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

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Supporting Information Placeholder

ABSTRACT: A cobalt–diphosphine catalyst promotes the addition of an arylzinc reagent to a norbornene derivative to afford *ortho*-(2-*exo*-norbornyl)arylcobalt 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 *ortho*-(2-*exo*-norbornyl)arylcobalt species and the arylzinc reagent. The *ortho*-(2-*exo*-norbornyl)arylcobalt 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 coworkers reported a rhodium-catalyzed merry-go-round addition reaction of an arylboronic acid to norbornene (Scheme 1a).⁴ The reaction affords multiply norbornylated 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 coworkers reported on rhodium-catalyzed hydroarylation of an internal 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 *ortho*-alkenylarylrhodium species.

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 *ortho*-alkenylarylcobalt species, which can be intercepted by an external electrophile. This "migratory arylzincation" also finds its application in modular synthesis of benzothiophene and benzoselenophene 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 *ortho*-(2-*exo*-norbornyl)arylcobalt 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

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

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 ZnCl₂•TMEDA and 4-MeOC₆H₄MgBr and denoted as type **A** reagent) to norbornene **2a**, which was conducted at 60 °C for 12 h (Table 1). A CoCl₂–Xantphos catalyst, which is the optimum catalyst for the migratory arylzincation to an internal alkyne,⁶ exhibited poor catalytic activity, affording the ary-

lation 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(diphenylphosphinomethyl)-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), produced a 1,2-di-2-norbornylated product in ca. 30–40% yield, as judged from GC and GCMS analysis of the reaction mixture (entries 4 and 7). Mono-dentate phosphines such as PPh₃ 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 ZnCl₂•TMEDA and 4-MeOC₆H₄MgBr (type **B** reagent) as well as one prepared from 4-MeOC₆H₄I and Zn•LiCl¹⁰ 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., Me₃SiCH₂MgCl. Thus, the mixed diorganozinc reagent (type **C** reagent) underwent addition to **2a**, and upon quenching with D₂O, afforded a deuterated adduct **3aa-d** in 82% yield (entry 13).¹¹ The ¹H 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 *ortho*-(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 ¹³C NMR spectrum, demonstrating that the 3-*exo*-position of the norbornyl group was virtually not deuterated.

Table 1. Screening of Reaction Conditions^a

(Type A–C , 1.7 equiv)			
Type A : ZnCl ₂ •TMEDA + 2ArMgBr Type B : ZnCl ₂ •TMEDA + ArMgBr Type C : ZnCl ₂ •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

^aUnless otherwise noted, the reaction was performed on a 0.3 mmol scale and was quenched with H₂O. ^bDetermined by GC using *n*-tridecane as an internal standard. ^c1,2-Di-2-norbornylated product was obtained (44% and 34% for entries 4 and 7, respectively). ^d10 mol % of PPh₃ was used. ^eThe reaction was performed with 1.2 equiv of arylzinc reagent at 40 °C for 18 h. ^fThe reaction was performed with 1.5 equiv of arylzinc reagent at 40 °C for 12 h and quenched with D₂O. The yield was determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

The putative 1,4-cobalt migration process was further supported by another deuterium-labeling experiment (Scheme 2). Thus, the addition of pentadeuteriophenylzinc reagent **1b-d₅** (type **A**) to **2a** under the cobalt–dppf catalysis took place with concomitant migration of one of the *ortho*-deuterium atoms to the *exo*-2-norbornyl position, as revealed by ¹H NMR analysis of the product **3ba-d₅**.

Scheme 2. Reaction of Pentadeuteriophenylzinc Reagent^a

^a The proton content on each carbon atom was estimated by ¹H 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 D₂O in order to confirm the 1,4-cobalt migration process. First, we performed reactions of a series of arylzinc reagents with norbornene **2a**. 4-Trimethylsilylphenylzinc 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 di-addition 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-trifluoromethylphenylzinc 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 tri-addition products **3ka-d**, **4ka-d**, and **5ka-d**, re-

spectively (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 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.

Scheme 3. Scope of Migratory Arylzincation

^aThe reaction was performed on a 0.5 mmol scale. Unless otherwise noted, type **A** arylzinc reagent was used, and the isolated yield is shown.

^bType **C** arylzinc reagent was used. ^cThe yield was determined by ¹H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

^dMerry-go-round addition was observed (see Scheme 4). ^eDppe was used instead of dppf. ^fObtained as a diastereomeric mixture.

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

^acat. Co = CoCl₂ (5 mol %), dppf (5 mol %). The identities and quantities of norbornylated products were estimated by ¹H NMR, GC and GCMS analysis of the product mixture. The yields in parentheses are based on **2a**.

The *ortho*-(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-trimethylsilylphenylzinc 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 *ortho*-(2-*exo*-norbornyl)arylzinc intermediate also participated in the Negishi coupling with ethyl 4-iodobenzoate under Pd/SPhos catalysis, affording the biaryl product **9** in a moderate yield.

Scheme 5. Electrophilic Trapping of *ortho*-Norbornylarylzinc Species

^aCuCN·2LiCl (20 mol %), allyl bromide (3 equiv), 60 °C, 8 h.
^bCuCN·2LiCl (20 mol %), benzoyl chloride (3 equiv), 60 °C, 8 h.
^cPd(OAc)₂ (4 mol %), SPhos (4 mol %), ethyl 4-iodobenzoate (3 equiv), 60 °C, 8 h.

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 *ortho*-(2-*exo*-norbornyl)arylcobalt species **D**. Subsequent transmetalation between **D** and the arylzinc reagent furnishes the *ortho*-(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 *ortho*-(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 ¹H NMR analysis of the thus-obtained sample using 1,1,2,2-tetrachloroethane as an internal standard. See the Supporting Information for the detail of each case.

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