Catalytic Asymmetric Synthesis of Zinc Metallacycles

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ABSTRACT: Transition-metal-catalyzed reductive coupling reactions of alkynes and imines are attractive methods for the synthesis of chiral allylic amines. Mechanistically, these reactions involve an oxidative cyclization of the alkyne and the imine to generate a metallacyclic intermediate, which then reacts with H_2 or an H_2 surrogate to form the product. As an alternative to this hydrogenolysis pathway, here we show that transmetallation to zinc can occur, forming a zinc metallacycle product. This organozinc product serves as a versatile nucleophile for carbon–carbon and carbon–heteroatom coupling reactions. Mechanistic studies based on isotopic labelling experiments and DFT calculations suggest that the key transmetallation step occurs between a Co(II) species and $ZnCl_2$.

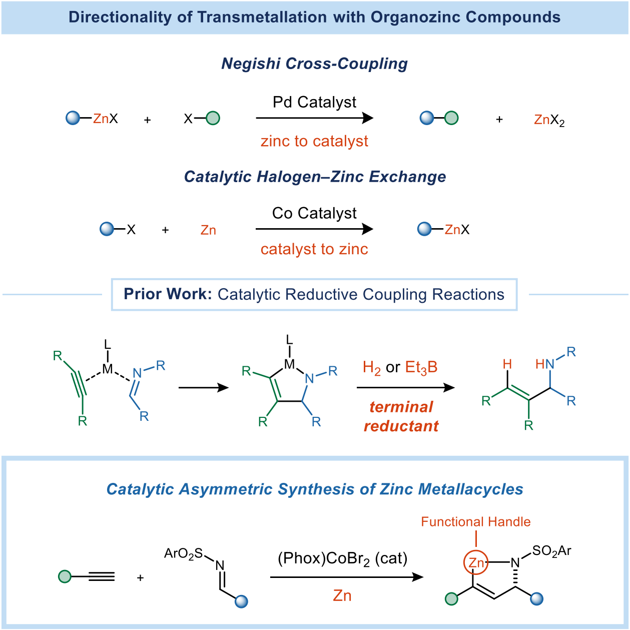
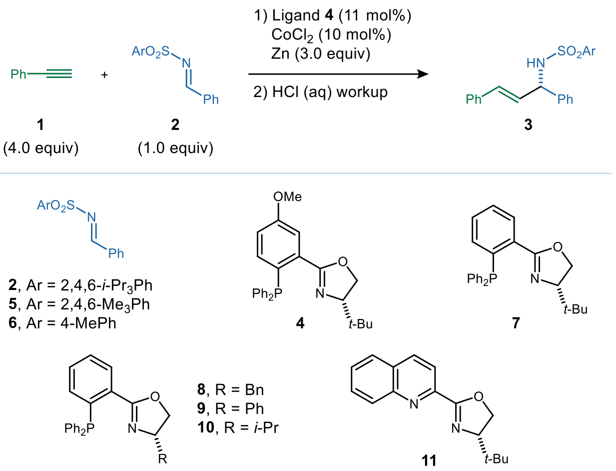


Figure 1. Catalytic asymmetric synthesis of zinc metallacycles.

Transmetallations from organometallic reagents to transition metal catalysts underlie numerous catalytic processes (Figure 1). For example, the Negishi cross-coupling reaction involves a transmetallation step from an organozinc nucleophile to a palladium catalyst.[1] In principle, the reverse process, transmetallation from a catalyst to a main group metal, would provide access to complex organometallic compounds that could function as intermediates for further functionalization. Achieving such a transformation would require careful consideration of the thermodynamics of metal–carbon and metal–halide bonds in order to control the directionality of transmetallation.[2]

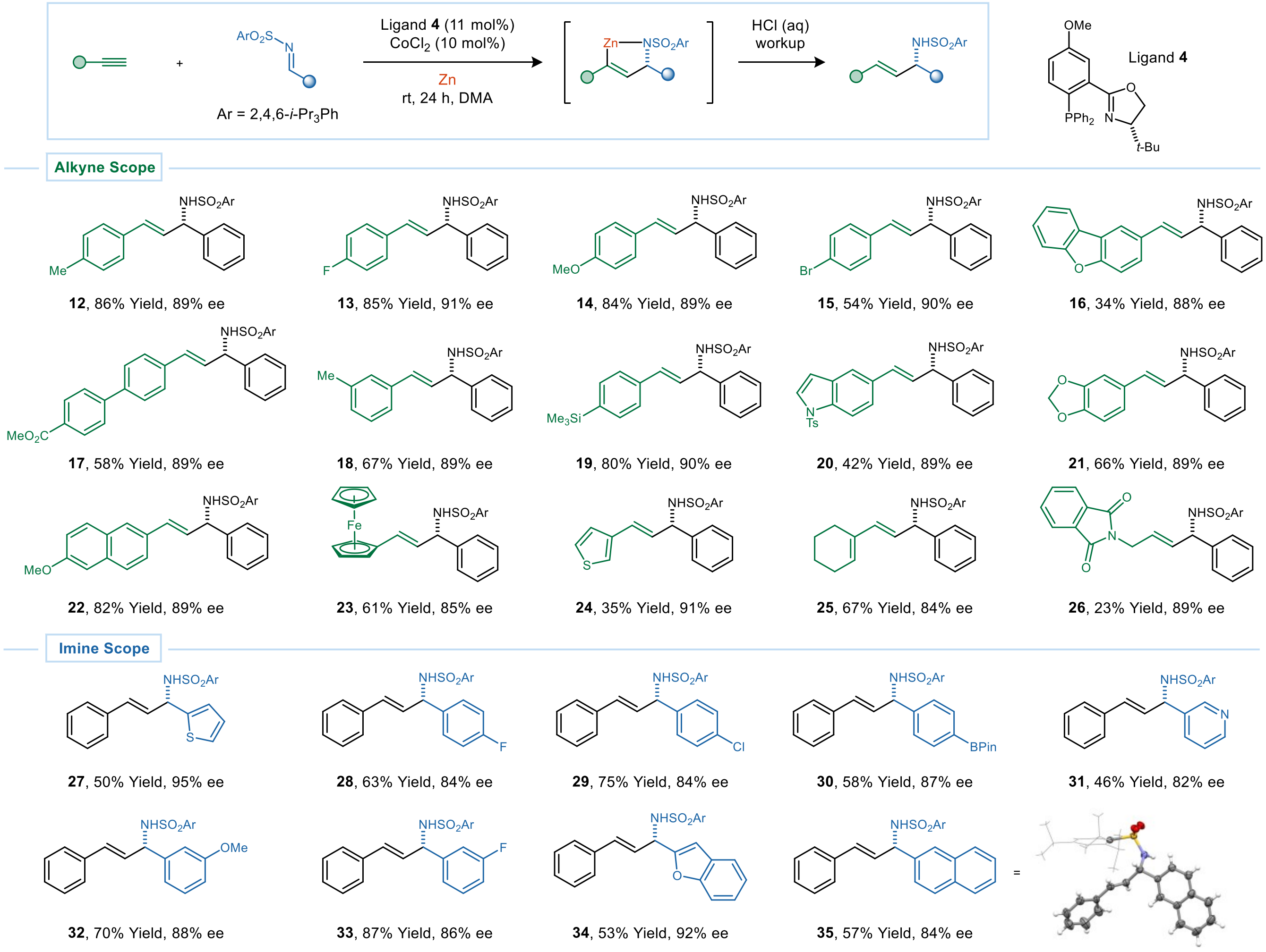
Table 1. Effect of Reaction Parameters



entry	variation from standard conditions [a]	yield (%)	ee (%)
1	none	79	91
2	no $CoCl_2$	0	–
3	no ligand **4**	0	–
4	2.0 equiv of **1**	53	91
5	Mn instead of Zn	0	–
6	imine **5** instead of **2**	81	85
7	imine **6** instead of **2**	79	45
8	ligand **7** instead of **5**	59	88
9	ligand **8** instead of **5**	60	59
10	ligand **9** instead of **5**	56	62
11	ligand **10** instead of **5**	45	39
12	ligand **11** instead of **5**	27	38

[a] Reaction conditions: **1** (0.8 mmol), **2** (0.2 mmol), Zn (0.6 mmol), $CoCl_2$ (10 mol%), ligand **4** (11 mol%); 24 h, rt, DMA (1 mL). Isolated yields determined after purification by column chromatography.

Table 2. Substrate Scope Studies



12, 86% Yield, 89% ee
13, 85% Yield, 91% ee
14, 84% Yield, 89% ee
15, 54% Yield, 90% ee
16, 34% Yield, 88% ee
17, 58% Yield, 89% ee
18, 67% Yield, 89% ee
19, 80% Yield, 90% ee
20, 42% Yield, 89% ee
21, 66% Yield, 89% ee
22, 82% Yield, 89% ee
23, 61% Yield, 85% ee
24, 35% Yield, 91% ee
25, 67% Yield, 84% ee
26, 23% Yield, 89% ee
27, 50% Yield, 95% ee
28, 63% Yield, 84% ee
29, 75% Yield, 84% ee
30, 58% Yield, 87% ee
31, 46% Yield, 82% ee
32, 70% Yield, 88% ee
33, 87% Yield, 86% ee
34, 53% Yield, 92% ee
35, 57% Yield, 84% ee

[a] Reaction conditions: **1** (0.8 mmol), **2** (0.2 mmol), Zn (0.6 mmol), CoCl$_2$ (10 mol%), ligand **4** (11 mol%); 24 h, rt, DMA. Isolated yields determined after purification by column chromatography. Enantiomeric excess (ee) values determined by HPLC analysis using chiral columns. [b] The absolute stereochemistry was established by XRD analysis. All other compounds are assigned by analogy.

Simple cobalt salts are known to catalyze the synthesis of arylzinc reagents from aryl halides and Zn metal.[3] In the proposed mechanism, a reduced Co species activates the aryl halide by oxidative addition. Transmetallation from the Co(II)–aryl intermediate to ZnX$_2$ generates the organozinc product. Here, we show that the favorable thermodynamics of transmetallation from Co(II) to Zn can be successfully merged with reductive C–C coupling[4] to achieve an asymmetric synthesis of Zn metallacycles. In previous examples of imine and alkyne reductive coupling reactions, a terminal reductant such as H$_2$ or an H$_2$ surrogate is used, and the products contain a hydrogen atom at the site of the M–C bond.[5] The same process has also been achieved in a redox-neutral fashion using an amine and an alkyne through a hydrogen borrowing strategy.[6] Alternatively, there are limited cases where a third organoboron component can be introduced to carry out tandem oxidative cyclization and C–C cross-coupling.[7,8] Finally, there is a singular example of transmetallation to form an aluminum metallacycle.[9] However, the need for Me$_3$Al limits functional group compatibility, and synthetic elaboration of the Al–C bond is limited to halogenation. By instead transmetallating to Zn, it is possible to incorporate a versatile functional handle to yield a diversity of allylic amine products[10] containing geometrically defined trisubstituted alkenes.

Under optimized reaction conditions, a (Phox)CoCl$_2$ catalyst promoted the reductive coupling of imine **2** and phenylacetylene (**1**) with Zn. During workup, the putative organozinc product was quenched with HCl (aq) to yield allylic amine **3** in 79% yield and 91% ee (Table 1, entry 1). When the crude reaction mixture was analyzed prior to the acidic quench, an intermediate species containing resonances at 6.55 ppm (d, $J = 3.1$ Hz) and 5.16 ppm (d, $J = 3.1$ Hz) was observed in the ^{1}H NMR spectrum. When PhCCD was used, the peak at 6.55 ppm was absent, and the peak at 5.16 ppm appeared as a singlet. Based on these data, we assign this intermediate as an organozinc species of the general form shown in Figure 1. The small J value is consistent with a HCCH dihedral angle of approximately 60°, which would be expected for a metallacyclic rather than an acyclic structure.

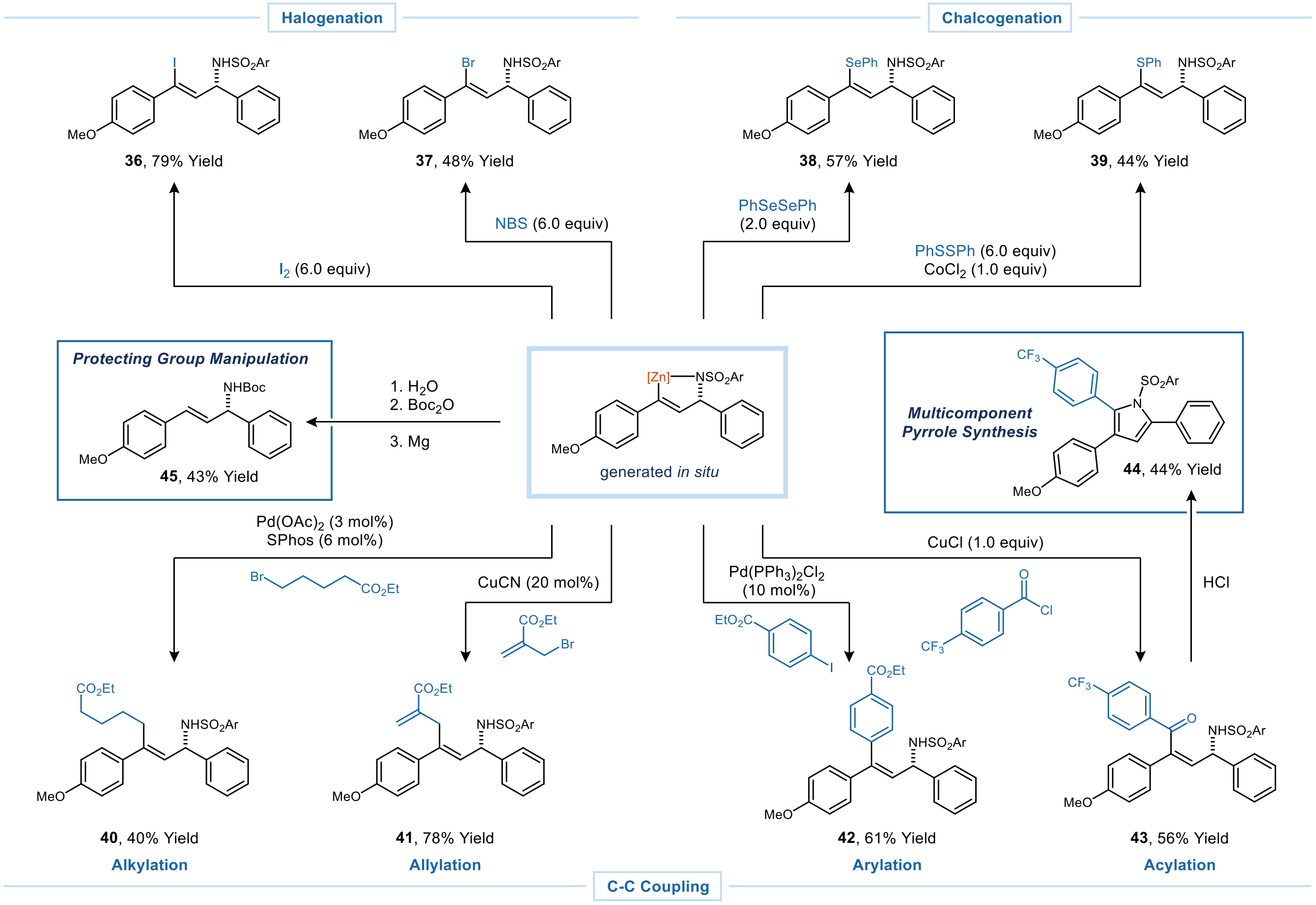


Figure 2. Functionalization experiments of the organozinc intermediate. Yields are of isolated products over the two-step sequence of reductive coupling and organozinc functionalization. See Supporting Information for experimental details.

No yield of product is observed in the absence of $CoCl_2$ or the Phox ligand (entries 2 and 3). Due to a competing alkyne homooligomerization process, the alkyne **1** is used in excess and added in two portions. Reducing the equivalency of the alkyne or adding it in a single portion lowers the yield (entry 4). Mn proved to be ineffective as a reductant (entry 5). A hindered sulfonyl group was critical for enantioselectivity. Less hindered groups provided similar yields but lower ee values (entries 6 and 7). Other Phox or Quinox ligands generated some amount of product but were inferior with respect to yield and ee (entries 8–12).

The substrate scope of the reaction is summarized in Table 2. Aryl, heteroaryl, and ferrocenyl-substituted acetylenes proved to be effective in the reaction. Notably, C(Ar)–Br bonds were tolerated (product **15**), despite the ability of CoX_2 to catalyze the synthesis of organozinc compounds from aryl bromides and Zn. An enyne substrate yielded a product containing a conjugated diene (product **25**). Finally, alkylacetylenes provided similar ee values to those observed with arylacetylenes but gave diminished yields (product **26**). Internal alkynes were ineffective, in striking contrast to other examples of catalytic imine–alkyne reductive coupling reactions, which require internal alkynes and are not viable for terminal alkynes.[5a-d,7-8] With regard to the imine partner, a variety of aryl and heteroaryl substituents were tolerated. Alkyl imines, on the other hand, proved to be unreactive.

The zinc metallacycles generated in this reaction serve as versatile intermediates for the synthesis of allylic amines containing trisubstituted alkenes (Figure 2).[11] For example, quenching of the reaction with I_2 or NBS instead of HCl (aq) yielded the halogenated products **36** and **37**, respectively. Related chalcogenations reactions were carried out with PhSSPh or PhSeSePh (products **38** and **39**). In the former case, the addition of $CoCl_2$ (1.0 equiv) was beneficial for yield.[12] There is no erosion in ee during the organozinc functionalization step.

Carbon–carbon cross-coupling reactions were also investigated. Alkyl cross-coupling with a primary alkyl halide electrophile was conducted using a (SPhos)Pd catalyst (product **40**). A Cu-catalyzed allylation provided skipped diene product **41**.[13] Negishi cross-coupling yielded product **42**, containing a trisubstituted alkene. Due to the metallacyclic nature of the organozinc intermediate, the alkene was obtained as a single geometric isomer despite the minimal differentiation between the two aryl groups. Acylation was achieved in high yield by transmetallating to a copper nucleophile.[14] Treatment of the acylated product **43** with HCl, induced cyclization to the pyrrole product **44**. This sequence represents a one-pot, three-component pyrrole synthesis from an alkyne, imine, and acyl chloride. Finally, the hindered sulfonyl group on the imine could be replaced with a Boc group by first treating with Boc_2O and then deprotecting under reducing conditions with Mg.[6a]

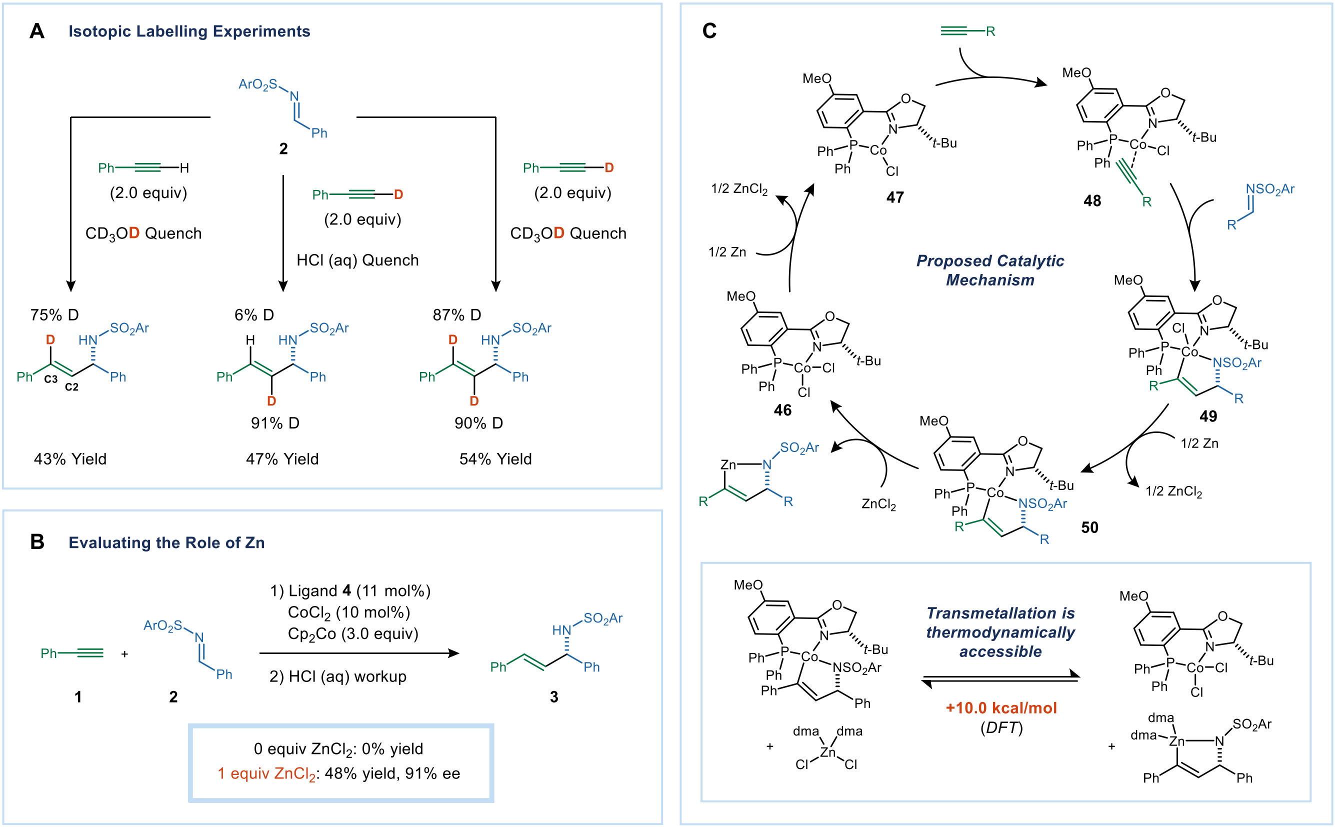


Figure 3. (A) Isotopic labelling experiments probing the structure of the proposed zinc metallacycle intermediate. (B) The dual role of zinc in the catalytic cycle can be replicated with Cp_2Co and $ZnCl_2$. (C) A proposed catalytic mechanism and DFT calculations for the transmetallation step from Co to Zn (M06-L-D3(SMD)/6-31g(d,p)).

Mechanistic details of the reaction were examined using deuterium-labelling experiments (Figure 3A). Quenching the reaction with CD_3OD in the glovebox yielded product **3** with 75% deuteration at C3, which is the expected position based on the proposed structure of the zinc metallacycle. Conversely, when PhCCD (92% D) was used as a substrate, 91% deuteration was observed at C2. Interestingly, there is 6% deuteration at C3, suggesting that the alkyne is sufficiently acidic to partially protonate the Zn metallacycle during the reaction. Finally, the combination of PhCCD and the CD_3OD quench led to high deuteration at both C2 and C3.

Zn plays a dual role in the catalytic mechanism. It serves as an electron source to turn over the catalyst. It is also required in the transmetallation step to generate the Zn metallacycle product. Accordingly, when Zn was replaced with Cp_2Co, there was no yield of coupled product, despite the fact that Cp_2Co is sufficiently reducing to access the reduced Co(I) state of the catalyst (Figure 3B). Using Cp_2Co in combination with $ZnCl_2$ restores the reactivity, and product **3** is generated in 48% yield and 91% ee.

A proposed catalytic mechanism is shown in Figure 3C. Reduction of the (Phox)$CoCl_2$ catalyst **46** generates Co(I) complex **47**, which can then induce oxidative coupling of the alkyne and imine to form a Co(III) metallacycle (**49**).[15] Transmetallation to $ZnCl_2$ could then occur to form the (Phox)$CoCl_3$ and the product. Alternatively, **49** could be reduced to a Co(II) metallacycle (**50**) prior to transmetallation. To distinguish between these two possibilities, we carried out DFT calculations to examine the thermodynamics of transmetallation. At the Co(III) oxidation state, transmetallation from Co to Zn is disfavored by 21.2 kcal/mol. By comparison, transmetallation from Co(II) to Zn is thermodynamically more favorable (+10.0 kcal/mol). We note that there is uncertainty regarding the precise nature of the Zn species in solution due to potential aggregation and variable solvent coordination. These issues would impact the absolute values of these calculated equilibrium constants. However, the relative energies nonetheless suggest that reduction from Co(III) to Co(II) may precede transmetallation.

In summary, reductive coupling reactions of π-systems provide an approach to C–C bond formation that takes advantage of readily available starting materials. Typically, the mechanism involves the formation of a metallacyclic intermediate that reacts with a terminal reductant, such as H_2, to form the coupled product. By using Zn as a reductant, it is possible to instead carry out a catalyst-to-Zn transmetallation, which furnishes an organozinc product that is poised for further functionalization. This process avoids the need to generate organozinc compounds using a pre-installed halide or by deprotonation using a strong base. Applications of this transmetallation to other multicomponent reductive coupling reactions are ongoing.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge at https://pubs.acs.org

Experimental details, characterization data, and computational details (PDF)

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Notes

The authors declare no competing financial interest.

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ArO$_2$S
N
Chiral Cobalt Catalyst
Zn
Zn
N
SO$_2$Ar