

Cobalt Catalyzed Enantioselective Reductive Coupling of Imines and Internal Alkynes

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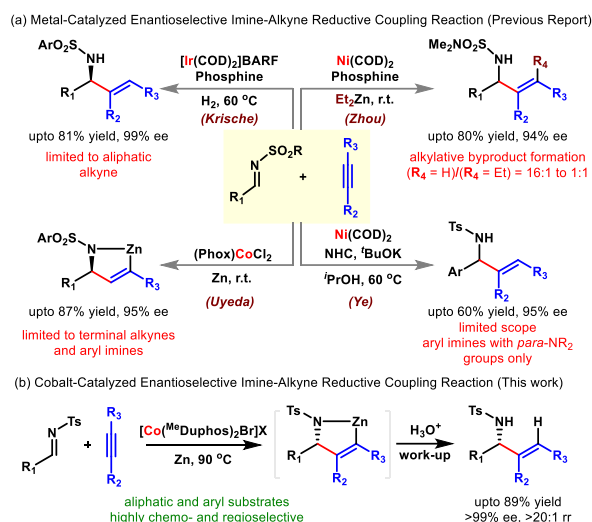
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Abstract: Chiral allylic amines hold significant importance as structural components in natural products, pharmaceuticals, and chiral catalysts. In this study, we have delved into cobalt-catalyzed enantioselective reductive coupling of imines with internal alkynes. The key to our success lies in developing a cobalt bisphosphine conglomerate catalyst and utilizing zinc as the electron donor. Our investigations have indicated that an in-situ cobalt(I) catalyst orchestrates the oxidative cyclization of alkynes and imines. Zinc plays a pivotal role in facilitating the transmetalation of the resulting azacobaltacycle. Subsequently, the organozinc intermediate is captured by a proton. Remarkably, the reaction proceeds under mild conditions and accommodates a wide range of substrates. Both symmetric and asymmetric alkyl and aryl alkynes have been successfully coupled with various imines. We have isolated tri- and tetrasubstituted allyl amines in exceptional yields exceeding 89%, with enantiomeric excess surpassing >99% and regioselectivities exceeding >20:1. These chiral allylic amines can serve as versatile platform molecules for subsequent transformations while preserving their stereochemical integrity to a high degree.

Introduction

Chiral allylic amines are attractive synthetic targets due to their diverse bioactivities and versatility as synthons for subsequent manipulations.^[1] Metal-catalyzed Tsuji-Trost amination^[2] and Overman rearrangement^[3] of allyl systems devised one of the highly effective protocols for their synthesis. Another popular alternative involved the asymmetric addition of vinyl organometallic to electrophilic imines.^[4] Among them, Noyori-type vinyl zinc addition^[5] and Nozaki-Hiyama-Kishi^[6] reactions are notable. While powerful, the pre-synthesis of starting materials, vinyl organometallic reagents, and associated stereoselectivity challenges advocated for benign options.

The imine vinylation *via* direct reductive coupling of imines with alkynes is logically uncovered as an exciting operationally simple approach.^[7] However, unlike the reductive coupling of alkynes with aldehydes,^[8] the coupling with imines is limited in its prominence. The racemic imine-alkyne coupling reaction is known using diverse stoichiometric metals.^[4a] Jamison first attempted a three-component alkylative coupling of alkynes, imines, and triethyl borane for synthesizing chiral allyl amine.^[9] In 2007, Krische pioneered the asymmetric imine-alkyne reductive coupling employing rhodium^[10] and iridium^[11] metal complexes using hydrogen as a benign reductant (Schemes 1a). Although versatile with diverse imine partners, the later reaction was limited to aliphatic alkynes only, and using 5d transition metal catalysts also campaigns for sustainable alternatives. Later, Zhou employed Et₂Zn as the terminal reductant for imine-alkyne reductive coupling using catalytic Ni(0)/phosphine (Scheme 1a).^[12] However, the methods suffer from chemoselectivity issues from the reductant-derived undesired alkylative cross-coupling product.



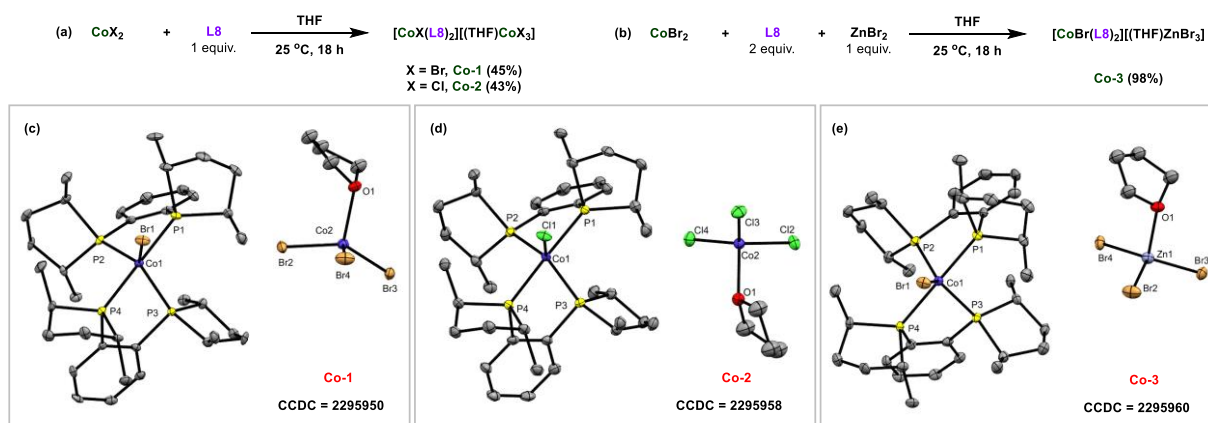
Scheme 1. Transition Metal Catalyzed Enantioselective Imine-Alkyne Reductive Coupling Reaction: (a) Previous Work, (b) This Work.

Recently, the Ye group modified the protocol using Ni(0)/NHC as the catalyst and isopropanol as a reductant (NHC = *N*-heterocyclic carbene, Scheme 1a).^[13] However, this method could only accommodate moderate enantioselectivity with few electron-rich amino-substituted imines. A redox-neutral reaction employing an amine and an alkyne via borrowing hydrogen strategy was recently reported.^[14] As we write this draft, an elegant synthesis of chiral zinc metallacycles via the reductive coupling of imines with terminal alkynes was disclosed by Uyeda (Scheme 1a).^[15] However, the reaction had its limitations, being applicable solely to internal alkynes and aryl imines. Nonetheless, all these previous reports are limited to either using precious metal catalysts or narrow scope or providing poor chemo- and enantioselectivity. There is a growing need for a highly chemo- and enantioselective approach to access these valuable molecule classes using catalysts based on base metals.

Low valent cobalt complexes have shown excellent reactivity toward coupling two π -components, and a plethora of transformations have been developed.^[16] In this context, we showcased cobalt-catalyzed stereoselective reactions involving ene-yne, ene-ene cross-coupling, and hydroarylate cyclization of 1,6-enynes.^[17] Recently, cobalt-catalyzed asymmetric reductive coupling of aldehydes and cyclic enones with internal alkynes was reported.^[18] However, to our knowledge, the cobalt-catalyzed reductive coupling of imines with internal alkynes synthesizing chiral allylamines has not been developed thus far. The challenges could be twofold. In addition to poor electrophilicity, imines are σ -coordinating ligands and could potentially deactivate or direct an undesired side reaction.^[19]

Lately, we have contemplated the notion that by carefully refining the cobalt catalyst and optimizing reaction conditions, it could be possible to overcome the previously mentioned challenges, ultimately facilitating the versatile synthesis of chiral allyl amines (Scheme 1b). This report introduces the discovery of an exceptionally efficient cobalt conglomerate catalyst for promoting the reductive coupling of internal alkynes and imines. Our mechanistic investigations reveal that the process begins with forming an in-situ cobalt(I) catalyst, initiating the oxidative cyclization of alkynes and imines to produce a cobaltallacyclic intermediate. Zinc plays a crucial role in mediating a transmetalation step, producing a chiral zinc metallacycle. Upon protonation, this organozinc intermediate facilitates product formation. Importantly, this reaction exhibits a wide substrate diversity, encompassing over 38 examples, including both symmetrical and asymmetrical alkyl and aryl alkynes paired with various imines. Impressively, it produced trisubstituted allyl amines with high yields and exceptional chemo-,

regio-, and enantioselectivities, achieving yields of up to 89%, a 99.9% enantiomeric excess, and a regioselectivity ratio exceeding 20:1.



Scheme 2. (a-b) Synthesis of Cobalt Complexes. (c-e) Molecular Structures of **Co-1-3** (50% probability ellipsoids).^[22]

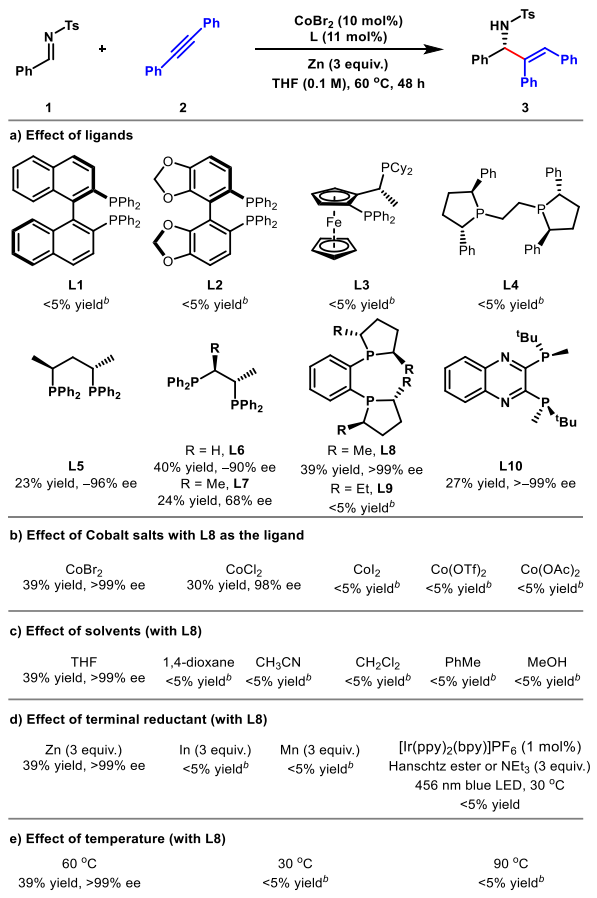
Results and Discussion

We have taken *N*-tosyl aldimine **1** and diphenyl acetylene **2** as the model substrate to investigate the proposed reaction (Table 1). The initial attempt using CoBr_2 as a cobalt precursor and (*S*)-BINAP (**L1**) as chiral ligands in the presence of zinc powder in THF at 60 °C was unsuccessful (Table 1a). The desired product **3** did not form, **2** remained unreacted, and **1** partly got reduced. The reaction using (*S*)-Segphos (**L2**), (*R*)-(*S*)-Josiphos (**L3**), and (*S,S*)-^{Ph}BPE (**L4**) also did not produce the allyl amine **3** (Table 1a). Pleasingly, when (*S,S*)-BDPP (**L5**) was used as a ligand, **3** was formed in 23% yield and 96% ee. While (*R*)-PropHos (**L6**) gave a higher 40% yield of **3**, the ee drops to 90% ee. An inferior result (24% yield, 68% ee) was also obtained when (*S,S*)-Chiraphos (**L7**) was used. Notably, the use of (*R,R*)-^{Me}Duphos (**L8**) ligand produced practically pure enantiomer (>99% ee) of **3** in 39% yield. In comparison, (*R,R*)-^{Et}Duphos (**L9**) did not produce **3** in appreciable yield. Using (*R,R*)-QuinoxP* (**L10**) also did not improve the reaction yield, although the enantioselectivity remained high. We have chosen **L8** for further work.

The reaction was found to be dependent on cobalt precursor. CoCl_2 gave a slightly inferior outcome (Table 1b). In comparison, other cobalt salts, including CoI_2 , $\text{Co}(\text{OTf})_2$, and $\text{Co}(\text{OAc})_2$ did not form active catalysts. The reaction was found to be highly sensitive to the medium (Table 1c). Except for THF, all other solvents gave inferior results. Poor results were also obtained when In and Mn were used as the sacrificial reductants (Table 1d). The product also did not form under our previously reported visible-light photoredox conditions employing $[\text{Ir}(\text{ppy})_2(\text{bpy})]\text{PF}_6$ (1 mol%) as the catalyst and Hanschtz ester, NEt_3 , and $^i\text{Pr}_2\text{NEt}$ as reducing agents under 456 nm blue light emitting diode irradiation.^[17b] Modulating the reaction temperature also did not promote the reaction (Table 1e).

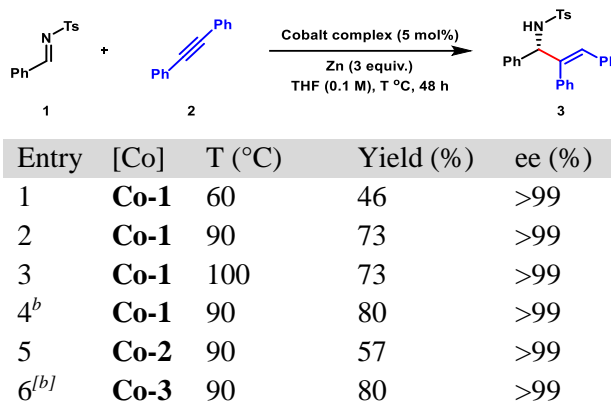
As we were unable to enhance the yield at this point, we opted to prepare the precatalyst by mixing CoBr_2 and **L8** in THF following a modified protocol inspired by Rajanbabu^[16a] and Chirik^[20] (Scheme 2a,b, Section-S3). The formation of the complex was characterized by blue to green color change. Filtration and washing with hexane resulted in a green color solid. The paramagnetic nature of the complex is indicated by electron paramagnetic resonance (EPR) spectroscopy (Figure S17).

Table 1. Initial Reaction Optimization for Cobalt Catalyzed Reductive Coupling of Imines and Alkynes.^[a]



^aReaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), CoX₂ (10 mol%), **L** (11 mol%), Zn powder (0.3 mmol), Solvent (1 mL), T °C, 48 h, then workup with water. Isolated yield. Enantiomeric excess (ee) was determined by HPLC analysis using a chiral stationary phase column. ^bee was not determined.

Table 2. Reductive Coupling of Imines and Alkynes Catalyzed by Cobalt Complexes.^[a]



^[a]Reaction condition: **1** (0.1 mmol), **2** (0.2 mmol), [Co] (5 mol%), Zn powder (0.3 mmol), Solvent (1 mL), T °C, 48 h, then workup with water. Isolated yield. ee was determined by HPLC analysis using a chiral stationary phase column. ^[b]**2** (0.12 mmol), Zn powder (0.22 mmol).

Characterization of the complex *via* single-crystal X-ray diffractometry revealed a conglomerate^[21] with the structure [CoBr(L8)₂][(THF)CoBr₃] (**Co-1**, Scheme 2c).^[22] The structure was found to be distorted trigonal bipyramidal geometry. Bond angles between the central cobalt, bromine, and the phosphorus

atoms (P1, P4) are 91.37° and 90.07°, respectively. In comparison, P2 and P3 make 125.74°, and 129.07° angles with central cobalt and bromine atom. The corresponding bond lengths are 2.23 Å for Co1-P1 and Co1-P4, 2.28 and 2.27 Å for Co1-P2 and Co1-P4, respectively.

When **Co-1** was used as the precatalyst, the yield improved slightly while the enantioselectivity remained high >99% ee even at 5 mol% Co-loadings (Table 2, entry 1). Notably, the product was obtained in 73% yields and >99% ee when the reaction was performed at 90 °C (entry 2). At 100 °C, the yield of the reaction remained the same (entry 3). We found that as the equivalency of **2** and Zn powder reduced to near stoichiometric amounts, the yield of the reaction improved to 80% yield, and the ee remained high (entry 4).

We have also prepared the precatalyst by using CoCl₂ as the precursor. The reaction similarly yield the complex [CoCl(L8)₂][(THF)CoCl₃] (**Co-2**, Scheme 2a). The structure of **Co-2** is also confirmed by single-crystal X-ray diffractometry^[22] (Scheme 2d). However, the reaction using **Co-2** as a precatalyst gave a lower yield of **3**, although the enantioselectivity remained unchanged (Table 2, entry 5).

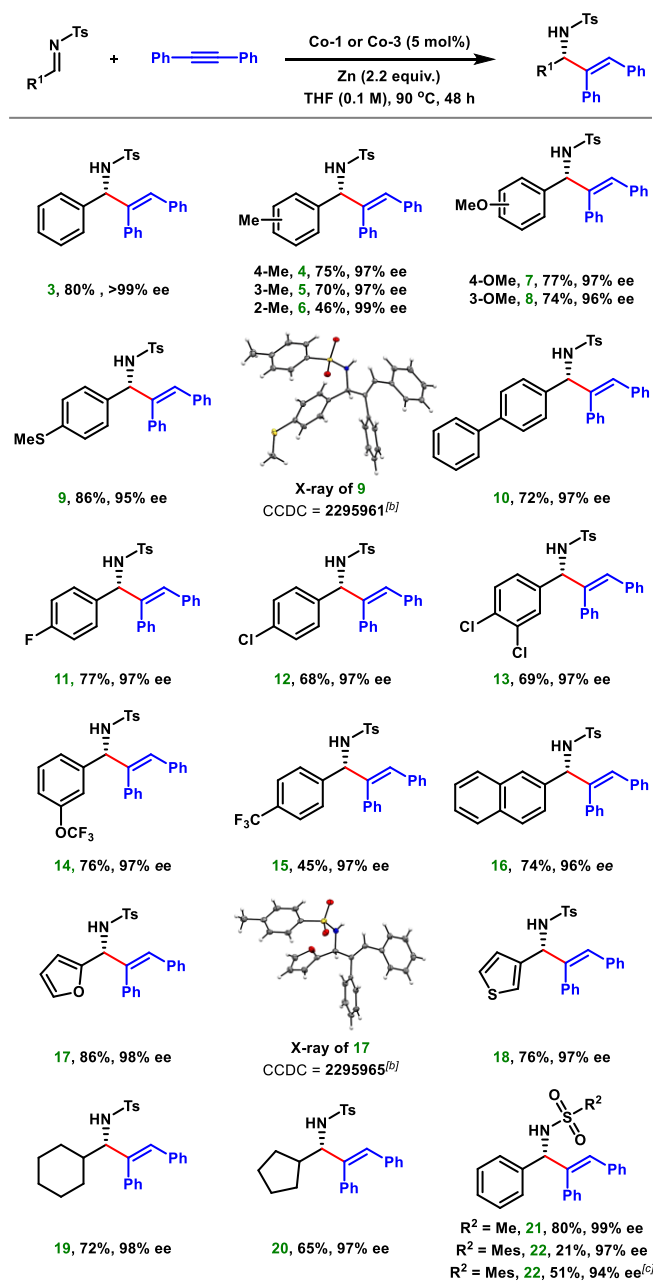
At this stage, we presume that if we use zinc bromide while preparing the cobalt complex, the anionic part might be independent of cobalt. Accordingly, we reacted CoBr₂ with two equivalents of **L8** in the presence of one equivalent of ZnBr₂ in THF (Scheme 2b). Characterization of the complex *via* single crystal X-ray diffractometry indicated the formation [CoBr(L8)₂][(THF)ZnBr₃] (**Co-3**, Scheme 2e).^[22] Introducing **Co-3** in the standard reaction condition delivered **3** in 80% yield >99% ee (Table 2, entry 6). Additionally, a kinetic study suggested that the initial rates of the reactions catalyzed by **Co-1** and **Co-3** are similar (Figures S12-S13). These clearly indicated anionic parts have negligible influence on the reactivity of [CoBr(L8)₂]⁺. Since **Co-1** and **Co-3** gave the highest yield and enantioselectivity, we conducted further studies with them as the precatalyst, and entries 4,6 (Table 2) were considered the optimum.

We then examined the scope for cobalt-catalyzed asymmetric imine-alkyne reductive coupling reaction (Table 3). Initially, the scope of imines was studied. The range of substituted imine is comprehensive, and chiral allylamines were isolated in high yields and enantioselectivities. Imines with a methyl substituent at the *para* and *meta* position in the phenyl ring delivered the intended products **4** and **5** in 75% and 70% yields with 97% ee and 97% ee, respectively. However, an *ortho* methyl-substituted imine gave a relatively lowered 46% yield of **6**, although the enantioselectivity remains high. The lesser product formation might be attributed to the bulkiness of the reaction center. Imines with *para*-, and *meta*-methoxy substituents also reacted at equal efficiencies, delivering the products **7-8** at high 77% and 74% yields with 97% and 96% ee, respectively. A thiomethoxy-substituted imine also reacted smoothly, yielding product **9** in high 86% yield and 97% ee. Notably, the sulfur substituent does not impact the catalysis.

An imine derived from biphenyl carbaldehyde also takes part in the reaction, giving **10** in 72% yield and 97% ee. Fluorine and chlorine substituents in the aromatic ring are also well tolerated, providing the desired product **11-13** in 68-77% yields with excellent 97% ee. An electron-withdrawing -OCF₃ group at the *meta* position of the aryl ring does not affect either the reactivity or the selectivity, and **14** was isolated in 76% yield and 97% ee. However, a trifluoromethyl group in the *para* position slows the reaction down, and **15** was isolated in 45% yield and high 97% ee. Imine derived from β-naphthaldehyde also reacted smoothly, producing **16** in 74% yield and 94% ee.

Heteroaryl imines, including 3-thienyl and 2-furyl groups, also responded firmly to the reaction condition, yielding the allylamines **17-18** in 76-86% yield and excellent 97-98% ee.

Table 3. Scope of Imines.^[a]



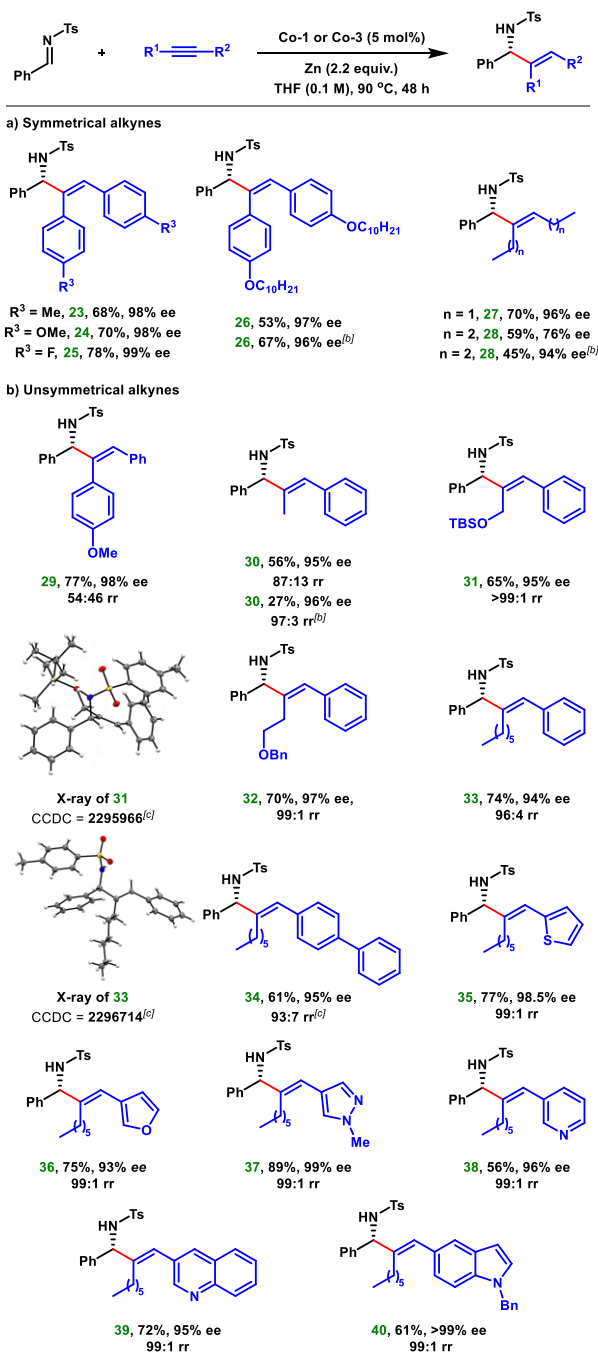
^[a] Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), [Co] (5 mol%), Zn powder (0.22 mmol), THF (1 mL), 90 °C, 48 h, then workup with water. Isolated yields. ee was determined by HPLC analysis using a chiral stationary phase column. ^[b] See ref. 22 for crystallographic information. ^[c] **Co-3** is used as the catalyst. Mes = 2,4,6-Me₃C₆H₂.

Not only aryl imines but also imines derived from aliphatic aldehydes also smoothly participated in this reaction. The products containing cyclohexyl (**19**) and cyclopentyl (**20**) groups were isolated in 72% and 65% yields and 98% and 97% ee, respectively. *N*-mesylate-protected imine can also be used to yield **21** in high 80% yield and 99% ee. However, with a bulkier protecting group, **22** was isolated in a slightly lower yield. Notably, using **Co-3** as the catalyst improved yield while maintaining a high 94% ee.

The absolute stereochemistry of products **9** and **17** was determined to be (*S*) from the single-crystal X-ray crystallography.^[22] Analogously, the configurations of the allymines in Table 3 were assigned.

Then, the scope of alkynes was tested (Table 4). Substituted diphenyl acetylenes, having *p*-methyl, *p*-methoxy, and *p*-fluoro substituents, are well tolerated under these conditions to give 68-78% yields of the desired allylic amines **23-25** with 96-99% ee (Table 4a). Furthermore, diphenyl acetylene containing long alkyl chain substituent also reacted at equal efficiencies with cobalt complexes **Co-1** and **Co-3**, yielding **26** in high yield and high ee.

Table 4. Scope of Alkynes.^[a]



^[a]Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), [Co] (5 mol%), Zn powder (0.22 mmol), THF (1 mL), 90 °C, 48 h, then workup with water. Isolated yields, ee and the regioisomeric ratio (rr) were determined by HPLC analysis using a chiral stationary phase column. ^[b] **Co-3** is used as the catalyst.

^[c] See ref. 22 for crystallographic information.

The reaction also accommodates alkyl acetylenes. Aliphatic alkynes such as 3-hexyne and 4-octyne give the reductive imine vinylated product **27** and **28** in 70% and 60% yields and 96 and 76% ee, respectively. Pleasingly, the enantioselectivity of product **28** was improved to 94% ee with **Co-3** as the precatalyst, albeit at the expense of a slight drop in yield.

We then considered unsymmetrically substituted acetylenes (Table 4b). Unsymmetrical diphenyl acetylene yielded **29** as a regioisomeric mixture (rr = 54:46) in the reaction condition with a combined 77% yield and a high 99% ee. Phenyl methyl acetylene was then subjected to the reaction conditions to check the regioselectivity further. With **Co-1** as the catalyst, product **30** was isolated in 56% yield and 95% ee with 87:13 rr, favoring the alkyl chain at the internal position. The regioselectivity improved to 97:3 rr as **Co-3** was used as the catalyst, albeit the yield dropped slightly, although the ee remained high. Notably, with the increasing aliphatic chain length, the regioselectivity is improved. Single regioisomeric product **31** having a silyl-protected alcohol was isolated in 65% yield and 95% ee. Similarly, high selectivity was also noticed for **32**, isolated in 70% yield, 97% ee, and 99:1 rr. Analogous observations were made for **33** and **34**, having long alkyl chains, isolated in 74% and 61% yields and 94% and 95% ee, respectively, with high rr.

The regioselectivity and absolute stereochemistry of products **31** and **33** were confirmed via single-crystal X-ray crystallography.^[22] The regioselectivity and configuration of the rest of the products in Table 4 were set *via* analogy. The preferential occupation of the aryl ring at the ortho-position-near to the cobalt center in azacobaltacyclopentene intermediate can explain the observed regioselectivity.^[23] We then performed the reaction with unsymmetrical alkynes containing several heteroaromatic groups to showcase further the scope, selectivity, and functional group compatibility. Notably, the products having 2-thienyl (**35**), 3-furyl (**36**), 4-*N*-methyl pyrazolyl (**37**), 3-pyridyl (**38**), 3-quinonyl (**39**), 5-*N*-benzyl indolyl (**40**) groups were isolated as single regioisomer (rr 99:1) in high 56-89% yields and excellent 93% to >99% ee.

Various synthetic transformations were done to demonstrate the synthetic utility of the protocol further (Figure 3). The Pd/C-catalyzed selective hydrogenation of the C=C in **3** results in the formation of **41** in 98% isolated yield and 1.3:1 diastereomeric ratio (dr). Reductive ozonolysis of **19** results in chiral 1,2-amino alcohol **42** in 65% yield with 11:1 dr favoring the *cis*-isomer. We then epoxidized the alkenyl double bond in **3** with *m*-chloro perbenzoic acid. The amine-bearing chiral epoxide **43** was isolated in 62% yield, and 3:1 dr favoring the *cis*-diastereomer. The relative and absolute stereochemistries of **42** and **43** were confirmed *via* single-crystal X-ray crystallography.^[22] Finally, using a ruthenium catalyst, we have oxidatively cleaved the C=C bond in **3**. The product α -amino ketone **44** was isolated in 57% yield and 96% ee.

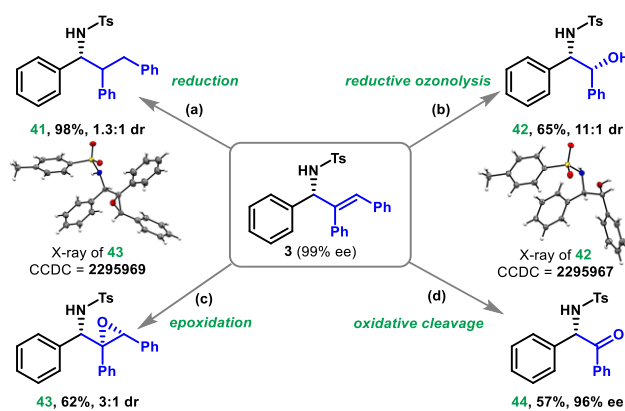


Figure 2. Derivatization of the allylamine 3. Reaction condition: (a) **3**, Pd/C (5 mol%), H₂ (balloon), MeOH, 60 °C, 4 h. (b) **19**, O₃, CH₂Cl₂, -78 °C, then Me₂S; NaBH₄, MeOH, r.t., 2 h. (c) **3**, mCPBA,

NaHCO₃, CH₂Cl₂, r.t., 12 h. (d) **3**, RuCl₃ (10 mol %), NaIO₄, MeCN/CCl₄/H₂O, 5 °C to r.t., 24 h. See ref. 22 for crystallographic information.

A catalytic cycle is proposed in Figure 3. It was hypothesized that initially, the reduction of the conglomerates **Co-1,3** by Zn would generate a Co(I) species. The complex **Co-3** shows an EPR signal with 2.09 g value at 80 K corresponding to Co(II)-distorted trigonal bipyramidal geometry (Figure S17). When we took an aliquot of the reaction mixture, froze it at 80 K, and recorded the EPR, a flat line was noticed (Figure S18). The EPR silent behavior indicates the existence of a diamagnetic low-spin Co(I)-complex during the catalysis. While an attempt to isolate was unsuccessful, we computed the Co(I) species as distorted square planar complex **45** (Section S11, B3LYP/6-311+G and SDD(Co) level of density functional theory, solvent THF). A similar complex was previously isolated.^[24]

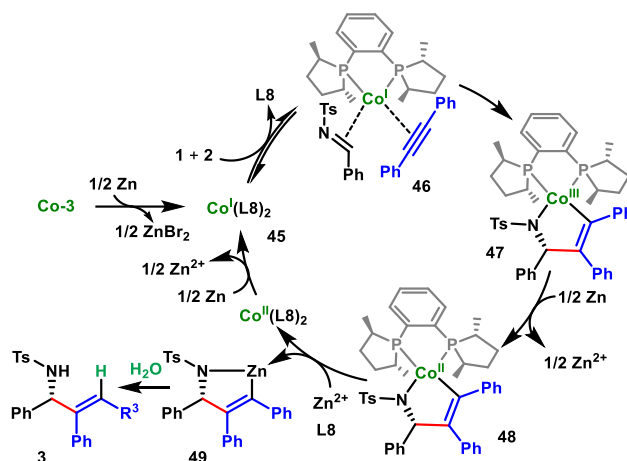


Figure 3. Proposed Mechanistic Cycle.

In the subsequent phase, our hypothesis revolves around the notion that **45** releases one ligand to accommodate both imine **1** and alkyne **2** (Figure 3). This situation creates a coordination equilibrium between the thermodynamically more stable and catalytically active species.^[24] To empirically investigate the metal-ligand ratio during catalysis, we examined the correlation between the ee of the catalysts and the ee of the allylic amine product **3** (Figure 4).^[25] Our findings indicate that the enantioselectivity of **Co-3** exhibits a perfectly linear relationship with the product's enantioselectivity. This observation suggests the presence of a catalytically active species with a Co/L8 ratio of 1:1 during the reaction, as outlined in Figure 3.

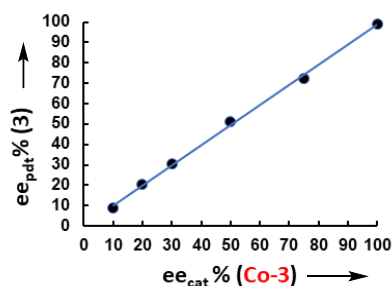


Figure 4. Non-Linear Effect Experiment.

In the next step, imine **1** and alkyne **2** are expected to undergo oxidative cyclization, yielding the azacobaltacyclopentene intermediate **47**, which should, upon reduction and protonation, release product **3** and regenerate the catalyst (Figure 3). At this juncture, we delved into the potential mechanism for product release. When deuterated imine **50-d** (98% D) reacted with **2**, it yielded **4-d** in a 67% yield with 100% D retention at the initial position (Figure 5a). This finding implies that the imine hydrogen is not involved in the reaction. Furthermore, when the reaction was conducted in THF- d_8 , no D incorporation was observed in isolated product **3**, which evidently denied the solvent as a proton source (Figure 5b). In contrast, with the addition of 1 equiv. D_2O to the reaction medium, we observed an 87% D incorporation in the olefinic proton (Figure 5c), indicating that water within the medium can serve as a proton source.

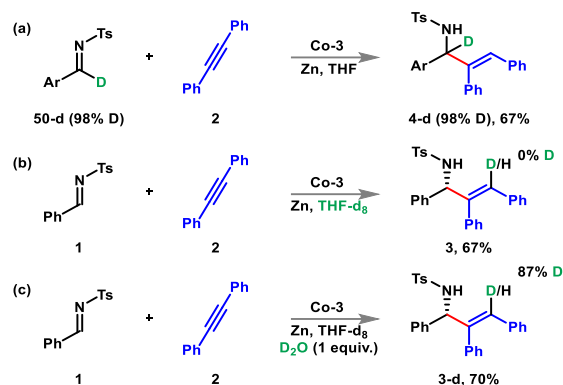


Figure 5. Deuterium Labelling Experiments.

Notably, when we terminated the reaction by adding D_2O after its completion, we observed a 74% D incorporation in the vinylic proton (Figure 6). This finding suggests that protonation of the azacobaltacyclopentene intermediate **47** occurs outside the catalytic cycle, and the turnover of the catalyst is facilitated by transmetalation with zinc, possibly involving intermediate **49** (Figure 3). Recent work by Uyeda involved the synthesis of chiral zinc metallacycles through the transmetalation of Co(II) species with $ZnCl_2$.^[15] While the precise nature of the zinc species could not be definitively determined due to potential aggregation and variable solvent coordination, it was proposed that the reduction of Co(III) species **47** to Co(II) species **48** might precede the transmetalation. To further investigate the chiral organozinc species **49**, we quenched the reaction with $PhSeSePh$, resulting in the isolation of an allylamine **51** containing a tetrasubstituted alkene in 40% yield (Figure 6). Furthermore, this highlights the multifaceted role of zinc in catalysis, serving as both an electron source and a transmetalating agent to facilitate catalyst turnover. Further work exploring the reactivity of zinc metallacycle is underway in this laboratory.

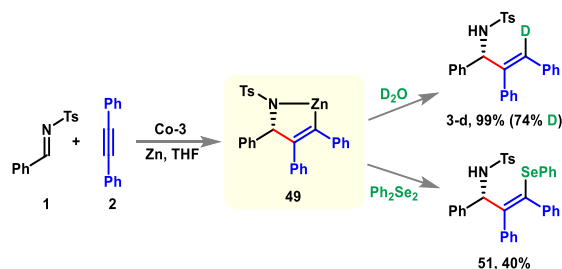


Figure 6. Experiments Probing the Proposed Zinc Metallacycle Intermediate.

Conclusion

In conclusion, we have explored cobalt-catalyzed enantioselective reductive coupling of imines with internal alkynes for the first time. A new conglomerate cobalt catalyst was developed, employing commercial salt and ligand. The reaction displayed impressive substrate scope, accommodating both symmetrical and unsymmetric aryl and alkyl alkynes. The trisubstituted allylic amines were produced in high yields and excellent control of regio- and enantioselectivities. Zinc serves a multifaceted role, acting as an electron source and a transmetallating agent for catalyst turnover. Selective quenching of the chiral organozinc intermediate allowed the synthesis of tetrasubstituted allylic amines in high yields.

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Keywords: Reductive Coupling • Cobalt Conglomerate • Cross-Electrophile Coupling • Chiral Zinc Metallacycle • Low-valent Cobalt

References

- [1] (a) T. C. Nugent, *Chiral amine synthesis: methods, developments and applications*, John Wiley & Sons, **2010**; (b) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257-10274.
- [2] (a) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395-422; (b) N. A. Butt, W. Zhang, *Chem. Soc. Rev.* **2015**, *44*, 7929-7967; (c) G. Lalic, S. A. Blum, R. G. Bergman, *J. Am. Chem. Soc.* **2005**, *127*, 16790-16791; (d) Y. Wei, F.-Y. Xiong, L.-Q. Lu, W.-J. Xiao, *Chem* **2023**, *9*, 559-561.
- [3] (a) R. A. Fernandes, P. Kattanguru, S. P. Gholap, D. A. Chaudhari, *Org. Biomol. Chem.* **2017**, *15*, 2672-2710; (b) X.-Y. Jiang, L. Chu, R.-W. Wang, F.-L. Qing, *Tetrahedron Lett.* **2012**, *53*, 6853-6857.
- [4] (a) R. Bloch, *Chem. Rev.* **1998**, *98*, 1407-1438; (b) P. Wipf, C. R. J. Stephenson, K. Okumura, *J. Am. Chem. Soc.* **2003**, *125*, 14694-14695; (c) Y. Huang, R.-Z. Huang, Y. Zhao, *J. Am. Chem. Soc.* **2016**, *138*, 6571-6576.
- [5] (a) A. E. Lurain, P. J. Walsh, *J. Am. Chem. Soc.* **2003**, *125*, 10677-10683; (b) Y. K. Chen, A. E. Lurain, P. J. Walsh, *J. Am. Chem. Soc.* **2002**, *124*, 12225-12231; (c) P. Wipf, S. Ribe, *J. Org. Chem.* **1998**, *63*, 6454-6455; (d) A. M. DeBerardinis, M. Turlington, L. Pu, *Angew. Chem. Int. Ed.* **2011**, *50*, 2368-2370.
- [6] (a) Q. Tian, G. Zhang, *Synthesis* **2016**, *48*, 4038-4049; (b) G. C. Hargaden, P. J. Guiry, *Adv. Synth. Catal.* **2007**, *349*, 2407-2424; (c) A. Gil, F. Albericio, M. Álvarez, *Chem. Rev.* **2017**, *117*, 8420-8446.
- [7] (a) M. Holmes, L. A. Schwartz, M. J. Krische, *Chem. Rev.* **2018**, *118*, 6026-6052; (b) E. Ortiz, J. Shezaf, Y.-H. Chang, M. J. Krische, *ACS Catal.* **2022**, *12*, 8164-8174; (c) E. Ortiz, J. Z. Shezaf, W. Shen, M. J. Krische, *Chem. Sci.* **2022**, *13*, 12625-12633.
- [8] (a) J. Montgomery, *Angew. Chem. Int. Ed.* **2004**, *43*, 3890-3908; (b) Y. Yang, S.-F. Zhu, C.-Y. Zhou, Q.-L. Zhou, *J. Am. Chem. Soc.* **2008**, *130*, 14052-14053; (c) M. R. Chaulagain, G. J. Sormunen, J. Montgomery, *J. Am. Chem. Soc.* **2007**, *129*, 9568-9569; (d) K. M. Miller, W.-S. Huang, T. F. Jamison, *J. Am. Chem. Soc.* **2003**, *125*, 3442-3443.
- [9] (a) S. J. Patel, T. F. Jamison, *Angew. Chem. Int. Ed.* **2003**, *42*, 1364-1367; (b) S. J. Patel, T. F. Jamison, *Angew. Chem. Int. Ed.* **2004**, *43*, 3941-3944.
- [10] E. Skucas, J. R. Kong, M. J. Krische, *J. Am. Chem. Soc.* **2007**, *129*, 7242-7243.
- [11] M.-Y. Ngai, A. Barchuk, M. J. Krische, *J. Am. Chem. Soc.* **2007**, *129*, 12644-12645.
- [12] C.-Y. Zhou, S.-F. Zhu, L.-X. Wang, Q.-L. Zhou, *J. Am. Chem. Soc.* **2010**, *132*, 10955-10957.
- [13] W.-W. Yao, R. Li, J.-F. Li, J. Sun, M. Ye, *Green Chem.* **2019**, *21*, 2240-2244.
- [14] L. Li, Y.-C. Liu, H. Shi, *J. Am. Chem. Soc.* **2021**, *143*, 4154-4161.
- [15] H. D. Bishop, Q. Zhao, C. Uyeda, *J. Am. Chem. Soc.* **2023**, *145*, 20152-20157.
- [16] (a) P. Gandeepan, C.-H. Cheng, *Acc. Chem. Res.* **2015**, *48*, 1194-1206; (b) W. G. Whitehurst, J. Kim, S. G. Koenig, P. J. Chirik, *J. Am. Chem. Soc.* **2022**, *144*, 4530-4540; (c) C. Wu, W. J. Teo, S. Ge, *ACS Catal.* **2018**, *8*, 5896-5900; (d) Z.-Y. Gu, W.-D. Li, Y.-L. Li, K. Cui, J.-B. Xia, *Angew. Chem. Int. Ed.* **2023**, *62*, e202213281; (e) J. Yang, Y. Sekiguchi, N. Yoshikai, *ACS Catal.* **2019**, *9*, 5638-5644; (f) W. Lu, Y. Zhao, F. Meng, *J. Am. Chem. Soc.* **2022**, *144*, 5233-5240; (g) H.-T. Chang, T. T. Jayanth, C.-C. Wang, C.-H. Cheng, *J. Am. Chem. Soc.* **2007**, *129*, 12032-12041; (h) M.-S. Wu, D. K. Rayabarapu, C.-H. Cheng, *Tetrahedron* **2004**, *60*, 10005-10009; (i) C.-H. Wei, S. Mannathan, C.-H. Cheng, *J. Am. Chem. Soc.* **2011**, *133*, 6942-6944; (j) G. Wu, A. Jacobi von Wangelin, *Chem. Sci.* **2018**, *9*, 1795-1802; (k) C.-C. Wang, P.-S. Lin, C.-H. Cheng, *J. Am. Chem. Soc.* **2002**, *124*, 9696-9697; (l) S. Mannathan, C.-H. Cheng, *Chem. Eur. J.* **2012**, *18*, 11771-11777; (m) T. Yasui, K. Yamada, R. Tatsumi, Y. Yamamoto, *ACS Catal.* **2021**, *11*, 11716-11722; (n) T. Yasui, R. Tatsumi, Y. Yamamoto, *ACS Catal.* **2021**, *11*, 9479-9484; (o) M. M. Parsutkar, T. V. RajanBabu, *J. Am. Chem. Soc.* **2021**, *143*, 12825-12835; (p) J. H. Herbolt, R. F. Lalisce, C.

- M. Hadad, T. V. RajanBabu, *ACS Catal.* **2021**, *11*, 9605-9617; (q) K. Cui, Y.-L. Li, G. Li, J.-B. Xia, *J. Am. Chem. Soc.* **2022**, *144*, 23001-23009; (r) K. Nogi, T. Fujihara, J. Terao, Y. Tsuji, *J. Am. Chem. Soc.* **2016**, *138*, 5547-5550.
- [17] (a) P. Rai, K. Maji, B. Maji, *Org. Lett.* **2019**, *21*, 3755-3759; (b) K. Maji, P. R. Thorve, P. Rai, B. Maji, *Chem. Commun.* **2022**, *58*, 9516-9519; (c) M. Maiti, S. K. Jana, B. Maji, *Chem. Commun.* **2023**, *59*, 9718-9721.
- [18] (a) Y.-L. Li, S.-Q. Zhang, J. Chen, J.-B. Xia, *J. Am. Chem. Soc.* **2021**, *143*, 7306-7313; (b) C.-H. Wei, S. Mannathan, C.-H. Cheng, *J. Am. Chem. Soc.* **2011**, *133*, 6942-6944.
- [19] (a) K. Gao, N. Yoshikai, *J. Am. Chem. Soc.* **2013**, *135*, 9279-9282; (b) M.-H. Chen, J.-C. Hsieh, Y.-H. Lee, C.-H. Cheng, *ACS Catal.* **2018**, *8*, 9364-9369.
- [20] M. R. Friedfeld, M. Shevlin, J. M. Hoyt, S. W. Krska, M. T. Tudge, P. J. Chirik, *Science* **2013**, *342*, 1076-1080.
- [21] G. Hilt, W. Hess, K. Harms, *Synthesis* **2008**, *2008*, 75-78.
- [22] *CCDC-2295950 (Co-1)*, *CCDC-2295958 (Co-2)*, *CCDC-2295960 (Co-3)*, *CCDC-2295961 (9)*, *CCDC-2295965 (17)*, *CCDC-2295966 (31)*, *CCDC-2296714 (33)*, *CCDC-2295967 (42)*, *CCDC-2295969 (43)* contain supplementary crystallographic data.
- [23] H. A. Reichard, M. McLaughlin, M. Z. Chen, G. C. Micalizio, *Eur. J. Org. Chem.* **2010**, *2010*, 391-409.
- [24] J. Xiao, M. Wang, X. Yin, S. Yang, P. Gu, X. Lv, Y. Zhao, Z. Shi, *Angew. Chem. Int. Ed.* **2023**, *62*, e202300743.
- [25] (a) D. Guillaneux, S.-H. Zhao, O. Samuel, D. Rainford, H. B. Kagan, *J. Am. Chem. Soc.* **1994**, *116*, 9430-9439; (b) C. Girard, H. B. Kagan, *Angew. Chem. Int. Ed.* **1998**, *37*, 2922-2959.