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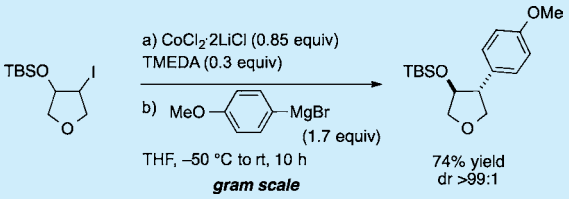
Cobalt-Mediated Diastereoselective Cross-Coupling Reactions between Cyclic Halohydrins and Arylmagnesium Reagents

Jeffrey M. Hammann, Andreas K. Steib, and Paul Knochel*

Department of Chemistry, Ludwig-Maximilians-Universität München, Butenandtstr. 5-13, Haus F, 81377 Munich, Germany

Supporting Information

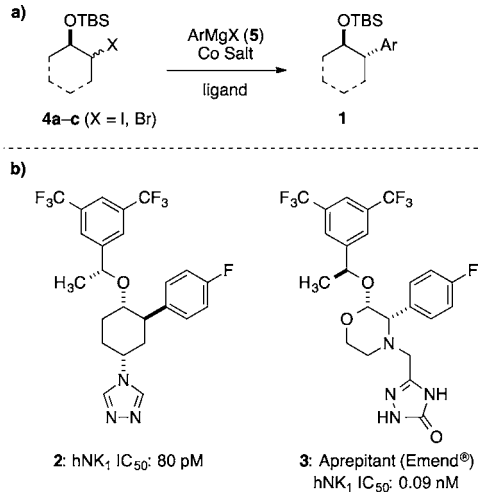
ABSTRACT: Cyclic TBS-protected iodohydrins (and bromohydrins) undergo a highly diastereoselective cross-coupling with various aryl- and heteroarylmagnesium reagents in the presence of THF-soluble $CoCl_2$·2LiCl and TMEDA as a ligand leading to *trans*-2-arylcyclohexanol derivatives in good yields and dr up to >99:1. A range of functional groups are tolerated in the Grignard reagent (e.g., COOR, CN, CF_3, SF_5). The use of heterocyclic iodohydrins leads to *trans*-3,4-disubstituted pyrrolidines and tetrahydrofurans.



Transition-metal-catalyzed cross-coupling reactions are indispensable tools for the construction of C−C bonds in organic synthesis.[1] Most of these reactions are catalyzed by Pd or Ni salts; however, these metals have the disadvantage of toxicity[2] and/or high costs.[3] In contrast, cobalt is an inexpensive and less toxic alternative for cross-coupling reactions. Recently, there has been much progress in Co-catalyzed coupling methods.[4] However, despite the spectacular advances and insights into the role of Co in coupling reactions, only a few diastereoselective Co-mediated or catalyzed transformations of this type have been described.[5,6] Previously, we have reported a diastereoselective Fe-mediated cross-coupling of cyclic iodohydrins with aryl Grignard reagents leading to products of type **1**.[7] Although very effective with electron-poor Grignard reagents, this method displays a limited reaction scope, and electron-rich arylmagnesium bromides give unsatisfactory results. Additionally, cyclic bromohydrins did not react. Herein, we report a new broadly applicable cobalt-mediated α-arylation of TBS-protected (TBS = *tert*-butyldimethylsilyl) cyclic bromo- and iodohydrins.[8] The structural unit present in **1** is found in a range of biologically active molecules, such as the NK_1 antagonists **2** and **3** (Scheme 1).[9]

In optimization studies, we have examined the arylation of **4a** (75:25 *cis*/*trans*, X = I) with 4-anisylmagnesium bromide (**5a**) in the presence of various transition-metal salts (Table 1). As mentioned above, the use of $FeCl_2$·2LiCl proved to be unsatisfactory, and the coupling of **4a** with **5a** furnished the expected product **1a** in only 18% yield (entry 1).[7] Changing the iron salt or the ligand was not satisfactory (entries 2 and 3).[10] Therefore, we examined other metallic salts. $MnCl_2$·2LiCl[11] and $CrCl_2$[12] gave poor results (entries 4 and 5), in contrast to cobalt salts. Thus, $CoCl_2$·2LiCl (0.85 equiv)[13] and 4-fluorostyrene (0.5 equiv) used as an additive[14] led to the product **1a** with a dr = 99:1, but with only 44% yield (entry 6). In the absence of 4-fluorostyrene, the yield improved to 62%. Finally, adding TMEDA as a ligand gave the best results (71% isolated yield, dr 95:5; entry 8).[5e,15]

Scheme 1. (a) Diastereoselective α-Arylation of Alcohol Derivatives and (b) Structure of Key NK_1 Antagonists 2 and 3



Thus, the dropwise addition of various Grignard reagents to a mixture of the protected iodohydrin **4a** (1.0 equiv), $CoCl_2$·2LiCl (0.85 equiv, 1 M in THF),[16] and TMEDA (0.3 equiv) in THF at −50 °C led to the *trans*-coupling products (**1a**−**k**) in 55−91% yield and excellent dr (dr >95:5, Table 2).[17] Both electron-poor or electron-rich arylmagnesium halides were used successfully. Furthermore, heterocyclic Grignard reagents obtained either by a directed magnesiation[18] or magnesium insertion[19] led to the desired cross-coupling product in very high diastereoselectivity (up to >99:1 dr). Thus, the magnesiation of the uracil derivative **6** with TMPMgCl·LiCl (1.1 equiv, THF, 0 °C, 0.5 h) led to the heterocyclic Grignard reagent **5b** (>90% yield).[18] Its coupling with **4a** under the

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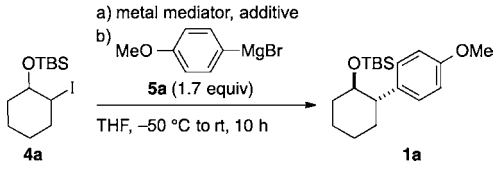
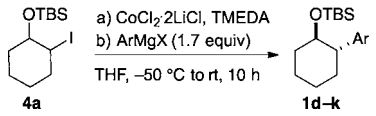
Table 1. Optimization of the Conditions for the Diastereoselective Cross-Coupling of 4a with 5a

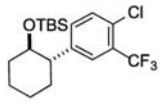
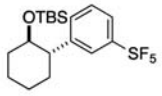
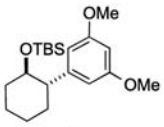
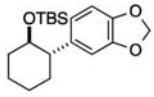
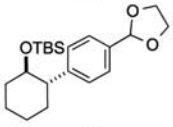
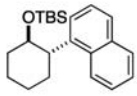
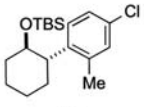
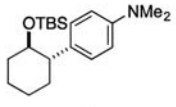


entry	metal mediator (equiv)	additive (equiv)	GC yield[a] (%)	dr[a]
1	$FeCl_2$·2LiCl (0.85)	4-fluorostyrene (0.50)	18	94:6
2	$FeCl_2$·2LiCl (0.85)	TMEDA (0.30)	53	88:12
3	$Fe(acac)_3$ (0.85)	TMEDA (0.30)	24	91:9
4	$MnCl_2$·2LiCl (0.85)	TMEDA (0.30)	0	nd
5	$CrCl_2$ (0.20)	TMEDA (0.30)	5	99:1
6	$CoCl_2$·2LiCl (0.85)	4-fluorostyrene (0.50)	44	99:1
7	$CoCl_2$·2LiCl (0.85)		62	99:1
8	$CoCl_2$·2LiCl (0.85)	TMEDA (0.30)	79 (71)[b]	95:5

[a]Determined by capillary GC analysis. Undecane ($C_{11}H_{24}$) was used as internal standard. [b]Isolated yield. TMEDA = *N,N,N′,N′*-tetramethylethane-1,2-diamine.

Table 2. Products Obtained by the Diastereoselective Cross-Coupling of 4a with Various Grignard Reagents



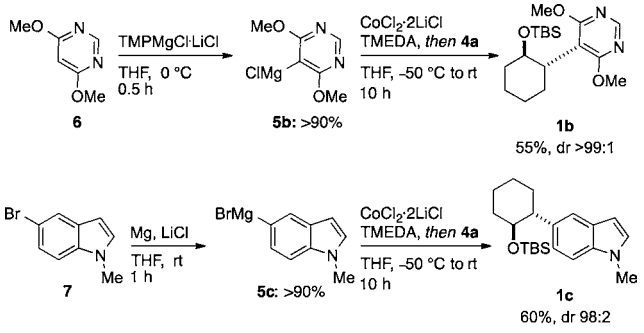
entry	product	yield (%)[a] dr[b]	entry	product	yield (%)[a] dr[b]
1	 1d	65 >99:1	5	 1h	67 98:2
2	 1e	71 95:5	6	 1i	70 98:2
3	 1f	73 97:3	7	 1j	91 >99:1
4	 1g	71 >99:1	8	 1k	63 99:1

[a]Isolated yield. [b]Determined by capillary GC and ^{1}H NMR analysis.

standard conditions furnished the pyrimidine **1b** in 55% yield (dr >99:1). Also, *N*-methyl 5-bromoindole **7** reacted with Mg and LiCl (25 °C, 1 h) to produce the corresponding Grignard reagent **5c** in >90% yield.[17] Coupling with **4a** under our standard conditions produced the indole **1c** (60% yield, dr 98:2, Scheme 2).

Extension of this coupling to the five-membered iodohydrin **4b** (X = I) led to the expected α-arylated or α-heteroarylated cyclopentanol silyl ethers **8a–j** in 52–80% yield (dr >97:3; Table 3). The mild conditions required for this cross-coupling allowed the presence of sensitive functional groups in the Grignard reagent. Thus, the treatment of the bromobenzonitrile

Scheme 2. Preparation of Heterocyclic Grignard Reagents and Their Diastereoselective Cross-Coupling with 4a



(**9**) with *i*PrMgCl·LiCl (1.1 equiv, THF, −20 °C, 0.5 h)[20] provides the corresponding Grignard reagent **5d** (>90%), which smoothly undergoes a Co-mediated cross-coupling, providing the cyclopentanol derivative **8a** in 67% yield (dr >99:1). Similarly, the arylmagnesium reagent **5e** (>90%) prepared from the iodobenzoate **10** by I/Mg-exchange furnished, after cross-coupling with **4b**, the cyclopentanol derivative **8b** in 52% yield (dr 97:3, Scheme 3).

The use of $CoCl_2$·2LiCl allows further expansion of the reaction scope of this coupling, and the iodohydrins **4a**,**b** can be replaced advantageously by the corresponding bromohydrin (**4c**, X = Br). Using the same reaction conditions, the cross-coupling products **11a–d** were obtained with high diastereoselectivities (dr >97:3, Scheme 4).

Remarkably, this cross-coupling can also be performed with heterocyclic iodohydrins such as **12** and **13**, leading to *trans*-3,4-disubstituted tetrahydrofurans (**14**) and pyrrolidines (**15**) as single diastereomers (71–74%, Scheme 5). The up-scaling of this cross-coupling is readily performed as indicated in Table 3 (entry 7) as well as in the synthesis of **14**, which has been performed on a 4 mmol scale (gram scale).

To demonstrate the synthetic potential of this method, we have prepared the functionalized arylated TBS-protected cyclohexanol,[16] which is a key intermediate for the synthesis of the NK_1 antagonist **2**. Thus, the commercially available ketone **17** was converted in four steps (37% overall yield) into the silyl-protected iodohydrin **18** (Scheme 6). Co-mediated cross-coupling with 4-fluorophenylmagnesium bromide (**5f**)

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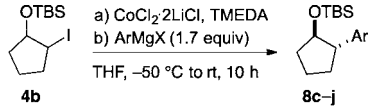
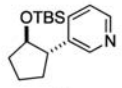
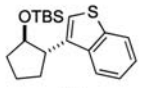
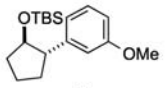
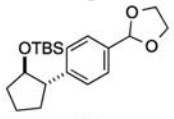
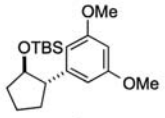
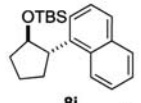
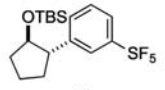
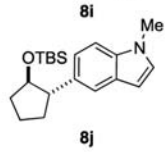
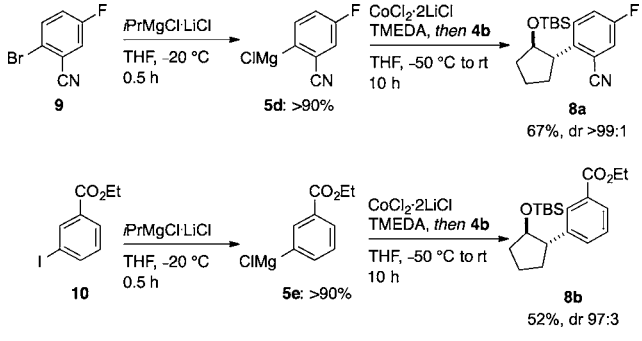
Table 3. Products Obtained by the Diastereoselective Cross-Coupling of 4b with Various Grignard Reagents



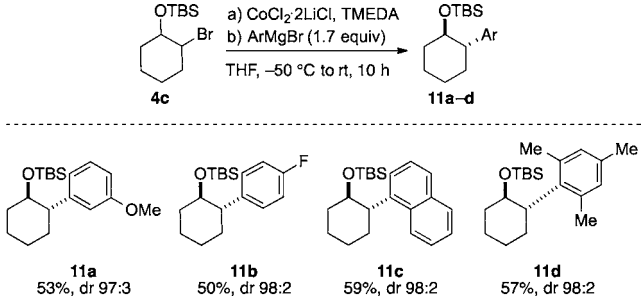
entry	product	yield (%)[a] dr[b]	entry	product	yield (%)[a] dr[b]
1	 8c	73 >99:1	5	 8g	58 98:2
2	 8d	79 >99:1	6	 8h	78 >99:1
3	 8e	74 99:1	7	 8i	80[c] >99:1
4	 8f	61 99:1	8	 8j	65 99:1

[a]Isolated yield. [b]Determined by capillary GC and ^{1}H NMR analysis. [c]Reaction performed on a 4 mmol scale.

Scheme 3. Preparation of Various Grignard Reagents and Their Diastereoselective Cross-Coupling with 4b



Scheme 4. Products of Type 11 Obtained by the Diastereoselective Cross-Coupling of Bromohydrin 4c with Arylmagnesium Reagents

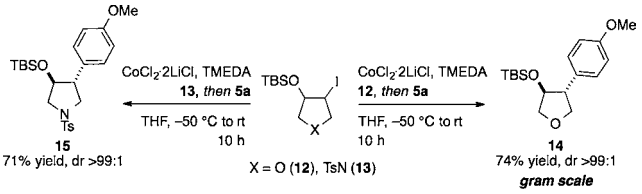


furnished the desired product **16** in 61% yield (dr 85:15). Although this diastereoselectivity is not perfect, it represents an improvement over the previously reported synthesis (dr 66:54).[9]

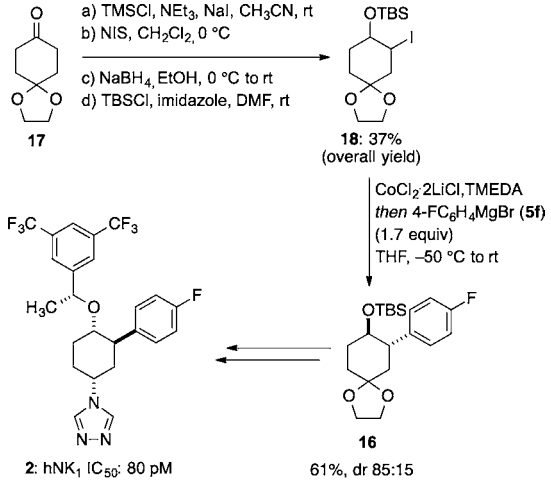
Preliminary mechanistic studies have shown that ArMgX and $CoCl_2$ readily react with each other, leading to the homocoupling products quantitatively. However, under the reaction conditions (slow addition of ArMgX to a mixture of the respective halohydrin, $CoCl_2$·2LiCl, and TMEDA), the desired cross-coupling is much faster. The stereoconvergence of the reaction may be the result of a radical generated at the α-position to oxygen.[4b,5]

In conclusion, we have reported a highly stereoselective cobalt-mediated arylation of TBS-protected cyclic bromo- and iodohydrins, leading to *trans*-α-arylated cyclic alcohols with high diastereoselectivity (up to dr >99:1). In contrast to the corresponding iron-mediated arylation, both electron-withdrawing and electron-donating substituents can be present in the Grignard reagent. Furthermore, heterocyclic iodohydrins are also excellent substrates for this cobalt-mediated arylation. Further extension of this method as well as mechanistic studies are currently underway.

Scheme 5. Diastereoselective Cross-Coupling of the Heterocyclic Halohydrins 12 and 13



Scheme 6. Synthesis of Key Intermediate 16 from Ketone 17



■ ASSOCIATED CONTENT

Supporting Information

Full experimental details; ^{1}H, ^{13}C, and ^{19}F NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: paul.knochel@cup.uni-muenchen.de.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) *Metal-Catalyzed Cross-Coupling Reactions*; Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004. (b) *Organotransition Metal Chemistry*; Hartwig, J. F., Ed.; University Science Books: Sausalito, CA, 2010.

(2) (a) *Handbook on the Toxicology of Metals*; Friberg, L., Nordberg, G. F., Vouk, V. B., Eds.; Elsevier: Amsterdam, 1986. (b) Hughes, M. N. *Compr. Coord. Chem. II* **1987**, *67*, 643. (c) *Nickel and the Skin: Absorption, Immunology, Epidemology, and Metallurgy*; Hostynek, J. J., Maibach, H. I., Eds.; CRC Press: Boca Raton, FL, 2002.

(3) (a) World market prices for Pd: \$834 per pound. (b) World market prices for Co: \$14 per pound.

(4) (a) Yorimitsu, H.; Oshima, K. *Pure Appl. Chem.* **2006**, *78*, 441. (b) Gosmini, C.; Begouin, J.-M.; Moncomble, A. *Chem. Commun.* **2008**, 3221. (c) Cahiez, G.; Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435. (d) Gosmini, C.; Moncomble, A. *Isr. J. Chem.* **2010**, *50*, 568.

(5) For recent cobalt-catalyzed cross-couplings and related reactions, see: (a) Cahiez, G.; Avedissian, H. *Tetrahedron Lett.* **1998**, *39*, 6159. (b) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374. (c) Shinokubo, H.; Oshima, K. *Eur. J. Org. Chem.* **2004**, 2081. (d) Ohmiya, H.; Tsuji, T.; Yorimitsu, H.; Oshima, K. *Chem.—Eur. J.* **2004**, *10*, 5640. (e) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2006**, *8*, 3093. (f) Ohmiya, H.; Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2006**, *62*, 2207. (g) Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 1565. (h) Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2007**, *63*, 8609. (i) Gosmini, C.; Bégouin, J.-M.; Moncomble, A. *Chem. Commun.* **2008**, *28*, 3221. (j) Usanov, D. L.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 8169. (k) Qian, X.; Auffrant, A.; Felouat, A.; Gosmini, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10402. (l) Gao, K.; Yoshikai, N. *Acc. Chem. Res.* **2014**, *47*, 1208. (m) Barré, B.; Gonnard, L.; Campagne, R.; Reymond, S.; Marin, J.; Ciapetti, P.; Brellier, M.; Guérinot, A.; Cossy, J. *Org. Lett.* **2014**, DOI: 10.1021/ol503043r. (n) Cahiez, G.; Chaboche, C.; Duplais, C.; Moyeux, A. *Org. Lett.* **2009**, *11*, 277.

(6) For diastereoselective cobalt-catalyzed cross-coupling reactions, see: (a) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 1886. (b) Nicolas, L.; Angibaud, P.; Stanfield, I.; Bonnet, P.; Meerpoel, L.; Reymond, S.; Cossy, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 11101. (c) Nicolas, L.; Izquierdo, E.; Angibaud, P.; Stansfield, I.; Meerpoel, L.; Reymond, S.; Cossy, J. *J. Org. Chem.* **2013**, *78*, 11807. (d) Despiau, C. F.; Dominey, A. P.; Harrowven, D. C.; Linclau, B. *Eur. J. Org. Chem.* **2014**, 4335.

(7) Steib, A. K.; Thaler, T.; Komeyama, K.; Mayer, P.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 3303.

(8) For examples of α-arylations to oxygen, see: (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108. (b) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360. (c) Ehrentraut, A.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 209. (d) Cossy, J.; de Filippis, A.; Pardo, D. G. *Org. Lett.* **2003**, *5*, 3037. (e) Navarro, O.; Marion, N.; Onishi, Y.; Kelly, R. A., III; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 685. (f) Su, W.; Raders, S.; Verkade, J. G.; Liao, X.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2006**, *45*, 5852. (g) Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 3302. (h) Lundin, P. M.; Esquivias, J.; Fu, G. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 154. (i) Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 1264.

(9) Dirat, O.; Elliott, J. M.; Jelley, R. A.; Jones, A. B.; Reader, M. *Tetrahedron Lett.* **2006**, *47*, 1295.

(10) Cahiez, G.; Habiak, V.; Duplais, C.; Moyeux, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4364.

(11) (a) Alami, M.; Ramiandrasoa, P.; Cahiez, G. *Synlett* **1998**, 325. (b) Cahiez, G.; Gager, O.; Lecomte, F. *Org. Lett.* **2008**, *10*, 5255.

(12) Steib, A. K.; Kuzmina, O. M.; Fernandez, S.; Flubacher, D.; Knochel, P. *J. Am. Chem. Soc.* **2013**, *135*, 15346.

(13) Cahiez, G.; Chaboche, C.; Duplais, C.; Giulliani, A.; Moyeux, A. *Adv. Synth. Catal.* **2008**, *350*, 1484.

(14) Jensen, A. E.; Knochel, P. *J. Org. Chem.* **2002**, *67*, 79.

(15) (a) The use of triisopropylsilyl-protected (TIPS-protected) 2-iodocyclohexanol led to a similar diastereoselectivity (dr 94:6), whereas protection with the bulky *tert*-butyldiphenylsilyl (TBDPS) group resulted in a decreased diastereoselectivity (dr 90:10). (b) The role of *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA) is to coordinate the low-valent cobalt intermediate.

(16) The use of catalytic amounts of $CoCl_2$·2LiCl (0.40 equiv) did not lead to a satisfactory conversion of **1a** (54% yield).

(17) Treatment of a mixture of $CoCl_2$·2LiCl (0.85 equiv), TMEDA (0.3 equiv), and ArMgCl (1.7 equiv) with the protected iodohydrin (1 equiv) in THF at −50 °C did not lead to the formation of the desired product.

(18) Mosrin, M.; Knochel, P. *Org. Lett.* **2008**, *10*, 2497.

(19) Piller, F. M.; Metzger, A.; Schade, M. A.; Haag, B. A.; Gavryushin, A.; Knochel, P. *Chem.—Eur. J.* **2009**, *15*, 7192.

(20) (a) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333. (b) Krasovskiy, A.; Straub, B. F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 159.