Cobalt-Catalyzed Arylative Cyclization of Acetylenic Esters and Ketones with Arylzinc Reagents through 1,4-Cobalt Migration

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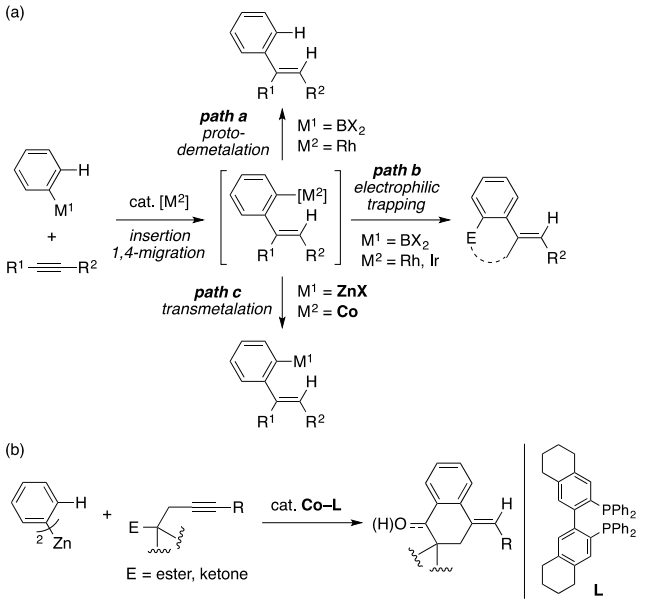
ABSTRACT: 1,4-Migrations of organopalladium and organorhodium species have been utilized for the development of various cascade reactions involving remote C–H bond activation. Recently, we reported a cobalt-catalyzed migratory arylzincation reaction of an alkyne that features alkenyl-to-aryl 1,4-cobalt migration and cobalt-to-zinc transmetalation as key steps. We report herein that the cobalt/arylzinc combination can also promote a cascade arylative cyclization reaction of alkynes bearing pendant ester or ketone moieties to afford benzo-fused cyclic ketone or alcohol products, respectively. The reaction is considered to proceed through insertion of the alkyne into an arylcobalt species, 1,4-cobalt migration, and intramolecular organocobalt addition to the carbonyl group. The present cobalt/arylzinc system may not only serve as an alternative to previously reported rhodium/arylboron and iridium/arylboron systems but also complement their scopes in the arylative cyclization.

KEYWORDS: *cobalt, organozinc reagents, alkynes, cascade reactions, C–H activation*

1,4-Metal migration of organotransition metal species has been extensively studied as an elementary process that is not only mechanistically intriguing but also uniquely useful for the development of novel catalytic cascade transformations involving remote C–H bond activation.[1] While the Catellani reaction and related reactions of organopalladium species are among representative examples,[2,3] 1,4-migration of organorhodium(I) species has also been extensively exploited for the development of novel cascade reactions for the synthesis of complex molecules and polymers.[4,5] For example, such cascade transformations are initiated by the insertion of an alkyne into an arylrhodium species generated by transmetalation between a rhodium(I) complex and an arylboron reagent and subsequent vinyl-to-aryl 1,4-rhodium migration of the resulting *cis*-β-styrylrhodium species (Scheme 1a). While the thus-formed *ortho*-alkenylarylrhodium species may be protodemetalated by a protic solvent (path a),[4b] pre-installation of an electrophilic moiety (e.g., ester, enone) into an appropriate position of the alkyne substrate enables intramolecular trapping of the nucleophilic aryl–rhodium bond, thus affording an arylative cyclization product (path b).[5a,j] Lam and coworkers have recently reported the feasibility of the latter type of cascade reaction using an iridium(I) catalyst and a cyclic 1,3-diketone moiety as an internal electrophile, which represents the first example of 1,4-iridium migration.[6,7]

Scheme 1. Group 9 Metal-Catalyzed Reaction of Arylmetal Reagents and Alkynes Involving 1,4-Metal Migration

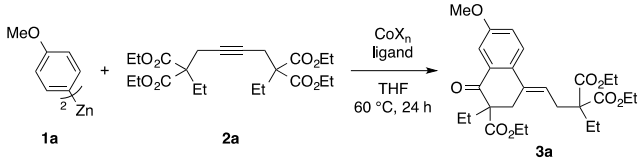


Recently, our group discovered the first example of 1,4-cobalt migration in a cobalt-catalyzed "migratory arylzincation" of an alkyne, where the addition of an arylzinc reagent to the alkyne occurs along with transposition of zinc atom to the *ortho* position (path c).[8] Compared with the above-discussed rhodium- or iridium-catalyzed reactions, this reaction features transmetalation between an *ortho*-alkenylarylcobalt species and the arylzinc reagent as a unique catalyst-turnover step. We have also demonstrated the feasibility of migratory arylzincation of a norbornene derivative involving alkyl-to-aryl 1,4-cobalt migration.[9] As a part of our continued studies on cobalt catalysis and its comparison with other Group 9 metal catalysis,[10,11] we report here that the combination of a cobalt catalyst and an arylzinc reagent allows cascade arylative cyclization reactions

involving 1,4-cobalt migration and nucleophilic organocobalt addition to an ester or ketone moiety (Scheme 1b). The cobalt/arylzinc system may not only serve as an alternative to the rhodium/arylboron and iridium/arylboron systems in the cascade arylative cyclizations, but also display unique reactivity and selectivity to complement the scope of the latter.

Our initial study was focused on the reaction of a diarylzinc reagent **1a** (prepared from a 1:2 mixture of $ZnCl_2$•TMEDA and 4-methoxyphenylmagnesium bromide) with a symmetric acetylenic tetraester **2a**, a type of substrates employed by Murakami and coworkers in the rhodium-catalyzed arylative cyclization.[5a] In light of our previous studies on migratory arylzincation,[8,9] the reaction was performed using a catalytic system comprising a cobalt salt and a diphosphine ligand (10 mol% each) in THF at 60 °C (Table 1). Xantphos and dppf, which were the optimum ligands for migratory arylzincation of alkyne and norbornene, respectively,[8,9] performed poorly, affording the desired product **3a** in only less than 5% yield (entries 1 and 2). Upon examination of other typical diphosphine ligands, we observed distinct improvement of the reaction using BINAP and BIPHEP ligands among others (entries 3–6). Further screening of binaphthyl- and biphenyl-diphosphine ligands including optically active ones led us to identify a modified BIPHEP ligand **L** (Scheme 1b)[12] as the optimum ligand, which affords **3a** in 78% isolated yield (entry 7). A monoarylzinc reagent prepared from a 1:1 mixture of $ZnCl_2$•TMEDA and 4-methoxyphenylmagnesium bromide did not afford **3a** at all (entry 8). A comparable catalytic activity was achieved using $CoBr_2$ instead of $CoCl_2$ (entry 9), while CoF_2 was entirely ineffective (entry 10). Note also that the reaction did not take place at all using 4-methoxyphenylboronic acid instead of the arylzinc reagent **1a** under otherwise identical conditions.

Table 1. Screening of Reaction Conditions for the Addition of 4-Methoxyphenylzinc Reagent to Acetylenic Tetraester[a]

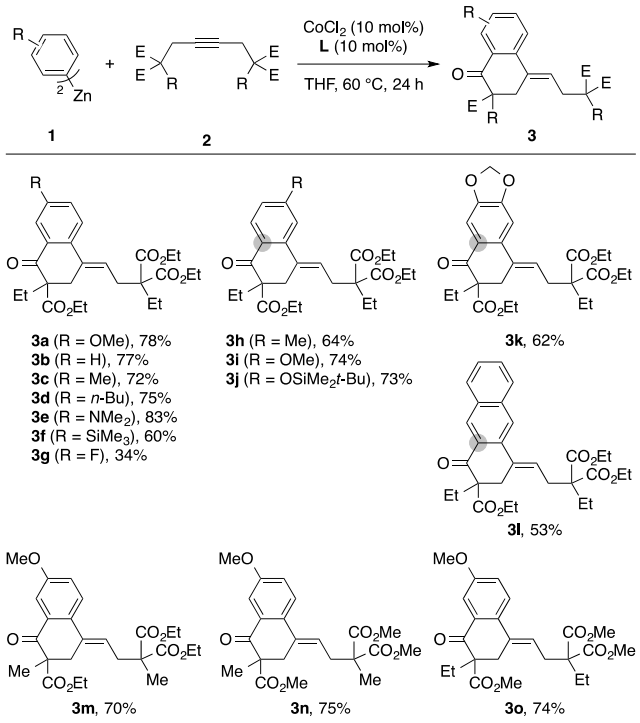


entry	CoX_n	ligand	yield (%)[b]
1	$CoCl_2$	Xantphos	1
2	$CoCl_2$	dppf	3
3	$CoCl_2$	dppe	2
4	$CoCl_2$	dppp	10
5	$CoCl_2$	(±)-BINAP	50
6	$CoCl_2$	BIPHEP	60
7	$CoCl_2$	**L**	78[c]
8[d]	$CoCl_2$	**L**	0
9	$CoBr_2$	**L**	70
10	CoF_2	**L**	2

[a]Reaction conditions: Arylzinc reagent prepared from $ZnCl_2$•TMEDA (0.3 mmol) and 4-$MeOC_6H_4MgBr$ (0.6 mmol), alkyne **2a** (0.2 mmol), CoX_n (10 mol %), ligand (10 mol %), THF, 60 °C, 24 h. [b]Determined by GC. [c]Isolated yield. [d]The reaction was performed using arylzinc reagent prepared from $ZnCl_2$•TMEDA (0.3 mmol) and 4-$MeOC_6H_4MgBr$ (0.3 mmol).

With the Co–**L** catalytic system in hand, we explored the scope of arylzinc reagents for the cascade arylation–cyclization reaction with **2a** (Table 2). A series of electron-rich and electron-neutral *para*-substituted arylzinc reagents participated in the reaction to afford the desired products **3a**–**3f** in moderate to good yields, while the reaction became relatively sluggish with a 4-fluorophenylzinc reagent (see **3g**). The cascade cyclization using *meta*-methyl, methoxy, and siloxy-substituted arylzinc reagents took place exclusively at the *ortho* position distal to the substituent, affording the products **3h**–**3j** in respectable yields. The same sense of regioselectivity was observed for the reaction of 3,4-methylenedioxyphenylzinc and 2-naphthylzinc reagents, which resulted in regioselective formation of the products **3k** and **3l**, respectively. As was the case with the migratory arylzincation reaction,[8] *ortho*-tolylzinc reagent did not afford the desired adduct at all. In addition to the alkyne **2a**, similar alkyne substrates having different alkyl or ester substituents reacted with the arylzinc reagent **1a** to afford the desired products **3m**–**3o** in comparable yields.

Table 2. Arylative Cyclization of Acetylenic Tetraester with Arylzinc Reagent[a]

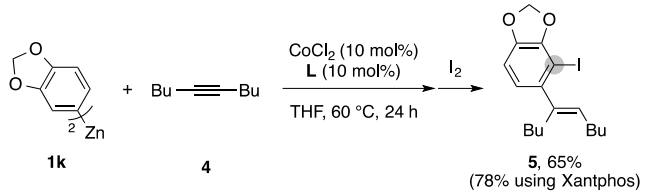


[a]The reaction was performed on a 0.2 mmol scale under the reaction conditions in Table 1, entry 7.

The regioselective formation of the products **3h**–**3l** may be simply explained by preferential 1,4-cobalt migration to the less hindered ortho position. However, the cases of 3-alkoxy, 3-siloxy, and 3,4-methylenedioxyphenylzinc reagents (**3i**–**3k**) deserve further discussion. This is because the same type of zinc reagent exhibits opposite regioselectivity (i.e., 1,4-migration to the proximity of the *meta*-oxygen atom) in the migratory arylzincation reaction with simple alkynes, which can be rationalized in terms of a secondary directing effect of the *meta*-oxygen atom during the 1,4-migration process.[8] To gain insight into the origin of this difference, we performed a reference experiment using 3,4-methylenedioxyphenylzinc

reagent **1k** and 5-decyne (**4**) under the present conditions, which was quenched by I_2 (Scheme 2). As was the case with the optimum catalytic system using Xantphos, the reaction afforded the adduct **5** with exclusive iodination of the more hindered *ortho* position. This result suggests that the regiochemistry of the product **3k** is not attributable to the specific nature of ligand **L**, but would originate from the nature of the substrate **2a** (vide infra).

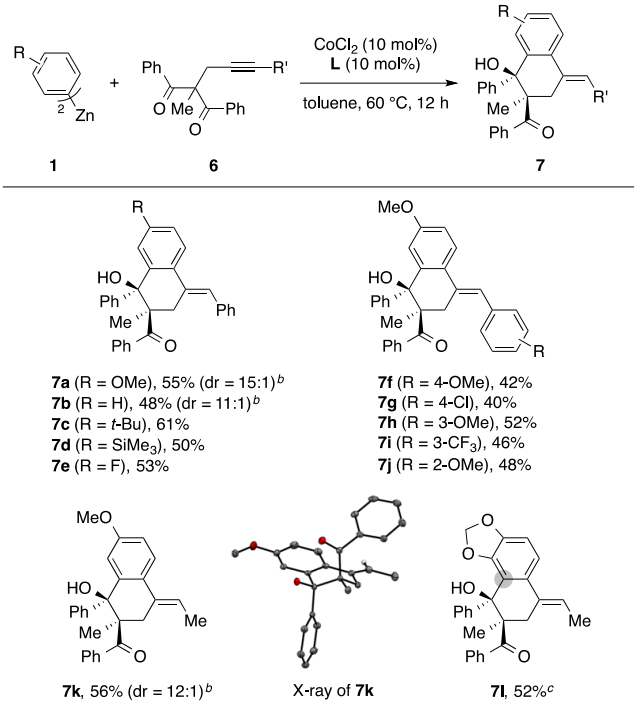
Scheme 2. Addition of Benzo[*d*][1,3]dioxol-5-ylzinc Reagent 1k to Unfunctionalized Alkyne



The scope of functionalized alkyne substrates for the cascade arylation–cyclization could be extended to ketone derivatives. Thus, the reaction of arylzinc reagents with homopropargyl diketones **6**, prepared through propargylation of 1,3-diketone derivatives, took place with the same Co–**L** catalytic system to afford bicyclic alcohol products **7**, albeit in moderate yields (Table 3). GC and GCMS analysis of the crude reaction mixtures for **7a**, **7b**, and **7k** indicated full consumption of the starting alkynes and high diastereoselectivity (≥ 10:1) of the cyclization. Although we were unable to characterize any other byproducts, the analysis of the reaction mixture at least suggested the absence of a hydroarylation product, which may arise from the addition of **1** to **6** with opposite regioselectivity. The geometry of the C=C bond and the diastereochemistry of **7k** were confirmed by X-ray crystallographic analysis.

Cobalt-catalyzed (migratory) arylzincation reactions of alkyl(aryl)alkynes are known to occur with regioselective arylation of the acetylenic carbon proximal to the alkyl group.[8,13] Given this regioselectivity trend, formation of the products **7a**–**7j** from homopropargyl diketones bearing aryl groups on the acetylenic termini was not unexpected. By contrast, formation of the products **7k** and **7l** is notable in light of poor regioselectivity of the migratory arylzincation with unsymmetrical dialkylalkynes.[8] The latter product, **7l**, is also notable for the regioselective 1,4-migration to the proximity of the methylenedioxy group, which is in line with the regioselectivity of the migratory arylzincation (Scheme 2)[8] but is opposite to that observed for **3k** (Table 2). We speculate that the regioselectivity of **3k** originates from coordination of the ester moiety of **2a** to the cobalt center, which would interfere with the secondary directing effect of the *meta*-oxygen (see the Supporting Information for detail). It should be noted that, in our hands, the present propargylic diketone substrates did not participate in arylative cyclization using an iridium or a rhodium catalyst and 4-methoxophenylboronic acid under Lam's conditions developed for substrates featuring cyclic 1,3-diketone moieties.[6]

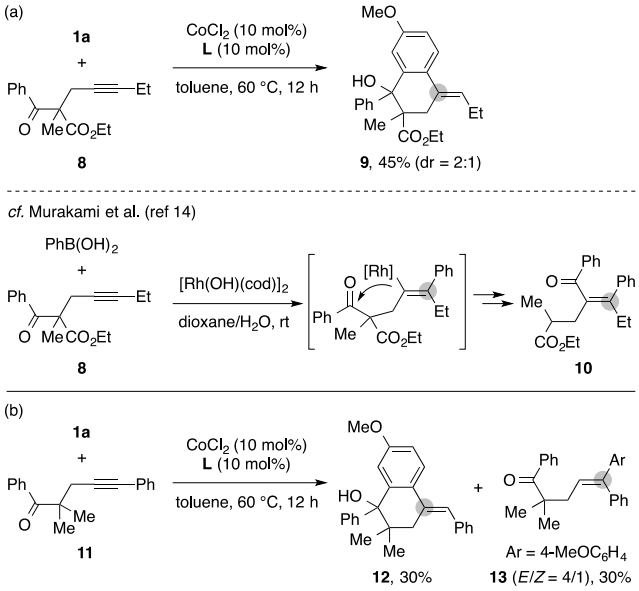
Table 3. Arylative Cyclization of Homopropargylic Diketone with Arylzinc Reagent



[a]The reaction was performed on a 0.2 mmol scale under the reaction conditions in Table 1, entry 7 with a slight modification (toluene instead of THF as the solvent). [b]Diastereomer ratio was determined for **7a**, **7b** and **7k** by GC and GCMS analysis of the crude product. [c]Estimated yield of the product containing impurities.

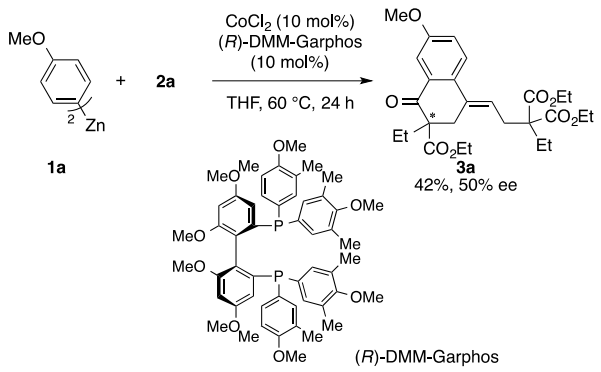
In addition to the above homopropargyl diketones, we examined a few additional structurally related substrates (Scheme 3). The reaction of arylzinc reagent **1a** with homopropargyl ketoester **8** resulted in chemoselective cyclization onto the keto moiety rather than the ester moiety, thus affording a cyclic alcohol product **9** in modest yield and diastereoselectivity (Scheme 3a). Once again, no other product could be characterized regardless of full consumption of the alkyne **8**, while formation of other types of 1:1 adducts could be excluded by GCMS analysis. The formation of the cyclic product **9** is in sharp contrast to the fate of the same substrate **8** under Rh-catalyzed reaction with phenylboronic acid.[14] The reaction, reported by Murakami and coworkers, afforded a tetrasubstituted alkene **10** as a main product through alkyne insertion into a phenylrhodium species with opposite regioselectivity. In contrast to the reaction of propargyl diketones **6**, a propargyl monoketone **11** afforded a mixture of the expected cascade cyclization product **12** and the simple hydroarylation product **13**, the latter being formed through alkyne insertion with the opposite regioselectivity (Scheme 3b).

Scheme 3. Reactions of Homopropargylic Ketoester and Monoketone Substrates



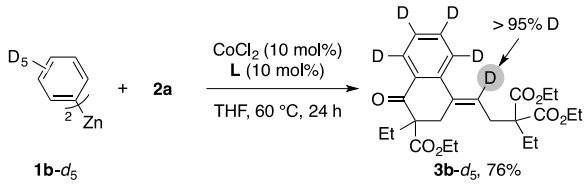
Given the effectiveness of the biphenyl-diphosphine **L** in the present cascade reactions, it was natural for us to explore the possibility of enantioselective variants by screening chiral BINAP- and BIPHEP-type ligands. Unfortunately, such attempts have not been very successful. For example, the reaction of homopropargyl diketone **6** using a typical chiral BINAP or BIPHEP derivative instead of **L** became too sluggish to determine any enantioselectivity. Nevertheless, a cobalt–(*R*)-DMM-Garphos catalyst promoted desymmetrizing arylative cyclization of acetylenic tetraester **2a** albeit with a modest enantioselectivity (Scheme 4; see the Supporting Information for additional ligand screening results). Though the enantioselectivity requires further improvement, this observation is mechanistically valuable. It supports the involvement of a diphosphine-ligated *ortho*-alkenylarylcobalt species in the cyclization process, while the modest enantioselectivity may not allow us to exclude an alternative pathway involving transmetalation of the *ortho*-alkenylarylcobalt species with the arylzinc reagent **1a** and subsequent intramolecular cyclization of the resulting *ortho*-alkenylarylzinc species.

Scheme 4. Enantioselective Arylative Cyclization of 2a



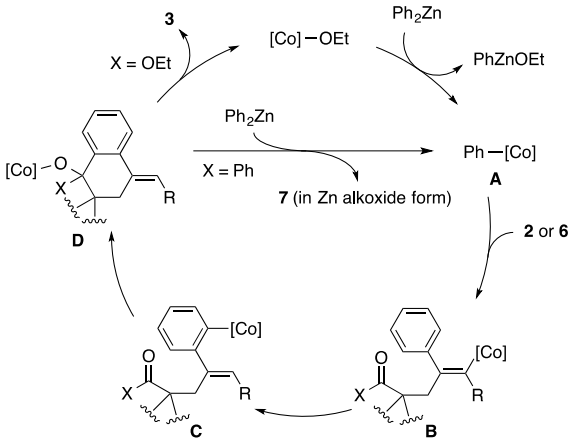
To confirm the 1,4-cobalt migration process in the present cascade reaction, a reaction between pentadeuteriophenylzinc reagent **1b**-d_5 and the tetraester **2a** was examined (Scheme 5). As expected, the cascade cyclization was accompanied by clean transfer of one of the *ortho*-deuterium atoms into the vinylic position of the product **3b**-d_5.

Scheme 5. Deuterium-Labeling Experiment



In light of the rhodium- and iridium-catalyzed precedents[5a,6] and our previous study on the cobalt-catalyzed migratory arylzincation,[8] we propose catalytic cycles outlined in Scheme 6 for the present cascade arylative cyclizations. A phenylcobalt species **A** generated from the cobalt precatalyst and phenylzinc reagent undergoes insertion of the alkyne substrate **2** or **6** to produce an alkenylcobalt intermediate **B**, which then rearranges to an *ortho*-alkenylarylcobalt species **C**. Intramolecular cyclization of the aryl–Co moiety of **C** onto the carbonyl group results in a cobalt alkoxide intermediate **D**. For the tetraester substrate **2**, this cyclization step is followed by β-alkoxy elimination, thus affording the ketone product **3** along with a Co–OEt species. Transmetalation of this species with phenylzinc reagent completes the catalytic cycle, regenerating the phenylcobalt species **A**. For the ketone substrate **6**, the intermediate **D** would directly undergo transmetalation with phenylzinc reagent to furnish the alcohol product **7** in the form of zinc alkoxide while regenerating the species **A**.

Scheme 6. Plausible Catalytic Cycle



The origin of the diastereoselectivity observed for the propargyl diketone substrates deserves additional discussion. With brief stereochemical analysis using ball-and-stick molecular models, we presume that the intramolecular cyclization of the arylcobalt species **C** onto the carbonyl moiety occurs when the aryl group and the C=O bond are in a parallel orientation with each other, and are both perpendicular to the olefinic plane (Fig. 1). Out of two possible transition state models with such structural configurations, the one with the bulkier benzoyl group pointing away from the aryl–cobalt moiety would be favored due to smaller steric repulsion. Such transition state would indeed lead to the observed diastereoselectivity, while the analysis does not exclude possible formation of the minor diastereomer. The same molecular model analysis on the cyclic diketone-containing substrate employed in Lam's Ir-catalyzed reaction[6] would

rationalize exclusive formation of the opposite type of diastereomer due to the conformational rigidity of the cyclic diketone moiety.

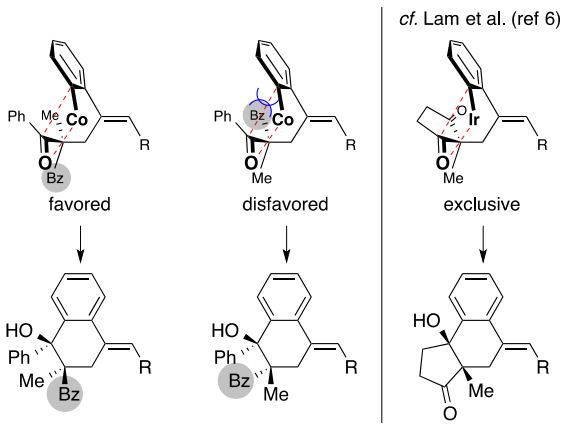


Figure 1. Plausible models for diastereoselectivity in intramolecular cyclization.

In summary, we have reported that 1,4-cobalt migration can be integrated into a cascade arylative cyclization process employing an arylzinc reagent and an acetylenic ester or ketone substrate, thus affording a benzo-fused carbocyclic product. The present study illustrates the parallelism between low-valent organocobalt species and organorhodium(I)/iridium(I) species in the context of nucleophilic addition to carbonyl groups. Furthermore, the performance of the present catalyst on some of the substrates such as **6** and **8** demonstrates the potential of cobalt catalysts to offer reactivity and selectivity complementary to that of rhodium(I) and iridium(I) catalysts. Given the synthetic versatility of organorhodium(I) species,[15] C–C bond forming reactions involving nucleophilic organocobalt species deserve further investigations.[16,17]

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of new compounds (PDF)

Crystallographic data (CIF)

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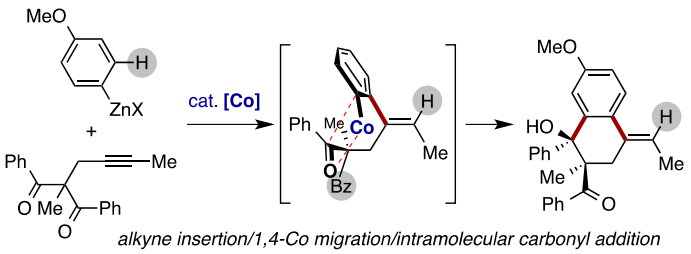

alkyne insertion/1,4-Co migration/intramolecular carbonyl addition