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Erika Diosdado Castro Date

Catalytic Process for Epoxide Ring-Opening with Terminal Alkynes for Carbon-Carbon Bond Formation

By

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Master of Science

Chemistry

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Erika Diosdado Castro

B.S., Georgia Gwinnett College, 2019

Advisor: Frank E. McDonald, Ph.D.

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A thesis submitted to the Faculty of the

James T. Laney School of Graduate Studies of Emory University

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Abstract

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By Erika Diosdado Castro

Carbon-carbon bond-forming reactions are challenging and demand the development of catalytic transformations. One of the primary gaps in knowledge is the lack of a known catalytic method for the ring-opening reaction of epoxides with terminal alkynes using mild and practical reaction conditions. The overall objective of this research project is to invent a catalytic method for the ring-opening reaction of epoxides with terminal alkynes to replace the known stoichiometric methods. We have successfully synthesized two novel pentadentate ligands that may promote a dual activation mechanism for epoxide ring-opening with terminal alkynes. Preliminary results show that both ligands in combination with diethylzinc promoted the ring-opening reaction of 1,2-epoxyhexane with phenylacetylene to give the homopropargylic alcohol; however, only the pseudoephedrine-derived ligand (L**2**) promoted full conversion to the homopropargylic alcohol. This supported that the pseudoephedrine-derived ligand (L**2**) was superior to the achiral analog of ProPhenol (L**1**) and thus, the substrate scope was extended with L**2**. The ligand-catalyzed reaction of styrene oxide and 1-decyne gave a 48 % yield of a major regioisomer from the addition to the more substituted carbon of styrene oxide and a 3.3 % yield of homopropargylic alcohol as the minor regioisomer. The pseudoephedrine derived ligand (L**2**) also promoted the epoxide ring-opening reaction of benzyl glycidyl ether with phenylacetylene and resulted in a 67 % yield of the corresponding homopropargylic alcohol. Finally, we have reported the first Zn-promoted epoxide ring-opening with terminal alkynes; it is a simplification from the stoichiometric method that used both *n*-butyllithium and BF_3-OEt_2.

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List of Abbreviations

BF_3-OEt_2	boron trifluoride etherate
BF_3-THF	boron trifluoride tetrahydrofuran
DMEDA	*N,N'*-dimethylethylenediamine
DMF	Dimethylformamide
Et	ethyl
EtOAc	ethyl acetate
h	hour
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
^{1}H NMR	proton nuclear magnetic resonance
PMA	phosphomolybdic acid
PMB	*para*-methoxybenzyl
ppm	parts per million
R_f	retention factor
r.t.	room temperature
TBS	*tert*-butyldimethylsilyl

THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate

Introduction: Our specific aim is a catalytic process for epoxide ring-opening with terminal alkynes. The justification for this specific aim is to replace the classical Yamaguchi-Hirao[1] stoichiometric reaction of lithium acetylides to BF_3-activated epoxides to prepare simple homopropargylic alcohols (Figure 1). The Yamaguchi-Hirao method uses acetylide anions generated with a strong base, *n*-butyllithium, as well as stoichiometric Lewis acid, boron trifluoride etherate, to activate the epoxide.[1] This reaction requires anhydrous solvent and low reaction temperatures (below 0 °C).[1] There are few applications that describe both alkyne and epoxide reactants containing multiple functional groups and chiral centers using this stoichiometric method.[2] Ideally, the proposed catalytic method aims for more user-friendly conditions to enable a broader substrate scope.

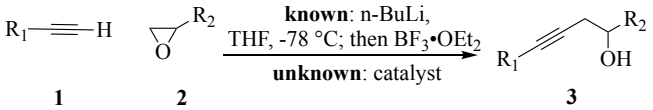


Figure 1. Known method versus the proposed catalytic method for epoxide ring-opening with terminal alkynes.

Previously, the McDonald group reported the iterative ring-opening reaction of epoxides with terminal alkynes for the synthesis of C9-C27 degradation product from aflastatin A.[2] Compound **4** and an electrophilic epoxide were coupled using 1 equivalent of *n*-butyllithium and BF_3-OEt_2 to form alkynyl alcohol **5**, which afforded compound **6** after a series of reactions (Figure 2). Some limitations included the use of *n*-butyllithium to deprotonate each alkyne, low reaction temperatures, and a second Lewis acid to activate each epoxide.[2] However, through this method, a protected polyhydroxyl-terminal alkyne **6** was linked with a protected electrophilic epoxide to form the alkynyl alcohol intermediate **7** with 11 chiral centers, although there was extensive optimization required for this transformation (Figure 2).[2] The transformation with BF_3-OEt_2 proceeded in much lower yield and was not highly reproducible; BF_3-THF was used instead.[2] Evans and Knight reported that the alkylation of lithium acetylides by monosubstituted

epoxides was more robust with the use of BF_3-THF.[3] Protective group manipulations were required to introduce substituents.[2] There was also extensive temperature control needed to deprotonate the alkyne. In some cases, side reactions were observed with *O*-protective groups such as *tert*-butyldimethylsilyl (TBS) and *para*-methoxybenzyl (PMB) ethers when the temperature was too high from -78 °C.[4,5] This was the motivation for the development of a catalyst that may allow this transformation to occur without the need for extensive optimization and harsh reaction conditions.

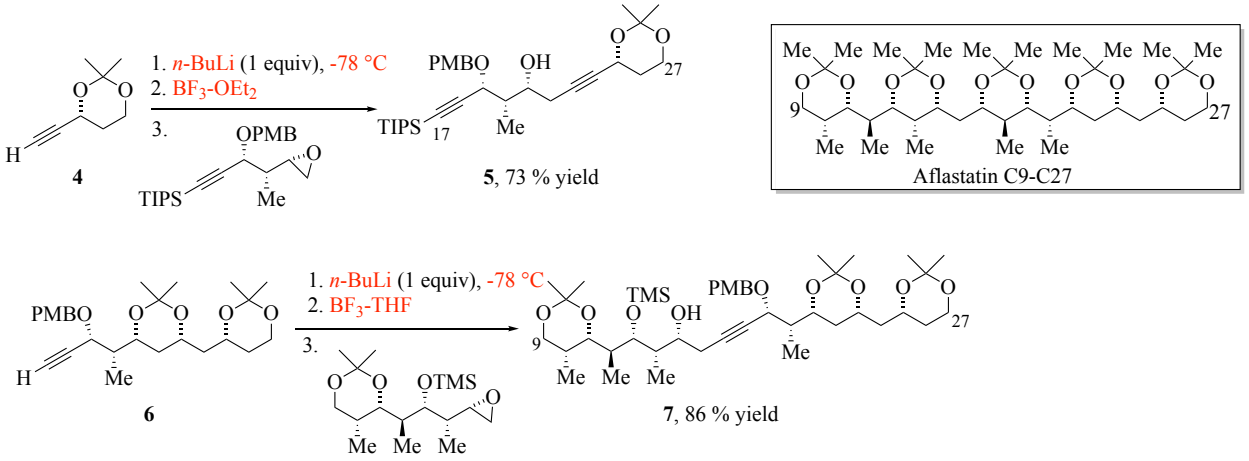


Figure 2. Alkyne-epoxide cross-coupling reactions used in the synthesis of aflastatin C9-C27.

Our long-term outcome is multiple iterations of the catalytic process to build linear carbon chains with multiple hydroxyl substituents. Our proposed catalytic method will form carbon-carbon bonds between chiral subunits containing terminal alkyne and epoxide functional groups. We can accomplish this using chiral non-racemic epoxyalkyne modules as trimethylsilyl-masked bifunctional modules that can be un-masked using mild base (Figure 3).

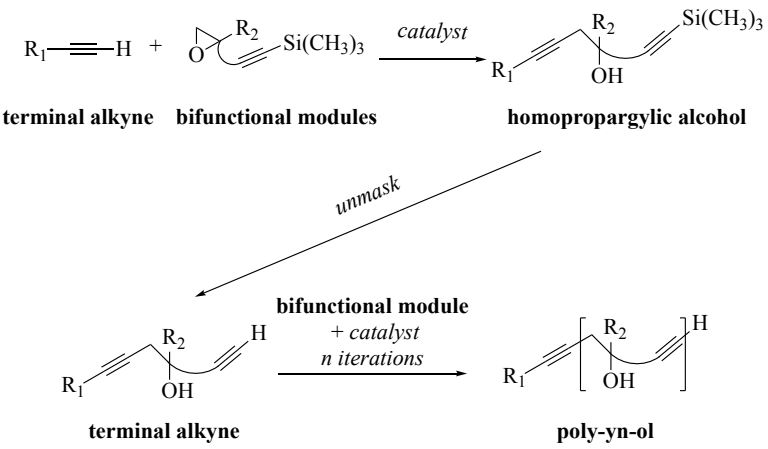


Figure 3. Iterative synthesis of poly-yn-ols to form carbon-carbon bonds.

One potential application of this work lies in synthesizing cyanobacterial 40-membered polyhydroxy macrolides (Figure 4). The efficient construction of these marine cyanobacterial derived natural products gained interest from the scientific community because of their biological relevance as antibiotics, immunosuppressants, and antifungals.[6] These natural products were cyclized into macrolides bearing a *tert*-butyl group and an α,β-unsaturated carboxyl group at similar positions and were structurally diverse in their arrangement and number of hydroxy groups.[6] The first total synthesis of Bastimolide A was reported by Cox and coworkers through a linear sequence of twenty steps that involved the implementation of five Type 1 Anion Relay Chemistry (ARC) protocols to establish the 1,5-stereodiol and 1,3,5-stereotriol units.[7] Our approach will introduce an efficient, quick, and stereoselective strategy for the complete synthesis of bastimolide A.

PM toxin, a corn-specific toxin caused by the fungal pathogen *Phyllosticta maydis*, was identified as another potential target (Figure 4).[8] The unique structure consisted of thirty-three linear carbons and four β-ketol groups and was synthesized from D-lactate through tandem aldol-type reactions and regiospecific reduction of consecutive α,β-epoxy ketone groups.[8] We envision

that molecules like this can be made by iterative additions of epoxide to terminal alkynes. The first step can be the alkyne addition of **8** to epoxide **9** followed by regioselective hydration to prepare the ketone (Figure 4).

Possible Targets: Bastimolide A & PM Toxin

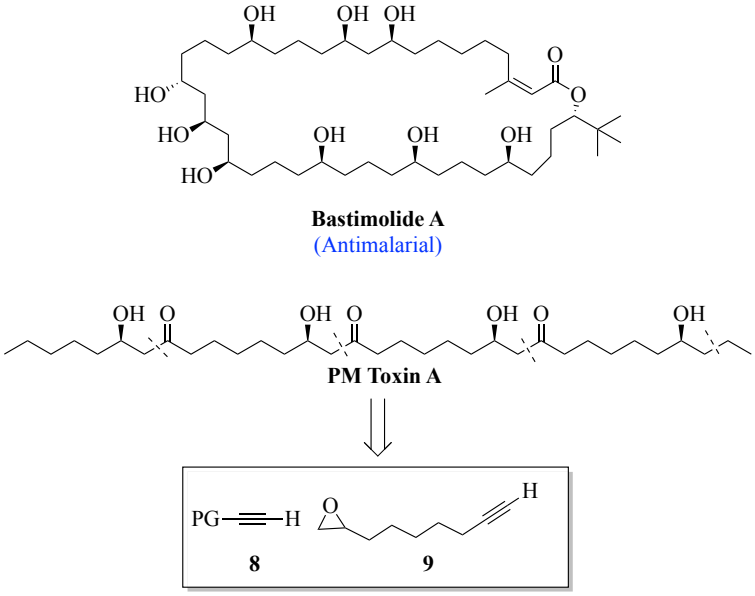
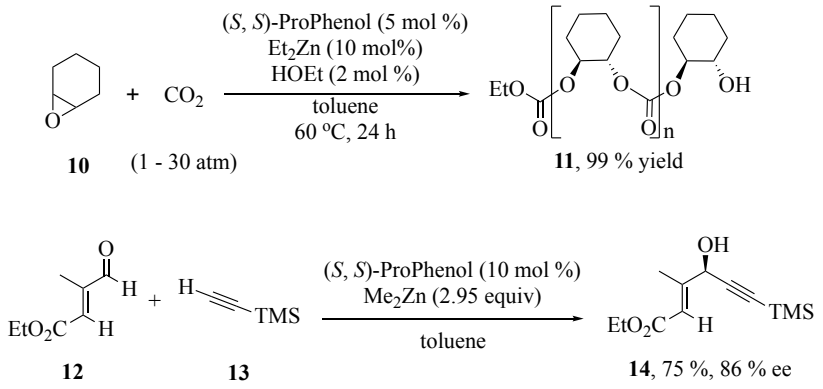


Figure 4. Potential natural product targets for iterative epoxide ring-opening with terminal alkynes.

The pre-catalyst chosen for the proof of principle experiment was inspired by the Zn_2-ProPhenol catalyst.[9,10,11,12] Catalytic reactions with Zn_2-ProPhenol included enantioselective direct aldol reactions, asymmetric additions to imines (Mannich reactions and Aza-Henry reactions), asymmetric conjugate additions, among others.[12] The relevance to this project was that the Zn_2-ProPhenol catalyst activated epoxides in one application, epoxide copolymerization with CO_2[10] and it activated alkynes in another application, the enantioselective alkynylation of aldehydes to prepare propargylic alcohols[13] (Figure 5). The key for our transformation was to have a catalyst that activated the epoxide and the alkyne to form the homopropargylic alcohol, which combined the substrates from the abovementioned reactions.

The intramolecular dinuclear zinc structure of the Zn_2-ProPhenol enabled CO_2 /cyclohexene oxide **10** copolymerization into the polycarbonate **11** (Figure 5).[10] This occurred through a dual activation mechanism for polymerization, where one zinc atom activated an alkyl carbonate nucleophile, and the second zinc atom activated the electrophilic epoxide in proximity to the carbonate nucleophile. This reaction occurred under mild conditions (1 atm of pressure) with good activity and excellent chemoselectivity.



10 **11**, 99 % yield

12 **13** **14**, 75 %, 86 % ee

Figure 5. Zn_2-ProPhenol catayzed cyclohexene oxide/CO_2 copolymerization and alkylaton of α,β-unsaturated aldehyde **12**.

The Zn_2-ProPhenol catalyst promoted aldehyde alkynylations. The basic alkyl-zinc deprotonated the terminal alkyne **13** to form nucleophilic zinc acetylide, and the Lewis acidic zinc activated the electrophilic aldehyde **12** and gave the alkynyl alcohol **14** (Figure 5).[13] The functionalized substrate gave a good yield and enantiomeric excess (*ee*) of **14**.[13] In this paper, a dual activation mechanism was proposed, where the Brønsted basic site activated the alkynylzinc nucleophile through a deprotonation, while the Lewis acidic site activated the aldehyde electrophile through coordination.[13] The coordination of the substrates promoted a nucleophilic addition to the *Si* face of the aldehyde and a metal exchange step gave product dissociation and formation of a propargylic zinc alkoxide species.

The ProPhenol catalyst used for cyclohexene oxide/CO_2 copolymerization and alkylation of α,β-unsaturated aldehyde was synthesized from the multidentate semi-azacrown ether ligand known as the (*S*, *S*)-ProPhenol ligand, which transformed into a bimetallic complex **15** with the addition of an alkyl metal reagent such as Et_2Zn (Figure 6).[12] The resulting complex contained a Brønsted basic site at one metal center and a Lewis acidic site at the other metal center.[12]

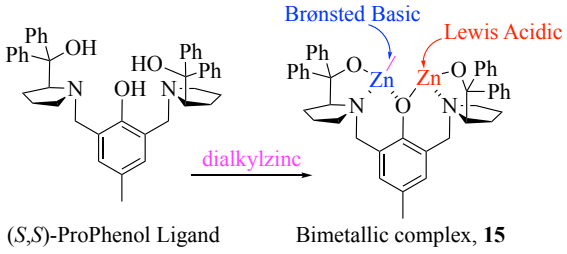


Figure 6. Transformation of (S,S)-ProPhenol ligand into a bimetallic complex.

Pre-catalyst **16** is chosen for the proof of principle experiment and is inspired by the Zn_2-ProPhenol catalyst, which reacts through a dual activation mechanism.[12,10] Thus, we propose a similar dual activation mechanism, where a Zn species activates the alkyne nucleophile, while another activates the epoxide. The species may be diethylzinc or an alkoxide. We propose that the addition of the terminal alkyne **17** activates the ethyl zinc pre-catalyst, generating zinc acetylide **19** (Figure 1). The epoxide **20** coordinates to the Lewis acidic zinc atom in intermediate **19**, activating the electrophilic epoxide in intermediate **21**. In the case of catalytic additions to aldehydes, d^{10} metal ions (Cu^+, Ag^+, Zn^{2+}, or In^{3+}) coordinate with terminal alkynes, increasing the acidity of the sp-hybridized C-H bond through backbonding with the alkyne π^* orbital, so that tertiary amines are sufficiently basic to generate metal acetylide.[14] Similarly, we intend to have an ethyl ligand that is sufficiently basic enough to effect deprotonation of the terminal alkyne, leaving

behind a Lewis acidic zinc to coordinate with the epoxide. Both directions of bonding are present, and an empty orbital accepts electrons from the π. The net effect is a π to σ rearrangement.

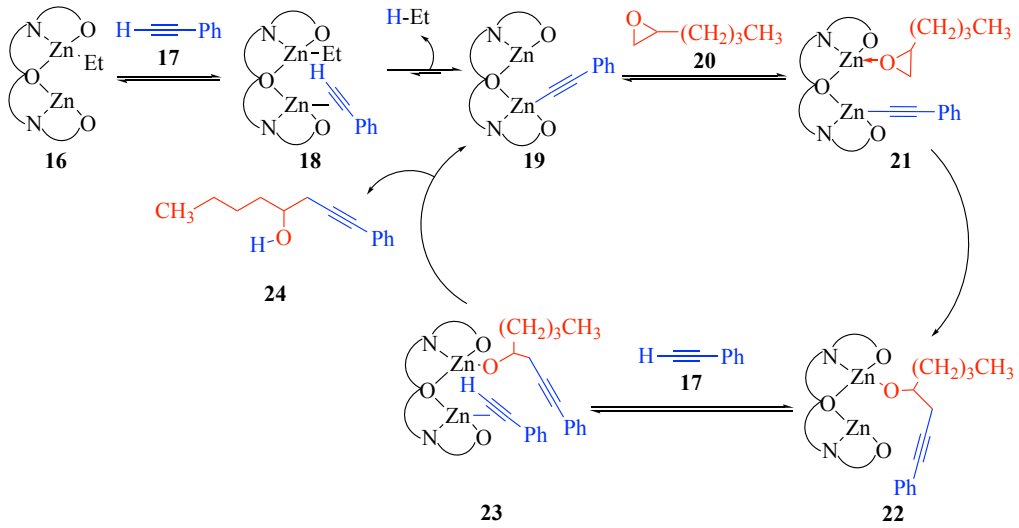


Figure 7. Proposed catalytic method for epoxide ring-opening with terminal alkynes. The catalytic cycle begins with the activated complex **19**.

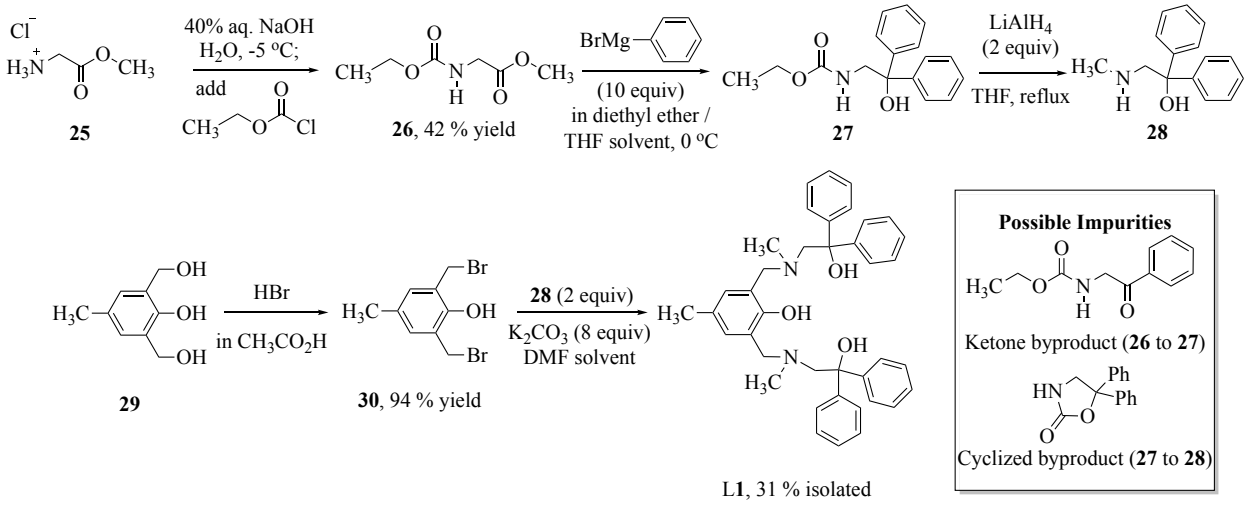
The proximity between the nucleophilic epoxide and the zinc acetylide promotes epoxide ring-opening and migratory insertion, producing the zinc alkoxide intermediate **22**. If another alkyne **17** can coordinate to the free zinc in complex **23** then the adjacent alkoxide may be basic enough to deprotonate the activated alkyne and that can turn over the catalytic process and release product **24**.

Results and Discussion:

I. Preparation of Novel and Achiral L1

The preliminary work began with precatalyst preparation of a novel achiral pentadentate ligand (L**1**). The achiral pre-catalyst was inspired by a Zn_2-ProPhenol catalyst (Figure 6).[9,10,11,12] An achiral ligand was initially chosen to avoid double diastereoselection in the presence of chiral

substrates. The catalyst was also designed with sterically bulky tertiary diphenylethanol groups to sterically steer coordination of two Zn^{2+} ions within a single ligand to avoid 2:2 dimerization between the zinc and ligand (Scheme 1).[15] Sugiyama and coworkers[16] reported the synthesis of 2-Methylamino-1,1-diphenylethanol **28** starting from *N*-(ethoxycarbonyl)glycine ethyl ester. While *N*-(ethoxycarbonyl)glycine ethyl ester was available for purchase, it was extraordinarily expensive, and thus, we chose to synthesize it instead.[17] Glycine methyl ester hydrochloride **25** and ethyl chloroformate were used to synthesize **26** (Scheme 1).[17] Currently, we obtained a 42 % yield of compound **26** using this method.



Scheme 1. Catalyst preparation of L**1** for epoxide ring-opening with terminal alkynes.

The synthesis of **28** from **26** was reported using phenylmagnesium bromide and a strong reducing agent, lithium aluminum hydride.[16] Compound **27** was synthesized through addition of Grignard reagent. Purification of crude **27** was attempted through silica gel chromatography (20% EtOAc: hexane), but **27** was inseparable from minor impurities. All the expected peaks of compound **27** were observed in the ^{1}H NMR spectrum; however, the number of hydrogens didn't add up to the expected number of hydrogens for some peaks. In addition, the integration for the

aromatic region was slightly higher than the expected 10H; the integration for the methylene hydrogens closest to the N-H group was 1H higher than expected, while the integration of the terminal methyl group was 1H lower. There were also minor impurities observed in the ^{1}H NMR spectrum. There was little if any evidence of the starting material (missing methoxy group or singlet at 3.70 ppm). A peak at 8.0 ppm was observed and can correspond to a small amount of a ketone byproduct. Compound **28** was synthesized from **27** using a strong reducing agent, lithium aluminum hydride ($LiAlH_4$). Aminoalcohol **28** could not be isolated due to its high polarity (R_f = 0) at different solvents such as 50 % EtOAc: hexane and 10 % methanol: EtOAc. The ^{1}H NMR showed the major product peaks for aminoalcohol **28**, but the NH and OH peaks weren't observed due to the presence of minor impurities. These minor impurities were observed on TLC plate (at least 6 spots present) and in the ^{1}H NMR spectrum, which made the preparation of the precatalyst difficult. A major impurity included the starting carbamate **27** along with the possible formation of a cyclized byproduct (5,5-diphenyl-1,3-oxazolidine).

We proceeded to prepare the achiral pentadentate ligand L**1**. Dibromide **30** was alkylated with the unpurified aminoalcohol **28**.[18] We prepared *para*-cresol **30** from commercially available **29** through a bromination step, which resulted in a 94% yield of pure **30**.[18]

*II. Preparation/Purification of Novel and Chiral L**2***

Novel, chiral pentadentate L**2** was initially prepared to assist with the purification of L**1** as the synthesis of L**2** was more straightforward and its polarity was similar. To prepare L**2**, commercially available (1*R*, 2*R*)-(-)-Pseudoephedrine **31** was alkylated with *para*-cresol **30** (Figure 8).[18] We anticipated some issues may arise from the chirality of L**2**, which was why this ligand was not initially proposed. Both the pseudoephedrine-derived ligand (L**2**) and L**1** are

novel ligands and thus, their ^{1}H NMR peaks weren't reported in the literature. Nevertheless, we assigned all ^{1}H NMR peaks. The ^{1}H NMR signals for (1*R*, 2*R*)-(-)-Pseudoephedrine **31** were observed in the crude spectrum along with new signals corresponding to the pseudoephedrine-derived ligand (L**2**).

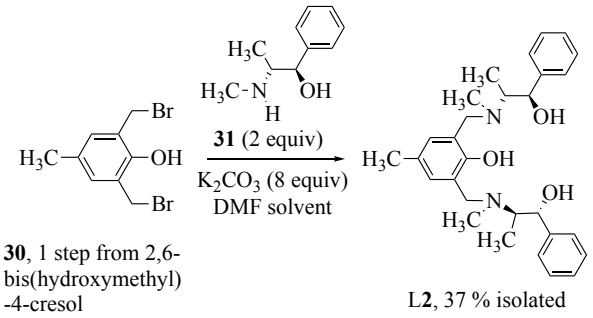


Figure 8. Catalyst preparation of L**2** for epoxide ring-opening with terminal alkynes.

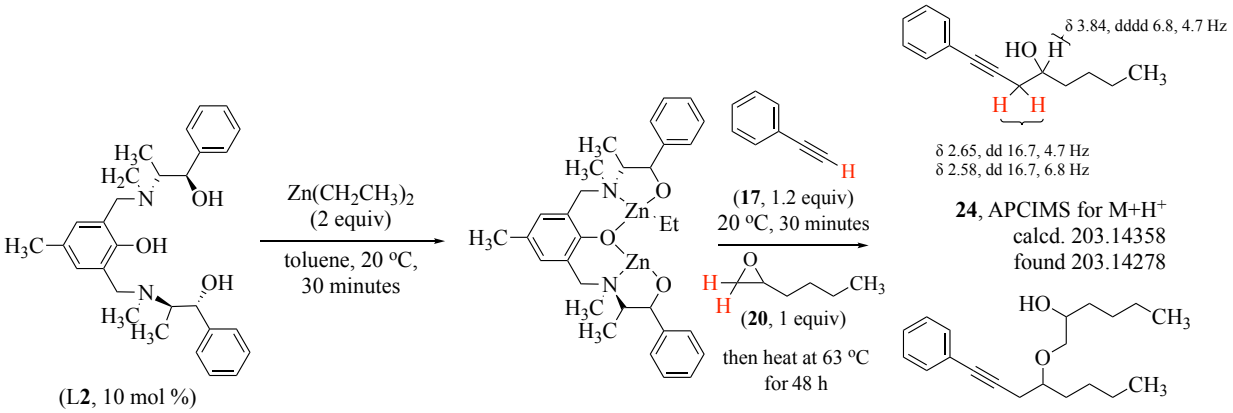
Pseudoephedrine **31** and **L2** were very polar and didn't move up the TLC plate. To purify, L**2** was dissolved in DCM and loaded on a grade III alumina column (3 inch) using 15-100 % EtOAc: hexane. It was found early on that grade I alumina was to be rendered less active to grade III alumina for pseudoephedrine **31** and L**2** to come off the column and be separated. Addition of 6% (w/w) of water converted grade I alumina to grade III alumina. The fractions were collected in test tubes and then spotted on a TLC plate without solvent elution and stained with phosphomolybdic acid (PMA) stain. The purification step resulted in a 37 % yield or 0.3126 g of L**2**. However, the reproducibility of this purification remained a challenge. The ^{1}H NMR peaks of L**2** were assigned and showed a higher integration for the aromatic hydrogens (12H observed and 10H expected). Ethyl acetate was the only impurity noted on the spectrum.

*III. Purification of Novel and Achiral **L1***

Just like L**2**, L**1** was difficult to purify. We validated the difficulty in purifying both L**1** and L**2** through a commercially available sample of (*S*, *S*)-ProPhenol ligand purchased from Sigma-Aldrich, which showed obvious impurities in the ^{1}H NMR spectrum. The (*S*, *S*)-ProPhenol ligand was purchased to perform control experiments on ligand-catalyzed reactions. This corroborated that these aminoalcohol, multidentate ligands were difficult to purify even for a specialized chemical company. After extensive experimentation with the purification of L**2**, the most successful process involved purification of L**1** through column chromatography (grade III alumina, 10% EtOAc: hexane) to yield L**1** as a crusty, white solid (31 % isolated). A short/narrow column was filled with ~3.0 inches of grade III alumina, which was necessary to elute L**1** off the column. The crude product was first dissolved with a couple of drops of ethyl acetate and ~1 mL of the 10 % EtOAc: hexane mixture right before being loaded onto the column. The fractions were collected in test tubes and then spotted on a TLC plate without solvent elution and stained with PMA stain like with L**2**. Aminoalcohol **28** and L**1** were very polar and didn't move up the TLC plate, but a break in spots on the TLC plate indicated separation. We originally hypothesized that the most polar material was L**1**; however, aminoalcohol **28** eluted off the column last. Impurities included ethyl acetate and an unknown impurity at 5.86 (s, 1H).

IV. Ligand Catalyzed Reactions and Control Reactions

Preliminary results from the initial proof of principle experiment showed that a combination of L**1** and diethylzinc promoted the ring-opening reaction of 1,2-epoxyhexane **20** with phenylacetylene **17** to give homopropargylic alcohol **24** (Figure 9). We chose to begin with this combination of alkyne and epoxide substrates because the product, **24**, was nonvolatile, which made it isolable. Also, these substrates did not have reactive functional groups that tend to promote side reactions. A temperature advantage was identified, where the reaction was slow at 52 °C as observed by the low ratio of conversion to the homopropargylic alcohol **24** (entries 1 and 2) and gave byproducts with ^{1}H NMR characteristics of alkenes. In the next experiment, the reaction was heated to 68 °C and aliquots were taken at 48 hours and 72 hours (entries 3 and 4). The desired transformations gave a higher ratio of homopropargylic alcohol **24,** and the 72-hour reaction gave the highest ratio of conversion to the homopropargylic alcohol **24**. At 48 hours, product **24** and small amounts of unreacted alkyne and epoxide were observed (entry 3). After 72 hours, epoxide **20** was almost completely consumed, although some alkyne **17** remained. This can be observed by the increase in the ratio of phenylacetylene, which implied a decrease in the presence of 1,2-epoxyhexane **20** (entry 4). Despite the use of two equivalents of diethylzinc, there was no evidence of ethyl addition to the epoxide, nor Meinwald rearrangement of epoxide to an aldehyde to give propargylic alcohols (no ^{1}H NMR resonances between 4 - 5 ppm).



Entry	Temp. (°C)	Time (h)	Ligand	**17**	**20**	**24**
1	52	24	L**1** (10 mol %)	1.3	1.0	2.1
2	52	48	L**1** (10 mol %)	0.63	1.0	0.50
3	68	48	L**1** (10 mol %)	1.4	1.0	4.6
4	68	72	L**1** (10 mol %)	1.7	1.0	8.0
5	63	48	L**2** (10 mol %)	0	0	full conversion to **24**
6	45	46	No ligand	0.80	1.0	0.57
7	60	48	No ligand	2.6	1.0	5.4

*Growth of the product was identified based on the integration of peaks corresponding to 1,2-epoxyhexane **20** (m at 2.38 and dtd at 2.67 ppm), phenylacetylene **17** (s at 3.11 ppm), and the homopropargylic alcohol **24** (2 dd at 2.58 and 2.65 ppm). Impurity **32** overlaps with diethyl ether impurity (q at 3.48 ppm) on ^{1}H NMR. The results are reported as relative ratios after normalizing 1,2-epoxyhexane **20** to 1.0.

Figure 9. Catalytic ring-opening reaction of 1,2-epoxyhexane **20** with phenylacetylene **17**.

It was important to determine early on which of the two ligands was superior in terms of the epoxide ring-opening reaction. To do this, an experiment with similar reaction conditions to entry 3 was performed, this time with the pseudoephedrine-derived ligand (L**2**). We found that L**2** promoted full conversion to the desired homopropargylic alcohol **24** in 48 hours (entry 5). This was a better reaction compared to the reaction with L**1** that gave a 4.6 ratio of product **24**. As a result, we moved forward to expand the substrate scope with L**2**. The crude product was purified by column chromatography (SiO_2, 20% EtOAc: hexane), and gave 0.1033 g (41%) of homopropargylic alcohol **24** and a minor, inseparable impurity **32**. The ^{1}H NMR peaks of impurity **32** overlapped with that of diethyl ether impurities in the spectrum and prevented an

accurate measurement of the ratio of this impurity. The desired product **24** was identified by the distinctive diastereotopic hydrogens from the methylene group (Figure 9). The presence of byproduct **32**, the alkoxide of **24** adding to another molecule of the epoxide, was supported by mass spectrometry data. The presence of byproduct **32** was also supported by additional multiplet peaks at 3.74 – 3.41 ppm (integration of 0.15) and the higher integration of the terminal carbon chain (11H versus expected 9H) observed on ^{1}H NMR.

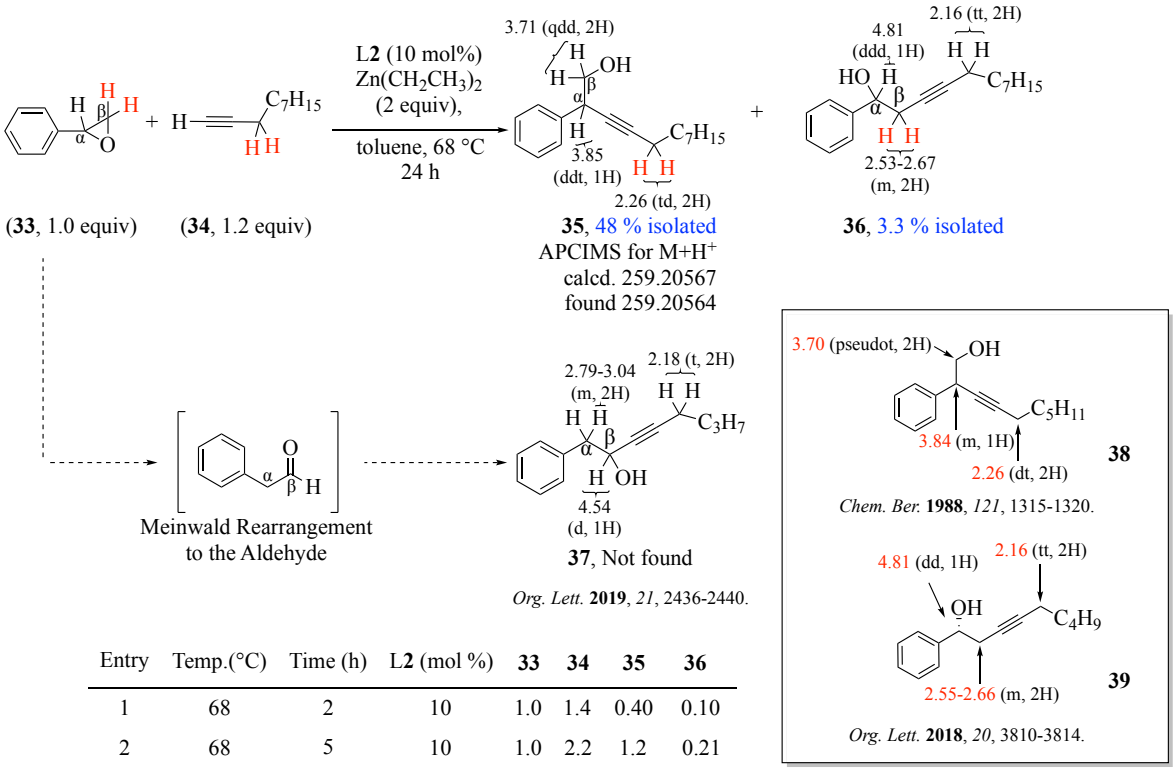
A series of control experiments were set up to determine the importance of L**2** with the substrate combination. Aliquot analysis for the reaction of phenylacetylene **17** and 1,2-epoxyhexane **20** in the absence of L**2** gave homopropargylic alcohol **24**. We observed slow conversion of phenylacetylene **24** and 1,2-epoxyhexane **25** and greater formation of the byproduct **32** compared to homopropargylic alcohol **24** at a ratio of 2:1. There was also a temperature advantage because the reaction worked at 45 ℃ and better at 60 ℃ (entries 6 and 7). Interestingly, a slightly higher ratio of the homopropargylic alcohol **24** was observed in the absence of ligand than in the presence of L**1** at lower temperatures (entries 2 and 6). Also, a 48-hour reaction of L**1** heated to 68 °C was comparable to the 48-hour reaction in the absence of ligand at 60 °C (entries 3 and 7).

Due to these results, a new hypothesis is introduced: A Zn species activates the alkyne nucleophile, while another activates the epoxide. Based on the reaction conditions in place, it is likely that zinc acetylide is present. However, it is less clear what source activates the epoxide to open. There is a possibility that diethylzinc, an alkoxyzinc, or the product itself activates the epoxide. It may be that the epoxide opening is slow, but as the product is generated, there is a zinc alkoxide that is more Lewis acidic than diethylzinc. We can still describe this system as dual

activation, but in a system that isn't tied together. This is the first Zn-promoted epoxide ring-opening with terminal alkynes and a simplification from the known stoichiometric reaction. While there is a literature report of zinc and allyl bromide promoting the addition of phenylacetylene **17** to styrene oxide **33** under mild conditions, the report includes misassigned spectral data for Meinwald rearrangement products.[19] Currently, the control reaction that uses diethylzinc isn't clean, but we aim to improve control conditions without the ligand.

To extend the substrate scope, we moved on to styrene oxide as a new substrate. Styrene oxide presented an equal form of the regioselectivity at either carbon and was prone to rearrangement to the aldehyde. Initially, we intended to use 1-heptyne and styrene oxide **33** because the desired product,1-phenylnon-3-yn-1-ol, was reported in the literature[20]; instead, we used 1-decyne **34** and styrene oxide **33** as these were readily available in our laboratory. A reaction at 68 ℃ was set up with these substrates and an ^{1}H NMR spectrum was taken at different time intervals (2 h, 5 h, 8 h, 24 h) through aliquot analysis. We expected the formation of homopropargylic alcohol **36** as the major product, but this wasn't observed. Comparison of early peaks (td at 2.26 ppm, qdd at 3.71 ppm, and ddt at 3.85 ppm) observed in ^{1}H NMR spectra to those of similar structures in the literature (**38** and **39**) [21,20] supported the presence of compound **35** as the major regioisomer. Both regioisomers are unknown in the literature, but similar structures with different carbon chains were found.[21,20] This compound **35** formed from the α-addition to the more substituted carbon of styrene oxide **33**. The growth of the product was identified based on the integration of peaks that corresponded to styrene oxide **33**, 1-decyne **34**, major regioisomer **35**, and minor regioisomer **36** (entries 1-3, Figure 10). After two hours, formation of major regioisomer **35** was observed with styrene oxide **33** and 1-decyne **34** present

(entry 1). At 2 hours, byproduct **36** was observed at a ratio of 4:1 (major regioisomer **35**: minor regioisomer **36**).



Entry	Temp.(°C)	Time (h)	L2 (mol %)	33	34	35	36
1	68	2	10	1.0	1.4	0.40	0.10
2	68	5	10	1.0	2.2	1.2	0.21
3	68	8	10	1.0	3.1	1.9	0.36
4	68	24	10	1.0	2.7	2.8	0.050
5	68	3	0	1.0	1.3	0	0
6	68	24	0	1.0	2.9	0.81	0.050

*Growth of the product was identified based on the integration of peaks corresponding to **33** (dd at 2.77 ppm), **34** (td at 2.18 ppm), major regioisomer **35** (dt at 2.26 ppm), and minor regioisomer **36** (m at 2.53-2.67). The results are reported as relative ratios after normalizing styrene oxide to 1.0

Figure 10. Catalytic ring-opening reaction of styrene oxide **33** with 1-decyne **34** using L**2**.

Styrene oxide continued to be consumed from 2 hours to 8 hours as observed by the increasing ratio of 1-decyne **34**, which suggested that styrene oxide was involved in a side reaction. It was unclear what happened to styrene oxide, but propargylic alcohol **37** from Meinwald rearrangement of styrene oxide **33** was not observed. The crude spectrum of the 24-hour reaction

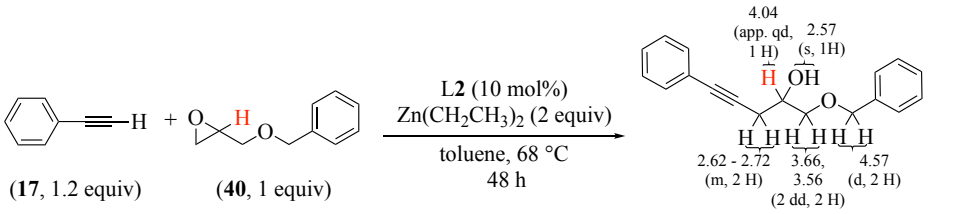
showed an overlap of major regioisomer **35** peaks with minor regioisomer **36** peaks, which interfered with the integration of the peaks used to calculate ratios for Figure 10. Therefore, the aliquot analysis at 24 hours wasn't included in Figure 10, but the crude ^{1}H NMR spectrum showed increased conversion to **35** and **36**.

A 24-hour reaction at 68 °C was set-up and the crude ^{1}H NMR spectrum showed a small amount of minor regioisomer **36** in comparison to regioisomer **35** (entry 4). The crude product was purified through silica gel chromatography (20% EtOAc: hexane) and gave 0.1514 g (48 % isolated) of major regioisomer **35** and 0.0108 g (3.3 %) of minor regioisomer **36**. High-resolution mass spectrometry (HRMS) and the ^{1}H NMR spectrum of the isolated compound confirmed the presence of major regioisomer **35**.[21] The tertiary proton at 3.85 ppm on the ^{1}H NMR spectrum coupled to four hydrogens and resulted in a doublet of doublet of triplets (ddt) (Figure 10). The signal at 2.26 ppm for **35** matched with the propargylic hydrogens even though they were diastereotopic. These hydrogens were far enough from the chiral center that the peaks overlapped to an apparent triplet of doublets (td); the doublet was from the long-range coupling to a single hydrogen and the triplet to coupling to adjacent hydrogens. The hydroxyl peak at 1.89 ppm of **35** showed triplet (t) character; this was consistent with coupling to two nearby hydrogens. Both the ^{1}H NMR and ^{13}C NMR spectra (16 unique carbon peaks observed) confirm the presence of minor regioisomer **36**.[20] The observed multiplicity (triplet of triplets) of the propargylic methylene hydrogens at 2.16 ppm were consistent with what was expected for the homopropargylic alcohol **36** and not the propargylic alcohol **37**, which will appear as a triplet of doublets (td). If instead propargylic alcohol **37** had formed as the minor regioisomer, the corresponding multiplet of the secondary protons adjacent to the hydroxyl group would be more deshielded than 2.53-2.67 ppm for **36** because the protons in **37** are secondary and benzylic.

After we determined that diethylzinc alone promoted the ring-opening reaction of the 1,2-epoxyhexane **20** with phenylacetylene **17**, we designed a similar control reaction with the new substrate combination. A 3-hour reaction heated to 68 °C showed presence of 1-decyne **34** and styrene oxide **33**, but major regioisomer **35** and minor regioisomer **36** peaks were not observed (entry 5). A 24-hour reaction, however, showed both major regioisomer **35** and minor regioisomer **36** peaks at a ratio of 0.81: 0.050 (entry 6). Although the major regioisomer **35** was clearly formed, the reaction proceeded slower than in the presence of L**2** (entries 4 and 6). This control experiment implied that diethylzinc alone doesn't work better than the combination of L**2** and diethylzinc.

Before this point, styrene oxide **33** and 1-decyne **34** were considered the best substrate combination. This led us to consider other alkyne and epoxide substrates to expand the substrate scope. Benzyl glycidyl ether **40**, an epoxide that has another Lewis basic group due to the ether lone pairs, was used in combination with phenylacetylene **17**. A 6-hour reaction heated to 70 ℃ was set up using the L**2** and diethylzinc (entry 1, Figure 11). The crude spectrum was observed to be cleaner than any of the other substrate combinations, which meant that L**2** may interact with the final product. Phenylacetylene **17** was not present on the crude ^{1}H NMR spectrum, but benzyl glycidyl ether **40** and homopropargylic alcohol **41** were observed at a 1.0:0.71 ratio. The ratio of homopropargylic alcohol **41** increased as we increased the reaction time to 48 hours (entry 2). The crude product of this 48-hour reaction was purified through silica gel chromatography (7.5 inches, 20 % EtOAc: hexane) and gave a 67 % yield of homopropargylic alcohol **41**. The ^{1}H NMR peaks and the high-resolution mass spectrometry (HRMS) of homopropargylic alcohol **41** agreed with those reported in the literature.[22] Homopropargylic

alcohol **41** has been prepared by epoxide alkylation with an alkynyllithium under catalytic trimethylaluminum via a pentacoordinate chelate complex.[22]



(**17**, 1.2 equiv) (**40**, 1 equiv)

41, 67 % isolated,
APCIMS for M+H$^+$calcd. 267.13796
found 267.13798

Entry	Temp. (°C)	Time (h)	L**2** (mol %)	**40**	**41**
1	70	6	10	1.0	0.71
2	68	48	10	1.0	5.6
3	66	24	0	1.0	1.8
4	66	48	0	1.0	3.0

*Growth of the product was identified based on the integration of peaks corresponding to **40** (m at 3.09 ppm), and homopropargylic alcohol **41** (apparent qd at 4.04 ppm). Phenylacetylene **17** wasn't observed in the crude ^{1}H NMR spectra. The results are reported as relative ratios after normalizing benzyl glycidyl ether **40** to 1.0.

Figure 11. Catalytic ring-opening reaction of benzyl glycidyl ether **40** with phenylacetylene **17**.

The control experiment for the phenylacetylene **17** and benzyl glycidyl ether **40** also showed clean formation of homopropargylic alcohol **41** after 24 hours and 48 hours (entries 3 and 4). The results of the 48-hour reaction in the absence of L**2** were promising as the ratio of homopropargylic alcohol **41** formation was high. Ooi and co-workers[22] developed a catalytic method for chelation-controlled alkylation of hetero-epoxy ethers with Me_3Al (Figure 12). The mechanism described the formation of a pentacoordinate chelate complex as the key intermediate followed by the attack of alkynyllithium on the epoxy ether at the less hindered site to give the alkynylation product (Figure 12). Similarly, there may be chelation between the zinc and the oxygens of benzyl glycidyl ether **40** to enhance reactivity for the epoxide (Figure 12). This may explain why the control reaction in the absence of L**2** works well even in the absence of L**2**,

making benzyl glycidyl ether **40** a good substrate for synthetic outcomes, but less ideal for testing ligand effects.

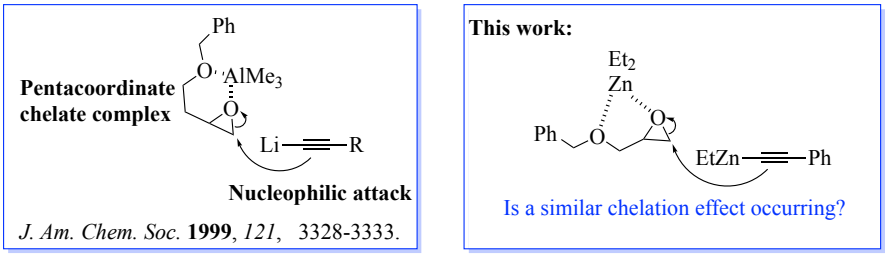


Figure 12. Proposed chelation effect between zinc and the oxygens of benzyl glycidyl ether **40**.

V. Experimentation to Improve the Zn-Catalyzed System

Based on the results that were obtained from the control experiments with the different substrate combinations, we decided to implement a series of strategies to improve the Zn-catalyzed system. It is known in the literature that a dialkylzinc and an alcohol gave monoalkylzinc alkoxide, with aliphatic alcohols and phenol.[23] In our case, it was found that alkynylzinc was formed at room temperature based on experiments ran by Emily Williamson (Figure 13); this implied that the challenge involved epoxide ring-opening.

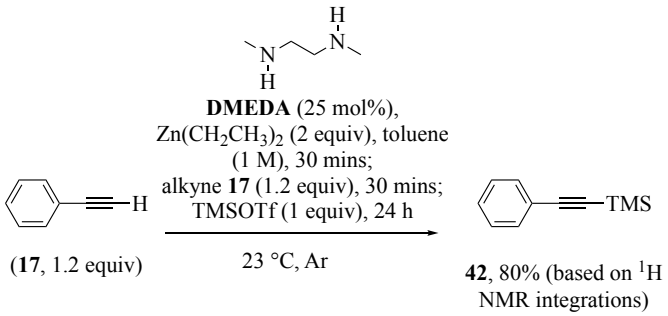


Figure 13. Control experiment for the formation of zinc acetylide. This work was performed by Emily Williamson from the McDonald Laboratory.

We reasoned that a secondary alkoxide may be generated to avoid a competing side reaction of alcohol with epoxide in situ by addition of isopropanol to diethylzinc and then reaction with the alkyne. The ethyl group or the alkoxide may then deprotonate the alkyne and follow with the ring-opening reaction of the epoxide at the least substituted carbon (Figure 14). To test this hypothesis out, a reaction with phenylacetylene **17** and benzyl glycidyl ether **40** was set up using isopropanol and diethylzinc (Figure 14). During aliquot analysis, possible product peaks were observed starting at 24 hours. Based on the crude ^{1}H NMR spectra, it was concluded that this method was not better than the diethylzinc control reaction nor the L**2**/diethylzinc combination as the conversion to **41** was low.

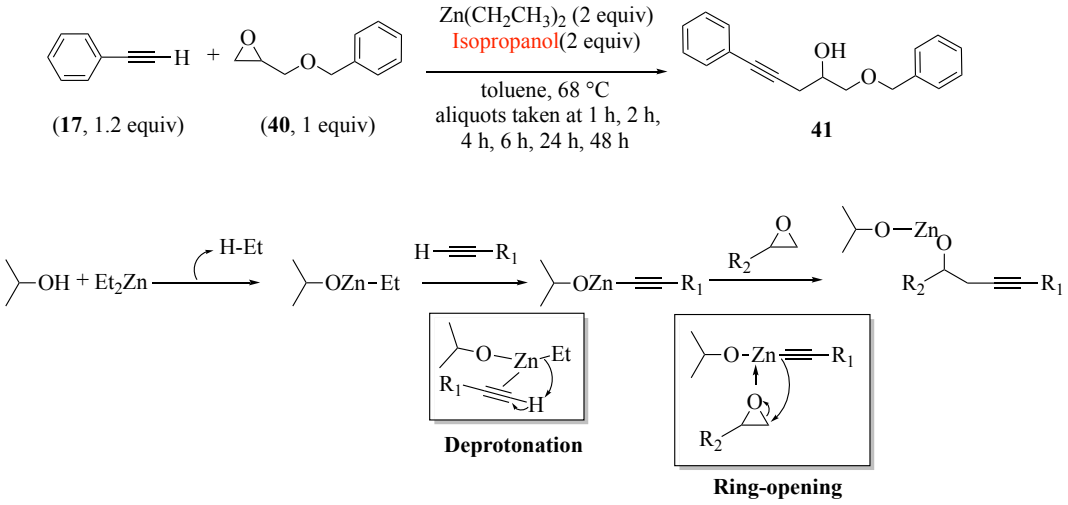
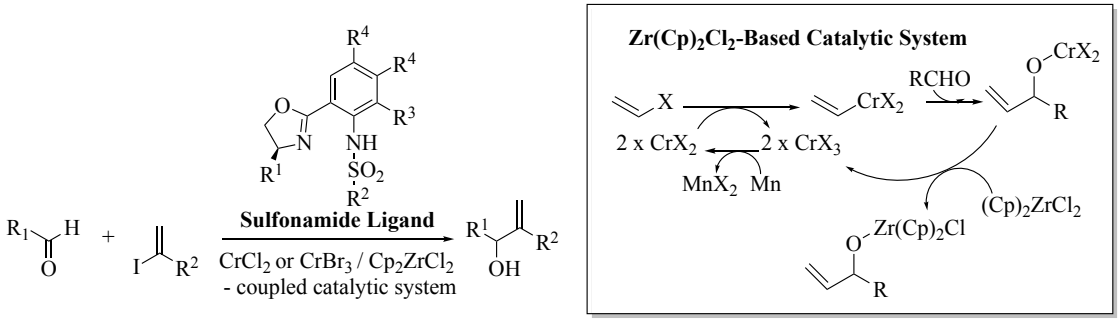


Figure 14. Aliquot analysis experiment and the proposed mechanism to generate a secondary alkoxide in situ using isopropanol and diethylzinc.

We then looked into activation of the epoxide with zirconocene dichloride since it was unclear whether diethylzinc alone was Lewis acidic enough to activate the epoxide. This idea came from an initial attempt to get catalytic turnover using zirconocene dichloride as a trapping reagent in combination with L**2**. A similar transmetallation step with zirconocene dichloride was

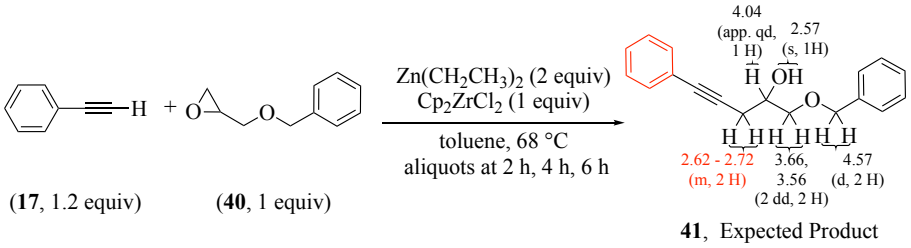
observed in the catalytic cycle for Cr-mediated Nozaki-Hiyama-Kishi coupling of aldehydes with different types of halides (Figure 15).[24]

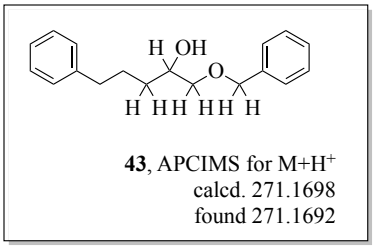


Org. Lett. **2004**, *6*(26), 5031-5033.

Figure 15. Zirconocene dichloride (Cp_2ZrCl_2) for Cr-mediated Nozaki-Hiyama-Kishi coupling of aldehydes with halides.

To test this hypothesis, a reaction with phenylacetylene **17** and benzyl glycidyl ether **40** was set up using zirconocene dichloride in combination with diethylzinc (Figure 16). The crude material for the 6-hour reaction was purified using silica gel chromatography (15-100 % EtOAc: hexanes) and resulted in a series of fractions.





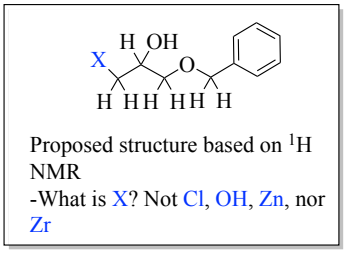
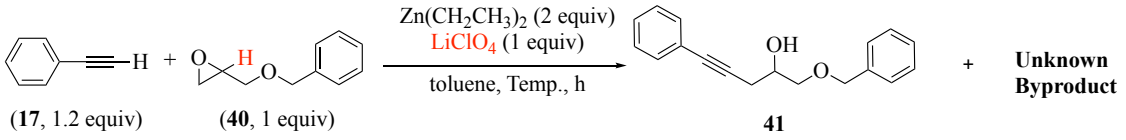


Figure 16. Zirconocene dichloride (Cp_2ZrCl_2) for the activation of benzyl glycidyl ether **40**.

One of the fractions was submitted for mass spectrometry and showed three major peaks (273.18467 m/z, 255.17436 m/z, and 271.16923 m/z). The peak at 271.16923 m/z corresponded to the reduced form of the homopropargylic alcohol (**43**, Figure 16). The ^{1}H NMR spectrum of the fraction was similar to the ^{1}H NMR spectrum of the isolated homopropargylic alcohol **41**, but it was missing the multiplet peak for the propargylic hydrogens (Figure 16, shown in red). In addition, the integration for the aromatic groups was 6H, which meant only one phenyl group for homopropargylic alcohol **41** was accounted for. Based on the ^{1}H NMR spectrum, it was determined that the reduced form of the homopropargylic alcohol **43** wasn't the main component in the fraction collected; instead, a structure with an electronegative atom (X) was proposed (Figure 16, shown in blue). The electronegative atom wasn't a chlorine, hydroxyl, zinc, nor zirconium although the expected mass of the proposed structure with zirconium as the electronegative atom was one mass unit off from the 255.17436 m/z peak.

We continued to search for a Lewis acid that effectively activated the epoxide. We hypothesized that lithium perchlorate ($LiClO_4$) may activate the epoxide and then transmetallate to prepare the zinc alkoxide species. The metal may need to react with another epoxide to have a catalytic system in the absence of L**2**. The procedure was modified to include addition of alkyne to diethylzinc to form the zinc acetylide and addition of epoxide to lithium perchlorate in a separate round-bottom flask to activate the epoxide (Figure 17, Reaction Set-up). Both mixtures were combined after being stirred separately for 30 minutes. The ^{1}H NMR spectra supported that $LiClO_4$ didn't effectively activate the epoxide at room temperature (entries 1 and 2). To speed up the reaction, two 24-hour reactions were set up at increased temperatures (39 ℃ and 70 ℃). The reaction at 39 ℃ gave a 1: 4: 2 ratio of **40**: **41**: byproduct, while the reaction at 70 ℃ gave conversion to the homopropargylic alcohol **41** and the byproduct without presence of starting

materials (entries 3 and 4). However, it was evident through analysis of crude ^{1}H NMR spectra that the unknown byproduct started to dominate as observed by the multiplet at 3.88 ppm and a peak that overlapped the two doublet of doublets at 3.63 ppm from the homopropargylic alcohol **41**. This unknown impurity may arise from side reactions with the 1 equivalent of Lewis acid.



Entry	Temp. (°C)	Time (h)	**40**	**41**	**Byproduct**
1	r.t.	2	1.0	0.020	0.010
2	r.t.	24	1.0	0.26	0.14
3	39	22	1.0	4.2	2.20
4	70	23	0	full conversion	full conversion

*Growth of the product was identified based on the integration of peaks corresponding to **40** (m at 3.09 ppm), homopropargylic alcohol **41** (apparent qd at 4.04 ppm), and an unknown byproduct (m at 3.88 ppm). Phenylacetylene **17** wasn't observed in the crude ^{1}H NMR spectra. The results are reported as relative ratios after normalizing benzyl glycidyl ether **40** to 1.0.

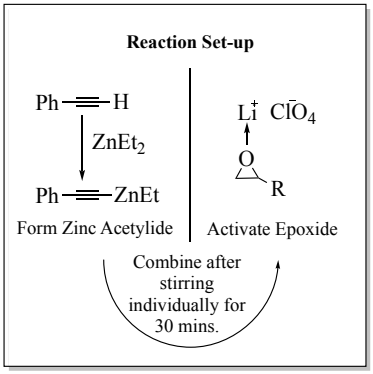


Figure 17. Progression of reaction with benzyl glycidyl ether **40** and phenylacetylene **17** using lithium perchlorate ($LiClO_4$) and diethylzinc.

Finally, we speculated that HFIP may protonate the epoxide without protonation of the alkynylzinc. It was hypothesized that the strong hydrogen bond donating abilities of HFIP may activate the electrophilic epoxide and the low solvent nucleophilicities may prevent competing addition of solvent.[25,26,27] HFIP replaced toluene as solvent in the reaction with benzyl glycidyl ether **40** and phenylacetylene **17**, but it was found to be incompatible with the reaction conditions used. After diethylzinc was added to HFIP, an opaque white solid was formed within the round-bottom flask. Based on this observation, it was possible that HFIP reacted with diethylzinc

before alkynylzinc was formed. There was also no product formation observed on ^{1}H NMR after 24 hours, but unreacted benzyl glycidyl ether **40** was observed.

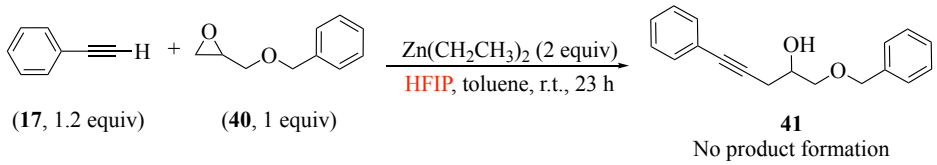


Figure 18: Reaction of benzyl glycidyl ether **40** and phenylacetylene **17** with HFIP.

Conclusion

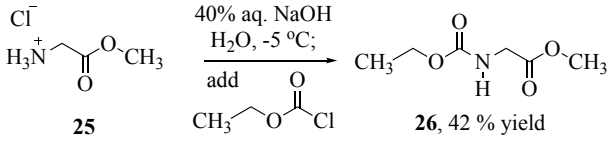
To conclude, we successfully synthesized and purified two novel pentadentate ligands that promoted epoxide ring-opening with terminal alkynes. The pseudoephedrine-derived ligand (L**2**) promoted the regioselective ring-opening reaction of 1, 2-epoxyhexane **20** with phenylacetylene **17** to give the homopropargylic alcohol **24** as the major product and styrene oxide **33** with 1-decyne **34** to give α-addition to styrene oxide as the major product **35**. The effect of the pseudoephedrine-derived ligand (L**2**) on the reaction of benzyl glycidyl ether and phenylacetylene was less clear as there may be a chelation effect between the zinc and the oxygens of benzyl glycidyl ether that facilitated the reaction. We also reported the first Zn-promoted epoxide ring-opening with terminal alkynes; it is a simplification from the stoichiometric method that uses both *n*-butyllithium and BF_3-OEt_2. Future goals for this project include redesigning the ligand to better facilitate the catalytic ring-opening reaction of epoxides with terminal alkynes and expanding the substrate scope to more relevant fragments for the synthesis of natural products like Bastimolide A and PM toxin A.

Experimental:

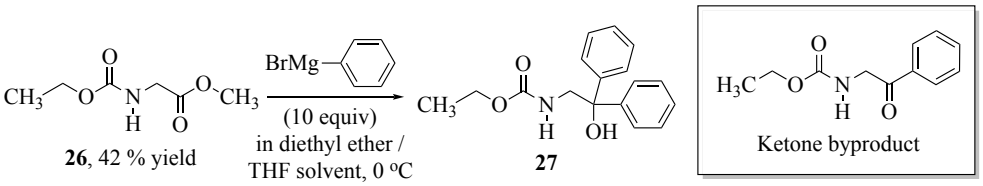
General Information:

Flash chromatography purification was carried out using Siliaflash® P60 silica gel obtained from Silicycle. ^{1}H NMR spectra were obtained from the Emory University NMR facility and recorded on INOVA 600 (600 MHz), INOVA 400 (400 MHz), and VNMR 400 (400 MHz). Chemical shifts (δ) are reported in ppm and referenced using $CDCl_3$ as solvent (δ ^{1}H NMR, 7.26 ppm; ^{13}C NMR, 77.16 ppm). Coupling constants *J* are given in Hz. Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; ddd, doublet of doublet of doublets; ddt, doublet of doublet of triplets; qdd, quartet of doublet of doublets; dt, doublet of triplets; m, multiplet. High Resolution Mass Spectrometry (HRMS) experiments were recorded on Thermo Scientific Exactive Plus (orbitrap) equipped with Atmospheric Pressure Chemical Ionization (APCI) source. Reaction progress was monitored via thin layer chromatography (TLC) on aluminum sheets coated with TLC Silica gel 60 F254 obtained from MilliporeSigma. Compounds were detected by staining mostly with phosphomolybdic acid (PMA) stain, although the *p*-Anisaldehyde stain was used for detection/purification of product in one catalytic reaction. All reactions were carried out with anhydrous toluene, Dimethylformamide (DMF), tetrahydrofuran (THF) from a solvent purification system. They were also carried out using oven-dried glassware and argon-charged (argon balloon or argon line) glassware. Organic solutions were concentrated using a rotary evaporator (rotovap) connected to a vacuum pump and a water bath for cooling/heating.

Precatalyst Preparation



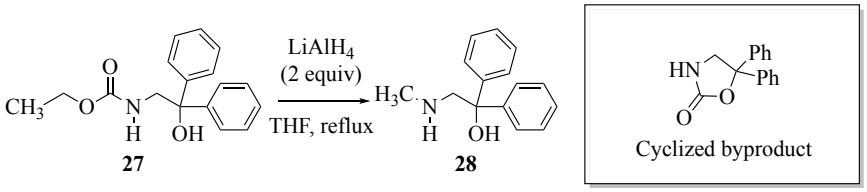
Preparation of N-(ethoxycarbonyl)-α-amino methyl carbonyl ester **26**.[17] A solution of glycine methyl ester hydrochloride **25** (1.56 g, 12.4 mmol) in distilled water (2.24 mL) cooled to 0 °C was carefully neutralized to a pH of 8 with a 40% aqueous sodium hydroxide solution (1.12 mL), keeping the internal temperature below 5 °C using a salt bath. Ethyl chloroformate (1.31 mL, 13.7 mmol, 1.1 equiv) was then added dropwise with vigorous stirring to maintain the internal temperature below 5 °C. After all the ethyl chloroformate was added, the temperature rose above 10 °C, at which time more ice was added to cool back down. The reaction mixture was stirred at 0 °C for 45 min, at which time a second portion of a 40% aqueous sodium hydroxide solution (1.23 mL) was added. The reaction mixture was extracted with ether. The organic layers were combined, dried with magnesium sulfate ($MgSO_4$), and concentrated through rotary evaporation to give **26** as the major compound (clear liquid, 0.848 g, 42% yield).). The temperature wasn't consistently maintained at <5 °C. Perhaps, this influenced the yield of the reaction. Synthesis of compound **26** followed a similar procedure to Kende et al.[17], who reported the synthesis of this compound from glycine ethyl ester hydrochloride and methyl chloroformate. Major component **26**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 1H), 4.09 (q, 2H), 3.91 (d, J = 5.8 Hz, 2H), 3.70 (s, 3H), 1.19 (t, 3H). Unknown impurity at δ 4.33 (q, J = 7.2 Hz, 0.07), 1.33 (t, 0.07H).



Preparation of ethyl (2-hydroxy-2,2-diphenyl ethyl) carbamate **27**.[16] A solution of 6.00 mL of phenylmagnesium bromide (3.0 M in diethyl ether, 37.5 mmol, 4.54 equiv.) was added dropwise to a solution of compound **26** (1.33 g, 8.27 mmol) in THF (16.3 mL) at 0 °C. The reaction was carried out in a 100 mL round-bottom flask (RBF) under argon flow through an argon line. After being stirred for 1 h at this temperature, the reaction was quenched with saturated, aqueous NH_4Cl. The mixture was extracted with diethyl ether. The extracts were combined, dried over $MgSO_4$, filtered, and concentrated through rotary evaporation to give **27** as a yellow oil. Purification of the crude product was attempted through column chromatography (SiO_2, 20% EtOAc: hexane, $R_f = 0.33$), but **27** was inseparable. 1.26 g of a white solid was collected from the column with all the expected hydrogen peaks of compound **27** observed in addition to minor impurities. Compound **27**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.39 (m, 5H, Ph), 7.39 – 7.22 (m, 6H, Ph), 4.88 (br s, 1H, NH), 4.08 (q, J = 7.1 Hz, 2H, CH_2O), 3.99 (d, J = 6.3 Hz, 3H, CH_2NH), 3.25 (s, 1H, OH), 1.19 (t, J = 7.1 Hz, 2H, CH_3). The number of H's didn't add up to the expected. There should be a total of 10H in the aromatic region and 2H corresponding to the methylene hydrogens closest to the N-H. The terminal methyl group should correspond to 3H. ^{1}H NMR peaks were assigned based on a literature reference.[28]

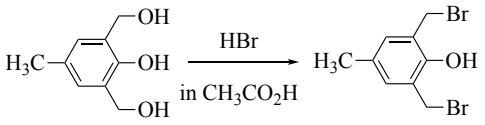
There was little if any evidence of the starting material (methoxy group or singlet at 3.7 ppm was absent). This indicated that peaks around 8.0 ppm could be a small amount of ketone byproduct. The ketone byproduct is not known. Impurities: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 –

7.91 (m, 0.26H), 7.62 (s, 0.06H), 7.55 – 7.48 (m, 0.21H), 5.68 (s, 0.12H), 5.11 (s, 0.11H), 4.71 (d, J = 4.5 Hz, 0.25H), 4.16 (dd, J = 11.0, 7.1 Hz, 0.32H), 3.76 (s, 0.34H), 1.56 (s, 1H, H_2O), 1.32 – 1.23 (m, 1H).



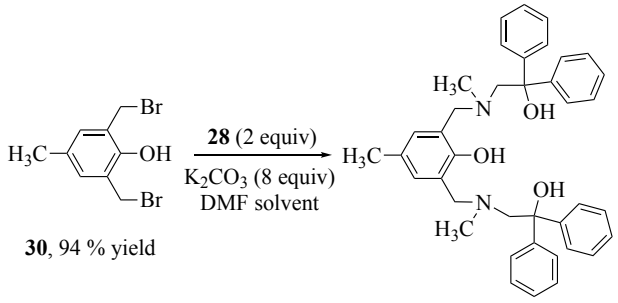
27 28

Preparation of 2-(methylamino)-1,1-diphenyl ethan-1-ol **28**.[16] A mixture of **27** (0.315 g, 1.10 mmol) and lithium aluminum hydride (0.0839 g, 2.21 mmol, 2 equiv.) in THF (4.0 mL) was refluxed for 22 h under argon. Solid lithium aluminum hydride was used despite safety concerns as attempts with lithium aluminum hydride solution (2.0M in THF) gave an 18% of crude aminoalcohol **28**. After cooling, the reaction mixture was diluted with diethyl ether (5.7 mL), water (0.10 mL), 15% aqueous sodium hydroxide (0.10 mL), and water (0.25 mL). After being stirred for 1 h, the mixture was filtered through a pad of Celite, and the filtrate was concentrated through rotary evaporation to give aminoalcohol **28** (0.216 g, 86% crude) as a colorless oil. Aminoalcohol **28** was not isolated through silica gel chromatography due to its high polarity (R_f = 0) at 50 % EtOAc: hexane. Purification of crude aminoalcohol **28** was also attempted through the following protocol: successive washes with water and 15% aqueous NaOH, extraction with aqueous HCl, treatment with Na_2CO_3, and recrystallization from hexanes.[28] The ^{1}H NMR spectrum showed minor impurities as well as the following product peaks of aminoalcohol **28**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, 4H), 7.35 – 7.26 (m, 4H), 7.24 – 7.18 (m, 2H), 3.29 (s, 2H, CH_2NH), 2.46 (s, 3H, CH_3). The NH and OH broad peaks weren't observed on ^{1}H NMR due to the presence of minor impurities.



29 **30**, 94 % yield

Preparation of 2,6-bis(bromomethyl)p-cresol **30**. The preparation of dibromide **30** was based on literature precedents.[18,29] 2,6-Bis(hydroxymethyl)-4-cresol **29** (1.355 g, 8.056 mmol) was dissolved in 7.4 mL of a HBr/acetic acid solution (33% HBr) and stirred overnight under argon. The reaction mixture was diluted with ~11 mL of H_2O, and the formed solid was filtered and dried to afford a light-yellow powder (94% yield, 2.220 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 2H, *m*-C_6H_2), 5.41 (s, 1H, OH), 4.54 (s, 4H, *CH*$_2$Br), 2.26 (s, 3H, Ar*CH*$_3$).

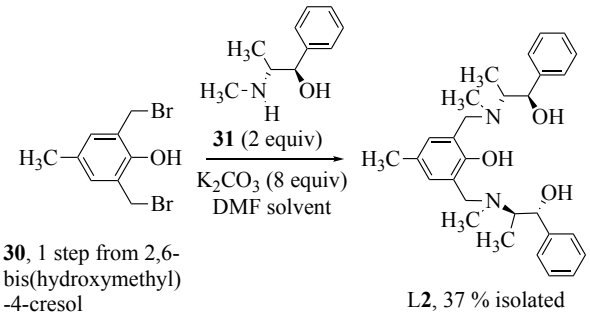


30, 94 % yield

L**1**, 31 % isolated

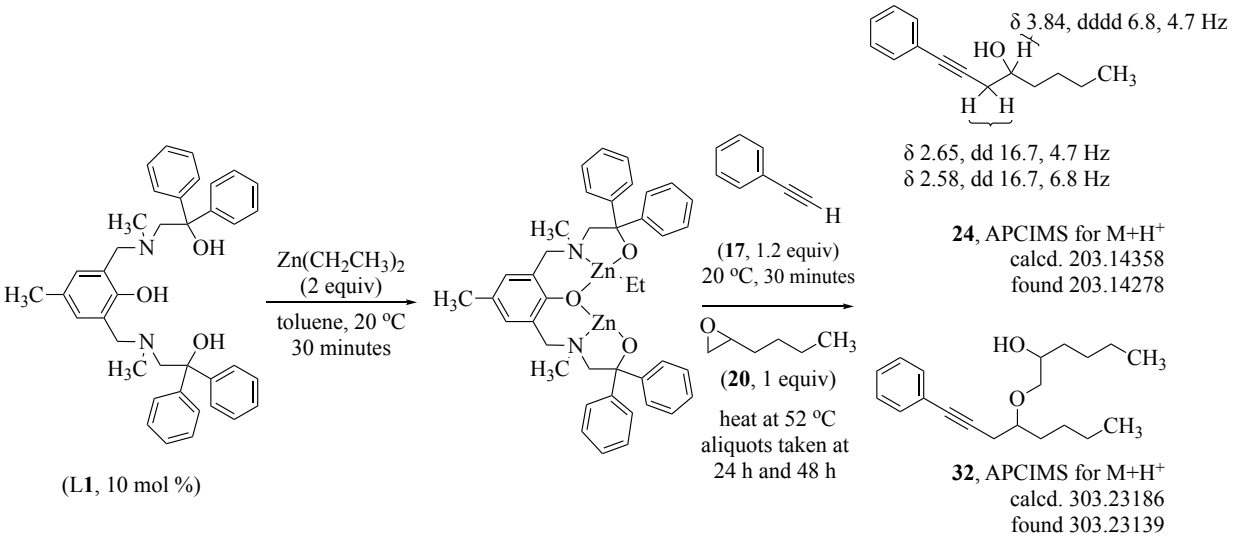
Preparation of Novel, Achiral L**1**.[18] Following a procedure for diphenylprolinol, dibromide **30** (0.1403 g, 0.4772 mmol) was added in one portion to a stirred and cooled solution of unpurified aminoalcohol **28** (2.0 equiv, 0.2160 g, 0.9503 mmol) and K_2CO_3 (8.0 equiv, 0.5262 g, 3.807 mmol) in dry DMF (1.95 mL) under argon. The ice bath was removed after the addition and the resulting solution stirred at room temperature for 48 h before it was diluted with water (9.2 mL) and diethyl ether (9.2 mL). The two phases were separated, and the aqueous phase was extracted with diethyl ether (3x). The combined organic phases were washed with water (2x) and brine (3x), dried ($MgSO_4$), and concentrated through rotary evaporation to form a sticky foam.

The crude product was purified through column chromatography (grade III alumina, 10% EtOAc: hexane) to yield L**1** as a crusty, white solid (31 %). Grade III alumina was prepared through the addition of 6% (w/w) of water (4.231 g) to grade I alumina (66.29 g). The mixture was stirred for an hour until all clumps of solid were removed. It was found early on through extensive experimentation with L**2** that grade I alumina must be rendered less active for aminoalcohol **28** and L**1** to come off the column and thus, be separated. A short/narrow column was filled with ~3.0 inches of grade III alumina. The crude product was first dissolved with a couple drops of ethyl acetate and ~1 mL of the 10 % EtOAc: hexane mixture right before being loaded onto the column. The fractions were collected in test tubes and then spotted on TLC plate without elution. The TLC plates were then stained with phosphomolybdic acid (PMA) stain. Aminoalcohol **28** and L**1** were very polar and didn't move up the TLC plate, and thus, a break in spots indicated separation between the two. It was originally hypothesized that the most polar material was L**1**; however, aminoalcohol **28** eluted off the column last, which made it more polar. L**1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.14 (m, 21H), 6.72 (s, 2H), 3.63 (s, 4H), 3.37 (s, 4H), 2.18 (s, 3H), 1.97 (s, 6H). Impurities included ethyl acetate as observed by the following peaks: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (q, J = 7.1 Hz, 1H), 2.05 (s, 1H), 1.26 (t, J = 7.1 Hz, 1H). There was also an impurity at 5.86 (s, 1H) that may correspond to a trisubstituted alkene.

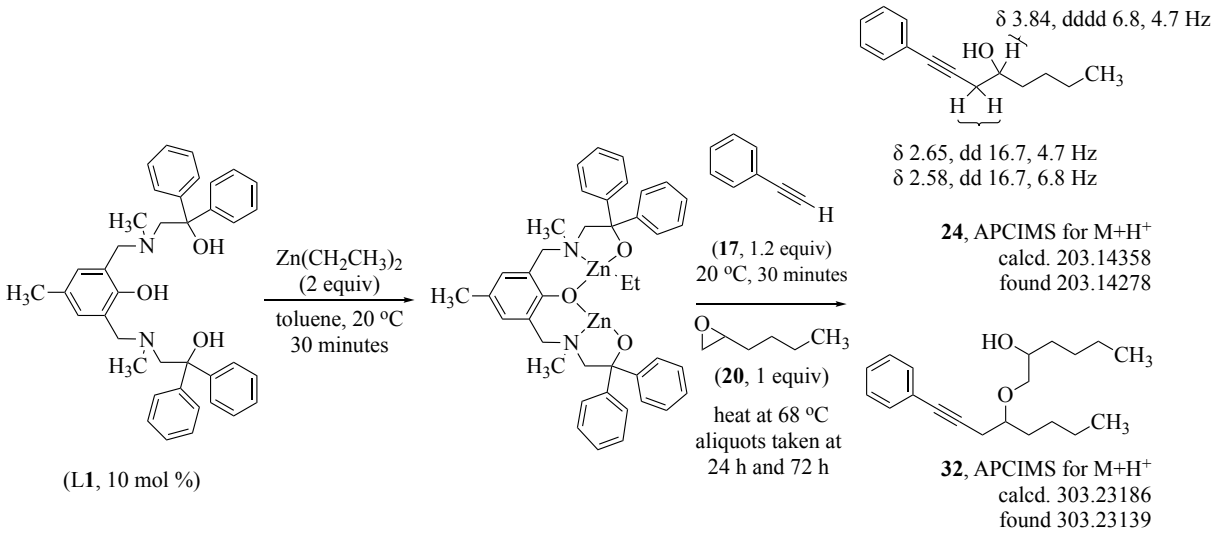


Preparation of Novel, Chiral ligand L**2**.[18] Dibromide **30** (0.5352 g, 1.817 mmol) was added in one portion to a stirred and cooled solution of **31** (2.0 equiv, 0.6042 g, 3.657 mmol) and K_2CO_3 (8.0 equiv, 1.995 g, 14.44 mmol) in dry DMF (7.0 mL) under argon. The ice bath was removed after the addition and the resulting solution was allowed to stir at room temperature for 48 h before it was diluted with water (12 mL) and diethyl ether (12 mL). The two phases were separated, and the aqueous phase was extracted with diethyl ether (3x). The combined organic phases were washed with water (2x) and brine (3x), dried ($MgSO_4$), and concentrated through rotary evaporation to form a sticky foam (0.6975 g, 83% crude yield). Pseudoephedrine **31** and **L2** were very polar and didn't move up the TLC plate. To purify, crude L**2** was dissolved in DCM and loaded on a grade III alumina column (3 inch) using 15-100 % EtOAc: hexane. The fractions were collected in large test tubes and then spotted on TLC plate to see if they stained without elution of the solvent up the TLC plate. The purification step resulted in a 37 % yield or 0.3126 g of L**2**. L**2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 12H), 6.88 (s, 2H), 4.47 (d, *J* = 9.6 Hz, 2H), 3.89 (d, *J* = 13.3 Hz, 2H), 3.60 (d, *J* = 13.2 Hz, 2H), 2.92 (dq, 2H), 2.30 (s, 6H), 2.27 (s, 3H), 0.78 (d, *J* = 6.7 Hz, 6H). The integration for the aromatic hydrogens from 7.38 – 7.25 ppm was slightly higher than the expected 10H. Ethyl acetate was the only impurity observed: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (q, *J* = 7.1 Hz, 1H), 2.05 (s, 2H), 1.26 (t, *J* = 7.1 Hz, 3H).

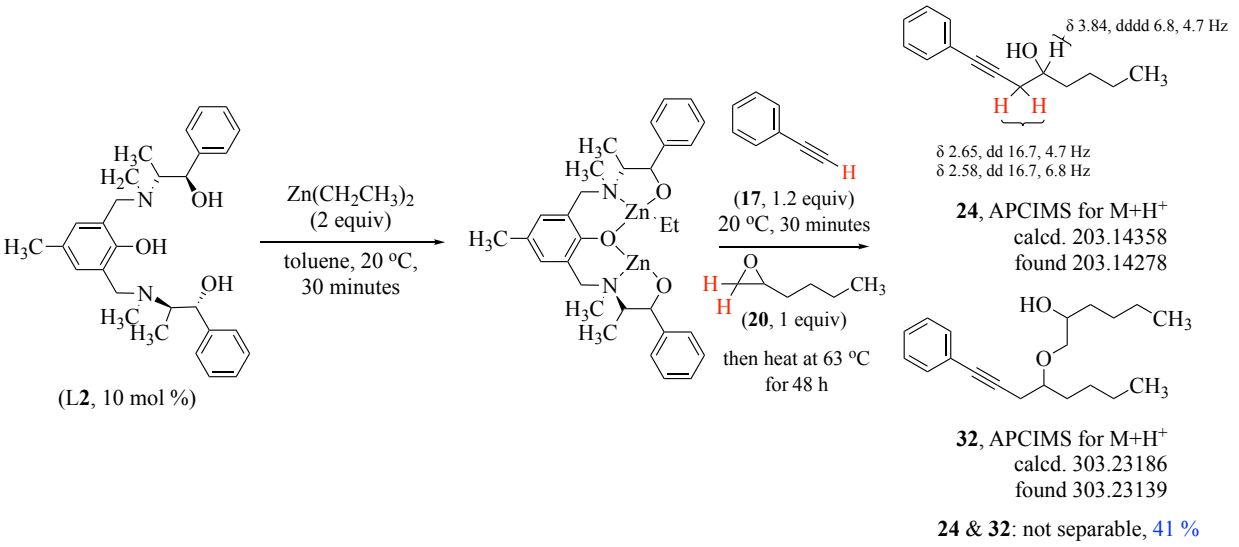
Ligand-catalyzed Reactions and Control Reactions



Under argon, a solution of $ZnEt_2$ (0.580 mL, 1.0M in hexane, 0.580 mmol, 2.0 equiv) was added to a stirred and cooled solution of L**1** (0.0172 g, 0.0293 mmol, 0.1 equiv) in anhydrous toluene (0.44 mL). The mixture was stirred at room temperature for 30 min. Phenylacetylene **17** (0.040 mL, 0.36 mmol, 1.2 equiv) was then added dropwise and stirred for 30 min at which time 1,2-epoxyhexane **20** (0.035 mL, 0.29 mmol) was added. After 24 h of stirring at 52 °C, half of the reaction was quenched with saturated, aqueous NH_4Cl. The organic phase was extracted 3x with diethyl ether and the combined organic layers were concentrated through rotary evaporation. The other half of the reaction was left to stir for a total of 48 h at the same temperature after which a similar workup was performed.

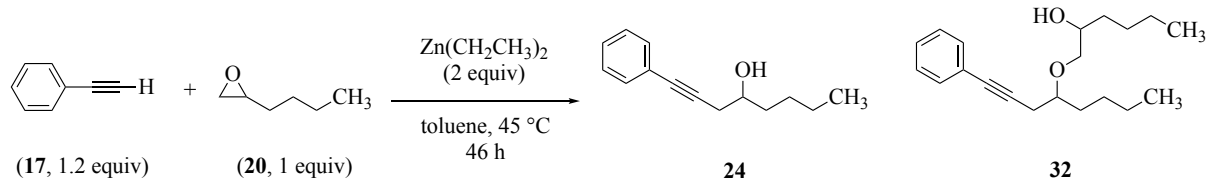


Under argon, a solution of $ZnEt_2$ (0.685 mL, 1.0M in hexane, 0.685 mmol, 2.0 equiv) was added to a stirred and cooled solution of L**1** (0.0201 g, 0.0343 mmol, 10 mol %) in anhydrous toluene (0.55 mL). The mixture was stirred at room temperature for 30 min. Phenylacetylene **17** (0.045 mL, 0.41 mmol, 1.2 equiv) was then added dropwise and stirred for 30 min at which time 1,2-epoxyhexane **20** (0.040 mL, 0.33 mmol) was added. After 48 h of stirring at 68 °C, half of the reaction was quenched with saturated, aqueous NH_4Cl. The organic phase was extracted 3x with diethyl ether and the combined organic layers were concentrated through rotary evaporation. The remaining amount of the reaction was left to stir for a total of 72 h at the same temperature after which a similar workup was performed. Purification of the crude products from the 48-h and 72-h reactions was attempted through column chromatography (SiO_2, 10% EtOAc: hexane). The TLC plate showed better separation with the 10% EtOAc: hexane mixture than with the pentane/ether solvent system. An 8 ½ inch SiO_2 column was used with smaller fractions collected, but separation was difficult as there were 3 spots (including **24** and **32**) very close together on the TLC plate. Mixed fractions were obtained (mostly **24** with some of **32**).



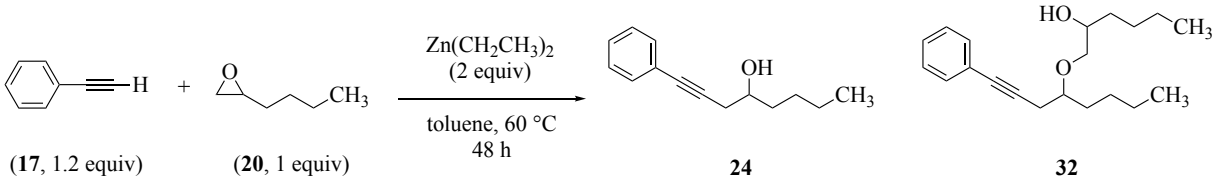
Under argon, a solution of $ZnEt_2$ (2.50 mL, 1.0M in hexane, 2.50 mmol, 2.0 equiv) was added to a stirred solution of L**2** (0.0575 g, 0.126 mmol, 10 mol %) in anhydrous toluene (1.2 mL). The mixture was stirred at room temperature for 30 min. Phenylacetylene **17** (0.166 mL, 1.51 mmol, 1.2 equiv) was then added dropwise and stirred for 30 min at which time 1,2-epoxyhexane **20** (1.50 mL, 1.26 mmol) was added. After 48 h of stirring at 63 °C, the reaction was quenched with saturated, aqueous NH_4Cl. The organic phase was extracted with diethyl ether and concentrated through rotary evaporation to give 0.2738 g of the crude product. The crude product was purified by column chromatography (SiO_2, 20% EtOAc: hexane) and gave 0.1033 g (41%) of homopropargylic alcohol **24** and a minor, inseparable impurity **32** (slightly yellow oil). There was one spot observed on TLC (R_f = 0.40, 20% EtOAc: hexane). Homopropargylic alcohol **24**: HRMS (APCI/FTMS) *m/z*: $[M + H]^+$ Calcd. for $C_{14}H_{19}O$, 203.14358; Found 203.14278. ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.35 (m, 2H), 7.34 – 7.15 (m, 3H), 3.84 (dddd, *J* = 6.8, 4.7 Hz, 1H), 3.74 – 3.41 (m, 0.15H), 2.65 (dd, *J* = 16.7, 4.7 Hz, 1 H), 2.58 (dd, *J* = 16.7, 6.8 Hz, 1H), 1.96 (dd, *J* = 5.3, 2.1 Hz, 1H), 1.69 – 1.52 (m, 3H), 1.49 – 1.30 (m, 5H), 1.00 – 0.83 (m, 3H).

Presence of byproduct **32** (alkoxide of **24** adding to another molecule of the epoxide) was supported by mass spectrometry peaks. Byproduct **32**: HRMS (APCI/FTMS) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{31}O_2$ 303.23186; Found 303.23139. The presence of a multiplet peak at 3.74 – 3.41 ppm (integrated to ~0.15) as well as the higher integration of the carbon chain (m at 1.69 – 1.52 ppm and m at 1.49 – 1.30 ppm) are also an indication of this byproduct.



(**17**, 1.2 equiv) (**20**, 1 equiv) **24** **32**

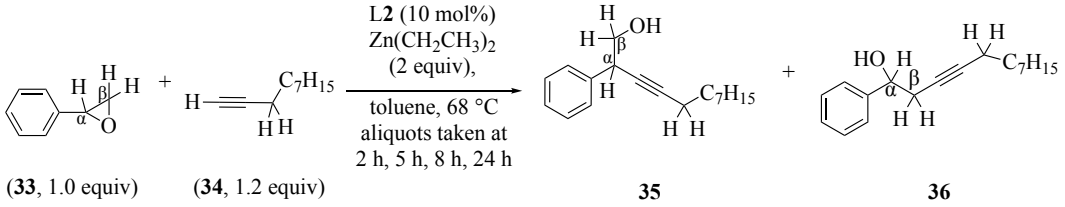
Under an argon balloon, a solution of $ZnEt_2$ (0.58 mL, 1.0M in hexane, 0.58 mmol, 2.0 equiv) was added to anhydrous toluene (0.40 mL). The mixture was stirred at room temperature for 30 minutes. Phenylacetylene **17** (0.040 mL, 0.36 mmol, 1.2 equiv) was then added dropwise and stirred for 30 min at which time 1,2-epoxyhexane **20** (0.035 mL, 0.29 mmol) was added. After 46 h of stirring at 45 °C, the reaction was quenched with saturated, aqueous NH_4Cl. The organic phase was extracted with diethyl ether and concentrated through rotary evaporation to give the crude product.



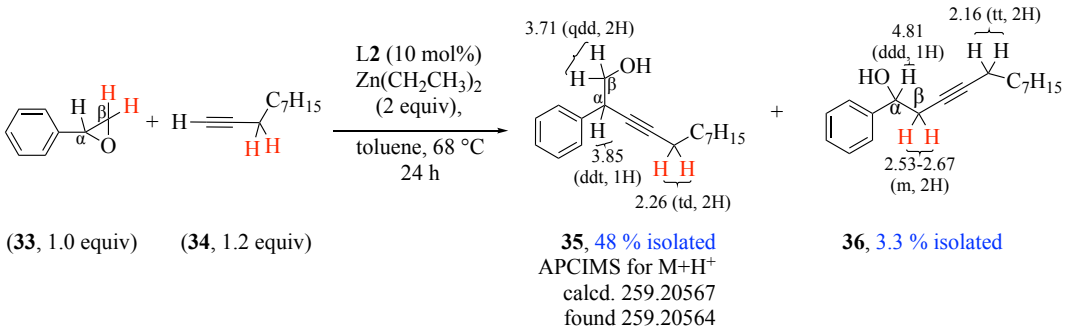
(**17**, 1.2 equiv) (**20**, 1 equiv) **24** **32**

Under an argon balloon, a solution of $ZnEt_2$ (0.685 mL, 1.0M in hexane, 0.685 mmol, 2.1 equiv) was added to anhydrous toluene (0.50 mL). The mixture was stirred at room temperature for 30 minutes. Phenylacetylene **17** (0.045 mL, 0.41 mmol, 1.2 equiv) was then added dropwise and stirred for 30 min at which time 1,2-epoxyhexane **20** (0.040 mL, 0.33 mmol) was added. After 48 h of stirring at 60 °C, the reaction was quenched with saturated, aqueous NH_4Cl. The organic

phase was extracted with diethyl ether and concentrated through rotary evaporation to give the crude product.



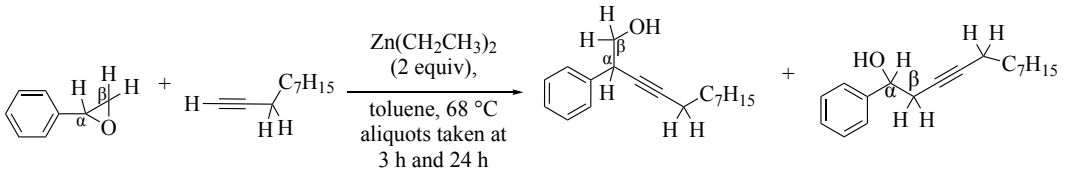
Under argon, a solution of $ZnEt_2$ (0.446 mL, 1.0 M in hexane, 0.446 mmol, 2.0 equiv) was added to a stirred solution of **L2** (0.0103 g, 0.0223 mmol, 10 mol %) in anhydrous toluene (0.35 mL). The mixture was stirred at room temperature for 30 min. 1-decyne **34** (0.048 mL, 0.27 mmol, 1.2 equiv) was added dropwise and stirred for 30 min at which time styrene oxide **33** (0.025 mL, 0.22 mmol) was added. The reaction was stirred for 24 h at 68 °C under a condenser However, aliquots were extracted at 2 h, 5 h, and 8 h and worked up in a scintillation vial. Each aliquot was quenched with saturated, aqueous NH_4Cl and the organic phase was extracted with diethyl ether. The organic layer was concentrated through rotary evaporation each time. The 24-h reaction was worked up in a similar manner.



Under an argon balloon, a solution of $ZnEt_2$ (2.50 mL, 1.0M in hexane, 2.50 mmol, 2.0 equiv) was added to a stirred and cooled solution of L**2** (0.0580 g, 0.125 mmol, 10 mol %) in anhydrous toluene (1.2 mL). The mixture was stirred at room temperature for 30 min. 1-decyne **34** (0.270 mL, 1.50 mmol, 1.2 equiv) was then added dropwise and stirred for 30 min at which time styrene oxide **33** (0.140 mL, 1.23 mmol) was added. After 24 h of stirring at 68 °C, the reaction was quenched with saturated, aqueous NH_4Cl. The organic phase was extracted with diethyl ether and concentrated through rotary evaporation to give 0.2542 g of the crude product. The crude product was purified by column chromatography (SiO_2, 20% EtOAc: hexane, R_f of **35** = 0.50), and gave 0.1514 g (48%) of the major regioisomer **35** (slightly yellow oil). The major regioisomer **35** is an unknown compound, but the ^{1}H NMR and ^{13}C NMR peaks observed were compared to a similar structure in the literature with a shorter carbon chain.[21] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.31 (m, 4H), 3.85 (ddt, *J* = 8.0, 5.9, 2.2 Hz, 1H), 3.71 (qdd, *J* = 10.4, 7.8, 5.9 Hz, 2H), 2.26 (td, *J* = 7.1, 2.2 Hz, 2H), 1.89 (t, *J* = 1.5 Hz, 1H), 1.67 – 1.49 (m, 3H), 1.47 – 1.18 (m, 10H), 0.98 – 0.81 (m, 3H). The integration of the multiplet at 1.67 – 1.49 ppm was slightly higher (3H) for the major regioisomer **35** and corresponded to a methylene group (2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.73, 134.47, 133.84, 130.30, 129.13, 128.73, 128.62, 128.04, 127.85, 127.39, 85.59, 68.05, 65.59, 41.68, 33.93, 31.97, 31.94, 29.35, 29.23, 29.21, 29.10, 29.06, 24.84, 22.81, 22.78, 18.97, 14.25, 14.23. There should be 16 unique carbon peaks shown

in the ^{13}C NMR spectrum of the major regioisomer **35**. There are substantially more carbon signals observed, which may indicate a possible contamination during submission for ^{13}C NMR. HRMS (APCI/FTMS) *m/z*: $[M + H]^+$ Calcd. for $C_{18}H_{27}O$, 259.20567; Found 259.20564.

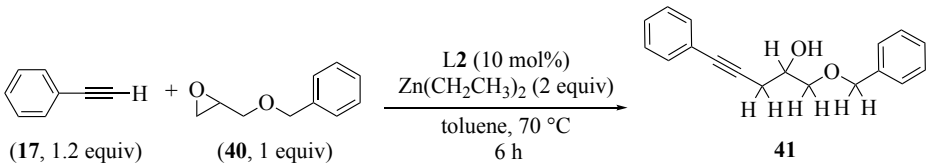
The minor regioisomer **36** (0.0108 g, ~3%) was isolated from the major regioisomer. The minor regioisomer **36** had an $R_f = 0.57$ at 20% EtOAc: hexane. Minor impurities were observed. ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.02 (m, 8H), 4.81 (ddd, J = 8.1, 5.1, 3.4 Hz, 1H), 2.67 – 2.53 (m, 2H), 2.43 (d, J = 3.4 Hz, 1H), 2.39 – 2.23 (m, 1H), 2.16 (tt, J = 7.1, 2.4 Hz, 2H), 1.52 – 1.43 (m, 2H), 1.42 – 1.14 (m, 12H), 0.89 (t, 3H). The observed multiplicity (triplet of triplets) of the propargylic methylene hydrogens at 2.16 ppm were consistent with what was expected for the homopropargylic alcohol **36** and not the propargylic alcohol from Meinwald rearrangement to the aldehyde, which we expected to show up as a triplet of doublets (td). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.0, 128.6, 127.9, 125.9, 83.9, 77.4, 72.8, 32.0, 30.3, 29.4, 29.3, 29.1, 29.1, 22.9, 18.9, 14.3. The minor regioisomer **36** is an unknown compound, but the ^1H NMR and ^{13}C NMR peaks observed were compared to a similar structure in the literature with a shorter carbon chain.[20]



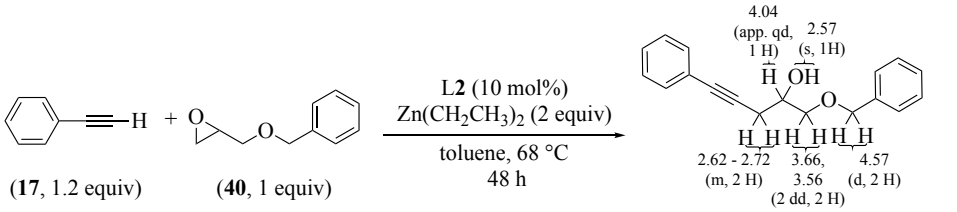
(**33**, 1.0 equiv) (**34**, 1.2 equiv) **35** **36**

Under an argon balloon, a solution of $ZnEt_2$ (0.450 mL, 1.0 M in hexane, 0.450 mmol, 2.0 equiv) was added to cooled, anhydrous toluene (0.35 mL). The mixture was stirred at room temperature for 30 min. 1-decyne **34** (0.048 mL, 0.27 mmol, 1.2 equiv) was then added dropwise and stirred

for 30 min at which time styrene oxide **33** (0.025 mL, 0.22 mmol) was added. The reaction was stirred for 3 h at 68 °C under a condenser. An aliquot was then quenched with saturated, aqueous NH_4Cl and the organic phase was extracted with diethyl ether. The organic layer was concentrated through rotary evaporation and submitted for ^1H NMR. After 24 h, the reaction was stopped and worked up. The work-up was similar, but the organic phase was passed through a fritted funnel before being concentrated through rotary evaporation and submitted for NMR.



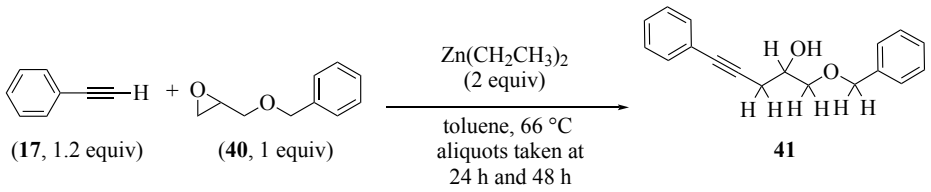
Under an argon balloon, a solution of $ZnEt_2$ (2.13 mL, 1.0M in hexane, 2.13 mmol, 2.0 equiv) was added to a stirred and cooled solution of L**2** (0.0493 g, 0.107 mmol, 10 mol %) in anhydrous toluene (1.05 mL). The mixture was stirred at room temperature for 30 min. Phenylacetylene **17** (0.140 mL, 1.27 mmol, 1.2 equiv) was then added dropwise and stirred for 30 min at which time benzyl glycidyl ether **40** (0.163 mL, 1.07 mmol) was added. After 6 h of stirring at 70 °C, the reaction was quenched with saturated, aqueous NH_4Cl. The organic phase was extracted with diethyl ether and concentrated through rotary evaporation.



(**17**, 1.2 equiv) (**40**, 1 equiv)

41, 67 % isolated,
APCIMS for $M+H^+$calcd. 267.13796
found 267.13798

Under an argon line, a solution of $ZnEt_2$ (2.518 mL, 1.0M in hexane, 2.518 mmol, 2.0 equiv) was added to a stirred and cooled solution of L**2** (0.0582 g, 0.1259 mmol, 10 mol %) in anhydrous toluene (1.2 mL). The mixture was stirred at room temperature for 30 min. Phenylacetylene **17** (0.1660 mL, 1.511 mmol, 1.2 equiv) was then added dropwise and stirred for 30 min at which time benzyl glycidyl ether **40** (0.1900 mL, 1.246 mmol) was added. After 48 h of stirring at 68 °C, the reaction was quenched with saturated, aqueous NH_4Cl. The organic phase was extracted with diethyl ether and concentrated through rotary evaporation and resulted in 0.3452 g of a crude yellow oil. The crude product was then purified by column chromatography (SiO_2, 20% EtOAc: hexane) and gave 0.2262 g (67 % yield) of a clear oil. The purification was simple as there was separation between four spots observed on the TLC plate after staining with the *p*-Anisaldehyde stain. Homopropargylic alcohol **41** stained as a bright yellow spot at an $R_f = 0.37$ using a 25% EtOAc: hexane mixture; benzyl glycidyl ether **40** had an $R_f = 0.26$. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 – 7.22 (m, 10H, 2Ph), 4.57 (d, J = 1.3 Hz, 2H, PhCH_2O), 4.04 (app qd, J = 6.5, 3.8 Hz, 1H, C*H*OH), 3.66 (dd, J = 9.6, 3.9 Hz, 1H, OC*H*), 3.56 (dd, J = 9.6, 6.5 Hz, 1H, OC*H*), 2.72 – 2.62 (m, 2H, 2 C*H*C≡C), 2.57 (s, J = 15.5 Hz, 1H, O*H*). ^{1}H NMR peaks of homopropargylic alcohol **41** agree with those reported in the literature.[22] HRMS (APCI/FTMS) *m/z*: $[M + H]^+$ Calcd. for $C_{18}H_{19}O_2$, 267.13796; Found 267.13798.



Under an argon line, a solution of $ZnEt_2$ (2.13 mL, 1.0M in hexane, 2.13 mmol, 2.0 equiv) was added to cooled, anhydrous toluene (1.05 mL). The mixture was stirred at room temperature for 30 min. Phenylacetylene **17** (0.140 mL, 1.27 mmol, 1.2 equiv) was then added dropwise and stirred for 30 min at which time benzyl glycidyl ether **40** (0.163 mL, 1.07 mmol) was added. After 24 h of stirring at 66°C, an aliquot from the reaction was quenched with saturated, aqueous NH_4Cl. The organic phase was extracted with diethyl ether and concentrated through rotary evaporation, allowing an ^1H NMR spectrum to be taken. After a total of 48 h of stirring, the rest of the reaction was worked up in a similar manner, resulting in 0.2715 g of a crude yellow oil.

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