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Cobalt(diamine)-Catalyzed Cross-coupling Reaction of Alkyl Halides with Arylmagnesium Reagents: Stereoselective Constructions of Arylated Asymmetric Carbons and Application to Total Synthesis of AH13205

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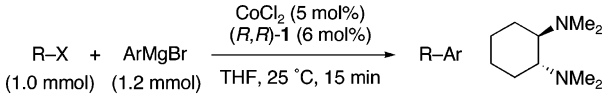
Abstract: A cobalt−diamine complex catalyzes the cross-coupling reactions of primary and secondary alkyl halides with aryl Grignard reagents. It is confirmed that oxidative addition of alkyl halide to cobalt proceeds via a radical process. Optically pure Ueno-Stork halo acetals undergo diastereoselective cross-coupling reactions, the products of which are transformed into optically active THF derivatives. A sequential radical cyclization/arylation reaction under cobalt catalysis provides extremely short access to a synthetic prostaglandin AH13205.

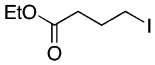
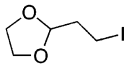
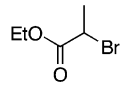
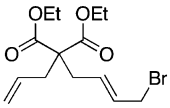
Introduction

Transition-metal-catalyzed cross-coupling reactions are indispensable tools for the construction of organic molecules. Use of alkyl halides that can suffer from β-elimination in cross-coupling reactions is now attracting increasing attention as a new repertoire of cross-coupling strategy.[1] Especially, coupling of secondary[2] and tertiary[2d,2e,2q,2r] alkyl halides with organometallic reagents is a challenging target to establish the universality of cross-coupling reactions.

During the course of our study on cobalt-catalyzed cross-coupling reactions,[2q,2r,3] we found that catalytic amounts of cobalt(II) chloride and diamine (*R*,*R*)-**1** promote cross-coupling reactions of alkyl halides with arylmagnesium reagents (Table 1). This will significantly expand the utility of cobalt as a catalyst.[4] Specifically, the present cobalt−diamine-catalyzed method allows us to arylate secondary alkyl halides whereas our previous arylation reaction[3a] is applicable to the reaction of primary alkyl halides.

Table 1. Cobalt−Diamine-Catalyzed Cross-coupling Reaction



entry	R–X	Ar	R–Ar
1		Ph	95 (X=I)
2		Ph	95(X=Br)[a]
3		2-naphthyl	93 (X=Br)
4	$^{n}C_6H_{17}$–X	Ph	99 (X=I)
5		Ph	80 (X=Br)
6		Ph	10 (X=Cl)
7		2-MeC_6H_4	99 (X=I)
8		2-thienyl	86 (X=I)
9		1-phenylvinyl	72 (X=I)[b]
10		Ph	73
11		4-MeOC_6H_4	87
12		Ph	91
13		Ph	86
14		Ph	88
15		Ph	56[c]

[a] When the reaction was performed on a 10 mmol scale, an 87% yield of the product was obtained. [b] $CoCl_2$ (10 mol %) and (*R*,*R*)-**1** (36 mol %) were used. [c] No cyclopentane ring was observed.

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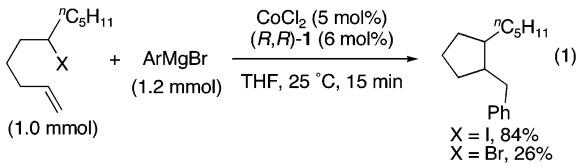
10.1021/ja057560o CCC: $33.50

Results and Discussion

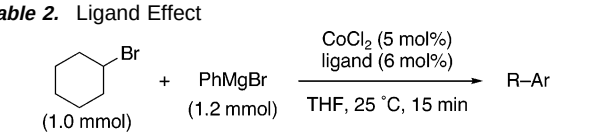
Scope and Limitation. Diamine **1** (0.06 mmol)[5] was added to a suspension of $CoCl_2$ (0.05 mmol) in THF (3 mL) to form a clear-blue solution. Substrate (1.0 mmol) and then a Grignard reagent (1.2 mmol, 1 M THF solution) were added over 5 s at 0 °C. An exothermic reaction immediately took place. After the mixture was stirred at 25 °C for 15 min, the usual workup followed by silica gel column purification afforded the corresponding coupling product. Representative examples are listed in Table 1. Several comments are worth noting: (1) Not only primary alkyl halides but also secondary ones underwent the cross-coupling reaction. In contrast, phenylation took place only with primary alkyl halides under our previous cobalt-diphosphine catalysis.[3a] Unfortunately, neither *tert*-butyl bromide nor iodide couple with any aryl Grignard reagents tested. (2) Alkyl iodides and bromides are the choice of the coupling partner. The reaction of 1-chlorooctane resulted in poor yield (entry 6). (3) The reaction was readily scalable. Treatment of 10 mmol of bromocyclohexane with phenylmagnesium bromide (12 mmol) in the presence of **1** (0.6 mmol) and $CoCl_2$ (0.5 mmol) in THF (30 mL) in a similar manner provided cyclohexylbenzene in 87% yield (entry 2). (4) An alkenylmagnesium reagent (entry 9) as well as arylmagnesium reagents were available for the cross-coupling reaction. (5) Functional groups such as an ester linkage were compatible. (6) Allylic bromide also underwent the phenylation reaction (entry 15), wherein no cyclization was observed (vide infra).[2n] On the other hand, a cyclic product was obtained exclusively in the reaction of 6-iodo-1-undecene to yield 1-benzyl-2-pentylcyclopentane (diastereomer ratio = 3:1) in good yield (eq 1).[2l,2n,2o,2q,2r,3a] The relevant bromide was less reactive.

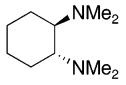
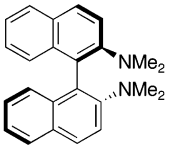
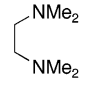
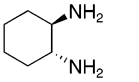
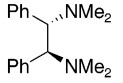
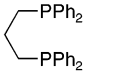
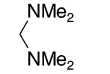
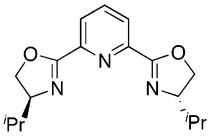
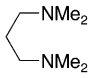


The diamine (*R*,*R*)-**1** is the best ligand among ligands we tested (Table 2). *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine and (1*S*, 2*S*)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diphenylethylenediamine were less effective (entries 2 and 3). The difference in efficiency would originate from the very subtle changes in the conformations, bite angles, and/or steric hindrance of the diamine ligands. Naturally, a shorter or a longer methylene tether completely deactivated the cobalt catalysts (entries 4 and 5). The reactions with the aid of primary 1,2-cyclohexanediamine (entry 7), a bidentate phosphine (entry 8), and a pybox ligand (entry 9) provided none of the coupling product.

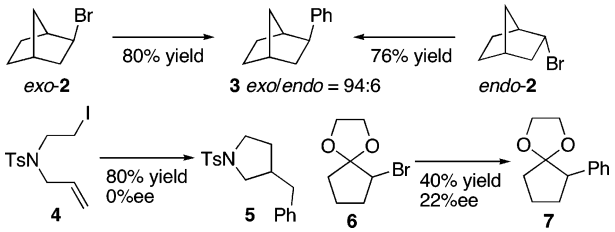
Evidence of Carbon-Centered Radical Intermediates. The intermediacy of a carbon-centered radical in the arylation reaction is strongly supported by the following new facts, in addition to our accumulative efforts to certify cobalt-mediated

Table 2. Ligand Effect



entry	ligand	yield /%	entry	ligand	yield /%
1		95	6		<1
2		43	7		<1
3		76	8		<1
4		<1	9		<1
5		<1			

Scheme 1. Justification of the Existence of Carbon-centered Radicals; Conditions Are the Same as Those in Table 1



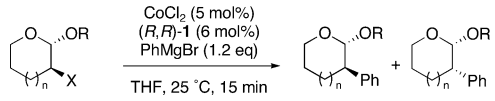
radical processes (Scheme 1): (1) The phenylations of *endo*- and *exo*-**2** yielded **3** with the same endo/exo selectivity, which indicates the existence of a planer carbon center with no original stereochemical information. (2) The reaction of **4** with phenylmagnesium bromide yielded cyclic product **5** in 80% yield. Notably, no enantioselectivity for the cyclization was observed. We tested several other cyclization reactions under the chiral cobalt catalysis. However, all the reactions exhibited no enantioselectivity. The complete lack of the enantioselectivity implies that the 5-*exo*-*trig* cyclization step proceeds via a free radical mechanism, not via enantioface-discriminating intramolecular carbocobaltation. (3) Some enantioselectivity was observed in the phenylations of cyclic halides such as **6**. The enantioselection would take place upon recombination of a cobalt complex with a planer carbon-centered radical.[2q,2r,3a] Unfortunately, no kinetic resolution of **6** was observed.

Cobalt-Catalyzed Highly Stereoselective Arylations and Their Applications. Next we turned our attention to the coupling reaction of Ueno-Stork halo acetals[6] that have a stereogenic center next to the halogenated carbons (Table 3). The coupling reactions proceeded smoothly without suffering from possible β-alkoxy elimination. Virtually no stereoselectivity was observed in the reactions of tetrahydropyran derivatives (entries 1 and 2). On the other hand, the phenylations of tetrahydrofurans were highly diastereoselective (entries 3 and

(4) For recent reports on cobalt-catalyzed coupling reactions, see: (a) Cahiez, G.; Avedissian, H. *Tetrahedron Lett.* **1998**, *39*, 6159−6162. (b) Avedissian, H.; Bérillon, L.; Cahiez, G.; Knochel, P. *Tetrahedron Lett.* **1998**, *39*, 6163−6166. (c) Nishii, Y.; Wakasugi, K.; Tanabe, Y. *Synlett* **1998**, 67−69. (d) Korn, T. J.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 2947−2951. (e) Sezen, B.; Sames, D. *Org. Lett.* **2003**, *5*, 3607−3610. (f) Gomes, P.; Gosmini, C.; Périchon, J. *Org. Lett.* **2003**, *5*, 1043−1045. (g) Amatore, M.; Gosmini, C.; Périchon, J. *Eur. J. Org. Chem.* **2005**, 989−992.

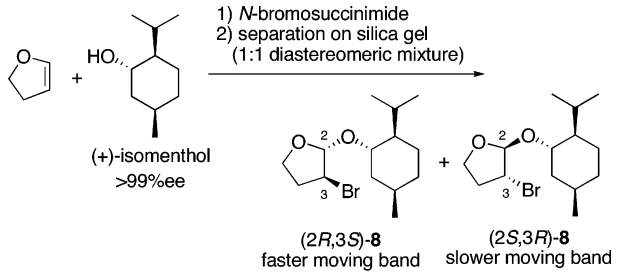
(5) Racemic diamine **1** worked as well.

Table 3. Diastereoselective Cross-coupling of Halo Acetals

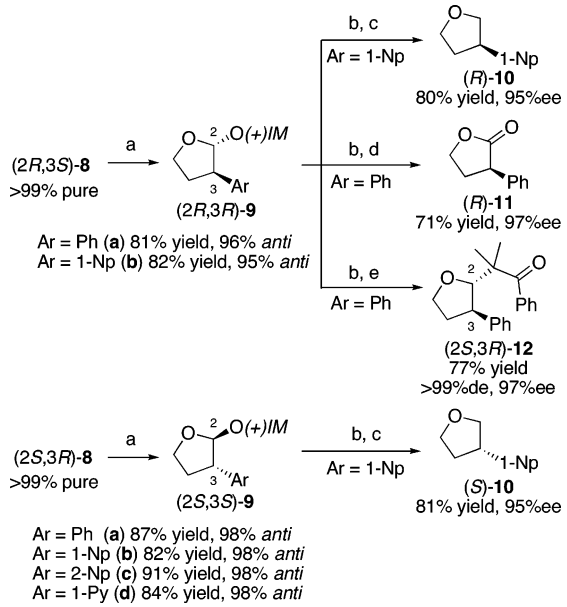


entry	n	X	R	yield	trans/cis
1	1	I	Me	83%	51:49
2	1	I	^{i}Pr	81%	60:40
3	0	Br	Me	82%	95:5
4	0	Br	^{i}Pr	80%	96:4

Scheme 2. Preparation of Bromo Acetal Having Chiral Auxiliary



Scheme 3. Arylation of Chiral Bromo Acetal **8**[a]

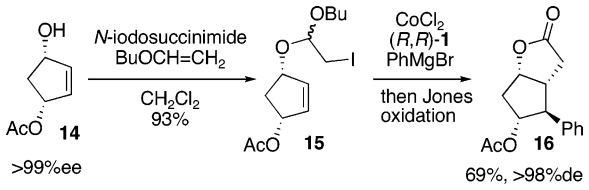


[a] Abbreviations: *(+)IM*, (+)-isomenthyl; 1-Np, 1-naphthyl; 2-Np, 2-naphthyl; 1-Py, 1-pyrenyl. Conditions: (a) $CoCl_2$ (5 mol %), (*R*,*R*)-**1** (12 mol %), ArMgBr (1.2 mmol), THF, 25 °C, 15 min; (b) chromatographic isolation of the anti-isomer; (c) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (d) CrO_3, acetone; (e) $Me_2C{=}C(Ph)OSiMe_3$ (**13**), $BF_3{\cdot}OEt_2$, CH_2Cl_2.

4). Five-membered rings have less flexibility than six-membered ones, which leads to the efficient shielding by the alkoxy group on one face of the ring. Note again that no kinetic resolution of the halo acetals was observed. Attempted butylation, vinylation, and allylation reactions resulted in failure, leaving most of the starting bromo acetal.

Bromoetherification with enantiomerically pure (+)-isomenthol allowed the separation of the diastereomers, (2*R*,3*S*)-**8** and (2*S*,3*R*)-**8**, from each other by purification on silica gel under atmospheric pressure (Scheme 2). With the enantiomerically pure bromo acetals in hand, the arylation reactions of **8** were examined (Scheme 3). As expected, (2*R*,3*S*)-**8** and (2*S*,3*R*)-**8** underwent highly diastereoselective arylation reactions, furnishing optically pure 2-alkoxy-3-aryl-1-oxacyclopentanes, (2*R*,3*R*)-**9** and (2*S*,3*S*)-**9**, respectively. The absolute stereochemistry of (2*R*,3*R*)-**9** was determined by X-ray crystallographic analysis.[7] The major isomers produced in the arylation reactions were separated from the minor isomers and were subjected to several transformations. Lewis-acid-mediated reductions of (2*R*,3*R*)-**9b** and (2*S*,3*S*)-**9b** furnished (*R*)-**10** and (*S*)-**10**, respectively, in excellent yield with high enantiomeric excess. Jones oxidation of (2*R*,3*R*)-**9a** afforded optically active lactone (*R*)-**11**. The reactions of (2*R*,3*R*)-**9a** with silyl enolate **13** constructed a new carbon−carbon bond diastereoselectively.

Scheme 4. Synthesis of a Corey Lactone Analogue

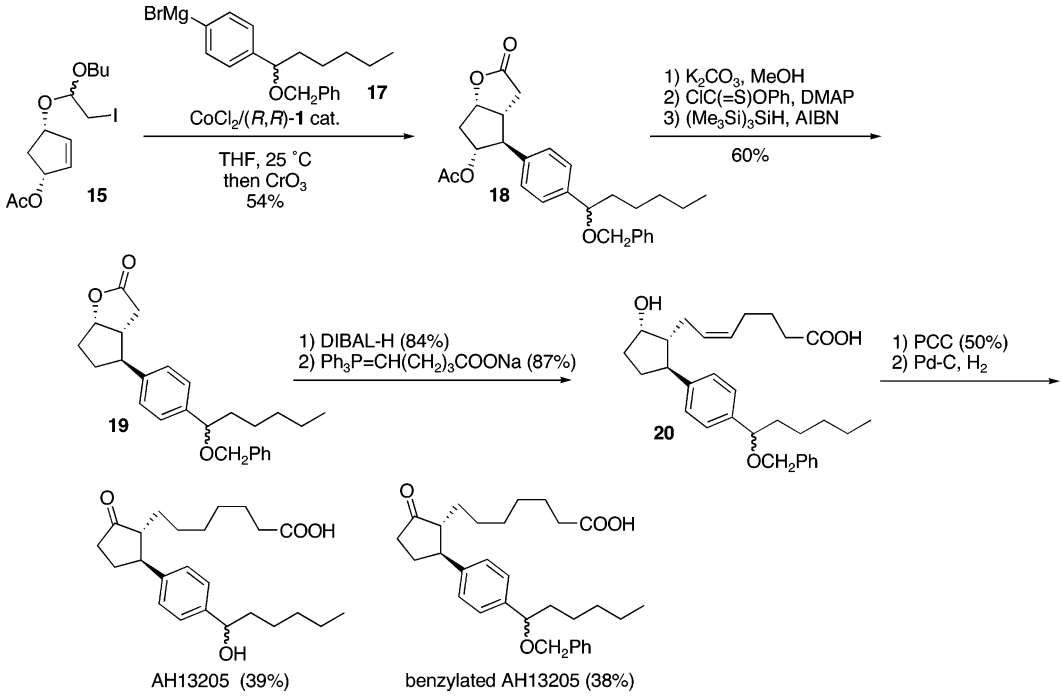


Sequential Cyclization/Arylation Reactions: Total Synthesis of AH13205. Iodoetherification of butyl vinyl ether with optically pure **14** yielded **15** (Scheme 4). Treatment of **15** under the present conditions leads to sequential radical cyclization/cross-coupling reaction to afford a phenylated analogue of Corey lactone[8] **16**. The sequential version also allowed the construction of a secondary alkyl−aryl bond in a highly stereoselective manner.

The sequential cyclization/arylation reaction is applicable for the synthesis of a synthetic prostaglandin AH13205, an EP_2-receptor agonist that lowers intraocular pressure.[9,10] The synthesis is outlined in Scheme 5. Cobalt-catalyzed reaction of **15** with Grignard reagent **17** followed by Jones oxidation provided bicyclic lactone **18** in 54% yield. Removal of the acetoxy group in **18** was performed in three steps. Namely, deacetylation, formation of thiocarbonate, and tin-free radical reduction[11] afforded lactone **19** in 60% overall yield. Reduction of **19** followed by Wittig olefination allowed installation of the α side chain of AH13205 with high efficiency. Hydroxy alcohol **20** was oxidized. Finally, simultaneous deprotection and reduction by catalytic hydrogenation completed the total synthesis of AH13205. The only byproduct identified was benzylated AH13205, which can be subjected to additional deprotection conditions. AH13205 is a mixture of epimers. The mixture was used to serve as the agonist.[9] The synthesis is extremely short, which highlights the synthetic utility of the cobalt-catalyzed arylation process.

(6) (a) Salom-Roig, X. J.; Dénès, F.; Renaud, P. *Synthesis* **2004**, 1903−1928. (b) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564−5566. (c) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741−3742.
(7) See Supporting Information.
(8) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley & Sons: New York, 1989; Chapter 11.
(9) (a) Nials, A. T.; Vardey, C. J.; Denyer, L. H.; Thomas, M.; Sparrow, S. J.; Shephaerd, G. D.; Coleman, R. A. *Cardiovasc. Drug Rev.* **1993**, *11*, 165−179. (b) Woodward, D. F. U.S. Patent, 5,462,968, Oct 31, 1995. (c) Borman, R. A.; Coleman, R. A.; Clark, K. L.; Mills, K.; Oxford, A. W.; Zhang, J. European Patent,WO2005061449, July 7, 2005. (d) Stumpff, F.; Boxberger, M.; Krauss, A.; Rosenthal, R.; Meissner, S.; Choritz, L.; Wiederholt, M.; Thieme, H. *Exp. Eye Res.* **2005**, *80*, 697−708. (e) Richter, M.; Krauss, A. H.-P.; Woodward, D. F.; Lütjen-Drecoll, E. *Invest. Ophthalmol. Vis. Sci.* **2003**, *44*, 4419−4426.
(10) The only published total synthesis of AH13205: Kobayashi, Y.; Nakata, K.; Ainai, T. *Org. Lett.* **2005**, *7*, 183−186.
(11) Robin, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059−4065.

Scheme 5. Total Synthesis of AH13205



Conclusion

The cobalt−diamine catalyst system is promising for combining aryl Grignard reagents with primary and secondary alkyl halides. The reaction is powerful and reliable enough to realize stereoselective construction of asymmetric carbon centers. The high stereoselectivity observed depends on the generation of planer carbon-centered radicals followed by approaches of cobalt complexes from the less congested faces. High stereoselectivity was also observed in the sequential cyclization/arylation reaction, leading to the short total synthesis of the synthetic prostaglandin AH13205.

Experimental Section

Typical Procedure for Cobalt-Catalyzed Arylation Reaction. The reaction of bromocyclohexane with phenyl Grignard reagent (Table 1, entry 2) is representative. Anhydrous cobalt(II) chloride (6.5 mg, 0.05 mmol) was placed in a 20-mL reaction flask and was heated with a hair-dryer in vacuo for 2 min. After the color of the cobalt salt became blue, anhydrous THF (3 mL) and (*R*,*R*)-**1** (10 mg, 0.06 mmol) were sequentially added under argon. The mixture was stirred for 3 min at room temperature. Bromocyclohexane (163 mg, 1.0 mmol) was added. Phenylmagnesium bromide (1.0 M THF solution, 1.2 mL, 1.2 mmol) was then added over 5 s to the reaction mixture at 0 °C. While the Grignard reagent was being added, the mixture turned brown. After being stirred for 15 min at 25 °C, the reaction mixture was poured into saturated ammonium chloride solution. The products were extracted with hexane (20 mL × 2). The combined organic layer was dried over Na_2SO_4 and concentrated. Silica gel column purification (hexane) of the crude product provided cyclohexylbenzene (152 mg, 0.95 mmol) in 95% isolated yield. The addition of phenylmagnesium bromide was performed over 10 s in the 10 mmol scale reaction (1.39 g, 8.7 mmol, 87% yield).

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Supporting Information Available: Experimental details, characterization data for new compounds, and assignment of the absolute configurations of **8** and **9** (PDF) and crystallographic data for **9** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org. See any current masthead page for ordering information and Web access instructions.

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