Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____

Bowen Zhang Date

Broadening the applications of rhodium donor/acceptor carbene mediated C—H functionalization

By

Bowen Zhang

Doctor of Philosophy

Chemistry

Huw M. L. Davies, Ph.D.

Advisor

Frank E. McDonald, Ph.D.

committee member

Nathan T. Jui, Ph.D.

committee member

Accepted:

Lisa A. Tedesco, Ph.D.

Dean of the James T. Laney School of Graduate Studies

Date

Broadening the applications of rhodium donor/acceptor carbene mediated C–H functionalization

By

Bowen Zhang

B.S., Nankai University, Tianjin, China, 2015

Advisor: Huw M. L. Davies, Ph.D.

An abstract of

A dissertation submitted to the Faculty of the

James T. Laney School of Graduate Studies of Emory University

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

in Chemistry

2020

ABSTRACT

The first chapter is a general review of rhodium stabilized carbenes and their reactions, including introduction of basic concepts, development of carbene reactions and metal catalysts as well as recent progress with rhodium donor/acceptor carbene in C–H functionalization.

The second chapter is focused on exploring new reactions with rhodium vinyl carbenes, a special type of donor/acceptor carbene. A novel reaction of siloxydienes with *E*-vinyldiazoacetates in the presence of the bulky chiral dirhodium tetracarboxylate catalyst, Rh_2(*R*-*p*-PhTPCP)$_4$ results in an enantioselective [4+2] cycloaddition, in which three new stereogenic centers are formed. The [4+2] cycloadducts are generated as single diastereomers with high enantiocontrol (95-98% ee). When the diene contains an additional stereogenic center, effective kinetic resolution can be achieved.

The third chapter is focused on solving the limitation of the fixed aryl-ester moiety in products from our rhodium donor/acceptor carbene chemistry. The first attempt was exploring the reactivity profile of acceptor only carbene under our latest dirhodium catalysts. Secondary and tertiary selective C–H insertion with 2-methylpentane were achieved in moderate to good site-selectivity. However, these results did not surpass previous studies with other metal catalysts. Further test reactions with pentane showed serious issues of site-selectivity compared to donor/acceptor carbenes. The second attempt was to check the behavior of asymmetric cyclopropanation with rarely used donor only carbenes generated from retro-Büchner reaction under rhodium catalysis. The best ee achieved is 30%, suggesting poor catalyst-controlled chiral induction for donor only carbenes. The third try of developing general derivatizations of products from our rhodium donor/acceptor carbene turned out to be successful. Firstly, derivatization by removing the aryl part through Ru(VIII) oxidation/decarboxylation was studied. A few examples were achieved but the strong Ru(VIII) oxidation has narrow functional group tolerance. Therefore, we moved our focus to removing the ester part and a general derivatization was developed using hydrolysis followed by a photoredox decarboxylation. Under these mild conditions, various unique C–H functionalization compounds reported by our group were transformed to formal benzylation type of products in good yield and with maintained high stereoselectivity.

The fourth chapter describes a C–H functionalization approach for the synthesis of chiral C_2 symmetric 1,5-cyclooctadienes ligands. This is an example of applying our rhodium donor/acceptor carbene chemistry on relatively simple molecules to generate valuable chiral products. Chiral cyclooctadiene (COD) derivatives are readily prepared by rhodium-catalyzed allylic C–H functionalization of COD. Either mono- or di-functionalization of COD is possible generating the products in high yield, diastereoselectivity and enantioselectivity. The double C–H functionalization generates C_2 symmetric COD derivatives with four new stereogenic centers in >99% ee, which can be readily converted to a series of chiral COD ligands. Preliminary evaluations revealed that these COD ligands can be used in rhodium-catalyzed asymmetric arylation of cyclohex-2-enone, leading to the conjugate addition products in up to 76% ee.

The last chapter covers my experimental studies with an unusual observation initially discovered by Dr. Wenbin Liu. A direct cyclopropanation with N-sulfonyl piperidines and rhodium donor/acceptor carbenes was observed as minor byproducts during her piperidine C2 insertion studies. This unexpected observation intrigued us to explore the possibility of a catalyst controlled direct cyclopropanation of protected piperidines, which would save the trouble of preparing enamines as substrates as described in our reported methodology. Therefore, a systematic optimization was performed with this reaction regarding factors such as dirhodium catalysts, aryldiazoacetates, and reaction solvents. The best ratio of desired cyclopropanation versus the standard C2 insertion obtained to date was 1.87 : 1, suggesting achieving clean cyclopropanation will be challenging. Miscellaneous studies with other protected cyclic amines under the same conditions observed no cyclopropanation, suggesting the unique structural properties of *N*-sulfonylpiperidines for this type of reaction.

Broadening the applications of rhodium donor/acceptor carbene mediated C–H functionalization

By

Bowen Zhang

B.S., Nankai University, Tianjin, China, 2015

Advisor: Huw M. L. Davies, Ph.D.

A dissertation submitted to the Faculty of the

James T. Laney School of Graduate Studies of Emory University

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

in Chemistry

2020

ACKNOWLEDGEMENT

With the achievement of the last degree in my life, I would like to acknowledge profusely all those who have been part of this experience without whom I could not have complete this task.

First and foremost, I would like to give my special thanks to Professor Huw M. L. Davies, my advisor. One of the luckiest decisions I've made during my Ph.D. is my choice of a thesis advisor. Prof. Davies is an amazing supervisor by all means. He can always provide stimulating suggestions when my project is facing challenges. I could not have finished my program so smoothly without his patience, kindness and endless encouragement. Also, I learnt from him that I should keep an enthusiastic, confident and cautious mind in my future scientific research, which I deeply believe is priceless.

My thanks also go to my committee members, prof. Frank McDonald and prof. Nathan T. Jui. Your organic chemistry courses during my first two years of Ph.D. opened the gate of knowledge as well as strengthened my interest for organic chemistry. Your following generous help on my annual evaluations really made me understand my responsibility and goal as Ph.D. candidate. Your patient and considerate suggestions on my proposals really cultivated my professional writing abilities an also taught me how to challenge new ideas in a sensible manner.

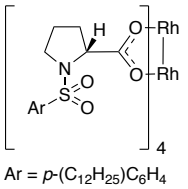
I would like to thank former group Postdocs that provided endless help on building my lab skills and knowledge of Chemistry. They are Dr. Wilkerson-Hill, Sidney, Dr. Jeffrey Mighion, Dr. Daniel Rackl, Dr. Sandeep Raikar, Dr. Cecilia Tortoreto and Dr. Solymer Negretti. It is your generous help that significantly contribute to my growing up as a qualified chemistry Ph.D. student.

I wish to thank all my past and current lab mates for daily help in life and academia. Thanks to all who has ever provided me with dirhodium catalysts and aryldiazoacetates. Thanks for all that taught me how to use group instruments. Thanks for sharing happiness and sadness during each group activities. You are all wonderful people and my daily memories with you are one of the shiniest part in my Ph.D. life. I would especially like to thank Dr. Jiantao Fu, who is not only my lab mate but also my best friend. I wish our friendship last forever.

Last but not least, my thanks to my family is beyond words. Thanks for support my choice of organic chemistry. It is no longer that hard a road with your comfort and understanding.

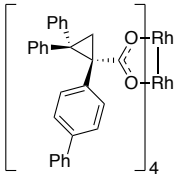
TABLE OF CONTENTS

LIST OF DIRHODIUM CATALYSTS

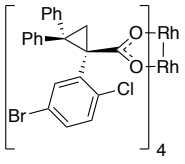


Ar = *p*-($C_{12}H_{25}$)C_6H_4

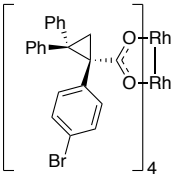
Rh_2(*R*-DOSP)$_4$



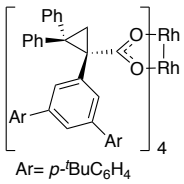
Rh_2[*R*-*p*-PhTPCP]$_4$



Rh_2(*R*-2-Cl-5-BrTPCP)$_4$

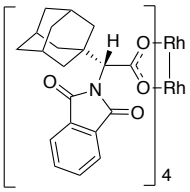


Rh_2[*R*-*p*-BrTPCP]$_4$

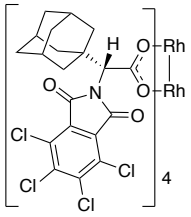


Ar= *p*-^{t}BuC_6H_4

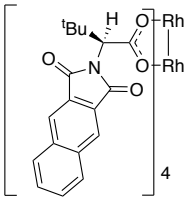
Rh_2[*R*-3,5-di(*p*-^{t}BuC_6H_4)TPCP]$_4$
Common name: Rh_2(Dibic)$_4$



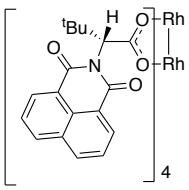
Rh_2(*R*-PTAD)$_4$



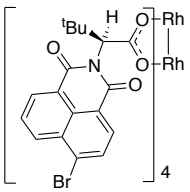
Rh_2(*R*-TCPTAD)$_4$



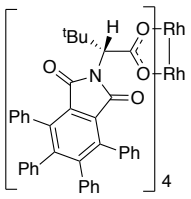
Rh_2(*S*-NaphTTL)$_4$



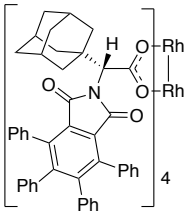
Rh_2(*R*-NTTL)$_4$



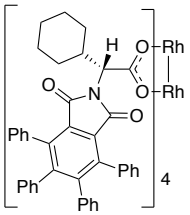
Rh_2(*S*-4-BrNTTL)$_4$



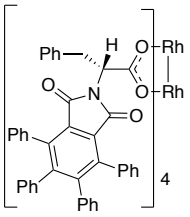
Rh_2(*R*-TPPTTL)$_4$



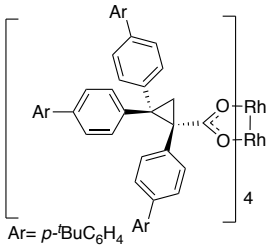
Rh_2(*R*-TPPTAD)$_4$



Rh_2(*R*-TPPTCL)$_4$

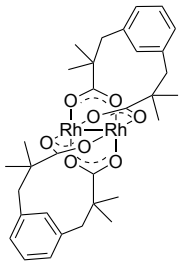


Rh_2(*R*-TPPTBL)$_4$

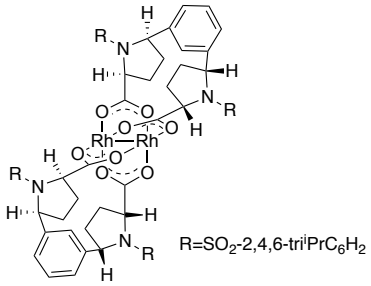


Ar= *p*-^{t}BuC_6H_4

Rh_2[*R*-tris(*p*-^{t}BuC_6H_4)TPCP]$_4$
Common name: Rh_2(Tribic)$_4$



Rh_2(esp)$_2$



R=SO_2-2,4,6-tri^{i}PrC_6H_2

Rh_2(S-biTISP)$_2$

Chapter One

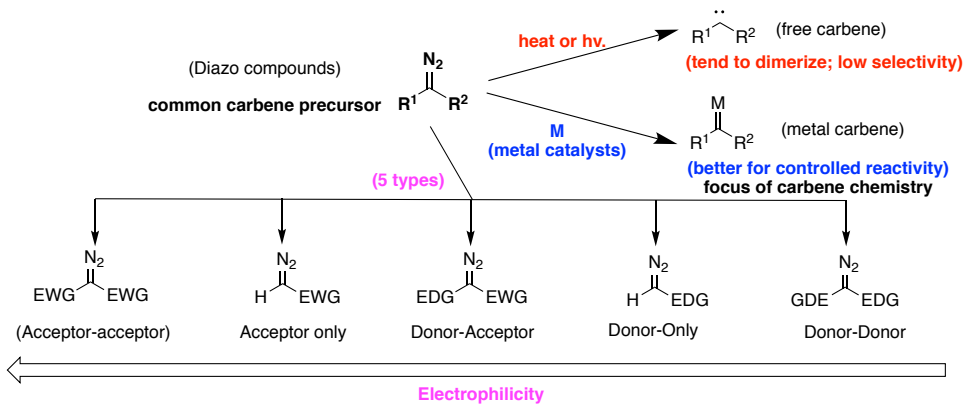
Overview of rhodium carbene chemistry

1.1 Introduction

Developing new methodologies is a continuous goal for synthetic organic chemists. We use these novel strategies to solve synthetic challenges of complicated molecules, optimize current synthetic routes to important medicinally related compounds as well as to test new chemical hypotheses and predictions. Metal-carbenoid mediated C–H functionalization has been an active focus of methodology studies since its discovery in the 1950s [1] and is becoming more valued in organic synthetic chemistry in recent years. The combination of rhodium tetracarboxylate catalysts with donor/acceptor type of carbene precursors has been shown by the Davies group to be applicable to w wider range of useful synthetic methods, such as, asymmetric cyclopropanation,[2-10] vinylogous reactions with rhodium vinyl carbene,[11-29] allylic C–H insertion followed by a Cope rearrangement[30-38] and site-selective C–H insertion of unactivated primary, secondary or tertiary C–H bonds.[39-43]

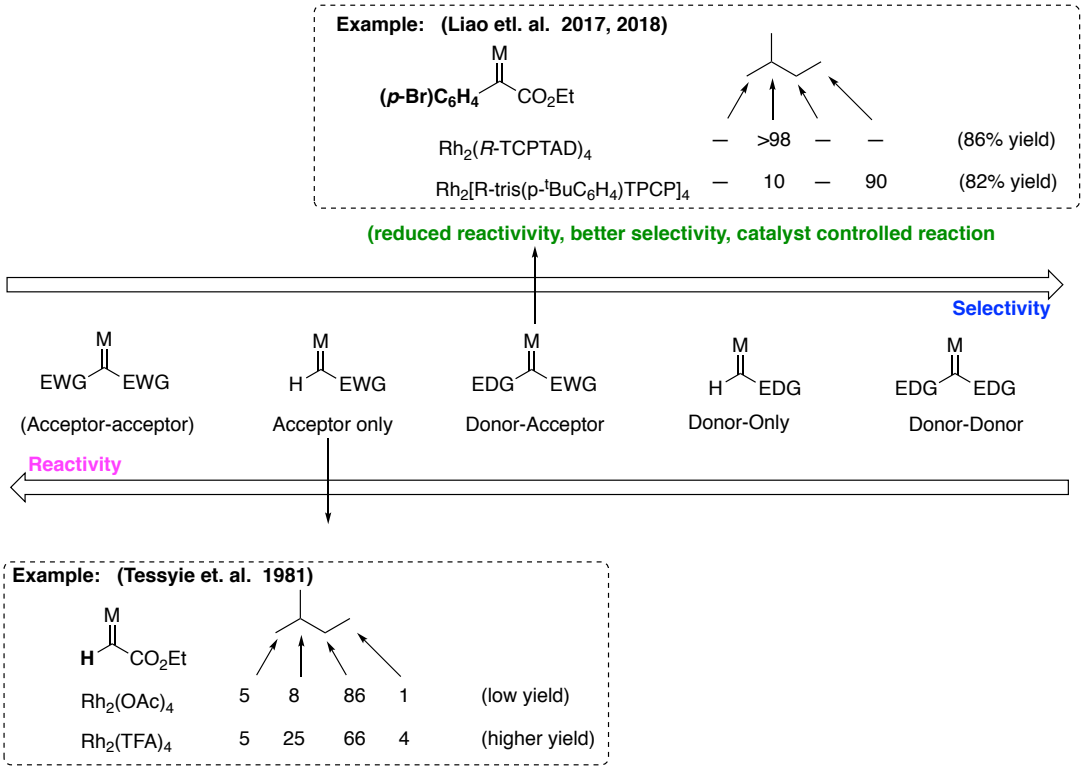
Electronic effects are decisive factors that influence the reactivity of carbenes. Based on this point, the carbenes generated from diazo compounds in **Figure 1** can be categorized into five types, acceptor/acceptor, acceptor only, donor/acceptor, donor only and donor/donor. Although free carbenes, generated from photodecomposition or thermal decomposition of diazo compounds, have shown to have some utility, including C–H functionalization,[44-45] free carbenes are still prone to self-dimerization and the reactions are not enantioselective.[46-48] Therefore, the background discussions will focus on the chemistry of metal-bonded carbenes.

Figure 1. Classification of diazo compounds based on electronic properties



Acceptor/acceptor and acceptor only carbenes are highly electrophilic and reactive. It is difficult to control the reactivity and selectivity of reactions with this type of carbene, as has been demonstrated in early studies of C–H insertion with alkanes (**Figure 2(a)**).[49-54] On the contrary, donor/acceptor carbenes developed by the Davies group can perform much more selective transformations. This is attributed to the reduced electrophilicity by the donor part, usually an aryl or a vinyl, that can donate electron density into the empty *p*-orbital of the carbene carbon.[55-56] The reduced electrophilicity leads to attenuated reactivity of donor/acceptor carbenes, enabling them to be delicately controlled by the steric and electronic features of different metal catalysts and eventually achieve highly site- and stereo-selective intermolecular reactions (**Figure 2(b)**).[39-41] A more detailed introduction to the reactivity profile of acceptor only carbenes versus donor/acceptor carbenes is illustrated in chapter three.

Figure 2 Reactivity and selectivity of different types of carbenes.

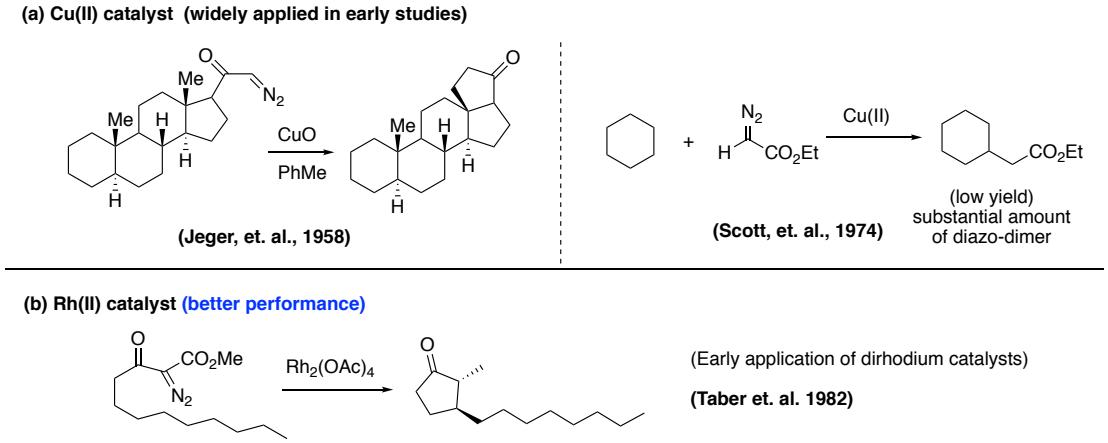


Donor only and donor/donor carbenes are the least electrophilic of the carbenes. Without any acceptor to balance the electronic properties of the carbene carbon, the reactivity of these carbenes is significantly inhibited. Although the Davies group recently has demonstrated that donor/donor carbene with both donors as aryl groups can perform asymmetric cyclopropanation with styrene as well as allylic C–H insertion to cyclohexadiene,[57] the intrinsic low reactivity of these carbenes still shows limited

applications. It would be very challenging to perform selective C–H insertion to unactivated C–H bonds like the donor/acceptor carbene did with donor only or donor/donor carbenes.

Copper catalysts are the most widely applied metal catalysts in early studies of carbene-induced C–H functionalization since the initial report of CuO-catalyzed intramolecular C–H insertion by Jeger et. al. in 1958.[1] Later Scott et. al. reported an early intermolecular reaction of ethyl diazoacetate with cyclohexane under Cu catalysis.[48] Wenkert et. al.[58] and Tabber et. al.[59] for the first time expanded the scope of transition metal catalysts to dirhodium catalysts in intramolecular metal-carbene reactions (**Figure 3**). The breakthrough to intermolecular rhodium-mediated carbene reactions was achieved by Teyssié et. al.[50-51] in the reaction of ethyl diazoacetates with alkanes. Although the selectivity is an issue with acceptor only type of carbenes, it was realized that rhodium(II) carboxylates can be more efficient for promoting carbene insertion compared to the early Cu catalysts. Since then, new dirhodium catalysts, especially chiral ones with better performance and selectivity have been developed by featuring different types of ligands.[60]

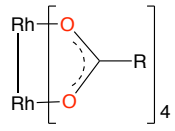
Figure 3 Metal catalysts for carbene reactions



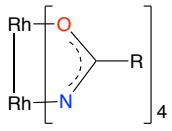
The most notable ligands of chiral dirhodium catalysts include three types, carboxylates, carboxamides, and phosphonates (**Figure 4**). Chiral dirhodium phosphonates were developed by Doyle[61] and Zhang[62] in 1992. However, these catalysts only achieved limited intramolecular reactions such as 2,3-sigmatropic rearrangement and C–H insertion with acceptor/acceptor carbenes.[61] Also, the asymmetric induction with chiral dirhodium phosphonates was generally very poor. Chiral dirhodium carboxyamidates were originally studied by the Doyle group and they can catalyze effective and highly

enantioselective intramolecular reactions with acceptor only carbenes.[63] Nevertheless, they did not show promising applications in intermolecular reactions.

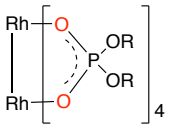
Figure 4 Classification of dirhodium catalysts based on ligand types.



Dirhodium carboxylates



Dirhodium carboxamidates

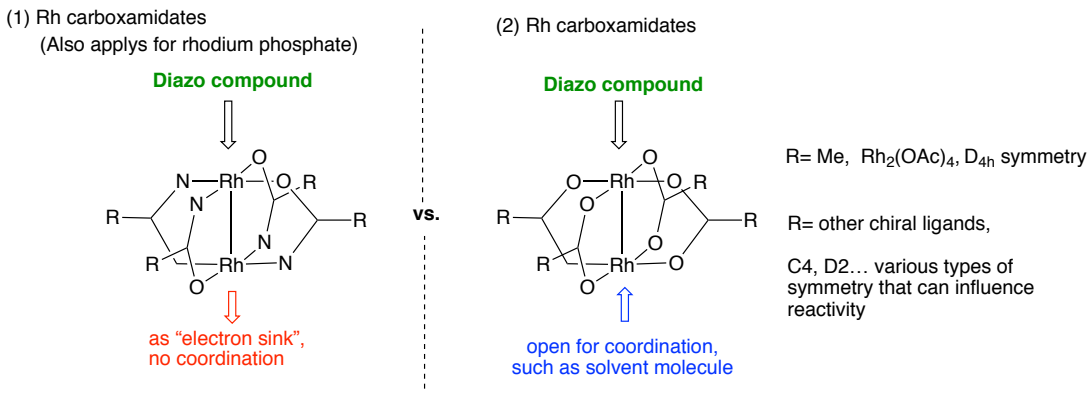


Dirhodium phosphates

Reactivity profile for carbene reaction	wide range of intra- and intermolecular reactions good enantioselectivity with chiral ligands	limited application, mostly for intramolecular reactions good enantioselectivity with chiral ligands	limited to intramolecular reactions Low enantioselectivity with chiral ligands

The most successful chiral dirhodium catalysts to date are dirhodium carboxylates. During a carbene reaction, unlike the former two types of dirhodium catalysts that have only one Rh site coordinated to the diazo compound while leaving the other Rh site open as an electron sink,[64] dirhodium carboxylates have both Rh sites open for coordination with diazo compounds or axial ligands (**Figure 5**). They are also considered to be kinetically more active towards diazo decomposition as well as the optimized type for selective C–H functionalization with donor/acceptor carbenes. Achiral $Rh_2(OAc)_4$ adopts a "paddlewheel complex" structure in strict D_{4h}-symmetry, however, different chiral ligands can alter the symmetry of the catalysts, which is illustrated in recent studies to be critical for the unique selectivity of each catalyst. [42, 43]

Figure 5 Structural features of dirhodium catalysts



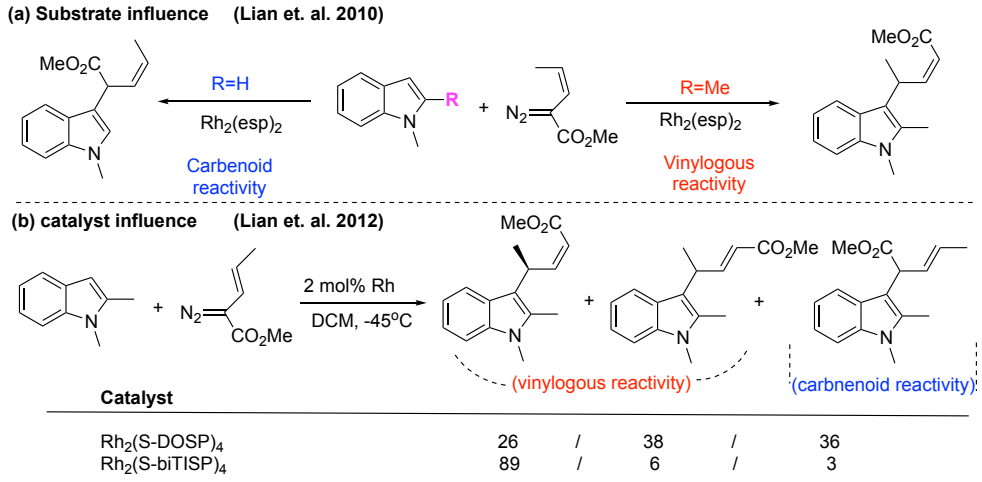
Applications of rhodium-carbene mediated C–H functionalization in the early days aware primarily limited to intramolecular reactions,[58,59,65-67] and the lack of selective intermolecular reactions was a limitation This is because intramolecular reactions generally require elaborate starting materials

bearing the diazo moiety. The synthesis of these compounds usually requires multiple steps and can be very challenging if the diazo-transfer step is not compatible with sensitive functional groups. Also, a successful intramolecular C–H functionalization is closely related to the steric properties around the diazo moiety within the specific starting material, yet it is impossible to develop a new C–H functionalization for each substrate. Therefore, more selective and generalizable intermolecular C–H functionalization methods were needed to build on Teyssié's early intermolecular reactions between ethyl diazoacetates and alkanes.[49-50]

The Davies group has achieved many remarkable intermolecular reactions through the use of a combination of donor/acceptor carbenes with newly developed tool box of chiral dirhodium catalysts featuring different reactivity and selectivity.[11-38, 39-43] Rhodium donor/acceptor carbenes applied in our chemistry can be categorized into two types based on the donor feature of diazo compounds. The first type is vinyldiazoacetates, which has an alkenyl group as the donor. The second type is aryldiazoacetates, in which the donor is an aryl or heteroaryl functional group.

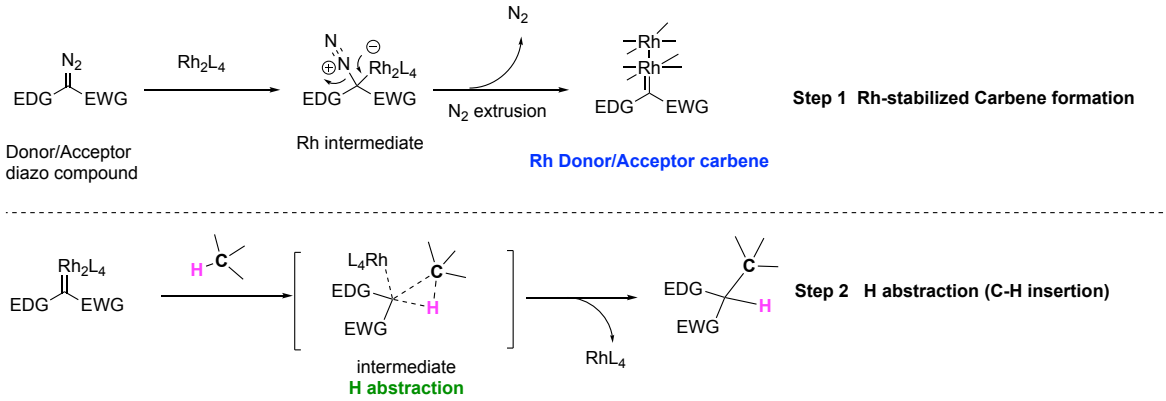
Vinyldiazoacetates react with dirhodium catalysts to form rhodium vinyl carbenes, which can participate in further reactions either initiated at the carbene carbon site or the vinylogous carbon site. the unique feature of two reactive sites within the rhodium-bound vinylcarbene intrigued us to explore catalyst-controlled site-selectivity. An early successful example is the reaction of rhodium vinylcarbene with substituted indoles, in which selective reactions at the carbenoid site and the vinylogous site can be achieved by modifying the steric feature of indole substrates and the dirhodium catalysts (**Figure 6**). It suggests that steric properties of substrates and the catalysts can have significant influence on the reaction outcome. Since then, many interesting reactions with rhodium vinylcarbene have been developed.[11-29] A limitation for vinyl carbene is that it tends to cyclize by itself to form byproducts, so the reaction generally requires reactive substrates such as alkene or allylic C–H bonds and lower reaction temperature. The reactivity profiles of these rhodium vinyl carbenes will be discussed in more detail in Chapter 2.

Figure 6 Examples of regioselective reactions with rhodium vinyl carbene



Rhodium donor/acceptor carbenes from aryldiazoacetates were more stable compared to the vinyl carbenes and are more frequently studied for asymmetric cyclopropanation as well as intermolecular C–H insertion reactions. The cyclopropanation is beyond the discussion of this thesis so it is not introduced in this overview. A general intermolecular C–H insertion reaction with rhodium donor/acceptor carbene involves two steps. The initial step is the formation of a transient rhodium-carbene intermediate *in situ* accompanied by the nitrogen extrusion. The second step is insertion of this highly reactive intermediate to a C–H bond through a hydride abstraction (**Figure 7**).[75]

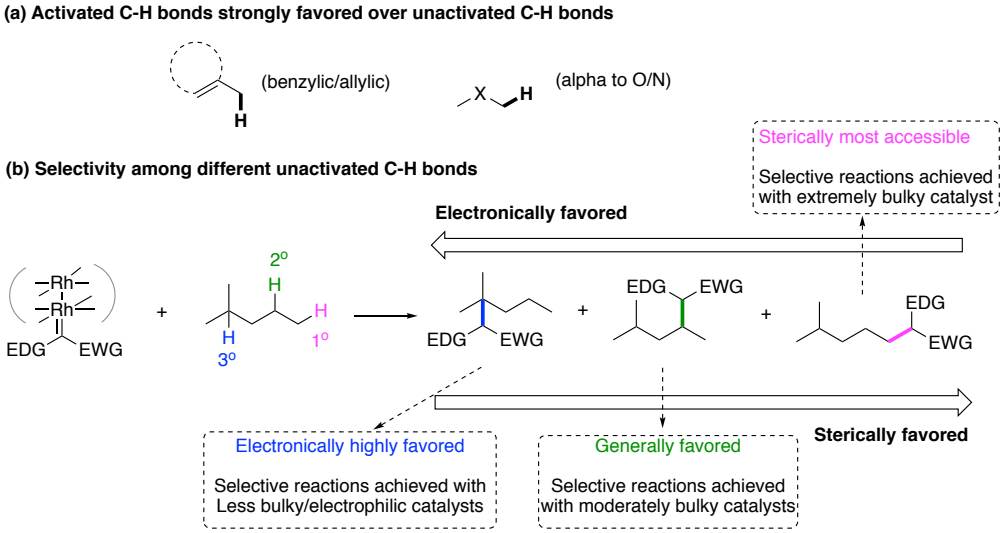
Figure 7 General mechanism for rhodium donor/acceptor carbene mediated C–H insertion



The specific site-selectivity of a reaction is mainly controlled by the electronic and steric features of the substrates and the rhodium carbenes (**Figure 8**). The site on the substrate that can better stabilize partial positive charge during the insertion of the electrophilic rhodium carbene into the C–H bond is

more favored. Therefore, electronically, the reactivity of a C–H bond toward functionalization is: activated (benzylic/allylic) > 3° > 2° > 1°. However, rhodium carbene surrounded with bulky chiral ligands can hinder the reaction with sterically congested sites such as a 3° C–H bond. A combination of these effects leave 2° C–H bonds to be commonly preferred reactive sites, and many 2° selective C–H insertion reactions have been developed by our group.[40,42,43] Highly sterically encumbered dirhodium tetracarboxylate catalysts can suppress the 2° C–H insertion and push the reaction to favor the most open 1° C–H bonds.[39]

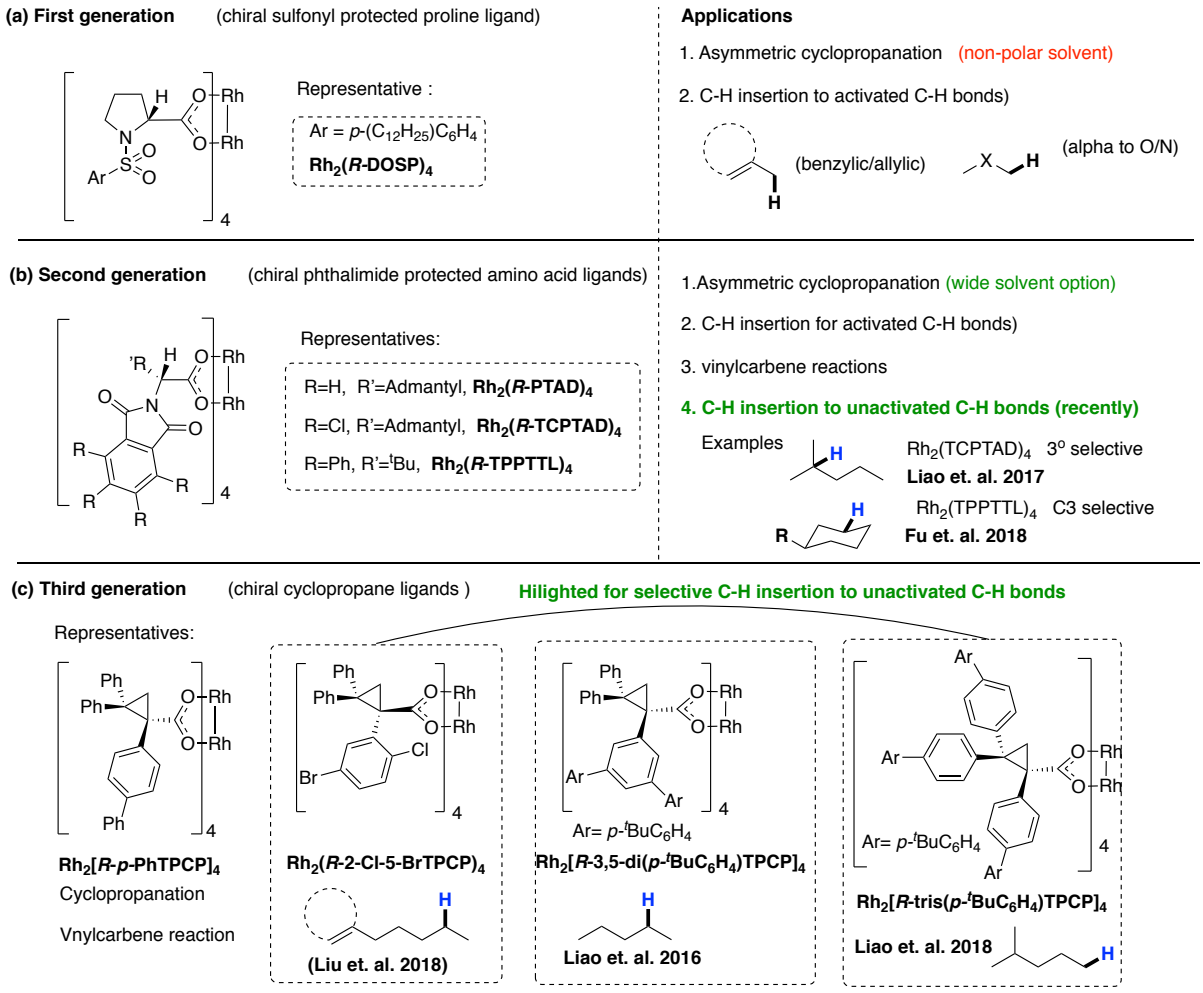
Figure 8 General trend for the site-selectivity of a C–H insertion reaction



A major goal of the Davies group is to develop a toolbox of dirhodium catalysts that can target different types of C–H bonds. There are three generations of chiral dirhodium tetracarboxylate catalysts commonly used based on the ligand type (**Figure 9**). The first generation includes chiral sulfonyl proline ligand-based catalysts developed by our group.[60,68] $Rh_2(DOSP)_4$ is the most widely applied one among this type that has a dodecyl chain on the sulfonyl proline ligand. This long aliphatic chain allows the catalyst to have good solubility in non-polar solvents, such as pentane, which is the optimized solvent for many reactions with $Rh_2(DOSP)_4$.[68] It can catalyze highly enantioselective cyclopropanation as well as C–H insertion reactions at activated C–H bonds (**Figure 9 (a)**).[60] The second generation includes chiral phthalimido protected amino acid ligand-based catalysts that originally developed by the Hashimoto group.[69-71] A representative catalyst is $Rh_2(PTAD)_4$, which adopts a C_4 symmetrical structure. The much more rigid ligand enables this catalyst to catalyze some unique reactions.[64] New

members of the 2nd generation catalysts developed by the Davies group further expanded the application to site-selective intermolecular C–H insertions with unactivated C–H bonds (**Figure 9 (b)**). The third generation are chiral triarylcyclopropane ligand-based catalysts (**Figure 9 (c)**). The chiral cyclopropane ligands are prepared from asymmetric cyclopropanation reactions under the catalysis of the first and the second generation of dirhodium catalysts.[39-42,73,74] These catalysts are generally considered to be sterically congested and they can adopt different symmetries depending on the substitution pattern of the triarylcyclopropane ligand. These catalysts are capable of achieving highly regioselective C–H insertion reactions towards unactivated 2° or 1° C–H bonds.[39-42] Some prominent C–H insertion reactions from our group in recent years are briefly noted in Figure 9, and in more detail in Chapter 3.

Figure 9 Three generation of chiral dirhodium catalysts in the Davies lab and their applications



1.2 Conclusion

Rhodium carbene chemistry has been a thriving field ever since its discovery decades ago and many novel methodologies have been developed that feature various C–H functionalization strategies. The Davies group achieved remarkable site- and stereoselective C–H functionalization reactions through the use of donor/acceptor carbenes and the development of new dirhodium catalysts. Some notable catalyst-controlled intermolecular C–H insertion reactions developed by the Davies group include primary, secondary or tertiary selective functionalization of pentane derivatives;[40] selective terminal C2 or benzylic functionalization of linear alkyl benzenes[42] and desymmetrization of substituted alkyl cyclohexane.[43]

Despite the unprecedented reactivity and selectivity of these novel reactions, several limitations remain to be explored in further studies. One major limitation is that C–H functionalization products contain the donor/acceptor moiety (aryl ester or vinyl ester). The substrate scope could also benefit from further expansion to sophisticated systems beyond hydrocarbons, which could limit late-stage applications.

In this thesis, the main focus of study is broadening the potential application of rhodium donor/acceptor carbene chemistry from three aspects. The first aspect is to take advantage of the vinylogous reactivity of rhodium vinyl carbene and develop novel reactions. The second aspect is to explore direct and indirect solutions to broaden the scope of the products formed in C–H functionalization beyond the standard donor/acceptor functionality. Specifically, the direct solution is to explore other types of carbenes such as acceptor only carbene using our latest toolbox of chiral dirhodium catalysts, and the indirect solution is to develop general derivatizations of successful and unique C–H functionalization products from donor/acceptor diazo compounds. In addition, this thesis will also cover some miscellaneous exploratory studies using rhodium carbene chemistry.

1.3 References

1. Greuter, F.; Kalvoda, J.; Jeger, O. *Proc. Chem. Soc.* **1958**, 349.

2. Davies, H. M.; Townsend, R. J. *J. Org. Chem.* **2001**, *66*, 6595.

3. Negretti, S.; Cohen, C. M.; Chang, J. J.; Guptilll, D. M.; Davies, H. M. L. *Tetrahedron*, **2015**, *71*,

7415.

4. Chepiga, K. M.; Qin, C.; Alford, J. S.; Chennamadhavuni, S.; Gregg, T. M.; Olson, J. P.; Davies, H. M. L. *Tetrahedron* **2013**, *69*, 27.

5. Wu, W.; Lin, Z.; Jiang, H. *Org. Biomol. Chem.* **2018**, *16*, 7315.

6. Wang, H.; Guptilll, D. M.; Alvarez, A. V.; Musaev, D. G.; Davies, H. M. L. *Chem. Sci.* **2013**, *4*, 2844.

7. Davies, H. M. L.; Lee, G. H. *Org. lett.* **2004**, *6*, 2117.

8. Denton, J. R.; Sukumaran, D.; Davies, H. M. L. *Org. lett.* **2007**, *9*, 2625.

9. Tinoco, A.; Steck, V.; Tyagi, V.; Fasan, R. *J. Am. Chem. Soc.* **2017**, *139*, 5293.

10. Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.

11. Davies, H. M. L.; Saikali, e.; Young, W. B. *J. Org. Chem.* **1991**, 56, 5696

12. Lian, Y. J.; Davies, H. M. L. *Org. Lett.* **2010**, 12, 924.

13. Lian, Y. J.; Davies, H. M. L. *Org. Lett.* **2012**, *14*, 1934.

14. Valette, D.; Lian, Y. J.; Haydek, J. P.; Hardcastle, K. I.; Davies, H.M. L. *Angew. Chem. Int. Ed.* **2012**, *51*, 8636.

15. Smith, A. G.; Davies, H.M. L. *J. Am. Chem. Soc.* **2012**, *134*, 18241.

16. Qian, Y.; Xu, X. F.; Wang, X. C.; Zavalij, P. J.; Hu, W. H.; Doyle, M. P. *Angew. Chem. Int. Ed.* **2012**, *51*, 5900.

17. Qian, Y.; Zavalij, P. J.; Hu, W. H.; Doyle, M. P. *Org. Lett.* **2013** *15*, 1564.

18. Wang, X. C.; Abrahams, Q. M.; Zavalij, P. J.; Doyle, M. P *Angew. Chem. Int. Ed.* **2012**, *51*, 5907.

19. Wang, X. C.; Xu, X. F.; Zavalij, P. Y.; Doyle, M. P *J. Am. Chem. Soc.* **2011**, *133*, 16402.

20. Xu, X. C.; Leszczynski, J. S.; Mason, S. M.; Zavalij, P. Y.; Doyle, M. P. *Chem. Commmun.* **2014**, *50*, 2462.

21. Xu, X. C.; Zavalij, P. Y.; Doyle, M. P. *J. Am. Chem. Soc.* **2013**, 1*35*, 12349.

22. Xu, X. F.; Doyle, M. P. *Acc. Chem. Res.* **2014**, *47,* 1396.

23. Xu, X. F.; Doyle, M. P. *Aust. J. Chem.* **2014**, *67*, 365.

24. Xu, X. F.; Ratnikov, M. O.; Zavalij, P. Y.; Doyle, M. P. *Org. Lett.* **2011**, *13*, 6122.

25. Xu, X. F.; Zavalij, P. Y.; Doyle, M. P *Angew. Chem. Int. Ed.* **2013**, *52*, 12664.

26. Xu, X. F.; Zavalij, P. Y.; Hu, W. H.; Doyle, M. P. *J. Org. Chem.* **2013**, *78*, 1583-1588.

27. Qin, C.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 14516.

28. Lian, Y. J.; Hardcastle, K. I.; Davies, H.M. L. **2011**, *50*, 9370.

29. Guzmán, P. E.; Lian, Y.; Davies, H. M. L. *Angew. Chem., Int. Ed.* **2014**, *53*, 13083.

30. Davies, H. M. L.; Beckwith, R. E. J. *J. Org. Chem.* **2004**, *69*, 9241.

31. Davies, H. M. L.; Lian, Y. *Acct. Chem. Res.* **2012**, *45*, 923.

32. Lian, Y.; Davies, H. M. L. *J. Am. Chem. Soc.* **2011**, 133, 11940.

33. Davies, H. M. L.; Lian, Y. *Acct. Chem. Res.* **2012**, *45*, 923.

34. Davies, H. M. L.; Dai, X.; Long, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 2485.

35. Lian, Y.; Hardcastle, K. I.; Davies, H. M. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 9370.

36. Hansen, J. H.; Gregg, T. M.; Ovalles, S. R.; Lian, Y.; Autschbach, J.; Davies, H. M. L. *J. Am. Chem. Soc. 2011*, **133**, 5076.

37. Hodgson, D. M.; Labande, A. H.; Pierard, F. Y. T. M.; Expósito Castro, M. Á. *J. Org. Chem.* **2003**, *68*, 6153.

38. Spangler, J. E.; Lian, Y.; Raikar, S. N.; Davies, H. M. L. *Org. lett.* **2014**, *16*, 4794.

39. Liao, K.; Yang, Y., Sander, J., Houk, K., Musaev, D. G,, Davies, H. M. L. *Nature Chemistry.* **2018**, *10*, 1048.

40. Liao, K.; Negretti, S.; Musaev, D. G.; Bacsa, J.; Davies, H. M. L. *Nature*, **2016**, *533*, 230

41. Liao, K.; Pickel, T. C.; Boyarskikh, V.; Bacsa, J.; Musaev, D. G.; Davies, H. M. L. *Nature*, **2017**, *551*, 609

42. Liu, W.; Ren, Z.; Bosse, A. T.; Goldstein, E. L.; Bacsa, J.; Musaev, D. G.; Stoltz, B. M.; Davies, H. M. L. *J. Am. Chem. Soc.* **2018**, *140*, 12247.

43. Fu, J.; Ren, Z. Bacsa, J.; Musaev, D. G.; Davies, H. M. L. *Nature*, **2018**, *564*, 395.

44. Tortoreto, C.; Rackl, D.; Davies, H. M. L. *Org. Lett.* **2017**, *19*, 770

45. Jurberg, I. D.; Davies, H. M. L. *Chem. Sci.*, **2018**, *9*, 5112

46. Moser, W. R. *J. Am. Chem. Soc.* **1969**, *91*, 1135.

47. Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765.

48. Scott, L. T.; DeCicco, G. J. *J. Am. Chem. Soc.* **1974**, *96*, 322.

49. Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssie, P. *J. Chem. Soc., Chem. Commun.* **1981**, 688.

50. Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssie, P. *Bull. Soc.Chim. Belg.* **1984**, *93*, 945

51. Demonceau, A.; Noels, A. F.; Teyssie´, P.; Hubert, A. *J. Mol. Catal.* **1988**, *49*, L13.

52. Demonceau, A.; Noels, A. F.; Hubert, A. *J. Mol. Catal.* **1989**, *57*, 149.

53. Demonceau, A.; Noels, A. F.; Costa, J. L.; Hubert, A. *J. Mol. Catal.* **1990**, *58*, 21.

54. Dı´az-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pe´rez, P. J. *J. Am. Chem. Soc*. **2002**, *124*, 896.

55. Davies, H. M. L.; Panaro, S. A. *Tetrahedron* **2000**, *56*, 4871.

56. Hansen, J.; Autschbach, J.; Davies, H. M. L. *J. Org. Chem.* **2009**, *74*, 6555

57. Lee, M.; Ren, Z.; Musaev, D. G.; Davies, H. M. L. *ACS Catalysis,* **2020**, *10*, 6240

58. Wenkert, E.; Davis, L. L.; Mylari, B. L.; Solomon, M. F.; Da Silva, R. R.; Shulman, S.; Warnet, R. J.; Ceccherelli, P.; Curini, M.; Pellicciari, R. *J. Org. Chem.* **1982**, *47*, 3242.

59. Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808.

60. Davies, H. M.; Beckwith, R. E. *Chem. Rev.* **2003**, *103*, 2861.

61. McCarthy, N.; McKervey, M. A.; Ye, T.; McCann, M.; Murphy, E.; Doyle, M. P. *Tetrahedron lett.* **1992**, *33*, 5983.

62. Pirrung, M. C.; Zhang, J. *Tetrahedron lett.* **1992**, *33*, 5987.

63. Timmons, D. J.; Doyle, M. P. *J. Organomet. Chem.* **2001**, *617*, 98.

64. Davies, H. M. L. *Chem. Soc. Rev.* **2011**, *40*, 1857.

65. Yoon, C. H.; Flanigan, D. L.; Chong, B.-D.; Jung, K. W. *J. Org.Chem.* **2002**, *67*, 6582.

66. Yoon, C. H.; Nagle, A.; Chen, C.; Gandhi, D.; Jung, K. W. *Org.Lett.* **2003**, *5*, 2259.

67. Jung, Y. C.; Yoon, C. H.; Turos, E.; Yoo, K. S.; Jung, K. W. *J. Org. Chem.* **2007**, *72*, 10114

68. Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.

69. Hashimoto, S.-i.; Watanabe, N.; Sato, T.; Shiro, M.; Ikegami, S. *Tetrahedron lett.* **1993**, *34*, 5109.

70. Yamawaki, M.; Tsutsui, H.; Kitagaki, S.; Anada, M.; Hashimoto, S. *Tetrahedron lett.* **2002**, *43*,

9561.

71. Tsutsui, H.; Abe, T.; Nakamura, S.; Anada, M.; Hashimoto, S. *Chem. Pharm. Bull.* **2005**, *53*, 1366.

72. DeAngelis, A.; Dmitrenko, O.; Yap, G. P. A.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, 131, 7230.

73. Qin, C.; Boyarskikh, V.; Hansen, J. H.; Hardcastle, K. I.; Musaev, D. G.; Davies, H. M. L. *J. Am. Chem. Soc.* **2011**, *133*, 19198.

74. Qin, C.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014**, *136*, 9792.

75. Davies, H. M.; Manning, J. R. *Nature* **2008**, *451*, 417.

Chapter Two

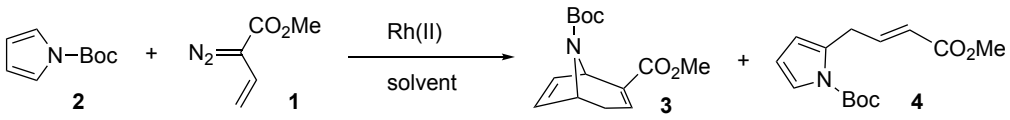
Enantioselective [4+2] Cycloaddition of Rh-vinylcarbenes with Dienes[31]

2.1 Introduction

In the mid 1980's, we began exploring intermolecular reactions of vinyldiazoacetates with dienes.[1] Since then, a large number of synthetically useful transformations of these vinylcarbenes have been developed, such as cyclopropanation,[2] tandem cyclopropanation/Cope rearrangement,[2,3] C–H functionalization,[4] combined C–H functionalization/Cope rearrangement and various more elaborate cascade reactions.[5,6]

The vinylogous reaction of Rh-vinylcarbene was initially observed in the reaction of unsubstituted vinyldiazoacetate **1** and N-Boc pyrrole **2**.[7] Besides the formation of the typical cycloadduct **3** from tandem cyclopropanation followed by Cope rearrangement, another product **4** with alkylation at the vinylogous position of the pyrrole was also observed (**Scheme 1**). This was viewed as a side reaction during these early studies of rhodium carbene chemistry because such transformations were limited to terminal unsubstituted vinylcarbenes, and consequently, do not generate any new stereogenic centers. In addition, conditions for clean vinylogous product formation was not available at that time.

Scheme 1 Early observation of vinylogous reactivity of rhodium vinylcarbene

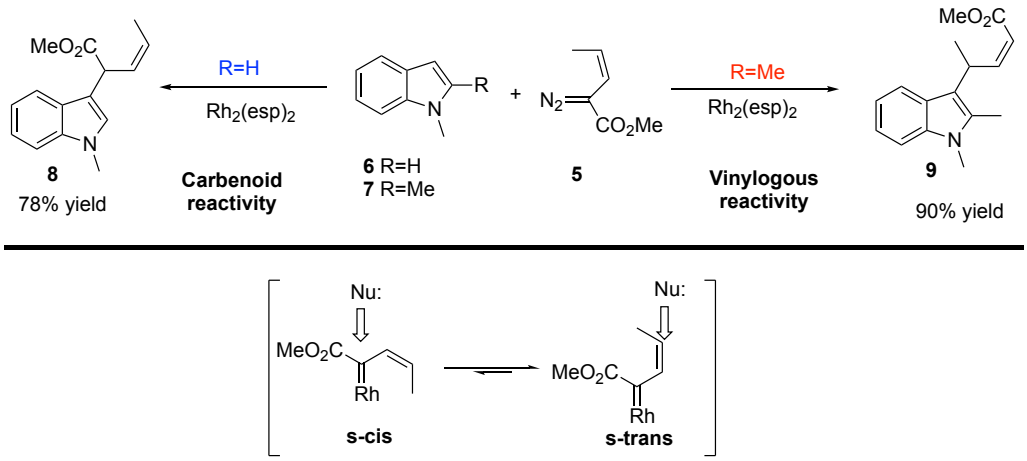


Cat. / Solvent	3		4
$Rh_2(OAc)_4$ / CH_2Cl_2	55	:	41
$Rh_2(TFA)_4$ / CH_2Cl_2	15	:	85
$Rh_2(OHex)_4$ / hexane	> 95	:	5

Recently, vinylogous reactions were successfully applied for developing new synthetic methods. In the reaction of *cis*-substituted vinyldiazoacetate **5** with indoles,[8] it was found that the reaction outcome was dependent on the steric hinderance around the indole. The reaction with *N*-methyl indole **6** occurred at the carbenoid site to give **8**, while the reaction with more sterically crowded 1,2-dimethylinodle **7** occurred at the vinylogous position to give **9** (**Scheme 2**). In the reaction with 1,2-dimethylindole **7**, the Z-isomer of product **9** was proposed to indicate that the *cis* conformation of **5**

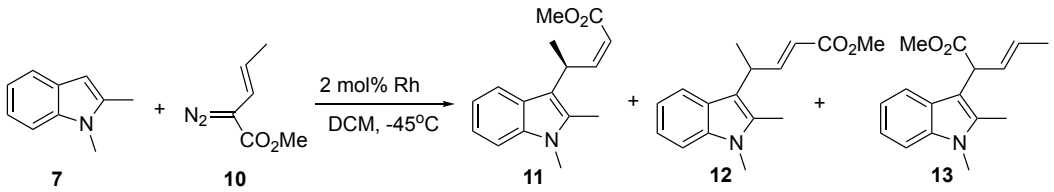
forced the rhodium carbene to prefer *s-trans* configuration, in which the carbenoid site is less accessible compared to the vinylogous site. This also indicates that resulting vinyl rhodium intermediate is protonated stereospecifically.

Scheme 2 reaction of cis-substituted vinyldiazoacetate with substituted indoles.



Asymmetric vinylogous reactions of rhodium vinylcarbene with the indole system was also developed using our chiral dirhodium catalysts.[9] Although the achiral vinylogous reaction was achieved with *cis*-vinyldiazoacetate **5**, attempts at achieving chiral reactions proceeded with low enantioselectivity. Therefore, the current study focused on *trans*-vinyldiazoacetate **10**. Unlike cis-vinyldiazoacetate **5**, **10** does not have internal steric factors that favor s-trans configuration of rhodium vinylcarbene, so the proposed controlling factor comes from the bulky dirhodium catalysts. The steric demanding ligand on the rhodium could push the rhodium vinylcarbene configuration to favor s-trans and enable the vinylogous reaction with 1,2-dimethylindole **7** to happen. The catalysts screening identified Rh_2(*S*-biTISP)$_4$ as the optimized catalyst to generate vinylogous reaction product **11** with good regio- and enantioselectivity.

Scheme 3 reaction of trans-substituted vinyldiazoacetate with substituted indole

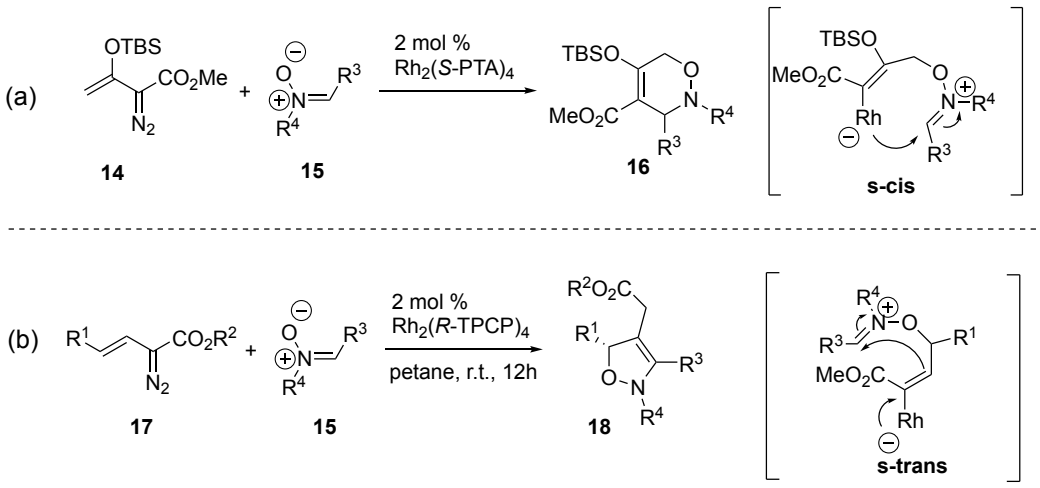


7 10 11 12 13

Catalyst	11 / 12 / 13	yield of 11	ee. of 11
$Rh_2(OAc)_4$	62 / 33 / 5	57	---
$Rh_2(TFA)_4$	49 / 44 / 7	43	---
$Rh_2(esp)_2$	74 / 26 / 0	52	---
Rh_2(S-PTAD)$_4$	76 / 16 / 8	55	-8
Rh_2(S-DOSP)$_4$	26 / 38 / 36	22	17
Rh_2(S-TISP)$_4$	89 / 6 / 5	66	39
Rh_2(S-biTISP)$_4$	**89 / 6 / 3**	**66**	**89**

The Davies group[10,11,23] and the Doyle group[12-22] in recent years have conducted independent studies on the reactions of siloxyvinyldiazoacetates with various trapping agents. These reactions are considered to proceed by means of vinylogous functionalization of the rhodium vinylcarbenes. Doyle et. al.[15] demonstrated a [3+3] cycloaddition between siloxyvinyldiazoacetate **14** and nitrones **15** (**Scheme 4(a)**), in which the rhodium vinylcarbenes were proposed to exist in the *s-cis* configuration. Davies et. al. tested this hypothesis[23] by using a *trans*-substituted vinyldiazoacetate **17** to react with the nitrone **15** under the catalysis of a bulky dirhodium catalyst Rh_2(*R*-TPCP)$_4$, which by analogy to the study with substituted indoles[9] would be expected to react through the rhodium vinylcarbene in the *s-trans* configuration. Indeed, a different [3+2] type of cycloadduct **18** was observed in this reaction **(Scheme 4(b)).**

Scheme 4 [3+3] and [3+2] cycloaddition between vinyldiazoacetates and nitrones

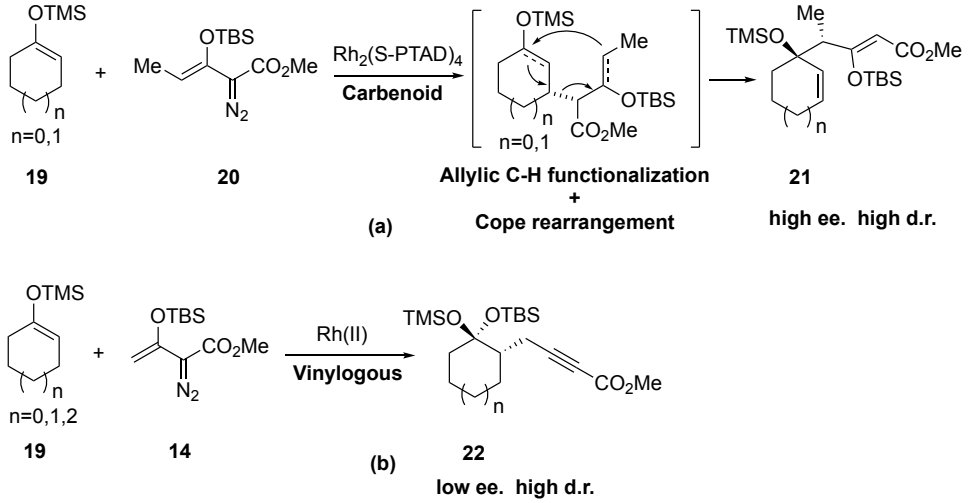


14 15 16 17 18

The reaction of siloxyvinyldiazoacetates with cyclic silyl enol ethers can generate different products depending on the terminal substitution of vinyldiazo compounds. Cyclic enol ether **19** reacts

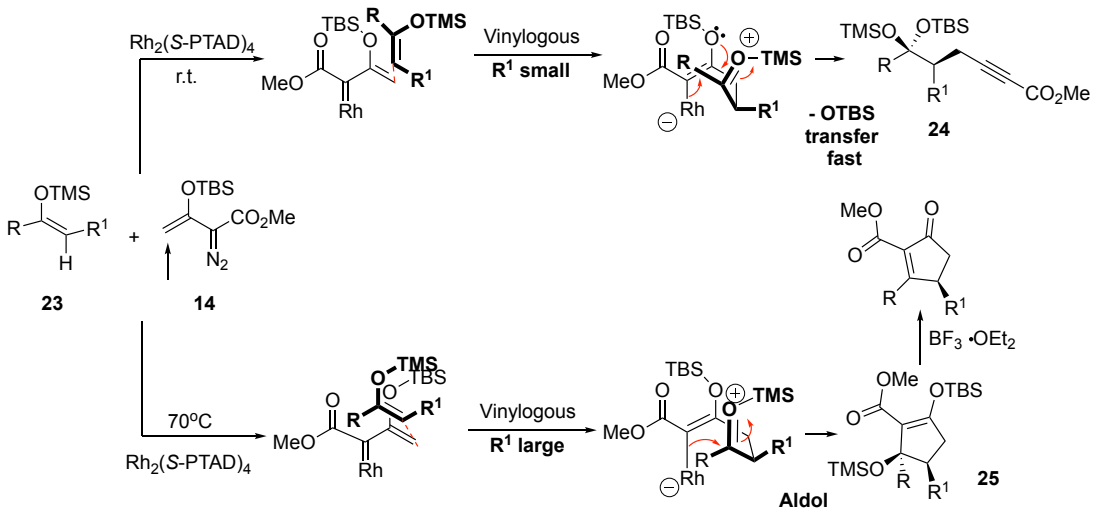
with terminal methyl substituted (Z)-siloxyvinyldiazoacetate **20** at the carbenoid site to give allylic C–H functionalization/Cope rearrangement product **21** with high ee. and d.r. under catalyst Rh_2(*S*-PTAD)$_4$ (**Scheme 5(a)**).[24] However, the reaction of the same cyclic enol ether **19** with terminal unsubstituted siloxyvinyldiazoacetate **14** occurs at the vinylogous position, followed by an unusual 1,4-siloxy group transfer, giving the final alkynolate product **22** with excellent diastereoselectivity but only low to moderate ee. (**Scheme 5(b)**).[10]

Scheme 5 Allylic C–H functionalization/Cope rearrangement vs. alkynoate formation for the reaction of siloxyvinyldiazoacetates with cyclic silyl enol ethers



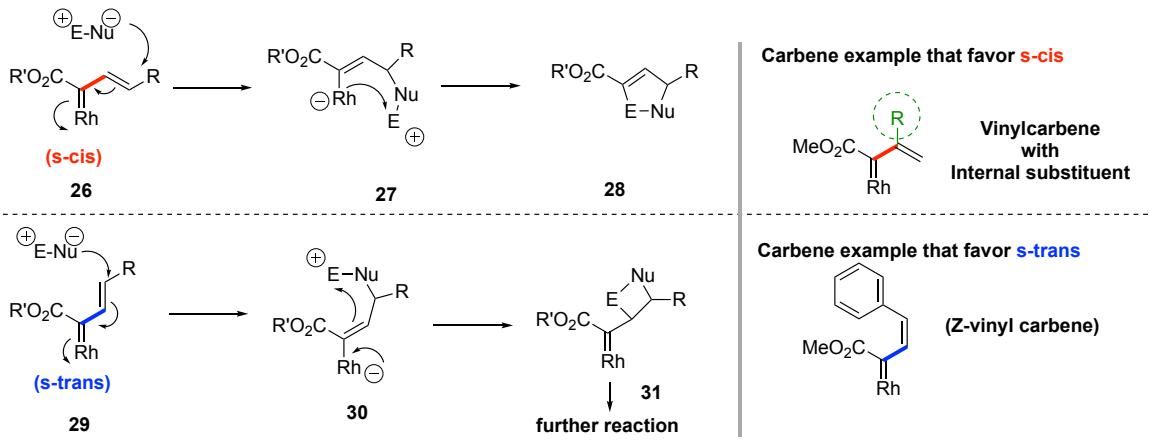
Further exploration of the reaction between siloxyvinyldiazoacetates and acyclic silyl enol ethers also shows that the steric factors associated with the diene substrates can influence the reaction outcome.[11] In the reaction of acyclic (Z)-silyl enol ethers **23** with terminal unsubstituted siloxyvinyldiazoacetate **14**, less crowded silyl enol ethers (**Scheme 6 (small R^1)**) at room temperature under Rh_2(*S*-PTAD)$_4$ catalyst will experience a fast 1,4-siloxy group transfer and generate the di-siloxy-ketal product **24**. However, more crowded silyl enol ethers (**Scheme 6 (large R^1)**) with elevated reaction temperature at 70 ºC will generate a formal [3+2] aldol type of reaction product **25**.

Scheme 6 Diverse reaction of acyclic enol ethers with siloxyvinyldiazoacetates



These results indicate that the configuration of rhodium vinylcarbene will significantly influence the geometry of vinyl rhodium intermediate and lead to a different reaction outcome. A general reaction pattern was proposed for the vinylogous reaction of rhodium vinylcarbene (**Scheme 7**). Vinylcarbenes with an internal substituent will preferentially adopt *s-cis* configuration **26** [8,25] while *Z*-vinylcarbene tends to react with s-*trans* configuration **29**.[23] *E*-vinylcarbene is more flexible and can react through s-*cis* or s-*trans* configuration.[9] The s-*cis* configuration **26** will lead to intermediate **27** that can directly cyclize to give product **28**,[11,15,26] while s-*trans* configuration **29** will generate intermediate **30** that cannot directly cyclize. It will form a temporary new rhodium carbene **31** and undergo further reactions such as 1,2 H-shift to give product with smaller-sized ring. Recently, we have found that bulky dirhodium catalysts can cause *E*-vinylcarbene to preferentially react in the s-*trans* conformation, [9, 23] and it has been confirmed by computational study.[27]

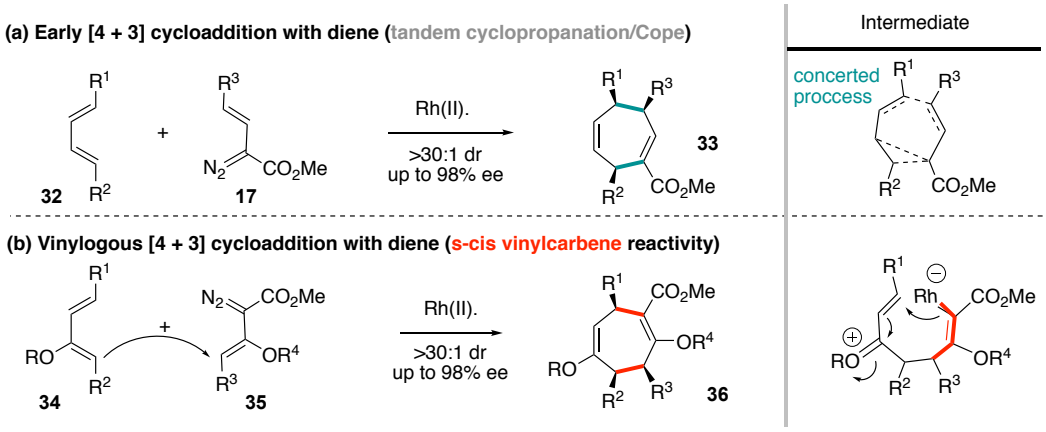
Scheme 7 General reaction pattern for s-*cis*/s-*trans* configuration of rhodium vinylcarbene



***E*-vinylcarbene can react in both configuration, but bulky dirhodium catalysts can pish it towards s-trans**

The Davies group also studied reactions of siloxyvinyldiazoacetates with siloxy dienes. An early example is the formal [4+3] cycloaddition from cyclopropanation/Cope rearrangement.[3] It does not engage the vinylogous reactivity of rhodium vinylcarbenes (**Scheme 8(a)**). Recently, a different [4+3] cycloaddition between rhodium vinylcarbenes and dienes that involves vinylogous reactivity was developed.[25] This reaction is conducted with a vinylcarbene that has an internal siloxy substituent, which would favor s-cis configuration during the reaction and generate the intermediate that can directly cyclize to form a seven membered ring product **36** with opposite regioselectivity compared to the earlier [4+3]. (**Scheme 8(b)**).

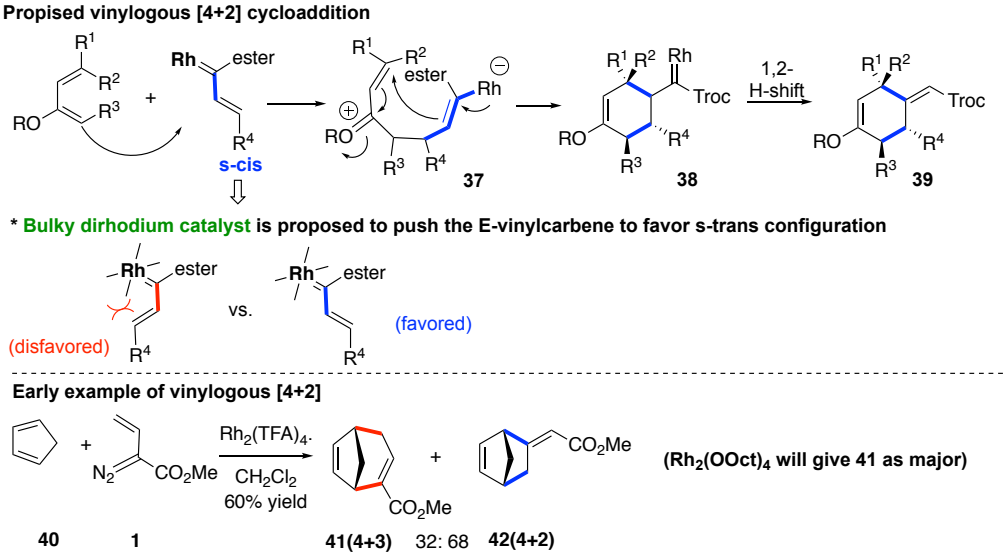
Scheme 8 [4+3] cycloaddition of siloxy dienes with siloxy vinyl diazoacetates



The study described in this chapter also focused on reactions of vinyldiazoacetates with dienes under rhodium catalysis , but instead of the cycloheptadiene products, a formal [4+2] cycloaddition reaction was developed. (**Scheme 9**).[3] We have proposed that the newly developed bulky chiral dirhodium catalysts forces the E-vinylcarbene to react through the s-trans configuration, which would give intermediate **37** that cannot cyclize directly to a seven-membered ring. It will instead form a new rhodium carbene **38**, followed by a 1,2-H shift to give a 6-membered ring product **39**. The only previous example[29] of this type of [4+2] cycloaddition is the $Rh_2(TFA)_4$-catalyzed reaction of the unsubstituted cyclopentadiene **40** with vinyldiazoacetate **1** in dichloromethane as solvent. This reaction gave a mixture of the [4+3] cycloadduct **41** and the [4+2] cycloadduct **42**. The [4+3] cycloadduct is the

dominant product when $Rh_2(OOct)_4$ in hexane was used as catalyst, and the scope of the diene [4+2] cycloaddition was not explored further.

Scheme 9 Proposed new formal 4+2 cycloaddition with bulky dirhodium catalysts.



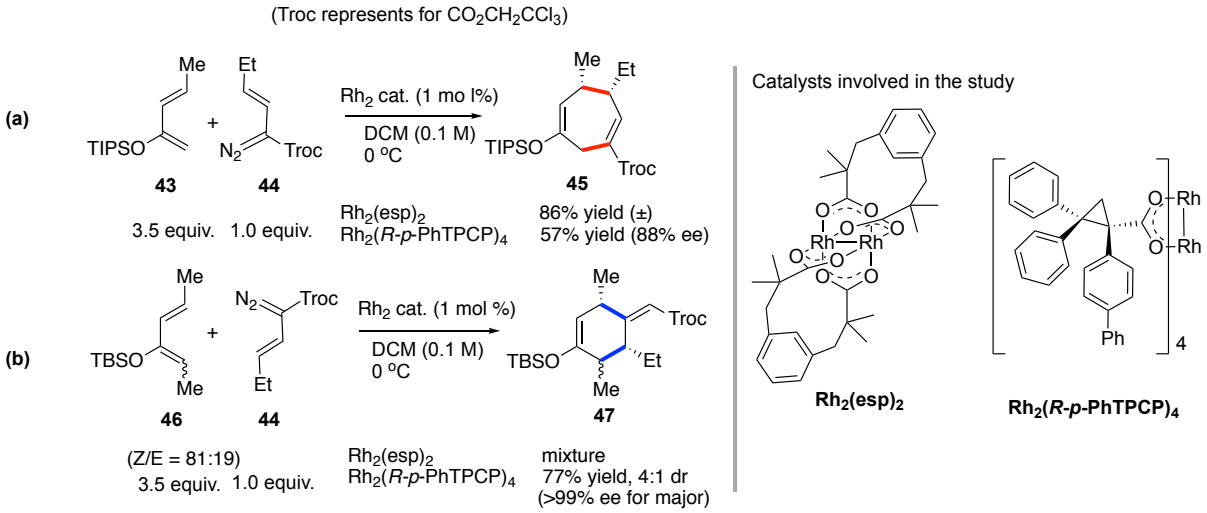
2.2 Early optimization study

The desired 4+2 cycloadduct will be generated as long as the reaction occurs through s-trans rhodium vinylcarbene. Such a vinylogous reaction would generate zwitterionic intermediates. We decided to use electron rich 2-siloxydienes as the trapping reagents because the zwitterionic intermediate would be stabilized. According to previous studies, carbenes substituted with trichloroethyl esters generally give cleaner reactions.[30] Therefore, initial test reaction was performed with vinyl diazo compound **44** with siloxy diene **43**. Two dirhodium catalysts were tested, Du Bois' $Rh_2(esp)_2$,[28] which is a relatively bulky achiral catalyst and the Rh_2(*R*-*p*-PhTPCP)$_4$, which is one of our recently reported bulky chiral catalysts.[30] Both catalysts successfully generated the 4+3 cycloadduct **45** as the product, which is formed through the previously reported cyclopropanation/Cope rearrangement.[3] This [4+3] cycloadduct is formed as a single diastereomer and Rh_2(*R*-*p*-PhTPCP)$_4$ catalyst can achieve an 88% ee (**Scheme 10(a)**).

To shift the reactivity from carbenoid site to the desired vinylogous position, we decided to use terminally substituted diene substrates., which would be sterically more demanding . This choice is based on our previous observation in alkylation reaction of vinylcarbenes with indoles, in which congested indoles caused a change from reaction at the carbene site to the vinylogous position.[8]

Congested diene **46** was reacted with the same vinyl diazo compound **44** under Rh_2(*R*-*p*-PhTPCP)$_4$ and Rh_2(esp)$_4$ catalysis. The two catalysts gave quite different results this time, Rh_2(esp)$_4$ gave a mixture of products while Rh_2(*R*-*p*-PhTPCP)$_4$ cleanly generated the desired 4+2 formal cycloaddition product **47** in 77% yield. The diene starting material is prepared in 81:19 *Z*/*E* mixture, which explains the 4:1 dr in the product. This observation also suggests that both *Z* and *E* isomer of the diene starting material react at similar rates. The major diastereomer of the product has >99% ee, showing that the reaction is highly enantioselective (**Scheme 10(b)**). Rh_2(*R*-*p*-PhTPCP)$_4$ was therefore chosen as the optimum catalyst for the following studies.

Scheme 10 Initial test reactions and optimization study

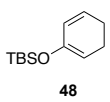
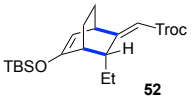
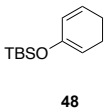
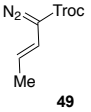
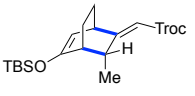
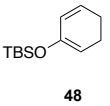
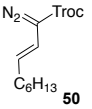
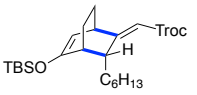
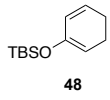
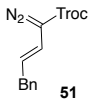
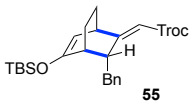
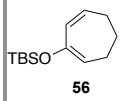
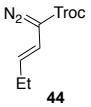
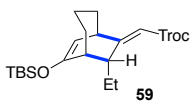
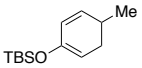
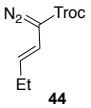
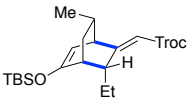
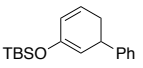
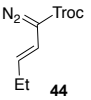
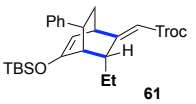


2.3 Reaction scope for the Rh_2(*S*-*p*-PhTPCP)$_4$ catalyzed [4+2] cycloaddition

The initial test reactions suggested that relatively bulky dienes (terminal substituted) would need to be used as substrates to favor the desired 4+2 cycloaddition, so the following studies focused on the reactions of cyclic siloxydienes because they are readily prepared as single stereoisomers. With the optimized Rh_2(*R*-*p*-PhTPCP)$_4$ catalyst, different cyclic siloxy dienes and different vinyl diazo compounds were examined to explore the reaction scope (**Scheme 11**). The Rh_2(*R*-*p*-PhTPCP)$_4$-catalyzed reaction of the vinyldiazoacetate **44** with cyclohexadiene **48** gave the [4+2] cycloadduct **52** in 74% yield as a single diastereomer with high enantioselectivity (97% ee). Different vinyldiazoacetates **49-51** also performed well and all gave the 4+2 cycloadducts as single diastereomers with high asymmetric induction (97-98% ee). The cycloheptadiene **56** is also effective and generated

product **59** in 96% ee. Racemic cyclohexadienes **57** and **58** are the most intriguing substrates because they have the possibility for the chiral catalyst to preferentially react with only one enantiomer. Indeed, the results show a high level of kinetic resolution, generating **60** and **61** that contain four stereogenic centers as single diastereomers with high asymmetric induction (95-96% ee). The absolute configuration of desilylated **52** was determined by X-ray crystallography and all the other [4+2] cycloadducts are tentatively assigned by analogy.

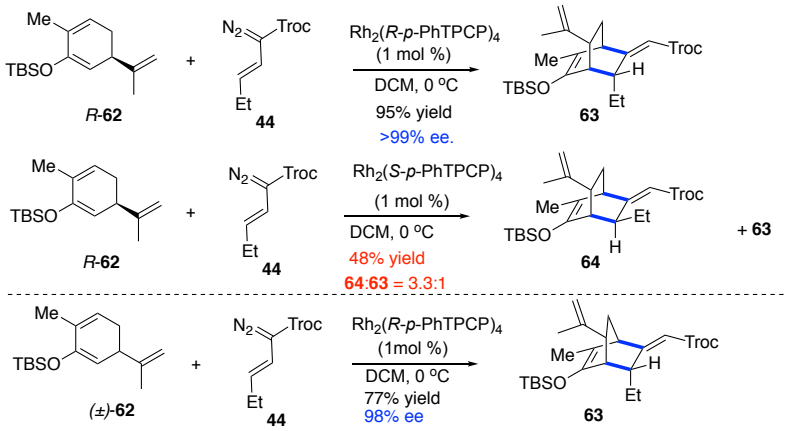
Scheme 11 Reaction scope for the 4+2 cycloaddition

diene	diazo	4+2 cycloadduct [a]	yield [b] (%)	ee (%)
 **48**	 **44**	 **52**	74	97
 **48**	 **49**	 **53**	60	97
 **48**	 **50**	 **54**	49	97
 **48**	 **51**	 **55**	62	98
 **56**	 **44**	 **59**	55	96 [c]
 **57**	 **44**	 **60**	53	95
 **58**	 **44**	 **61**	80	96 [c]

2.4 Detailed study for the kinetic resolution in the 4+2 cycloaddition

Given the excellent kinetic resolution observed with diene substrates **57** and **58,** we examined the reaction of enantiomerically pure diene **62** derived from *R*-(+)-carvone (**Scheme 12**). The Rh_2(*R-p*-PhTPCP)$_4$ catalyzed reaction cleanly generated the desired [4+2] cycloadduct **63** in high yield (95%). In contrast, the reaction with opposite enantiomer catalyst Rh_2(*S-p*-PhTPCP)$_4$ performed much poorly with regards to the yield and gave a mixture of two [4+2] cycloadducts **64** and **63** in a 3.3:1 ratio. Then a control experiment of Rh_2(*S-p*-PhTPCP)$_4$ catalyzed reaction with a racemic mixture of the diene **62** was performed and generated cleanly the cycloadduct **63** in 98% ee. These results show that racemic diene **62** tends to experience kinetic resolution during the reaction and the reaction of the *R* isomer of the catalyst with R-diene **66** is considered as a "matched" reaction.

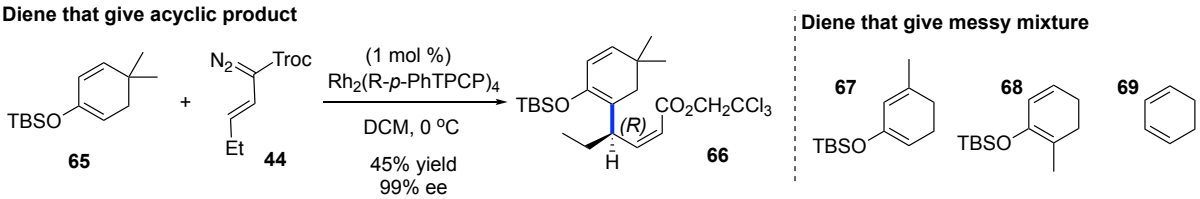
Scheme 12. Kinetic resolution with (±)-66 (derived from natural compound carvone)



2.5 Diene steric influence on the 4+2 cycloaddition

The steric features of the dienes can significantly influence this [4+2] cycloaddition. We have already shown that less crowded diene **43** only demonstrated normal carbene reactivity and generated [4+3] cycloadduct. However, further test studies with sterically crowded diene substrates also gave unsatisfactory results (**Scheme 12**). The [4+2] cycloaddition will be blocked as can be seen in the reaction with the cyclohexadienes **65**, in which alkylation product **66** is generated in 45% yield and 99% ee (**Scheme 13**). This product indeed indicated initial vinylogous attack, but the final cyclization is blocked by the geminal dimethyl group and so following protonation/deprotonation leads to the non-cyclized product **66**. Such cis-enoate conformation can be related to a similar type of reaction that has been observed in the reaction of vinylcarbene with indoles.[8,9] This result is good supporting evidence that the reaction occurs through E-vinylrhodium conformer. For more highly substituted diene substrates **67** and **68**, a messy mixture of products was observed. Again, the steric hindrance may block the attack of the diene onto the vinylcarbene. Finally, it is found that the diene needs to be electron rich as attempted reaction with cyclohexadiene **69** shows no sign of [4+2] cycloadduct.

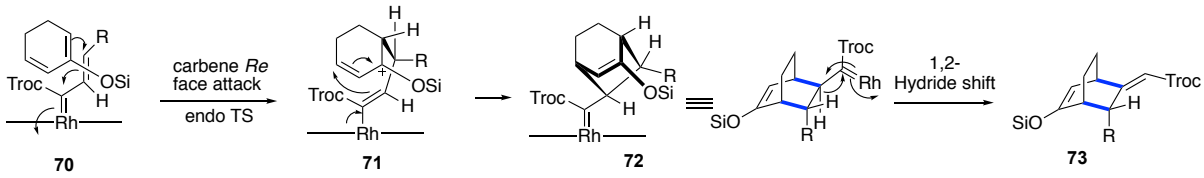
Scheme 13. Diene steric influence on the 4+2 reaction



2.6 Proposed reaction mechanism

The proposed mechanism of this reaction is illustrated in the **Scheme 14**. Initial attack of the diene active site occurs at the vinylogous position of the s-*trans* vinylcarbene **73**. Our hypothesis that bulky dirhodium catalysts lead to preferential attack at the s-trans conformer of the E-vinylcarbenes[9] was also supported by recent computational studies[27] for the 3+2 cycloaddition between vinylcarbenes and nitrones. The stereochemistry is determined by the reaction proceeding via *endo* transition state occurring at the *Re* face of the carbene. Following this initial attack, the resulting intermediate **71** directly cyclizes towards the cyclohexene intermediate bearing a new rhodium[23] carbene **72**. Finally, the intermediate **72** would undergo a 1,2-hydride shift to generate the 4+2 cycloadduct **73**. This final step would be different from the 1,3-hydride shift[23, 27] followed by proton transfer observed in the nitrone [3+2] cycloaddition reaction.

Scheme 14. Mechanistic model for the formal 4+2 cycloaddition



2.7 Conclusion

In this study the vinylogous reactivity of rhodium mediated vinylcarbenes was successfully engaged into reaction with diene substrates to generate a new type of formal [4+2] cycloadduct in good yield, single diastereomer and excellent enantioselectivity. The study shows that the vinylogous reactivity is susceptible to a variety of factors, including the steric influences of the dirhodium catalyst as well as the steric feature within the diene substrates. The bulky dirhodium catalyst is critical to ensure that the *E*-vinylcarbene reacts at the vinylogous position through the *s-trans* configuration, which is required for a successful [4+2] cycloaddition reaction. This new 4+2 cycloaddition is complementary to the previous 4+3 cycloaddition with vinylcarbene and broadens the synthetic application of rhodium mediated vinylcarbene chemistry.

References:

1. Davies, H. M. L.; Clarke, D. M.; Thuy K. S. *Tetrahedron Lett.* **1985**, *26*, 5659.

2. Davies H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, 57, 1-326.

3. Stafford, D. G.; Doan, B. D.; Houser, J. H.; Davies, H. M. L. *J. Am. Chem. Soc.* **1998**, *120*, 3326.

4. Davies H. M. L.; Pelphrey, P. *Org. React.* **2011**. *75*, 75-212.

5. Davies, H. M. L.; Lian, Y. J. *Acc. Chem. Res.* **2012**, *45*, 923.

6. Manning, J. R.; Davies, H. M. L. *J. Am. Chem. Soc.* **2008**, *130*, 8602.

7. Davies, H. M. L.; Saikali, e.; Young, W. B. *J. Org. Chem.* **1991**, 56, 5696

8. Lian, Y. J.; Davies, H. M. L. *Org. Lett.* **2010**, 12, 924.

9. Lian, Y. J.; Davies, H. M. L. *Org. Lett.* **2012**, *14*, 1934.

10. Valette, D.; Lian, Y. J.; Haydek, J. P.; Hardcastle, K. I.; Davies, H.M. L. *Angew. Chem. Int. Ed.* **2012**, *51*, 8636.

11. Smith, A. G.; Davies, H.M. L. *J. Am. Chem. Soc.* **2012**, *134*, 18241.

12. Qian, Y.; Xu, X. F.; Wang, X. C.; Zavalij, P. J.; Hu, W. H.; Doyle, M. P. *Angew. Chem. Int. Ed.* **2012**, *51*, 5900.

13. Qian, Y.; Zavalij, P. J.; Hu, W. H.; Doyle, M. P. *Org. Lett.* **2013** *15*, 1564.

14. Wang, X. C.; Abrahams, Q. M.; Zavalij, P. J.; Doyle, M. P *Angew. Chem. Int. Ed.* **2012**, *51*, 5907.

15. Wang, X. C.; Xu, X. F.; Zavalij, P. Y.; Doyle, M. P *J. Am. Chem. Soc.* **2011**, *133*, 16402.

16. Xu, X. C.; Leszczynski, J. S.; Mason, S. M.; Zavalij, P. Y.; Doyle, M. P. *Chem. Commmun.* **2014**, *50*, 2462.

17. Xu, X. C.; Zavalij, P. Y.; Doyle, M. P. *J. Am. Chem. Soc.* **2013**, 1*35*, 12349.

18. Xu, X. F.; Doyle, M. P. *Acc. Chem. Res.* **2014**, *47,* 1396.

19. Xu, X. F.; Doyle, M. P. *Aust. J. Chem.* **2014**, *67*, 365.

20. Xu, X. F.; Ratnikov, M. O.; Zavalij, P. Y.; Doyle, M. P. *Org. Lett.* **2011**, *13*, 6122.

21. Xu, X. F.; Zavalij, P. Y.; Doyle, M. P *Angew. Chem. Int. Ed.* **2013**, *52*, 12664.

22. Xu, X. F.; Zavalij, P. Y.; Hu, W. H.; Doyle, M. P. *J. Org. Chem.* **2013**, *78*, 1583-1588.

23. Qin, C.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 14516.

24. Lian, Y. J.; Hardcastle, K. I.; Davies, H.M. L. **2011**, *50*, 9370.

25. Guzmán, P. E.; Lian, Y.; Davies, H. M. L. *Angew. Chem., Int. Ed.* **2014**, *53*, 13083.

26. Deng, Y.; Yglesias, M. V.; Arman H.; Doyle, M. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 10108.

27. (a) Yang, X.; Yang, Y. S.; Rees, R. J.; Yang, Q.; Tian, Z. Y.; Xue, Y. *J. Org. Chem.* **2016**, *81*, 8082.

(b) Ma, L. L.; Wang, W.; Wang G. C. *RSC Advances* **2016**, *6*, 53839.

28. Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378.

29. Davies, H. M. L.; Saikali, E.; Clark, T. J.; Chee, E. H. *Tetrahedron Lett.* **1990**. *31*, 6299.

30. Guptill, D. M.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014,** *136*, 17718.

31. Zhang, B., Davies, H.M.L. *Angew. Chem. Int. Ed.* **2020**, *59*, 4937

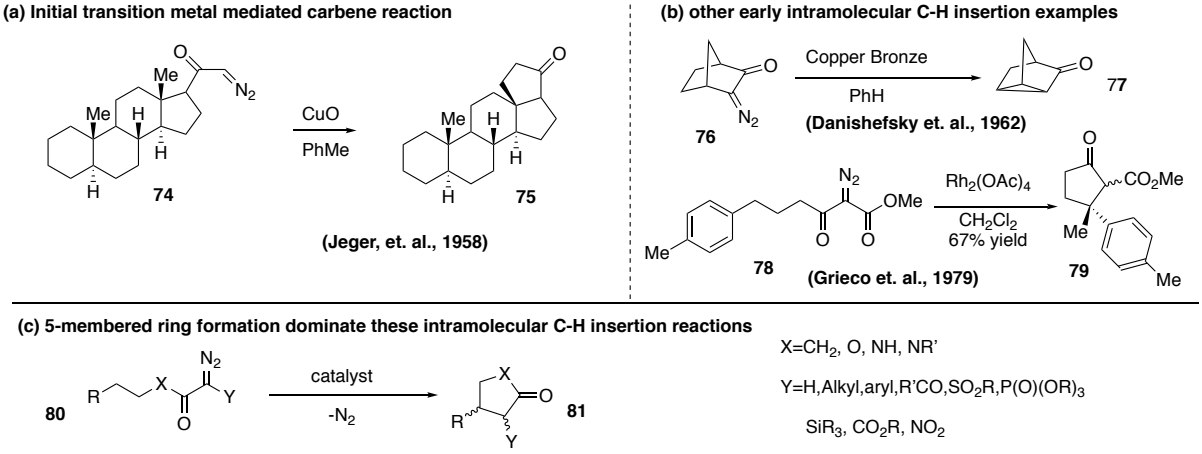
Chapter Three

Broadening the application of Rh-carbene mediated C–H functionalization

3.1 Introduction

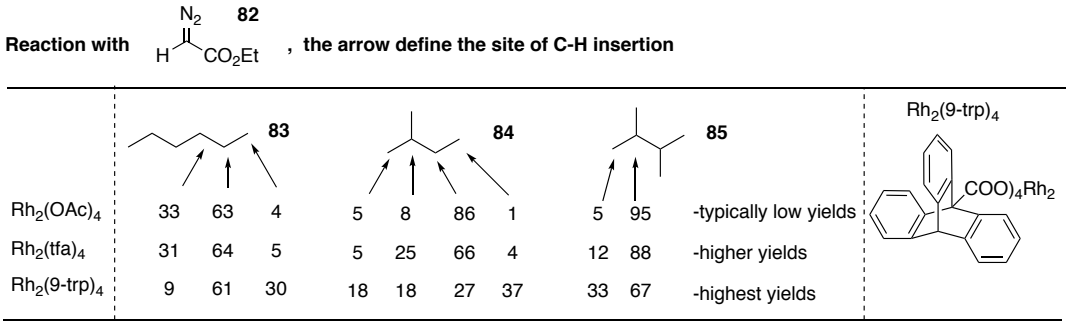
Since the initial reported transition metal mediated carbene insertion reaction in 1958,[1] early synthetically useful C–H insertion examples with diazo compounds were limited to intramolecular reactions in geometrically rigid systems (**Scheme 15(a),(b)**).[2-4] Copper and nickel (II)[5] catalysts are effective for systems such as diazocamphor[2] **76** and the scope of transition metal was expanded to dirhodium(II) acetate by Wenkert[6] and Taber.[7] These intramolecular C–H insertion reactions tend to occur at the gamma position to form five membered rings (**Scheme 15(c)**).[8-10]

Scheme 15 Early transition metal mediated intramolecular carbene insertion reactions.



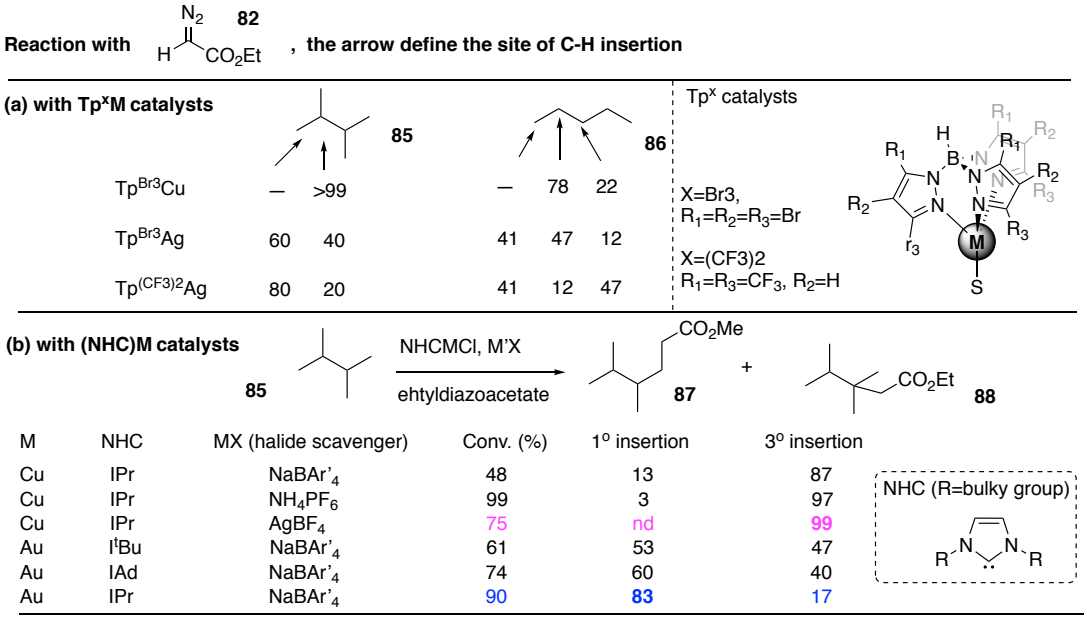
The Teyssie group first studied the intermolecular C–H insertion reaction of ethyl diazoacetates **82** with alkanes catalyzed by dirhodium tetracarboxylate catalysts (**Scheme 16**).[11] Hexane (**83**), 2-methylbutane **84** and 2,3-dimethylbutane **85** were tested as substrates with increasing steric hindrance. Although the three dirhodium catalysts tested all gave a mixture and mostly favored more substituted positions, these initial results showed that the identity of catalyst ligand can influence regioselectivity. In addition, the higher yields for $Rh_2(tfa)_4$ compared to $Rh_2(OAc)_4$ suggest that electron withdrawing ligands attached to the rhodium center can provide higher conversion of alkanes into functionalized products. Such effect was observed by their following studies as well.[12-15]

Scheme 16 Teyssie's initial study of C−H reaction of ethyl diazoacetates with alkanes



Perez et. al. have also studied C–H insertion of ethyl diazoacetate with simple aliphatic substrates, but using copper or silver based catalysts containing a trispyrazolylborate ligand.[16-18] Their studies indicated that C–H insertion of ethyl diazoacetate **82** with 2,3-dimethylbutane **85** could achieve excellent tertiary selective C–H insertion (3° : 1° > 99 : 1, Cu-based catalyst) or relatively good primary selective C–H insertion (3° : 1° = 20 : 80, Ag-based catalyst). However, for linear aliphatic system like pentane (**86**), the best selectivity among terminal 2° (methylene), internal 2° (methylene) or 1° (methyl) C–H bond is only moderate (**Scheme 17(a)**). Later on, the Perez group also explored copper and gold-based catalysts with N-heterocyclic carbene (NHC) as ligands for C–H insertion of ethyl diazoacetate **82** with 2,3-dimethylbutane **85**. The regioselectivity between tertiary and primary C–H insertion ranges from 3° : 1° >99 : 1 (Cu-based catalyst) to 3° : 1° = 17 : 83 (Au based catalyst)(**Scheme 17(b)**).

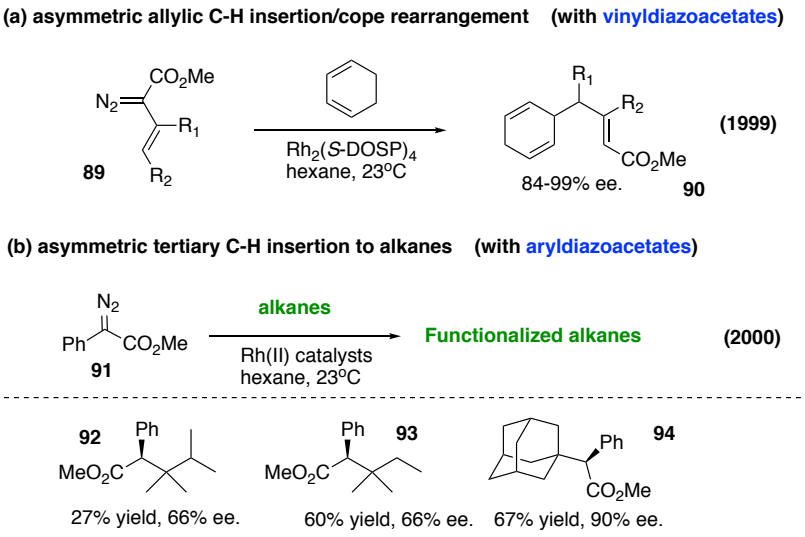
Scheme 17 Perez's study of C–H reaction of ethyl diazoacetates with alkanes



Both Teyssie and Perez's work have demonstrated the possibility of controlling regioselectivity of C–H insertion by modifying the ligands on the metal catalysts. Although clean tertiary C–H insertion reactions were achieved with certain alkanes, the regioselectivity had always been a challenge for acceptor only type of carbene, for example, in terms of distinguishing different methylene sites. On the basis of these early investigations that generally demonstrated limited selectivity profiles,[11-18,20] Doyle concluded that "Intermolecular C–H insertion reactions are of mechanistic interest but are not synthetically useful".[21]

However, the Davies group demonstrated that regioselective and enantioselective intermolecular C–H insertion reactions can be achieved with aryldiazoacetates and vinyldiazoacetates (**Scheme 18**).[22,26] The electron-donating nature of aryl (see **91**) and vinyl groups (see **89**) tempers the reactivity of these donor/acceptor carbene, enabling them to be delicately controlled by dirhodium catalysts with different ligands and perform selective C–H insertion.[23-25]

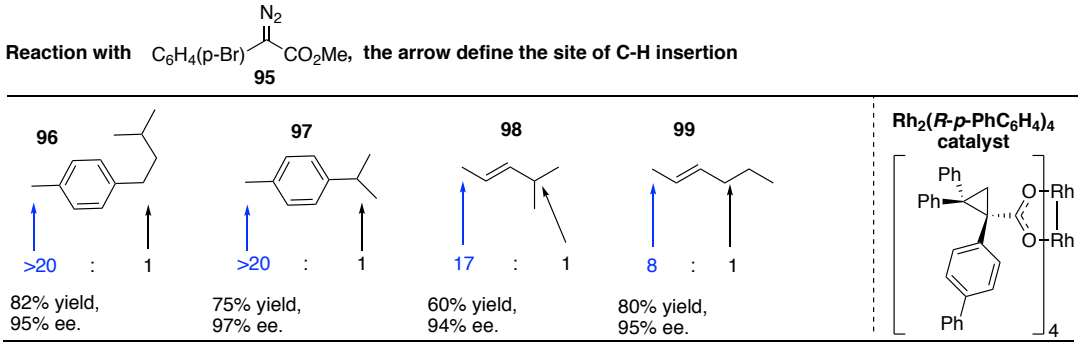
Scheme 18 Davies' early studies of regio- and enantioselective C–H insertion reactions.



The regioselectivity of donor/acceptor rhodium carbenes in early studies was still not ideal, especially for primary or secondary C–H bonds in aliphatic substrates like 2-methyl pentane.[26] This challenge motivated our group to develop novel chiral dirhodium catalysts with various bulkier ligands. Another breakthrough is the development of the latest triarylcyclopropane (TPCP) series of chiral dirhodium catalysts.[27] These catalysts nicely illustrate the possibility of using enantioselective

cyclopropanation reactions to enable the design of new chiral catalysts, they can catalyze highly regio-, diastereo- and enantioselective intermolecular C–H insertion reactions.[28] In the reaction of aryldiazoacetate **95** with substituted benzenes **96-99**, Rh_2(*R*-*p*-PhTPCP)$_4$ primary benzylic/allylic C–H insertion was highly favored over secondary or tertiary benzylic/allylic C–H bonds (**Scheme 19**).

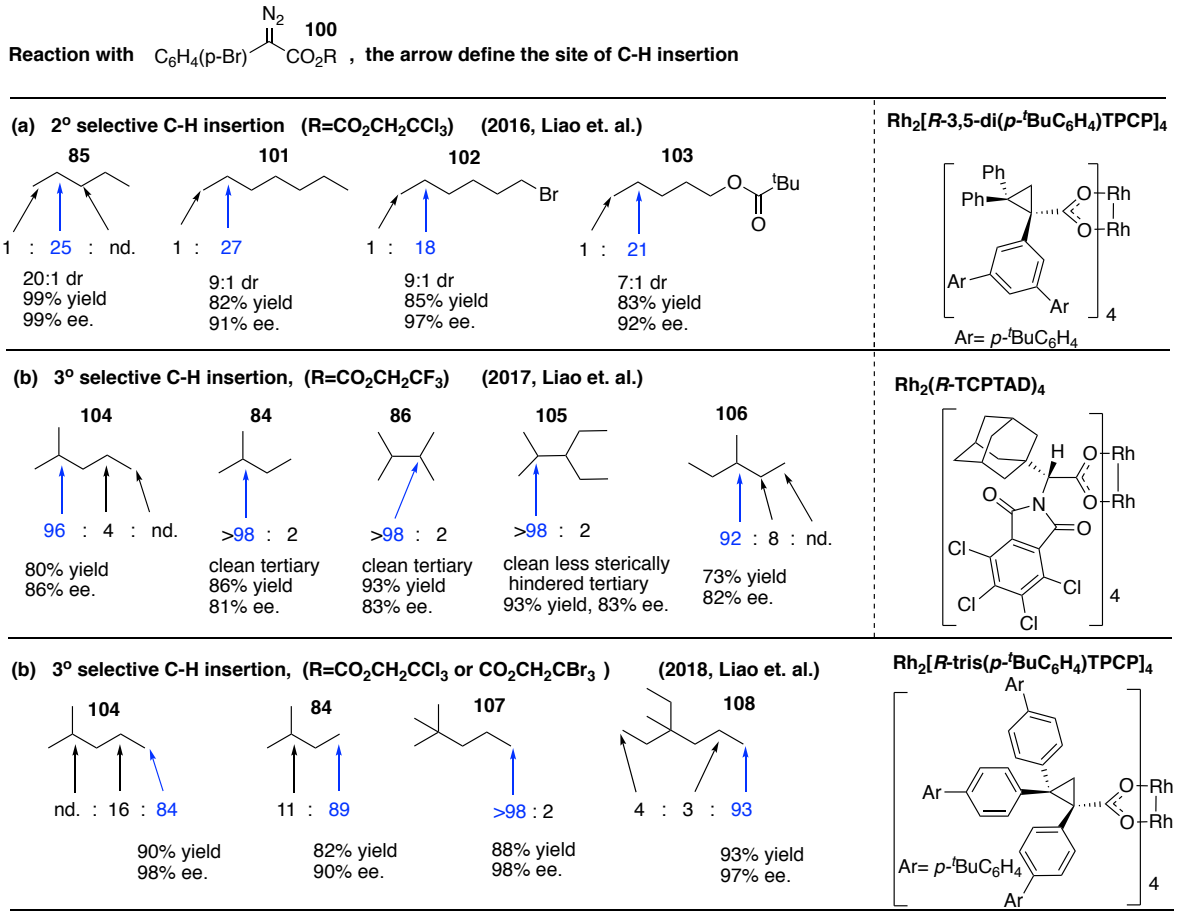
Scheme 19 Davies's regioselective primary benzylic C–H insertion reactions.



Later on, the Davies group explored more TPCP ligand-based as well as phthalimido ligand-based chiral dirhodium catalysts and has achieved great success on site- and stereo-selective C–H insertion of more challenging aliphatic substrates.[29-33] Some prominent examples include regioselective C–H insertion of the most accessible primary,[29] secondary[30] and tertiary C–H bonds;[31] functionalization of the terminal methylene C–H bond in the presence of activated benzylic C–H bonds;[32] and desymmetrization of substituted cyclohexanes).[33] Site- and regioselective secondary C–H insertion was first achieved with a bulky TPCP ligand-based dirhodium catalyst Rh_2(*R*-3,5-di(^{t}BuC$_6$H$_4$)TPCP)$_4$.[30] This catalyst can control C–H insertion reactions of aryl diazoacetate **100** with linear aliphatic substrates (**85, 101-103**) to occur selectively at the terminal methylene site. Only minimum primary C–H insertion was observed and no internal methylene C–H insertion was detected,[30] which was unprecedented in the previous studies with ethyl diazoacetate (**Scheme 20(a)**).[11-18] Site- and stereoselective tertiary C–H insertion was achieved with Rh_2(*R*-TCPTAD)$_4$.[31] The reaction with 2-methylpentane **104** showed a remarkable ratio of 3° : 2°(terminal) =96 : 4 and no primary or internal methylene C–H insertion was observed. The reaction with 2,3-dimethylbutane **86** can achieve not only exclusive 3° C–H insertion,[11,16] but also with unprecedented high enantioselectivity. The reaction with 2-methylbutane **84** gave clean 3° C–H insertion, which is far better than the behavior of acceptor only carbene (**Scheme 20(b)**).[11] The electronically challenging site- and stereo-selective primary C–H insertion was achieved with another

bulky TPCP type catalyst Rh_2(*R*-tris-(*p*-^{t}BuC_6H_4)TPCP)$_4$.[29] The reaction with 2-methylbutane **84** gave a 1° : 3° = 9 : 1, which is remarkable for the electronically disfavored primary C–H bond. Reactions with other alkane substrates (**104, 107, 108**) also achieved good regioselectivity (**Scheme 20(c)**).

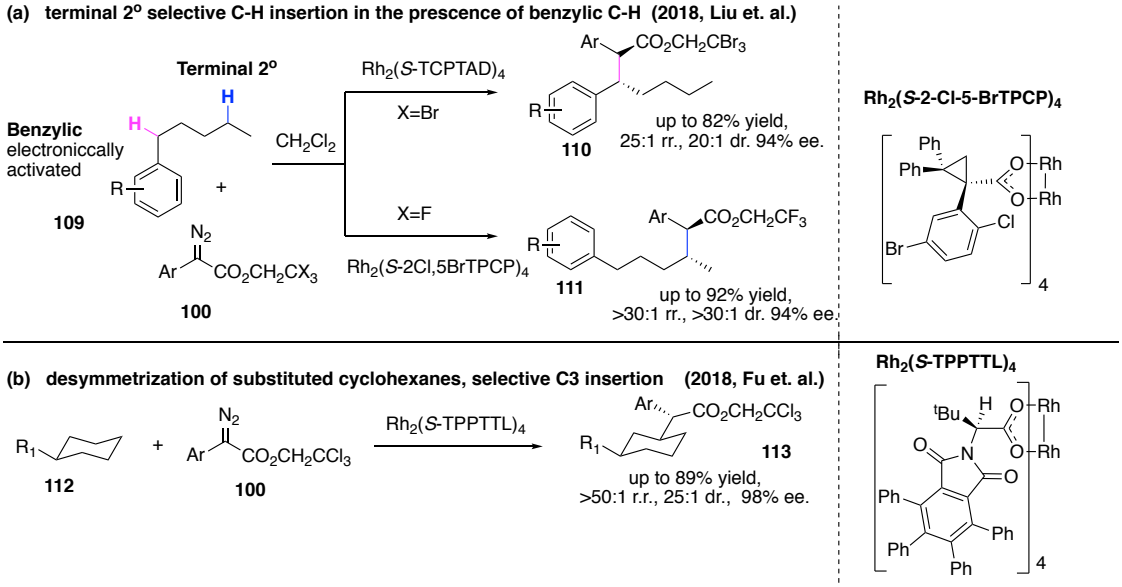
Scheme 20 Davies's stereo- and enantio-selective C–H insertion reactions with alkanes



More recently, selective terminal methylene functionalization of a linear aliphatic chain in the presence of benzylic C–H bonds was achieved with a TPCP catalyst, Rh_2(*S*-2Cl,5BrTPCP)$_4$.[32] In the reaction of alkylbenzene **109** with aryldiazoacetates **100**, Rh_2(*R*-TCPTAD)$_4$ favored the electronically activated benzylic C–H insertion, while the new catalyst Rh_2(*S*-2Cl,5BrTPCP)$_4$ can overcome such electronic bias and cleanly reacted at the terminal methylene site (**Scheme 21(a)**). In another example, desymmetrization of substituted cyclohexanes with C3 selective C–H functionalization was achieved by a phthalimido ligand-based catalyst Rh_2(*S*-TPPTTL)$_4$.[33] The arrangement of peripheral phenyl rings makes this catalyst unique in terms of suppressing the C4 regioisomer as well as C5 diastereomer

(**Scheme 21(b)**). Such excellent site- and stereo-selectivity for C–H insertion of cyclic alkanes was unprecedented in previous studies.[34,35]

Scheme 21 Davies's recent breakthrough on site and stereo selective C–H insertion reactions



Nevertheless, despite the success and novelty of these new catalysts and methodologies, a long-term challenge still exists within our group, which is to broaden the application scope of rhodium carbene chemistry. Most of our C–H functionalization products contain the aryl-ester moiety derived from the aryldiazoacetates. This fixed substructure could be a limitation for a general synthetic application. One solution would be to explore other types of rhodium carbenes beyond the donor/acceptor type, such as acceptor only carbenes or the donor only carbenes. Another indirect solution would be to develop general derivatizations to the successful C–H functionalization products from donor/acceptor carbene. In this chapter, both solutions have been explored to address the problem.

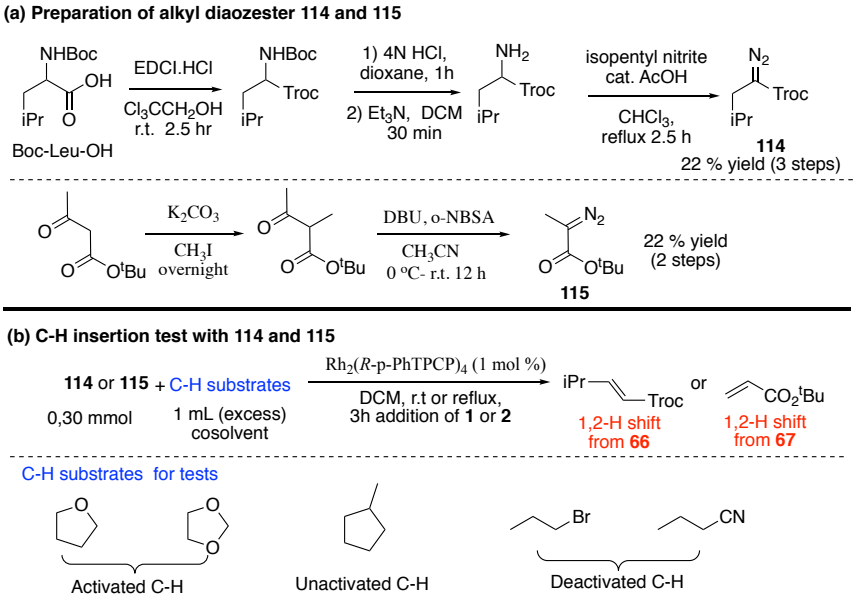
3.2 Exploring site-selective intermolecular C–H insertion with Rh acceptor only carbene

Recently developed bulky dirhodium catalysts in the Davies group can enable rhodium donor/acceptor carbene to achieve highly site-selective intermolecular C–H insertion reactions.[29-33] These catalysts have not been applied to intermolecular C–H insertion reactions with rhodium acceptor only carbene. Given the current limitation that acceptor only carbenes are unable to react in a site-selective manner, it would be worthwhile to test if promising results can be achieved with these novel catalysts, which will also directly broaden the synthetic application of rhodium carbene chemistry.

3.2.1 Early study of alkyl diazoester as carbene precursor

Diazo compounds **114** and **115** were prepared for the C–H insertion test reactions (**Scheme 22 (a)**). Substrates for tests include ones that contain activated C–H bond (THF, 1,3-dioxane); ones that only contain unactivated C–H bonds (Methylcyclopentane); ones that contain deactivated C–H bonds (alkyl halides). Recently developed Rh_2(*R*-*p*-PhTPCP)$_4$ was chosen as the dirhodium catalyst for all the test reactions. However, Intramolecular 1,2-H shift dominate the reaction no matter what type of substrates are applied. The only product observed is the trans-alkene (**Scheme 22 (b)**).

Scheme 22 Preparation of alkyl-diazoester and their C–H insertion performance



3.2.2 Rh acceptor-only carbene mediated site-selective C–H insertion reactions

3.2.2.1 Test reactions with 2-methylpentane as substrate

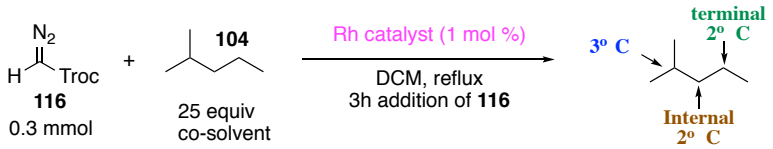
2-methylpentane is a common substrate used for study site selective C–H insertion with donor/acceptor carbene[31] as it contains competitive primary, secondary and tertiary C–H bonds. Diazo compound **116** (2,2,2-trichloroethyl 2-diazoacetate) with trichloroethyl as ester part is commonly used in the Davies lab to prepare donor/acceptor diazo compounds through cross-coupling. Therefore, this readily available acceptor only diazo compound was applied as the carbene precursor.

3.2.2.1.1 Study of site-selective tertiary (3°) C–H insertion

(1) Dirhodium catalyst influence

Dirhodium catalyst is the key element for achieving various site-selective C–H insertion with donor/acceptor carbene. So, the investigation began by doing a broad screening for the reaction of 2-methylpentane with diazo compound **116** (**Scheme 16)**. All of the catalysts generated substantial amount of diazo dimerization byproduct, with Rh_2(*R*-NTTL)$_4$ giving almost exclusively the dimer. As for the C–H insertion products, internal 2° C–H is always the minor reaction site, so the focus was the ratio of terminal 2° C–H functionalization to 3° C–H functionalization. The highest 3° to terminal 2° ratio is 2.15 : 1 achieved with Rh_2(*R*-TCPTAD)$_4$ catalyst; while the lowest 3° to terminal 2° ratio is 0.44 : 1 achieved with Rh_2(*S-2-Cl,5-Br*TPCP)$_4$. Therefore, Rh_2(*R*-TCPTAD)$_4$ was chosen as the optimized catalyst for further study of tertiary selective C–H functionalization.

Scheme 23 Catalyst screening for the reaction of diazo compound 116 with 2-methyl pentane



Rh Catalyst	Dimerization	Terminal 2° C	:	3° C	:	Internal 2° C
Rh_2(*S*-DOSP)$_4$	1.18	1		1.81		0.35
Rh_2(*R*-PTAD)$_4$	0.92	1		1.32		0.36
Rh_2(*R*-TCPTAD)$_4$	0.86	1		2.15		0.49
Rh_2(*S*-NTTL)$_4$	2.16	1		1.38		0.40
Rh_2(*R-p*-PhTPCP)$_4$	0.97	1		1.85		0.28
Rh_2(*S*-2Cl,5BrTPCP)$_4$	0.59	1		0.44		0.25
Rh_2(*S*-TPPTTL)$_4$	1.83	1		1.33		0.44
Rh_2(*S*-Dibic)$_4$	0.68	1		0.65		0.30
Rh_2(*S*-Tribic)$_4$	0.94	1		1.81		0.25

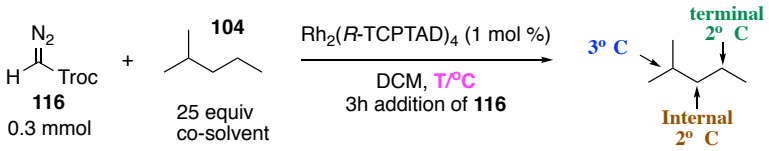
* Rh_2(S-Dibic)$_4$ is common name for Rh_2[*S*-3,5-di(p-^{t}BuC$_6$H$_4$)TPCP]$_4$
* Rh_2(S-Tribic)$_4$ is common name for Rh_2[*S*-tris(p-^{t}BuC$_6$H$_4$)TPCP]$_4$

(2) Reaction temperature influence

Acceptor only carbenes are generally considered to be more reactive compared to donor/acceptor carbenes. In addition, reaction temperature may also have a substantial influence on the reaction outcome, as it was discovered that diazo dimerization byproduct may be reduced by lowering the

reaction temperature. Therefore, a comparison study was performed at 40 °C, 0 °C and -20 °C. The test results confirmed that low temperature (-20 °C) significantly suppressed the side reaction. Also, this temperature seems to improve the 3° to terminal 2° ratio to 2.80 : 1 (**Scheme 24**). Based on these results, -20 °C was chosen as the optimized reaction temperature for further study with 3° C–H insertion.

Scheme 24 Temperature influence (find optimized T/°C for tertiary insertion)



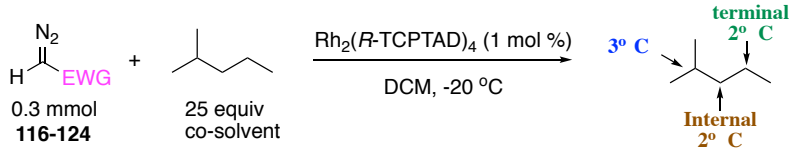
T/ °C	Dimerization	Terminal 2° C	:	3° C	:	Internal 2° C
40	0.86	1		2.15		0.49
0	0.15	1		2.51		0.50
-20	0.02 (suppressed)	1		2.80		0.54

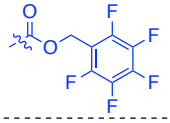
(3) Influence of the electron-withdrawing group (EWG) within the diazo compound

The EWG in the diazo compound can also significantly influence the site-selectivity. With the optimized Rh_2(*R*-TCPTAD)$_4$ catalyst and -20 °C reaction temperature, a series of electron withdrawing groups (**116-124**) were screened to compare the 3° selectivity. ^{t}Bu group (**117**) seems more favor the 3° insertion than the Trichloroethyl (Troc) group, but the formation of intramolecular insertion byproduct limits its application. Trifluoroethyl group (**118**) is also better for 3° C–H insertion than Troc group, which seems to indicate that stronger EWG may be helpful for selective 3° C–H insertion. Amides as EWG (**122-124**) generally tend to work poorly due to intramolecular reactions and dimerization. The optimized EWG identified is the pentafluorobenzyl group (**119**), which can increase the ratio of 3° to 2° (terminal) to 5.95 : 1 (3° : 2° (combined) = 3.54 : 1, also the highest achieved). An internal standard, 1,3,5-trimethoxybenzene, was used in this study to measure the NMR yield for 3° insertion product. Using pentafluorobenzyl group gave the product in 71% NMR yield, which is also very high among all the results (**Scheme 25(a)**). The 3° insertion product was then isolated and compared with the authentic sample **125** prepared using traditional chemistry. The matched ^{1}HNMR confirmed the structure to be correct (**Scheme 25(b)**).

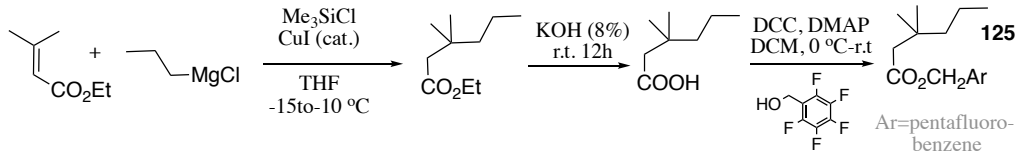
Scheme 25 Influence of the EWG within the diazo compound

(a) EWG screening for 3° C-H insertion



Diazo compound	EWG	3° : ter 2° : int 2° : Intra	^{1}H NMR yield for C3/ %
117	-$CO_2{}^t$Bu	5.88 : (1*) : 1.53	55
118	-$CO_2CH_2CF_3$	5.44 : 1 : 0.82 : --	54
116	-$CO_2CH_2CCl_3$	2.80 : 1 : 0.56 : --	41
119 (optimized)		5.95 : 1 : 0.68 : --	71
120	-CO_2CH_2(*p*-Cl)C_6H_4	5.30 : 1 : 0.62 : --	44
121	-$CO_2CH(CF_3)_2$	5.44 : 1 : 0.55 : --	74
122	-$CON(Et)_2$	messy reaction	--
123	-$CON(Bn)_2$	only cyclopropanation/cope prodcut	--
124	-$CON(CH_2CF_3)_2$	3.33 : 1 : dimeization(1.83) (2-methylpentane as solvent)	40%*

(b) Synthesis of authentic sample for 3° insertion product from diazo 6



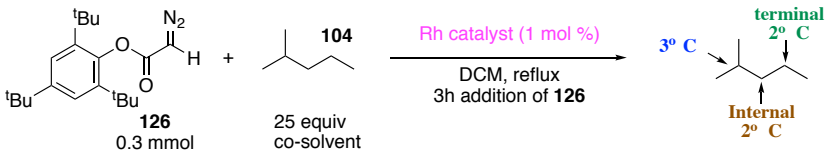
3.2.2.1.2 Study of site-selective secondary (2°) C–H insertion

In the previous study with 2,2,2-trichloroethyl 2-diazoacetate, catalyst screening shows that Rh_2(*S*-2Cl,5BrTPCP)$_4$ seems to give the highest ratio for 2° C–H insertion (3°: 2° (combined)=0.33:1). Although this ratio is not too bad, Troc group as EWG is not an ideal diazo compound to start exploring selective 2° C–H insertion. This is because Troc has strong electron-withdrawing capability with little steric influence, which would make a very electrophilic carbene that tend to be unselective. A new diazoester **126** was designed to perform the following studies. The reduced electrophilicity is achieved by using a more electron rich aryl ester. In addition, the 1,3,5-tri-tert-butyl groups on the Ar ring increased the steric size, which may help the carbene to react at less sterically hindered secondary sites.

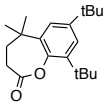
(1) Dirhodium catalyst influence (part I)

Similar to the study of tertiary C–H insertion, various dirhodium catalysts from the Davies lab were examined for the reaction of diazoester **126** with 2-methylpentane **104** to compare the site-selectivity (**Scheme 26**). Unfortunately, many dirhodium catalysts gave only intramolecular cyclopropanation side products, including the Rh_2(*S*-2Cl,5BrTPCP)$_4$ that showed the most 2° C–H selective reaction with 2,2,2-trichloroethyl 2-diazoacetate (**116**). But we are delighted to find that some catalysts [Rh_2(*S*-DOSP)$_4$, Rh_2(*R*-PTAD)$_4$, Rh_2(*R*-TCPTAD)$_4$, Rh_2(*S*-TPPTTL)$_4$] did give desired intermolecular C–H insertion, and the 2° C–H insertion dominate the reaction. Another good sign is that no catalyst gave diazo dimerization byproduct. The best 2° C–H insertion result was again given by the Rh_2(*R*-TCPTAD)$_4$ catalyst with the ratio of 2° : 3°= 8.33 : 1. Although the crude ^{1}HNMR indicated that the major 2° C–H insertion product is the terminal 2° one , the actual ratio of terminal 2° to internal 2° is hard to determine in this system. Therefore, all the ratio in following studies use combined 2° insertion.

Scheme 26 Catalyst screening for the reaction of diazo compound 126 with 2-methyl pentane



Rh Catalyst	2° (terminal+internal)**	:	3°	Intra 1°
Rh_2(*S*-DOSP)$_4$	5.56		1	4.17
Rh_2(*R*-PTAD)$_4$	4.35		1	4.22
Rh_2(*S*-TCPTAD)$_4$	8.33		1	2.25
Rh_2(*S*-NTTL)$_4$	--		--	only intra
Rh_2(*S*-p-PhTPCP)$_4$	--		--	only intra
Rh_2(*S*-2Cl,5BrTPCP)$_4$	--		--	only intra
Rh_2(*S*-TPPTTL)$_4$	7.14		1	7.14
Rh_2(*S*-Dibic)$_4$	--		--	only intra
Rh_2(*S*-Tribic)$_4$	--		--	only intra



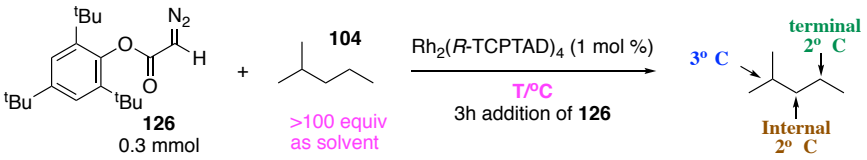
* Rh_2(S-Dibic)$_4$ is common name for Rh_2[*S*-3,5-di(p-^{t}BuC$_6$H$_4$)TPCP]$_4$
* Rh_2(S-Tribic)$_4$ is common name for Rh_2[*S*-tris(p-^{t}BuC$_6$H$_4$)TPCP]$_4$
** Although mainly terminal 2°, but still have internal 2° and hard to determine the ratio, so use combined 2°

(2) Reaction temperature influence

Reaction temperature can influence the 2° : 3° ratio as well as the byproduct formation, as has been demonstrated with the **3**° C–H insertion study. The side product in this system is not from diazo

dimerization, but the intramolecular primary insertion to the ortho ^{t}Bu group. It is possible that lower reaction temperature combined with using 2-methyl pentane (**104**) as solvent can suppress the byproduct formation. Therefore, a comparison experiment with the same reaction under 0 °C, and -20 °C was performed (**Scheme 27**). The test results show that byproduct is well suppressed under low temperature with 2-methyl pentane directly as solvent. Also, both 0 °C and -20 °C enhanced the ratio of 2° insertion to 3° insertion. Although -20 °C gave highest 2° : 3° ratio and lowest side product formation, the ^{1}HNMR yield dropped significantly. So, 0 °C is chosen as optimized reaction temperature for good ratio, low byproduct and good ^{1}HNMR yield.

Scheme 27 Reaction temperature influence



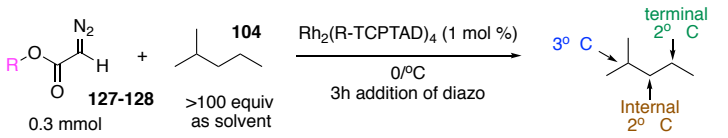
T/ °C	2° (terminal+internal)*	:	3°	Intra 1°	^{1}HNMR yield for 2°
0	10.0		1	0.80	64%
-20	11.1		1	0.56	34%

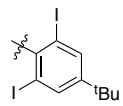
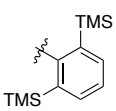
* Although mainly terminal 2°, but still have internal 2° and hard to determine the ratio, so use combined 2°

(3) Screening diazo compounds other bulky aryl ester as EWG for comparison

Two diazo compounds (**127-128**) with different aryl ester as EWG were tested, considering that other ortho functionalized Ar may also give good secondary selectivity without the intramolecular side reaction given by 2,4,6-tri^{t}BuAr. However, the test results show that they both gave much worse ratio compared to the diazo compound **126** (**Scheme 28**).

Scheme 28 Comparison of more aryl ester type of EWG for secondary insertion

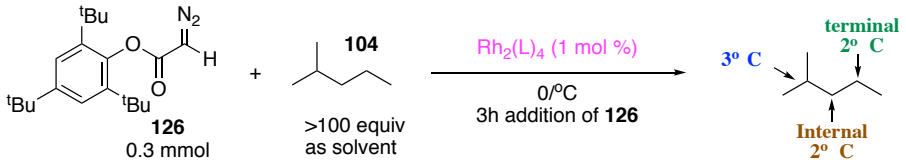


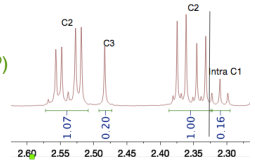
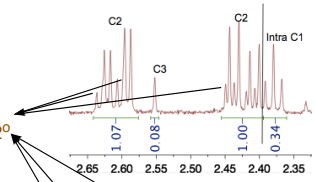
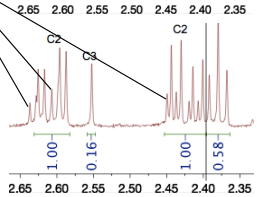
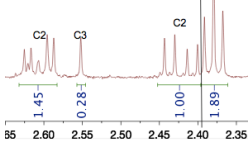
	R	2° (ter+int)	:	3°	:	intra 1°
127		1.1		1		--
128		1.2		1		--

(4) Dirhodium catalyst influence (part II)

In catalyst screening part I, Rh_2(*R*-TCPTAD)$_4$ achieved best secondary C–H insertion and Rh_2(*S*-TPPTTL)$_4$ behaved the second-best result. Inspired by the fact that they are both phthalimido-based dirhodium catalysts, three dirhodium catalysts of this series were further tested (**Scheme 29**). Among the three new catalyst, Rh_2(*R*-TPPTBL)$_4$ **131** gave worse 2° insertion compared to Rh_2(*R*-TCPTAD)$_4$; Rh_2(*R*-TPPTCL)$_4$ **130** and Rh_2(*R*-TPPTAD)$_4$ **129** gave better 2° insertion compared to Rh_2(*R*-TCPTAD)$_4$ with Rh_2(TPPTAD)$_4$ **129** being the best (2° : 3° = 25 : 1). However, the intramolecular side reaction product for catalyst **129** is heavier than Rh_2(*R*-TCPTAD)$_4$. Another disadvantage is that from crude ^{1}HNMR these catalysts seems to give bad ratio of internal 2° to terminal 2°, suggesting bad selectivity between different secondary sites.

Scheme 29 Study of more phthalimido ligand based dirhodium catalyst



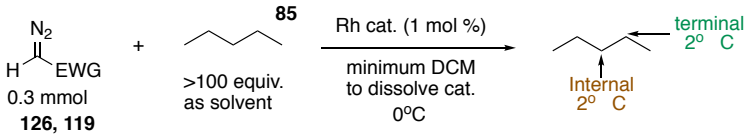
$Rh_2(L)_4$	2°(ter+int) : 3° : Intra 1°	^{1}H NMR yield for 2° (ter+ int)	crude ^{1}HNMR
Rh_2(*R*-TCPTAD)$_4$	10.5 : 1 : 0.89	64 % (cleaner ter 2° vs. int 2°)	
Rh_2(*R*-TPPTAD)$_4$ **129**	25 : 1 : 4.2 (ter C2 and int C2 mixture)	50 %	
Rh_2(*R*-TPPTCL)$_4$ **130**	12.5 : 1 : 3.63 (ter C2 and int C2 mixture)	58 %	
Rh_2(*R*-TPPTBL)$_4$ **131**	7.14 : 1 : 6.79 (ter C2 and int C2 mixture)	29 %	

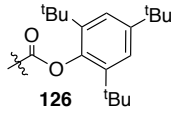
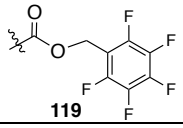
these small peaks are int 2°

3.2.2.2 Preliminary test reactions with pentane as substrate.

Two reactions with pentane as substrates were performed to have an initial understanding of acceptor only rhodium carbene's selectivity between terminal and internal secondary C–H sites (**Scheme 30**). The first reaction followed the optimized 2° insertion from the study with 2-methylpentane (diazo compound **126**, Rh_2(*R*-TCPTAD)$_4$ catalyst). The reaction gave a ratio of 2° (terminal) to 2° (internal) as 2.85 : 1. Considering that there are two terminal methylene sites, the selectivity is considered poor (ter : int = 1.4 : 1). The second reaction use (perfluoro phenyl)methyl 2-diazoacetate **119** to react with pentane under Rh_2(*S*-Dibic)$_4$ catalyst, which is a good comparison to Rh_2(*S*-Dibic)$_4$ catalyzed pentane insertion reaction with donor/acceptor carbene. The ratio 2° (terminal) : 2° (internal) = 6.07 : 1. Considering that there are two terminal 2° sites, the selectivity is only moderate.

Scheme 30 Two preliminary reactions of acceptor-only Rh carbene with pentane



Entry	EWG	Rh catalyst	2° (terminal) : 2° (internal)
1	 **126**	Rh_2(R-TCPTAD)$_4$	2.85 : 1
2	 **119**	*Rh_2(*S*-dibic)$_4$	6.07 : 1

* Rh_2(S-Dibic)$_4$ is common name for Rh_2[*S*-3,5-di(p-^{t}BuC$_6$H$_4$)TPCP]$_4$

However, the pentane system deserves a future systematic study to gain more conclusions. Different EWGs within diazo compound should be screened again as there is no more tertiary C–H site and the only focus now is selectivity between terminal 2° and internal 2°. Also, TPCP series of dirhodium catalysts that failed in the reaction of 2-methylpentane with diazo compound **126** due to intramolecular side reaction should be re-studied for pentane reaction. For example, in previous study with diazo compound **116** (Troc as EWG), Rh_2(*S*-2-Cl,5-BrTPCP)$_4$ is the most secondary C–H selective catalyst, which could be a very promising catalyst for pentane reaction system as well.

3.2.2.3 Preliminary test reactions for benzylic C–H insertion

Donor/acceptor rhodium carbene has achieved high diastereoselectivity and enantioselectivity for many benzylic C–H insertions, so it is natural to test if acceptor only rhodium carbene can achieve good selectivity for benzylic C–H insertion. 4-methoxyanisole and 4-Br ethylbenzene were chosen to represent electron rich and electron deficient aryl substrates and they were reacted with diazo compound **116** (Troc as EWG) using various dirhodium catalysts. However, the results were not promising, 4-methoxyanisole gave substantial cyclopropanation on benzene ring with no sign of the desired benzylic C–H insertion; while 4-Br ethylbenzene gave substantial diazo dimer byproduct, minor cyclopropanation on benzene ring and still no benzylic C–H insertion. Therefore, benzylic substrates are considered to be not suitable for acceptor only rhodium carbene C-H functionalization.

3.2.3 Conclusion for site-selective C–H insertion with Rh acceptor-only carbene

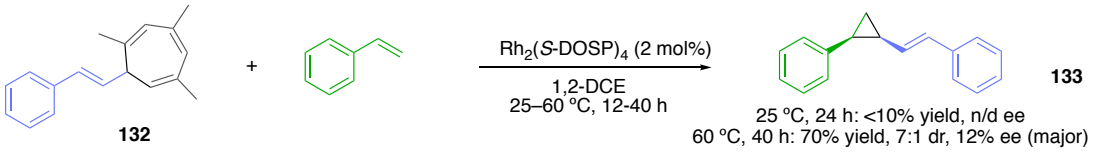
For 2-methylpentane system, both optimized selective 2° and 3° C–H insertion have been achieved with Rh_2(*R*-TCPTAD)$_4$ catalyst but with different ester group of the diazo compounds. The optimized 3° insertion is obtained with pentafluorobenzyl ester as EWG (3° : 2° (ter): 2° (int) = 5.95 : 1 : 0.68). This ratio is good but did not surpass previous best result from other metal catalysts.[11,16] The optimized 2° insertion is obtained with 2,4-6-tri^{t}BuPhenyl ester as EWG and the ratio 2° (combined) : 3° is 10.5 : 1. This high ratio for secondary C–H insertion is unprecedented, but the reaction requires to use 2-methylpentane as solvent to suppress intramolecular side reaction. Also, the overlap of terminal 2° and internal 2° insertion peak in ^{1}HNMR makes it difficult to study the selectivity between different 2° C–H sites. For the pentane system, the poor regioselectivity indicates that it is still difficult to distinguish between terminal 2° and internal 2° even with these newly developed bulky dirhodium catalysts. However, more studies are needed based on this very preliminary study. For the benzylic C–H insertion. The messy mixture without observation of desired insertion products indicate that rhodium acceptor only carbene behave poor for these substrates.

3.3 Asymmetric cyclopropanation with Rh donor-only carbene generated from retro-Büchner reaction

3.3.1 Introduction

Rhodium donor-only carbenes have no precedence of applications in C–H insertion. To better understand the reactivity profile of this type of carbene, it is more reasonable to study if it can achieve asymmetric cyclopropanation first. Professor Antonio Echavarren's group has discovered that retro-Büchner reaction from compound **132** can generate donor-only type metal carbenoid and further react with styrene to form cyclopropanes.[36,37] Several attempts to achieve the enantioselective version have been made, including a gold(I) catalyst that gave up to 30% ee.[36] The best result so far was a 44% ee obtained with a stoichiometric Zinc-BINOL lewis acid.[36] Later on, they found that the same reaction can be carried out under Rh_2(DOSP)$_4$ catalyst, giving product **133** in 7:1 dr and 12% ee (major) (**Scheme 31**).[37] The possibility of inducing enantioselectivity with Rh(II) complexes was proved, and it would be worthwhile to explore new chiral dirhodium catalysts developed from the Davies lab to see if better asymmetric induction can be achieved.

Scheme 31 Model reaction to study enantioselective retro-Büchner cyclopropanation

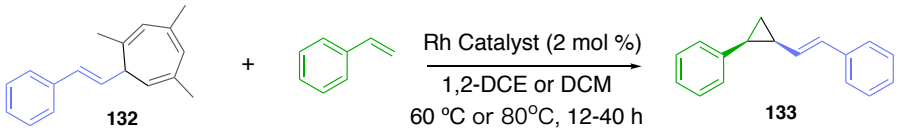


3.3.2 Chiral dirhodium catalysts screening

Various chiral dirhodium catalysts from the Davies group were screened to see if higher enantioselectivity can be achieved (**Scheme 32**). The new chiral dirhodium catalysts involved in the screening tests were Rh_2(*R*-TCPTAD)$_4$, Rh_2(*R*-*p*-BrTPCP)$_4$, Rh_2(*R*-TPPTTL)$_4$, Rh_2(*R*-2Cl,5BrTPCP)$_4$. Racemic sample was obtained by using the reported reaction with Rh_2(TFA)$_4$ (16:1 dr).[ref] It was shown that these newer chiral dirhodium catalysts were not able to significantly increase the enantioselectivity compared to Rh_2(*S*-DOSP)$_4$ (12% ee. 7:1 dr.). The best results among these catalysts is achieved with Rh_2(*R*-2Cl,5BrTPCP)$_4$ (32% ee. 8:1 dr.), which is comparable to the previous best result by

Echavarren's group using Au(I) catalyst. All TPCP catalysts require higher temperature (80 °C) to complete the reaction, possibly due to increased steric demand from the catalysts.

Scheme 32 Catalyst screening results with new chiral dirhodium catalysts from Davies group



132

0.2 mmol
1.0 equiv

0.8 mmol
4.0 equiv

133

75-80% yield, didn't separate celan, focused on ee. and dr.

Rh cat.	T / °C	time / h	dr.	ee. / %
Rh_2(TFA)$_4$	23	18	16:1	0
Rh_2(*R*-TCPTAD)$_4$	60	16	5:1	30
Rh_2(*R*-*p*-BrTPCP)$_4$	80 60(not complete after 40 h)	36	3.2:1	22
Rh_2(*R*-TPPTTL)$_4$	80	22	5.8:1	~0
Rh_2(*R*-2-Cl,5-BrTPCP)$_4$	80	18	8:1 (optimized result with ee.)	32

Recently the Davies group reported increased ee in cyclopropanation with donor-acceptor carbene with dimethyl carbonate (DMC) solvent,[38] so a reaction with Rh_2(*R*-TCPTAD)$_4$ catalyst was also run in DMC as comparison. However, the ee turned out to be 25%, which is lower compared to 30% ee in CH_2Cl_2. Therefore, DMC solvent is not helpful for this reaction system.

3.3.3 Conclusion for asymmetric cyclopropanation with Rh donor-only carbene

Asymmetric cyclopropanation with rhodium donor carbene can be achieved. However, only low ee can be achieved even with our latest bulky chiral dirhodium catalysts. This suggests that this type of carbene is very difficult to achieve catalyst-controlled selectivity. Therefore, no further study was carried on with rhodium donor only carbene.

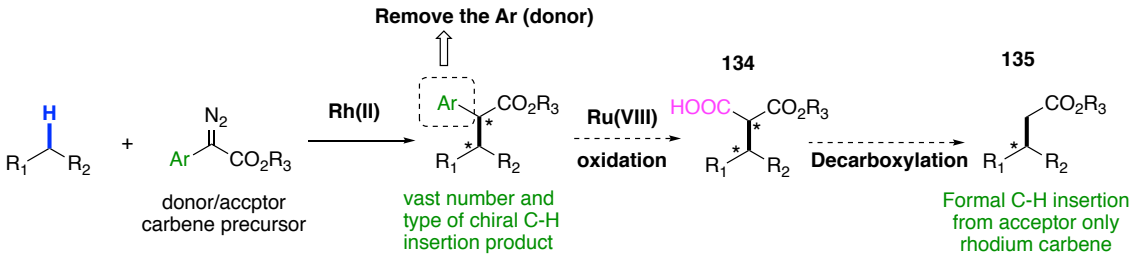
3.4 Derivatization of C–H insertion products from Rh donor/acceptor carbene

Given the unsatisfactory site-selective C–H insertion results obtained directly with acceptor only rhodium carbene, it is reasonable to consider derivatizing successful C–H insertion products from donor/acceptor rhodium carbene, which can also broaden the application of our rhodium carbene chemistry. Two types of derivatizations are studied in this section. The first derivatization is removing the aryl group (donor) of C–H insertion products from rhodium donor/acceptor carbenes, which will generate formal C–H insertion products from previously studied acceptor only carbenes. The second derivatization is removing the ester part (acceptor) of C–H insertion products from rhodium donor/acceptor carbene, which will generate formal benzylation products. Such derivatizations could be synthetically very useful if they can be generalized to C–H insertion products obtained from unique reactivity and selectivity of rhodium donor/acceptor carbenes.

3.4.1 Remove aryl of C–H insertion products from Rh donor/acceptor carbene

The aryl group is usually a very stable group and there are currently no methods for removing the aryl group in one step. A viable 2-step method to achieve the goal is to perform a Ru(VIII) oxidation to transform the aryl group into carboxylic acid first[39-44] followed by a decarboxylation. The combination of catalytic amount of $RuCl_3$ and excess amount of $NaIO_4$ as oxidant are used to generate RuO_4 in-situ in the first oxidation step, but it requires the aryl rings to be electron rich.[39] Therefore, in the initial C–H insertion step we need to use aryldiazoacetates that have electron donating groups on the aromatic ring. The oxidation step would generate a malonate type of intermediate **134**, so the following decarboxylation step requires a methodology that is more suitable for malonate type of product. In this study, we chose to use microwave-assisted fast decarboxylation reported by Tellitu et. Al.[45] to perform the following decarboxylation towards the final product **135**. (**Scheme 33**).

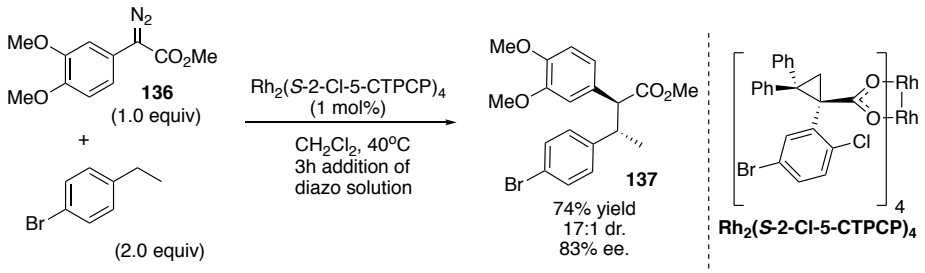
Scheme 33. General scheme of removing the aryl (donor) of Donor/acceptor Rh carbene mediated C–H insertion products



3.4.1.1 Ru(VIII) oxidation/decarboxylation with benzylic C–H insertion products.

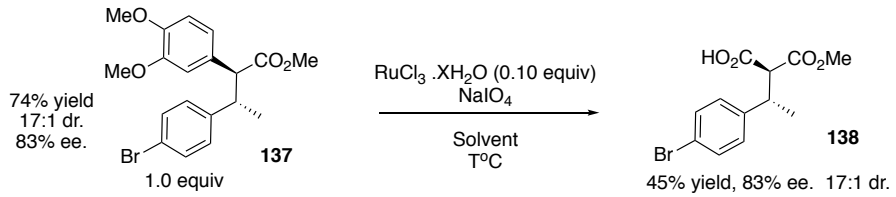
The aromatic ring needs to be electron rich for Ru(VIII) oxidation to work, and selective cleavage of electron-rich aromatic rings in the presence of electron-deficient aromatic rings has been demonstrated.[41] It would be reasonable to test the Ru(VIII) oxidation/decarboxylation derivatization with a benzylic C–H insertion product first so that the final product would still be UV active and can measure ee. The specific benzylic C–H insertion reaction engaged for the study is developed by Dr. Wenbin Liu[46] (**Scheme 34**). The C–H insertion product **137** is obtained in 74% yield, 83% ee (for the major) and 17:1 dr.

Scheme 34. Benzylic C–H insertion (preparing substrate for following derivatization)



The obtained C–H insertion product **137** was subjected to Ru(VIII) oxidation (**Scheme 35**). The electron rich aromatic ring from the diazo compound **136** was oxidized in the Ru(VIII) oxidation step, while the electron-deficient aromatic ring from substrate 4-ethyl toluene survived the oxidation. Early test reaction gave desired product in relatively low yield, so an optimization study was performed by changing reaction temperature, stoichiometry of $NaIO_4$ and reaction solvent. The optimized yield achieved for product **138** is 45%. The ee and dr remain unchanged in this reaction.

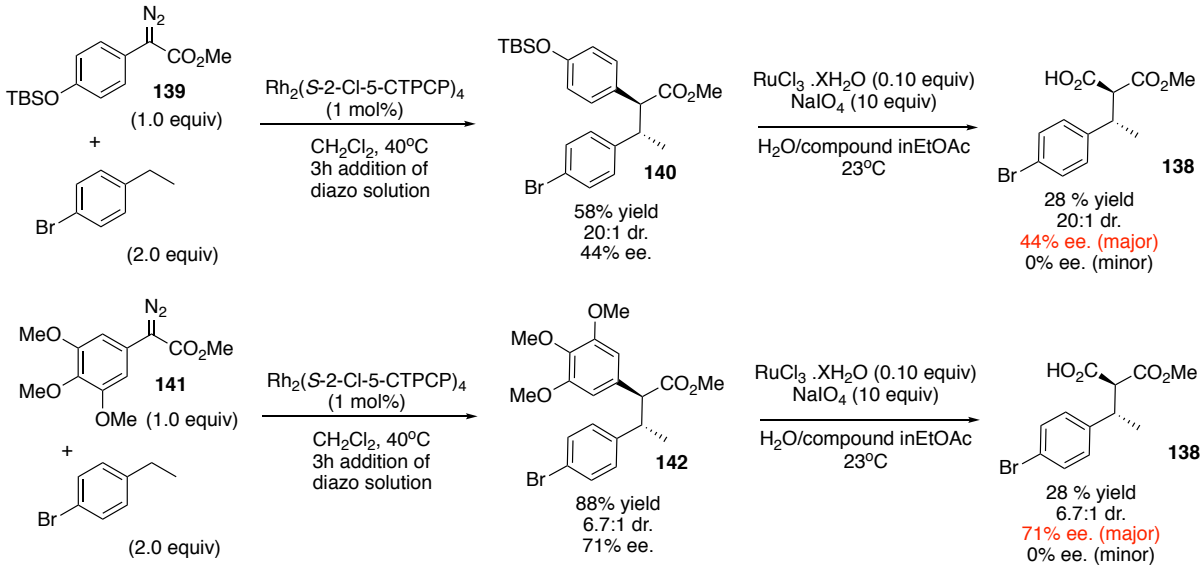
Scheme 35. Optimization study for the Ru(VIII) mediated oxidation of electron rich Ar ring



Equiv of $NaIO_4$	Solvent	T/°C	Reaction time	Yield (isolated)	Unreacted S.M.
5.0	CCl_4:CH_3CN:H_2O =2:2:3	23	12 h	no reaction	Yes,all S.M.
5.0	H_2O compound in EtOAc	23	2 h	low	Yes, significant amount
10.0	H_2O compound in EtOAc	23	2 h	34%	No
10.0	Ch_3CN:H_2O=1:2 compound in EtOAc	23	2 h	32%	No
10.0	H_2O compound in EtOAc	0-23	2 h	45%	No

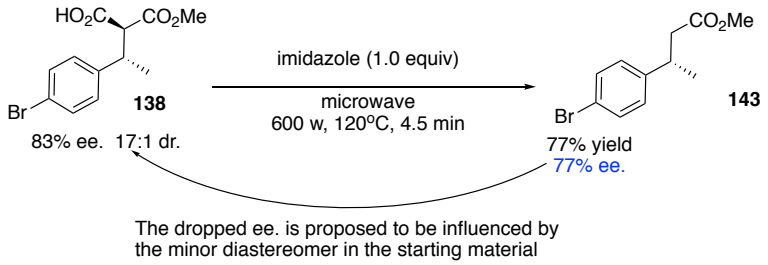
Two other diazo compounds with electron rich aryl rings were also tested as a comparison (**Scheme 36**). Diazo compound **139** gave C–H insertion product **140** in 58% yield and 20:1 dr The Ru(VIII) oxidation step then gave malonate type product **138** in 28% isolated yield and 44% ee (for the major). Diazo compound **141** gave C–H insertion product **142** in 88% yield and 6.7:1 dr Following Ru(VIII) oxidation gave malonate type product **138** in 37% isolated yield and 71% ee (for the major). Both diazo compounds show less promising ee. and low yields, therefore the optimized reaction remains unchanged.

Scheme 36. Comparison study with other diazo compounds bearing electron-rich aromatic ring



Microwave-assisted decarboxylation developed by Tellitu et. Al.[45] were then applied to the malonate type of intermediate from Ru(VIII) oxidation (**Scheme 37**). With the optimized **138** (17:1 dr, 83% ee) that come from **137**, clean decarboxylation product **143** can be achieved in 77% yield and 77% ee. The dropped ee. is proposed to be caused by the minor diastereomer in the insertion step as one stereocenter is burned during the reaction.

Scheme 37. Microwave-assisted decarboxylation to generate formal C–H insertion product from acceptor only carbene

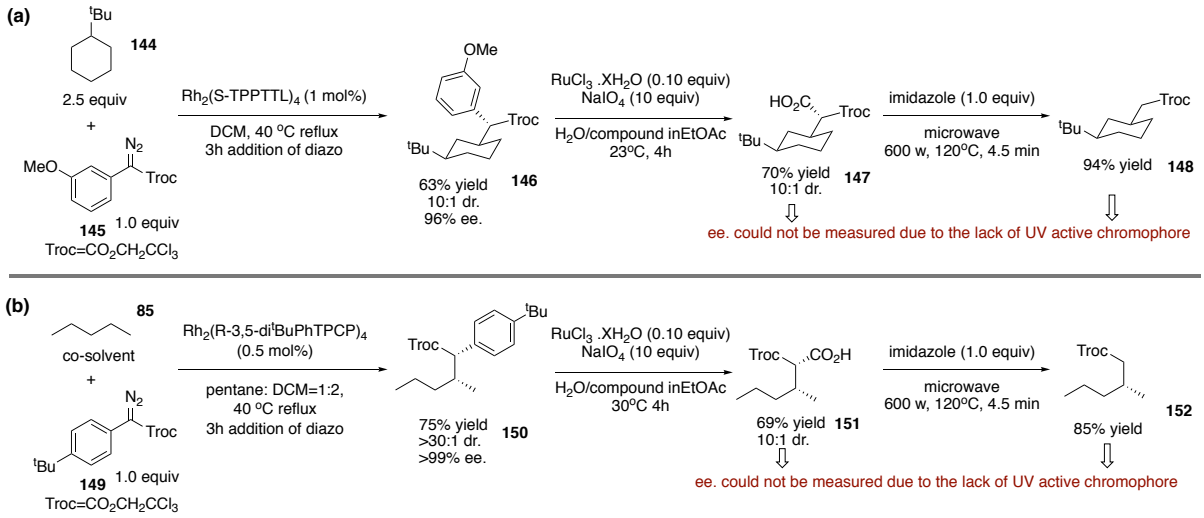


3.4.1.2 Ru(VIII) oxidation/decarboxylation with other C–H insertion products.

The successful Ru(VIII) oxidation/decarboxylation derivatization with benzylic C–H insertion product prompted us to apply the strategy to other C–H insertion products from the Davies lab. C3 functionalized ^{t}Bu-cyclohexane[33] was first tested. Diazo compound **145** was reacted with ^{t}Bu-cyclohexane **144** following the published procedure, giving C–H insertion product **146** in 63% yield, 10:1 dr and 96% ee. This compound was subjected to Ru(VIII) oxidation and gave the malonate type of product **147** in 70% yield, 10:1 dr. Then, microwave-assisted decarboxylation gave the final product **148** in 94% yield (**Scheme 38(a)**). Due to a lack of UV active chromophore, the ee. for the products in oxidation and decarboxylation steps were not able to be measured on our HPLC. Terminal methylene functionalized pentane derivatives[30] was also tested. However, the C–H insertion step behaves poorly if the aryl ring of the diazo compound is too electron rich (such as previous **136**, **139**, **141**), so the one chosen for test is **149**, in which the aryl group is moderately electron-rich (p-^{t}BuC$_6$H$_4$). C–H insertion product **150** following published procedure was obtained in 75% yield, >30:1 dr and >99% ee. This compound was subjected to Ru(VIII) oxidation and gave the malonate type of product **151** in 69% yield, >30:1 dr. Noticing that elevated temperature was used for oxidizing this less electron rich aryl

part. Following microwave-assisted decarboxylation gave final product **152** in 85% yield (**Scheme 38(b)**). Again, the ee was not measured due to the lack of UV active chromophore.

Scheme 38. Application of Ru(VIII) oxidation/decarboxylation to other C–H insertion products



3.4.1.3 Conclusion for the Ru(VIII) oxidation/decarboxylation derivatization.

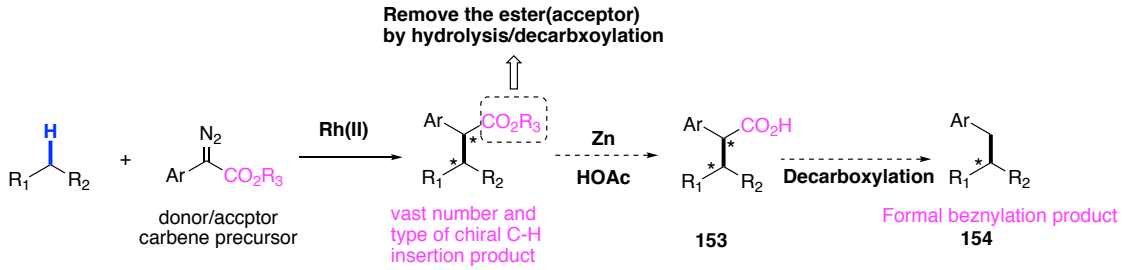
A few examples have been achieved for removing the aryl groups of C–H insertion products from rhodium donor acceptor carbenes. These examples were achieved through Ru(VIII) oxidation (transform aryl part into carboxylic acid) followed by microwave-assisted decarboxylation. However, aryl diazoacetates with electron rich aryl parts behave poorly for many C–H insertion reactions developed in the Davies lab, so there are not many choices of substrates to be tested. In addition, the strong Ru(VIII) oxidizing condition required limits the functional group tolerance as well as possible application to late stage functionalization of complicated molecules. Therefore, this strategy was considered a non-generalizable derivatization.

3.4.2 Remove ester of C–H insertion products from Rh donor/acceptor carbene

Given the lack of generality in the previous strategy of removing aryl (donor) part of C–H insertion product from rhodium donor/acceptor carbene, it is reasonable to consider removing the ester (acceptor) part, which would generate formal benzylation products. This strategy could be very useful for broadening the application of current rhodium donor/acceptor carbene. It is important to develop a convenient and generalizable strategy to achieve the goal. Many C–H insertion reactions developed by

the Davies group give optimized results (ee, dr or yield) with 2,2,2-trichloroethyl aryl diazoacetates.[47] Zn/AcOH condition are frequently used to hydrolyze 2,2,2-trichloroethyl esters into carboxylic acids **153**. Therefore, it is natural to consider a 2-step hydrolysis/decarboxylation derivatization to remove the ester part and generate the formal benzylation products **154**. A mild decarboxylation with wide functional group tolerance is important for the strategy to be general. The Nicewicz group recently developed a photoredox decarboxylation that is carried under very mild conditions and are applied to complicated molecules in the late stage functionalization.[48] Therefore, Zn/AcOH hydrolysis was combined with this photoredox decarboxylation as the strategy for the desired derivatization of removing the ester part of C–H insertion products from Rh donor/acceptor carbenes. (**Scheme 39**)

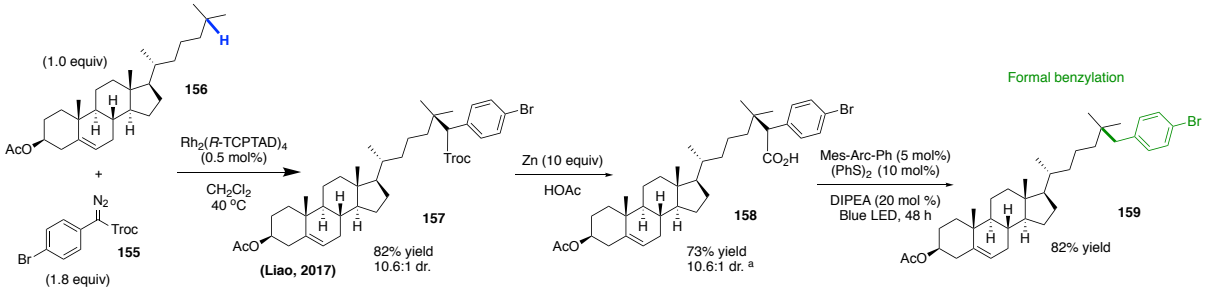
Scheme 39. General scheme of removing the ester (acceptor) of Donor/acceptor Rh carbene mediated C–H insertion products



3.4.2.1 Hydrolysis/decarboxylation with 3° C–H insertion products

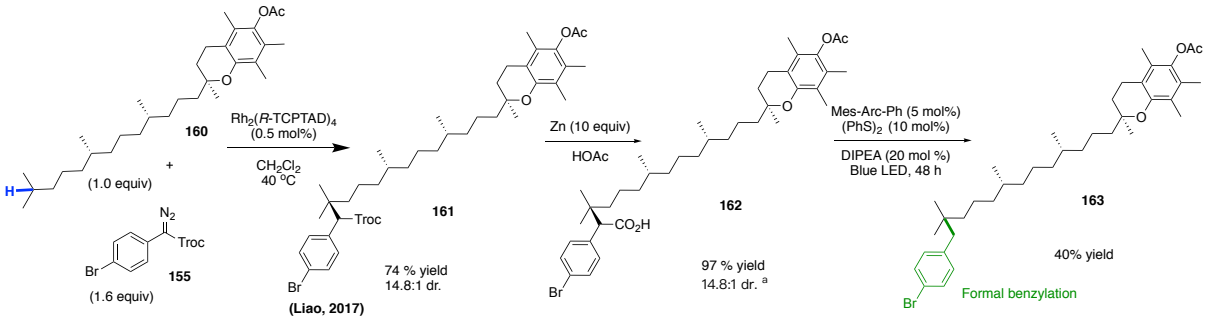
Site- and stereo-selective tertiary (3°) C–H insertion to acyl-protected Vitamin E and acyl-protected cholesterol were reported by Dr. Kuangbiao Liao.[31] These C–H insertion products were successfully derivatized to formal benzylation compounds with the hydrolysis/decarboxylation strategy. For a tertiary C–H insertion product, the final decarboxylation step will remove the benzylic chiral center, so the dr in the insertion step does not influence the final product. The first tested substrate is 3° C–H insertion product (**157**) of acyl-protected cholesterol, which was prepared in 82% yield and 10.6:1 dr. The following Zn/AcOH hydrolysis of **157** gave carboxylic acid intermediate **158** in 73% yield. The final photoredox decarboxylation of **158** gave the formal benzylation compound **159** in 82% yield. (**Scheme 40**)

Scheme 40. Derivatization with 3° C–H insertion products from Acyl-protected cholesterol



The next substrate tested is acyl-protected vitamin E 3° C–H insertion product. C–H insertion product **161** was initially prepared in 74% yield and 14.8:1 dr. The following Zn/AcOH hydrolysis of **161** gave carboxylic acid intermediate **162** in 97% yield. Final photoredox decarboxylation of **161**gave the formal benzylation product **163** in 40% yield. It was noticed that there was benzyl aldehyde type of side product, which could be the reason for the dropped yield. (**Scheme 41**)

Scheme 41. Hydrolysis/decarboxylation with 3° C–H insertion products from Acyl-Vitamin E



a. The dr. was measured by HPLC after $LiAlH_4$ reduction, transforming the OAc and Troc to alcohol at the sametime

3.4.2.2 Hydrolysis/decarboxylation with 2° C–H insertion products

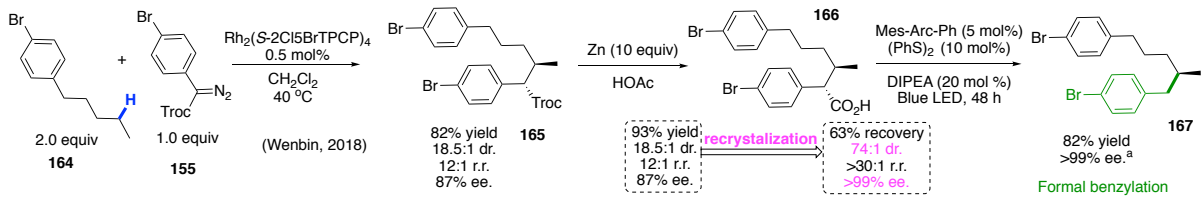
Products from secondary (2°) C–H insertion are more valuable for hydrolysis/decarboxylation derivatization as the final formal benzylation products will still remain a new chiral center. However, the minor diastereomer for many secondary (2°) C–H insertion reactions could give rise to a problem that after decarboxylation the ee. may drop. Moreover, initial test results showed that the racemate of formal benzylation products could not be separated on chiral HPLC due to a lack of nearby polar binding functional group. Therefore, recrystallization of carboxylic acid intermediates was considered as a solution. With enhanced dr to over 50:1, the ee of carboxylic acid intermediates, it is reasonable to

assume that the ee will keep unchanged after decarboxylation. The products of decarboxylation indeed show optical activity, but it is difficult to assess the degree of enantiopurity of these compounds.

3.4.2.2.1 Derivatization of products from Rh_2(*S*-2-Cl,5-BrTPCP)$_4$ catalysts.

Rh_2(*S*-2-Cl-5-BrTPCP)$_4$ catalyst is developed by Dr. Wenbin Liu.[32] This catalyst tends to perform C–H functionalization on the most accessible secondary C–H bond. For substrates containing an aliphatic chain, this catalyst can overcome electronically favored site and perform C–H insertion at the terminal methylene site.[32] The first substrate tested is 2° C–H insertion product (**165)** of 1-bromo-4-pentylbenzene**,** which was prepared in 82% yield, 18.5:1 dr, 12:1 r.r., and 86% ee. The following Zn/AcOH hydrolysis of **165** gave carboxylic acid intermediate **166** in 93% yield, 18.5:1 dr, 12:1 r.r. and 86% ee. Recrystallization of the acid **166** gave 63% recovered yield with significantly enhanced 74:1 dr, >30:1 r.r. and >99% ee. Final photoredox decarboxylation of **166** gave the formal benzylation product **167** in 82% yield. Given the high dr for recrystallized acid, the ee can be considered unchanged (>99% ee). (**Scheme 42**)

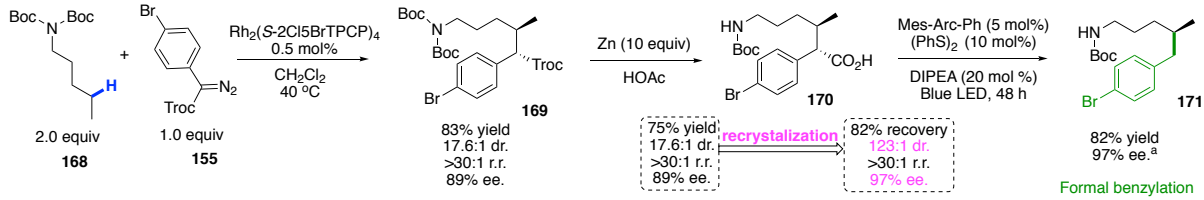
Scheme 42 Derivatization for 2° C–H insertion product of 4-Br,n-pentylbenzene



a. The maintained ee. is assuming that the decarboxylation does not influence the chiral center

The second substrate tested is 2° C–H insertion product (**169**) of a di-Boc protected amine,[50] which was obtained in 83% yield, 17.6:1 dr, >30:1 r.r. and 89% ee. The following Zn/AcOH hydrolysis of **169** gave carboxylic acid intermediate **170** in 93% yield, 17.6:1 dr, >30:1 r.r. and 89% ee. One of the two Boc protecting group was also cleaved off under the condition. Recrystallization of the acid **170** gave 63% recovered yield with significantly enhanced 123:1 dr and 97% ee. Final photoredox decarboxylation of **170** gave the formal benzylation product **171** in 82% yield. Given the high dr for recrystallized acid, the ee is considered unchanged (97% ee). (**Scheme 43**)

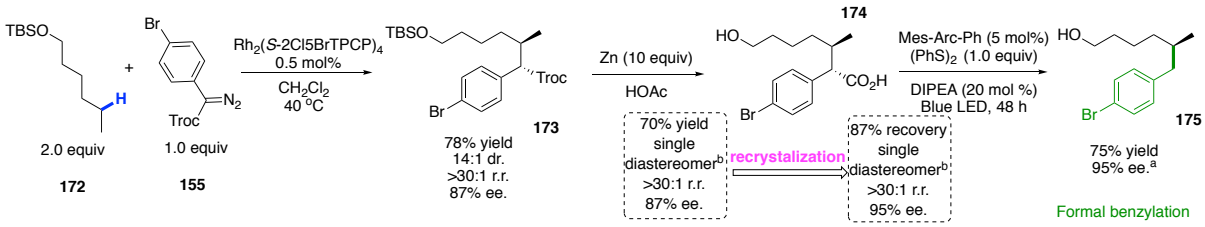
Scheme 43 Derivatization for 2° C–H insertion product of di-Boc protected amyl amine



a. The maintained ee. is assuming that the decarboxylation does not influence the chiral center

The third substrate tested is 2° C–H insertion product (**173**) of TBS protected 1-hexanol,[49] which was obtained in 78% yield, 14:1 dr, >30:1 r.r. and 87% ee. The following Zn/AcOH hydrolysis of **173** gave carboxylic acid intermediate **174** in 70% yield, as a single diastereomer, >30:1 r.r. and 87% ee. The TBS protecting group was also cleaved off under this condition and the major diastereomer of **174** can be directly isolated via column on silica gel. Recrystallization of the acid **174** gave 87% recovered yield with enhanced 95% ee. Final photoredox decarboxylation of **174** gave the formal benzylation product **175** in 75% yield. The ee is considered unchanged (95% ee.) (**Scheme 44**).

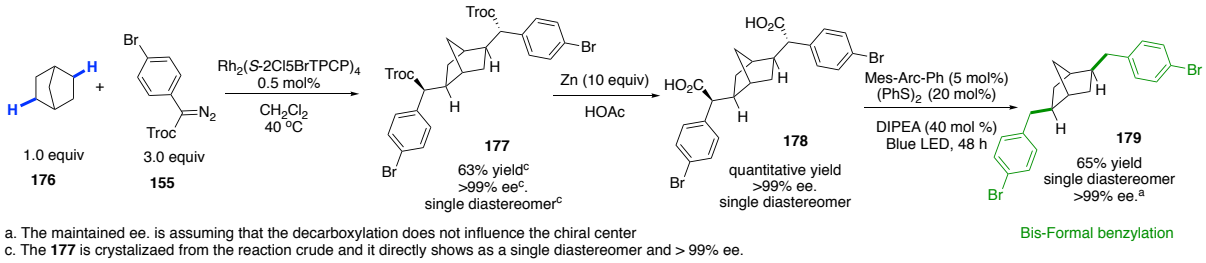
Scheme 44 Derivatization for 2° C–H insertion product of TBS protected 1-hexanol



a. The maintained ee. is assuming that the decarboxylation does not influence the chiral center
b. For **174,** the crude ^{1}HNMR shows 14:1 dr. but column chromatography was able to isolate the major diastereomer cleanly.

The fourth substrate tested is bis- 2° C–H insertion product (**177) of** norbornane. Although the crude NMR showed 29:2:2:1 dr, direct crystallization from the reaction crude can obtain **177** in 63% yield as a single diastereomer, regioisomer in >99% ee.[52] The following Zn/AcOH hydrolysis of **177** gave bis-carboxylic acid intermediate **178** in quantitative yield. Final photoredox bis-decarboxylation of **178** gave the bis-formal benzylation product **179** in 65% yield. The ee is considered unchanged (>99% ee). (**Scheme 45**)

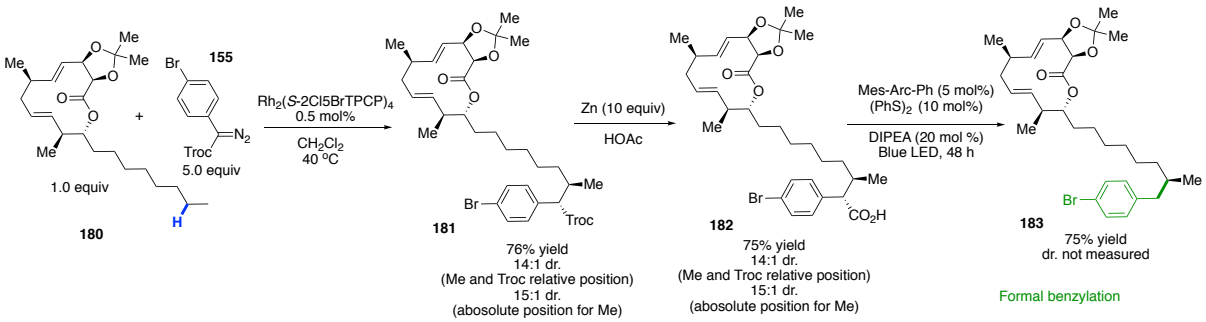
Scheme 45 Derivatization for 2° C–H insertion product of TBS protected 1-hexanol



a. The maintained ee. is assuming that the decarboxylation does not influence the chiral center
c. The **177** is crystalizaed from the reaction crude and it directly shows as a single diastereomer and > 99% ee.

The fifth substrate tested is 2° C–H insertion product (**181**) of a natural compound **180** (from the Bill Wuest lab), which was obtained in 14:1 dr (by ^{1}H NMR, for relative position of terminal methyl and Troc group) and 15:1 dr (by HPLC, for the absolute stereochemistry of the terminal methyl).[51] The following Zn/AcOH hydrolysis of **181** gave carboxylic acid intermediate **182** in 75%. Unfortunately, acid **182** is not a solid cannot be recrystallized to enhance the dr. Final photoredox decarboxylation of **182** gave formal benzylation product **183** in 75% yield. The dr was not determined. (**Scheme 46**)

Scheme 46 Derivatization for 2° C–H insertion product of a nature product 180

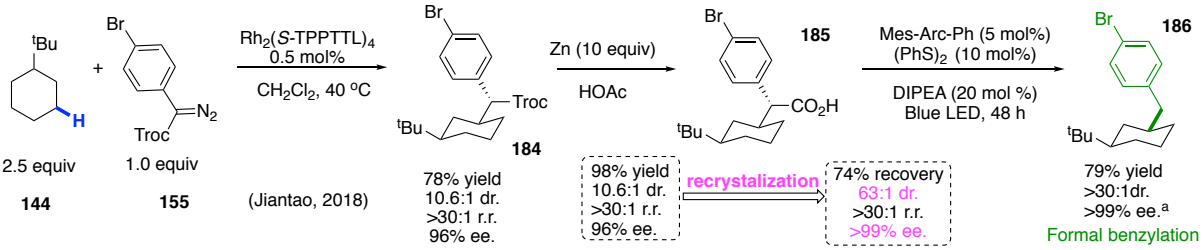


3.4.2.2.2 Derivatization of products from Rh$_2$(*S*-TPPTTL)$_4$ catalysts.

Rh$_2$(*S*-TPPTTL)$_4$ has demonstrated superior site- and stereoselectivity for desymmetrization of substituted cyclohexane.[33] It can achieve C3 secondary C–H insertion to substituted cyclohexanes with high regioselectivity, diastereoselectivity and enantioselectivity.[33] Two Rh$_2$(*S*-TPPTTL)$_4$ catalyzed C–H insertion products were successfully derivatized to formal benzylation compounds with the hydrolysis/decarboxylation strategy (**Scheme 47**). The first substrate tested is ^{t}Bu cyclohexane C3 insertion product **184**, which was obtained in 78% yield, 10.6:1 dr, >30:1 r.r. and 95% ee. The following Zn/AcOH hydrolysis of **184** gave carboxylic acid intermediate **185** in 98% yield, 10.6:1 dr and 95% ee. Recrystallization of the acid **185** gave 74% recovered yield with enhanced 63:1 dr and >99% ee. Final

photoredox decarboxylation of **185** gave the formal benzylation product **186** in 79% yield. Given the high dr for recrystallized acid, the ee is considered unchanged (>99% ee). (**Scheme 47**)

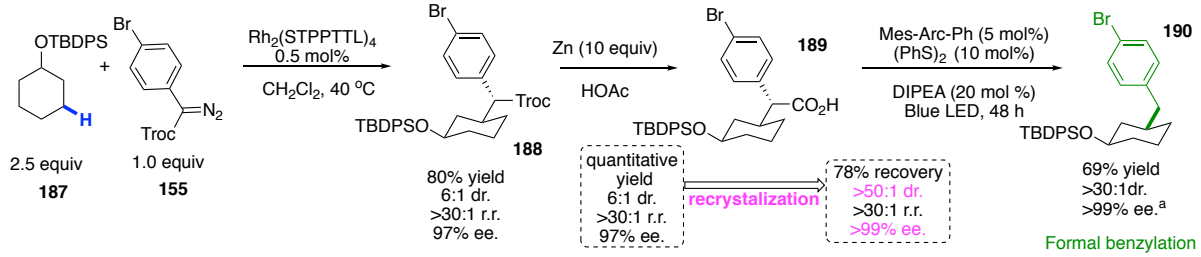
Scheme 47 Derivatization for C3 2° C–H insertion products of tert-Butyl cyclohexane



a. The maintained ee. is assuming that the decarboxylation does not influence the chiral center

The second substrate tested is C3 insertion product (**188)** of TBDPS protected cyclohexanol[53], which was obtained in 74% yield, 6:1 dr, >30:1 r.r. and 97% ee. The following Zn/AcOH hydrolysis of **188** gave carboxylic acid intermediate **189** in quantitative yield, 10:1 dr and 97% ee. Recrystallization of the acid **189** gave 78% recovered yield with enhanced >50:1 dr and >99% ee. Final photoredox decarboxylation of **189** gave the formal benzylation product **190** in 69% yield. Given the high dr for recrystallized acid, the ee is considered unchanged (>99% ee). (**Scheme 48**)

Scheme 48 Derivatization for C3 insertion products of TBDPS protected cyclohexanol

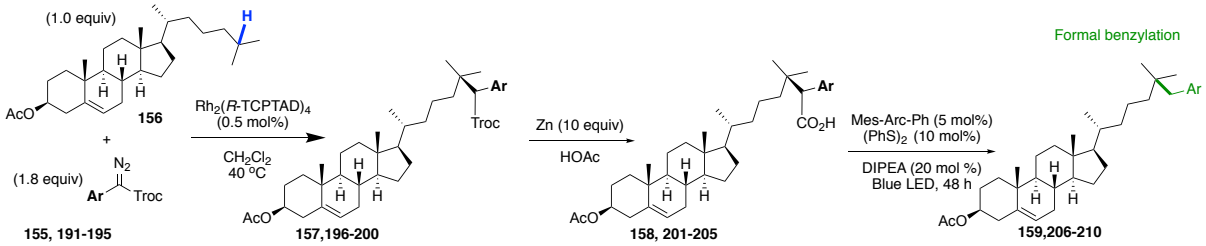


a. The maintained ee. is assuming that the decarboxylation does not influence the chiral center

3.4.2.3 Demonstrating the aryl scope with acyl- cholesterol 3° C–H formal benzylation

With the successful formal benzylation from 3° C–H insertion product of Ac-protected cholesterol example (**Scheme 40**), aryl diazoacetates (**191-195**) bearing different aromatic groups were tested to demonstrate the diazo compound scope (**Scheme 49**). It can be seen that the formal benzylation strategy "Hydrolysis/decarboxylation" is compatible with different electronic feature on the aryl ring.

Scheme 49. Aryldiazoacetates scope for acyl-cholesterol 3° C–H formal benzylation



Ar	C-H insertion	Hydrolysis	Decarboxylation
Br **155**	82% yield 10.6:1 dr. [c] >30:1 r.r. **157**	75% yield 10.6:1 dr. >30:1 r.r. **158**	82% yield >30:1 r.r. **159**
F **191**	81% yield 20:1 dr. [c] >30:1 r.r. **196**	80% yield 20:1 dr. >30:1 r.r. **201**	69% yield >30:1 r.r. **206**
AcO **192**	74% yield 5.3:1 dr. [b] >30:1 r.r. **197**	quantitative yield 5.3:1 dr. >30:1 r.r. **202**	87% yield >30:1 r.r. (Ar=*p*-OHC_6H_4)[a] **207**
AcO **193**	67% yield 5.6:1 dr. [b] >30:1 r.r. **198**	94% yield 5.6:1 dr. >30:1 r.r. **203**	81% yield >30:1 r.r. (Ar=*m*-OHC_6H_4)[a] **208**
Me **194**	61% yield 3.1:1 dr. [c] >30:1 r.r. **199**	94% yield 3.1:1 dr. >30:1 r.r. **204**	74% yield >30:1 r.r. **209**
195	75% yield 4.1:1 dr. [c] >30:1 r.r. **200**	90% yield 4.1:1 dr. >30:1 r.r. **205**	72% yield >30:1 r.r. **210**

a. The OAc on the phenol is labile, the photodecarboxylation step casued the OAc on aromatic ring to fall off, therefore the **207** and **208** has Ar=phenol
b. For **197** and **198**, the dr. was measured directly by HPLC, and this dr. represent the dr. of carboxylic acid **202** and **203**
c. For **157**, **196**, **199, 200**, the dr. was measured with $LiAlH_4$ reduced by HPLC, and this dr. represent the dr. of carboxylic acid **158, 201, 204, 205**

3.4.2.4 Conclusion for hydrolysis/decarboxylation derivatization

The Zn/AcOH hydrolysis of trichloroethyl ester moiety followed by a mild photoredox decarboxylation proved to be a desired general derivatization strategy. Multiple unique C–H insertion products achieved with the Davies' rhodium donor/acceptor chemistry were successfully derivatized to formal benzylation products with good yield. The recrystallization of carboxylic acid intermediates can significantly enhance the dr so that final products are considered to maintain the high ee. In general, this strategy is very promising for late stage benzylation and also achieved the goal of broadening the application of our rhodium carbene chemistry.

References:

1. Greuter, F.; Kalvoda, J.; Jeger, O. *Proc. Chem. Soc.* **1958**, 349.

2. Yates, P.; Danishefsky, S. *J. Am. Chem. Soc.* **1962**, *84*, 879.

3. Burke, S. D.; Grieco, P. A. *Org. React.* **1979**, *26*, 361.

4. Bredt, J.; Holz, W. J. *Prakt. Chem*. **1917**, *95*, 133.

5. Maas, G. *Top. Curr. Chem.* **1987**, *137*, 75.

6. Wenkert, E.; Davis, L. L.; Mylari, B. L.; Solomon, M. F.; Da Silva, R. R.; Shulman, S.; Warnet, R. J.; Ceccherelli, P.; Curini, M.; Pellicciari, R. *J. Org. Chem.* **1982**, *47*, 3242.

7. Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808.

8. Yoon, C. H.; Flanigan, D. L.; Chong, B.-D.; Jung, K. W. *J. Org.Chem.* **2002**, *67*, 6582.

9. Yoon, C. H.; Nagle, A.; Chen, C.; Gandhi, D.; Jung, K. W. *Org.Lett.* **2003**, *5*, 2259.

10. Jung, Y. C.; Yoon, C. H.; Turos, E.; Yoo, K. S.; Jung, K. W. *J. Org. Chem.* **2007**, *72*, 10114

11. Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssie, P. *J. Chem. Soc., Chem. Commun.* **1981**,688.

12. Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssie, P. *Bull. Soc.Chim. Belg.* **1984**, *93*, 945

13. Demonceau, A.; Noels, A. F.; Teyssie´, P.; Hubert, A. *J. Mol. Catal.* **1988**, *49*, L13.

14. Demonceau, A.; Noels, A. F.; Hubert, A. *J. Mol. Catal.* **1989**, *57*, 149.

15. Demonceau, A.; Noels, A. F.; Costa, J. L.; Hubert, A. *J. Mol. Catal.* **1990**, *58*, 21.

16. Dı´az-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pe´rez, P. J. *J. Am. Chem. Soc*. **2002**, *124*, 896.

17. Trofimenko, S. Scorpionates, The Coordination Chemistry of Polypyrazolylborate Ligands; *Imperial College Press: London*,**1999**.

18. Díaz-Requejo, M. M., Pérez, P. *J. Chem. Rev*. **2008**, *108*, 3379.

19. Gava, R., Olmos, A., Noverges, B., Varea, T., Álvarez, E., Belderrain, T. R., Caballero, A., Asensio, G., Pérez, P. J. *ACS Catal*. **2015**, *5*, 3726.

20. Callot, H. J.; Metz, F. Tetrahedron Lett. **1982**, *23*, 4321.

21. Doyle, M. P.; McKervey, M. A.; Ye, T. Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides; Wiley-Interscience: New York, 1998.

22. Davies, H. M. L.; Stafford, D. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 233.

23. Davies, H. M. L.; Antoulinakis, E. G. *J. Organomet. Chem.* **2001**, *47*, 617

24. Davies, H. M. L.; Hansen, T. *J. Am. Chem. Soc.***1997**, *119*, 9075

25. Davies, H. M. L. In Advances in Cycloaddition; Haramata, M. E., Ed.; *JAI Press Inc.*, **1999**; Vol. 5, p 119

26. Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063.

27. Qin, C., Boyarskikh,V., Hansen, J. H., Hardcastle, K. I., Musaev, D. G., Davies, H. M. L. *J. Am. Chem. Soc.* **2011**, *133*, 19198

28. Qin, C., Davies, H. M. L. *J. Am. Chem. Soc.* **2014**, *136*, 9792

29. Liao, K.; Yang, Y., Sander, J., Houk, K., Musaev, D. G,, Davies, H. M. L. *Nature Chemistry.* **2018**, *10*, 1048.

30. Liao, K.; Negretti, S.; Musaev, D. G.; Bacsa, J.; Davies, H. M. L. *Nature*, **2016**, *533*, 230

31. Liao, K.; Pickel, T. C.; Boyarskikh, V.; Bacsa, J.; Musaev, D. G.; Davies, H. M. L. *Nature*, **2017**, *551*, 609

32. Liu, W.; Ren, Z.; Bosse, A. T.; Goldstein, E. L.; Bacsa, J.; Musaev, D. G.; Stoltz, B. M.; Davies, H. M. L. *J. Am. Chem. Soc.* **2018**, *140*, 12247.

33. Fu, J.; Ren, Z. Bacsa, J.; Musaev, D. G.; Davies, H. M. L. *Nature*, **2018**, *564*, 395.

34. Czaplyski, W. L., Na, C. G. & Alexanian, E. J. *J. Am. Chem. Soc.* **138**, 13854

35. Schmidt, V. A., Quinn, R. K., Brusoe, A. T. & Alexanian, E. J. *J. Am. Chem. Soc.* **2014**, *136*, 14389

36. Mato, M., Herlé, B., Echavarren, A. M. *Org. Lett.* **2018**, *20*, 4341.

37. Mato, M., Echavarren, A. M., *Angew. Chem. Int. Ed.* **2019**, *58*, 2088.

38. Wei, B., Sharland, J. C., Lin, P., Wilkerson-Hill, S. M., Fullilove, F. A., Mckinnon, S., Blackmond, D. G., Davies, H. M. L. *ACS Catal.* **2020**, *10*, 1161.

39. Kasai, M., Ziffer, H. *J. Org. Chem.* **1983**, *48*, 2346.

40. Nunez, M. T., Martin, V. S. *J. Org. Chem.* **1990**, *55*, 1928

41. Clayden, J., Menet, C. J., Tchabanenko, M. K., *Tetrahedron*, **2002**, *58*, 4727

42. Mander, L. N., Williams, C. M. *Tetrahedron*, **2003**, *59*, 1105

43. Pagliaro, M., Campestrini, S., Ciriminna, R. *Chem. Soc. Rev.* **2005**, *34*, 837.

44. Plietker, B. *Synthesis*, **2005**, *15*, 2453.

45. Tellitu, I., Beitia, I., Diaz, M., Alonso, A., Moreno, I., Dominguez, E., *Tetrahedron*, **2015**, *43*, 8251

46. Liu, W. *The Synthesis and Application of a Series of C_4-Symmetric Dirhodium Catalysts Derived from 1-(2-Chlorophenyl)-2,2-Diphenylcyclopropanecabroxylate Ligands* ; Emory University, GA., **2019**; pp 41.

47. Guptill, D. M.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014,** *136*, 17718.

48. Griffin, J. D., Zeller, M. A., Nicewicz, D. A. *J. Am. Chem. Soc.* **2015**, *137*, 11340.

49. This insertion reaction is performed by Boni, Y. T. (the Davies group) and has not been published.

46. Liu, W. *The Synthesis and Application of a Series of C_4-Symmetric Dirhodium Catalysts Derived from 1-(2-Chlorophenyl)-2,2-Diphenylcyclopropanecabroxylate Ligands* ; Emory University, GA., **2019**; pp 54.

51. This insertion reaction is performed by Dr. Liu Wenbin and has not been published.

52. This insertion reaction is unpublished result in the Davies group.

46. Fu, J. *Development and Applications of a New Dirhodium Tetracarboxylate Catalyst and Asymmetric Cyclopropanation of Heterocyclic Compound*; Emory University, GA., **2020**; pp 68.

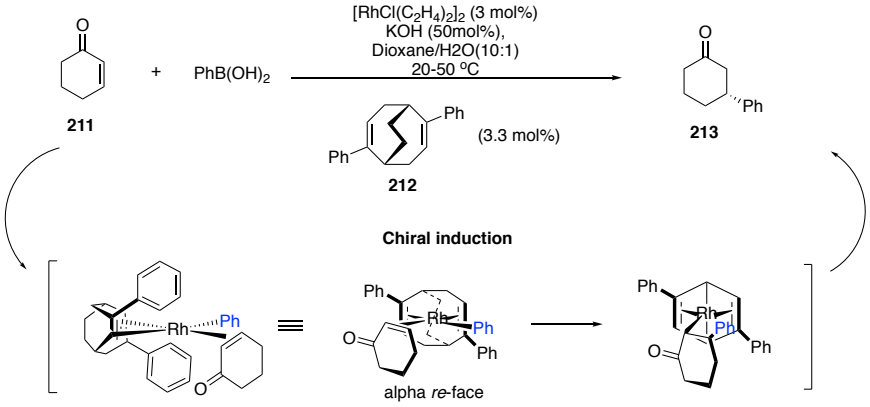
Chapter Four

C–H Functionalization Approach for the Synthesis of Chiral C_2 symmetric 1,5-Cyclootadienes (COD) Ligands[28]

4.1 Introduction

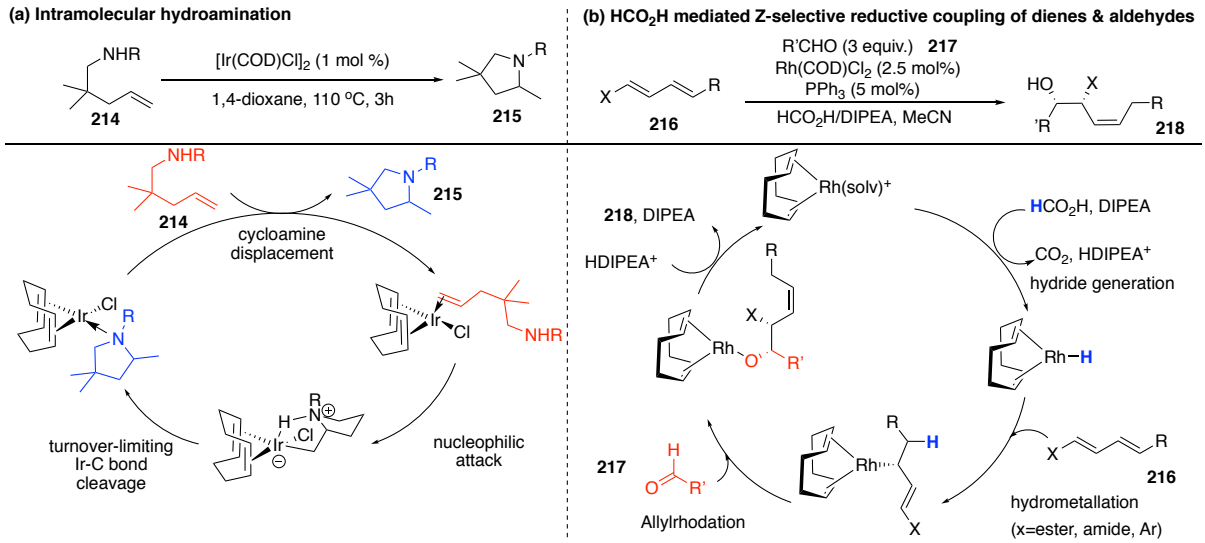
Metal-COD complexes are useful because many are stable to isolate, easily handled, and often more robust than the related ethylene complexes because of chelation. Even though the metal-COD complexes were initially considered as stable precursors to active catalysts, it became clear in many instances that the COD ligand participated in the entire catalytic cycle.[2-4] One classic example is rhodium catalyzed asymmetric conjugate addition of cyclohexa-2-enone **211** with phenyl boronic acid. The chiral pocket from the rhodium-chiral COD ligand complex only allows the enone **211** to approach at alpha-*Re* face, inducing the enantioselectivity (**Scheme 50**).

Scheme 50 Rh-catalyzed asymmetric conjugate addition



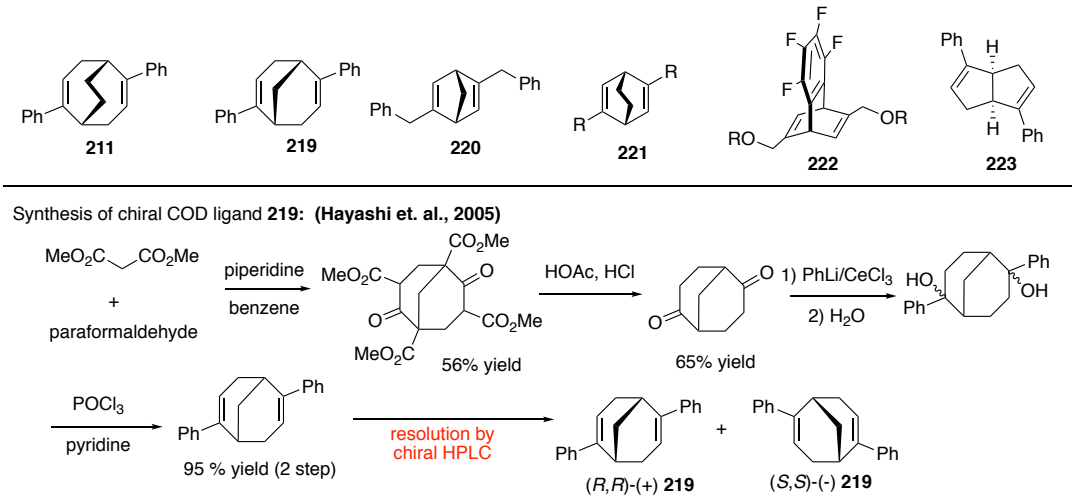
Recently, more transition-metal catalyzed reactions emerged in which the COD ligand was an integral part of the catalytic cycle.[2,3] One example would be the intramolecular hydroamination of compound **214**, where one COD ligand is always bound to the iridium center during the catalytic cycle (**Scheme 51(a)**).[2] In the reaction of formic acid-mediated *Z*-selective reductive coupling of dienes **216** and aldehydes **217**, it is also proposed in the mechanism that the COD ligand is binding to rhodium center throughout the reaction**(Scheme 51(b))**.[3] It would be worthwhile to consider the asymmetric version of such reactions using chiral COD ligands. Consequently, there has been an increased interest in designing chiral COD ligands for asymmetric catalysis.

Scheme 51 Recent reactions with a binding M-COD complex during the catalytic cycle



The chiral COD ligands **211** and **219** have shown considerable promise but their synthesis requires multiple steps and a chiral resolution.[5] This has led to the synthesis of other cyclic dienes as chiral ligands,[4-6] including a number of C_2 symmetric ligands (**211-223**).[3-6] (**Scheme 52**).

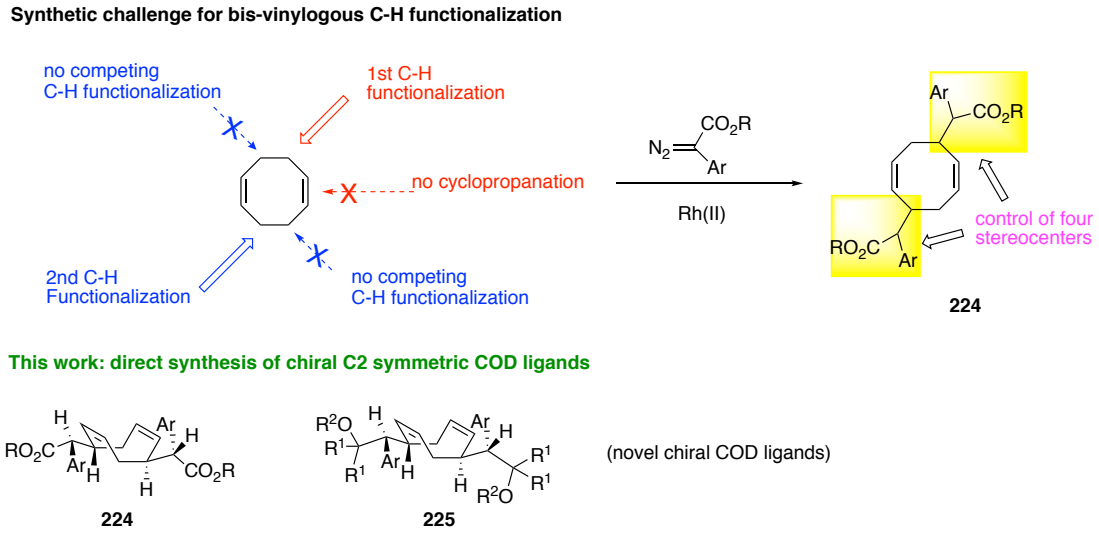
Scheme 52 Previous cyclic chiral diene ligands and the challenging synthesis



We realized that COD would be an intriguing substrate to challenge catalyst-controlled C–H functionalization by rhodium-stabilized donor/acceptor carbenes (**Scheme 53**).[7,8] The Davies group have recently shown that dirhodium catalysts with defined shapes are capable of selecting between primary, secondary and tertiary unactivated C–H bonds.[8-12] We have also demonstrated that different secondary C–H bonds can be distinguished in C–H insertion reactions by using different dirhodium

catalysts.[10,13,14] COD was considered to be an interesting substrate because even though the methylene sites are allylic and activated, the *cis* alkene would be expected to be a competing site for cyclopropanation. Therefore, we would need to identify a catalyst that would lead to selective C–H functionalization instead of cyclopropanation. Then, ideally once the mono C–H functionalization has occurred, the catalyst would select the C5 site for a second C–H functionalization, over the two other allylic methylene sites at C3 and C6 to generate the COD derivative **224**. In this chapter, the challenge of controlling the stereochemistry of the four newly formed stereogenic centers was successfully solved using our rhodium donor acceptor carbene chemistry, where C_2-symmetric **224** along with their derivatives **225** were obtained as novel chiral COD ligands.

Scheme 53 Synthetic challenge and the achievement of this work

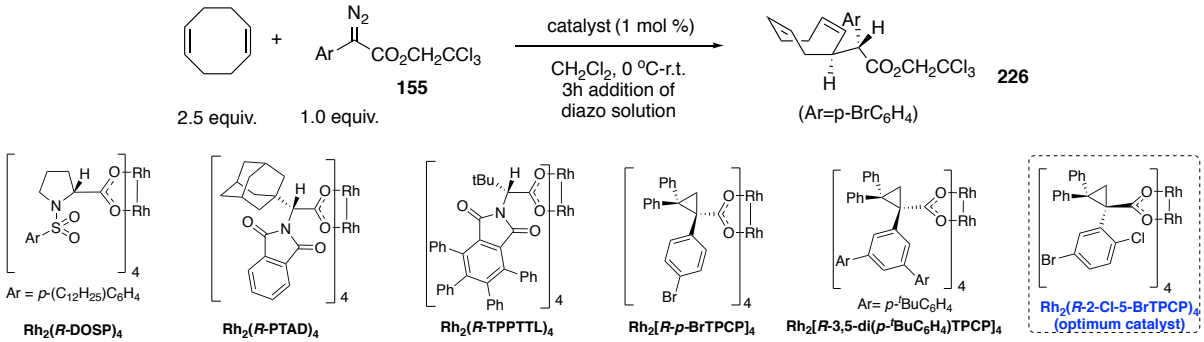


4.2 Mono-allylic C–H functionalization experiments

4.2.1 Catalyst optimization study

We proposed that the dirhodium catalysts are important for the reaction to achieve the desired vinylogous C–H insertion cleanly. Therefore, the initial study focused on a catalyst screening for the mono-allylic C–H functionalization. Several promising dirhodium catalysts developed by the Davies lab that target the methylene sites were chosen to perform the optimization studies (**Scheme 54**). Rh_2(*S*-DOSP)$_4$ is our first generation of chiral dirhodium catalysts that demonstrate wide applications for methylene C–H functionalization.[7b] Rh_2(*S*-PTAD)$_4$ is our second generation of chiral dirhodium catalyst that give different reactivity as well as stereochemistry compared to the Rh_2(*S*-DOSP)$_4$ with regards to methylene C–H functionalization.[7b] Rh_2(*R*-TPPTTL)$_4$ is more recently developed that demonstrate outstanding site and stereo selectivity for C3 over C4 C–H functionalization of substituted cyclohexanes.[13] The triaryl-cyclopropanecarboxylates (TPCP) series of catalysts are the latest generation that are considered to be the most sterically congested. Rh_2(*R*-*p*-BrTPCP)$_4$ was the first developed among this type of catalysts and it preferred to react at sterically less crowded C–H bonds.[8-9] Other TPCP series of dirhodium catalysts tested include Rh_2(*R*-3,5-(*p*-^{t}BuC$_6$H$_4$)TPCP)$_4$[10] and Rh_2(*R*-2-Cl-5-BrTPCP)$_4$.[14] These two have shown great success for functionalization of unactivated C–H bonds and they both tend to react at the most accessible methylene site. Rhodium donor/acceptor carbenes with trichloroethyl ester as the electron withdrawing group have been shown to give better yield and selectivity in many situations,[9] and therefore, the initial reaction was conducted with trichloroethyl aryldiazoacetate **155** with 2.5 equiv of COD substrate. Most catalysts gave undefined mixture of products (see supporting information for crude ^{1}H NMR), but the Rh_2(*R*-2-Cl-5-BrTPCP)$_4$-catalyzed reaction cleanly generated the desired mono C–H functionalization product **226** in 72% isolated yield, >30:1 dr and 91% ee. Therefore, Rh_2(*R*-2-Cl-5-BrTPCP)$_4$ was chosen as the optimized catalyst for the following studies.

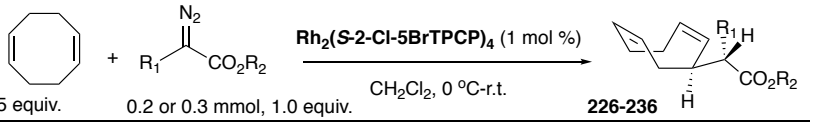
Scheme 54 Catalysts screening for the mono-allylic C–H functionalization



4.2.2 Diazo compound scope for the mono allylic C–H functionalization

The scope of the mono-allylic C–H insertion was then investigated with various aryldiazoacetates using Rh_2(*R*-2-Cl-5-BrTPCP)$_4$ as the optimal catalyst (**Scheme 55**). The influence of the ester functionality was initially examined (entries 1-3). By comparing the dr and ee of the C–H functionalization products **226-236**, we found that the trifluoroethyl aryldiazoacetate was the most effective and gave the allylic C–H insertion product **228** with the highest enantioselectivity (93% ee) and excellent diastereoselectivity (>30:1 dr). Therefore, the following studies focused on the trifluoroethyl derivatives. A series of *p*-substituted aryl and a pyridyl derivative were applied to the reaction under optimized condition and they all generate the desired product **229-234** in high yield and dr, with the asymmetric induction in the range of 79-95% ee. The *meta*-substituted aryldiazoacetate behaved poorer with regard to the enantioselectivity, giving product **235** in 63% ee. A styryldiazoacetate was also tested and it gave an effective reaction towards allylic insertion product **236** in 67% yield, >30:1 dr, 88% ee.

Scheme 55 Diazo compound scope for the mono C–H functionalization of COD



2.5 equiv. 0.2 or 0.3 mmol, 1.0 equiv. **226-236**

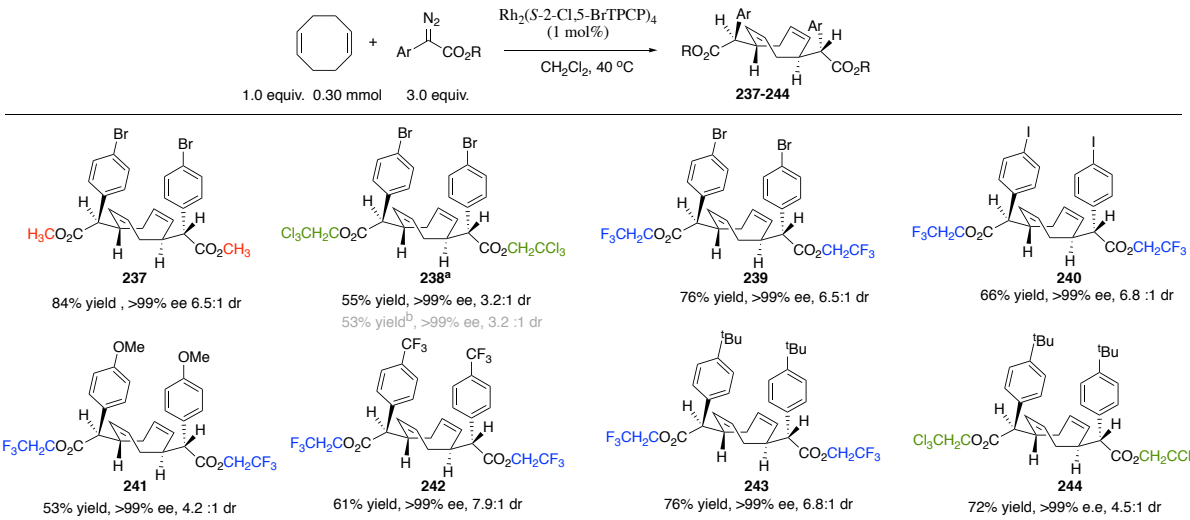
Entry	product	R_1	R_2	yield, %	dr	ee, %
1	**226**	*p*-BrC_6H_4	CH_2CCl_3	72/80*	>30:1	91/89*
2	**227**	*p*-BrC_6H_4	CH_3	73	11.6:1	72
3	**228**	*p*-BrC_6H_4	CH_2CF_3	83	>30:1	93
4	**229**	*p*-IC_6H_4	CH_2CF_3	78	>30:1	95
5	**230**	*p*-$(MeO)C_6H_4$	CH_2CF_3	72	>30:1	81
6	**231**	*p*-$(CF_3)C_6H_4$	CH_2CF_3	78	>30:1	94
7	**232**	*p*-$tBuC_6H_4$	CH_2CF_3	85	>30:1	88
8	**233**	*p*-$(AcO)C_6H_4$	CH_2CF_3	70	>30:1	79
9	**234**	*6*-(2-Clpyridine)	CH_2CF_3	72	>30:1	87
10	**235**	*m*-BrC_6H_4	CH_2CF_3	64	>30:1	63
11	**236**	styryl	CH_2CF_3	67	>30:1	88

* larger scale reaction at 3.0 mmol of diazo compound

4.3 Double-allylic C–H functionalization experiments

With the goal of designing C2 symmetric chiral COD ligands, we then focused on exploring the possibility of achieving a double C–H functionalization, which would be a direct synthesis of C2 symmetric ligands. It was initially considered challenging because the second allylic C–H insertion would need to be regio- and stereoselective in the presence of two other allylic methylene sites. Nevertheless, the double allylic C–H insertion turned out to be very effective (**Scheme 56**). The limiting reagent was switched and 3 equiv of the diazo compound was reacted with 1 equiv of COD at elevated temperature (40 °C). The bis C–H insertion products **237-244** were formed in good yield with very high levels of enantioselectivity (>99% ee) even though the enantioselectivity for mono C–H functionalization was considerably lower (72-95% ee). This is because the minor enantiomer of the mono-insertion product would be primarily transformed into the *meso* diastereomer of the final bis C–H insertion compound. Such enantio-enrichment is known as the Horeau Principle.[15] Therefore, bis C–H insertion products **237-244** were obtained in high ee but with moderate diastereoselectivity. Nevertheless, the target major diastereomer can be easily isolated using $AgNO_3$-impreganated silica gel.

Scheme 56 Diazo compound scope for the double- C–H functionalization of COD

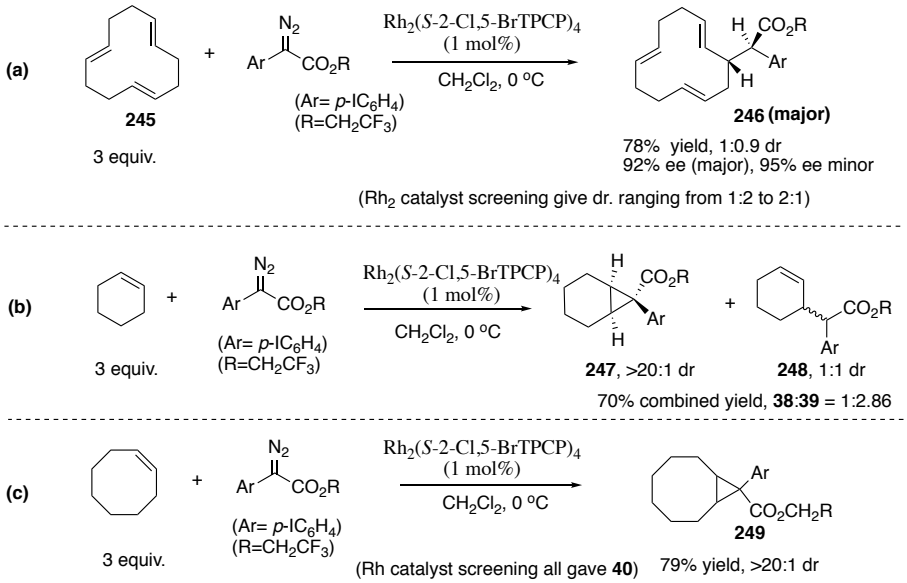


a. The only minor diastereomer can be observed is a meso compound, such minor diastereomer for **238** is isolated and characterized in supporting information. Other possible minor diastereomer can not be observed in the crude ^{1}HNMR. b. Larger scale of reaction at 0.8 mmol scale of COD

4.4 Evaluation of related cycloalkanes

The excellent site- and stereoselectivity for the allylic functionalization of COD is unprecedented, which prompted us to explore the reactivity of other related cycloalkanes. A series of control experiments were conducted using Rh_2(*S*-2-Cl,5-BrTPCP)$_4$ (**Scheme 57**). 1E,5E,9E-Cyclododecatriene (**245**) was found to be an effective substrate that generate cleanly the allylic C–H insertion product **246** with poor diastereoselectivity but high enantioselectivity. Catalyst screening for this reaction showed that the diastereomeric ratio can only vary slightly from 2:1 to 1:2, which suggest that no catalyst can render the reaction highly diastereoselective (**Scheme 57 (a)**). The reaction with cyclohexene generated a mixture of cyclopropanation (**247**) and allylic C–H insertion products (**248**), ranging from 1.27:1 to 1:2.85, and the dr was also poor ranging from 3.11:1 to 1:3.12 (see supporting information) (**Scheme 57 (b)**). The reaction with cis-cyclooctene, however, exclusively gave cyclopropanation product (**249**) (**Scheme 57 (c)**). Such results seem to suggest that the structural features of 1,5-cyclooctadiene are uniquely suitable for stereoselective allylic C–H functionalization, while other cycloalkenes tend to react in a very different manner.

Scheme 57 Diazo compound scope for the double- C–H functionalization of COD

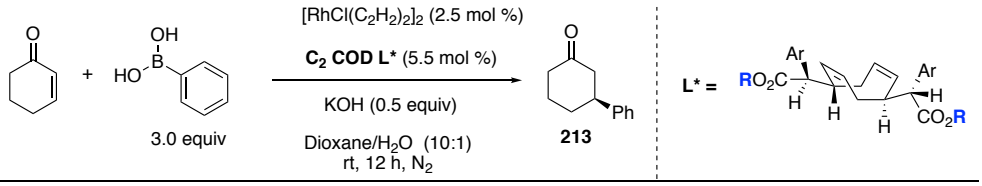


4.5 Evaluation of chiral COD ligands for enantioselective conjugate addition reaction

4.5.1 Evaluation of chiral COD ligands directly from bis-allylic C–H insertion

The new C2 symmetric chiral COD ligands **237-243** derived from double allylic C–H functionalization was first evaluated by Michael R. Hollerbach from the Blakey Group. The reaction chosen for the evaluation study was enantioselective conjugate addition of cyclohexenone to phenyl boronic acid (**Scheme 58**). The reaction with these ligands, except for the aryl iodide derivative **240**, all generated product in reasonable yield (43-84%) but low enantioselectivity (22-45% ee.)

Scheme 58. Enantioselective conjugate addition (part 1)

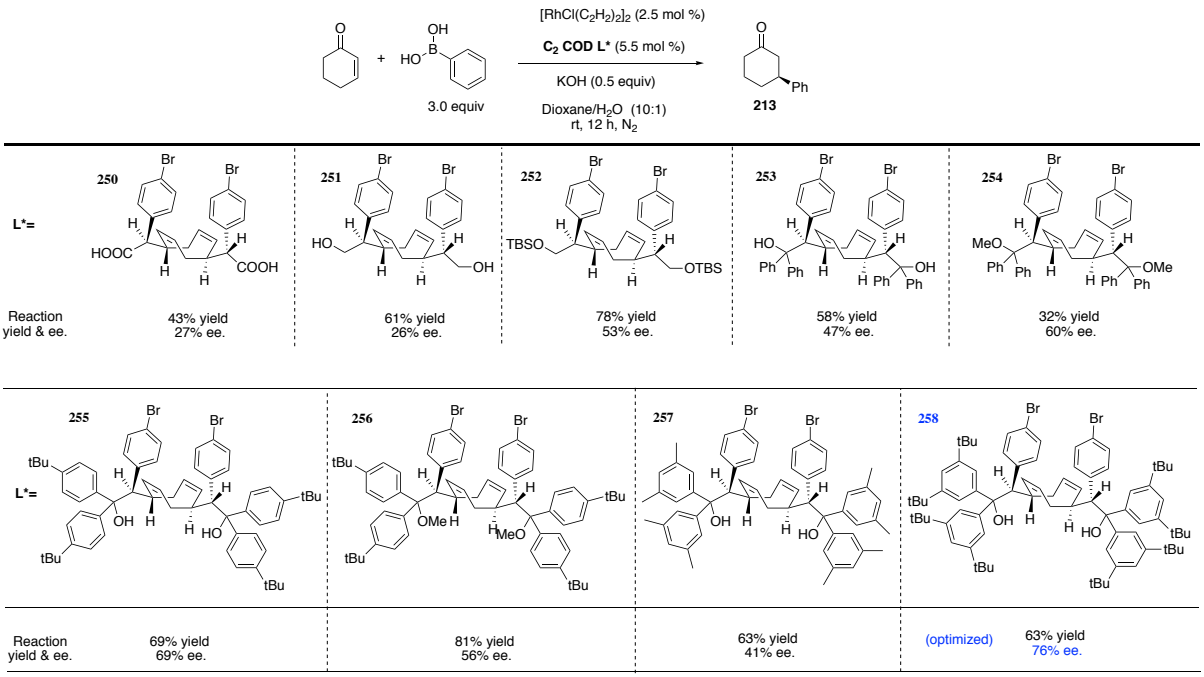


L*	Ar	R	yield / %	ee. / %
237	*p*-BrC_6H_4	CH_3	67	39
238	*p*-BrC_6H_4	CH_2CCl_3	84	34
239	*p*-BrC_6H_4	CH_2CF_3	81	36
240	*p*-IC_6H_4	CH_2CF_3	~2	45
241	*p*-$OMeC_6H_4$	CH_2CF_3	68	30
242	*p*-$CF_3C_6H_4$	CH_2CF_3	60	33
243	*p*-$^tBuC_6H_4$	CH_2CF_3	45	22

4.5.2 Evaluation of the further derivatized C2 symmetric chiral COD ligands.

The bis C–H functionalization products obtained from double allylic C–H insertion can be further derivatized through ester hydrolysis, reduction, or aryllithium addition. The alcohol formed from ester reduction or aryllithium addition can also be protected with silyl groups. Such derivatization successfully gave a variety of C_2-symmetric chiral COD ligands (**250-258**). These derivatized ligands, again can enable the conjugate addition product to be formed in reasonable yield (26-76%). (**Scheme 59**) The enantioselectivity is more variable, with the ee. ranging from 26-76%. It seems that sterically congested ligands tended to give higher enantioselectivity. The most promising ligand has been **258**, which resulted in the formation of **213** in 63% yield, 76% ee.

Scheme 59. Enantioselective conjugate addition (part 2)



4.6 Conclusion

In conclusion, a one-step enantioselective synthesis of C_2-symmetric chiral COD ligands was achieved with rhodium donor/acceptor carbene mediated double allylic C–H functionalization of COD. This transformation illustrates that C–H functionalization can rapidly generate synthetic complexity from a very simple starting molecule. Initial evaluation of these chiral COD ligands along with their

derivatives revealed they were highly effective in the rhodium-catalyzed asymmetric arylation of cyclohex-2-enone.

References

1. Hartwig, J. F. *Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books: Sausalito, CA., 2010; pp 48.
2. Hesp, K. D.; Tobisch, S.; Stradiotto, M. *J. Am. Chem. Soc*. **2010**, *132*, 413.
3. Cooze, C.; Dada, R.; Lundgren, R. J. *Angew. Chem. Int. Ed.* **2019**, *58*, 12246.
4. Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc*. **2003**, *125*, 11508.
5. Otomaru, Y.; Kina, A.; Shintani, R.; Hayashi, T. *Tetrahedron Asymm*. **2005**, *16*, 1673.
6. Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503.
7. Nishimura, T.; Nagaosa, M.; Hayashi, T. *Chem. Lett.* **2008**, *37*, 860.
8. Helbig, S.; Sauer, S.; Cramer, N.; Laschat, S.; Baro, A.; Frey, W., *Adv. Synth. Catal.* **2007**, *349*, 2331.
9. Feng, C.; Wang, Z..; Tian, P.; Xu, M.; Lin, G. *Chem. Asian J.* **2008**, *3*, 1511.
10. Defieber C.; Paquin, J. F.; Serna, S.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 3873.
11. Paquin, J. F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc*. **2005**, 127, 10850.
12. Paquin, J. F.; Stephenson, C. R. J.; Defieber, C.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 3821.
13. Defieber, C.; Grutzmacher,H.; Carreira, E. M., *Angew. Chem. Int. Ed*. **2008**, *47*, 4482.
14. Nagamoto M.; Nishimura, T., *ACS Catal.* **2017**, *7*, 833.
15. Davies, H. M. L.; Liao, K., *Nat. Rev. Chem.* **2019**, *3*, 347.
16. Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011**, *40*, 1857-1869.
17. Qin, C. M.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014**, *136*, 9792.
18. Guptilll, D. M.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014**, *136*, 17718.
19. Liao, K. B.; Negretti, S.; Musaev, D. G.; Bacsa, J.; Davies, H. M. L. *Nature* **2016**, *533*, 230.
20. Liao, K.; Pickel, T. C.; Boyarskikh, V.; Bacsa, J.; Musaev, D. G.; Davies, H. M. L. *Nature*, **2017**, *551*, 609.
21. Liao, K.; Yang, Y.-F.; Li, Y.; Sanders, J. N.; Houk, K. N.; Musaev, D. G.; Davies, H. M. L.

Nature Chem. **2018**, *10*, 1048.

22. Fu, J.; Ren, Z.; Bacsa, J.; Musaev, D. G.; Davies, H. M. L. *Nature* **2018**, *564*, 395.
23. Liu, W.; Ren, Z.; Bosse, A. T.; Liao, K.; Goldstein, E. L.; Bacsa, J.; Musaev, D. G.; Stoltz, B. M.; Davies, H. M. L. *J. Am. Chem. Soc.* **2018**, *140*, 12247-12255.
24. Vigneron, J.P.; Dhaenens, M.; Horeau, A. *Tetrahedron*, **1973**, *29*, 1055-1059.
25. D'Arrigo, P.; Fliciotti, L.; Pedrocchi-Fantoni, G.; Servi, S. *J. Org. Chem.* **1997**, *62*, 6394-6396.
26. Heller, D.; Drexler, H-J.; Fischer, C.; Buschmann, H.; Baumann, W.; Heller, B. *Angew. Chem. Int. Ed.* **2000**, *39*, 495-499.
27. Huo, S.; Negishi, E. *Org. Lett.* **2001**, *3*, 3253-3256.
28. Zhang, B., Hollerbach, M.R., Blakey, S.B., Davies, H.M.L. *Org. Lett*. **2019**, 21, 24, 9864

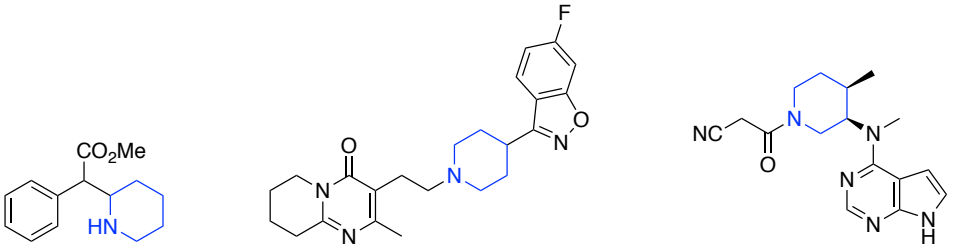
Chapter Five

Exploring the direct cyclopropanation with N-sulfonyl protected piperidines

5.1 Introduction

Substituted piperidine rings are prominent structural elements in various pharmaceutical molecules,[1] such as Ritalin (methylphenidate) for treating attention deficit hyperactivity disorder,[2] Risperidone for treating schizophrenia, bipolar disorder and irritability caused by autism[3] and Tofacitinib (CP-690,550) for treating rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and ulcerative colitis ((**Scheme 60**).[4] Traditional synthesis usually involves the ring construction or directly start with functionalized piperidines.[2,5] The latter one could be especially challenging due to a lack of readily available enantiopure piperidine precursors.

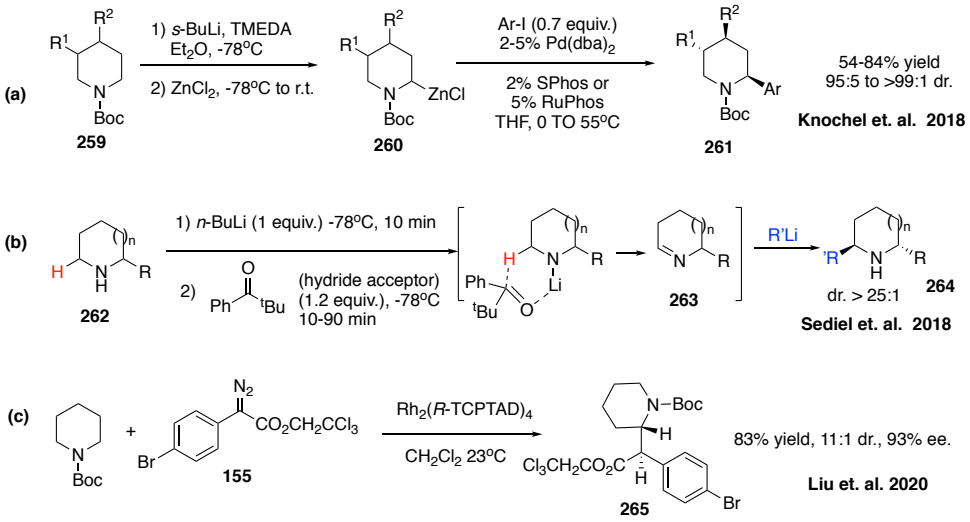
Scheme 60 examples of pharmaceutical molecules with substituted piperidine ring



Ritalin Risperidone Tofacitinib

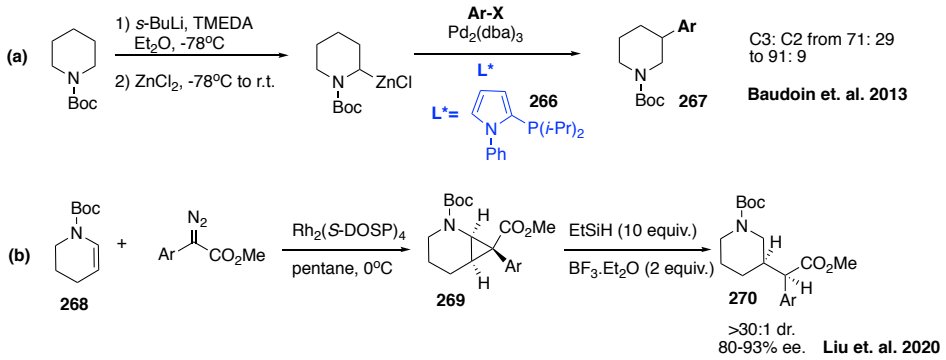
In recent years, site-selective C–H functionalization has emerged as a new tool for building substituted piperidine rings, where most successful examples include the functionalization at the C2 position. Knochel et. al. developed the highly diastereoselective arylation of substituted piperidines[6] through an initial formation of zinc complex **260** followed by a Pd-catalyzed asymmetric cross-coupling. (**Scheme 61(a)**) Seidel et. al. achieved direct C–H functionalization at the C2 position of unprotected piperidines and other cyclic amines[7] through enamine intermediate **263** (**Scheme 61(b)**). Later on, the Davies group successfully achieved highly enantioselective selective piperidine C2 functionalization[8] using rhodium donor/acceptor carbenes. This reaction can directly generate Ritalin-related piperidine drug molecule **265** in high yield, dr. and ee.(**Scheme 61(C)**).

Scheme 61 Selective piperidine C–H functionalization at the C2 position



Selective piperidine C3 functionalization was limited during early studies. The Baudoin group reported a ligand controlled C3-selective arylation of N-Boc piperidines.[9] This reaction is very similar to Knochel's work[6] by forming the same zinc-complex first before Pd-catalyzed cross coupling, but the flexible biarylphosphine ligand **266** applied in this work favor the formation of C3 arylation products **267** (**Scheme 62(a)**). The Davies and the Reiser groups introduced an indirect way of synthesizing C3 functionalized piperidines through cyclopropanation with enamine **268** followed by a ring opening process.[8] C3-substituted piperidines **269** can be obtained in high ee as a single diastereomer (**Scheme 62(b)**). One factor that may limit the application of this work is that starting material enamine **268** is not readily available and need to be prepared using electrochemistry.

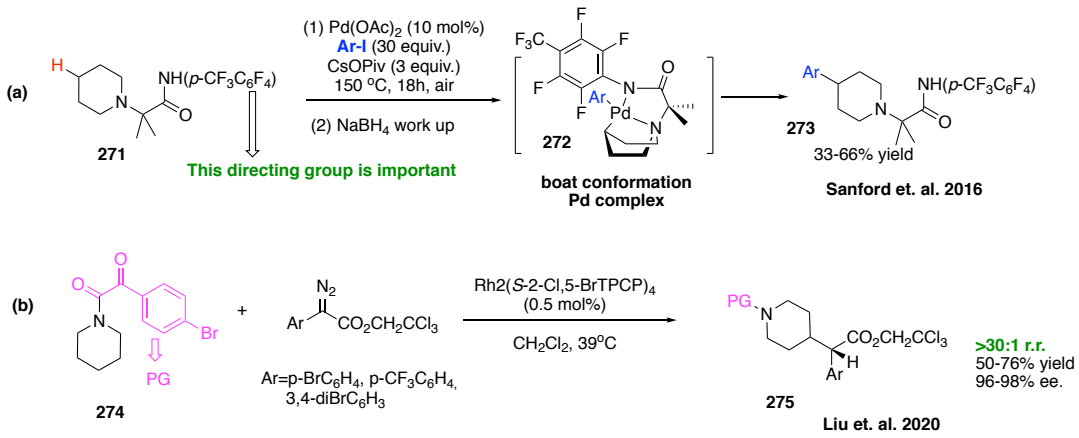
Scheme 62 Selective piperidine C–H functionalization at the C3 position



Selective C4 functionalization of piperidines was also a challenge given the difficulty to control the reaction at the distant position. The Sanford group made a breakthrough by achieving Pd-catalyzed transannular C–H functionalization of cyclic amines. The unique amide directing group in **271** is

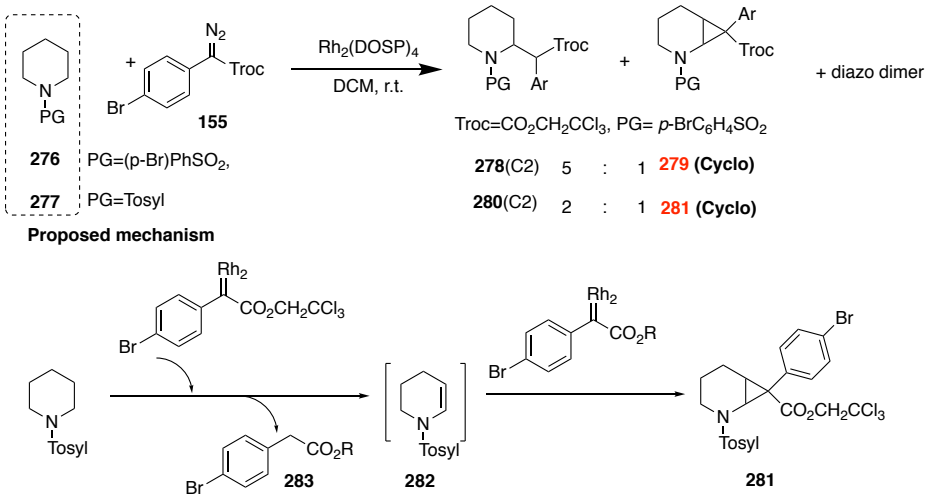
important to form the boat shaped Pd-complex **272**, which is proposed to lead to the formation of C4 arylation products **273** (**Scheme 63(a)**).[10] Their following optimization with the second generation catalyst combined with pyridine or quinoline ligands increased the reaction rate, yield and application scope.[11] The Davies group recently developed an enantioselective C4-selective piperidine C–H functionalization with rhodium donor/acceptor carbene.[8] Piperidine substrate **274** with a special a-oxoarylacetyl protecting group was reacted with aryldiazoacetates under a recently developed catalyst Rh_2(*S*-2Cl,5-BrTPCP)$_4$ that favors most accessible methylene site[11] to give exclusively piperidine C4-insertion product **275** with excellent ee.(**Scheme 63(b)**).

Scheme 63 Selective piperidine C–H functionalization at the C4 position



The Davies group recently observed unexpected cyclopropanation as a side reaction during the C2 insertion study of sulfonyl protected piperidine substrates.[12] In the reaction of protected piperidines (**276, 277**) with aryldiazoacetate **155** under Rh_2(*S*-DOSP)$_4$ catalysis,[12] unusual cyclopropanation products (**279, 281**) were generated besides the normal C2-insertion products (**278, 280**). This direct cyclopropanation of protected piperidines was not observed when using carbamate protecting groups such as Boc or CBz (benzyl carbamate). Cyclopropanation was also not observed when using sterically congested TPCP (triarylcyclopropane) ligand-based dirhodium catalysts. The proposed mechanism involves an important enamine intermediate **282** that was generated by full H abstraction from the first molecule of rhodium carbenoid. The second molecule of rhodium carbenoid then reacted with enamine **282** immediately to give the final cyclopropanation product **281**. The observation of *p*-Br-benzyl ester **283** in the ^{1}H NMR of reaction mixture also support the initial full H-abstraction step.

Scheme 64 Early study of the reaction and proposed mechanism.



This direct cyclopropanation between aryldiazoacetates and sulfonyl-protected piperidines intrigued us to further explore this reaction. In this chapter, a systematic optimization study was performed for this reaction to enhance the ratio of desired cyclopropanation over the C2 insertion. This study can save the step of preparing enamine starting material that is required in our previously reported piperidine C3 functionalization (enamine cyclopropanation/ring opening).[8]

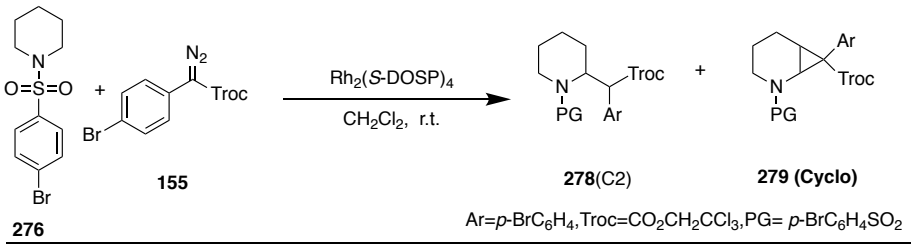
5.2 Optimization study (to achieve higher ratio of desired cyclopropanation)

Factors that may influence the ratio of the cyclopropanation to C2-insertion include stoichiometry, piperidine protecting groups (**PG**), solvents, dirhodium catalysts and reaction temperature. A series of controlled studies were performed to investigate the reaction parameters and optimize toward cyclopropanation.

5.2.1 Stoichiometry influence

The stoichiometry ratio of sulfonyl piperidine to diazo compound was varied from 2:1 to 1:3 in a given reaction (**Scheme 65**), but the product ratio **278** : **279** is fixed at around 5:1. This suggests that stoichiometry has little to no influence on the product composition. It is proposed that the competition between partial and complete H abstraction (lead to **279**) in the first step determines the product ratio. Once the enamine intermediate is formed, following cyclopropanation occurred at a much faster rate than C2-insertion, so all the enamine intermediates are consumed immediately.

Scheme 65 Study of stoichiometry influence

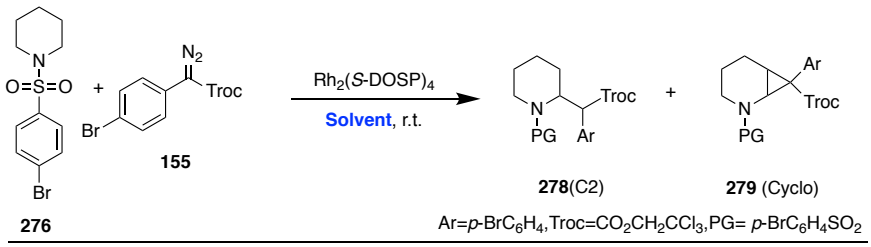


stoichiometry			
equiv	equiv	ratio	ratio
2	1	~ 5 :	1
1	1	~ 5 :	1
1	3	~ 5 :	1

5.2.2 Solvent influence

It is proposed that more polar solvent could better stabilize charged intermediates generated from the full H abstraction and favor the formation of cyclopropanation product **279**. Therefore, several more polar solvents (compared to CH_2Cl_2) were tested for the reaction system (**Scheme 66**). 1,2-DCE gave worse ratio for desired cyclopropanation product **279**. Ethyl acetate and nitromethane gave messy reaction mixture, neither **278** nor **279** can be observed in the crude ^{1}HNMR. 1,2-dioxane was chosen considering that the two internal methylene were generally inactive towards carbenoid chemistry, however, the diazo compound seemed to have reacted with solvent 1,2-dioxane in this reaction.

Scheme 66 Study of solvent influence

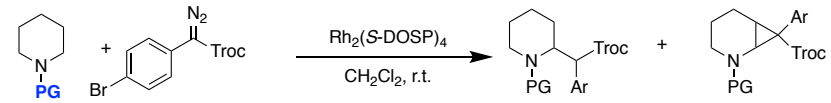


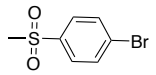
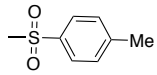
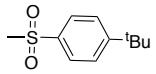
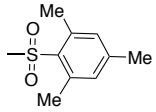
solvent	ratio	ratio
CH_2Cl_2	~ 5 :	1
1,2-DCE	~ 9 :	1
EtOAc	messy, couldn't see A or B	
CH_3NO_2	messy, couldn't see A or B	
1,4-dioxane	diazo reaction with solvent	

5.2.3 N-sulfonyl protecting group (PG) influence (Part I)

Protecting groups can influence the product ratio, which has been observed in Liu's preliminary studies. Sulfonyl PGs can generate the cyclopropanation product while carbamate PGs cannot. It was also observed that (*p*-Br)$C_6H_4SO_2$ PG (**276**) gave C2 insertion (C2) : Cyclopropanation (Cyclo) at around 5:1 while (*p*-Methyl)$C_6H_4SO_2$ (Tosyl) PG (**277**) give C2 : Cyclo at around 2:1. Two other sulfonyl protected piperidines **282** and **283** were also tested as a comparison (**Scheme 67**). Piperidine substrate **282** gave C2 : Cyclo at 2.2:1, which is similar to **277**. Piperidine substrate **283** reacted to give a messy mixture. The better performance of **277** and **282** towards cyclopropanation suggests that electron donating group (EDG) on the sulfonyl aromatic ring may contribute to the cyclopropanation. The messy results with **283** indicates that bulky aryl sulfonyl protecting groups may hinder the approach of rhodium carbene. More studies of protecting group's influence were shown later in part II.

Scheme 67 Study of N-sulfonyl protecting group influence (Part I)

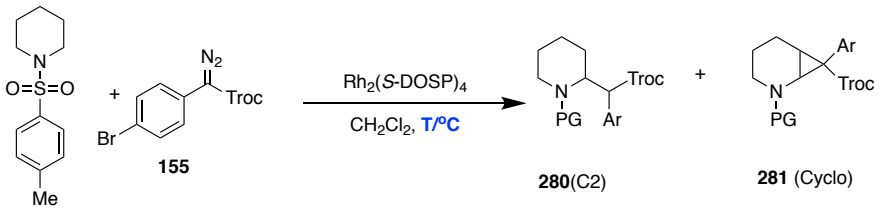


PG		ratio		ratio
	**276**	**(278)**		**(279)**
		~5	:	1
	**277**	**(280)**		**(281)**
		2.02	:	1
	**282**	**(284)**		**(285)**
		2.25	:	1
	**283**	messy peaks, can see C2		

5.2.4 Temperature influence

Both room temperature (23 °C) and refluxing dichloromethane (40 °C) were tested with piperidine substrate **277** (**Scheme 68**). It can be seen that higher temperature slightly disfavored cyclopropanation by dropping the ratio of **281** : **280** from 1:2.02 to 1:2.31. However, the crude ^{1}H NMR showed higher combined conversion at 40 °C. Considering that another big challenge of this reaction is low yield (diazo compound mostly converted to dimer), 40 °C was eventually chosen to be the optimized temperature for following studies.

Scheme 68 Study of temperature influence



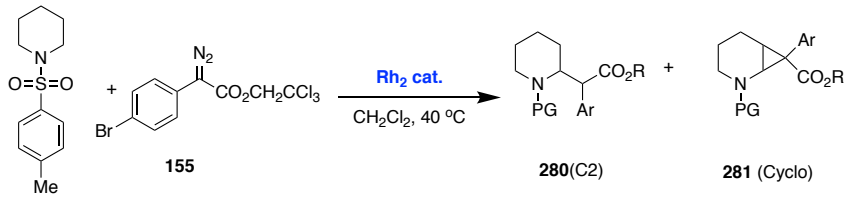
Ar=*p*-BrC_6H_4,Troc=$CO_2CH_2CCl_3$,PG= *p*-$MeC_6H_4SO_2$

T	ratio		ratio
23 °C	2.02	:	1
40 °C	2.31	:	1

5.2.5 Dirhodium catalyst influence (part I)

Dirhodium catalyst is an important factor that can influence the composition of reaction products. In Liu's preliminary studies, it has been observed that the new generation TPCP series of catalysts from Davies lab gave no cyclopropanation and generated mainly diazo dimer.[12] $Rh_2(PTAD)_4$ indeed gave cyclopropanation but the ratio is much worse compared to $Rh_2(DOSP)_4$. There is a lack of systematic catalyst screening in early studies. Therefore, it is necessary to test more dirhodium catalysts for this reaction. Simple achiral catalysts such as $Rh_2(OAc)_4$ and $Rh_2(TFA)_4$ were initially tested for the reaction of piperidine substrate **277** and aryldiazoacetate **155** (**Scheme 69**). It is interesting that $Rh_2(OAc)_4$ favored more for the cyclopropanation compared to Rh_2(*S*-DOSP)$_4$, enhanced the ratio of Cyclo : C2 from 1:2.02 to 1:1.25. The reaction using $Rh_2(TFA)_4$ generated the desired cyclopropanation product **281** without undesired C2 insertion product **280**, but diazo dimerization dominated the reaction. This study indicates that the more electron-deficient catalyst may favor the desired cyclopropanation ($Rh_2(TFA)_4$> $Rh_2(OAc)_4$> Rh_2(*S*-DOSP)$_4$), but too much electrophilic feature can hinder the intermolecular reaction. Rh_2(*S*-F-DOSP)$_4$ (**286**), a catalyst structurally similar to Rh_2(*S*-DOSP)$_4$ but more electron deficient, was also tested. Again, the more electron-deficient Rh_2(*S*-F-DOSP)$_4$ gave higher ratio of **281** (Cyclo) compared to Rh_2(*S*-DOSP)$_4$. The most optimized result came from a bridged catalyst Rh_2(*S*-BiTISP)$_2$ (**287**) developed earlier by Davies group,[13] which gave a ratio of Cyclo : C2 at 1:1.10. More dirhodium catalysts were investigated later in part II.

Scheme 69 Study of dirhodium catalyst influence (part 1)

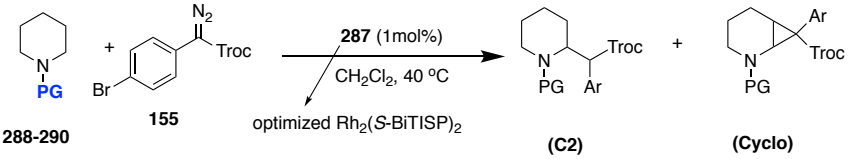


	Rh2 cat.	ratio		ratio
	Rh_2(*S*-DOSP)$_4$	2.02	:	1
	Rh_2(*S*-F-DOSP)$_4$ from postdoc Sidney (**286**)	1.70	:	1
	$Rh_2(OAc)_4$	1.25	:	1
	$Rh_2(TFA)_4$	—		**281 observed, but messy reaction, mostly dimer!**
(**287**)	Rh_2(*S*-BiTISP)$_2$ L=	1.10	:	1

5.2.6 N-sulfonyl protecting group (PG) influence (part II)

Three aryl sulfonyl protected piperidine substrates with strong electron donating groups on the aromatic ring were further tested with optimized Rh_2(*S*-BiTISP)$_2$ (**287**) catalyst. Using (*p*-OMe)$C_6H_4SO_2$ as PG (**288**) reversed the ratio of two products (C2 : Cyclo at 1:1.20). More electron donating Benzoin-sulfonyl protected piperidine (**89**) was even more promising (C2 : Cyclo at 1:1.35). (2,4-dimethoxy)$C_6H_4SO_2$ as PG (**290**) gave a messy crude ^{1}HNMR with no evidence for the formation of either cyclopropanation or C2-insertion product (**Scheme 70**).

Scheme 70 Study of N-sulfonyl protecting group influence (part II)



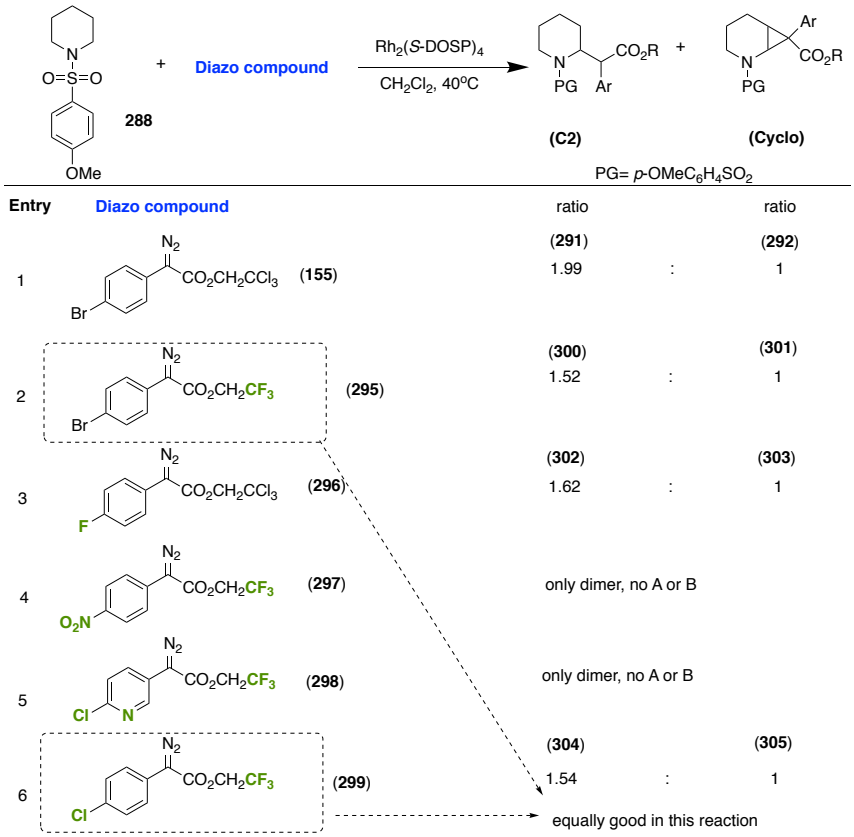
	PG		ratio		ratio
			(**291**)		(**292**)
(**288**)			1	:	1.20
			(**293**)		(**294**)
(**289**)		(optimzed PG)	1	:	1.35
(**290**)			messy results, could not oversve A or B		

Benzoin-sulfonyl protected piperidine **289** is so far the most optimized piperidine substrate for the cyclopropanation reaction from combined protecting group study in part I and II. Although sulfonyl protecting groups with more electron donating aromatic ring can be tested, the trend of adding EDG to the sulfonyl aryl ring seems difficult to promote a clean cyclopropanation.

5.2.7 Aryl diazoester influence

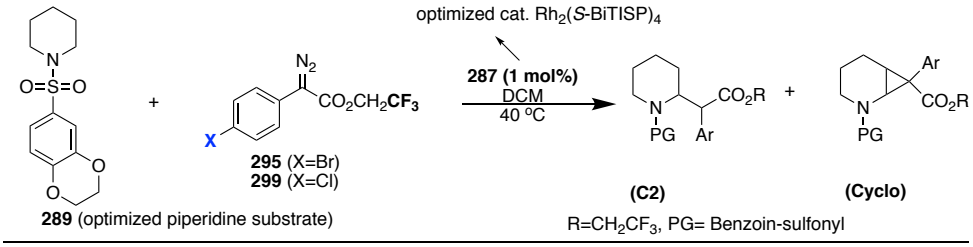
The electronic features of an aryldiazoacetate is directly related to the reactivity of the rhodium carbenoid, and therefore, can influence the reaction outcome. Studies on dirhodium catalysts have shown that cyclopropanation is more favored with more electrophilic rhodium carbene. Therefore, electron-deficient aryldiazoacetates (compared **155**) should also improve the chemoselectivity. This can be achieved either by incorporating a more electron-deficient aryl group or a more electron-withdrawing ester group into the diazo design. Because Rh_2(*S*-BiTISP)$_2$ is a relatively precious catalyst (**287**), Rh_2(*S*-DOSP)$_4$ was used for the initial screening (**Scheme 71**). Comparison of entries 2 and 1 confirmed that more electrophilic **295** indeed gave better ratio for cyclopropanation. The same trend applies to **296** versus **155**. However, too electron-deficient **297** and **298** gave only diazo dimer side product.

Scheme 71 Aryldiazoacetate influence (Initial screening)



Diazo compounds **295** and **299** showed similar ratio of C2-insertion versus cyclopropanation in the above reaction, so further test reaction with the optimized reaction condition was performed to select the best diazo compound (**Scheme 72**). We found that aryldiazoacetate **299** performed better than **295** for cyclopropanation (C2 : Cyclo at 1:1.87). This is also the highest ratio for cyclopropanation achieved so far.

Scheme 72 Comparison of aryldiazoacetate 295 and 299 in the optimized reaction

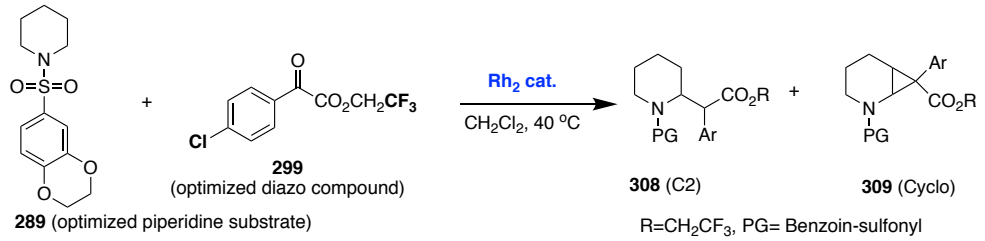


Diazo compound			ratio (306)		ratio (307)
X=Br	(295)		1	:	1.58
X=Cl	(299)	most opimized diazo	(308) 1	:	(309) 1.87

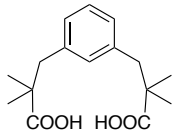
5.2.8 Dirhodium catalyst influence (part II)

More dirhodium catalysts were screened with the optimized reaction (**Scheme 73**). Rh_2(NTTL)$_4$ is a catalyst widely used for *N*-sulfonyl triazole chemistry.[14] However, it strongly favored C2-insertion in this reaction. Rh_2(*S*-TCPTAD)$_4$ is considered to be an electron-deficient catalyst which should favor ~~the~~ cyclopropanation, however, it did not perform better than Rh_2(*S*-DOSP)$_4$. Inspired by the optimized result from bridged-ligand catalyst Rh_2(*S*-BiTISP)$_2$ (**287**), a similar achiral ~~bridged ligand~~ catalyst Rh_2(esp)$_2$ was also tested (**Entry 2**). Unfortunately, they both failed to outperform the Rh_2(*S*-BiTISP)$_2$. Therefore, studies from part I and II show that Rh_2(*S*-BiTISP)$_2$ (**287**) is the optimized catalyst so far.

Scheme 73 Study of dirhodium catalyst influence (part II)



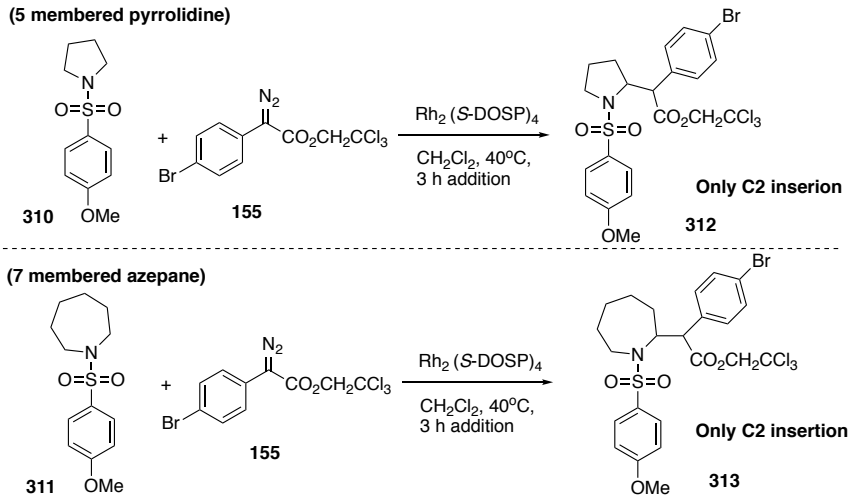
	Rh2 cat.	ratio		ratio
1	$Rh_2(BiTISP)_4$ (**287**) optimized cat.	1	:	1.87
2	$Rh_2(esp)_2$ (bridged ligand)	6.64	:	1
3	$Rh_2(NTTL)_4$	~40	:	1
4	$Rh_2(TCPTAD)_4$	2.81 (seems to haveone more unknown new compound)	:	1

L= 

5.3 Miscellaneous reactions with other protected cyclic amines

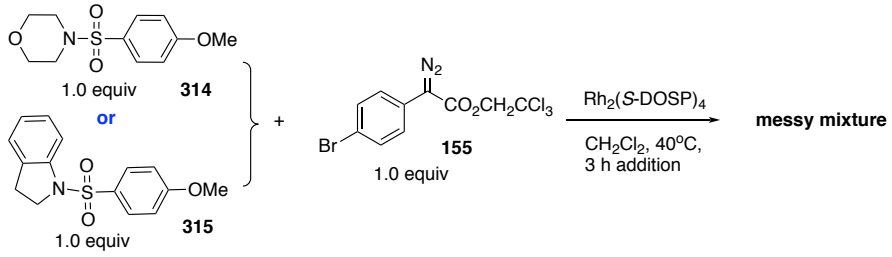
Five- and seven-membered cyclic amines were firstly tested to see if the cyclopropanation is uniquely observed for 6 membered piperidine (**Scheme 74**). Sulfonyl protected pyrrolidine (**310**) and azepane (**311**) were reacted with 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate **155** using Rh_2(*S*-DOSP)$_4$ in refluxing CH_2Cl_2, but only C2-insertion products were observed for both substrates.

Scheme 74 Miscellaneous tests with sulfonyl protected pyrrolidine and azepane



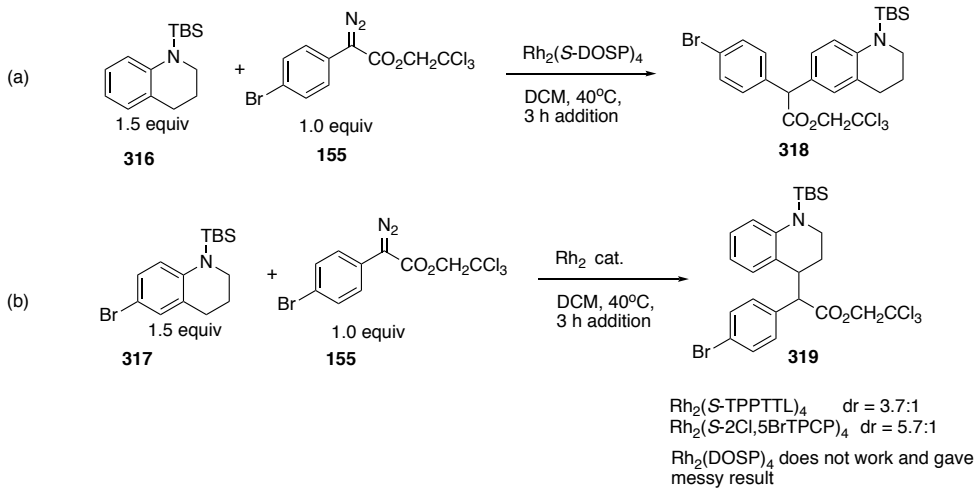
Sulfonyl protected morpholine (**314**) and indoline (**315**) were then tested under the same reaction condition (**Scheme 75**). The substrates were chosen for a competition reaction between 2 reactive C–H site (alpha to N vs. alpha to O or alpha to N vs. benzylic). Both substrates gave messy mixtures.

Scheme 75 Miscellaneous tests with sulfonyl protected morpholine and indoline



Two TBS protected tetrahydroquinoline substrates **316** and **317** were also tested under the same reaction conditions (**Scheme 76**). Substrate **316** reacted to give alkylated product **318** at the 6-position of the aromatic ring, which is proposed to happen through an ylide reaction. Substrate **317** has a blocking "Br" on the 6-position of aromatic ring, and it reacted to give clean benzylic C–H insertion product **319** under Rh_2(*S*-TPPTTL)$_4$ catalysis (3.7:1 dr.) or Rh_2(2-Cl,5-BrTPCP)$_4$ catalysis (5.7:1 dr.) The ee. was not measured for these reactions.

Scheme 76 Miscellaneous tests with TBS protected tetrahydroquinoline substrates



5.4 Conclusion

The reaction of N-sulfonyl piperidine with aryldiazoacetates under certain dirhodium catalysts can directly generate cyclopropanation products, which is unprecedented. However, this reaction is usually accompanied by competitive C2-insertion and difficult to optimize toward a clean cyclopropanation. The highest cyclopropanation to C2-insertion products ratio achieved in this study is 1.87:1, with approximately 24% conversion of sulfonyl piperidine (limiting reagent) based on crude ^{1}H NMR. The low conversion rate is mainly caused by significant diazo-dimerization side reaction, suggesting low

reactivity between the substrate and the carbene. Such direct cyclopropanation reaction is not observed with other protected cyclic amine substrates, suggesting that sulfonyl protected piperidines are structurally unique for the reaction to happen.

References:

1. Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*,10257;

2. Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845.

3. Prashad, M. *Adv.Synth. Catal.* **2001**, *343*, 379.

4. Leucht S.; Cipriani, A.; Spineli, L.; Marvridis, D.; Örey, D.; Richter, F. *Lancet*. **2013**, *382*, 951.

5. *"FDA approves new treatment for moderately to severely active ulcerative colitis"*. U.S. Food and Drug Administration (FDA) (Press release). 30 May **2018.**

5. Vo, C.-V.T.; Bode, J. W. *J. Org. Chem.* **2014**, *79*, 2809;

6. Eicher, T., Hauptmann, S., Speicher, A. *The Chemistry of Heterocycles: Structure, Reactions, Synthesis and Applications. Wiley -VCH,* Weinheim, **2003**;

7. Wolfe, J. P.; *Synthesis of Heterocycles via Metal-Catalyzed Reactions That Gen-erate One or More Carbon-Heteroatom Bonds*, Springer, Heidelberg, **2013**.

8. Seel, S.; Thaler, T.; Takatsu, K.; Zhang, C.; Zipse, H.; Straub, B. F.; Mayer, P.; Knochel, P. *J. Am.Chem. Soc.* **2011**, *133*, 4774

9. Chen, W.; Ma, L.; Paul, A.; Seidel, D. *Nat. Chem.* **2018**, *10*, 165.

10. Liu, W., Babl, T., Röther, A., Reiser, O. *Chem. Eur. J.* **2020**, *26*, 4236.

11. Millet, A.; Larini, P.; Clot, E.; Baudoin, O. *Chem.Sci.* **2013**, *4*, 2241.

12. Topczewski, J.J.; Cabrera, P. J.; Saper, N. I.; Sanford, M.S. *Nature* **2016** , *531*, 220.

13. Cabrera, P.J.; Lee, M.; Sanford, M. S. *J. Am. Chem. Soc.* **2018**, *140*, 5599.

14. Liu, W. Unpublished results in the Davies group.

15. Lian, Y.; Davies, H. M. L. *Org. Lett.* **2012**, *14*, 1934

16. Kubiak, R. W.; Mighion, J. D.; Wilkerson-Hill, S. M.; Alford, J. S.; Yoshidomi, T. *Org.Lett.* **2016**, *18*, 3118.

Chapter Six

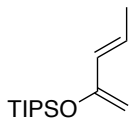
Experimental procedure

6.1 Chapter 2 (Experimental procedure)

6.1.1 General procedure for diene synthesis

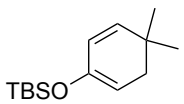
(1) Diene 43 & 65

Starting material enone (10 mmol) was dissolved in 30 mL anhydrous dichloromethane. The solution was cooled to 0 °C and Et_3N (1.4 equiv.) was added. Keep the solution stirring for 5 min and then TBSOTf or TIPSOTf (1.15 equiv.) was added in one portion. The reaction was kept running for 30 min. Dilute the mixture with 20 mL pentane, wash with saturated $NaHCO_3$ solution (50 mL×2) and then dry over $MgSO_4$. Filter and the filtrate were concentrated under vacuum. Pure product is obtained through basified column chromatography (Et_3N:Pentane =1:99)



43

(*E*)-triisopropyl(penta-1,3-dien-2-yloxy)silane 43: derived from (*E*)-pent-3-en-2-one (10 mmol) with general procedure, yield 96 %. All spectra matched the reference[1].



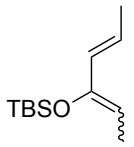
65

***tert*-butyl((4,4-dimethylcyclohexa-1,5-dien-1-yl)oxy)dimethylsilane 65**: derived from 4,4-dimethylcyclohex-2-enone (10 mmol) with general procedure, yield 93%. All spectra matched the reference[5].

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.53 (m, 2H), 4.77 (m, 1H), 2.09 (d, *J* = 4.7 Hz, 2H), 0.99 (s, 6H, **2 methyl**), 0.91 (s, 9H, **TBS**), 0.11 (S, 6H, **TBS**) ; ^{13}C NMR(100 MHz, CDCl3): δ 147.4, 140.0, 123.9, 101.4, 37.0, 31.2, 27.7, 25.7, 18.1, -4.49

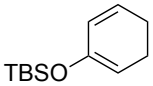
(2) Diene 46, 48, 56-58, 62, 67, 68

Diisopropylamine (1.2 equiv.) was added to 40 mL anhydrous THF. The solution was cooled to -78 °C for 5 min and then n-BuLi (2.5 M in hexane, 1.2 equiv.) was added dropwisely. The mixture was warmed up to 0 °C for 15min and then cooled back to -78 °C followed by slow addition of starting material enone (purchased or prepared from reported references) (10 mmol). The reaction was kept running for 1 h, and then TBSOTf (1.15 equiv.) was added in one portion. After stirring for another 1 h, the solution was warmed to room temperature, diluted with 40 mL pentane and then washed with saturated $NaHCO_3$ solution (50 mL×3). Dry the solution over $MgSO_4$ and then filter. The filtrate was concentrated under vacuum, and pure product was obtained through basified column (Et_3N:Pentane =1:99) or kugelrhor distillation.



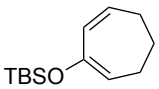
46

***tert*-butyl((4*E*)-hexa-2,4-dien-3-yloxy)dimethylsilane 46**: derived from (*E*)-hex-4-en-3-one (10 mmol) with general procedure, purified through basified column, *Z*/*E*=81:19, yield 60 %. ^{1}HNMR spectra matched the reference[1].



48

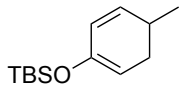
***tert*-butyl(cyclohexa-1,5-dien-1-yloxy)dimethylsilane 48**: derived from cyclohex-2-enone (20 mmol) with general procedure, purified through kugelrhor distillation, yield 81 %. All spectra matched the reference[2].



56

***tert*-butyl(cyclohepta-1,6-dien-1-yloxy)dimethylsilane 56**: derived from cyclohept-2-enone (10 mmol) with general procedure, purified through basified column, yield 93 %. All spectra matched the reference[5].

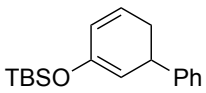
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.79 ((dt, *J* = 12.0, 5.2 Hz, 1H), 5.65 (dq, *J* = 12.0, 1.8 Hz, 1H), 5.18 (dt, *J* = 6.0, 2.0 Hz, 1H), 2.29 (q, *J* = 5.8 Hz, 2H), 2.16 (q, *J* = 5.8 Hz, 2H), 1.82 (p, *J* = 5.8 Hz, J=2H), 0.92 (s, 9H, **TBS**), 0.11 (S, 6H, **TBS**) ; ^{13}C NMR(100 MHz, CDCl3): δ 148.3, 133.3, 128.2, 112.7, 31.4, 27.0, 26.7, 25.8, 18.0, -4.5



57

***tert*-butyldimethyl((4-methylcyclohexa-1,5-dien-1-yl)oxy)silane 57**: derived from 4-methyl-cyclohex-2-enone (10 mmol, prepared through reported procedure[3]) with general procedure, purified through basified column, yield 45 %.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.70 (dd, *J* = 9.9, 3.6 Hz, 1H), 5.65 (dt, *J* = 9.9, 2.1 Hz, 1H), 4.83 (m, 1H), 2.36 (m, 1H), 2.25 (m, 1H), 1.96 (m, 2H), 1.01 (d, *J* = 7.03 Hz, 3H, **methyl**), 0.93 (s, 9H, **TBS**), 0.13 (s, 6H, **TBS**); ^{13}C NMR(100 MHz, CDCl3): δ 148.0, 135.3, 125.4, 101.7, 30.2, 28.4, 26.3, 25.7, 19.6, -4.5; IR(neat): 2957, 2929, 2857, 2822, 1739, 1661, 1472, 1397, 1252, 1195, 1112, 920; HRMS-(APCI) m/z: 225.1667 [$(M+H)^+$: $[C_{13}H_{25}OSi]^+$ requires 225.1669]

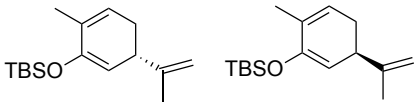


58

***tert*-butyl((1,6-dihydro-[1,1'-biphenyl]-3-yl)oxy)dimethylsilane 58**: derived from 1,6-dihydro-[1,1'-biphenyl]-3(2H)-one (10 mmol, prepared through reported procedure[4]) with general procedure, purified through basified column, yield 78 %. All spectra matched the reference[5].

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.18-7.29 (m, 5H, **Ph ring**), 5.78 (m, 2H), 4.93 (m, 1H), 3.68 (ddd, *J* = 12.3, 9.0, 2.9 Hz, **benzylic**), 2.46 (m, 1H), 2.23 (m, 1H), 0.99 (s, 6H, **2 methyl**), 0.93 (s, 9H, **TBS**),

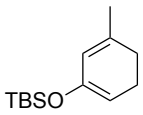
0.15 (S, 6H, **TBS**) ; ^{13}C NMR(100 MHz, CDCl3): δ 149.0, 145.2, 128.4, 127.6, 127.5, 126.3, 126.2, 106.7, 40.2, 32.4, 25.7, 18.1, -4.5



62 S **62 R**

***tert*-butyldimethyl((6-methyl-3-(prop-1-en-2-yl)cyclohexa-1,5-dien-1-yl)oxy)silane 62**: derived from *S*-(+)-carvone or *R*-(-)-carvone (10 mmol) with general procedure, purified through basified column, yield 74 %. All spectra matched the reference[11].

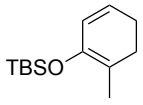
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.57 (m, 1H), 4.78 (m, 1H), 4.75 (d, J=3.80 Hz, 1H), 4.72 (m, 1H), 3.02 (ddd, *J* = 12.3, 8.3, 3.7 Hz,1H), 2.05-2.21 (m, 2H), 1.74 (s, 6H, **2 methyl**), 0.95 (s, 9H, **TBS**), 0.18 (S, 6H, **TBS**) ; ^{13}C NMR(100 MHz, CDCl3): δ 150.0, 148.7, 132.1, 123.1, 109.9, 105.1, 42.0, 28.7, 25.8, 22.3, 20.6, 18.2, 17.7, 14.1, -4.6



67

***tert*-butyldimethyl((5-methylcyclohexa-1,5-dien-1-yl)oxy)silane 67**: derived from 3-methyl-cyclohex-2-enone (10 mmol) with general procedure, purified through kugelrhor distillation, yield 45 %. All spectra matched the reference[9].

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.43 (s, 1H), 4.71 (m, 1H), 2.15 (m, 2H), 2.15 (m, 2H), 2.00 (m, 2H), 1.77 (s, 3H, **methyl**), 0.96 (s, 9H, **TBS**), 0.11 (S, 6H, **TBS**); ^{13}C NMR(100 MHz, CDCl3): δ 149.0, 138.9, 121.1, 99.1, 28.5, 25.7, 23.0, 22.2, 18.1, -4.5

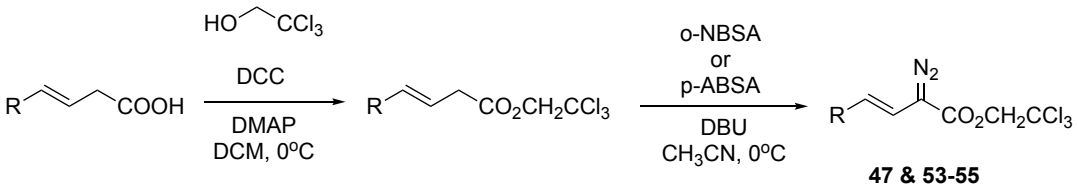


68

***tert*-butyldimethyl((2-methylcyclohexa-1,5-dien-1-yl)oxy)silane 68**: derived from 6-methyl-cyclohex-2-enone (10 mmol, prepared through reported procedure[6]) with general procedure, purified through basified column, yield 70 %. All spectra matched the reference[10].

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.68 (m, 2H), 2.10 (m, 4H), 1.67 (s, 3H, **methyl**), 0.96 (s, 9H, **TBS**), 0.11 (s, 6H, **TBS**) ; ^{13}C NMR(100 MHz, CDCl3): δ 142.0, 126.4, 125.2, 112.4, 28.6, 26.3, 25.8, 23.0, 18.1, 16.2, -4.2

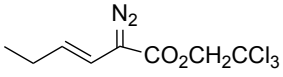
6.1.2 General procedure for vinyl diazo compounds



47 & 53-55

Starting material β, γ-unsaturated carboxylic acid was directly purchased or prepared from reported procedures. First step is a DCC-coupled esterification. β, γ-unsaturated carboxylic acid (15 mmol), 2,2,2-trichloroethanol (1.2 equiv.), DCC (1.1 equiv.) were dissolved in 35 mL anhydrous dichloromethane. The mixture was cooled to 0 °C and kept stirring. DMAP (0.1 equiv.) was dissolved in 5 mL dichloromethane and added to the solution. The reaction was kept running for 4 hrs. Filter and the filtrate was concentrated under vacuum. Pure ester was obtained by flushing column with 1 % Et_2O in pentane.

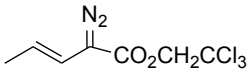
Obtained Ester (10 mmol) were directly dissolved in 30 mL anhydrous acetonitrile along with diazo transfer reagent o-NBSA (1.2 equiv.) or p-ABSA (1.2 equiv.). The solution was cooled to 0 °C and kept stirring for 5 min. DBU (1.2 equiv.) was then added dropwisely, and the colorless solution gradually changed to yellow and eventually bright orange. The reaction was kept running for 1hr and quenched by diluting with Et_2O (20 mL). Wash the organic layer with Saturated NH_4Cl (20 mL×2), brine (20 mL×2) and then dried over $MgSO_4$. Filter and the filtrate were concentrated under vacuum. The pure vinyl diazo compound was obtained by flushing column with 3-5 % Et_2O in pentane.



44

(*E*)-2,2,2-trichloroethyl 2-diazohex-3-enoate 44: derived from (*E*)-hex-3-enoic acid (20 mmol) with general procedure, diazo transfer reagent is o-NBSA, yield (2 step) 74%.

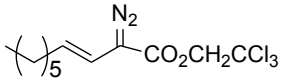
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.72 (dq, *J* = 15.8, 1.5 Hz, 1H), 5.45 (dq, *J* = 15.8, 6.5 Hz, 1H), 4.84 (s, 2H, **trichloroethyl**), 2.21 (m, 2H ethyl **CH_2**), 1.05 (t, *J* = 7.5 Hz, 3H, **ethyl CH_3**) ; ^{13}C NMR(100 MHz, CDCl3): δ 128.2, 110.1, 95.0, 73.9, 25.9, 13.7; IR(neat): 2956, 2082, 1708, 1450, 1375, 1336, 1306, 1248, 1121, 950, 795, 715; HRMS-(APCI) m/z: 270.9729, 272.9699 (M+2 for Cl), 274.9670 (M+4 for Cl) [$(M+H)^+$: $[C_8H_{10}Cl_3N_2O_2]^+$ requires 270.9730]



49

(*E*)-2,2,2-trichloroethyl 2-diazopent-3-enoate 49: derived from (*E*)-pent-3-enoic acid (20 mmol, prepared from reported procedures[7]), diazo transfer reagent is o-NBSA, yield (2 step) 63%.

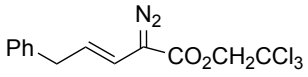
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.74 (dq, *J* = 15.8, 1.7 Hz, 1H), 5.44 (dq, *J* = 15.8, 6.7 Hz, 1H), 4.84 (s, 2H, **trichloroethyl**), 1.86 (dd, *J* = 6.7, 1.7 Hz, 3H, **methyl**) ; ^{13}C NMR(100 MHz, CDCl3): δ 121.5, 111.9, 95.0, 73.9, 18.3; IR(neat): 2955, 2080, 1704, 1450, 1374, 1336, 1247, 1118, 1058, 949, 794, 714; HRMS-(APCI) m/z: 256.9647, 258.9617 (M+2 for Cl), 260.9588 (M+4 for Cl) [$(M+H)^+$: $[C_7H_8Cl_3N_2O_2]^+$ requires 256.9647]



50

(*E*)-2,2,2-trichloroethyl 2-diazoundec-3-enoate 50: derived from (*E*)-undec-3-enoic acid (10 mmol, prepared from reported procedures[7]), diazo transfer reagent is o-NBSA, yield (2 step) 49%.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.72 (dt, *J* = 15.8, 1.4 Hz, 1H), 5.41 (dt, *J* = 15.8, 6.8 Hz,1H), 4.84 (s, 2H, **trichloroethyl**), 2.19 (qd, *J* = 7.1, 1.5 Hz, 2H), 1.40 (m, 2H), 1.24-1.33 (m, 6H), 0.88 (t, *J* = 7.0 Hz, 3H, **methyl**) ; ^{13}C NMR(100 MHz, CDCl3): δ 127.0, 110.8, 95.0, 73.9, 32.8, 31.7, 29.4, 28.8, 22.6, 14.1; IR(neat): 2955, 2926, 2855, 2081, 1713, 1455, 1376, 1234, 1129, 1108, 949, 712; HRMS-(APCI) m/z: 327.0431, 329.0401 (M+2 for Cl), 331.0372 (M+4 for Cl) [$(M+H)^+$: $[C_{12}H_{18}Cl_3N_2O_2]^+$ requires 327.0428]



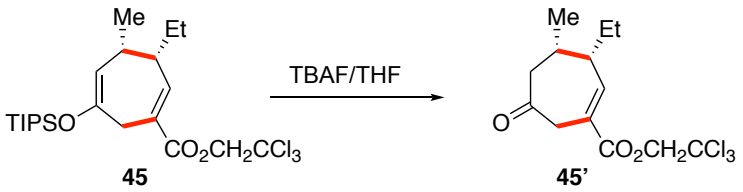
51

(*E*)-2,2,2-trichloroethyl 2-diazo-5-phenylpent-3-enoate 51: derived from (*E*)-5-phenylpent-3-enoic acid (10 mmol, prepared from reported procedures[8]), diazo transfer reagent is o-NBSA, yield (2 step) 75%.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.18-7.34 (m, 5H, **Ph ring**), 5.82 (dt, *J* = 15.8, 1.4 Hz, 1H), 5.58 (dt, *J* = 15.8, 6.9 Hz, H), 4.84 (s, 2H, **trichloroethyl**), 3.51 (d, *J* = 6.6 Hz, 2H, **benzylic**) ; ^{13}C NMR(100 MHz, CDCl3): δ171.3, 139.7, 128.6, 128.5, 128.3, 126.4, 124.9, 112.5, 95.0, 74.0, 39.1; IR(neat): 3028, 2954, 2082, 1703, 1646, 1603, 1495, 1453, 1378, 1247, 1113, 950, 697; HRMS-(APCI) m/z: 330.9819, 332.9790 (M+2 for Cl), 334.9761 (M+4 for Cl) [$(M-H)^-$: $[C_{13}H_{10}Cl_3N_2O_2]^+$ requires 330.9813]

6.1.3 General Procedure for 4+2 cycloaddition products & miscellaneous compounds

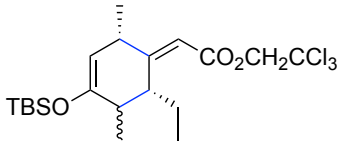
Cross-conjugated siloxy diene (1.05 mmol, 3.5 equiv.) was dissolved in 2.5 mL anhydrous dichloromethane in a dry 10 mL round bottom flask. R- or S- Rh_2(p-PhTPCP)$_4$ was then added, and the flask was degassed and filled with Ar for several times. The solution was cooled to 0 °C and kept stirring for 5min. Vinyl diazo compound (0.30 mmol, 1.0 equiv.) was then dissolved in 2.5 mL anhydrous dichloromethane and added to the round bottom flask over 1hr using the syringe pump. The reaction was kept running for 4hrs. The solution was later concentrated under vacuum to give crude mixture. Pure [4+2] cycloadducts and other compound **45** (4+3), **66** (open chain) was obtained through column chromatography (0.5-1.0 % Et_2O in pentane).



45 **45'**

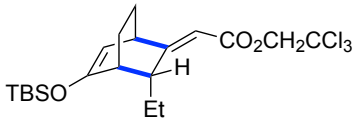
(3*R*,4*R*)-2,2,2-trichloroethyl 3-ethyl-4-methyl-6-oxocyclohept-1-enecarboxylate 45': **45** (characterized as **45'** after desilylation) derived from diene **43** (1.05 mmol) and vinyl diazoacetate **44** (0.30 mmol) with general procedure, isolated product: 110.1 mg, yield 76% ($Rh_2(esp)_2$); 83.2 mg, yield 53% ($Rh_2(R\text{-}p\text{-}PhTPCP)_4$).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.13 (dd, *J* = 7.1 Hz, 2.5 Hz, 1H, **alkene H**), 4.83 (d, *J* = 11.9 Hz, 1H, **trichloroethyl**), 4.82 (d, *J* = 11.9 Hz, 1H, **trichloroethyl**), 3.59 (d, *J* = 18.7 Hz, 1H, **CH_2 between carbonyl and alkene**), 3.36 (d, *J* = 18.8 Hz, 1H, **CH_2 between carbonyl and alkene**), 2.53 (m, 1H), 2.42-2.48 (m, 3H), 1.50-1.62 (m, 2H), 0.95 (t, *J* = 7.45 Hz, 3H, **methyl on Et**), 0.92 (d, *J* = 6.3 Hz, 3H, **Me on ring**); ^{13}C NMR(100 MHz, CDCl3): δ 208.7 (**ketone carbonyl**), 164.5 (**ester carbonyl**), 149.7, 127.3, 94.9, 74.6, 49.2, 43.55,43.50, 36.5, 25.1, 15.8, 12.4; IR(neat): 2961, 2932, 2875, 1714, 1636, 1457, 1381, 1228, 1154, 1099, 798, 718; HRMS-(APCI) m/z: 327.0242, 329.0213 (M+2 for Cl), 331.0191 (M+4 for Cl) [$(M+H)^+$: $[C_{13}H_{18}Cl_3O_3]^+$ requires 327.0243]



47

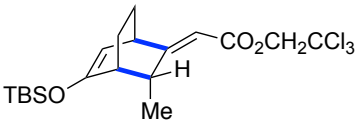
(*Z*)-2,2,2-trichloroethyl 2-((2*S*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-ethyl-2,5-dimethylcyclohex-3-en-1-ylidene)acetate 47: derived from diene **46** (1.05 mmol) and vinyl diazoacetate **44** (0.30 mmol) with general procedure, isolated yield 77%. Since diene **46** was prepared as mixture of *Z*/*E* isomers, **44** was obtained as a mixture of diastereomers with regards to the 5-methyl group. ^{1}H NMR was attached with major and minor product noted in the spectra, stereochemistry of 2-methyl and 6-ehtyl was based on analogy of [4+2] product **52**. Distinctive peaks for the [4+2] was noted in spectra, some detailed peaks were not further analyzed.



52

(*Z*)-2,2,2-trichloroethyl 2-((1*R*,3*R*,4*R*)-5-((*tert*-butyldimethylsilyl)oxy)-3-ethylbicyclo[2.2.2]oct-5-en-2-ylidene)acetate 52: derived from diene **48** (1.05 mmol) and vinyl diazoacetate **44** (0.30 mmol) with general procedure with Rh_2(*R*-*p*-PhTPCP)$_4$ cat., isolated product: 100.4 mg, yield 74%.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.77 (d, *J* = 1.9 Hz, 1H, **H next to trichloroethyl**), 4.90 (dd, *J* = 6.7 Hz, 2.3 Hz, 1H, **alkene H next to TBS**), 4.78 (d, *J* = 12.1 Hz, 1H, **trichloroethyl**), 4.74 (d, *J* = 12.1 Hz, 1H, **trichloroethyl**), 3.10 (dt, *J* = 6.8, 2.7 Hz, 1H), 2.91 (ddd, *J* = 10.4, 4.9, 2.7 Hz, 1H), 2.65 (m, 1H), 1.50-1.66 (m, 4H), 1.43 (m, 1H), 1.11 (m, 1H), 1.03 (t, *J* = 7.1 Hz, 3H, **methyl**), 0.93 (s, 9H, **TBS**), 0.17 (s, 3H, **TBS**), 0.16 (s, 3H, **TBS**),; ^{13}C NMR(100 MHz, CDCl3): δ 175.3, 165.1, 157.3, 109.1, 98.6, 95.7, 73.8, 48.5, 43.5, 40.3, 29.7, 27.1, 25.8, 23.5, 18.2, 12.9, -4.5; IR(neat): 2954, 2931, 2860, 1731, 1636, 1462, 1369, 1250, 1222, 1138, 1098, 905, 863; HRMS-(APCI) m/z: 453.1179, 455.1150 (M+2 for Cl), 457.1128 (M+4 for Cl) [$(M+H)^+$: $[C_{20}H_{32}Cl_3O_3Si]^+$ requires 453.1181]; $[\alpha]^{20}_D$: -19.2^o (c=1.00, $CHCl_3$);

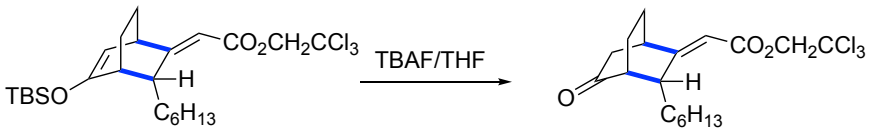


53

(*E*)-2,2,2-trichloroethyl 2-((1*R*,3*R*,4*R*)-5-((*tert*-butyldimethylsilyl)oxy)-3-methylbicyclo[2.2.2]oct-5-en-2-ylidene)acetate 53: derived from diene **48** (1.05 mmol) and vinyl diazoacetate **49** (0.30 mmol) with general procedure with Rh_2(*R*-*p*-PhTPCP)$_4$ cat., isolated product: 79.6 mg, yield 60%.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.78 (d, *J* = 1.8 Hz, 1H, **H next to trichloroethyl**), 4.90 (dd, *J* = 7.0, 2.2 Hz, 1H, **alkene H next to TBS**), 4.79 (d, *J* = 12.0 Hz, 1H, **trichloroethyl**), 4.73 (d, *J* = 12.0 Hz, 1H, **trichloroethyl**), 3.10 (m, 2H), 2.36 (m, 1H), 1.48-1.58 (m, 4H), 1.10 (d, *J* = 6.8 Hz, 3H, **methyl**), 0.93 (s, 9H, **TBS**), 0.17 (s, 3H, **TBS**), 0.16 (s, 3H, **TBS**); ^{13}C NMR(100 MHz, CDCl3): δ 174.8, 164.5, 157.4, 109.0, 98.2, 95.5, 73.6, 44.8, 43.2, 41.0, 28.7, 25.6, 23.6, 18.9, 18.0, -4.5; IR(neat): 2951, 2930,

2858, 1734, 1637, 1463, 1368, 1252, 1229, 1196, 1139, 903, 839; HRMS-(APCI) m/z: 439.0950, 440.0921 (M+2 for Cl), 443.0899 (M+4 for Cl) [(M+H)$^+$: [$C_{19}H_{30}Cl_3O_3Si$]$^+$ requires 439.0952]

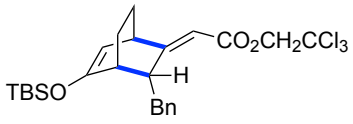


54 **54'**

(*Z*)-2,2,2-trichloroethyl 2-((1*R*,3*R*,4*R*)-3-hexyl-5-oxobicyclo[2.2.2]octan-2-ylidene)acetate 54':

54 (characterized after desilylation as **54'**) derived from diene **48** (1.05 mmol) and vinyl diazoacetate **50** (0.30 mmol) with general procedure with Rh_2(*R*-*p*-PhTPCP)$_4$ cat., isolated product: 75.6 mg, yield 49%.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.94 (d, *J* = 1.8 Hz, 1H, **H next to trichloroethyl**), 4.82 (d, *J* = 11.9 Hz, 1H, **trichloroethyl**), 4.76 (d, *J* = 11.93 Hz, H, **trichloroethyl**), 3.37 (ddd, *J* = 11.7, 5.2, 3.1 Hz, 1H), 2.83 (m, 1H), 2.64 (m, 1H), 2.32 (m, 2H, **2H next to carbonyl**) 1.93 (m, 1H), 1.72-1.84 (m, 4H), 1.46 (m, 1H), 1.18-1.38 (m, 7H), 1.02 (m, 1H), 0.86 (t, *J* = 7.1 Hz, 3H, **methyl**) ; ^{13}C NMR(100 MHz, CDCl3): δ 214.1 (**ketone carbonyl**), 171.2 (**trichloroethyl carbonyl**), 163.9, 112.2, 95.2, 73.7, 47.0, 43.3, 42.1, 40.9, 34.1, 31.7, 29.0, 27.3, 27.2, 22.63, 22.60, 14.1; IR(neat): 2953, 2927, 2858, 1729, 1640, 1448, 1383, 1205, 1142, 1119, 1084, 1036, 810; HRMS-(APCI) m/z: 395.0868, 397.0840 (M+2 for Cl), 399.0817 (M+4 for Cl) [(M+H)$^+$: [$C_{18}H_{26}Cl_3O_3$]$^+$ requires 395.0869]; [α]$^{20}_D$: -22.5^o (c=1.00, $CHCl_3$);

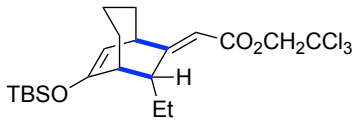


55

(*Z*)-2,2,2-trichloroethyl 2-((1*R*,3*R*,4*R*)-3-benzyl-5-((*tert*-butyldimethylsilyl)oxy)bicyclo[2.2.2]oct-5-en-2-ylidene)acetate 55: derived from diene **48** (1.05 mmol) and vinyl diazoacetate **51** (0.30 mmol) with general procedure with Rh_2(*R*-*p*-PhTPCP)$_4$ cat., isolated product: 95.5 mg, yield 62%.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.50 (m, 2H, **Ph ring**), 7.29 (m, 2H, **Ph ring**), 7.20 (m, 1H, **Ph ring**), 5.90 (d, *J* = 1.8 Hz, 1H, **H next to trichloroethyl**), 5.01 (dd, *J* = 6.8, 2.3 Hz, 1H, **alkene H next to**

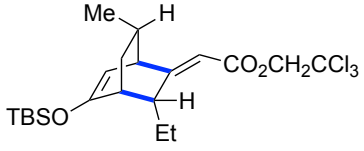
TBS), 4.86 (d, *J* = 12.1 Hz, 1H, **trichloroethyl**), 4.79 (d, *J* = 12.1 Hz, 1H, **trichloroethyl**), 3.17 (m, 2H, **benzylic**), 2.98 (dd, *J* = 13.2, 2.6 Hz, 1H), 2.39 (m, 1H, **H next to benzyl**), 2.28 (dd, *J* = 13.1, 11.2 Hz, 1H), 1.41-1.54 (m, 2H), 1.30 (m, 2H), 0.99 (s, 9H, **TBS**), 0.23 (s, 3H, **TBS**), 0.17 (s, 3H, **TBS**); ^{13}C NMR(100 MHz, CDCl3): δ 173.9, 164.8, 157.4, 140.9, 129.7, 128.0, 125.9, 109.4, 99.8, 95.5, 73.6, 49.1, 43.3, 39.9, 31.2, 29.7, 29.4, 25.7, 23.2, 22.7, 18.1, 14.1, -4.25, -4.76; IR(neat): 2952, 2929, 2858, 1727, 1636, 1462, 1368, 1252, 1224, 1194, 1139, 1105, 896; HRMS-(APCI) m/z: 515.1263, 517.1234 (M+2 for Cl), 519.1212 (M+4 for Cl) [(M+H)$^+$: [$C_{25}H_{34}Cl_3O_3Si$]$^+$ requires 515.1265]; [α]$^{20}_D$: +52.8° (c=1.00, $CHCl_3$);



59

(*Z*)-2,2,2-trichloroethyl 2-((1*R*,5*R*,9*R*)-6-((*tert*-butyldimethylsilyl)oxy)-9-ethylbicyclo[3.2.2]non-6-en-8-ylidene)acetate 59: derived from diene **56** (1.05 mmol) and vinyl diazoacetate **44** (0.30 mmol) with general procedure with Rh_2(*R*-*p*-PhTPCP)$_4$ cat., isolated product: 80.0 mg yield 57%.

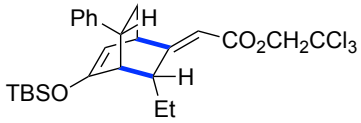
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.79 (d, *J* = 1.6 Hz, 1H, **H next to trichloroethyl**), 4.83 (d, *J* = 12.0 Hz, 1H, **trichloroethyl**), 4.80 (dd, *J* = 7.0, 2.1 Hz, 1H, **alkene H next to TBS**), 4.74 (d, *J* = 12.0 Hz, 1H, **trichloroethyl**), 3.26 (ddd, *J* = 10.6, 4.3, 2.0 Hz, 1H), 3.00 (m, 1H), 2.35 (m, 1H, **H next to ethyl**), 1.75 (m, 1H), 1.58-1.69 (m, 3H), 1.49-1.55 (m, 2H), 1.32 (m, 2H), 1.01 (t, *J* = 7.5 Hz, 3H, **methyl**), 0.93 (s, 9H, **TBS**), 0.20 (s, 3H, **TBS**), 0.17 (s, 3H, **TBS**); ^{13}C NMR(100 MHz, CDCl3): δ 176.5, 164.5, 157.8, 111.0, 98.6, 95.5, 73.5, 47.6, 42.6, 39.8, 33.2, 28.6, 26.3, 25.6, 22.0, 17.9, 13.0, -4.54, -4.47; IR(neat): 2955, 2930, 2858, 1732, 1628, 1462, 1375, 1257, 1229, 1177, 1129, 882, 839; HRMS-(APCI) m/z: 467.1264, 469.1236 (M+2 for Cl), 471.1213 (M+4 for Cl) [(M+H)$^+$: [$C_{21}H_{34}Cl_3O_3Si$]$^+$ requires 467.1265]; [α]$^{20}_D$: +9.7° (c=1.00, $CHCl_3$);



60

(*E*)-2,2,2-trichloroethyl 2-((1*R*,3*R*,4*R*,7*S*)-5-((*tert*-butyldimethylsilyl)oxy)-3-ethyl-7-methyl-bicyclo[2.2.2]oct-5-en-2-ylidene)acetate 60: derived from diene **57** (1.05 mmol) and vinyl diazoacetate **44** (0.30 mmol) with general procedure with Rh_2(*R*-*p*-PhTPCP)$_4$ cat., isolated product: 75.4 mg, yield 53%. The steric position of 7-methyl group was determined by NOE experiment.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.78 (d, *J* = 1.9 Hz, 1H, **H next to trichloroethyl**), 4.77 (d, *J* = 12.0 Hz, 1H, **trichloroethyl**), 4.75(dd, *J* = 6.6, 2.3 Hz, 1H, **alkene H next to TBS**), 4.74 (d, *J* = 12.02 Hz, 1H, **trichloroethyl**), 2.86 (dd, *J* = 6.8, 2.4 Hz, 1H), 2.81 (ddd, *J* = 10.3, 4.9, 2.7 Hz, 1H, **H next to ethyl**), 2.59 (m, 1H), 1.81 (m, 1H, **H next to methyl on the ring**), 1.63-1.72 (m, 2H, **ethyl CH_2, ring CH_2**), 1.08 (m, 1H, **ethyl CH_2**), 1.01 (t, *J* = 7.2 Hz, 3H, **methyl**), 1.01 (m, 1H, **ring CH_2**), 0.93 (s, 9H, **TBS**), 0.87 (d, *J* = 6.8 Hz, 3H, **methyl on the ring**), 0.18 (s, 3H, **TBS**), 0.18 (s, 3H, **TBS**); ^{13}C NMR(100 MHz, CDCl3): δ 175.6, 164.9, 156.9, 108.7, 95.1, 73.5, 50.0, 48.8, 40.7, 34.8, 32.9, 26.9, 25.6, 21.3, 12.7, -4.7; IR(neat): 2956, 2929, 2859, 1731, 1637, 1462, 1372, 1250, 1213, 1130, 998, 893, 818, 719; HRMS-(APCI) m/z: 467.1264, 469.1235 (M+2 for Cl), 471.1213 (M+4 for Cl) [$(M+H)^+$: $[C_{21}H_{34}Cl_3O_3Si]^+$ requires 467.1265]; $[\alpha]^{20}_D$: +9.5° (c=1.00, $CHCl_3$);

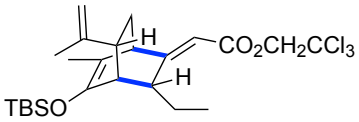


61

(*Z*)-2,2,2-trichloroethyl 2-((1*R*,3*R*,4*S*,8*R*)-5-((*tert*-butyldimethylsilyl)oxy)-3-ethyl-8-phenylbicyclo[2.2.2]oct-5-en-2-ylidene)acetate 61: derived from diene **58** (1.05 mmol) and vinyl diazoacetate **44** (0.30 mmol) with general procedure with Rh_2(*R*-*p*-PhTPCP)$_4$ cat., isolated product: 127.3 mg, yield 80%. Stereochemistry of 8-phenyl was determined by NOE.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.17-7.22 (m, 5H, **Ph ring**), 5.86 (d, *J* = 1.7 Hz, 1H, **H next to trichloroethyl**)), 5.01(dd, *J* = 6.8, 2.5 Hz, 1H, **alkene H next to TBS**), 4.81(d, *J* = 12.2 Hz, 1H, **trichloroethyl**), 4.76(d, *J* = 12.2 Hz, 1H, **trichloroethyl**), 3.17 (td, *J* = 6.8, 2.8 Hz, 1H), 3.10 (ddd, *J* = 10.7, 4.8, 2.8 Hz, 1H, **H next to Et**), 2.89 (dt, *J* = 6.8, 1.6 Hz, 1H, **benzylic**), 2.79 (m, 1H, **H next to ethyl**), 2.15 (dt, *J* = 9.7, 3.8 Hz, 1H, **ring CH_2**), 1.67 (m, 2H, **ethyl CH_2, ring CH_2**), 1.15 (m, 1H, **ethyl CH_2**), 1.02 (t, *J* = 7.3 Hz, 3H, **methyl**), 0.86 (s, 9H, **TBS**), 0.18 (s, 3H, **TBS**), 0.17 (s, 3H, **TBS**); ^{13}C

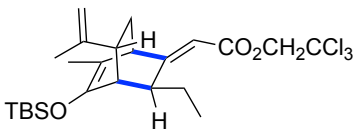
NMR(100 MHz, CDCl3): δ 174.0, 164.8, 155.4, 146.5, 128.2, 127.4, 126.0, 109.7, 97.7, 95.4, 73.7, 49.1, 47.0, 43.3, 42.4, 39.4, 29.7, 26.3, 25.4, 17.8, 12.5, -4.9; IR(neat): 2955, 2929, 2858, 1730, 1637, 1472, 1462, 1374, 1252, 1120, 910, 878, 781; HRMS-(APCI) m/z: 529.1419, 531.1390 (M+2 for Cl), 533.1369 (M+4 for Cl) [$(M+H)^+$: $[C_{26}H_{36}Cl_3O_3Si]^+$ requires 529.1421]; $[\alpha]^{20}_D$: +11.7° (c=1.00, $CHCl_3$);



63

(*E*)-2,2,2-trichloroethyl 2-((1*S*,3*S*,4*R*,8*R*)-5-((*tert*-butyldimethylsilyl)oxy)-3-ethyl-8-(prop-1-en-2-yl)bicyclo[2.2.2]oct-5-en-2-ylidene)acetate 63: derived from diene **62(*R*)** (1.05 mmol) and vinyl diazoacetate **44** (0.30 mmol) under Rh_2(***R***-*p*-PhTPCP)$_4$ with general procedure, isolated product: 145.1 mg, yield 95%. Stereochemistry of 3- and 8-position is determined by NOE.

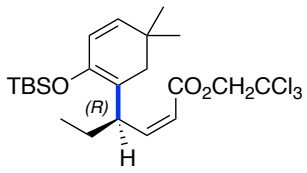
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.82 (d, *J* = 1.8 Hz, 1H, **H next to trichloroethyl**), 4.79 (d, *J* = 12.1 Hz, 1H, **trichloroethyl**), 4.75 (m, 1H, **alkene H**), 4.74 (d, *J* = 12.1 Hz, 1H, **trichloroethyl**), 4.72 (m, 1H, **alkene H**), 2.92 (t, *J* = 2.9 Hz, 1H), 2.89 (ddd, *J* = 10.1, 4.7, 2.4 Hz, 1H, **H next to ethyl**), 2.63 (m, 1H,), 2.16 (t, *J* = 8.3 Hz, 1H, **next to 8-(prop-1-en-2-yl)**), 1.75 (s, 3H, **methyl next to open alkene**), 1.73 (m, 1H), 1.66 (s, 3H, **methyl on alkene next to TBS**), 1.56 (m, 1H, **ethyl H**), 1.52 (m, 1H), 1.13 (m, 1H, **ethyl H**), 1.05 (t, *J* = 7.1 Hz, 3H, **methyl of ethyl**), 0.92 (s, 9H, **TBS**), 0.12 (s, 3H, **TBS**), 0.12 (s, 3H, **TBS**); ^{13}C NMR(100 MHz, CDCl3): δ 174.3, 164.7, 148.1, 147.2, 110.2, 109.4, 108.5, 95.5, 73.6, 53.4, 50.5, 49.9, 45.2, 44.4, 34.5, 27.0, 25.6, 22.8, 18.3, 13.4, 13.2, -3.7; IR(neat): 2957, 2930, 2857, 1730, 1677, 1634, 1462, 1381, 1354, 1254, 1221, 1117, 922; HRMS-(APCI) m/z: 507.1577, 509.1548 (M+2 for Cl), 511.1527 (M+4 for Cl) [$(M+H)^+$: $[C_{24}H_{38}Cl_3O_3Si]^+$ requires 507.1578]; $[\alpha]^{20}_D$: +38.1° (c=1.00, $CHCl_3$);



64

(*E*)-2,2,2-trichloroethyl 2-((1*S*,3*S*,4*R*,8*R*)-5-((*tert*-butyldimethylsilyl)oxy)-3-ethyl-8-(prop-1-en-2-yl)bicyclo[2.2.2]oct-5-en-2-ylidene)acetate 64: derived from diene **62(*R*)** (1.05 mmol) and vinyl diazoacetate **44** (0.30 mmol) under Rh_2(***S***-*p*-PhTPCP)$_4$ with general procedure, isolated product: 78.5 mg, yield 51%. Stereochemistry of 3- and 8-position is determined by NOE.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.69 (d, *J* = 2.2 Hz, 1H, **H next to trichloroethyl**), 4.82 (d, *J* = 12.1 Hz, 1H, **trichloroethyl**), 4.76 (m, 1H, **alkene H**), 4.71 (m, 1H, **alkene H**), 4.70 (d, *J* = 12.1 Hz, 1H, **trichloroethyl**), 3.01 (ddd, *J* = 11.2, 5.7, 3.5 Hz, 1H, **H next to ethyl**), 2.83 (dd, *J* = 3.1, 2.5 Hz, 1H), 2.61 (m, 1H, **next to 8-(prop-1-en-2-yl)**), 2.59 (m, 1H), 2.08 (m, 1H, **ethyl CH_2**), 1.77 (m, 1H), 1.74 (s, 3H, **methyl next to open alkene**), 1.61 (s, 3H, **methyl on alkene next to TBS**), 1.55 (m, 1H), 1.20 (m, 1H, **ethyl CH_2**), 0.98 (t, *J* = 7.4 Hz, 3H, **methyl of ethyl**), 0.92 (s, 9H, **TBS**), 0.10 (s, 3H, **TBS**), 0.06 (s, 3H, **TBS**) ; ^{13}C NMR(100 MHz, CDCl3): δ 172.7, 164.8, 150.4, 148.3, 112.5, 110.3, 107.5, 95.4, 73.7, 53.4, 50.0, 43.8, 42.5, 38.6, 28.5, 25.6, 23.7, 22.0, 18.0, 12.8, 12.1, -3.6, -4.1; IR(neat): 2956, 2931, 2858, 1728, 1678, 1631, 1462, 1380, 1347, 1252, 1221, 1119, 834; HRMS-(APCI) m/z: 507.1577, 509.1548 (M+2 for Cl), 511.1527 (M+4 for Cl) [$(M+H)^+$: $[C_{24}H_{38}Cl_3O_3Si]^+$ requires 507.1578]; $[\alpha]^{20}_D$: +105.0° (c=1.00, $CHCl_3$);



66

(*R*,*Z*)-2,2,2-trichloroethyl 4-(2-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethylcyclohexa-1,3-dien-1-yl)hex-2-enoate 66: derived from diene **65** (1.05 mmol) and vinyl diazoacetate **44** (0.30 mmol) with general procedure with Rh_2(*R*-*p*-PhTPCP)$_4$ cat., isolated product: 65.2 mg, yield 45%.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.33 (dd, *J* = 11.5, 10.1 Hz, 1H, **alkene next to ester**), 5.87 (dd, *J* = 11.5, 1.1 Hz, 1H, **alkene next to ester**), 5.61(d, *J* = 9.9 Hz, 1H, **alkene in ring**), 5.47 (d, *J* = 9.9 Hz, 1H, **alkene in ring**), 4.76 (s, 2H, **trichloroethyl CH_2**), 4.56 (m, 1H, **H next to Ethyl**), 2.07 (d, *J* = 16.3 Hz, 1H, **ring CH_2**), 2.04 (d, *J* = 16.3 Hz, 1H, ring **CH_2**), 1.51 (m, 2H, **Ethyl CH_2**), 1.03 (s, 3H, **Me on ring**), 1.00 (s, 3H, **Me on ring**), 0.94 (s, 9H, **TBS**), 0.89 (t, *J* = 7.4 Hz, 3H, **Me on Ethyl**), 0.13 (s, 3H,

TBS), 0.09 (s, 3H, **TBS**) ; ^{13}C NMR(100 MHz, CDCl3): δ 163.8, 153.8, 143.2, 137.6, 124.0, 116.9, 113.0, 95.3, 73.6, 39.0, 37.4, 31.5, 27.8, 27.2, 25.9, 25.6, 18.1, 12.0, -3.8; IR(neat): 2957, 2930, 2858, 1741, 1652, 1463, 1400, 1377, 1253, 1140, 962, 839, 779; HRMS-(APCI) m/z: 481.1419, 483.1398 (M+2 for Cl), 485.1368 (M+4 for Cl) [$(M+H)^+$: $[C_{22}H_{36}Cl_3O_3Si]^+$ requires 481.1421]

References

1. Guzmán, P. E.; Lian, Y.; Davies, H. M. L. *Angew Chem Int Ed.* **2014**; *53*, 13083

2. Yuan, M.; Schreiber, J. V.; Corey, E. J. *J. Am. Chem. Soc.*, **2013**, *124*, 11290

3. Olga, L.; Manuel, M.; Reisinger, C. M.; Lee, A.; Christophe F.; Iakov, P.; Gopinadhanpillai, G.; Walter, T.; Benjamin, L. *J. Am. Chem. Soc.*, **2013**, *135*, 6677

4. Tatjana, H.; Daniel, K.; Jens, R; Thomas, M. *J.. Org. Chem.* **2015**, *80*, 2281

5. Biplab, M.; Hisashi, Y.; *J. Am. Chem. Soc.*, **2015**, *137*, 15957-15953

6. Marques, F. A.; Lenz, C. A.; Fabio, S.; Maia, B. H. L.; Sales, N.; Vellasco, A. P.; Eberlin, M. N. *J. Nat. Prod.* **2004**, *67*, 1939

7. Zhang, T.; Dai, Y.; Cheng, S.; Liu, Y.; Yang, S.; Sun, B.; Tian, H. *Synthesis*, **2017**, *6*, 1380

8. Kumar, H. M. S.; Reddy, B. V. S.; Reddy, E. J.; Yadav, J. S. *Tetrahedron Lett.* **1999**, *40*, 2401

9. Ihara, M.; Ishida, Y.; Fukumoto, K.; Kametani, T. *Chemical & Pharmaceutical Bulletin*, **1985,** *33*, 410

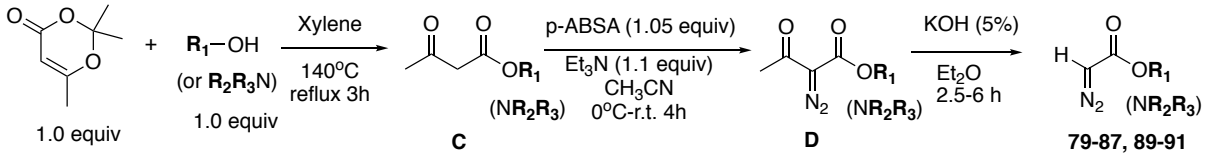
10. Carreno, M. C.; Ruano, J. G.; Remor, C. Z.; Urbano A. *Tetrahedron: Asymm.* **2000**, *11*, 4279

11. Morrison, C. F.; Vaters, J. P.; Miller, D. O.; Burnell, D. J. *Org. & Biomol. Chemi.* **2006**, 4, 1160

6.2 Chapter 3 (Experimental procedure)

6.2.1 Exploring site-selective C–H insertion with Rh acceptor only carbene

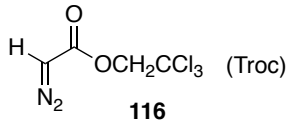
***General method for the preparation of acceptor-only diazo compounds**



2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (technical grade 87%, 20 mmol, 1.0 equiv) and nucleophile R_1OH or R_2R_3N (in accordance to the EWG of final acceptor only diazoacetate) (20 mmol, 1.0 equiv) were dissolved in 50 mL xylene. The solution was heated to 140 °C and kept reflux for 3h. The solution after the reaction was concentrated to give crude **C**. purification of C was done by column chromatography or simple silica plug (ether/hexane) over silica gel.

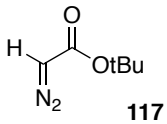
C (10 mmol, 1.0 equiv), p-ABSA (10.5 mmol, 1.05 equiv) were dissolved in 100 mL acetonitrile and the solution was cooled to 0 °C with ice/water bath. Et_3N (11 mmol, 1.1 equiv) was added to the solution and the reaction mixture was kept stirring for 4 h, meanwhile, gradually warmed to r.t. or NMR is attached for representative silyl ketene acetals involved in experiments. ^{1}H NMR for those reported matched the reference [1] or the database, others can be directly confirmed by analysis of the attached ^{1}H NMR. They are all prepared following the general procedure above, the yield ranged from 40% to 80%. The solution was filtered to remove white precipitation, and then concentrated to give crude **D**. purification of **D** was done by simple silica plug (ether/hexane) over silica gel.

D (5-10 mmol, 1.0 equiv**)** was dissolved in 50 mL ether. 50 mL KOH (5%) solution was added and the reaction mixture was stirred for 2.5 to 6 h at r.t. The organic layer was extracted with ether (20 mL*3), combined and dried over $MgSO_4$. The filtrate was concentrated to yield crude final acceptor only diazoacetate. Pure diazo compound for test was obtained by column chromatography (ether/pentane) over silica gel.



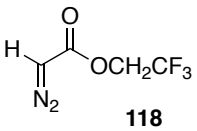
116

2,2,2-trichloroethyl 2-diazoacetate 116: Derived from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one and 2,2,2-trichloroethanol according to the general procedure. This specific diazoacetate was prepared and shared among the group. The ^{1}HNMR checked and matched the reference[1].



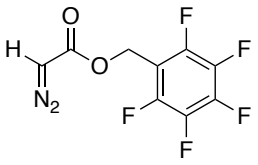
117

***tert*-butyl 2-diazoacetate 117:** Derived from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one and tert-butanol according to the general procedure. This specific diazoacetate was prepared and shared among the group. The ^{1}HNMR checked and matched the reference[2].



118

2,2,2-trifluoroethyl 2-diazoacetate 81: Derived from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one and 2,2,2-trifluoroethanol according to the general procedure. This specific diazoacetate was prepared by Dr. Wenbin Liu. The ^{1}HNMR checked and matched the reference[1].

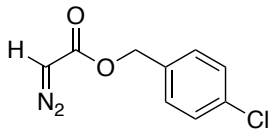


119

2,2,2-trifluoroethyl 2-diazoacetate 119: Derived from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (25 mmol, 1.0 equiv) and (perfluorophenyl)methanol (25 mmol, 4.95 g, 1.0 equiv) according to the general procedure. **119** is obtained as yellow oil, 2.39 g, 36% yield (3 step combined).

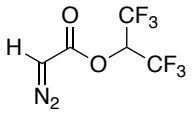
^{1}H NMR (600 MHz, Chloroform-*d*) δ 5.28 (s, 2H), 4.79 (s, 1H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 166.1, 145.7 (dddt, *J* = 251.4, 11.6, 7.9, 4.0 Hz), 141.8 (dtt, *J* = 256.0, 13.4, 5.2 Hz), 138.6 – 136.3 (m), 109.4 (td, *J* = 17.3, 3.9 Hz), 53.5, 46.3; IR(neat): 3132, 2111, 1695, 1658, 1523, 1504, 1391, 1352,

1338, 1309, 1230, 1167, 1129, 1054. HRMS-(APCI) m/z: calcd for $C_9H_4O_2N_2F_5$ $(M+H)^+$ 267.0184; found 267.0186;



120

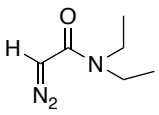
4-chlorobenzyl 2-diazoacetate 120: Derived from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (20 mmol, 1.0 equiv) and (4-chlorophenyl)methanol (20 mmol, 2.85 g, 1.0 equiv) according to the general procedure. **120** is obtained as yellow oil, the yield was not measured. The ^{1}HNMR checked and matched the reference[3].



121

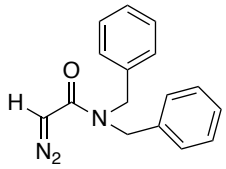
1,1,1,3,3,3-hexafluoropropan-2-yl 2-diazoacetate 121: Derived from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (30 mmol, 1.0 equiv) and 1,1,1,3,3,3-hexafluoropropan-2-ol (45 mmol, 7.56 g, 1.0 equiv) according to the general procedure. **121** is obtained as yellow oil, the yield was low and not measured. This diazo compound seems volatile under the vacuum.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 5.82 (hept, J = 6.1 Hz, 1H), 5.10 (s, broad, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.5, 120.4 (d, J = 282.1 Hz), 66.4 (p, J = 34.8 Hz), 46.9. IR(neat): 3141, 2972, 2124, 1716, 1376, 1361, 1343, 1268, 1229, 1192, 1138, 1104, 1076, 972; HRMS-(APCI) m/z: calcd for $C_5H_3O_2N_2F_6$ $(M+H)^+$ 236.0020; found 236.0018.



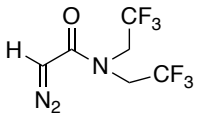
122

2-diazo-*N*,*N*-diethylacetamide 122: This specific diazo compound is directly derived from commercially available **C** intermediate *N*,*N*-diethyl-3-oxobutanamide (40 mmol, 6.29 g). **122** is obtained as yellow oil, the yield was not measured. The ^{1}HNMR checked and matched the reference[4].



123

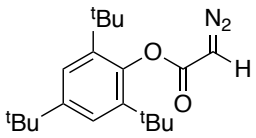
***N*,*N*-dibenzyl-2-diazoacetamide 123:** Derived from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (20 mmol, 1.0 equiv) and dibenzylamine (20 mmol, 3.95 g, 1.0 equiv) according to the general procedure. **123** is obtained as yellow oil, 1.16 g, 22% yield (3 step combined), this is the clean fraction, the actual yield should be higher. The ^{1}HNMR checked and matched the reference[5].



124

2-diazo-*N*,*N*-bis(2,2,2-trifluoroethyl)acetamide 124: Derived from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (20 mmol, 1.0 equiv) and bis(2,2,2-trifluoroethyl)amine (20 mmol, 3.62 g, 1.0 equiv) according to the general procedure. **124** is obtained as light yellow solid. The yield was not measured

^{1}H NMR (600 MHz, Chloroform-*d*) δ 5.12 (s, 1H), 4.01 (s, 4H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 166.6, 124.1 (q, J = 281.3 Hz), 47.7, 47.1; IR(neat): 3100, 2980, 2116, 1628, 1435, 1417, 1323, 1267, 1240, 1155, 1134, 1109, 1032, 899; HRMS-(APCI) m/z: calcd for $C_6H_5ON_3F_6{}^{23}Na$ $(M+Na)^+$ 272.0229; found 272.0227. m.p. 66-68 °C



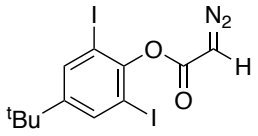
126

2,4,6-tri-tert-butylphenyl 2-diazoacetate 126: Derived from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (20 mmol, 1.0 equiv) and 2,4,6-tri-*tert*-butylphenol (20 mmol, 5.25 g, 1.0 equiv) according to the general procedure. **126** is obtained as light yellow solid. The yield was not measured.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.32 (s, 2H), 5.01 (s, 1H, broad peak), 1.36 (s, 18H), 1.31 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.3, 147.3, 145.0, 141.7, 123.4, 47.5, 35.6, 34.8, 31.5; IR(neat):3096,

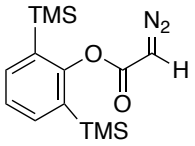
2954, 2909, 2108, 1717, 1594, 1479, 1428, 1394, 1363, 1333, 1247, 1223, 1202, 1184, 1105. HRMS-(APCI) m/z: calcd for $C_{20}H_{30}O_2N_2{}^{23}Na$ $(M+Na)^+$ 353.2200; found 353.1194. m.p. 124-126 °C



127

4-(*tert*-butyl)-2,6-diiodophenyl 2-diazoacetate 127: Derived from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (10 mmol, 1.0 equiv) and 4-(*tert*-butyl)-2,6-diiodophenol (10 mmol, 4.70 g, 1.0 equiv) according to the general procedure. **127** is obtained as light yellow solid. The yield was not measured.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.76 (s, 2H), 5.08 (s, 1H), 1.29 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.9, 152.9, 148.6, 136.9, 90.4, 47.8, 34.5, 31.2; IR(neat):3118, 2963, 2867, 2115, 1709, 1574, 1539, 1475, 1442, 1361, 1340, 1260, 1190, 1136, 1115; HRMS-(APCI) m/z: calcd for $C_{12}H_{12}O_2N_2{}^{127}I_2{}^{23}Na$ $(M+Na)^+$ 492.8880; found 492.8876. m.p. 118-120 °C



128

2,6-bis(trimethylsilyl)phenyl 2-diazoacetate 128: Derived from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (20 mmol, 1.0 equiv) and 2,6-bis(trimethylsilyl)phenol (20 mmol, 4.77 g, 1.0 equiv) according to the general procedure. **128** is obtained as light yellow solid. The yield was not measured.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 7.3 Hz, 2H), 7.11 (t, *J* = 7.3 Hz, 1H), 0.14 (s, 18H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.9, 137.6, 137.4, 133.0, 126.2, 47.3, -0.0. IR(neat): 3111, 2955, 2898, 2110, 1705, 1576, 1382, 1352, 1336, 1248, 1223, 1168, 1144, 1116, 971; HRMS-(APCI) m/z: calcd for $C_{14}H_{23}O_2N_2{}^{28}Si_2$ $(M+H)^+$ 307.1293; found 307.1290. m.p. 64-66 °C

6.2.2 Asymmetric cyclopropanation with Rh donor-only carbene generated from retro-Büchner reaction

***General procedure for the retro-buchner reaction**.

Precursor (E)-1,3,5-trimethyl-7-styrylcyclohepta-1,3,5-triene (0.20 mmol, 1.0 equiv, 47.3 mg) and styrene (0.8 mmol, 4.0 equiv, 83.3 mg) were dissolved in 2 mL anhydrous 1,2-DCE in a 8 mL glass reaction vial. $Rh_2(L)_4$ or $Rh_2(L)_2$ (2 mol %) was then added and the solution was kept stirring at 60 or 80 °C for 16-36 h (monitor by TLC). After the reaction, the solution was concentrated and pure cyclopropanation products are isolated through flash column chromatography on silica gel (0.2% ether in pentane). The 1HNMR matched the reference[6].

References for 6.2.1 and 6.2.2

1. Liu, W., Babl, T., Rother, A., Reiser, O*., Davies, H. M. L*. *Chem. Eur. J.* **2020**, *26*, 4236.

2. Dadabhau, K. D., Liu, R. *Org. Lett.*, **2019**, 21, 6452

3. Han, M., Xie, X., Zhou, D., Li, P., Wang, L., *Org. Lett.*, **2017**, *19*, 2282

4. Doeben, N., Yan, H. Kischkewitz, M., Mao, J., Studer, A., *Org. Lett.*, **2018**, *20*, 7933

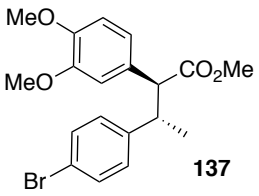
5. Liu, Q., Li, M., Xiong, R., Mo, F., *Org. Lett.*, **2017,** *19*, 6756

6. Mato, M., Herle, B., Echavarren, A. M. *Org. Lett.* **2018**, *20*, 4341–4345

6.2.3 Derivatization of C–H insertion products from Rh donor/acceptor carbene

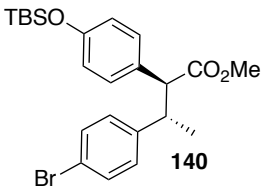
6.2.3.1 Remove the aryl of insertion products from Rh donor/acceptor carbene

6.2.3.1.1 Experimental procedure for the C–H insertion reactions.



137

methyl (2*S*,3*S*)-3-(4-bromophenyl)-2-(3,4-dimethoxyphenyl)butanoate 137: 4-Br ethylbenzene (0.75 mmol, 139 mg, 1.5 equiv) and Rh_2(*S*-2-Cl-5BrTPCP)$_4$ (1 mol%) were dissolved in 1 mL anhydrous CH_2Cl_2 and the solution was kept stirring at 40 °C (reflux temperature). Aryl diazoacetate **136** (0.50 mmol, 118 mg, provided by Dr. Wenbin Liu) was dissolved in 5 mL anhydrous CH_2Cl_2 and the solution was added dropwisely to the previous substrate solution over 3 h (via syringe pump). The reaction was kept running for another 2 h after the addition of diazo compound solution is finished. The reaction mixture was concentrated and the pure C–H insertion product **137** was isolated by column chromatography over silica gel (25-30% ether in pentane), 146 mg, 74% yield, 17:1 dr, 83% ee. The ^{1}HNMR matched the reported data by Dr. Wenbin Liu[1].

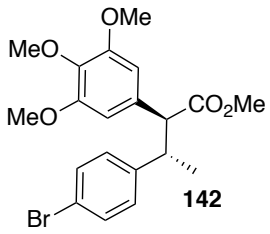


140

methyl (2*S*,3*S*)-3-(4-bromophenyl)-2-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)butanoate 101: 4-Br ethylbenzene (1.67 mmol, 0.24 mL, 1.5 equiv) and Rh_2(*S*-2-Cl-5BrTPCP)$_4$ (1 mol%) were dissolved in 1 mL anhydrous CH_2Cl_2 and the solution was kept stirring at 40 °C (reflux temperature). Aryl diazoacetate **139** (1.12 mmol, 342 mg, provided by Dr. Wenbin Liu) was dissolved in 5 mL anhydrous CH_2Cl_2 and the solution was added dropwisely to the previous substrate solution over 3 h (via syringe pump). The reaction was kept running for another 2 h after the addition of diazo compound solution is finished. The reaction mixture was concentrated and the pure C–H insertion product **140** was isolated by column chromatography over silica gel (25-30% ether in pentane), 298 mg, 58% yield, >20:1 dr, 44%

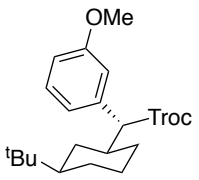
ee (**ee. is based on the malonic-type 138 formed after Ru Oxidation, the Ru(VIII) oxidation is proved to maintain the ee. from 137**).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.21 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 6.60 (d, *J* = 8.6 Hz, 2H), 3.71 (s, 3H), 3.55 (d, *J* = 11.1 Hz, 1H), 3.36 (dq, *J* = 11.0, 6.7 Hz, 1H), 1.34 (d, *J* = 6.8 Hz, 3H), 0.92 (s, 9H), 0.12 (**two Methyl of TMS(117, 0.119)**, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.1, 154.7, 142.7, 131.1, 130.0, 129.3, 120.0, 58.4, 52.0, 43.6, 25.7, 20.6, 18.2, -4.45, -4.46. IR(neat): 2954, 2930, 2858, 1735, 1607, 1508, 1489, 1472, 1463, 1406, 1343, 1254, 1157, 1074, 1010. HRMS-(APCI) m/z: calcd for $C_{23}H_{32}O_3{}^{79}Br^{28}Si$ $(M+H)^+$ 463.1299; found 463.1290. m.p. 80-83 °C



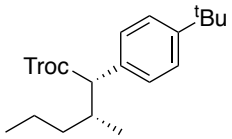
142

methyl (2*S*,3*S*)-3-(4-bromophenyl)-2-(3,4,5-trimethoxyphenyl)butanoate 142: 4-Br ethylbenzene (1.67 mmol, 0.24 mL, 1.5 equiv) and Rh_2(*S*-2-Cl-5BrTPCP)$_4$ (1 mol%) were dissolved in 1 mL anhydrous CH_2Cl_2 and the solution was kept stirring at 40 °C (reflux temperature). Aryl diazoacetate **141** (1.12 mmol, 342 mg, provided by Dr. Wenbin Liu) was dissolved in 5 mL anhydrous CH_2Cl_2 and the solution was added dropwisely to the previous substrate solution over 3 h (via syringe pump). The reaction was kept running for another 2 h after the addition of diazo compound solution is finished. The reaction mixture was concentrated and the pure C–H insertion product **142** was isolated by column chromatography over silica gel (25-30% ether in pentane), 411 mg, 88% yield, 6.7:1 dr, 71% ee. (**ee. is based on the malonic-type 138 formed after Ru Oxidation, the Ru(VIII) oxidation is proved to maintain the ee. from 137**). The ^{1}HNMR matched the reported data by Dr. Wenbin Liu[1].



146

2,2,2-trichloroethyl (*R*)-2-((1*S*,3*R*)-3-(*tert*-butyl)cyclohexyl)-2-(3-methoxyphenyl)acetate 146: tert-butyl cyclohexane (1.25 mmol, 175 mg, 2.5 equiv) and Rh_2(*R*-TPPTTL)$_4$ (1 mol%) were dissolved in 1 mL anhydrous CH_2Cl_2 and the solution was kept stirring at 40 °C (reflux temperature). Aryl diazoacetate **145** (0.50 mmol, 162 mg, from Davies lab diazo-inventory) was dissolved in 5 mL anhydrous CH_2Cl_2 and the solution was added dropwisely to the previous substrate solution over 3 h (via syringe pump). The reaction was kept running for another 4 h after the addition of diazo compound solution is finished. The reaction mixture was concentrated and the pure C–H insertion product **146** was isolated by column chromatography over silica gel (25-30% ether in pentane), 137 mg, 63% yield, 10:1 dr, >30:1 r.r., 96% ee. The ^{1}HNMR matched the reported data by Dr. Jiantao Fu[2].



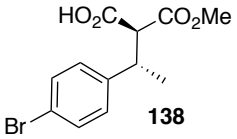
150

2,2,2-trichloroethyl (2*S*,3*R*)-2-(4-(*tert*-butyl)phenyl)-3-methylhexanoate 150: Rh_2(*R*-3,5-di^{t}BuPhTPCP)$_4$ (0.5 mol%) were dissolved in 0.5 mL anhydrous CH_2Cl_2 and 0.5 mL pentane mixed solvent. the solution was kept stirring at 40 °C (reflux temperature). Aryl diazoacetate **149** (0.50 mmol, 174 mg, from Davies lab diazo-inventory) was dissolved in 5 mL anhydrous CH_2Cl_2 and the solution was added dropwisely to the previous substrate solution over 3 h (via syringe pump). The reaction was kept running for another 4 h after the addition of diazo compound solution is finished. The reaction mixture was concentrated and the pure C–H insertion product **150** was isolated by column chromatography over silica gel (25-30% ether in pentane), 139 mg, 71% yield, >20:1 dr, >30:1 r.r., 99% ee. The ^{1}HNMR matched the reported data by Kuangbiao Liao[3].

6.2.3.1.2 General procedure for the Ru(VIII) mediated oxidation

$NaIO_4$ (1 mmol, 10 equiv.) was dissolved in 1 mL H_2O, followed by addition of $RuCl_3.XH_2O$ (10 mol%). The solution was kept stirring vigorously.(T/°C depend on the substrate). C–H insertion

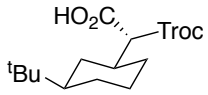
product (0.1 mmol, 1.0 equiv) was dissolved in 0.5 mL ethyl acetate and added dropwisely to the previous stirring solution in 1 min[4]. The reaction was monitored by TLC and stopped when the reaction is finished (maximum 6h if not complete). The organic phase was extraced with ethyl acetate (1mL*5), combined and dried over $MgSO_4$. The solution was evaporated to give crude mixture and pure oxidation product was isolated via column chromatography over silica gel (ether/pentane system).



138

(2*S*,3*S*)-3-(4-bromophenyl)-2-(methoxycarbonyl)butanoic acid 138: Derived from C–H insertion product **137** (78 mg, 0.2 mmol) following the general Ru(VIII) oxidation procedure. The product **138** was isolated as sticky oil in 27 mg, 45% yield. 17:1 dr, 83% ee.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 3.78 (s, 3H), 3.61 (d, *J* = 9.9 Hz, 1H), 3.51 – 3.46 (m, 1H), 1.32 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.6, 168.5, 141.6, 131.7, 129.1, 120.9, 58.4, 52.9, 39.5, 19.7. IR(neat): 2969, 2495(broad), 1733, 1590, 1489, 1457, 1435, 1374, 1285, 1261, 1191, 1161, 1072, 1010. HRMS-(ESI negative) m/z: calcd for $C_{12}H_{12}O_4{}^{79}Br$ $(M-H)^-$ 298.9924; found 298.9928.

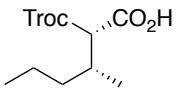


147

(*R*)-2-((1*S*,3*R*)-3-(*tert*-butyl)cyclohexyl)-3-oxo-3-(2,2,2-trichloroethoxy)propanoic acid 147: : Derived from C–H insertion product **146** (44 mg, 0.1 mmol) following the general Ru(VIII) oxidation procedure. The product **147** was isolated as sticky oil in 26 mg, 70% yield. 7.3:1 dr. (dropped compared to the insertion compound **106**'s 10:1 dr, but this is probably because the malonic chiral center itself epimerizes over time)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.88 (d, *J* = 11.9 Hz, 1H), 4.73 (d, *J* = 11.9 Hz, 1H), 3.43 (d, *J* = 7.7 Hz, 1H), 2.16 (tdt, *J* = 11.5, 7.5, 3.3 Hz, 1H), 1.88 – 1.82 (m, 2H), 1.80 – 1.74 (m, 2H), 1.33 – 1.23 (m, 1H), 1.16 – 1.03 (m, 2H), 0.96 – 0.86 (m, 2H), 0.83 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.3,

167.4, 94.4, 74.5, 57.7, 47.8, 38.9, 32.6, 31.7, 30.2, 27.5, 26.7, 26.2. IR(neat): 2941(a broad plus a sharp), 2859, 1757, 1713, 1448, 1413, 1394, 1367, 1285, 1242, 1223, 1198, 1142, 1125, 1028. HRMS-(APCI) m/z: calcd for $C_{15}H_{24}O_4{}^{35}Cl_3$ $(M+H)^+$ 373.0735; found 373.0732.



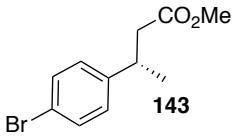
151

(2*S*,3*R*)-3-methyl-2-((2,2,2-trichloroethoxy)carbonyl)hexanoic acid 151: Derived from C–H insertion product **150** (39 mg, 0.1 mmol) following the general Ru(VIII) oxidation procedure. The product **151** was isolated as sticky oil in 21 mg, 69% yield. 7.5:1 dr. (dropped compared to the insertion compound **150**'s >20:1 dr, but this is probably because the malonic chiral center itself epimerizes over time)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.86 (d, *J* = 11.9 Hz, 1H), 4.74 (d, *J* = 11.9 Hz, 1H), 3.50 (d, *J* = 7.1 Hz, 1H), 2.38 – 2.28 (m, 2H), 1.50 – 1.40 (m, 2H), 1.35 – 1.27 (m, 2H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.91 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) 173.0, 167.2, 94.4, 74.5, 56.7, 36.4, 33.6, 20.0, 16.9, 14.0. IR(neat): 2960 (a broad plus a sharp), 2933, 2874, 1759, 1714, 1467, 1457, 1414, 1377, 1272, 1202, 1146, 1128, 1037, 921. HRMS-(APCI) m/z: calcd for $C_{10}H_{15}O_4{}^{35}Cl_3{}^{23}Na$ $(M+Na)^+$ 326.9928; found 326.9925.

6.2.3.1.3 General procedure for the microwave-assisted decarboxylation

Malonate type of intermediate from the oxidation step (1.0 equiv) and imidazole (1.0 equiv) was added to a 8 mL microwave tube and sealed with the cap. The microwave reaction condition was set as 120 °C. 600 W, 4.5 min[5]. After the program is finished, the reaction mixture was directly subjected to small pipette column (pentane/ether system) for isolation of pure decarboxylation product.



143

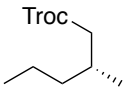
methyl (*S*)-3-(4-bromophenyl)butanoate 143: Derived from carboxylic acid intermediate **138** (18.7 mg, 0.062 mmol, from **137**) following the general procedure. The product **143** was isolated as colorless oil in 11.4 mg, 71% yield. 77% ee.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.34 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 3.55 (s, 3H), 2.51 (dd, *J* = 15.3, 7.3 Hz, 1H), 2.47 (dd, *J* = 15.3, 7.8 Hz, 1H), 1.21 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.5, 144.6, 131.6, 128.5, 120.1, 51.6, 42.5, 36.0, 21.8. IR(neat): 2954, 2925, 1737, 1490, 1456, 1436, 1407, 1377, 1362, 1287, 1262, 1166, 1100, 1010; HRMS-(APCI) m/z: calcd for $C_{11}H_{14}O_2{}^{79}Br$ $(M+H)^+$ 257.0172; found 257.0169.

148

2,2,2-trichloroethyl 2-((1*S*,3*R*)-3-(*tert*-butyl)cyclohexyl)acetate 148: Derived from carboxylic acid intermediate **147** (18.9 mg, 0.051 mmol) following the general procedure. The product **148** was isolated as colorless oil in 15.7 mg, 94% yield.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 4.76 (d, *J* = 12.0 Hz, 1H), 4.72 (d, *J* = 12.0 Hz, 1H), 2.35 (dd, *J* = 6.8, 1.6 Hz, 2H), 1.84 – 1.80 (m, 2H), 1.78 – 1.73 (m, 2H), 1.26 (qt, *J* = 12.6, 3.4 Hz, 2H), 1.06 (tt, *J* = 11.9, 2.9 Hz, 1H), 0.94 – 0.86 (m, 3H), 0.83 (s, 9H), 0.73 (q, *J* = 12.4 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.4, 95.1, 73.9, 47.7, 42.1, 35.4, 34.1, 32.9, 32.5, 27.5, 26.9, 26.3. IR(neat):2926, 2856, 1753, 1478, 1448, 1366, 1280, 1261, 1241, 1222, 1178, 1139, 1111, 1029; HRMS-(APCI) m/z: calcd for $C_{14}H_{24}O_2{}^{35}Cl_3$ $(M+H)^+$ 329.0836; found 329.0835.



152

2,2,2-trichloroethyl (*R*)-3-methylhexanoate 152: Derived from carboxylic acid intermediate **151** (12.4 mg, 0.041 mmol) following the general Ru(VIII) oxidation procedure. The product **152** was isolated as colorless oil in 9.0 mg, 85% yield.

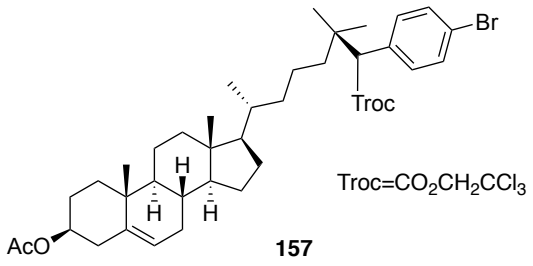
^{1}H NMR (600 MHz, Chloroform-*d*) δ 4.74 (s, 2H), 2.45 (dd, *J* = 15.0, 6.0 Hz, 1H), 2.27 (dd, *J* = 15.0, 8.0 Hz, 1H), 2.04 (dq, *J* = 13.0, 6.2, 5.8 Hz, 1H), 1.39 – 1.28 (m, 3H), 1.26 – 1.21 (m, 1H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.6, 95.1, 73.9, 41.4, 38.8, 30.0, 20.0, 19.7, 14.1. IR(neat): 2959, 2930, 2874, 1756, 1458, 1378, 1262, 1226, 1149, 1106, 1060, 1033, 879. HRMS-(APCI) m/z: calcd for $C_9H_{16}O_2{}^{35}Cl_3$ $(M+H)^+$ 262.0210; found 262.0208.

6.2.3.2 Remove the ester of insertion products from Rh donor/acceptor carbene

6.2.3.2.1 Experimental procedure for C–H insertion reactions

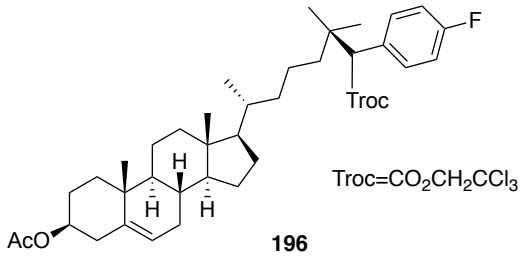
(1) General procedure for Ac-cholesterol tertiary C–H insertion

Acyl protected cholesterol (0.54 mmol, 1.8 equiv), stir bar and Rh_2(R-TCPTAD)$_4$ (1 mol%) was added to a 16 mL glass vial. The vial was degassed and filled with nitrogen several times. Anhydrous CH_2Cl_2 (2 mL) was added to the vial via a syringe. The solution was kept stirring at refluxing temperature (40 °C). Aryldiazoacetate (0.3 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (4 mL) and added to the reaction solution dropwisely over 3 h. The reaction was let run for further 6 h after the addition is finished. The solution was concentrated to give crude material and the pure C–H insertion product was isolated via column chromatography over silica gel (pentane/ether or pentane/hexanes).



157

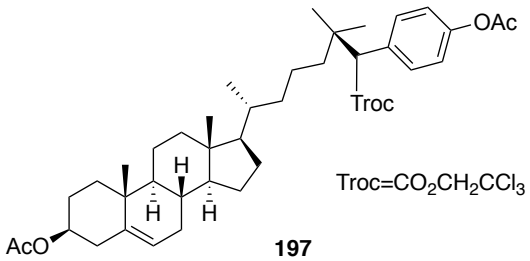
2,2,2-trichloroethyl (2*R*,7*R*)-7-((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-(4-bromophenyl)-3,3-dimethyloctanoate 157: Derived following the general procedure with Ac-cholesterol **156** (171 mg, 0.4 mmol) and aryldiazoacetate **155** (268 mg, 0.72 mmol). The product is isolated (5-10% ether in pentane for column chromatography) as white solid in 254 mg, 82% yield, dr.=10.6: 1(measured after $LiAlH_4$ reduction), r.r. >30:1. The ^{1}HNMR matched to the reference[6].



196

2,2,2-trichloroethyl (2*R*,7*R*)-7-((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-(4-fluorophenyl)-3,3-dimethyloctanoate 196: Derived following the general procedure with Ac-cholesterol **156** (129 mg, 0.3 mmol) and aryldiazoacetate **191** (168 mg, 0.54 mmol). The product is isolated (2-5% ether in hexanes for column chromatography) as white solid in 174 mg, 81% yield, dr.=20:1(measured after $LiAlH_4$ reduction), r.r. >30:1.

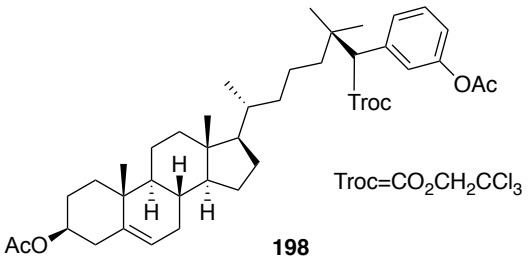
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.38 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.00 (t, *J* = 8.7 Hz, 2H), 5.37 (d, *J* = 5.0 Hz, 1H), 4.81 (d, *J* = 12.0 Hz, 1H, **CH_2 of Troc**), 4.61 (d, *J* = 12.0 Hz, 1H, **CH_2 of Troc**), 4.63 – 4.56 (m, 1H), 3.65 (s, 1H), 2.35 – 2.28 (m, 2H), 2.03 (s, 3H), 2.02 – 1.94 (m, 2H), 1.88 – 1.83 (m, 2H), 1.82 – 1.76 (m, 1H), 1.62 – 1.06 (m, 17H), 1.05 (s, 3H), 1.02 (s, 3H), 1.01 – 0.93 (m, 3H), 0.92 (m, 6H), 0.67 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.4, 170.5, 162.3 (d, *J* = 246.2 Hz), 139.7, 131.7 (d, *J* = 7.8 Hz), 131.0, 122.6, 114.8 (d, *J* = 21.2 Hz)， 94.8, 74.1, 74.0, 59.5, 56.7, 56.1, 50.0, 42.3, 41.2, 39.7, 38.1, 37.4, 37.0, 36.7, 36.6, 35.8, 31.89, 31.86, 28.3, 27.8, 24.6, 24.3, 21.5, 21.0, 20.3, 19.3, 18.8, 11.9. IR(cm^{-1}): 2941, 2868, 1749, 1733, 1605, 1508, 1467, 1374, 1243, 1161, 1120, 1033, 840, 808. HRMS (APCI) m/z: calcd for $C_{39}H_{58}O_4N^{35}Cl_3$ $(M+NH_4)^+$ 728.3410; found 728.3382. $[\alpha]^{20}_D$: -16.0° (c=1.00, $CHCl_3$); m.p. 42-45 °C



197

2,2,2-trichloroethyl (2*R*,7*R*)-7-((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-(4-acetoxy phenyl)-3,3-dimethyloctanoate 197: Derived following the general procedure with Ac-cholesterol **156** (129 mg, 0.3 mmol) and aryldiazoacetate **192** (190 mg, 0.54 mmol). The product is isolated (18-25% ether in hexanes for column chromatography) as white solid in 166 mg, 74% yield, dr.=5.3:1(measured after $LiAlH_4$ reduction), r.r. >30:1.

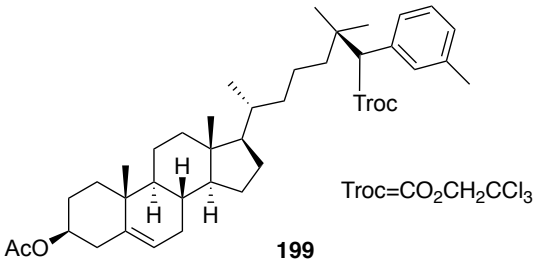
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.42 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 8.7 Hz, 2H), 5.37 (d, *J* = 5.0 Hz, 1H), 4.84 (d, *J* = 12.0 Hz, 1H, **CH_2 of Troc**), 4.60 (m, 1H), 4.55 (d, *J* = 12.0 Hz, 1H, **CH_2 of Troc**), 3.67 (s, 1H), 2.34 – 2.30 (m, 2H), 2.29 (s, 3H), 2.03 (s, 3H), 2.02 – 1.93 (m, 2H), 1.89 – 1.82 (m, 2H), 1.83 – 1.75 (m, 1H), 1.62 – 1.07 (m, 17H), 1.05 (s, 3H), 1.02 (s, 3H), 1.01 – 0.94 (m, 3H), 0.94 – 0.91 (m, 6H), 0.67 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.3, 170.5, 169.4, 150.0, 139.7, 132.7, 131.2, 122.6, 120.9, 94.8, 74.2, 74.0, 59.7, 56.7, 56.1, 50.0, 42.3, 41.2, 39.7, 38.1, 37.5, 37.0, 36.7, 36.6, 35.9, 31.89, 31.86, 28.3, 27.8, 24.6, 24.3, 24.2, 21.5, 21.2, 21.0, 20.4, 19.3, 18.8, 11.9. IR(cm^{-1}): 2941, 2867, 1750, 1732, 1506, 1468, 1439, 1370, 1242, 1200, 1170, 1118, 1033, 1020. HRMS (APCI) m/z: calcd for $C_{41}H_{58}O_6{}^{35}Cl_3$ $(M+H)^+$ 751.3294; found 751.3268. $[\alpha]^{20}_D$: -12.4° (c=1.00, $CHCl_3$); m.p. 53-56 °C



198

2,2,2-trichloroethyl (2*R*,7*R*)-7-((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-(3-acetoxy phenyl)-3,3-dimethyloctanoate 198: Derived following the general procedure with Ac-cholesterol **156** (107 mg, 0.25 mmol) and aryldiazoacetate **193** (158 mg, 0.45 mmol). The product is isolated (20% ether in hexanes for column chromatography) as white solid in 126 mg, 67% yield, dr.=5.6:1(measured after $LiAlH_4$ reduction), r.r. >30:1.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.31 (t, *J* = 7.9 Hz, 1H), 7.26 – 7.24 (m, 1H), 7.20 – 7.16 (m, 1H), 7.03 (ddd, *J* = 8.0, 2.3, 1.0 Hz, 1H), 5.37 (d, *J* = 5.0 Hz, 1H), 4.84 (d, *J* = 12.0 Hz, 1H, **CH_2 of Troc**), 4.64 – 4.58 (m, 1H, **CH_2 of Troc**), 4.57 (d, *J* = 12.0 Hz, 1H), 3.67 (s, 1H), 2.33 – 2.30 (m, 2H), 2.29 (s, 3H), 2.03 (s, 3H), 2.02 – 1.93 (m, 2H), 1.88 – 1.83 (m, 2H), 1.83 – 1.77 (m, 1H), 1.61– 1.07 (m, 17H), 1.06 (s, 3H), 1.02 (s, 3H), 1.01 – 0.94 (m, 3H), 0.94 – 0.91 (m, 6H), 0.67 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.1, 170.6, 169.3, 150.2, 139.7, 136.8, 128.7, 127.8, 123.3, 122.6, 120.6, 94.8, 74.1, 74.0, 59.9, 56.7, 56.1, 50.0, 42.3, 41.3, 39.7, 38.1, 37.6, 37.0, 36.64, 36.59, 35.9, 31.89, 31.87, 28.3, 27.8, 24.7, 24.3, 24.3, 21.5, 21.2, 21.0, 20.4, 19.3, 18.8, 11.9. IR(cm^{-1}): 2940, 2867, 1769, 1749, 1732, 1608, 1588, 1468, 1444, 1371, 1241, 1200, 1118, 1032. HRMS (APCI) m/z: calcd for $C_{41}H_{58}O_6{}^{35}Cl_3$ $(M+H)^+$ 751.3280; found 751.3292. $[\alpha]^{20}_D$: -13.5° (c=1.00, $CHCl_3$); m.p. 48-51 °C

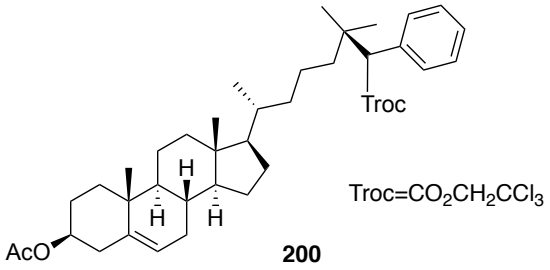


199

2,2,2-trichloroethyl (2*R*,7*R*)-7-((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-3,3-dimethyl-2-(*m*-tolyl)octanoate 199: Derived following the general procedure with Ac-cholesterol **156** (129 mg, 0.3 mmol) and aryldiazoacetate **194** (175 mg, 0.57 mmol). The product is isolated (5-10% ether in hexanes for column chromatography) as white solid in 130 mg, 61% yield, dr.=3.1:1(measured after $LiAlH_4$ reduction), r.r. >30:1.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.23 – 7.17 (m, 3H), 7.10 (d, *J* = 6.6 Hz, 1H), 5.40 – 5.36 (m, 1H), 4.86 (d, *J* = 12.0 Hz, 1H, **CH_2 of Troc**), 4.64 – 4.56 (m, 1H), 4.54 (d, *J* = 12.0 Hz, 1H, **CH_2 of Troc**), 3.64 (s, 1H), 2.35 (s, 3H), 2.33 – 2.29 (m, 2H), 2.03 (s, 3H), 2.02 – 1.94 (m, 2H), 1.88 – 1.83 (m, 2H), 1.84 – 1.77 (m, 1H), 1.63 – 1.08 (m, 17H), 1.06 (s, 3H), 1.02 (s, 3H), 0.97 (d, *J* = 37.7 Hz, 3H), 0.94 – 0.91 (m, 6H), 0.67 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.5, 170.5, 139.7, 137.4, 135.1, 130.9, 128.9, 127.7, 127.3, 122.6, 95.0, 74.1, 74.0, 60.2, 56.7, 56.1, 50.0, 42.3, 41.3, 39.7, 38.1,

37.3, 37.0, 36.7, 36.6, 35.8, 31.90, 31.87, 28.3, 27.8, 24.8, 24.4, 24.3, 21.5, 21.5, 21.0, 20.3, 19.3, 18.8, 11.9. IR(cm^{-1}): 2942, 1868, 1749, 1734, 1466, 1440, 1374, 1243, 1119, 1033, 959, 905. HRMS (APCI) m/z: calcd for $C_{40}H_{61}O_4N^{35}Cl_3$ $(M+NH_4)^+$ 724.3661; found 724.3658. $[\alpha]^{20}_D$: -16.7° (c=1.00, $CHCl_3$); m.p. 45-47 °C

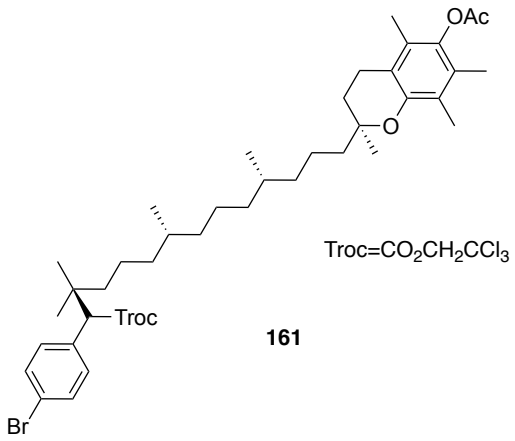


200

2,2,2-trichloroethyl (2*R*,7*R*)-7-((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-3,3-dimethyl-2-phenyloctanoate 200: Derived following the general procedure with Ac-cholesterol **156** (129 mg, 0.23mmol) and aryldiazoacetate **195** (167 mg, 0.57 mmol). The product is isolated (2.5% ether in hexanes for column chromatography) as white solid in 155 mg, 75% yield, dr.=4.1:1(measured after $LiAlH_4$ reduction), r.r. >30:1.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.41 (m, 2H), 7.33 – 7.27 (m, 3H), 5.37 (d, *J* = 5.0 Hz, 1H), 4.84 (d, *J* = 12.0 Hz, 1H, **CH_2 of Troc**), 4.64 – 4.58 (m, 1H), 4.57 (d, *J* = 12.0 Hz, 1H, **CH_2 of Troc**), 3.67 (s, 1H), 2.35 – 2.27 (m, 2H), 2.03 (s, 3H), 2.02 – 1.94 (m, 2H), 1.88 – 1.83 (m, 2H), 1.84 – 1.75 (m, 1H), 1.62 – 1.07 (m, 17H), 1.06 (s, 3H), 1.02 (s, 3H), 1.01 – 0.94 (m, 3H), 0.94 – 0.90 (m, 6H), 0.67 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.5, 170.5, 139.7, 135.2, 130.2, 127.9, 127.4, 122.6, 94.9, 74.1, 74.0, 60.3, 56.7, 56.1, 50.0, 42.3, 41.3, 39.7, 38.1, 37.4, 37.0, 36.7, 36.6, 35.8, 31.90, 31.87, 28.3, 27.8, 24.8, 24.3, 24.4, 21.5, 21.0, 20.4, 19.3, 18.8, 11.9. IR(cm^{-1}): 2939, 2867, 1749, 1732, 1468, 1455, 1374, 1240, 1116, 1032, 958, 904. HRMS (APCI) m/z: calcd for $C_{39}H_{59}O_4N^{35}Cl_3$ $(M+NH_4)^+$ 710.3504; found 710.3500. $[\alpha]^{20}_D$: -13.8° (c=1.00, $CHCl_3$); m.p. 41-44 °C

(2) Experimental procedure for Ac-vitamin E tertiary C–H insertion

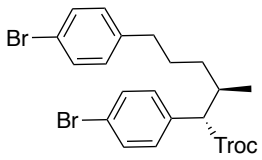


161

2,2,2-trichloroethyl (2*S*,7*R*,11*S*)-14-((*S*)-6-acetoxy-2,5,7,8-tetramethylchroman-2-yl)-2-(4-bromo phenyl)-3,3,7,11-tetramethyltetradecanoate 161: Acyl protected vitamin E **160** (189 mg, 0.64 mmol, 1.6 equiv), stir bar and Rh_2(R-TCPTAD)$_4$ (1 mol%) was added to a 16 mL glass vial. The vial was degassed and filled with nitrogen several times. Anhydrous CH_2Cl_2 (2 mL) was added to the vial via a syringe. The solution was kept stirring at refluxing temperature (40 °C). Aryldiazoacetate **155** (238 mg, 0.4 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (4 mL) and added to the reaction solution dropwisely over 3 h. The reaction was let run for further 6 h after the addition is finished. The solution was concentrated to give crude material and the pure C–H insertion product was isolated via column chromatography over silica gel (2.5-10% ether in pentane). The product **161** is obtained in 240 mg as sticky oil, 74% yield, 14.8:1 dr. (measured by HPLC), >30:1 r.r. The ^{1}HNMR matched the reference[6].

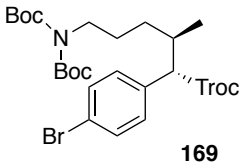
(3) General procedure for Rh_2(*S*-2-Cl-5-BrTPCP)$_4$ mediated secondary C–H insertion

Substrates (for C–H insertion) (0.6 mmol, 2.0 equiv), stir bar and Rh_2(*S*-2-Cl-5-BrTPCP)$_4$ (1 mol%) was added to a 16 mL glass vial. The vial was degassed and filled with nitrogen several times. Anhydrous CH_2Cl_2 (2 mL) was added to the vial via a syringe. The solution was kept stirring at refluxing temperature (40 °C). Aryldiazoacetate (0.3 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (4 mL) and added to the reaction solution dropwisely over 3 h. The reaction was let run for further 6 h after the addition is finished. The solution was concentrated to give crude material and the pure C–H insertion product was isolated via column chromatography over silica gel (pentane/ether system).



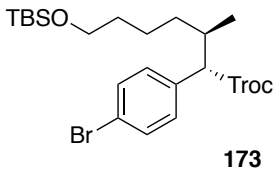
165

2,2,2-trichloroethyl (2*S*,3*R*)-2,6-bis(4-bromophenyl)-3-methylhexanoate 165: Derived following the general procedure with 1-bromo-4-pentylbenzene **164** (136 mg, 0.6 mmol) and aryldiazoacetate **155** (112 mg, 0.3 mmol). The product is isolated (2.5% ether in pentane for column chromatography) as colorless oil in 141 mg, 82% yield, 18.5:1 dr, 12:1 r.r., 87% ee. The ^{1}HNMR matched the reference[7].



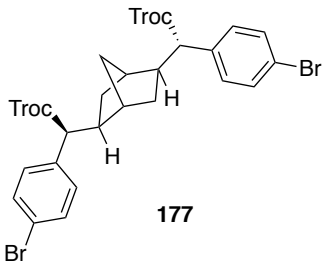
169

2,2,2-trichloroethyl (2*S*,3*R*)-6-(bis(*tert*-butoxycarbonyl)amino)-2-(4-bromophenyl)-3-methyl hexanoate 169: Derived following the general procedure with *tert*-butyl (*tert*-butoxycarbonyl) (pentyl)carbamate **168** (172 mg, 0.6 mmol) and aryldiazoacetate **155** (112 mg, 0.3 mmol). The product is isolated (15% ether in pentane for column chromatography) as sticky oil (slight purple due to coelution with catalyst) in 159 mg, 83% yield, 17:1 dr, >30:1 r.r., 89% ee. The ^{1}HNMR matched the reference[1].



173

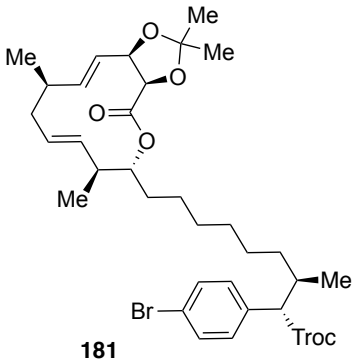
2,2,2-trichloroethyl (2*S*,3*R*)-2-(4-bromophenyl)-7-((*tert*-butyldimethylsilyl)oxy)-3-methylheptanoate 173: Derived following the general procedure with *tert*-butyl(hexyloxy)dimethylsilane **172** (216 mg, 1.0 mmol) and aryldiazoacetate **155** (186 mg, 0.5 mmol). The product is isolated (15% ether in pentane for column chromatography) as colorless sticky oil in 219 mg, 78% yield, 14:1 dr, >30:1 r.r., 87% ee. The ^{1}HNMR matched the reference[8].



177

bis(2,2,2-trichloroethyl) 2,2'-((1*R*,2*S*,4*R*,5*S*)-bicyclo[2.2.1]heptane-2,5-diyl)(2*S*,2'*S*)-bis(2-(4-bromophenyl)acetate) 177: Derived following the general procedure with norbornane **176** (48 mg, 0.5 mmol 1.0 equiv) and aryldiazoacetate **155** (596 mg, 1.6 mmol, 3.2 equiv). Analysis of the crude material shows 29:2:2:1 dr. The crude material was directly subjected to Pd/C (10 wt.%) catalyzed hydrogenation (H_2 balloon) for 4 h to reduce the azine byproduct so that a following silica plug (5-10% ether in pentane) can be used to obtain product in relative clean fractions. The fractions that contain the product was combined and evaporated to remove the solvent to yield a sticky oil compound. Directly dissolve the sticky oil compound in minimum amount of CH_2Cl_2 at 40 °C, keep stirring while adding hexanes dropwisely until no more white solid precipitate out. Filter and wash the white solid with hexanes. This crystallization was repeated again with the mother liquor. The obtained white solid is the pure product as a single diastereomer in 248 mg, 63% yield, >30:1 r.r., >99% ee.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.46 (d, *J* = 8.5 Hz, 4H), 7.23 (d, *J* = 8.4 Hz, 4H), 4.73 (d, *J* = 12.0 Hz, 2H, **CH_2 of Troc**), 4.59 (d, *J* = 12.0 Hz, 2H, **CH_2 of Troc**), 3.29 (d, *J* = 11.8 Hz, 2H), 2.27 (ddd, *J* = 12.3, 8.1, 5.1 Hz, 2H), 1.82 (d, *J* = 4.3 Hz, 2H), 1.60 (dd, *J* = 12.7, 8.2 Hz, 2H), 1.29 (s, 2H), 1.16 (dt, *J* = 12.7, 4.7 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.2, 136.7, 131.9, 130.1, 121.7, 94.7, 74.1, 57.0, 44.5, 39.2, 37.3, 32.5. IR(cm^{-1}): 2954, 2866, 1750, 1488, 1450, 1408, 1372, 1317, 1273, 1218, 1184, 1150, 1127, 1074, 1012. HRMS (APCI) m/z: calcd for $C_{27}H_{25}O_4{}^{79}Br_2{}^{35}Cl_6(M+H)^+$ 780.8245; found 780.8235. $[\alpha]^{20}_D$: +20.1° (c=1.00, $CHCl_3$); m.p. >200 °C

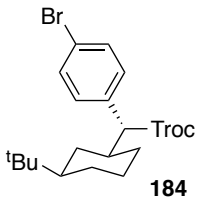


181

2,2,2-trichloroethyl (2*S*,3*R*)-2-(4-bromophenyl)-3-methyl-9-((3a*R*,6*R*,7*S*,8*E*,11*R*,12*E*,13a*R*)-2,2,7,11-tetramethyl-4-oxo-3a,6,7,10,11,13a-hexahydro-4*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclododecin-6-yl)nonanoate 181: Derived following the general procedure with substrate **180** (35 mg, 0.089 mmol, 1.0 equiv) and aryldiazoacetate **155** (166 mg, 0.446 mmol, 5.0 equiv). The reaction was performed in a 4 mL glass vial and the CH_2Cl_2 is used in half amount (1 mL +3 mL). The product is isolated (15% ether in pentane for column chromatography) as colorless sticky oil in 50 mg, 76% yield, 14:1 dr. (Me and Troc relative position, by ^{1}HNMR), 15:1 dr. (absolute position of Me, by HPLC), >30:1 r.r. The ^{1}HNMR matched the reference[1].

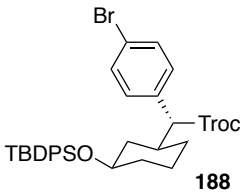
(4) General procedure for Rh_2(*S*-TPPTTL)$_4$ mediated secondary C–H insertion

Substrates (for C–H insertion) (0.75 mmol, 2.5 equiv), stir bar and Rh_2(*S*-TPPTTL)$_4$ (0.5 mol%) was added to a 16 mL glass vial. The vial was degassed and filled with nitrogen several times. Anhydrous CH_2Cl_2 (2 mL) was added to the vial via a syringe. The solution was kept stirring at refluxing temperature (40 °C). Aryldiazoacetate (0.3 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (4 mL) and added to the reaction solution dropwisely over 3 h. The reaction was let run for further 6 h after the addition is finished. The solution was concentrated to give crude material and the pure C–H insertion product was isolated via column chromatography over silica gel (pentane/ether system).



184

2,2,2-trichloroethyl (*R*)-2-(4-bromophenyl)-2-((1*S*,3*R*)-3-(*tert*-butyl)cyclohexyl)acetate 184: Derived following the general procedure with *tert*-butyl cyclohexane **144** (175 mg, 1.25 mmol) and aryldiazoacetate **155** (186 mg, 0.5 mmol). The product is isolated (1-5% ether in pentane for column chromatography) as colorless sticky oil in 189 mg, 78% yield, 10:1 dr, >30:1 r.r., 96% ee. The ^{1}HNMR matched the reference[2].

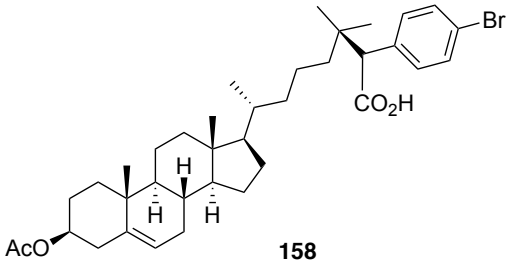


188

2,2,2-trichloroethyl (*R*)-2-(4-bromophenyl)-2-((1*S*,3*R*)-3-((*tert*-butyldiphenylsilyl)oxy)cyclohexyl) acetate 188: Derived following the general procedure with substrate **187** (254 mg, 0.75 mmol) and aryldiazoacetate **155** (112 mg, 0.3 mmol). The product is isolated (1-5% ether in pentane for column chromatography) as colorless sticky oil in 163 mg, 80% yield, 10:1 dr, >30:1 r.r., 96% ee. The ^{1}HNMR matched the reference[9].

6.2.3.2.2 General procedure for the Zn/AcOH hydrolysis

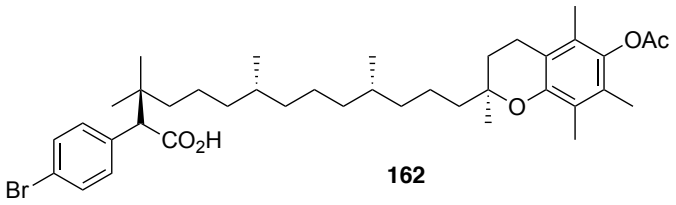
The TCE ester from C–H insertion (1.0 equiv) was dissolved in AcOH. Zn powder (10 equiv) was added and the solution was kept stirring vigorously at r.t. overnight. After the reaction, the solution was diluted with DCM and pass through a short pipette cotton plug to remove solid. The clear solution was concentrated to give crude acid product. The pure acid product was obtained through column chromatography on silica gel.



158

(2*R*,7*R*)-7-((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-(4-bromophenyl)-3,3-dimethyl-octanoic acid 158: Following general procedure, TCE ester **157** (0.30 mmol, 230 mg, 1.0 equiv) from Rh_2(*R*-TCPTAD)$_4$ catalyzed tertiary C–H insertion was dissolved in 4 mL AcOH, reacting with Zn powder (2.97 mmol, 195 mg, 10.0 equiv). Pure product was isolated through column chromatography (20% $CHCl_3$ in pentane with 0.5% AcOH to pure $CHCl_3$) on silica gel as white powder, 140 mg, 73% yield, 10.6:1 dr. (based on the TCE ester **157**), >30:1 r.r.

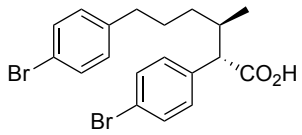
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.43 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 5.37 (d, *J* = 4.9 Hz, 1H), 4.60 (tdd, *J* = 10.5, 6.4, 4.1 Hz, 1H), 3.51 (s, 1H), 2.36 – 2.27 (m, 2H), 2.03 (s, 3H), 2.02 – 1.93 (m, 2H), 1.86 (d, *J* = 10.0 Hz, 2H), 1.84 – 1.75 (m, 1H), 1.63 – 1.41 (m, 7H), 1.40 – 1.32 (m, 3H), 1.30 – 1.04 (m, 10H), 1.02 (s, 6H), 1.01 – 0.93 (m, 3H), 0.92 – 0.90 (m, 6H), 0.67 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.8, 170.6, 139.7, 134.5, 131.8, 131.0, 122.6, 121.5, 74.0, 59.3, 56.7, 56.0, 50.0, 42.3, 41.2, 39.7, 38.1, 37.1, 37.0, 36.7, 36.6, 35.8, 31.89, 31.87, 28.2, 27.8, 24.5, 24.34, 24.28, 21.5, 21.0, 20.2, 19.3, 18.8, 11.9. IR(cm^{-1}): 3000(br, COOH), 2940, 1720, 1686, 1488, 1464, 1439, 1375, 1286, 1243, 1198, 1177, 1147, 1075. HRMS (APCI) m/z: calcd for $C_{37}H_{52}O_4{}^{79}Br$ $(M-H)^-$ 639.3054; found 639.3058. $[\alpha]^{20}_D$: -12.4° (c=1.00, $CHCl_3$); m.p. >200 °C.



162

(2*S*,7*R*,11*S*)-14-((*S*)-6-acetoxy-2,5,7,8-tetramethylchroman-2-yl)-2-(4-bromophenyl)-3,3,7,11-tetramethyltetradecanoic acid 162: Following general procedure, TCE ester **161** (0.24 mmol, 199 mg, 1.0 equiv) from Rh_2(*R*-TCPTAD)$_4$ catalyzed tertiary C–H insertion was dissolved in 4 mL AcOH, reacting with Zn powder (2.4 mmol, 159 mg, 10.0 equiv). Pure product was isolated through column chromatography (10-20% ether in pentane with 0.5% AcOH) on silica gel as slightly yellow sticky oil, 240 mg, 97% yield, 14.8:1 dr. (based on TCE ester **161**), >30:1 r.r.

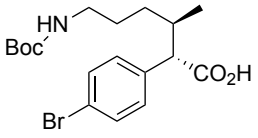
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.42 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 3.50 (s, 1H), 2.59 (t, *J* = 6.8 Hz, 2H), 2.33 (s, 3H), 2.09 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.81 (dt, *J* = 14.0, 7.2 Hz, 1H), 1.74 (dt, *J* = 13.3, 5.7 Hz, 1H), 1.55 (tt, *J* = 15.0, 7.1 Hz, 2H), 1.51 – 1.25 (m, 12H), 1.21 – 1.04 (m, 7H), 1.02 (s, 3H), 0.91 (s, 3H), 0.89 – 0.82 (m, 8H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.5, 169.8, 149.4, 140.5, 134.6, 131.8, 131.0, 126.7, 124.9, 123.0, 121.5, 117.4, 75.1, 59.6, 41.0, 39.4, 37.8, 37.44, 37.42, 37.0, 32.9, 32.8, 32.8, 28.0, 24.4, 24.3, 22.74, 22.65, 21.3, 21.0, 20.61, 20.58, 19.8, 19.7, 13.0, 12.1, 11.9. IR(cm^{-1}): 3000(br, COOH),2928, 2867, 1757, 1705, 1488, 1462, 1368, 1208, 1166, 1109, 1076, 1011, 922. HRMS (APCI) m/z: calcd for $C_{39}H_{56}O_5{}^{79}Br$ $(M-H)^-$ 683.3317; found 683.3318. $[\alpha]^{20}_D$: +9.0° (c=1.00, $CHCl_3$).



166

(2*S*,3*R*)-2,6-bis(4-bromophenyl)-3-methylhexanoic acid 166: Following general procedure, TCE ester **165** (0.095 mmol, 54 mg, 1.0 equiv) from Rh_2(*S*-*2*-Cl,*5*-BrTPCP)$_4$ catalyzed secondary C–H insertion was dissolved in 4 mL AcOH, reacting with Zn powder (0.95 mmol, 62 mg, 10.0 equiv). Pure product was isolated through column chromatography (10% ether in pentane with 0.5% AcOH) on silica gel as sticky oil to white solid, 38 mg, 90% yield, 18.5:1 dr, 86% ee, 20:1 r.r.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.43 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 3.20 (d, *J* = 10.6 Hz, 1H), 2.45 (ddd, *J* = 14.6, 9.1, 5.9 Hz, 1H), 2.32 (ddd, *J* = 14.0, 9.1, 6.7 Hz, 1H), 2.16 (dddq, *J* = 12.9, 9.7, 6.5, 3.2 Hz, 1H), 1.56 (dddd, *J* = 15.6, 13.6, 6.8, 4.6 Hz, 1H), 1.46 – 1.37 (m, 1H), 1.16 (dddd, *J* = 13.8, 10.6, 5.8, 3.3 Hz, 1H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.95 – 0.88 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 178.7, 141.1, 136.3, 131.8, 131.3, 130.3, 130.0, 121.6, 119.4, 57.8, 35.9, 35.0, 32.6, 27.9, 17.8. IR(cm^{-1}): 3000(br, COOH), 2933, 2858, 1703, 1488, 1404, 1281, 1073, 1022, 951, 817, 751. HRMS (APCI) m/z: calcd for $C_{19}H_{21}O_2{}^{79}Br_2$ $(M+H)^+$ 438.9903; found 438.9906. $[\alpha]^{20}_D$: +36.5° (c=1.00, $CHCl_3$). m.p. 98-101°C

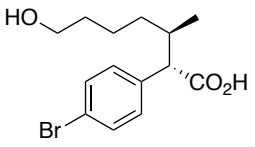


170

(2*S*,3*R*)-2-(4-bromophenyl)-6-((*tert*-butoxycarbonyl)amino)-3-methylhexanoic acid 170:

Following general procedure, TCE ester **169** (0.27 mmol, 170 mg, 1.0 equiv) from Rh_2(*S*-*2*-Cl,*5*-BrTPCP)$_4$ catalyzed secondary C–H insertion was dissolved in 4 mL AcOH, reacting with Zn powder (2.15 mmol, 141 mg, 8.0 equiv). Pure product was isolated through column chromatography (10% ether in pentane with 0.5% AcOH) on silica gel as white solid, 81 mg, 75% yield, 89% ee, 17.6:1 dr. (dr. didn't change compared to TCE ester), >30:1 r.r.

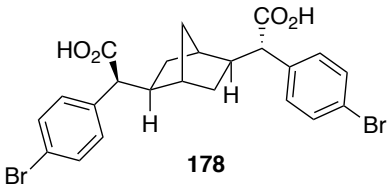
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 4.37 (s, 1H), 3.23 (d, *J* = 10.5 Hz, 1H), 3.07 – 2.95 (m, 1H), 2.89 (dt, *J* = 12.6, 6.5 Hz, 1H), 2.16 (dddq, *J* = 13.0, 9.8, 6.5, 3.2 Hz, 1H), 1.53 – 1.42 (m, 1H), 1.41 (s, 9H), 1.36 – 1.27 (m, 1H), 1.16 (dddd, *J* = 13.9, 10.7, 5.7, 3.3 Hz, 1H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.89 (dtd, *J* = 13.8, 10.2, 4.7 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.6, 155.9, 136.4, 131.8, 130.3, 121.6, 79.2, 57.8, 40.4, 35.8, 30.3, 28.4, 26.9, 17.8. IR(cm^{-1}): 3300(br, amide NH), 3000(br, COOH), 2974, 2933, 1706, 1519, 1489, 1454, 1408, 1367, 1276, 1252, 1167, 1011. HRMS (APCI) m/z: calcd for $C_{18}H_{25}O_4N^{79}Br$ $(M-H)^-$ 398.0972; found 398.0971. $[\alpha]^{20}_D$: +30.0° (c=1.00, $CHCl_3$); m.p. 99-102 °C.



174

(2*S*,3*R*)-2-(4-bromophenyl)-7-hydroxy-3-methylheptanoic acid 174: Following general procedure, TCE ester **173** (0.36 mmol, 200 mg, 1.0 equiv) from Rh_2(*S*-*2*-Cl,*5*-BrTPCP)$_4$ catalyzed secondary C–H insertion was dissolved in 4 mL AcOH, reacting with Zn powder (3.56 mmol, 233 mg, 8.0 equiv). Pure product was isolated through column chromatography (40-60 % ether in pentane with 1% AcOH) on silica gel as white solid, 57 mg, 70% yield, single diastereomer (The major diastereomer can be directly isolated cleanly via column over silica gel), 87% ee.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 3.54 (td, *J* = 6.3, 1.5 Hz, 2H), 3.24 (d, *J* = 10.5 Hz, 1H), 2.16 (m, 1H), 1.50 – 1.31 (m, 3H), 1.24 – 1.11 (m, 2H), 1.05 (d, *J* = 6.5 Hz, 3H), 0.97 – 0.86 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.5, 136.5, 131.7, 130.4, 121.6, 62.8, 57.7, 36.0, 33.0, 32.6, 22.5, 17.8. IR(cm^{-1}): 3350(broad), 2935, 2861, 2591(broad), 1702, 1488, 1461, 1406, 1382, 1295, 1276, 1216, 1178, 1095, 1048, 1011. HRMS (APCI) m/z: calcd for $C_{14}H_{19}O_3{}^{79}Br$ $(M-H)^-$ 313.0445; found 313.0448. $[\alpha]^{20}_D$: +32.5° (c=1.00, $CHCl_3$); m.p. 92-94 °C

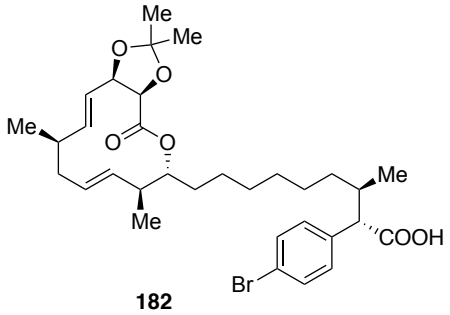


178

(2*S*,2'*S*)-2,2'-((1*R*,2*S*,4*R*,5*S*)-bicyclo[2.2.1]heptane-2,5-diyl)bis(2-(4-bromophenyl)acetic acid) 178: Following general procedure, TCE ester **177** (0.53 mmol, 416 mg, 1.0 equiv) from Norbornane bis-C–H insertion with Rh_2(*S*-*2*-Cl,*5*-BrTPCP)$_4$ catalyst was dissolved in 5 mL AcOH and 1 mL DCM mixed solvent, reacting with Zn powder (5.3 mmol, 347 mg, 10.0 equiv). Pure product was isolated through column chromatography (40% ether in pentane with 1% AcOH) on silica gel as white powder 278 mg, quantitative yield. Single diastereomer and >99.5% ee. (based on TCE ester **177**)

^{1}H NMR (600 MHz, DMSO-d_6) δ 12.35 (s, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 3.18 (d, *J* = 11.7 Hz, 1H), 2.07 (ddd, *J* = 12.3, 8.0, 5.1 Hz, 1H), 1.58 (d, *J* = 4.1 Hz, 1H), 1.44 (dd, *J* = 12.2, 8.1 Hz, 1H), 1.26 (s, 1H), 1.06 (dt, *J* = 12.3, 4.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 174.3, 139.4,

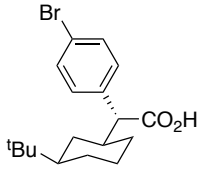
131.8, 130.8, 120.6, 56.7, 44.8, 39.0, 37.3, 32.3. IR(cm^{-1}): 3000(br, COOH), 2953, 2865, 1702, 1488, 1450, 1405, 1278, 1181, 1100, 1074, 1011, 933, 817. HRMS (APCI) m/z: calcd for $C_{23}H_{23}O_4{}^{79}Br_2$ $(M+H)^+$ 520.9969; found 520.9962. $[\alpha]^{20}_D$: +30.7° (c=1.00, ether); m.p. 163-166 °C.



182

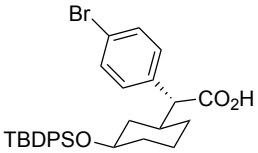
(2*S*,3*R*)-2-(4-bromophenyl)-3-methyl-9-((3a*R*,6*R*,7*S*,8*E*,11*R*,12*E*,13a*R*)-2,2,7,11-tetramethyl-4-oxo-3a,6,7,10,11,13a-hexahydro-4*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclododecin-6-yl)nonanoic acid 182: Following general procedure, TCE ester **181** (0.088 mmol, 65 mg, 1.0 equiv) from Rh_2(*S*-*2*-Cl,*5*-BrTPCP)$_4$ catalyzed secondary C–H insertion was dissolved in 3 mL AcOH, reacting with Zn powder (8.8 mmol, 58 mg, 10.0 equiv). Pure product was isolated through column chromatography (10% ether in pentane with 0.5% AcOH) on silica gel as colorless oil 40 mg, 75% yield, 14:1 dr.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 5.73 (dd, *J* = 15.7, 7.6 Hz, 1H), 5.25 (dd, *J* = 16.6, 6.9 Hz, 1H), 5.13 – 5.04 (m, 2H), 4.79 – 4.70 (m, 2H), 4.52 (d, *J* = 6.7 Hz, 1H), 3.25 (d, *J* = 10.3 Hz, 1H), 2.23 – 2.08 (m, 4H), 1.99 – 1.90 (m, 1H), 1.69 (s, 3H), 1.60 (dddt, *J* = 13.0, 8.7, 5.9, 2.7 Hz, 1H), 1.41 (S, 3H), 1.41– 1.32 (m, 1H), 1.24 – 1.07 (m, 9H), 1.05 (d, *J* = 6.7 Hz, 3H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.91 – 0.80 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.9, 170.1, 138.5, 136.4, 134.9, 131.6, 130.3, 129.7, 123.3, 121.4, 110.9, 78.5, 78.3, 78.2, 57.6, 42.3, 38.7, 36.0, 35.9, 33.0, 32.3, 29.2, 29.2, 26.7, 26.0, 25.8, 24.7, 21.1, 18.0, 17.7. IR(cm^{-1}): 3000(br, COOH),2930, 2856, 1747, 1706, 1489, 1459, 1380, 1189, 1086, 1011, 969, 881, 816. HRMS (APCI) m/z: calcd for $C_{32}H_{44}O_6{}^{79}Br$ $(M-H)^-$ 603.2327; found 603.2331. $[\alpha]^{20}_D$: +8.5° (c=1.00, $CHCl_3$).



185

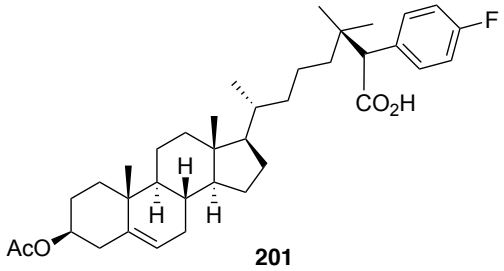
(*R*)-2-(4-bromophenyl)-2-((1*S*,3*R*)-3-(*tert*-butyl)cyclohexyl)acetic acid 185: Following general procedure, TCE ester **184** (0.4 mmol, 196 mg, 1.0 equiv) from Rh_2(*S*-TPPTTL)$_4$ catalyzed secondary C–H insertion was dissolved in 4 mL AcOH, reacting with Zn powder (2.0 mmol, 132 mg, 5.0 equiv). Pure product was isolated through column chromatography (10% ether in pentane with 0.5% AcOH) on silica gel as white powder, 140 mg, 98% yield, 10:1 dr (dr. didn't change compared to TCE ester) ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 3.20 (d, *J* = 10.3 Hz, 1H), 1.94 (tdd, *J* = 11.8, 7.6, 3.2 Hz, 1H), 1.89 – 1.78 (m, 2H), 1.74 (d, *J* = 12.5 Hz, 1H), 1.42 (d, *J* = 12.6 Hz, 1H), 1.27 (dddd, *J* = 16.6, 13.1, 8.4, 3.6 Hz, 1H), 1.01 – 0.87 (m, 2H), 0.87 (dd, *J* = 12.4, 9.0 Hz, 1H), 0.71 (s, 9H), 0.45 (q, *J* = 11.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.8, 136.2, 131.6, 130.3, 121.4, 58.3, 47.7, 41.2, 32.5, 31.7, 31.2, 27.4, 27.0, 26.3. IR(cm^{-1}): 3000(br, COOH), 2929, 2856, 1704, 1488, 1447, 1404, 1366, 1286, 1242, 1201, 1073, 1012, 941, 818. HRMS (APCI) m/z: calcd for $C_{18}H_{26}O_2{}^{79}Br$ $(M+H)^+$ 353.1111; found 353.1111. $[\alpha]^{20}_D$: -18.8° (c=1.00, $CHCl_3$); m.p. 145-148 °C.



189

(*R*)-2-(4-bromophenyl)-2-((1*S*,3*R*)-3-((*tert*-butyldiphenylsilyl)oxy)cyclohexyl)acetic acid 189: Following general procedure, TCE ester **188** (0.177 mmol, 121 mg, 1.0 equiv) from Rh_2(*S*-TPPTTL)$_4$ catalyzed secondary C–H insertion was dissolved in 4 mL AcOH, reacting with Zn powder (1.77 mmol, 116 mg, 10.0 equiv). Pure product was isolated through column chromatography (2.5-5% ether in pentane with 0.5% AcOH) on silica gel as sticky oil to white solid 98 mg, quantitative yield, 7:1 dr. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.53 (d, *J* = 6.7 Hz, 2H), 7.46 (d, *J* = 6.7 Hz, 2H), 7.41 – 7.33 (m, 4H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.6 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 3.45 (tt, *J* = 10.5, 4.2

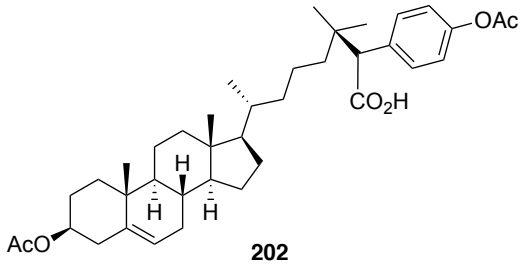
Hz, 1H), 3.10 (d, *J* = 10.5 Hz, 1H), 1.88 (d, *J* = 12.0 Hz, 1H), 1.69 (d, *J* = 9.9 Hz, 3H), 1.33 – 1.28 (m, 1H), 1.28 – 1.22 (m, 1H), 1.13 (qd, *J* = 13.2, 3.4 Hz, 1H), 0.96 (s, 9H), 0.91 – 0.84 (m, 1H), 0.75 (q, *J* = 12.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 144.8, 135.7, 135.5, 134.4, 131.7, 130.0, 129.4, 127.4, 127.3, 121.5, 71.8, 57.4, 39.5, 39.4, 35.5, 30.7, 26.9, 23.7, 19.0. IR(cm^{-1}): 3000(br, COOH), 2930, 2856, 1704, 1488, 1472, 1463, 1448, 1427, 1376, 1275, 1105, 1073, 1011. HRMS (APCI) m/z: calcd for $C_{30}H_{34}O_3{}^{79}Br^{28}Si$ $(M-H)^-$ 549.1466; found 549.1468. $[\alpha]^{20}_D$: +8.9° (c=1.00, $CHCl_3$). m.p. 130-133 °C



201

(2*R*,7*R*)-7-((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15, 16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-(4-fluorophenyl)-3,3-dimethyl-octanoic acid 201: Following general procedure, TCE ester **196** (0.140 mmol, 100 mg, 1.0 equiv) from Rh_2(*R*-TCPTAD)$_4$ catalyzed tertiary C–H insertion was dissolved in 4 mL AcOH, reacting with Zn powder (1.40 mmol, 92 mg, 10.0 equiv). Pure product was isolated through column chromatography (50% $CHCl_3$ in pentane with 1% AcOH to pure $CHCl_3$) on silica gel as white powder, 65 mg, 80% yield, 20:1 dr. (based on the TCE ester **196**)

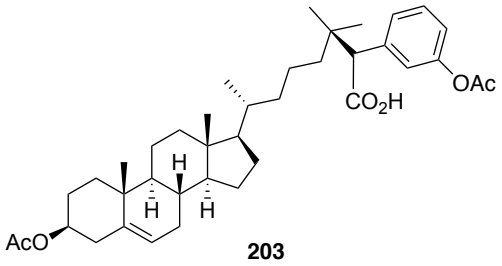
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.37 (dd, *J* = 8.7, 5.4 Hz, 2H), 6.99 (t, *J* = 8.7 Hz, 2H), 5.42 – 5.33 (m, 1H), 4.65 – 4.56 (m, 1H), 3.54 (s, 1H), 2.35 – 2.27 (m, 2H), 2.03 (s, 3H), 2.02 – 1.93 (m, 2H), 1.89 – 1.83 (m, 2H), 1.83 – 1.76 (m, 1H), 1.62 – 1.04 (m, 17H), 1.02 (6H, **2 CH_3 singlet quite close to each other, 1.023(s, 3H), 1.019 (s, 3H)**), 1.01 – 0.93 (m, 3H), 0.94 – 0.88 (m, 6H), 0.67 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.9, 170.6, 162.2 (d, *J* = 246.1 Hz), 139.7, 131.7 (d, *J* = 7.8 Hz), 131.2 (d, *J* = 3.0 Hz), 122.6, 114.7 (d, *J* = 21.1 Hz), 74.0, 65.9, 59.0, 56.7, 56.0, 50.0, 42.3, 41.2, 39.7, 38.1, 37.0, 36.7, 36.6, 35.8, 31.9, 31.9, 28.2, 27.8, 24.6, 24.3, 24.3, 21.5, 21.0, 20.3, 19.3, 18.8, 15.3, 11.9. IR(cm^{-1}): 2941, 1733, 1705, 1508, 1467, 1440, 1375, 1241, 1161, 1034, 908, 838. HRMS (APCI) m/z: calcd for $C_{37}H_{52}O_4F$ $(M-H)^-$ 579.3855; found 579.3846. $[\alpha]^{20}_D$: -5.6° (c=1.00, $CHCl_3$); m.p. >200 °C



202

(2*R*,7*R*)-7-((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-(4-acetoxyphenyl)-3,3-dimethyl-octanoic acid 202: Following general procedure, TCE ester **197** (0.19 mmol, 140 mg, 1.0 equiv) from Rh_2(*R*-TCPTAD)$_4$ catalyzed tertiary C–H insertion was dissolved in 4 mL AcOH, reacting with Zn powder (1.86 mmol, 122 mg, 10.0 equiv). Pure product was isolated through column chromatography (3% AcOH in $CHCl_3$) on silica gel as white powder, 120 mg, quantitative yield, 5.3:1 dr. (based on TCE ester **197**), >30:1 r.r.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.41 (d, *J* = 8.7 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 2H), 5.37 (d, *J* = 5.0 Hz, 1H), 4.65 – 4.56 (m, 1H), 3.55 (s, 1H), 2.34 – 2.29 (m, 2H), 2.29 (s, 3H), 2.03 (s, 3H), 2.01 – 1.93 (m, 2H), 1.89 – 1.83 (m, 2H), 1.83 – 1.77 (m, 1H), 1.62 – 1.05 (m, 17H), 1.03 (s, 3H), 1.02 (s, 3H), 1.01 – 0.93 (m, 3H), 0.93 – 0.89 (m, 6H), 0.67 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.5, 170.6, 169.4, 150.0, 139.7, 133.0, 131.2, 122.6, 120.9, 74.0, 59.4, 56.7, 56.0, 50.0, 42.3, 41.2, 39.7, 38.1, 37.1, 37.0, 36.7, 36.6, 35.9, 31.89, 31.87, 28.2, 27.8, 24.6, 24.30, 24.28, 21.5, 21.2, 21.0, 20.3, 19.3, 18.8, 11.9. IR(cm^{-1}): 2941, 2868, 1766, 1733, 1707, 1506, 1468, 1439, 1367, 1240, 1201, 1168, 1033, 1021. HRMS (APCI) m/z: calcd for $C_{39}H_{55}O_6$ $(M-H)^-$ 619.4004; found 619.3996. $[\alpha]^{20}_D$: -3.2° (c=1.00, $CHCl_3$); m.p. >200 °C

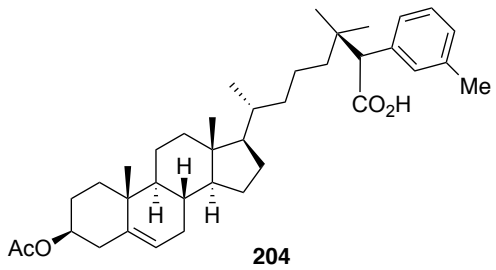


203

(2*R*,7*R*)-7-((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-(3-acetoxyphenyl)-3,3-dimethyl-

octanoic acid 203: Following general procedure, TCE ester **198** (0.15 mmol, 110 mg, 1.0 equiv) from Rh_2(*R*-TCPTAD)$_4$ catalyzed tertiary C–H insertion was dissolved in 4 mL AcOH, reacting with Zn powder (1.53 mmol, 99 mg, 10.0 equiv). Pure product was isolated through column chromatography (3% AcOH in $CHCl_3$) on silica gel as white powder, 89 mg, 94% yield, 5.6:1 dr. (based on TCE ester **198**), >30:1 r.r.

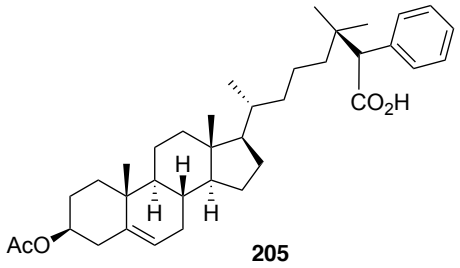
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.30 (t, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 7.17 (t, *J* = 1.9 Hz, 1H), 7.02 (ddd, *J* = 8.1, 2.2, 0.9 Hz, 1H), 5.39 – 5.35 (m, 1H), 4.64 – 4.57 (m, 1H), 3.56 (s, 1H), 2.34 – 2.28 (m, 5H), 2.29 (s, 3H), 2.03 (s, 3H), 2.02 – 1.94 (m, 2H), 1.88 – 1.83 (m, 2H), 1.83 – 1.76 (m, 1H), 1.62 – 1.05 (m, 17H), 1.04 (s, 3H), 1.02 (s, 3H), 1.01 – 0.93 (m, 3H), 0.93 – 0.90 (m, 6H), 0.67 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.6, 170.6, 169.4, 150.2, 139.7, 137.1, 128.6, 127.8, 123.3, 122.6, 120.5, 74.0, 59.4, 56.7, 56.0, 50.0, 42.3, 41.3, 39.7, 38.1, 37.2, 37.0, 36.7, 36.6, 35.9, 31.89, 31.87, 28.2, 27.8, 24.6, 24.31, 24.29, 21.5, 21.2, 21.0, 20.3, 19.3, 18.8, 11.9. IR(cm^{-1}): 2940, 2868, 1769, 1732, 1706, , 1608, 1587, 1471, 1446, 1368, 1242, 1202, 1142, 1034. HRMS (APCI) m/z: calcd for $C_{39}H_{55}O_6$ $(M-H)^-$ 619.4004; found 619.4007. $[\alpha]^{20}_D$: -3.6° (c=1.00, $CHCl_3$); m.p. >200 °C



204

(2*R*,7*R*)-7-((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-3,3-dimethyl-2-(*m*-tolyl)octanoic acid 204: Following general procedure, TCE ester **199** (0.13 mmol, 92 mg, 1.0 equiv) from Rh_2(*R*-TCPTAD)$_4$ catalyzed tertiary C–H insertion was dissolved in 4 mL AcOH, reacting with Zn powder (1.3 mmol, 85 mg, 10.0 equiv). Pure product was isolated through column chromatography (3% AcOH in $CHCl_3$) on silica gel as white powder, 71 mg, 94% yield, 3.1:1 dr. (based on TCE ester **199**), >30:1 r.r.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.19 (m, 3H), 7.12 – 7.05 (m, 1H), 5.37 (d, *J* = 4.8 Hz, 1H), 4.64 – 4.57 (m, 1H), 3.51 (s, 1H), 2.34 (s, 3H), 2.33 – 2.27 (m, 2H), 2.03 (s, 3H), 2.02 – 1.94 (m, 2H), 1.86 (m, 2H), 1.83 – 1.76 (m, 1H), 1.61 – 1.06 (m, 17H), 1.04 (s, 3H), 1.02 (s, 3H), 1.01 – 0.93 (m, 3H), 0.92 (m, 6H), 0.67 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.8, 170.6, 139.7, 137.4, 135.5, 130.9, 128.0, 127.7, 127.3, 122.6, 74.0, 59.9, 56.7, 56.1, 50.0, 42.3, 41.3, 39.7, 38.1, 37.0, 36.9, 36.7, 36.6, 35.8, 31.9, 31.9, 28.2, 27.8, 24.7, 24.4, 24.3, 21.5, 21.5, 21.0, 20.3, 19.3, 18.8, 11.9. IR(cm^{-1}): 2941, 2868, 1734, 1705, 1467, 1442, 1374, 1367, 1243, 1135, 1034, 716. HRMS (APCI) m/z: calcd for $C_{38}H_{55}O_4$ $(M-H)^-$ 575.4106; found 575.4109. $[\alpha]^{20}_D$: -8.9° (c=1.00, $CHCl_3$); m.p. 180-183 °C



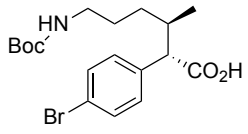
205

(2*R*,7*R*)-7-((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15, 16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-3,3-dimethyl-2-phenyloctanoic acid 205: Following general procedure, TCE ester **200** (0.14 mmol, 100 mg, 1.0 equiv) from Rh_2(*R*-TCPTAD)$_4$ catalyzed tertiary C–H insertion was dissolved in 4 mL AcOH, reacting with Zn powder (1.44 mmol, 94 mg, 10.0 equiv). Pure product was isolated through column chromatography (2% AcOH in $CHCl_3$) on silica gel as white powder, 74 mg, 91% yield, 4.1:1 dr. (based on TCE ester **200**), >30:1 r.r.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.43 – 7.34 (m, 2H), 7.32 – 7.26 (m, 3H), 5.37 (d, *J* = 4.9 Hz, 1H), 4.66 – 4.56 (m, 1H), 3.55 (s, 1H), 2.36 – 2.27 (m, 2H), 2.03 (s, 3H), 2.01 – 1.93 (m, 2H), 1.89 – 1.82 (m, 2H), 1.84 – 1.75 (m, 1H), 1.62 – 1.05 (m, 17H), 1.04 (s, 3H), 1.02 (s, 3H), 1.03 – 0.92 (m, 10H), 0.91 (m, 6H), 0.67 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.8, 170.6, 139.7, 135.6, 130.2, 127.9, 127.3, 122.6, 74.0, 60.0, 56.7, 56.0, 50.0, 42.3, 41.3, 39.7, 38.1, 37.0, 36.7, 36.6, 35.8, 31.90, 31.87, 28.2, 27.8, 24.7, 24.4, 24.3, 21.5, 21.0, 20.3, 19.3, 18.8, 11.9. IR(cm^{-1}): 2939 (a broad and a sharp), 2851, 1732, 1704, 1467, 1456, 1415, 1374, 1366, 1241, 1168, 1136, 1033, 977. HRMS (ESI

negative) m/z: calcd for $C_{37}H_{53}O_4$ $(M-H)^-$ 561.3949; found 561.3951. $[\alpha]^{20}_D$: -16.4° (c=1.00, $CHCl_3$); m.p. 198-200 °C

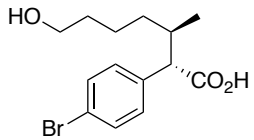
6.2.3.2.3 Procedure for recrystallization of carboxylic acid intermediates



170

[Starting acid compound: 61 mg (from Rh_2(*S*-2-Cl-5BrTPCP)$_4$ catalyst) 17:1 dr. 89% ee.]

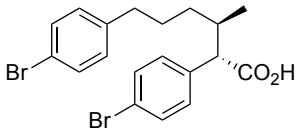
The original acid **170 (**61 mg**)** was dissolved with minimum amount of ether (add dropwisely) and diluted with 1 mL pentane in a 4 mL glass vial. The solution was heated at 40 °C for reflux until slight turbidity appears. The vial was capped and cooled to r.t. naturally with slow stir. Meanwhile, white precipitation is formed during the process. The suspension was filtered with a pipette that blocked with cotton at the front. The mother liquor was repeated for the recrystallization procedure above twice. After the last filtration, the white solid left on the cotton of the pipette was flushed with ether and concentrated to give recrystallized acid **170** at 49.9 mg, 82% recovered yield. 160:1 dr. (measured by HPLC), 97% ee.



174

[Starting acid compound: 51 mg (from Rh_2(*S*-2-Cl-5BrTPCP)$_4$ catalyst) single diastereomer, 89% ee.]

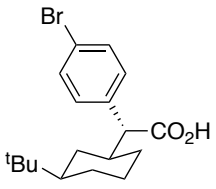
The original acid **174 (**61 mg**)** was dissolved with minimum amount of ether (add dropwisely) in a 4 mL glass vial. The solution was heated at 40 °C for reflux and pentane was added dropwisely until slight turbidity appears. The vial was capped and cooled to r.t. naturally with slow stir. Meanwhile, white precipitation is formed during the process. The suspension was filtered with a pipette that blocked with cotton at the front. The mother liquor was repeated for the recrystallization procedure above twice. After the last filtration, the white solid left on the cotton of the pipette was flushed with ether and concentrated to give recrystallized acid **174** at 44.5 mg, 87% recovered yield. Single diastereomer, 95% ee.



166

[starting acid compound: 70 mg (from Rh_2(*S*-2-Cl-5BrTPCP)$_4$ catalyst) 17:1 dr, 87% ee.]

The original acid **166 (**70 mg**)** was dissolved with 1 drop of ether and diluted with 1 mL pentane in a 4 mL glass vial. The solution was heated at 40 °C for reflux until slight turbidity appears. The vial was capped and cooled to r.t. naturally with slow stir. Meanwhile, white precipitation is formed during the process. The suspension was filtered with a pipette that blocked with cotton at the front. The white solid left on the cotton was obtained at 11 mg (HPLC analysis shows ~13% ee. suggesting that enantiomers of this acid tend to pair when crystalize, so the ee. of the mother liquor should be enhanced.) Then the mother liquor (59 mg) was concentrated to sticky solid and re-dissolved with minimum amount of ether followed by dilution with 1 mL pentane. This solution was kept stirring at 40 °C in the open air until the clear solution become turbid. Another 2 mL pentane was added in one time and the white precipitation formed quickly. The suspension was cooled to r.t. naturally and then filtered. The white solid left on the cotton of the pipette was collected at 44.5 mg, 64% recovered yield, 66:1 dr, >99% ee. (The difference between the recrystallization of original acid and the following mother liquor is very subtle, but this is the accurate procedure and the final recrystallized acid **166** indeed has significantly enhanced dr and ee)

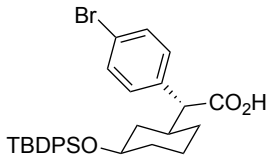


185

[Starting acid compound: 42 mg (from Rh_2(*S*-TPPTTL)$_4$ catalyst) 10:1 dr, 96% ee.]

The original acid **185 (**42 mg**)** was dissolved with one drop of ether and diluted with 1 mL pentane in a 4 mL glass vial. The solution was heated at 40 °C for reflux until slight turbidity appears. The vial was capped and cooled to r.t. naturally with slow stir. Meanwhile, white precipitation is formed during the

process. The suspension was filtered with a pipette that blocked with cotton at the front. The mother liquor was repeated for the recrystallization procedure above twice. After the last filtration, the white solid left on the cotton of the pipette was flushed with ether and concentrated to give recrystallized acid **185** at 36.0 mg, 86% recovered yield. 64:1 dr, (measured by HPLC), >99% ee.



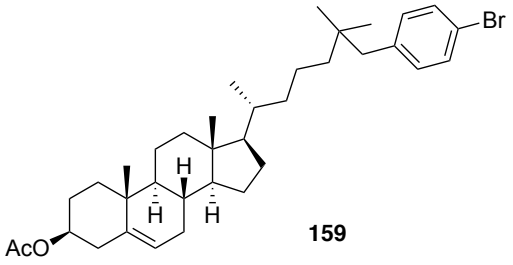
189

[Starting acid compound: 72 mg (from Rh_2(*S*-TPPTTL)$_4$ catalyst) 6:1 dr, 97% ee.]

The original acid **189 (**72 mg**)** was dissolved with 1 mL pentane in a 4 mL glass vial. The solution was heated at 40 °C for reflux until slight turbidity appears. The vial was capped and cooled to r.t. naturally with slow stir. Meanwhile, white precipitation is formed during the process. The suspension was filtered with a pipette that blocked with cotton at the front. The mother liquor was repeated for the recrystallization procedure above twice. After the last filtration, the white solid left on the cotton of the pipette was flushed with ether and concentrated to give recrystallized acid **189** at 56.5 mg, 78% recovered yield. >50:1 dr, >99% ee (measured after desilylation).

6.2.3.2.4 General procedure for the photoredox decarboxylation

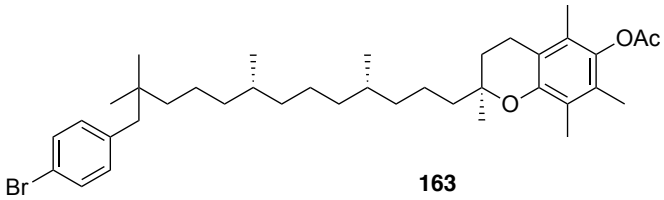
Trifluoroethanol(TFE) and ethyl acetate(EtOAc) solvents are purged with dry N_2 for 10 min. Carboxylic acid (0.05 mmol), $(PhS)_2$ (1.09 mg, 10 mol%) and photo catalyst Ar-Mes-Ph (1.15 mg, 5 mol%) were added to an 8 mL glass reaction vial. Stir bar was added and the vial was sealed with a cap. Purge the vial with gentle N_2 flow for 5 min. TFE:EtOAc=2:1 mixed solvent (0.25 mL) was added and the mixture was stirred at r.t. till all the solid is dissolved. Diisopropylethylamine(DIPEA)(1.29 mg, 20 mol% was added to the solution and the vial was placed 2-3 cm in front of a 15 W blue LED lamp. The reaction was let run for 48 h and then concentrated to remove solvent for analysis and purification. Pure product is isolated via column chromatography over silica gel (pentane/ether system)



159

(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-17-((*R*)-7-(4-bromophenyl)-6,6-dimethylheptan-2-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate 159: Following general procedure, target carboxylic acid **158** (32.1 mg, 0.05 mmol, 1.0 equiv) was decarboxylated to the product **159**. The product is isolated (2-5% ether in pentane for column) as white solid in 24.6 mg, 82% yield.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.37 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 5.38 (d, *J* = 5.0 Hz, 1H), 4.61 (tdd, *J* = 10.4, 6.5, 4.2 Hz, 1H), 2.44 (s, 2H), 2.36 – 2.27 (m, 2H), 2.03 (s, 3H), 2.02 – 1.93 (m, 2H), 1.90 – 1.78 (m, 3H), 1.61 – 1.04 (m, 18H), 1.02 (s, 3H), 1.01 – 0.94 (m, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.82 (s, 6H), 0.68 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.5, 139.7, 138.5, 132.2, 130.7, 122.6, 119.6, 74.0, 56.7, 56.1, 50.0, 47.8, 42.5, 42.3, 39.7, 38.1, 37.0, 36.8, 36.6, 35.9, 34.2, 31.90, 31.87, 28.3, 27.8, 26.81, 26.78, 24.3, 21.5, 21.0, 20.6, 19.3, 18.8, 11.9. IR(cm^{-1}): 2937, 2866, 1733, 1488, 1468, 1439, 1373, 1364, 1241, 1119, 1073, 1033, 1012, 840. HRMS (APCI) m/z: calcd for $C_{36}H_{54}O_2{}^{79}Br$ $(M+H)^+$ 597.3302; found 597.3307. $[\alpha]^{20}_D$: -30.4° (c=1.00, $CHCl_3$); m.p. 125-127 °C.

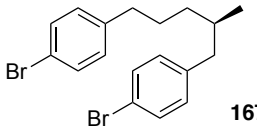


163

(*S*)-2-((4*S*,8*R*)-13-(4-bromophenyl)-4,8,12,12-tetramethyltridecyl)-2,5,7,8-tetramethylchroman-6-yl acetate 163: Following general procedure, target carboxylic acid **162** (34.3 mg, 0.05 mmol, 1.0 equiv) was decarboxylated to the product **163**. The product is isolated (5% ether in pentane for column) as colorless sticky oil 13.1 mg, 40% yield.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.37 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 2.59 (t, *J* = 6.8 Hz, 2H), 2.45 (s, 2H), 2.33 (s, 3H), 2.09 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.81 (dt, *J* = 14.1, 7.1 Hz, 1H), 1.74 (dt, *J* = 12.8, 6.1 Hz, 1H), 1.49 – 1.02 (m, 23H), 0.86 (d, *J* = 6.6 Hz, 6H), 0.82 (s, 6H).

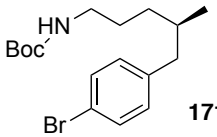
^{13}C NMR (151 MHz, $CDCl_3$) δ 169.8, 149.4, 140.5, 138.5, 132.2, 130.7, 126.7, 124.9, 123.0, 119.6, 117.4, 75.1, 47.8, 42.4, 37.9, 37.5, 37.5, 34.2, 32.8, 32.7, 26.8, 26.7, 24.5, 21.5, 21.0, 20.60, 20.58, 19.8, 19.7, 13.0, 12.1, 11.8. IR(cm^{-1}): 2927, 2865, 1757, 1488, 1461, 1366, 1333, 1206, 1158, 1109, 1074, 1012, 921, 841. HRMS (APCI) m/z: calcd for $C_{38}H_{58}O_3{}^{79}Br$ $(M+H)^+$ 641.3564; found 641.3565. $[\alpha]^{20}_D$: -30.4° (c=1.00, $CHCl_3$).



167

(*R*)-4,4'-(2-methylpentane-1,5-diyl)bis(bromobenzene) 167: Following general procedure, target carboxylic acid **166** (22.0 mg, 0.05 mmol, 1.0 equiv) was decarboxylated to the product **167**. The product is isolated (1% ether in pentane for column) as colorless oil 16.3 mg, 82% yield.

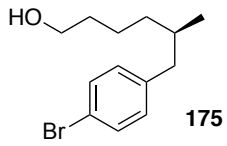
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.38 (dd, *J* = 8.4, 2.0 Hz, 4H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 2.58 – 2.46 (m, 3H), 2.32 (dd, *J* = 13.5, 8.0 Hz, 1H), 1.72 – 1.61 (m, 2H), 1.61 – 1.54 (m, 1H), 1.38 – 1.29 (m, 1H), 1.16 (tdd, *J* = 13.2, 6.7, 4.0 Hz, 1H), 0.83 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 141.5, 140.3, 131.3, 131.2, 130.9, 130.1, 119.43, 119.36, 43.0, 35.9, 35.5, 34.8, 28.8, 19.3. IR(cm^{-1}): 2926, 2855, 1487, 1460, 1403, 1377, 1202, 1109, 1072, 1011, 826, 796. HRMS (APCI) m/z: calcd for $C_{18}H_{20}{}^{79}Br_2$ (M) 393.9926; found 393.9930. $[\alpha]^{20}_D$: +13.9° (c=1.00, $CHCl_3$).



171

***tert*-butyl (*R*)-(5-(4-bromophenyl)-4-methylpentyl)carbamate 171:** Following general procedure, target carboxylic acid **170** (25.0 mg, 0.05 mmol, 1.0 equiv) was decarboxylated to the product **171**. The product is isolated (10% ether in pentane for column) as colorless oil 18.3 mg, 80% yield.

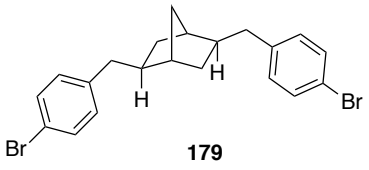
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 4.48 (s, 1H), 3.14 – 2.98 (m, 2H), 2.56 (dd, *J* = 13.5, 6.2 Hz, 1H), 2.33 (dd, *J* = 13.5, 8.1 Hz, 1H), 1.69 (dh, *J* = 13.2, 6.6 Hz, 1H), 1.54 (td, *J* = 12.9, 12.2, 6.3 Hz, 1H), 1.44 (s, 9H), 1.34 (ddt, *J* = 13.4, 10.7, 5.3 Hz, 1H), 1.14 (dddd, *J* = 13.3, 10.7, 8.0, 5.1 Hz, 1H), 0.84 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.9, 140.2, 131.2, 130.9, 119.45 79.1, 43.0, 40.8, 34.7, 33.5, 28.4, 27.7, 19.3. IR(cm^{-1}): 3350 (br, amide NH), 2968, 2928, 2869, 1692, 1512, 1488, 1455, 1391, 1365, 1250, 1171, 1072, 1011. HRMS (APCI) m/z: calcd for $C_{18}H_{20}{}^{79}Br_2$ $(M-H)^-$ 354.1074; found 354.1077. $[\alpha]^{20}_D$: +6.9° (c=1.00, $CHCl_3$).



175

(*R*)-6-(4-bromophenyl)-5-methylhexan-1-ol 175: Following general procedure, use $(Ph_2S)_2$ (0.06 mmol, 13 mg, 1.0 equiv), target carboxylic acid **174** (16 mg, 0.06 mmol, 1.0 equiv) was decarboxylated to the product **175**. The product is isolated (5% ether in pentane for column) as colorless oil 12 mg, 75% yield.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.5 Hz, 2H), 3.63 (t, *J* = 6.6 Hz, 2H), 2.58 (dd, *J* = 13.5, 6.2 Hz, 1H), 2.33 (dd, *J* = 13.4, 8.1 Hz, 1H), 1.75 – 1.63 (m, 1H), 1.58 – 1.49 (m, 2H), 1.47 – 1.41 (m, 1H), 1.37 – 1.31 (m, 2H), 1.20 – 1.13 (m, 1H), 0.84 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 140.4, 131.2, 130.9, 119.4, 63.0, 43.0, 36.3, 34.9, 33.0, 23.2, 19.3. IR(cm^{-1}): 3352(broad), 2926, 2857, 1488, 1459, 1403, 1377, 1349, 1202, 1109, 1071, 1050, 1011, 936. HRMS (ESI) m/z: calcd for $C_{13}H_{19}O^{79}Br^{23}Na$ $(M+Na)^+$ 293.0512; found 293.0511. $[\alpha]^{20}_D$: +7.2° (c=1.00, $CHCl_3$).

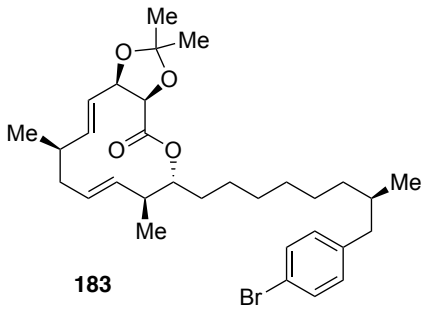


179

(1*R*,2*R*,4*R*,5*R*)-2,5-bis(4-bromobenzyl)bicyclo[2.2.1]heptane 179: Following general procedure, use $(PhS)_2$(20 mol%), DIPEA (40 mol%), target carboxylic acid **178** (26.1 mg, 0.04 mmol, 1.0 equiv) was

decarboxylated to the product **179**. The product is isolated (100% pentane for column) as white solid 14.0 mg, 65% yield.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.37 (d, *J* = 8.4 Hz, 4H), 7.02 (d, *J* = 8.5 Hz, 4H), 2.49 (dd, *J* = 13.9, 8.3 Hz, 2H), 2.38 (dd, *J* = 13.9, 7.5 Hz, 2H), 1.97 (d, *J* = 4.3 Hz, 2H), 1.66 (qd, *J* = 8.2, 5.1 Hz, 2H), 1.34 – 1.30 (m, 4H), 1.08 (dt, *J* = 12.6, 4.6 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 139.6, 130.2, 129.6, 118.3, 75.8, 41.8, 40.9, 39.9, 37.0, 30.9. IR(cm^{-1}): 3000(br, COOH), 2953, 2865, 1702, 1488, 1450, 1405, 1278, 1181, 1100, 1074, 1011, 933, 817. HRMS (APCI) m/z: calcd for $C_{11}H_{22}{}^{79}Br_2$ (M) 432.0083; found 432.0089. $[\alpha]^{20}_D$: -39.5° (c=1.00, $CHCl_3$); m.p. 71-73 °C.

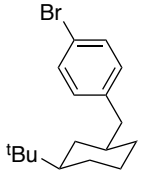


183

(3a*R*,6*R*,7*S*,8*E*,11*R*,12*E*,13a*R*)-6-((*R*)-8-(4-bromophenyl)-7-methyloctyl)-2,2,7,11-tetramethyl-3a,6,7,10,11,13a-hexahydro-4*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclododecin-4-one 183: Following general procedure, target carboxylic acid **182** (24.2 mg, 0.04 mmol, 1.0 equiv) was decarboxylated to the product **183**. The product is isolated (2-5% ether in pentane for column) as colorless oil 17.0 mg, 76% yield.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 5.73 (dd, *J* = 15.2, 7.2 Hz, 1H), 5.25 (ddd, *J* = 15.6, 6.9, 1.0 Hz, 1H), 5.13 – 5.07 (m, 2H), 4.78 (ddd, *J* = 10.8, 8.5, 2.7 Hz, 1H), 4.74 (td, *J* = 6.8, 1.1 Hz, 1H), 4.52 (d, *J* = 6.7 Hz, 1H), 2.57 (dd, *J* = 13.5, 6.1 Hz, 1H), 2.30 (dd, *J* = 13.5, 8.2 Hz, 1H), 2.24 – 2.15 (m, 3H), 1.98 – 1.90 (m, 1H), 1.70 (s, 3H), 1.68 – 1.61 (m, 2H), 1.49 – 1.42 (m, 1H), 1.41 (s, 3H), 1.35 – 1.17 (m, 10H), 1.15 – 1.07 (m, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.3, 140.6, 138.6, 135.0, 131.1, 130.9, 129.8, 123.4, 119.3, 111.0, 78.6, 78.44, 78.35, 43.0, 42.3, 38.7, 36.5, 36.0, 34.9, 32.4, 29.6, 29.6, 27.0, 26.8, 25.9, 24.9, 21.1, 19.3, 18.1. IR(cm^{-1}): 2926, 2854, 1748, 1488, 1457,

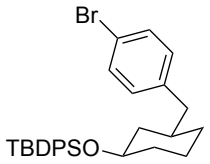
1378, 1253, 1223, 1186, 1085, 1011, 968, 880, 794. HRMS (APCI) m/z: calcd for $C_{31}H_{46}O_4{}^{79}Br$ $(M+H)^+$ 561.2574; found 561.2579. $[\alpha]^{20}_D$: -5.0° (c=1.00, $CHCl_3$).



186

1-bromo-4-(((1*S*,3*R*)-3-(*tert*-butyl)cyclohexyl)methyl)benzene 186: Following general procedure, target carboxylic acid **185** (17.7 mg, 0.05 mmol, 1.0 equiv) was decarboxylated to the product **186**. The product is isolated (100% pentane for column) as colorless oil 12.2 mg, 79% yield.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 8.3 Hz, 2H), 7.01 (d, *J* = 8.2 Hz, 2H), 2.50 (dd, *J* = 13.4, 6.3 Hz, 1H), 2.38 (dd, *J* = 13.4, 7.8 Hz, 1H), 1.80 – 1.68 (m, 3H), 1.63 – 1.56 (m, 1H), 1.51 – 1.41 (m, 1H), 1.14 (qt, *J* = 13.6, 3.7 Hz, 1H), 0.99 (tt, *J* = 11.9, 2.9 Hz, 1H), 0.92 – 0.85 (m, 1H), 0.82 (s, 9H), 0.80 – 0.72 (m, 1H), 0.67 (q, *J* = 11.9 Hz, 1H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 140.3, 131.1, 130.9, 119.3, 47.9, 43.9, 40.2, 34.4, 32.7, 32.5, 27.5, 27.2, 26.5. IR(cm^{-1}): 2922, 2853, 1487, 1467, 1447, 1403, 1393, 1365, 1240, 1202, 1113, 1097, 1072, 1012. HRMS (APCI) m/z: calcd for $C_{17}H_{25}{}^{79}Br$ (M) 308.1145; found 308.1138. $[\alpha]^{20}_D$: -7.1° (c=1.00, $CHCl_3$); m.p. 163-166 °C.

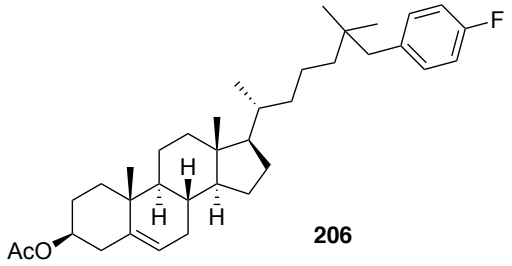


190

(((1*R*,3*R*)-3-(4-bromobenzyl)cyclohexyl)oxy)(*tert*-butyl)diphenylsilane 190: Following general procedure, target carboxylic acid **189** (27.6 mg, 0.05 mmol, 1.0 equiv) was decarboxylated to the product **190**. The product is isolated (100% pentane for column) as colorless oil 17.5 mg, 69% yield.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.62 (td, *J* = 7.9, 1.4 Hz, 4H), 7.40 (td, *J* = 7.5, 0.9 Hz, 2H), 7.36 – 7.28 (m, 6H), 6.89 (d, *J* = 8.4 Hz, 2H), 3.52 (tt, *J* = 10.7, 4.3 Hz, 1H), 2.41 (dd, *J* = 13.4, 7.1 Hz, 1H), 2.35 (dd, *J* = 13.4, 7.1 Hz, 1H), 1.83 (d, *J* = 12.4 Hz, 1H), 1.74 (d, *J* = 13.8 Hz, 1H), 1.62 (dp, *J* = 13.6, 3.4 Hz, 1H), 1.48 (d, *J* = 12.8 Hz, 1H), 1.34 – 1.21 (m, 2H), 1.03 (s, 9H), 1.02 – 0.96 (m, 2H), 0.78 (qd, *J* = 12.9, 3.7 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 139.7, 135.7, 135.7, 134.71, 134.70, 131.1,

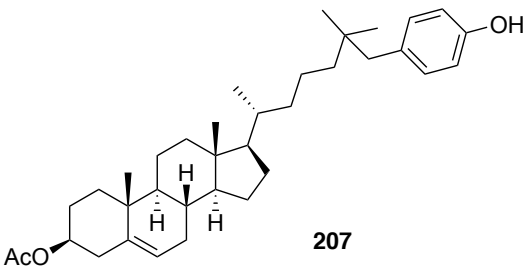
130.8, 129.4, 127.4, 119.4, 72.2, 42.9, 42.3, 38.3, 35.8, 31.8, 27.0, 23.9, 19.1. IR(cm^{-1}): 3070, 2928, 2855, 1487, 1472, 1462, 1448, 1427, 1373, 1262, 1189, 1104, 1074, 1049. HRMS (APCI) m/z: calcd for $C_{29}H_{54}O^{79}Br^{28}Si$ $(M-H)^-$ 505.1568; found 505.1573. $[\alpha]^{20}_D$: +23.6° (c=1.00, $CHCl_3$).



206

(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-17-((*R*)-7-(4-fluorophenyl)-6,6-dimethylheptan-2-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanth -ren-3-yl acetate 206: Following general procedure, target carboxylic acid **201** (29 mg, 0.05 mmol, 1.0 equiv) was decarboxylated to the product **206**. The product is isolated (2-3% ether in pentane for column) as white solid in 19 mg, 69% yield.

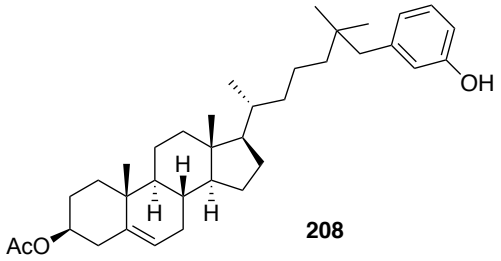
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.08 – 7.03 (m, 2H), 6.97 – 6.90 (m, 2H), 5.38 (d, *J* = 5.1 Hz, 1H), 4.65 – 4.56 (m, 1H), 2.46 (s, 2H), 2.34 – 2.27 (m, 2H), 2.03 (s, 3H), 2.03 – 1.94 (m, 2H), 1.88 – 1.79 (m, 3H), 1.61 – 1.05 (m, 17H), 1.02 (s, 3H), 1.02 – 0.95 (m, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.82 (6H, 2 CH_3 singlet, not a doublet, 0,824 ppm and 0.826 ppm), 0.68 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.5, 161.3 (d, *J* = 243.3 Hz), 139.6, 135.1 (d, *J* = 3.2 Hz), 131.7 (d, *J* = 7.7 Hz), 122.6, 114.3 (d, *J* = 20.9 Hz), 74.0, 56.7, 56.1, 50.0, 47.5, 42.5, 42.3, 39.7, 38.1, 37.0, 36.8, 36.6, 35.9, 34.2, 31.88, 31.85. IR(cm^{-1}):2937, 2867, 2850, 1733, 1606, 1508, 1469, 1439, 1374, 1365, 1241, 1223, 1158, 1033. HRMS (APCI) m/z: calcd for $C_{36}H_{57}O_2NF$ $(M+NH_4)^+$ 554.4368; found 554.4353. $[\alpha]^{20}_D$: -34.2° (c=1.00, $CHCl_3$). m.p. 119-121 °C



207

(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-17-((*R*)-7-(4-hydroxyphenyl)-6,6-dimethylheptan-2-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate 207: Following general procedure, target carboxylic acid **202** (31.0 mg, 0.05 mmol, 1.0 equiv) was decarboxylated to the product **207**. The product is isolated (20% ether in pentane) as white solid in 23.4 mg, 87% yield.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.97 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 8.5 Hz, 2H), 5.38 (d, *J* = 5.0 Hz, 1H), 4.78 (s, 1H), 4.65 – 4.56 (m, 1H), 2.42 (s, 2H), 2.37 – 2.27 (m, 2H), 2.03 (s, 3H), 2.04 – 1.93 (m, 5H), 1.88 – 1.79 (m, 3H), 1.62 – 1.04 (m, 17H), 1.02 (s, 3H), 1.01 – 0.94 (m, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.82 (6H, 2 CH_3 singlet, not a doublet, 0.817 ppm and 0.819 ppm), 0.68 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6, 153.5, 139.6, 131.7, 131.5, 122.6, 114.4, 74.0, 56.6, 56.1, 49.9, 47.4, 42.4, 42.3, 39.7, 38.0, 36.9, 36.8, 36.5, 35.8, 34.1, 31.81, 31.78, 28.2, 27.7, 26.74, 26.72, 24.2, 21.4, 21.0, 20.5, 19.2, 18.7, 11.8. IR(cm^{-1}): 3394(broad), 2935, 2867, 2850, 1732, 1711, 1615, 1596, 1514, 1469, 1442, 1375, 1365, 1270, 1172, 1035. HRMS (APCI) m/z: calcd for $C_{36}H_{55}O_3$ $(M-H)^-$ 535.4146; found 535.4130. $[\alpha]^{20}_D$: -30.6° (c=1.00, $CHCl_3$). m.p. 140-142 °C

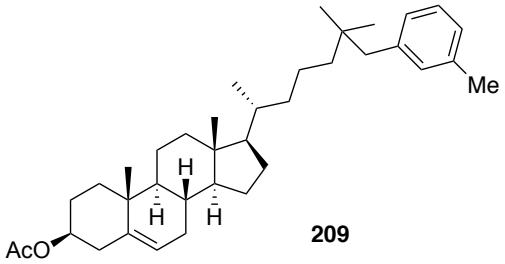


208

(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-17-((*R*)-7-(3-hydroxyphenyl)-6,6-dimethylheptan-2-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate 208: Following general procedure, target carboxylic acid **203** (18.6 mg, 0.03 mmol, 1.0 equiv) was decarboxylated to the product **208**. The product is isolated (20% ether in pentane) as white solid in 13.0 mg, 81% yield.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.12 (t, *J* = 7.8 Hz, 1H), 6.75 – 6.62 (m, 2H), 6.63 – 6.55 (m, 1H), 5.37 (d, *J* = 5.0 Hz, 1H), 4.75 (s, 1H), 4.65 – 4.57 (m, 1H), 2.45 (s, 2H), 2.35 – 2.27 (m, 2H), 2.03 (s, 3H), 2.03 – 1.94 (m, 2H), 1.89 – 1.79 (m, 3H), 1.64 – 1.58 (m, 1H), 1.55 – 1.04 (m, 17H), 1.02 (s, 3H), 1.01 – 0.94 (m, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.84 (6H, 2 CH_3 singlet, not a doublet, 0.844 ppm and

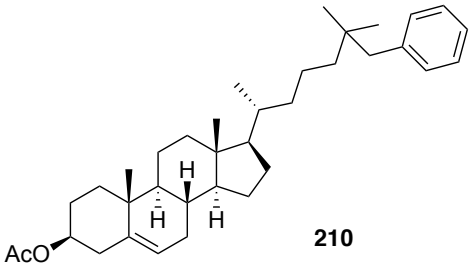
0.846 ppm), 0.68 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6, 154.9, 141.6, 139.7, 128.6, 123.2, 122.7, 117.5, 112.6, 74.0, 56.7, 56.2, 50.0, 48.3, 42.7, 42.3, 39.7, 38.1, 37.0, 36.9, 36.6, 35.9, 34.3, 31.90, 31.87, 28.3, 27.8, 27.0, 26.9, 24.3, 21.5, 21.0, 20.6, 19.3, 18.8, 11.9. IR(cm^{-1}): 3379(broad), 2936, 2867, 2849, 1733, 1707, 1598, 1587, 1488, 1457, 1375, 1365, 1269, 1243, 1158, 1034. HRMS (ESI) m/z: calcd for $C_{36}H_{55}O_3$ $(M+H)^+$ 535.4146; found 535.4144. $[\alpha]^{20}_D$: -31.0° (c=1.00, $CHCl_3$). m.p. 150-152 °C



209

(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-17-((*R*)-6,6-dimethyl-7-(*m*-tolyl)heptan-2-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate 209: Following general procedure, target carboxylic acid **204** (28.8 mg, 0.05 mmol, 1.0 equiv) was decarboxylated to the product **209**. The product is isolated (2-4% ether in pentane) as white solid in 19.7 mg, 74% yield.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.15 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.92 (m, 2H), 5.42 – 5.34 (m, 1H), 4.67 – 4.55 (m, 1H), 2.46 (s, 2H), 2.34 – 2.38 (m, 2H), 2.33 (s, 3H), 2.03 (s, 3H), 2.03 – 1.94 (m, 2H), 1.90 – 1.79 (m, 3H), 1.64 – 1.03 (m, 17H), 1.02 (s, 3H), 1.02 – 0.95 (m, 3H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.84 (6H, 2 CH_3 singlet, not a doublet, 0.842 ppm and 0.844 ppm), 0.69 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.5, 139.7, 139.5, 137.0, 131.4, 127.7, 127.4, 126.4, 122.7, 74.0, 56.7, 56.1, 50.1, 48.2, 42.6, 42.3, 39.7, 38.1, 37.0, 36.9, 36.6, 35.9, 34.2, 31.91, 31.88, 28.3, 27.8, 27.0, 24.3, 21.47, 21.45, 21.1, 20.6, 19.3, 18.8, 11.9 . IR(cm^{-1}): 2938, 2867, 2850, 1735, 1607, 1468, 1439, 1374, 1364, 1241, 1136, 1033, 959. HRMS (APCI) m/z: calcd for $C_{37}H_{60}O_2N$ $(M+NH_4)^+$ 550.4619; found 550.4619. $[\alpha]^{20}_D$: -33.0° (c=1.00, $CHCl_3$). m.p. 109-111 °C



210

(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-17-((*R*)-6,6-dimethyl-7-phenylheptan-2-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate 210: Following general procedure, target carboxylic acid **205** (28.1 mg, 0.05 mmol, 1.0 equiv) was decarboxylated to the product **210**. The product is isolated (23% ether in pentane) as white solid in 18.8 mg, 72% yield.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.26 – 7.23 (m, 2H), 7.21 – 7.17 (m, 1H), 7.13 – 7.10 (m, 2H), 5.38 (d, *J* = 5.0 Hz, 1H), 4.65 – 4.56 (m, 1H), 2.50 (s, 2H), 2.36 – 2.27 (m, 2H), 2.03 (s, 3H), 2.03 – 1.94 (m, 2H), 1.89 – 1.80 (m, 3H), 1.63 – 1.04 (m, 17H), 1.02 (s, 3H), 1.03 – 0.94 (m, 8H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.84 (6H, 2 CH_3 singlet, not a doublet, 0.842 ppm and 0.844 ppm), 0.68 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.5, 139.7, 130.6, 127.6, 125.6, 122.7, 74.0, 56.7, 56.2, 50.0, 48.4, 42.6, 42.3, 39.7, 38.1, 37.0, 36.9, 36.6, 35.9, 34.3, 31.91, 31.88, 28.3, 27.8, 26.91, 26.90, 24.3, 21.5, 21.0, 20.6, 19.3, 18.8, 11.9. IR(cm^{-1}): 2937, 2866, 2850, 1733, 1495, 1469, 1454, 1439, 1373, 1364, 1240, 1033, 979. HRMS (APCI) m/z: calcd for $C_{36}H_{58}O_2N$ $(M+NH_4)^+$ 536.4462; found 536.4461. $[\alpha]^{20}_D$: -30.7° (c=1.00, $CHCl_3$). m.p. 80-82 °C

References for 6.2.3

1. These early studies were performed by Dr. Wenbin Liu and are not published

2. Fu, J.; Ren, Z.; Bacsa, J.; Musaev, D. G.; Davies, H. M. L., *Nature* **2018**, *564*, 395-399.

3. Liao, K. B.; Negretti, S.; Musaev, D. G.; Bacsa, J.; Davies, H. M. L., *Nature* **2016**, *533*, 230-234.

4. Clayden, J., Menet, C. J., Tchabanenko, M. K., *Tetrahedron*, **2002**, *58*, 4727

5. Tellitu, I., Beitia, I., Diaz, M., Alonso, A., Moreno, I., Dominguez, E., *Tetrahedron*, **2015**, *43*, 8251

6. Liao, K.; Pickel, T. C.; Boyarskikh, V.; Bacsa, J.; Musaev, D. G.; Davies, H. M. L. *Nature*, **2017**, *551*, 609.

7. Liu, W.; Ren, Z.; Bosse, A. T.; Liao, K.; Goldstein, E. L.; Bacsa, J.; Musaev, D. G.; Stoltz, B. M.; Davies, H. M. L., *J. Am. Chem. Soc.* **2018**, *140*, 12247-12255.

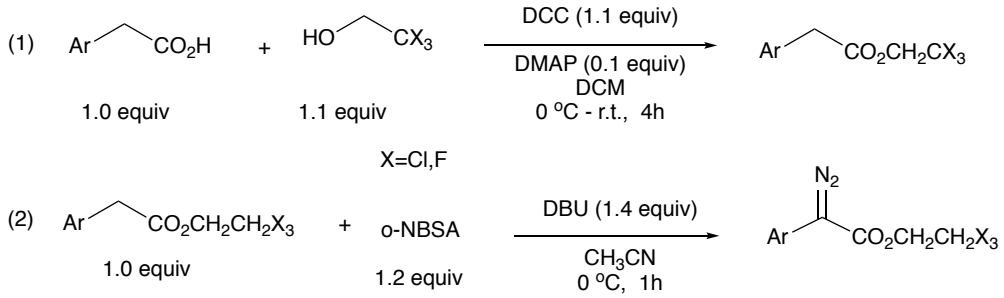
8. This insertion reaction is performed by Boni, Y. T. (the Davies group) and has not been published.

9. Fu, J. *Development and Applications of a New Dirhodium Tetracarboxylate Catalyst and Asymmetric Cyclopropanation of Heterocyclic Compound*; Emory University, GA., **2020**; (Supporting information).

6.3 Chapter 4 (Experimental procedures)

6.3.1 General procedure for diazo compounds synthesis

Diazo compound **155, I-XI** used in this work were pre-synthesized by group in storage following the general procedure below.

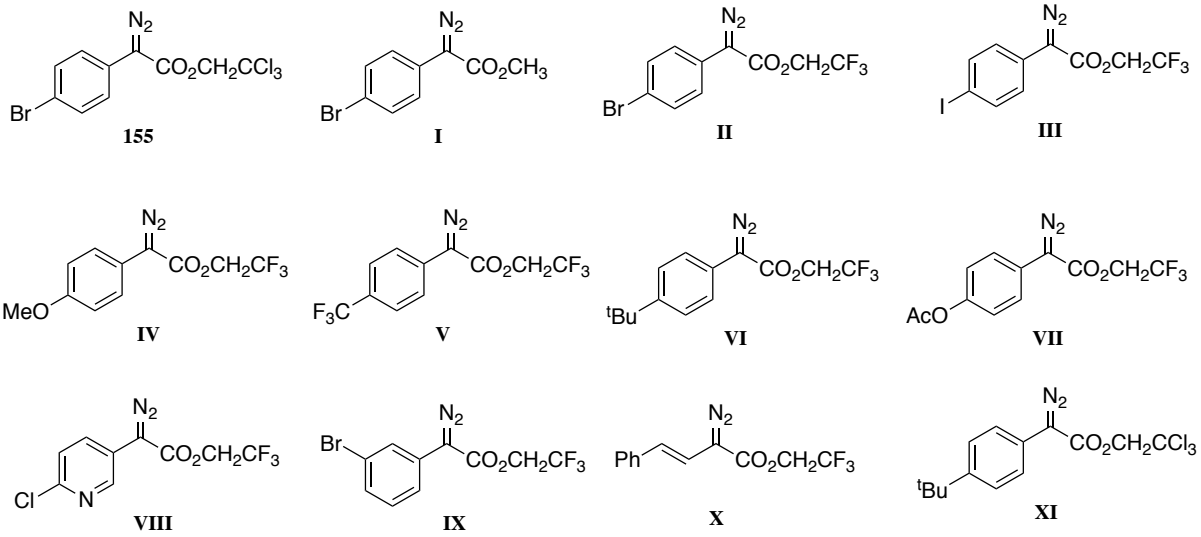


(1) Aryl acetic acid (1.0 equiv, 20 mmol) and 2,2,2-trihaloethanol (1.1 equiv, 22 mmol) were dissolved in 50 mL dichloromethane and stirred at 0 °C in ice/water bath. N,N'-Dicyclohexylcarbodiimide (DCC) (1.1 equiv. 22 mmol) was then added to the stirring solution carefully. Catalytic DMAP (0.1 equiv, 2.0 mmol) was then dissolved in 2 mL DCM and added to the solution. The white precipitation forms rapidly, and the solution become milk color. The reaction was kept running for 4 h and warm to r.t. naturally. Filter and concentrate the solution give the crude ester product. Purify the ester with a quick silica plug (5% Et_2O/Pentane) and then concentrate under vacuum, yielding the ester as colorless oil, which is directly used for the following diazo transfer step.

(2) Ester from step (1) (1.0 equiv, 10 mmol) and ortho-nitrobenzenesulfonyl azide (o-NBSA) (1.2 equiv, 12 mmol) were dissolved in 30 mL anhydrous CH_3CN. The solution was kept stirring at 0 °C and DBU (1.4 equiv, 14 mmol) was added dropwisely to the solution. The color of the solution gradually turned orange and it is quenched after 1 h by diluting with 100 mL Et_2O followed by adding 100mL NH_4Cl (sat.) solution. Extract the aqueous layer with Et_2O (30 mLx3), combined the organic layers and dry it over $MgSO_4$. Silica plug and concentrate give the crude diazo product as orange oil or solid. Further purification was done by flash column chromatography (2-5% Et_2O/Pentane)

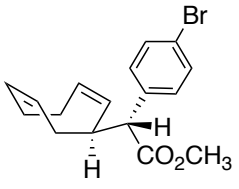
*For spectra information of these diazo compounds, refer to the references[1-3].

(below are all diazo compounds involved in this study)



6.3.2 General Procedure for mono-allylic-insertion

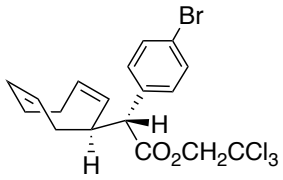
To a 16 mL glass reaction vial was added stir bar, 1,5-cyclooctadiene (COD) (0.75 mmol, 2.5 equiv, 81 mg/~0.1 mL) and Rh_2(*R*-2-Cl,5-BrTPCP)$_4$ (0.1 mol %). The vial was degassed and filled with Ar for several times. 2mL anhydrous DCM was then added to the vial and the solution was kept stirring at 0 °C for 5 min. Aryl diazo ester (0.3 mmol, 1.0 equiv) was dissolved in 4 mL DCM and added dropwisely to the vial over 3 h via syringe pump. The reaction was kept running for 2 h after the addition of diazo compound is finished. The solution was concentrated to give oil mixture and the crude ^{1}H NMR was obtained for dr analysis. Further purification was done by column chromatography (0.8-10% Et_2O in pentane depending on substrate), giving product as colorless oil.



227

(*R*)-methyl 2-(4-bromophenyl)-2-((*S*,2*Z*,6*Z*)-cycloocta-2,6-dien-1-yl)acetate 227: Derived from the reaction of diazo **I** (0.3 mmol, 77 mg) and COD (0.75 mmol, 81 mg) following general procedure, purified by column chromatography (2.5% Et_2O in pentane). Product: 74 mg, 73% yield; 72% ee.; 11.6:1 dr, colorless oil.

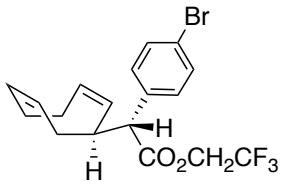
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (m, 2H), 7.22 (m, 2H), 5.57 (q, *J* = 4.5 Hz, 2H), 5.49 – 5.42 (m, 1H), 5.01 (dd, *J* = 11.6, 6.9 Hz, 1H), 3.67 (s, 3H), 3.51 – 3.44 (m, 1H), 3.39 (d, *J* = 10.5 Hz, 1H), 2.55 – 2.46 (m, 1H), 2.38 (dq, *J* = 13.7, 3.6, 2.7 Hz, 1H), 2.35 – 2.24 (m, 3H), 2.22 – 2.16 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.50, 136.55, 131.58, 130.46, 129.96, 129.35, 129.28, 127.23, 121.41, 57.48, 52.10, 42.16, 33.05, 27.91, 27.46. IR: 3010, 2949, 2885, 1732, 1488, 1433, 1340, 1266, 1153, 1073, 1011, 813, 763 (cm^{-1}); HRMS-(APCI) m/z: found at 335.0643 [$(M+H)^+$: $[C_{17}H_{20}O_2Br]^+$ calculates to be 335.0641]; $[\alpha]^{20}_D$: -35.1° (c=1.00, $CHCl_3$);



226

(R)-2,2,2-trichloroethyl 2-(4-bromophenyl)-2-((S,2Z,6Z)-cycloocta-2,6-dien-1-yl)acetate 226: Derived from the reaction of diazo **155** (0.2 mmol, 75 mg) and COD (0.5 mmol, 81 mg) following general procedure, purified by column chromatography (1-2% Et_2O in pentane). Product: 66 mg, 72% yield; 91% ee.; dr > 30:1, colorless oil. A large-scale reaction was also performed for this reaction. Diazo **I** (3.0 mmol, 1.12 g) and COD (6.0 mmol, 650 mg) was reacted to generate the product at yield: 1.08 g, 80% yield; 89% ee.; dr > 30:1, colorless oil.

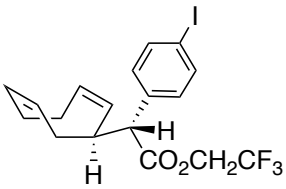
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.26 (m, 2H), 5.58 (q, *J* = 6.1, 5.7 Hz, 2H), 5.48 (dt, *J* = 13.0, 7.1 Hz, 1H), 5.03 (dd, *J* = 11.6, 6.7 Hz, 1H), 4.77 (d, *J* = 12.0 Hz, 1H, **H of CH_2 next to CCl_3**), 4.66 (d, *J* = 12.0 Hz, 1H, **H of CH_2 next to CCl_3**), 3.58 (td, *J* = 10.4, 5.4 Hz, 1H), 3.53 (d, *J* = 10.5 Hz, 1H), 2.57 – 2.44 (m, 2H), 2.38 – 2.26 (m, 3H), 2.24 – 2.16 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.3, 135.6, 131.7, 130.6, 129.7, 129.4, 127.0, 121.8, 94.7, 74.2, 57.4, 41.8, 33.1, 27.9, 27.5. IR: 3012, 2888, 1749, 1488, 1428, 1407, 1371, 1270, 1200, 1134, 1074, 1012, 824 (cm^{-1}); HRMS-(APCI) m/z: found at 450.9632 [$(M+H)^+$: $[C_{18}H_{19}O_2BrCl_3]^+$ calculates to be 450.9629]; $[\alpha]^{20}_D$: -24.8° (c=1.00, $CHCl_3$);



228

(R)-2,2,2-trifluoroethyl 2-(4-bromophenyl)-2-((S,2Z,6Z)-cycloocta-2,6-dien-1-yl)acetate 228: Derived from the reaction of diazo **II** (0.3 mmol, 97 mg) and COD (0.75 mmol, 81 mg) following general procedure, purified by column chromatography (0.8-1.5% Et_2O in pentane). Product: 100 mg, 83% yield; 93% ee.; dr > 30:1, colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 7.44 (m, 2H), 7.24 – 7.20 (m, 2H), 5.61 – 5.53 (m, 2H), 5.51 – 5.46 (m, 1H), 5.02 (dd, *J* = 11.6, 6.1 Hz, 1H), 4.56 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH_2 next to CF_3**), 4.35 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH_2 next to CF_3**), 3.53 – 3.46 (m, 2H), 2.49 (ddt, *J* = 17.9, 11.9, 5.7 Hz, 1H), 2.42 – 2.17 (m, 5H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.5, 135.5, 131.8, 130.4, 129.8, 129.5, 129.3, 126.8, 122.8 (q, J=277.8 Hz, **C of CF_3**), 121.8, 60.5 (q, J=36.7 Hz, **C of CH_2 next to CF_3**), 56.9, 42.2, 32.7, 28.0, 27.4. IR: 3014, 2889, 1751, 1488, 1407, 1280, 1164, 1131, 1071, 1036, 1011, 978, 812 (cm^{-1}); HRMS-(APCI) m/z: found at 401.0361 [$(M-H)^-$: $[C_{18}H_{17}O_2BrF_3]^-$ calculates to be 401.0359]; $[\alpha]^{20}_D$: -39.2° (c=1.00, $CHCl_3$);

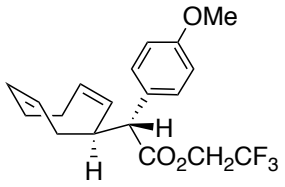


229

(R)-2,2,2-trifluoroethyl 2-((S,2Z,6Z)-cycloocta-2,6-dien-1-yl)-2-(4-iodophenyl)acetate 229: Derived from the reaction of diazo **III** (0.3 mmol, 111 mg) and COD (0.75 mmol, 81 mg) following general procedure, purified by column chromatography (2% Et_2O in pentane). Product: 117 mg, 78% yield; 95% ee.; dr > 30:1, colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 – 7.60 (m, 2H), 7.14 – 7.04 (m, 2H), 5.56 (tq, *J* = 11.6, 5.9 Hz, 2H), 5.52 – 5.44 (m, 1H), 5.02 (dd, *J* = 10.9, 5.5 Hz, 1H), 4.56 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH_2 next to CF_3**), 4.34 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH_2 next to CF_3**), 3.53 – 3.44 (m, 2H), 2.48 (ddt, *J* = 17.6,

11.9, 5.7 Hz, 1H), 2.42 – 2.16 (m, 5H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.5, 137.7, 136.1, 130.7, 129.8, 129.5, 129.3, 126.8, 122.8 (q, J=277.8 Hz, **C of CF_3**), 93.5, 60.5 (q, J=36.7 Hz, **C of CH_2 next to CF_3**), 57.0, 42.1, 32.7, 28.0, 27.4. IR: 3013, 2887, 1750, 1485, 1404, 1279, 1164, 1129, 1062, 1006, 977, 810, 758 (cm^{-1}); HRMS-(APCI) m/z: found at 451.0379 $[(M+H)^+ : [C_{18}H_{19}O_2F_3I]^+$ calculates to be 451.0376]; $[\alpha]^{20}_D$: -36.5° (c=1.00, $CHCl_3$);

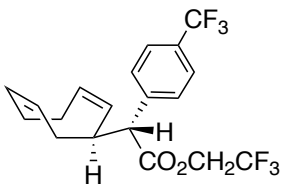


230

(R)-2,2,2-trifluoroethyl 2-((S,2Z,6Z)-cycloocta-2,6-dien-1-yl)-2-(4-methoxyphenyl)acetate 230: Derived from the reaction of diazo **IV** (0.3 mmol, 82 mg) and COD (0.75 mmol, 81 mg) following general procedure, purified by column chromatography (2-4% Et_2O in pentane). Product: 77 mg, 72% yield; 81% ee.; dr > 30:1, colorless oil.

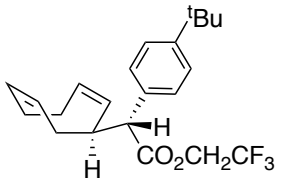
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (m, 2H), 6.88 – 6.82 (m, 2H), 5.61 – 5.53 (m, 2H), 5.51 – 5.43 (m, 1H), 5.06 (dd, *J* = 11.6, 6.3 Hz, 1H), 4.56 (dq, *J* = 12.7, 8.5 Hz, 1H, **H of CH_2 next to CF_3**), 4.33 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH_2 next to CF_3**), 3.79 (s, 3H), 3.55 – 3.45 (m, 2H), 2.51 (ddt, *J* = 17.2, 11.6, 5.8 Hz, 1H), 2.40 (dt, *J* = 15.1, 3.9 Hz, 1H), 2.36 – 2.24 (m, 3H), 2.20 (dq, *J* = 16.8, 4.8 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.1, 159.1, 129.9, 129.8, 129.4, 129.3, 128.5, 127.1, 122.9 (q, J=277.4 Hz, **C of CF_3**), 114.0, 60.3 (q, J=36.6 Hz, **C of CH_2 next to CF_3**), 56.7, 55.2, 42.1, 32.8, 28.0, 27.4. IR: 3012, 2891, 1750, 1610, 1511, 1465, 1407, 1283,1249, 1163, 1128, 1034, 978 (cm^{-1});

HRMS-(APCI) m/z: found at 355.1517 $[(M+H)^+ : [C_{19}H_{22}O_3F_3]^+$ calculates to be 355.1516]; $[\alpha]^{20}_D$: -34.5° (c=1.00, $CHCl_3$);



231

(R)-2,2,2-trifluoroethyl 2-((S,2Z,6Z)-cycloocta-2,6-dien-1-yl)-2-(4-(trifluoromethyl)phenyl) acetate 231: Derived from the reaction of diazo **V** (0.3 mmol, 94 mg) and COD (0.75 mmol 81 mg) following general procedure, purified by column chromatography (1-2% Et_2O in pentane). Product: 91 mg, 78% yield; 94% ee.; dr > 30:1, white solid. (Single Crystal structure obtained for this compound); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 5.63 – 5.53 (m, 2H), 5.49 (dddd, *J* = 11.6, 7.6, 5.9, 1.1 Hz, 1H), 5.01 (dd, *J* = 11.7, 6.8 Hz, 1H), 4.57 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH_2 next to CF_3 in ester**), 4.36 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH_2 next to CF_3 in ester**), 3.62 (d, *J* = 10.3 Hz, 1H), 3.54 (tt, *J* = 10.6, 5.5 Hz, 1H), 2.49 (ddt, *J* = 16.6, 11.8, 5.4 Hz, 1H), 2.43 – 2.18 (m, 5H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.3, 140.4, 130.0 (q, J=32.5 Hz, **C on Ar ring next to CF_3**), 130.1, 129.6, 129.2, 129.1, 126.7, 125.5 (q, J=3.7 Hz, **C on Ar ring next to the 130.02 C**), 124.0 (q, J=272.3 Hz, **C of CF_3 on the Ar ring**), 122.8 (q, J=277.7 Hz, **C of CF_3 in the ester**), 60.6 (q, J=36.7 Hz, **C of CH_2 next to CF_3 in ester**), 57.3, 42.3, 32.7, 28.0, 27.3. IR: 3017, 2893, 1755, 1619, 1422, 1326, 1286, 1166, 1130, 1069, 1020, 980, 838 (cm^{-1}); HRMS-(APCI) m/z: found at 393.1284 [$(M+H)^+$: $[C_{19}H_{19}O_2F_6]^+$ calculates to be 393.1284]; $[\alpha]^{20}_D$: -43.5° (c=1.00, $CHCl_3$); m.p. 58-60 °C

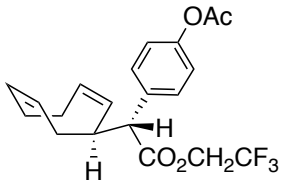


232

(R)-2,2,2-trifluoroethyl 2-(4-(tert-butyl)phenyl)-2-((S,2Z,6Z)-cycloocta-2,6-dien-1-yl)acetate 232: Derived from the reaction of diazo **VI** (0.3 mmol, 90 mg) and COD (0.75 mmol, 81 mg) following general procedure, purified by column chromatography (0.8-1.5% Et_2O in pentane). Product: 98 mg, 85% yield; 88% ee.; dr > 30:1, colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 2H), 7.27 – 7.23 (m, 2H), 5.63 – 5.52 (m, 2H), 5.51 – 5.43 (m, 1H), 5.08 (dd, *J* = 11.0, 5.5 Hz, 1H), 4.58 (dq, *J* = 12.7, 8.5 Hz, 1H, **H of CH_2 next to CF_3**), 4.30 (dq, *J* = 12.9, 8.5 Hz, 1H, **H of CH_2 next to CF_3**), 3.55 – 3.48 (m, 2H), 2.50 (ddt, *J* = 16.8, 11.2, 5.3 Hz, 1H), 2.45 – 2.17 (m, 5H), 1.30 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 150.5, 133.2, 129.9, 129.4, 129.2, 128.3, 127.1, 125.5, 122.9 (q, J=277.5 Hz, **C of CF_3**), 77.0, 60.3 (q, J=37.1 Hz, **C**

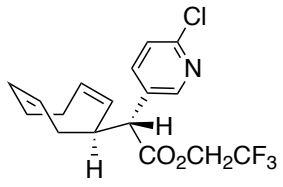
of CH_2 next to CF_3), 57.0, 42.10, 34.5, 32.5, 31.3, 28.0, 27.3. IR: 3014, 2964, 2890, 1753, 1508, 1408, 1365, 1283, 1166, 1131, 1062, 979, 841 (cm^{-1}); HRMS-(APCI) m/z: found at 381.2037 $[(M+H)^+$: $[C_{22}H_{28}O_2F_3]^+$ calculates to be 381.2036]; $[\alpha]^{20}_D$: -33.2° (c=1.00, $CHCl_3$);



233

(R)-2,2,2-trifluoroethyl 2-(4-acetoxyphenyl)-2-((S,2Z,6Z)-cycloocta-2,6-dien-1-yl)acetate 233: Derived from the reaction of diazo **VII** (0.2 mmol, 60 mg) and COD (0.5 mmol, 54 mg) following general procedure, purified by column chromatography (6-10% Et_2O in pentane). Product: 53 mg, 70% yield; 79% ee.; dr > 30:1, colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 2H), 7.09 – 7.02 (m, 2H), 5.62 – 5.52 (m, 2H), 5.48 (dddd, *J* = 11.7, 7.7, 6.0, 1.1 Hz, 1H), 5.05 (dd, *J* = 11.6, 6.5 Hz, 1H), 4.58 (dq, *J* = 12.7, 8.4 Hz, 1H), 4.33 (dq, *J* = 12.7, 8.4 Hz, 1H), 3.54 (d, *J* = 10.4 Hz, 1H), 3.49 (m, 1H), 2.49 (ddt, *J* = 17.9, 11.9, 5.8 Hz, 1H), 2.43 – 2.24 (m, 7H, 2.29 (s, **3H for Me in OAc**)), 2.24 – 2.17 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.7, 169.3, 150.2, 133.9, 129.8, 129.6, 129.5, 129.5, 126.9, 122.9 (q, J=277.4 Hz, **C of CF_3**), 121.6, 60.4 (q, J=36.6 Hz, **C of CH_2 next to CF_3**), 56.9, 42.3, 32.6, 28.0, 27.3, 21.2. IR: 3014, 2891, 1752, 1507, 1408, 1370, 1283, 1198, 1166, 1132, 1018, 978, 912 (cm^{-1}); HRMS-(APCI) m/z: found at 383.1465 $[(M+H)^+$: $[C_{20}H_{22}O_4F_3]^+$ calculates to be 383.1465]; $[\alpha]^{20}_D$: -32.4° (c=1.00, $CHCl_3$);

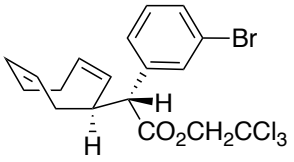


234

(R)-2,2,2-trifluoroethyl 2-((S,2Z,6Z)-cycloocta-2,6-dien-1-yl)-2-(6-(trifluoromethyl)pyridin-3-yl)acetate 234: Derived from the reaction of diazo **VIII** (0.3 mmol, 84 mg) and COD (0.75 mmol, 81

mg) following general procedure, purified by column chromatography (5-8% Et_2O in pentane). Product: 78 mg, 72% yield; 87% ee.; dr > 30:1, colorless oil.

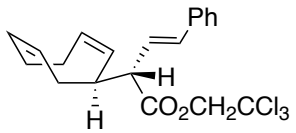
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 (d, *J* = 2.4 Hz, 1H), 7.71 (dd, *J* = 8.3, 2.5 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 1H), 5.62 – 5.50 (m, 3H), 5.03 (dd, *J* = 11.6, 6.9 Hz, 1H), 4.58 (dq, *J* = 12.7, 8.3 Hz, 1H, **H of CH_2 next to CF_3**), 4.40 (dq, *J* = 12.7, 8.3 Hz, 1H, **H of CH_2 next to CF_3**), 3.58 (d, *J* = 9.8 Hz, 1H), 3.48 (p, *J* = 7.9 Hz, 1H), 2.44 (td, *J* = 13.6, 11.5, 8.5 Hz, 1H), 2.37 – 2.32 (m, 2H), 2.32 – 2.18 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.9, 151.0, 150.0, 138.8, 131.1, 130.8, 129.7, 128.4, 126.4, 124.2, 122.7 (q, J=278.6 Hz, **C of CF_3**), 60.7 (q, J=36.8 Hz, **C of CH_2 next to CF_3**), 54.0, 42.4, 32.7, 27.9, 27.2. IR: 3014, 2891, 1752, 1584, 1565, 1462, 1410, 1391, 1278, 1166, 1138, 1107, 1023, 978 (cm^{-1}); HRMS-(APCI) m/z: found at 360.0971 $[(M+H)^+ : [C_{17}H_{18}O_2NClF_3]^+$ calculates to be 360.0973]; $[\alpha]^{20}_D$: -33.4° (c=1.00, $CHCl_3$);



235

2,2,2-trichloroethyl (R)-2-(3-bromophenyl)-2-((S,2Z,6Z)-cycloocta-2,6-dien-1-yl)acetate 235: Derived from the reaction of diazo **IX** (0.3 mmol, 97 mg) and COD (0.75 mmol, 81 mg) following general procedure, purified by column chromatography (6-10% Et_2O in pentane). Product: 78 mg, 64% yield; 63% ee.; dr > 30:1, colorless oil.

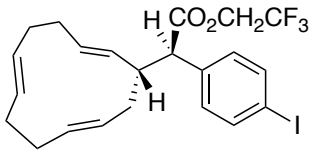
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.50 (t, *J* = 1.8 Hz, 1H), 7.42 (ddd, *J* = 7.9, 2.0, 1.1 Hz, 1H), 7.28 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 5.63 – 5.53 (m, 2H), 5.53 – 5.47 (m, 1H), 5.04 (dd, *J* = 11.6, 6.3 Hz, 1H), 4.59 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH_2 next to CF_3**), 4.35 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH_2 next to CF_3**), 3.54 – 3.42 (m, 2H), 2.48 (ddt, *J* = 17.5, 11.8, 5.6 Hz, 1H), 2.43 – 2.17 (m, 5H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.4, 138.6, 131.8, 130.9, 130.1, 129.9, 129.6, 129.2, 127.4, 126.7, 122.8 (q, *J* =277.3 Hz, **C of CF_3**),122.6, 60.5 (q, *J* =36.7 Hz, **C of CH_2 next to CF_3**), 57.0, 42.3, 32.5, 28.0, 27.3. IR: 3014,2890, 1754, 1593, 1570, 1475, 1429, 1408, 1282, 1169, 1136, 1075, 997, 979 (cm^{-1}); HRMS-(APCI) m/z: found at 403.0510 $[(M+H)^+ : [C_{18}H_{19}O_2F_3Br]^+$ calculates to be 403.0515]; $[\alpha]^{20}_D$: -39.9° (c=1.00, $CHCl_3$);



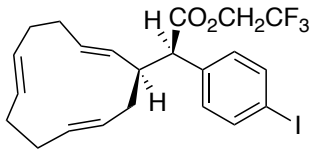
236

bis(2,2,2-trichloroethyl) 2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)(2S,2'S,3E,3'E)-bis(4-phenylbut-3-enoate) 236: Derived from the reaction of diazo **X** (0.2 mmol, 67 mg) and COD (0.5 mmol, 54 mg) following general procedure, purified by column chromatography (6-10% Et_2O in pentane). Product: 53 mg, 67% yield; 88% ee.; dr > 30:1, colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.37 (m, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.26 – 7.23 (m, 1H), 6.55 (d, *J* = 15.8 Hz, 1H), 6.25 (dd, *J* = 15.8, 9.5 Hz, 1H), 5.67 – 5.61 (m, 1H), 5.61 – 5.54 (m, 2H), 5.42 (dd, *J* = 11.6, 6.8 Hz, 1H), 4.83 (d, *J* = 12.0 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 3.35 (td, *J* = 11.8, 7.1 Hz, 1H), 3.28 – 3.21 (m, 1H), 2.44 (dtt, *J* = 16.8, 7.5, 4.4 Hz, 3H), 2.36 – 2.26 (m, 2H), 2.22 (dt, *J* = 15.4, 3.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.6, 136.6, 134.2, 129.9, 129.4, 129.2, 128.6, 127.8, 127.1, 126.5, 124.9, 94.9, 74.1, 55.3, 41.5, 32.8, 27.9, 27.5. IR: 3011, 2952, 2888, 1747, 1496, 1449, 1428, 1373, 1257, 1196, 1133, 966, 802 (cm^{-1}); HRMS-(APCI) m/z: found at 399.0682 [$(M+H)^+$: $[C_{20}H_{22}O_2Cl_3I]^+$ calculates to be 399.0680]; $[\alpha]^{20}_D$: -39.9° (c=1.00, $CHCl_3$);



246 (major)



246 (minor)

(R)-2,2,2-trifluoroethyl 2-((R,2E,6E,10E)-cyclododeca-2,6,10-trien-1-yl)-2-(4-iodophenyl)acetate 246 (major) & (R)-2,2,2-trifluoroethyl 2-((S,2E,6E,10E)-cyclododeca-2,6,10-trien-1-yl)-2-(4-iodophenyl)acetate 186 (minor): Derived from the reaction of diazo **V** (0.3 mmol, 111 mg) and Triene **245** (0.75 mmol, 122 mg) following general procedure, purified by column chromatography (2% Et_2O in pentane). Product: 118 mg (combined for **246 (major)** and **246 (minor)**), 78% yield; dr =1:0.86 [**186 (major):246 (minor)]**; 92% ee. for **246 (major)**, 96% ee. for **246 (minor)**; white solid. The 2

diastereomers were fully separated and characterized using prep HPLC. (Single crystal structure obtained for **246 (major)**.)

246(major):

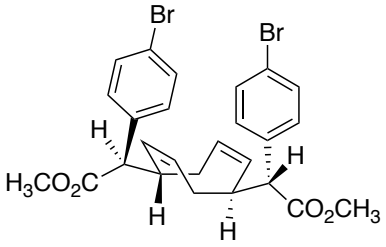
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 – 7.58 (m, 2H), 7.03 – 6.98 (m, 2H), 5.08 – 4.91 (m, 4H), 4.88 (ddd, *J* = 14.7, 10.6, 3.9 Hz, 1H), 4.59 (ddd, *J* = 15.0, 9.9, 1.4 Hz, 1H), 4.52 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH_2 next to CF_3**), 4.35 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH_2 next to CF_3**), 3.47 (d, *J* = 9.8 Hz, 1H), 2.72 (qd, *J* = 10.0, 2.7 Hz, 1H), 2.25 – 2.17 (m, 3H), 2.18 – 2.12 (m, 1H), 2.05 – 2.00 (m, 1H), 1.90 – 1.82 (m, 2H), 1.82 – 1.74 (m, 2H), 1.67 (tdd, *J* = 13.2, 10.8, 2.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.5, 137.4, 136.2, 134.1, 132.3, 131.3, 130.9, 130.7, 129.6, 122.8 (q, J=277.5 Hz, **C of CF_3**), 93.1, 65.9, 60.4 (q, J=36.6 Hz, **C of CH_2 next to CF_3**), 56.2, 46.8, 37.3, 32.2, 32.14, 32.12, 31.9, 29.7, 15.3. IR: 2971, 2929, 2913, 2847, 1748, 1485, 1445, 1433, 1410, 1347, 1277, 1146, 1132, 1007, 981 (cm^{-1}); HRMS-(APCI) m/z: found at 505.0846 $[(M+H)^+ : [C_{22}H_{25}O_2F_3I]^+$ calculates to be 505.0846]; $[\alpha]^{20}_D$: -175.5° (c=1.00, $CHCl_3$); m.p. 126-131°C

246 (minor):

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 – 7.63 (m, 2H), 7.16 – 7.09 (m, 2H), 5.17 (ddd, *J* = 14.3, 10.0, 3.9 Hz, 1H), 5.05 – 4.94 (m, 3H), 4.93 – 4.84 (m, 2H), 4.44 (dq, *J* = 12.7, 8.5 Hz, 1H, **H of CH_2 next to CF_3**), 4.27 (dq, *J* = 12.7, 8.4 Hz, 1H, **H of CH_2 next to CF_3**), 3.41 (d, *J* = 10.8 Hz, 1H), 2.63 (qd, *J* = 11.1, 3.0 Hz, 1H), 2.26 – 2.12 (m, 4H), 1.92 – 1.78 (m, 5H), 1.57 – 1.48 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.1, 137.8, 136.0, 133.6, 132.4, 131.8, 131.4, 131.2, 130.61, 130.60, 129.4, 122.9 (q, J=277.4 Hz, **C of CF_3**), 93.4, 65.9, 60.4 (q, J=36.6 Hz, **C of CH_2 next to CF_3**), 56.7, 47.2, 35.8, 32.22, 32.19, 32.1, 31.2, 29.7, 15.3; IR: 2912, 2844, 1753, 1485, 1436, 1404, 1279, 1168, 1128, 1063, 1007, 978, 958 (cm^{-1}); HRMS-(APCI) m/z: found at 505.0846 $[(M+H)^+ : [C_{22}H_{25}O_2F_3I]^+$ calculates to be 505.0846]; $[\alpha]^{20}_D$: +103.2° (c=1.00, $CHCl_3$); m.p. 85-87°C

6.3.3 General Procedure for bis-allylic-insertion

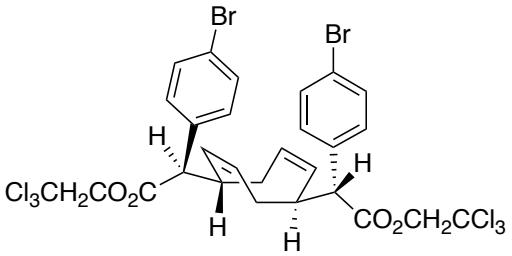
To a 16 ml glass reaction vial was added stir bar, 1,5-cyclooctadiene (COD) (0.3 mmol, 1.0 equiv, 32 mg) and Rh_2(2-Cl,5-BrTPCP)$_4$ (0.1 mol%). The vial was degassed and filled with Ar several times. 2mL anhydrous DCM was then added to the vial and the solution was kept stirring at 40 °C for 5min. Aryl diazo ester (0.9 mmol, 3.0 equiv) was dissolved in 4ml DCM and added dropwisely to the vial over 3 h via syringe pump. The reaction was kept running for 2 h after the addition of diazo compound is finished. The solution was concentrated to give oil crude, ^{1}HNMR was obtained for dr analysis. Further purification was done by column chromatography (2-4% Et_2O in pentane) or 5% $AgNO_3$ on silica column chromatography (4-10% Et_2O in pentane), giving product as sticky oil or white solid.



237

dimethyl 2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)(2R,2'R)-bis(2-(4-bromophenyl)acetate) 237: Derived from the reaction of diazo **I** (0.9 mmol, 230 mg, 3.0 equiv) and COD (0.3 mmol, 32 mg, 1.0 equiv) following general procedure, major dr purified by normal column chromatography (6-8% Et_2O in pentane). Product: 141 mg, 84% yield; >99% ee.; dr = 6.5:1, white foam solid.

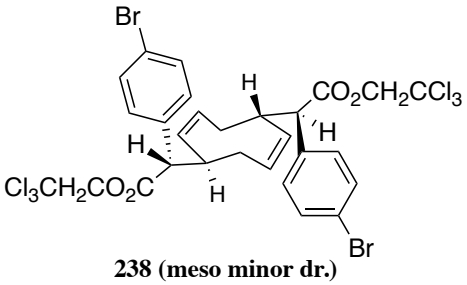
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.5 Hz, 4H), 7.20 (d, *J* = 8.5 Hz, 4H), 5.44 (ddd, *J* = 11.6, 7.9, 6.0 Hz, 2H), 5.04 (dd, *J* = 11.6, 6.6 Hz, 2H), 3.67 (s, 6H), 3.41-3.35 (m, 2H), 3.37 (d, *J* = 2.8 Hz, 2H), 2.28 – 2.11 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.3, 136.2, 131.6, 130.4, 130.4, 128.4, 121.5, 57.4, 52.2, 42.0, 32.7. IR: 2950, 1734, 1590, 1488, 1434, 1407, 1339, 1264, 1156, 1073, 1011, 908, 819 (cm^{-1}); HRMS-(APCI) m/z: found at 561.0275 $[(M+H)^+$: $[C_{26}H_{27}O_4Br_2]^+$ calculates to be 561.0271]; $[\alpha]^{20}_D$: -55.8° (c=1.00, $CHCl_3$); m.p. 66-70 °C



238

(2R,2'R)-bis(2,2,2-trichloroethyl) 2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-bromophenyl)acetate) 238: Derived from the reaction of diazo **155** (0.9 mmol, 335 mg, 3.0 equiv) and COD (0.3 mmol, 32 mg, 1.0 equiv) following general procedure, major dr purified by normal column chromatography (2% Et_2O in pentane). Product: 152 mg, 55% yield; >99% ee.; dr = 3.2:1, white foam solid. A larger scale of reaction at COD (0.8 mmol, 86 mg) and diazo**113** (2.4 mmol, 3.0 equiv 893 mg) was performed, given 340 mg product, 53% yield , >99% ee. dr = 3.2:1.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 – 7.41 (m, 4H), 7.26 – 7.23 (m, 4H), 5.51 – 5.41 (m, 2H), 5.04 (dd, *J* = 11.3, 7.9 Hz, 2H), 4.76 (d, *J* = 12.0 Hz, 2H, **H of CH_2 next to CCl_3**), 4.68 (d, *J* = 12.0 Hz, 2H, **H of CH_2 next to CCl_3**), 3.67 (qd, *J* = 10.1, 8.0, 5.4 Hz, 2H), 3.47 (d, *J* = 10.2 Hz, 2H), 2.47 – 2.36 (m, 2H), 2.14 (ddd, *J* = 15.9, 12.5, 8.0 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.8, 135.2, 131.8, 130.6, 130.0, 128.6, 121.9, 94.7, 74.3, 57.7, 41.1, 33.4. IR: 2924, 1750, 1489, 1408, 1371, 1262, 1216, 1136, 1074, 1012, 826, 762, 719 (cm^{-1}); HRMS-(APCI) m/z: found at 792.8262 $[(M+H)^+ : [C_{28}H_{25}O_4Br_2Cl_6]^+$ calculates to be 792.8245]; $[\alpha]^{20}_D$: +21.8° (c=1.00, $CHCl_3$); m.p. 48-52 °C

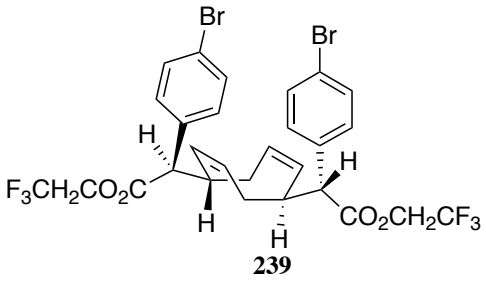


238 (meso minor dr.)

(2R,2'S)-bis(2,2,2-trichloroethyl) 2,2'-((1R,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-bromophenyl)acetate) 238 (meso minor dr): Originally isolated from the reaction that give **238 (major)**. Clean preparation of **238 (minor)** is derived from mono insertion product **226** (0.4 mmol, 181 mg, 1.0 equiv) and diazo **155** (0.8 mmol, 298 mg, 2.0 equiv) following general procedure using the

different enantiomer of catalyst. Purify this meso product with column chromatography (2% Et_2O in pentane). Product: 168 mg, 53% yield, white foam solid.

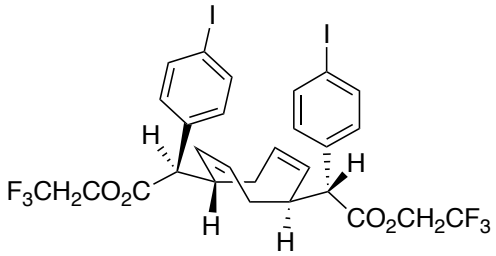
^1H NMR (600 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 4H), 7.26 – 7.22 (m, 4H), 5.57 (dtd, *J* = 10.7, 8.8, 1.8 Hz, 2H), 5.15 (dd, *J* = 11.7, 4.3 Hz, 2H), 4.79 (d, *J* = 12.0 Hz, 2H), 4.63 (d, *J* = 12.0 Hz, 2H), 3.62 (d, *J* = 10.8 Hz, 2H), 3.24 – 3.15 (m, 2H), 2.53 (ddd, *J* = 13.9, 9.1, 4.7 Hz, 2H), 2.46 – 2.35 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.1, 135.3, 131.8, 130.9, 130.6, 127.3, 122.0, 94.6, 74.2, 56.0, 43.2, 30.2. IR: 2952, 2874, 1748, 1488, 1447, 1408, 1371, 1331, 1269, 1206, 1130, 1074, 1011 (cm^{-1}); HRMS-(APCI) m/z: found at 792.8262 $[(M+H)^+ : [C_{28}H_{25}O_4Br_2Cl_6]^+$ calculates to be 792.8245]; m.p. 50-55 °C



239

(2R,2'R)-bis(2,2,2-trifluoroethyl) 2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-bromophenyl)acetate) 239: Derived from the reaction of diazo **II** (0.9 mmol, 290 mg, 3.0 equiv) and COD (0.3 mmol, 32 mg, 1.0 equiv) following general procedure, major dr purified by $AgNO_3$ column chromatography (4-8% Et_2O in pentane). Product: 160 mg, 76 % yield; >99% ee.; dr = 6.5:1, sticky oil to half solid.

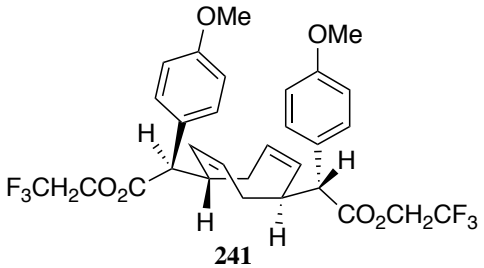
^1H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.42 (m, 4H), 7.24 – 7.14 (m, 4H), 5.46 (ddd, *J* = 12.6, 7.9, 5.3 Hz, 2H), 5.04 (dd, *J* = 11.5, 7.3 Hz, 2H), 4.50 (ddd, *J* = 13.1, 8.7, 4.5 Hz, 2H, **H of CH_2 next to CF_3**), 4.44 (ddd, *J* = 12.7, 8.7, 4.5 Hz, 2H, **H of CH_2 next to CF_3**), 3.58 – 3.47 (m, 3H), 3.46 (d, *J* = 10.0 Hz, 2H), 2.25 (dt, *J* = 15.4, 4.6 Hz, 2H), 2.14 (ddd, *J* = 15.5, 12.0, 8.2 Hz, 2H). ^{13}C NMR (126 MHz, $cdcl_3$) δ 171.0, 135.0, 131.8, 130.4, 129.8, 128.5, 122.8 (q, J=277.7 Hz, **C of CF_3**), 122.0, 60.5 (q, J=36.6 Hz, **C of CH_2 next to CF_3**), 57.0, 41.6, 32.7. IR: 3017, 1753, 1489, 1408, 1282, 1168, 1138, 1074, 1012, 978, 817, 760, 644 (cm^{-1}); HRMS-(APCI) m/z: found at 694.9880 $[(M-H)^- : [C_{28}H_{23}O_4Br_2F_6]^+$ calculates to be 694.9873]; $[\alpha]^{20}_D$: -10.2° (c=1.00, $CHCl_3$);



240

(2R,2'R)-bis(2,2,2-trifluoroethyl) 2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-iodophenyl)acetate) 240: Derived from the reaction of diazo **III** (0.9 mmol, 333 mg, 3.0 equiv) and COD (0.3 mmol, 32 mg, 1.0 equiv) following general procedure, major dr purified by $AgNO_3$ column chromatography (4-8% Et_2O in pentane). Product: 156 mg, 66 % yield; >99% ee.; dr = 6.8:1, white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 – 7.64 (m, 4H), 7.08 – 7.05 (m, 4H), 5.46 (ddd, *J* = 12.4, 7.8, 5.4 Hz, 2H), 5.04 (dd, *J* = 11.5, 7.4 Hz, 2H), 4.50 (dq, *J* = 12.7, 8.4 Hz, 2H, **H of CH_2 next to CF_3**), 4.43 (dq, *J* = 12.7, 8.4 Hz, 2H, **H of CH_2 next to CF_3**), 3.55 – 3.47 (m, 2H), 3.44 (d, *J* = 10.0 Hz, 2H), 2.24 (dt, *J* = 15.3, 4.7 Hz, 2H), 2.14 (ddd, *J* = 15.6, 12.3, 8.2 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.0, 137.8, 135.7, 130.6, 129.8, 128.6, 122.8 (q, J=277.7 Hz, **C of CF_3**), 93.6, 60.6 (q, J=36.7 Hz, **C of CH_2 next to CF_3**), 57.1, 41.6, 32.7. IR: 3017, 1752, 1485, 1405, 1281, 1168, 1138, 1063, 1007, 978, 815, 757, 644 (cm^{-1}); HRMS-(APCI) m/z: found at 792.9745 $[(M+H)^+$: $[C_{28}H_{25}O_4F_6I_2]^+$ calculates to be 792.9741]; $[\alpha]^{20}_D$: -7.1° (c=1.00, $CHCl_3$); m.p. 113-116 °C;

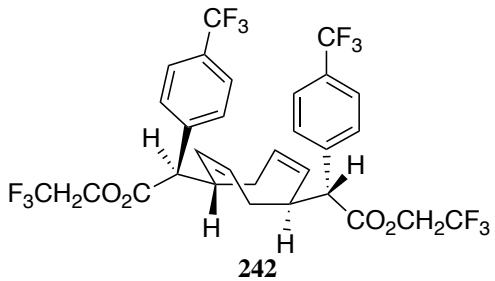


241

(2R,2'R)-bis(2,2,2-trifluoroethyl) 2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-methoxyphenyl)acetate) 241: Derived from the reaction of diazo **IV** (0.9 mmol, 247 mg, 3.0 equiv) and COD (0.3 mmol, 32 mg, 1.0 equiv) following general procedure, major dr purified by $AgNO_3$

column chromatography (4-8% Et_2O in pentane). Product: 96 mg, 53% yield; >99% ee.; dr = 4.2:1, white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 – 7.23 (m, 4H), 6.90 – 6.83 (m, 4H), 5.45 (ddd, *J* = 12.1, 7.7, 5.1 Hz, 2H), 5.05 (dd, *J* = 11.5, 7.6 Hz, 2H), 4.49 (dq, *J* = 12.7, 8.4 Hz, 2H, **H of CH_2 next to CF_3**), 4.42 (dq, *J* = 12.7, 8.4 Hz, 2H, **H of CH_2 next to CF_3**), 3.80 (s, 6H), 3.63 – 3.52 (m, 2H), 3.44 (d, *J* = 10.3 Hz, 2H), 2.31 (dt, *J* = 15.4, 4.5 Hz, 2H), 2.19 (ddd, *J* = 15.7, 12.3, 8.1 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.8, 159.2, 130.3, 129.7, 128.2, 122.9 (q, J=277.7 Hz, **C of CF_3**), 114.1, 60.4 (q, J=36.6 Hz, **C of CH_2 next to CF_3**), 56.9, 55.2, 41.6, 32.9. IR: 2962, 2839, 1750, 1610, 1511, 1464, 1408, 1283, 1249, 1164, 1133, 1034, 977 (cm^{-1}); HRMS-(APCI) m/z: found at 601.2021 [$(M+H)^+$: $[C_{30}H_{31}O_6F_6]^+$ calculates to be 601.2029]; $[\alpha]^{20}_D$: -17.2° (c=1.00, $CHCl_3$); m.p. 89-93 °C

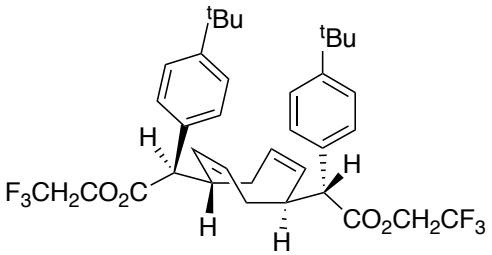


242

(2R,2'R)-bis(2,2,2-trifluoroethyl) 2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-(trifluoromethyl)phenyl)acetate) 242: Derived from the reaction of diazo **V** (0.9 mmol, 281 mg, 3.0 equiv) and COD (0.3 mmol, 32 mg, 1.0 equiv) following general procedure, major dr purified by $AgNO_3$ column chromatography (3-6% Et_2O in pentane). Product: 123 mg, 61 % yield; >99 % ee.; dr = 7.9:1, white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.1 Hz, 4H), 7.45 (d, *J* = 8.1 Hz, 4H), 5.49 (ddd, *J* = 11.7, 8.0, 5.5 Hz, 2H), 5.06 (dd, *J* = 11.5, 7.0 Hz, 2H), 4.52 (dq, *J* = 12.7, 8.4 Hz, 2H, **H of CH_2 next to CF_3**), 4.44 (dq, *J* = 12.7, 8.4 Hz, 2H, **H of CH_2 next to CF_3**), 3.59 (d, *J* = 9.7 Hz, 2H), 3.58 – 3.50 (m, 3H), 2.25 (dt, *J* = 14.4, 4.3 Hz, 2H), 2.16 (ddd, *J* = 15.1, 11.6, 8.4 Hz, 2H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 170.8, 139.8, 130.1 (q, J=32.5 Hz, **C on Ar ring next to CF_3**), 129.6, 129.1, 128.7, 125.6 (q, J=3.6 Hz, **C on Ar ring next to the 130.13 C**), 124.0 (q, J=272.3 Hz, **C of CF_3 on the Ar ring**), 122.7 (q, J=277.4 Hz, **C of CF_3 in the ester**), 60.6 (q, J=36.7 Hz, **C of CH_2 next to CF_3 in ester**), 57.2, 41.8, 32.5. IR:

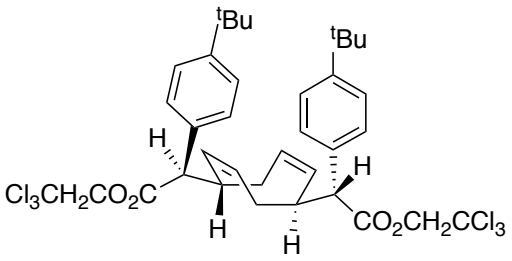
3021, 1754, 1619, 1422, 1325, 1285, 1163, 1127, 1069, 1020, 979, 827, 723 (cm^{-1}); HRMS-(APCI) m/z: found at 677.1551 [$(M+H)^+$: $[C_{30}H_{25}O_4F_{12}]^+$ calculates to be 677.1556]; $[\alpha]^{20}_D$: -35.8° (c=1.00, $CHCl_3$); m.p. 96-101 °C



243

(2R,2'R)-bis(2,2,2-trifluoroethyl) 2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-(tert-butyl)phenyl)acetate) 243: Derived from the reaction of diazo **VI** (0.9 mmol, 270 mg, 3.0 equiv) and COD (0.3 mmol, 32 mg, 1.0 equiv) following general procedure, major dr purified by $AgNO_3$ column chromatography (2-6% Et_2O in pentane). Product: 150 mg, 76 % yield; >99 % ee.; dr = 6.8:1, sticky oil to half solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 4H), 7.25 – 7.22 (m, 4H), 5.45 (ddd, *J* = 12.6, 7.6, 5.7 Hz, 2H), 5.07 (dd, *J* = 11.6, 7.2 Hz, 2H), 4.51 (dq, *J* = 12.7, 8.4 Hz, 2H, **H of CH_2 next to CF_3**), 4.37 (dq, *J* = 12.7, 8.4 Hz, 2H, **H of CH_2 next to CF_3**), 3.53 (m, 2H), 3.48 (d, *J* = 10.2 Hz, 2H), 2.33 – 2.19 (m, 4H), 1.30 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 150.6, 132.9, 130.4, 128.2, 128.1, 125.5, 122.9 (q, J=277.6 Hz, **C of CF_3**), 60.4 (q, J=36.5 Hz, **C of CH_2 next to CF_3**), 57.2, 41.6, 34.5, 32.6. IR: 2965, 1753, 1509, 1408, 1365, 1283, 1167, 1134, 1065, 1019, 978, 842, 823 (cm^{-1}); HRMS-(APCI) m/z: found at 653.3066 [$(M+H)^+$: $[C_{36}H_{43}O_4F_6]^+$ calculates to be 653.3060]; $[\alpha]^{20}_D$: -31.0° (c=1.00, $CHCl_3$);

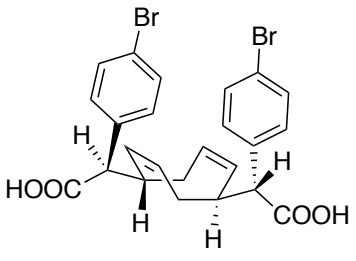


244

(2R,2'R)-bis(2,2,2-trichloroethyl) 2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-(tert-butyl)phenyl)acetate) 244: Derived from the reaction of diazo **XI** (0.9 mmol, 315 mg, 3.0 equiv) and COD (0.3 mmol, 32 mg, 1.0 equiv) following general procedure, major dr purified by normal column chromatography (4-8% Et_2O in pentane). Product: 231 mg, 72 % yield; >99 % ee.; dr = 4.5:1, white foam solid. (Single crystal structure obtained for the reduction product of this compound.)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 9H), 5.46 (ddd, *J* = 11.9, 7.2, 4.9 Hz, 2H), 5.08 (dd, *J* = 11.6, 7.5 Hz, 2H), 4.73 (d, *J* = 12.0 Hz, 3H, **H of CH_2 next to CCl_3**), 4.69 (d, *J* = 12.0 Hz, 3H, **H of CH_2 next to CCl_3**), 3.78 – 3.68 (m, 2H), 3.50 (d, *J* = 10.5 Hz, 2H), 2.52 – 2.44 (m, 2H), 2.22 (ddd, *J* = 15.8, 12.2, 7.9 Hz, 2H), 1.31 (s, 18H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.6, 150.6, 133.2, 130.5, 128.5, 128.1, 125.5, 94.8, 74.3, 58.0, 41.0, 34.5, 33.4, 31.3. IR: 2963, 1749, 1516, 1461, 1366, 1269, 1200, 1131, 1058, 915, 827, 771, 721 (cm^{-1}); HRMS-(APCI) m/z: found at 749.1296 $[(M+H)^+$: $[C_{36}H_{43}O_4Cl_6]^+$ calculates to be 749.1287]; $[\alpha]^{20}_D$: +10.2° (c=1.00, $CHCl_3$); m.p. 72-77 °C

6.3.4 Derivatization for Bis-insertion C2 symmetric chiral COD ligand

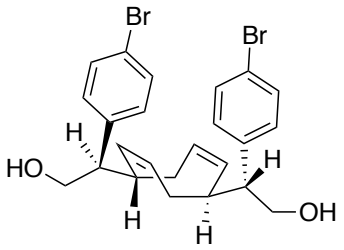


250

(2R,2'R)-2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-bromophenyl)acetic acid) 250: Bis-insertion compound **238** (0.053 mmol, 41.9 mg, 1.0 equiv) was dissolved in 1 mL AcOH. Zn powder (34.4 mg, 10 equiv) was added to the solution, and the suspension was kept stirring overnight.

Crude material was obtained by filtration and concentration under reduced pressure. Further column chromatography (50% Et_2O in pentane with 0.5% AcOH) gave pure product as white powder 17.2 mg, 61% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.3 Hz, 4H), 7.23 (d, *J* = 8.6 Hz, 4H), 5.58 – 5.37 (m, 2H), 5.18 – 4.99 (m, 2H), 3.44 (d, *J* = 9.5 Hz, 2H), 3.40 – 3.25 (m, 2H), 2.49 – 2.31 (m, 2H), 2.32 – 2.21 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 178.9, 135.5, 131.8, 130.5, 130.3, 128.5, 121.8, 57.0, 42.2, 31.9, 20.6. IR: 2921, 2851, 1725, 1488, 1409, 1263, 1098, 1012, 800, 730 (cm^{-1}); HRMS-(APCI) m/z: found at 530.9817 [$(M-H)^-$: $[C_{24}H_{21}O_4Br_2]^-$ calculates to be 530.9812]; $[\alpha]^{20}_D$: -14.0° (c=1.00, acetone); m.p. > 200 °C

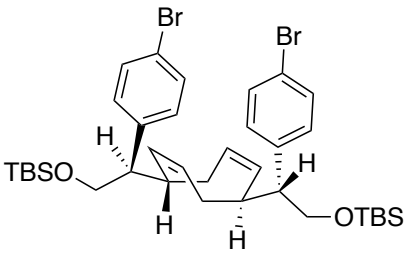


251

(2R,2'R)-2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-bromophenyl)ethan-1-ol) 251: Bis-insertion compound **238** (0.065 mmol, 51.9 mg, 1.0 equiv) was dissolved in 1 mL anhydrous THF, and the solution was cooled to -78 °C. $LiAlH_4$ (1.0 M THF solution) (0.18 mL, 2.5 equiv) was slowly added to the stirring solution. The reaction was kept running for 2 h at -78 °C, then raised to r.t. for 15 min and quenched with 1mL sodium potassium tartrate solution(saturated) and 1.0 mL HCl(1.0 M). The organic phase was extracted with Et_2O multiple times, combined and dried over $MgSO_4$. Crude material was obtained through filtration and concentration under reduced pressure. Further column chromatography (60% Et_2O in pentane) gave pure product 27.5 mg as white powder, 84% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.5 Hz, 4H), 6.94 (d, *J* = 8.4 Hz, 4H), 5.54 (ddd, *J* = 11.4, 9.0, 7.4 Hz, 2H), 5.32 (dd, *J* = 11.4, 6.3 Hz, 2H), 3.83 (dq, *J* = 7.5, 4.1, 3.5 Hz, 4H), 2.73 (dp, *J* = 11.8, 5.7 Hz, 4H), 1.72 (ddd, *J* = 12.2, 7.1, 4.9 Hz, 2H), 1.64 (dt, *J* = 13.2, 6.8 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.4, 131.2, 130.7, 129.52, 129.48, 120.7, 64.4, 53.0, 41.1, 31.6. IR: 3342 (broad OH), 3006, 2930, 2874, 1488, 1408, 1105, 1073, 1027, 1007, 819, 754 (cm^{-1}); HRMS-(APCI) m/z: found at

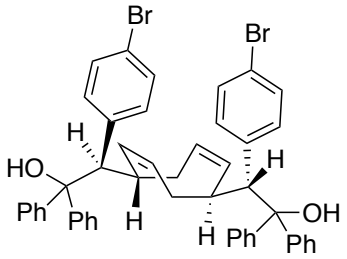
505.0376 [$(M+H)^+$: $[C_{24}H_{27}O_2Br_2]^+$ calculates to be 505.0372]; $[\alpha]^{20}_D$: -129.2° (c=1.00, $CHCl_3$); m.p. 69-73 °C



252

(1Z,3S,5Z,7S)-3,7-bis((R)-1-(4-bromophenyl)-2-((tert-butyldimethylsilyl)oxy)ethyl)cycloocta-1,5-diene 252: The di-ol starting material **251** (0.063 mmol, 31.7 mg, 1.0 equiv) was dissolved in 1 mL DCM, and the solution was cooled to 0 °C. Imidazole (0.158 mmol, 10.8 mg, 2.5 equiv) and TBSCl (0.139 mmol, 21.0 mg, 2.2 equiv.) was added to the solution, and the solution was kept stirring overnight. Crude material was obtained by filtration and concentration under reduced pressure. Further column chromatography (100% pentane) gave pure product as white solid. 42.0 mg, 90% yield.

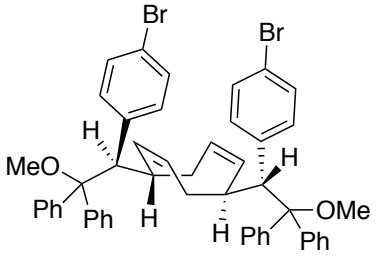
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.4 Hz, 4H), 6.92 (d, *J* = 8.4 Hz, 4H), 5.54 (ddd, *J* = 11.3, 8.7, 7.0 Hz, 2H), 5.32 (dd, *J* = 11.4, 7.1 Hz, 2H), 3.76 (dd, *J* = 10.0, 7.2 Hz, 2H), 3.70 (dd, *J* = 10.0, 6.0 Hz, 2H), 2.93 (dq, *J* = 12.6, 6.2 Hz, 2H), 2.59 (q, *J* = 6.4 Hz, 2H), 1.79 (dt, *J* = 12.2, 6.0 Hz, 2H), 1.61 (td, *J* = 14.0, 9.2 Hz, 2H), 0.84 (s, 18H), -0.03 (s, 6H), -0.04 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 139.8, 130.7, 130.7, 129.9, 129.5, 120.1, 64.5, 53.0, 40.0, 32.1, 25.9, 18.2, 0.0, -5.5. IR: 3008, 2953, 2928, 2885, 2856, 1488, 1471, 1408, 1361, 1254, 1097, 1074, 1010 (cm^{-1}); HRMS-(APCI) m/z: found at 733.2095 [$(M+H)^+$: $[C_{36}H_{55}O_2Br_2Si_2]^+$ calculates to be 733.2102]; $[\alpha]^{20}_D$: -109.0° (c=1.00, $CHCl_3$); m.p. 67-69 °C



253

(2R,2'R)-2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-bromophenyl)-1,1-diphenylethan-1-ol) 253: The bis-insertion compound **226** (0.756 mmol, 380 mg, 1.0 equiv) was dissolved in 4 mL anhydrous THF. The solution was kept stirring under Ar at -78 °C. PhLi (1.9 M purchased from Sigma Aldrich) in THF 2.6 mL was slowly added to the stirring solution over 30 min. The reaction was maintained at -78 °C for 3 h. After that, the solution was diluted with 4 mL Et_2O and quenched with HCl (1.0 M). The organic layer was extracted 3 times with Et_2O (1 mL), combined and dried over $MgSO_4$. Flash cotton pipette (a layer of silica) plug and concentration under reduced pressure gave crude sticky oil. Flash column chromatography (15% Et_2O/pentane) for the crude to remove nonpolar impurity and gave greenish yellow solid. Pure product was further obtained through recrystallization with ether/pentane system (40 °C cool to 0 °C) as white solid, 275mg, 50% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 8.4, 1.1 Hz, 4H), 7.33 (t, *J* = 7.8 Hz, 4H), 7.24 – 7.19 (m, 6H), 7.18 – 7.14 (m, 4H), 7.11 – 6.99 (m, 8H), 6.93 (t, *J* = 7.3 Hz, 2H), 5.48 (dd, *J* = 11.3, 7.2 Hz, 2H), 5.45 – 5.36 (m, 2H), 3.58 (d, *J* = 3.3 Hz, 2H), 2.67 (s, 2H), 2.66 – 2.54 (m, 2H), 1.46 – 1.32 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 146.7, 146.1, 136.9, 133.1, 130.2, 130.0, 129.8, 128.5, 127.8, 126.8, 126.1, 125.4, 125.1, 120.3, 81.4, 58.2, 40.2, 33.3. IR: 3586(Broad), 3057, 3021, 2974, 2868, 1597, 1488, 1447, 1157, 1112, 1075, 1068, 1010 (cm^{-1}); HRMS-(ESI) m/z: found at 843.1261 [$(M+Cl)^-$: $[C_{48}H_{42}O_2Br_2Cl]^-$ calculates to be 843.1246]; $[\alpha]^{20}_D$: -94.3° (c=1.00, $CHCl_3$); m.p. > 200 °C

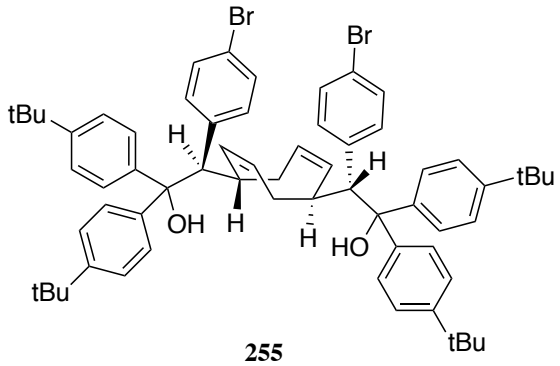


254

(1Z,3S,5Z,7S)-3,7-bis((R)-1-(4-bromophenyl)-2-methoxy-2,2-diphenylethyl)cycloocta-1,5-diene 254: The di-ol starting material **253** (59.7 mg, 0.074 mmol, 1 equiv) was dissolved in 1.5 mL anhydrous DCM. NaH (17.8 mg, 60% wt in mineral oil, 0.74 mmol, 10 equiv) was added into the solution, and the suspension was kept stirring at 0 °C. CH_3I (52.5 mg, 0.37 mmol, 5 equiv) was then added to the solution. The reaction was let warm up to r.t. naturally and run overnight. After that, the reaction was

quenched with NH_4Cl(saturated) and extracted with Et_2O multiple times. The organic layer was combined and dried over $MgSO_4$. Crude material was obtained through filtration and concentration under reduced pressure. Further column chromatography (5% ether in pentane)gave pure product as white solid 50.8 mg, 82% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (s, 10H), 7.24 (d, *J* = 8.6 Hz, 4H), 7.22 – 7.11 (m, 10H), 6.80 (d, *J* = 7.8 Hz, 4H), 5.09 – 4.97 (m, *J* = 7.9 Hz, 4H), 3.32 (d, *J* = 4.1 Hz, 2H), 2.78 (s, 6H), 2.64 – 2.44 (m, 2H), 1.37 – 1.29 (m, 2H), 1.18 (td, *J* = 13.8, 7.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.3, 138.0, 133.9, 130.7, 129.6, 129.0, 128.0, 127.5, 127.38, 127.35, 127.2, 120.1, 87.3, 60.8, 52.5, 40.5, 34.1, 29.7. IR: 3021, 2929, 2826, 1488,1446, 1407, 1193, 1074, 1010, 828, 756, 729, 702 (cm^{-1}); HRMS-(APCI) m/z: found at 871.1572 $[(M+Cl)^-$: $[C_{50}H_{46}O_2Br_2Cl]^-$ calculates to be 871.1559]; $[\alpha]^{20}_D$: -75.7° (c=1.00, $CHCl_3$); m.p. 91-96 °C

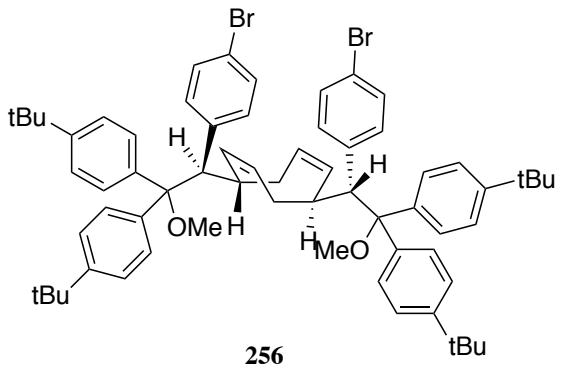


255

(2R,2'R)-2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-bromophenyl)-1,1-bis(4-(tert-butyl)phenyl)ethan-1-ol) 255: The bis-insertion compound **226** (0.1 mmol, 56.0 mg, 1.0 equiv) was dissolved in 1 mL anhydrous THF, and the solution was cooled to -78 °C**.** ^{t}BuPhLi solution (prepared from Li and 4-^{t}BuPhBr, 0.94 M) (0.6 mL, 5.5 equiv) was added to the stirring solution, and the reaction was let run for 2 h at -78 °C. After that, the reaction was quenched with NH_4Cl (saturated) 1 mL , HCl (1.0 M) 1 mL and extracted with Et_2O multiple times. The organic phase was combined, dried over $MgSO_4$, filtered and concentrated to obtain crude material. Further column purification (5-8% Et_2O in pentane) gave pure product as white powder 43.5 mg, 42% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.6 Hz, 4H), 7.32 (d, *J* = 8.5 Hz, 4H), 7.16 (d, *J* = 8.7 Hz, 4H), 7.11 (d, *J* = 8.8 Hz, 4H), 7.03 (d, *J* = 8.8 Hz, 8H), 5.52 (dd, *J* = 11.3, 7.2 Hz, 2H), 5.46 – 5.35 (m,

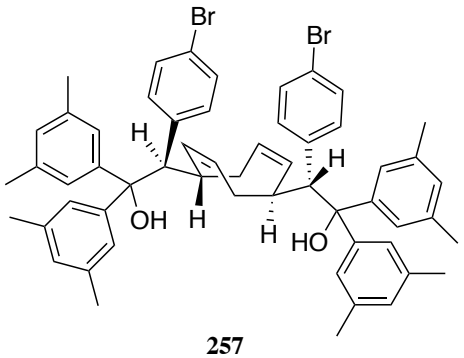
2H), 3.51 (d, J = 3.3 Hz, 2H), 2.67 (s, 2H), 2.56-2.60 (m, 2H), 1.36 – 1.31 (m, 4H), 1.30 (s, 18H), 1.15 (s, 18H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.2, 148.6, 143.6, 143.3, 137.3, 133.1, 130.1, 129.7, 125.3, 125.1, 124.8, 124.6, 120.1, 81.2, 58.5, 40.3, 34.4, 34.1, 33.2, 31.4, 31.2. IR: 3580, 2962, 2867, 1509, 1487, 1404, 1363, 1269, 1109, 1076, 1010, 909, 839 (cm^{-1}); HRMS-(APCI) m/z: found at 1050.4424 [$(M+NH_4)^+$: $[C_{64}H_{78}O_2NBr_2]^+$ calculates to be 1050.4394]; $[\alpha]^{20}_D$: -98.5° (c=1.00, $CHCl_3$); m.p. > 200 °C



256

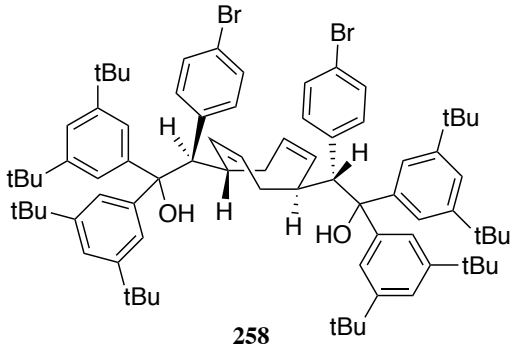
(1Z,3S,5Z,7S)-3,7-bis((R)-1-(4-bromophenyl)-2,2-bis(4-(tert-butyl)phenyl)-2-methoxyethyl)cycloocta-1,5-diene 256: The di-ol starting material **255** (37.9 mg, 0.037 mmol, 1 equiv) was dissolved in 1.5 mL anhydrous DCM. NaH (15 mg, 60% wt in mineral oil, 0.37 mmol, 10 equiv) was added into the solution, and the reaction was kept stirring at 0 °C. CH_3I (20.8 mg, 0.148 mmol, 4 equiv) was then added to the solution and the reaction was let warm up to r.t. overnight. After that, the reaction was quenched with NH_4Cl(saturated) 1 mL and extracted with Et_2O multiple times. The organic layer was combined and dried over $MgSO_4$, filtered and concentrated to yield crude material. Further column chromatography purification gave pure product 33.2 mg, 90% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (d, J = 8.7 Hz, 4H), 7.24 (dd, J = 8.8, 1.8 Hz, 9H), 7.09 (d, J = 8.8 Hz, 4H), 6.95 (d, J = 8.7 Hz, 8H), 5.12 (qd, J = 11.6, 7.0 Hz, 4H), 3.15 (d, J = 2.4 Hz, 2H), 2.82 (s, 6H), 2.29 – 2.19 (m, 2H), 1.30 (s, 18H), 1.24 (s, 18H), 1.11 – 0.95 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.9, 149.6, 139.5, 138.4, 138.0, 134.2, 130.4, 129.7, 129.6, 128.4, 128.2, 124.4, 123.9, 120.0, 87.7, 60.9, 52.9, 41.2, 34.4, 34.3, 33.1, 31.4, 31.3. IR: 2962, 2903, 2868, 1508, 1486, 1403, 1363, 1271, 1110, 1083, 1011, 966, 833 (cm^{-1}); HRMS-(APCI) m/z: found at 1083.4276 [$(M+Na)^+$: $[C_{66}H_{78}O_2Br_2Na]^+$ calculates to be 1083.4261]; $[\alpha]^{20}_D$: -132.7° (c=1.00, $CHCl_3$); m.p. 159-163 °C



257

(2R,2'R)-2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-bromophenyl)-1,1-bis(3,5-dimethylphenyl)ethan-1-ol) 257: Bis-insertion ester **226** (0.1 mmol, 56.0 mg, 1.0 equiv.) was dissolved in 1 mL anhydrous THF, and the solution was cooled to -78 °C. 3,5-diMePhLi solution (prepared from Li and 3,5-di-Methyl-4-Br-benzene, 0.73 M) (0.75 mL, 5.5 equiv.) was slowly added to the stirring solution, and the reaction was let run for 2 h at -78 °C. After that, the reaction was quenched with NH_4Cl (saturated) 1 mL, HCl (1.0 M) 1mL and extracted with Et_2O multiple times. The organic phase was combined, dried over $MgSO_4$, and concentrated to give crude material. Further column purification (2-5% Et_2O in pentane) gave pure product as white solid 52.1 mg, 56% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.7 Hz, 4H), 7.13 (s, 4H), 7.11 – 6.98 (m, 4H), 6.82 (d, *J* = 7.7 Hz, 6H), 6.56 (s, 2H), 5.51 (dd, *J* = 11.4, 7.1 Hz, 2H), 5.44 – 5.33 (m, 2H), 3.51 (d, *J* = 3.2 Hz, 2H), 2.54 – 2.49 (m, 2H), 2.50 (s, 2H), 2.29 (s, 12H), 2.10 (s, 12H), 1.38 – 1.27 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 146.8, 146.2, 137.7, 137.4, 136.9, 133.1, 130.1, 130.0, 129.7, 128.3, 127.7, 123.4, 122.8, 120.1, 81.3, 58.4, 40.4, 33.4, 21.7, 21.5. IR: 3586, 2007, 2916, 1597, 1487, 1408, 1376, 1216, 1157, 1111, 1075, 1010, 843 (cm^{-1}); HRMS-(APCI) m/z: found at 920.2830 [(M) : [$C_{56}H_{58}O_2Br_2$] calculates to be 920.2809]; $[\alpha]^{20}_D$: -121.0° (c=1.00, $CHCl_3$); m.p. 140-144 °C



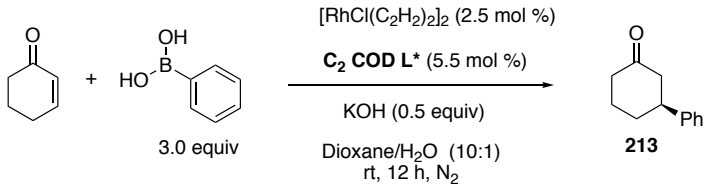
258

(2R,2'R)-2,2'-((1S,2Z,5S,6Z)-cycloocta-2,6-diene-1,5-diyl)bis(2-(4-bromophenyl)-1,1-bis(3,5-di-tert-butylphenyl)ethan-1-ol) 258: Bis-insertion ester **177** (0.1 mmol, 56.0 mg, 1.0 equiv.) was dissolved in 1 mL anhydrous THF, and the solution was cooled to -78 °C. 3,5-ditBuPhLi solution (prepared from Li and 3,5-di-tBu-4-Br-benzene, 1.1 M) (0.5 mL, 5.5 equiv.) was slowly added to the stirring solution, and the reaction was let run for 4 h at -78 °C. After that, the reaction was quenched with NH_4Cl (saturated) 1 mL, HCl (1.0 M) 1mL. The organic phase was extracted with Et_2O multiple times, combined, dried over $MgSO_4$, and concentrated to give crude material. Further column purification (0-2% Et_2O in pentane) gave pure product as white solid 55.3 mg, 44% yield.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, *J* = 1.7 Hz, 4H), 7.25 (t, *J* = 1.7 Hz, 2H), 7.11 (d, *J* = 8.7 Hz, 4H), 6.96 (dd, *J* = 13.7, 1.7 Hz, 10H), 5.46 (dd, *J* = 11.4, 6.7 Hz, 2H), 5.43 – 5.37 (m, 2H), 3.36 (d, *J* = 3.2 Hz, 2H), 2.60 – 2.53 (m, 2H), 2.55 (s, 2H), 1.44 – 1.32 (m, 4H), 1.30 (s, 36H), 1.09 (s, 36H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.2, 149.4, 145.0, 144.9, 137.3, 133.2, 130.2, 129.8, 129.6, 120.3, 120.23, 120.20, 120.0, 119.78 82.3, 60.1, 40.8, 35.0, 34.7, 33.5, 31.6, 31.3. IR: 3609, 2962, 2904, 2866, 1598, 1487, 1477, 1393, 1362, 1248, 1109, 1076, 1011, 879 (cm^{-1}); HRMS-(APCI) m/z: found at 1279.6415 [$(M+Na)^+$: $[C_{80}H_{106}O_2Br_2Na]^+$ calculates to be 1279.6452] $[\alpha]^{20}_D$: -35.8° (c=1.00, $CHCl_3$); m.p. 128-131 °C

6.3.5 General Procedure for conjugate addition test (Arylation of cyclohex-2-enone)

To an oven dried 4 mL vial with a stir bar was weighed di-μ-chlorotetraethylene dirhodium (0.025 equiv) and cyclooctadiene derived ligand (0.055 equiv). The vial was wrapped with Teflon™ thread tape, fitted with a septum cap and the atmosphere was exchanged for a dry N_2 atmosphere (3 cycles, 1 minute per cycle). Dry, nitrogen sparged 1,4-dioxane (1.8 mL) was then added to the vial and placed on a preheated hotplate at 50 °C to stir for 20 minutes under N_2. Aqueous potassium hydroxide (0.18 mL, 56.1 mg/mL, 0.50 equiv, sparged with N_2) was added to the reaction vial via syringe and allowed to stir for an additional 10 minutes at temperature. The vial was opened for addition of solid phenylboronic acid (3 equiv), then quickly resealed and the headspace was purged under positive pressure with addition of a vent needle for 1 minute. To the vial was added cyclohex-2-enone (0.2

mmol, 1 equiv) via syringe and the vial was fitted with a N_2 balloon and allowed to stir at temperature for 12 hours. The reaction was removed from heat, allowed to cool, and diluted with diethyl ether and passed through a silica plug. The combined organics were dried over sodium sulfate and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography on silica gel in a gradient of Hexanes: EtOAc (97:3 → 90:10) to afford the pure 3-phenylcyclohexan-1-one.



Ligand	**177**	**178**	**179**	**180**	**181**	**182**	**183**	**190**	**191**	**192**	**193**	**194**	**195**	**196**	**197**	**198**
yield	67	84	81	~2	68	60	45	43	61	78	58	32	69	81	63	**63**
ee.	39	34	36	45	30	33	22	27	26	53	47	60	69	59	41	**76**

References

1. Liu, W.; Ren, Z.; Bosse, A. T.; Goldstein, E. L.; Bacsa, J.; Musaev, D. G.; Stolz, B. M.; Davies, H. M. L. *J. Am. Chem. Soc.* **2018**, *140*, 12247

2. Fu, L.; Mighion, J. D.; Voight, E. A.; Davies, H. M. L. *Chem. Eur. J.* **2017***, 23,* 1

3. Guptill, D. M.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014,** *136*, 17718.

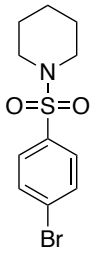
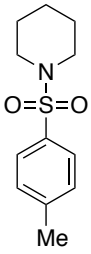
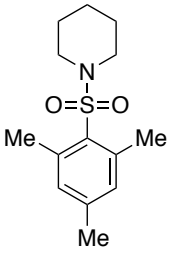
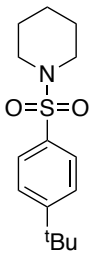
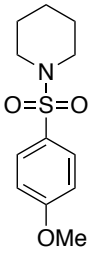
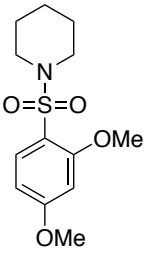
4. Liao, K.; Yang, Y.-F.; Li, Y.; Sanders, J. N.; Houk, K. N.; Musaev, D. G.; Davies, H. M. L. *Nature Chem.* **2018***, 10,* 1048.

6.4 Chapter 5 (Experimental procedures)

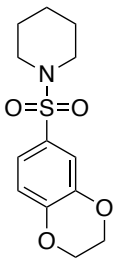
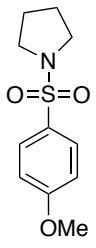
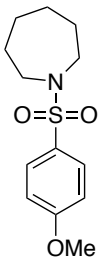
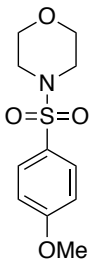
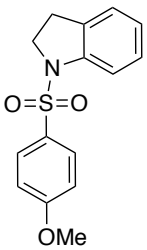
6.4.1 General procedure for sulfonyl cyclic amine substrates.

Sulfonyl chloride (20 mmol, 1.0 equiv) was dissolved in 100 mL anhydrous DCM, the solution was kept stirring at r.t. Piperidine (24 mmol, 1.2 equiv, 2.4 ml) was slowly added to the stirring solution. (white fume generated) Et_3N (30 mmol, 1.5 equiv) was then added into the mixture. The solution was heated to 40 °C and kept refluxing for 2.5 h. The solution was cooled to r.t. and concentrated to give crude material. Pure compounds were obtained through silica plug or flash column chromatography (10-20 % EtOAc in hexane)

N-sulfonyl piperidine table for the study:

						
	276	**277**	**283**	**282**	**288**	**290**
scale	20 mmol	20 mmol	20 mmol	20 mmol	20 mmol	1 mmol
yield	quantitative	94%	92%	quantitative	quantitative	—*
Ref	**1**	**1**	**2**	**3**	**4**	**—**

* crystalization from crude for fast use, did not do full isolation and calculate yield

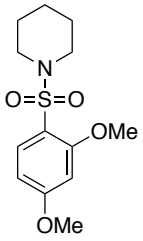
					
	289	**310**	**311**	**314**	**315**
scale	3.5 mmol	20 mmol	20 mmol	10 mmol	10 mmol
yield	89%	—*	—*	—*	—*
Ref	**—**	**4**	**5**	**4**	**6**

* crystalization from crude for fast use, did not do full isolation and calculate yield

(All sulfonyl protected substrates above are prepared according to the general procedure.)

The HNMR matched the reference[1-6] 290 and 289 have no reference and they are characterized.

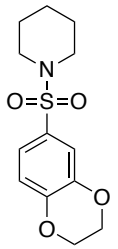
6.4.2 Procedure for sulfonyl protected piperidine substrates 290 and 289.



290

1-((2,4-dimethoxyphenyl)sulfonyl)piperidine 290: Derived from piperidine (12 mmol) and 2,4-dimethoxybenzenesulfonyl chloride (10 mmol) following the general procedure as white solid. The yield was not measured.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.6 Hz, 1H), 6.52 – 6.46 (m, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.16 – 3.11 (m, 4H), 1.59 (p, *J* = 5.8 Hz, 4H), 1.47 (p, *J* = 5.7 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.4, 158.4, 133.4, 119.0, 104.1, 99.4, 55.9, 55.7, 46.8, 25.7, 23.9. IR(neat):2938, 2851, 1592, 1676, 1465, 1439, 1415, 1330, 1322, 1310, 1287, 1256, 1160, 1140, 1074, 1049, 1023; HRMS-(APCI) m/z: calcd for $C_{13}H_{20}O_4N^{32}S$ $(M+H)^+$ 286.1108; found 286.1103; m.p. 80-82 °C

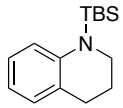


289

1-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)sulfonyl)piperidine 289: Derived from piperidine (4.2 mmol) and 2,3-dihydrobenzo[*b*][1,4]dioxine-6-sulfonyl chloride (3.5 mmol) following the general procedure as white solid, 746 mg, 89% yield.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.26 (d, *J* = 2.0 Hz, 1H), 7.22 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 4.33 – 4.30 (m, 2H), 4.30 – 4.27 (m, 2H), 3.02 – 2.90 (m, 4H), 1.63 (p, *J* = 5.9 Hz, 4H), 1.45 – 1.37 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.3, 143.5, 128.8, 121.4, 117.6, 117.2, 64.5, 64.2, 47.0, 25.2, 23.5. IR(neat):2939, 2840, 1582, 1491, 1460, 1418, 1336, 1315, 1287, 1254, 1214, 1160, 1125, 1079. HRMS-(APCI) m/z: calcd for $C_{13}H_{18}O_4N^{32}S$ $(M+H)^+$ 284.0951; found 284.0948; m.p. 118-120 °C

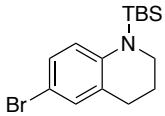
6.5.2 Procedure for TBS protected cyclic amine substrates.



316

TBSOTf (11 mmol, 1.3 g, 1.1 equiv) was added dropwisely to the solution of tetrahydroquinoline (10 mmol, 1.2 mL, 1.0 equiv) in 20 mL anhydrous DCM. Et_3N (15 mmol, 2.1 mL, 1.5 equiv) was then added and the solution was heated to 40 °C and kept refluxing for 2.5 h. The solution was concentrated and then dissolved with 10 mL pentane. The solution was then washed with saturated $NaHCO_3$ solution and dried over $MgSO_4$. Pure product was obtained by flash column chromatography (2.5% Et_3N in pentane) as colorless oil 2.1 g, 85% yield.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.10 (t, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.88 – 6.78 (m, 1H), 3.46 – 3.37 (m, 2H), 2.95 (t, *J* = 6.8 Hz, 2H), 2.01 – 1.91 (m, 2H), 1.16 (s, 9H), 0.42 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 146.9, 129.9, 125.7, 125.5, 119.8, 118.2, 46.1, 27.7, 27.3, 24.4, 20.6, -3.1. IR(neat):2927, 2854, 1601, 1573, 1489, 1472, 1463, 1451, 1360, 1305, 1279, 1244, 1187, 1123, 1090. HRMS-(APCI) m/z: calcd for $C_{15}H_{26}N^{28}Si$ $(M+H)^+$ 248.1829; found 248.1825;



317

TBSOTf (1.1 mmol, 291 mg, 1.1 equiv) was added dropwisely to the solution of tetrahydroquinoline (1.0 mmol, 212 mg, 1.0 equiv) in 5 mL anhydrous DCM. Et_3N (1.5 mmol, 0.2 mL, 1.5 equiv) was then added and the solution was heated to 40 °C and kept refluxing for 2.5 h. The solution was concentrated and then dissolved with 10 mL pentane. The solution was then washed with saturated $NaHCO_3$ solution and dried over $MgSO_4$. Pure product was obtained by recrystallisation with DCM/pentane solvent system as white crystal 252 mg, 77% yield.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.11 – 7.05 (m, 1H), 7.02 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.62 (d, *J* = 8.7 Hz, 1H), 3.30 – 3.19 (m, 2H), 2.76 (t, *J* = 6.8 Hz, 2H), 1.79 (dtd, *J* = 10.5, 6.9, 3.1 Hz, 2H), 0.98 (s, 9H), 0.24 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 145.9, 132.1, 128.1, 127.8, 121.0, 109.9, 45.9, 27.4,

27.1, 23.7, 20.4, -3.4. IR(neat):2927, 2854, 1590, 1560, 1483, 1408, 1361, 1302, 1276, 1254, 1187, 1135, 1095, 1082, 982. HRMS-(APCI) m/z: calcd for $C_{15}H_{25}N^{79}Br^{28}Si$ $(M+H)^+$ 326.0934; found 326.0930; m.p. 54-56 °C

6.5.3 General procedure for N-sulfonyl piperidine cyclopropanation

N-sulfonyl piperidine (0.20 mmol, 1.0 equiv) and Rh cat. (2 mol%) was dissolved in 1.5 mL anhydrous DCM, and the solution was kept stirring under Ar at r.t. The diazo compound (0.20 mmol, 1.0 equiv) was then dissolved in 2.5 mL anhydrous DCM and add dropwisely to the stirring solution over 2h. The reaction was let run overnight before concentration and crude ^{1}HNMR analysis.

*The ^{1}HNMR matched the reported reference by Dr. Wenbin Liu[8]

References

1. Liu, W., Babl, T., Röther, A., Reiser, O. *Chem. Eur. J.* **2020**, *26*, 4236.

2. Naik, P. U.; Harjani, J. R.; Nara, S. J.; Salunkhe, M. M. *Tetrahedron Letters*, **2004**, *45*, 1933

3. Chen, Y.; Willis, M. C.; *Chemical Science*, **2017**, *8*, 3249.

4. Poeira, D. L.; Macara, J.; Faustino, H.; Coelho, J. A. S.; Gois, P. M. P.; Marques, M. M. B. *Eur. J. Org. Chem.*, **2019**, 2695

5. Whitehouse, A. J.; Libardo, M. D. J.; Kasbekar, M.; Brear, P. D.; Fischer, G.; Thomas, C. J.; Barry III, C. E.; Boshoff, H. I. F.; Coyne, A. G.; Abell, C. *Journal of Medicinal Chemistry*, **2019,** *62*, 10586

6. Wilden, J. D.; Judd, D. B.; Caddick, S. *Tetrahedron Letters*, **2005**, *46*, 7637

7. Aizpurua, J. M.; Claudio, P. *Tetrahedron Letters*, **1985**, *26*, 475

8. Liu, W. *The Synthesis and Application of a Series of C_4-Symmetric Dirhodium Catalysts Derived from 1-(2-Chlorophenyl)-2,2-Diphenylcyclopropanecabroxylate Ligands* ; Emory University, GA., **2019**; pp 227-230.