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Cobalt-Catalyzed Addition of Arylzinc Reagents to Norbornene Derivatives through 1,4-Cobalt Migration

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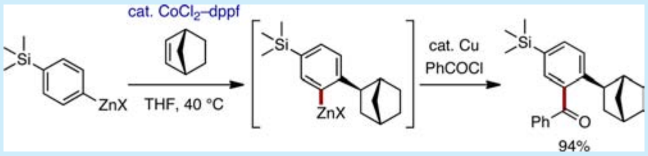
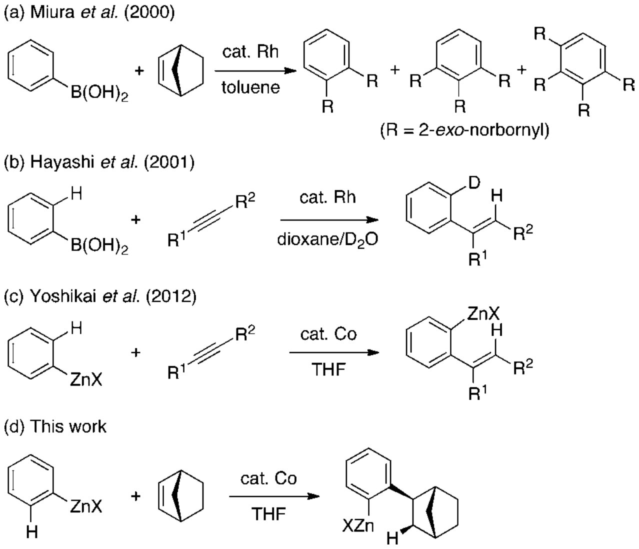
Ⓢ *Supporting Information*

ABSTRACT: A cobalt−diphosphine catalyst promotes the addition of an arylzinc reagent to a norbornene derivative to afford *o*-(2-*exo*-norbornyl)arylzinc species. This "migratory arylzincation" reaction is considered to involve insertion of norbornene into an arylcobalt species, alkyl-to-aryl 1,4-cobalt migration, and transmetalation between the resulting *o*-(2-*exo*-norbornyl)arylcobalt species and the arylzinc reagent. The *o*-(2-*exo*-norbornyl)arylzinc species can be intercepted by common organic electrophiles under copper or palladium catalysis.



Remote metal migrations of organorhodium and -palladium species, 1,4-migration in particular, have been extensively utilized to achieve novel catalytic transformations involving C−H activation and cascade bond forming processes.[1−3] With respect to the rhodium catalysis, the origin of this particular area of research dates back to two seminal reports in the early 2000s. In 2000, Miura and co-workers reported a rhodium-catalyzed merry-go-round addition reaction of an arylboronic acid to norbornene (Scheme 1a).[4] The reaction affords multiply norbonylated arenes through repetition of a sequence consisting of insertion of norbornene into arylrhodium species and alkyl-to-aryl 1,4-rhodium migration. One year later, Hayashi and co-workers reported on rhodium-catalyzed hydroarylation of an intenal alkyne with an arylboronic acid, revealing its mechanism involving 1,4-rhodium migration (Scheme 1b).[5] Thus, this apparently simple reaction goes through insertion of the alkyne into an arylrhodium species, vinyl-to-aryl 1,4-rhodium migration, and protoderhodation of the resulting *o*-alkenylarylrhodium species.

Scheme 1. Rhodium and Cobalt Catalysis Involving 1,4-Metal Migration



Recently, we disclosed the first example of 1,4-cobalt migration in a cobalt-catalyzed addition of an arylzinc reagent to an internal alkyne (Scheme 1c).[6,7] Compared to the rhodium-catalyzed hydroarylation, the reaction is unique in that it produces *o*-alkenylarylzinc species, which can be intercepted by an external electrophile. This "migratory arylzincation" also finds its application in modular synthesis of benzoheterole derivatives.[8] Here, we report that a cobalt complex is also capable of catalyzing migratory arylzincation of norbornene derivatives (Scheme 1d). Thus, unlike the rhodium-catalyzed merry-go-round addition, the present reaction affords *o*-(2-*exo*-norbornyl)-arylzinc species through alkyl-to-aryl cobalt migration and subsequent cobalt-to-zinc transmetalation. The reaction is also reminiscent of Catellani's palladium-catalyzed coupling reactions involving norbornene.[9]

The present study began with a screening of cobalt catalysts for the addition of 4-methoxyphenylzinc reagent (**1a**, 1.7 equiv; prepared from a 1:2 mixture of $ZnCl_2$·TMEDA and 4-$MeOC_6H_4MgBr$ and denoted as type **A** reagent) to norbornene **2a**, which was conducted at 60 °C for 12 h (Table 1). A $CoCl_2$−Xantphos catalyst, which is the optimum catalyst for the migratory arylzincation to an internal alkyne,[6] exhibited poor catalytic activity, affording the arylation product **3aa** only in a low yield of 2% (entry 1). Upon subsequent screening of common diphosphine ligands (entries 2−8), we identified dppf as the most effective ligand, which promoted the addition reaction to afford **3aa** in 69% yield (entry 3). Among other diphosphine ligands, dppp, dppb, and BISBI (2,2′-bis(diphenylphosphino-

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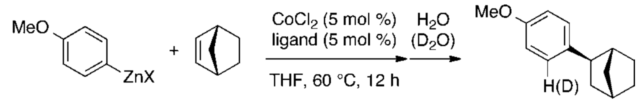
Table 1. Screening of Reaction Conditions[a]



1a (Type **A**–**C**, 1.7 equiv) **2a** **3aa** (**3aa**-*d*)

Type **A**: ZnCl$_2$•TMEDA + 2ArMgBr
Type **B**: ZnCl$_2$•TMEDA + ArMgBr
Type **C**: ZnCl2•TMEDA + ArMgBr + Me$_3$SiCH$_2$MgCl

entry	ArZnX type	ligand	yield[b] (%)
1	**A**	Xantphos	2
2	**A**	DPEphos	6
3	**A**	dppf	69
4	**A**	dppe	18[c]
5	**A**	dppp	38
6	**A**	dppb	35
7	**A**	dppbz	3[c]
8	**A**	BISBI	42
9[d]	**A**	PPh$_3$	7
10	**A**	none	1
11[e]	**A**	dppf	76
12[e]	**B**	dppf	<1
13[f]	**C**	dppf	82

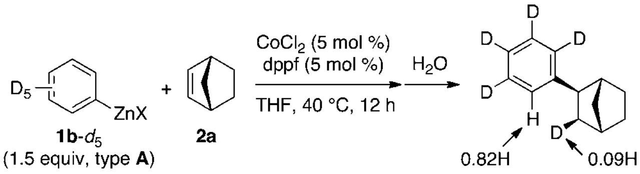
[a] Unless otherwise noted, the reaction was performed on a 0.3 mmol scale and was quenched with H$_2$O. [b] Determined by GC using *n*-tridecane as an internal standard. [c] 1,2-Di-2-norbonylated product was obtained (44% and 34% for entries 4 and 7, respectively). [d] 10 mol % of PPh$_3$ was used. [e] The reaction was performed with 1.2 equiv of arylzinc reagent at 40 °C for 18 h. [f] The reaction was performed with 1.5 equiv of arylzinc reagent at 40 °C for 12 h and quenched with D$_2$O. The yield was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

methyl)-1,1′-biphenyl) exhibited moderate performances, affording **3aa** in ca. 40% yield (entries 5, 6, and 8), while DPEphos was almost ineffective (entry 2). Interestingly, the reaction using dppe or dppbz as the ligand produced, like Miura's merry-go-round reaction (Scheme 1a), a 1,2-di-2-norbonylated product in ca. 30−40% yield, as judged from GC and GCMS analysis of the reaction mixture (entries 4 and 7). Monodentate phosphines such as PPh$_3$ as well as a ligand-free system were not effective (entries 9 and 10).

Upon further examination of reaction conditions, we found that the Co−dppf-catalyzed addition reaction could be achieved with a reduced amount of the type **A** arylzinc reagent (1.2−1.5 equiv) at a lower temperature of 40 °C (entry 11). Unlike the migratory arylzincation reaction to internal alkynes,[6] a monoarylzinc reagent prepared from a 1:1 mixture of ZnCl$_2$·TMEDA and 4-MeOC$_6$H$_4$MgBr (type **B** reagent) as well as one prepared from 4-MeOC$_6$H$_4$I and Zn·LiCl[10] were almost unreactive (entry 12), indicating that only one of two aryl groups on the type **A** reagent is transferable in the present reaction. The reactivity of this unreactive reagent could be restored by the addition of a "dummy" Grignard reagent, i.e., Me$_3$SiCH$_2$MgCl. Thus, the mixed diorganozinc reagent (type **C** reagent) underwent addition to **2a**, and upon quenching with D$_2$O, afforded a deuterated adduct **3aa**-*d* in 82% yield (entry 13).[11] The ^{1}H NMR spectrum of **3aa**-*d* showed an integration of 1.12 for the position ortho to the 2-norbornyl group, indicating substantial deuterium incorporation into this position and hence formation of an *o*-(2-*exo*-norbornyl)arylzinc species via 1,4-cobalt migration. Consistent with this, all of the norbornyl carbon atoms of **3aa**-*d* appeared as clear singlet signals in the ^{13}C NMR spectrum, demonstrating that the 3-*exo*-position of the norbornyl group was virtually not deuterated.

The putative 1,4-cobalt migration process was further supported by another deuterium-labeling experiment (Scheme 2). Thus, the addition of pentadeuteriophenylzinc reagent **1b**-d_5 (type **A**) to **2a** under the cobalt−dppf catalysis took place with concomitant migration of one of the *o*-deuterium atoms to the *exo*-2-norbornyl position, as revealed by ^{1}H NMR analysis of the product **3ba**-d_5.

Scheme 2. Reaction of Pentadeuteriophenylzinc Reagent[a]



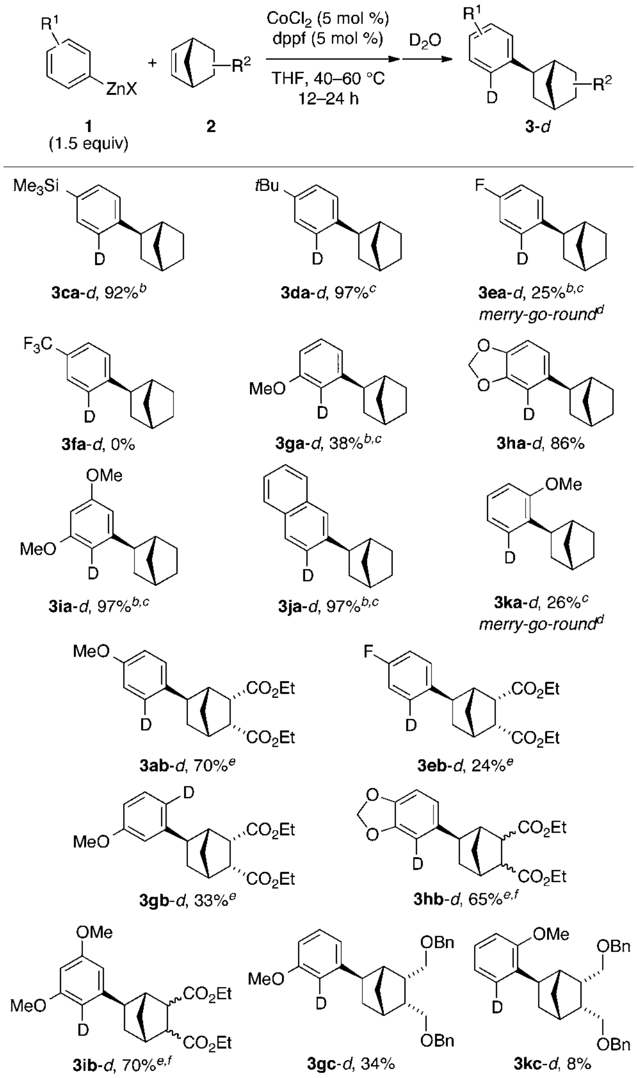
1b-d_5 (1.5 equiv, type **A**) **2a** **3ba**-d_5, 72%

[a] The proton content on each carbon atom was estimated by ^{1}H NMR analysis.

Having established the cobalt−diphosphine catalytic system, we next explored the scope of the present migratory arylzincation reaction using different arylzinc reagents and norbornene derivatives (Scheme 3). Note that each reaction was quenched with D$_2$O in order to confirm the 1,4-cobalt migration process. First, we performed reactions of a series of arylzinc reagents with norbornene **2a**. 4-(Trimethylsilyl)phenylzinc and 4-*tert*-butylphenylzinc reagents afforded the desired adducts **3ca**-*d* and **3da**-*d* in excellent yields. On the other hand, the reaction of 4-fluorophenylzinc reagent resulted in the formation of a mixture of mono- and diaddition products **3ea**-*d* and **4ea**-*d* in an approximate ratio of 1:1 (Scheme 4a). The latter product would have been formed through a merry-go-round process as proposed for Miura's rhodium-catalyzed reaction.[4] No desired reaction was observed with electron-poor 4-(trifluoromethyl)-phenylzinc reagent. As was the case with the migratory arylzincation of alkynes,[6] the *meta*-oxygen atom of 3-methoxy- and 3,4-methylenedioxyphenylzinc reagents caused secondary directing effect to induce regioselective 1,4-metal migration to its proximity (see **3ga**-*d* and **3ha**-*d*). 3,5-Dimethoxyphenylzinc reagent also afforded the desired adduct **3ia**-*d* in an excellent yield. The reaction of 2-naphthylzinc reagent took place cleanly through exclusive 1,4-migration to the less hindered 3-position, thus affording the adduct **3ja**-*d*. Like the case of 4-fluorophenylzinc reagent (Scheme 4a), a merry-go-round process was observed in the reaction of 2-methoxyphenylzinc reagent, which afforded a mixture of mono-, di-, and triaddition products **3ka**-*d*, **4ka**-*d*, and **5ka**-*d*, respectively (Scheme 4b). Note that mesitylzinc reagent failed to participate in the reaction.

A norbornene derivative bearing an *endo*-diester moiety **2b** failed to participate in the reaction with 4-methoxyphenylzinc reagent under the Co−dppf catalysis. However, the use of dppe instead of dppf promoted the reaction to afford the desired product **3ab**-*d* in 70% yield. 4-Fluoro-, 3-methoxy-, 3,4-methylenedioxy-, and 3,5-dimethoxyphenylzinc reagents also underwent addition to **2b** to afford the corresponding adducts **3eb**-*d*, **3gb**-*d*, **3hb**-*d*, and **3ib**-*d*, respectively, albeit in modest yields. Curiously, the reaction of 3-methoxyphenylzinc reagent and **2b** exhibited the opposite regioselectivity to that observed in the reaction of the same reagent with **2a** (see **3ga**-*d*), thus resulting in deuteration of the position distal to the methoxy

Scheme 3. Scope of Migratory Arylzincation[a]

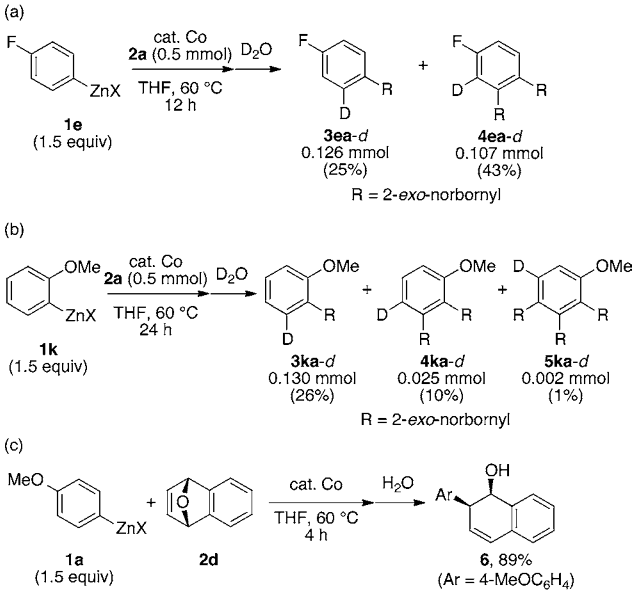


[a]The reaction was performed on a 0.5 mmol scale. Unless otherwise noted, type **A** arylzinc reagent was used, and the isolated yield is shown. [b]Type **C** arylzinc reagent was used. [c]The yield was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [d]Merry-go-round addition was observed (see Scheme 4). [e]Dppe was used instead of dppf. [f]Obtained as a diastereomeric mixture.

group (see **3gb**-*d*), while the regioselectivity did not change for 3,4-methylenedioxyphenylzinc reagent (see **3ha**-*d* and **3hb**-*d*). Note that some of these reactions produced a mixture of diastereomers, presumably due to epimerization of the α-positions of the diester moiety. The reactions of 3-methoxyphenyl- and 2-methoxyphenylzinc reagents with an *endo*-diether **2c** took place under the Co−dppf catalysis and afforded the corresponding adducts **3gc**-*d* and **3kc**-*d*, respectively, albeit in low yields. In the former case, deuteration took place at the position proximal to the methoxy group. Note also that, in these low-yielding cases, the norbornene derivative was largely recovered without affording any byproducts.

The reaction of 4-methoxyphenylzinc reagent **1a** with oxabicyclic alkene **2d** did not afford a migratory arylzincation product, but resulted in a ring-opening arylation product **6** (Scheme 4c).[12] Attempts to suppress the β-oxygen elimination process by using less reactive arylzinc reagent (i.e., type **B** reagent) or by lowering the reaction temperature did not change the course of the reaction.[13]

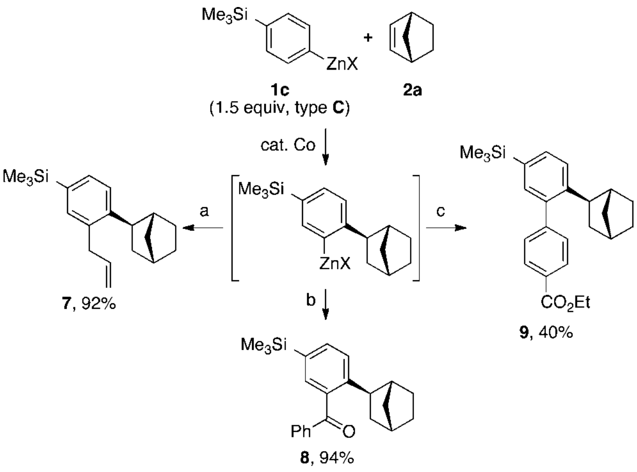
Scheme 4. Merry-Go-Round Addition to Norbornene and Ring-Opening Arylation of Oxabicyclic Alkene[a]



[a]cat. Co = $CoCl_2$ (5 mol %), dppf (5 mol %). The identities and quantities of norbornylated products were estimated by ^{1}H NMR, GC, and GCMS analysis of the product mixture. The yields in parentheses are based on **2a**.

The *o*-(2-*exo*-norbornyl)arylzinc species formed by the present reaction is amenable to transition-metal-catalyzed cross-coupling with organic electrophiles (Scheme 5).[14] The reaction of 4-(trimethylsilyl)phenylzinc reagent **1c** and **2a** was followed by copper-catalyzed allylation with allyl bromide and acylation with benzoyl chloride to afford the desired products **7** and **8**, respectively, in excellent yields.[15] The same *o*-(2-*exo*-norbornyl)arylzinc intermediate also participated in the Negishi

Scheme 5. Electrophilic Trapping of *o*-Norbornylarylzinc Species[a]

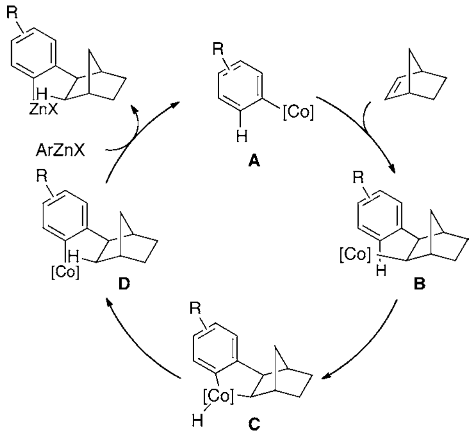


[a]CuCN·2LiCl (20 mol %), allyl bromide (3 equiv), 60 °C, 8 h. [b]CuCN·2LiCl (20 mol %), benzoyl chloride (3 equiv), 60 °C, 8 h. [c]$Pd(OAc)_2$ (4 mol %), SPhos (4 mol %), ethyl 4-iodobenzoate (3 equiv), 60 °C, 8 h.

coupling with ethyl 4-iodobenzoate under Pd/SPhos catalysis, affording the biaryl product **9** in a moderate yield.

A proposed catalytic cycle for the present migratory arylzincation is shown in Scheme 6. An arylcobalt species **A** generated from the cobalt precatalyst and the arylzinc reagent undergoes insertion of norbornene to give a norbornylcobalt species **B**. This species undergoes alkyl-to-aryl 1,4-cobalt migration presumably through a C−H oxidative addition intermediate **C**,[2d,4] thus affording an *o*-(2-*exo*-norbornyl)-arylcobalt species **D**. Subsequent transmetalation between **D** and the arylzinc reagent furnishes the *o*-(2-*exo*-norbornyl)-arylzinc species and regenerates the arylcobalt species **A**.

Scheme 6. Proposed Catalytic Cycle



In summary, we have reported on a cobalt−diphosphine-catalyzed addition reaction of an arylzinc reagent to a norbornene derivative, which involves alkyl-to-aryl 1,4-cobalt migration and cobalt-to-zinc transmetalation as key steps, thus affording *o*-(2-*exo*-norbornyl)arylzinc species. The arylzinc product is amenable to common electrophilic trapping reactions under copper or palladium catalysis. Further mechanistic and synthetic investigations into catalytic transformations involving 1,4-cobalt migration are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) In this and some other cases, it was difficult to isolate the addition product in a pure form because of small polarity differences among the product and hydrolyzed/homocoupling products of the arylzinc reagent. In such cases, the crude product mixture was subjected to short silica gel chromatography, and the yield was determined by ^{1}H NMR analysis of the thus-obtained sample using 1,1,2,2-tetrachloroethane as an internal standard. See the Supporting Information for the details of each case.

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