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Diastereoselective Cobalt-Mediated Cross-Couplings of Cycloalkyl Iodides with Alkynyl or (Hetero)Aryl Grignard Reagents

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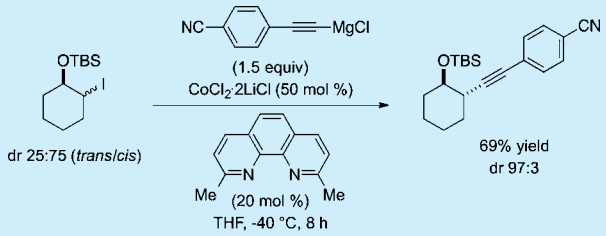
Supporting Information

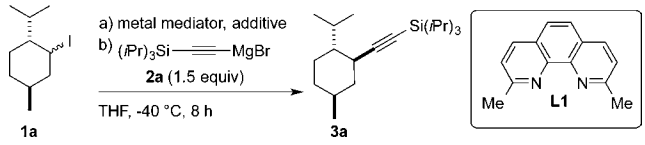
ABSTRACT: A highly diastereoselective cross-coupling of variously substituted cycloalkyl iodides with alkynyl and (hetero)aryl Grignard reagents using cobalt(II) chloride has been successfully developed. With the THF-soluble $CoCl_2$·LiCl and the inexpensive *ortho*-phenanthroline derivative, neocuproine, as a ligand, diastereomeric ratios of up to 99:1 were achieved. A range of functional groups are tolerated in the Grignard reagent (e.g., CF_3, Piv, CN, OPiv, NMe_2, CO_2NEt_2, SF_5, OTBS).



Transition metal catalyzed cross-coupling reactions are indispensable tools for the construction of carbon−carbon bonds in organic synthesis.[1] However, most of these couplings rely on Pd or Ni catalysts, which have the disadvantage of toxicity[2] and/or high costs.[3] Thus, there is a need for cheaper transition metal catalysts for such couplings, and cobalt salts have proven to be a powerful alternative.[4] Despite the diversity of various Co-catalyzed[5] cross-couplings, only a few stereoselective transformations have been described.[6] Recently, we reported a Co-mediated diastereoselective cross-coupling of substituted cyclic iodohydrins with (hetero)aryl Grignard reagents.[7] This method, however, gave unsatisfactory results with alkynylmagnesium reagents. Thus, the development of a novel method for the stereoselective C−C coupling is of great interest. Herein, we report a new broadly applicable stereoconvergent cobalt-mediated cross-coupling of alkynyl or (hetero)aryl magnesium halides and variously substituted cycloalkyl iodides.

In optimization studies, we examined the alkynylation of menthyl iodide **1a** (dr 1:99) with ((triisopropylsilyl)ethynyl)-magnesium bromide (1.5 equiv, **2a**) at −40 °C, in the presence of various transition metal salts (Table 1). The use of $CrCl_2$,[8] $MnCl_2$·2LiCl,[9] or $FeCl_2$·2LiCl[10] proved to be unsatisfactory, and the coupling of **1a** with **2a** furnished the expected product **3a** in only 27% yield at best when using 20 mol % of $FeCl_2$·2LiCl (entries 1−3). A general and more broad screening of reaction conditions using cobalt salts showed that $Co(acac)_3$[11] (acac = acetylacetonate) or cobalt halides[12] gave much better results (entries 4−6). Also, the THF-soluble $CoCl_2$·2LiCl[7] affords the coupling product **3a** in 42% yield with 99:1 dr (entry 7). Switching to more polar cosolvents such as DMPU[13] or NMP[14] leads to the formation of the desired product (**3a**) in up to 48% yield and a diastereoselectivity of up to 91:9 dr (entries 8 and 9). The use of 4-fluorostyrene[10] resulted in a yield of 44% and an excellent diastereoselectivity of 99:1 (entry 10). The addition of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA)[7] led to a deterioration of the diastereoselectivity (90:10 dr, entry 11). Changing the additive to neocuproine (**L1**, 20 mol %)[15] gave the best result, leading to product **3a** in 63% yield and high dr (dr = 93:7, entry 12). Significant improvements were achieved by using substoichiometric amounts (0.50 equiv) of the complex $CoCl_2$·2LiCl, which is highly soluble in THF; this complex leads exclusively to the thermodynamically more stable *trans*-isomer **3a** in 83% isolated yield and 99:1 dr (entry 13).

Table 1. Optimization of the Conditions for the Diastereoconvergent Cross-Coupling of 1a with 3a



entry	metal mediator (equiv)	additive (equiv)	GC yield[a] (%)	dr[a]
1	$CrCl_2$ (0.20)		trace	nd
2	$MnCl_2$·2LiCl (0.20)		0	nd
3	$FeCl_2$·2LiCl (0.20)		19	99:1
4	$Co(acac)_3$ (0.20)		28	83:17
5	$CoBr_2$ (0.20)		22	85:15
6	$CoCl_2$ (0.20)		36	86:14
7	$CoCl_2$·2LiCl (0.20)		42	88:12
8	$CoCl_2$·2LiCl (0.20)	DMPU (0.20)	48	90:10
9	$CoCl_2$·2LiCl (0.20)	NMP (0.20)	41	91:9
10	$CoCl_2$·2LiCl (0.20)	4-fluorostyrene (0.20)	44	99:1
11	$CoCl_2$·2LiCl (0.20)	TMEDA (0.20)	34	90:10
12	$CoCl_2$·2LiCl (0.20)	neocuproine (0.20)	63	93:7
13	$CoCl_2$·2LiCl (0.20)	neocuproine (0.20)	88(83)[b]	99:1

[a]Determined by capillary GC and ^{1}H NMR analysis. Undecane ($C_{11}H_{24}$) was used as internal standard. [b]Isolated yield.

With these optimized reaction conditions in hand, we performed a range of coupling reactions using various alkynylmagnesium halides. Alkynyl Grignard reagents obtained

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Scheme 1. Diastereoselective Cross-Coupling of 1a and 1b with the Alkynyl Grignard Reagent 2b

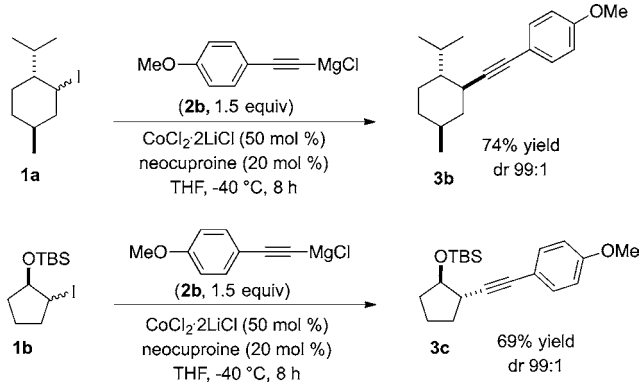
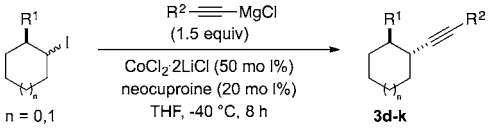
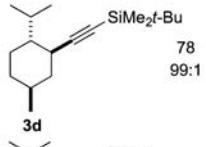
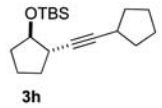
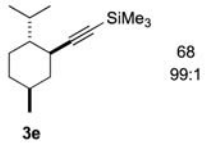
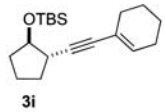
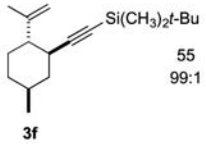
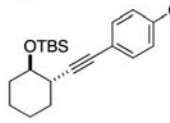
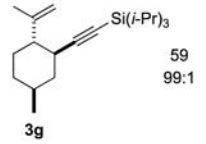
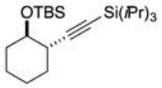


Table 2. Coupling of 1,2-Substituted Cycloalkyl Iodides with Various Alkynyl Grignard Reagents



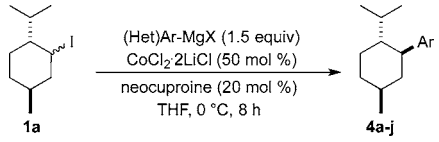
entry	product	yield (%)[a] dr[b]	entry	product	yield (%)[a] dr[b]
1	 3d	78 99:1	5	 3h	68 99:1
2	 3e	68 99:1	6	 3i	68 99:1
3	 3f	55 99:1	7	 3j	69 97:3
4	 3g	59 99:1	8	 3k	77 99:1 [gram scale]

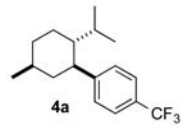
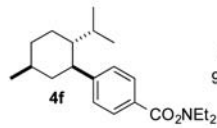
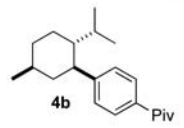
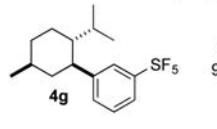
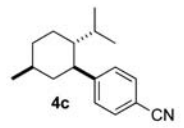
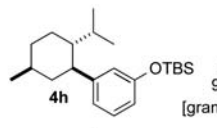
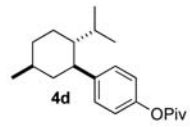
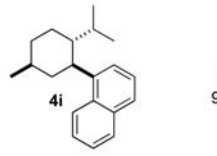
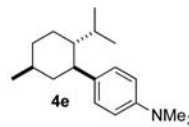
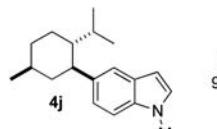
[a]Isolated yield. [b]Determined by capillary GC and ^{1}H NMR analysis.

by magnesiation using TMPMgCl·LiCl (1.1 equiv, THF, 0 °C, 3 h) led to the desired *trans*-cross-coupling products in very high diastereoselectivity. Thus, the coupling of ((4-mthoxyphenyl)-ethynyl)magnesium chloride (**2b**) with **1a** (dr 1:99) or **1b** (dr 99:1) using standard conditions furnished the coupling products **3b,c** in 69−74% yield (dr 99:1, Scheme 1). We have further extended this Co-mediated coupling reaction to various alkynyl Grignard reagents (see Table 2). Thus, alkynylmagnesium reagents bearing silyl (entries 1−4 and 8), aliphatic (entries 5 and 6), and aromatic substituents (entry 7) were successfully coupled, leading to the desired products (**3d−k**) in up to 83% yield and a dr up to 99:1 even on a gram scale (entry 8).

To underline its synthetic utility, we extended this reaction to the cross-coupling of cycloalkyl iodides such as **1a** with heterocyclic and aryl magnesium reagents. Thus, the dropwise addition of various Grignard reagents (1.5 equiv) to a mixture of the cycloalkyl iodide **1a** (1.0 equiv), $CoCl_2$·2LiCl (0.50 equiv, 1

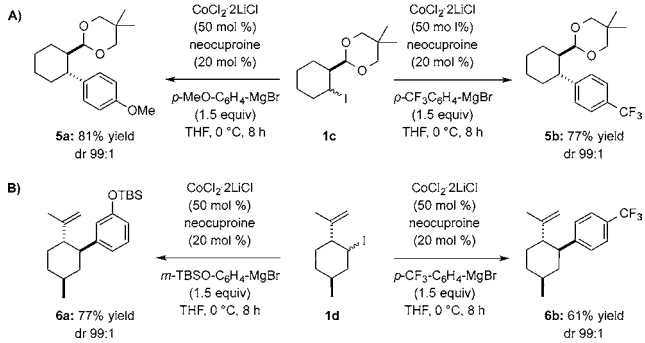
Table 3. Products Obtained by the Diastereoselective Cross-Coupling with Various Substituted Grignard Reagents



entry	product	yield (%)[a] dr[b]	entry	product	yield (%)[a] dr[b]
1	 4a	71 99:1	6	 4f	75 99:1
2	 4b	70 99:1	7	 4g	68 99:1
3	 4c	61 99:1	8	 4h	73 99:1 [gram scale]
4	 4d	75 99:1	9	 4i	62 99:1
5	 4e	62 91:9	10	 4j	75 96:4

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

Scheme 2. Diastereoselective Cross-Coupling of Cyclic 1,2-Substituted Alkyl Iodides with Various Magnesium Halides



Scheme 3. Diastereoselective Cross-Coupling of 1e with *p*-MeOC$_6$H$_4$MgBr

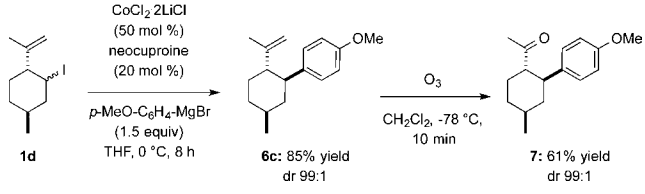


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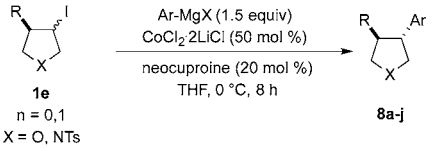
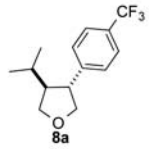
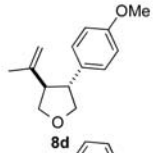
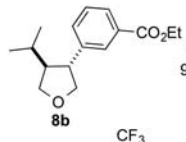
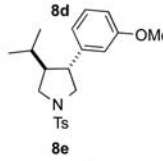
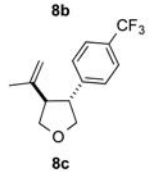
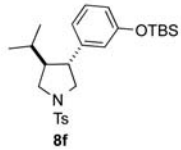
Table 4. Coupling of Various 1,2-Substituted Heterocyclic Alkyl Iodides with Aryl Grignard Reagents



entry	product	yield (%)[a] dr[b]	entry	product	yield (%)[a] dr[b]
1	 8a	71 97:3	4	 8d	57 99:1
2	 8b	64 99:1	5	 8e	66 99:1
3	 8c	54 99:1	6	 8f	88 99:1

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

M in THF), and neocuproine (20 mol %) in THF at 0 °C led to the desired *trans*-coupling products (**4a**−**j**) in 61−75% yield and a dr >91:9 (Table 3). Both, electron-poor or electron-rich arylmagnesium halides were employed successfully, and a range of functional groups such as CF_3, Piv, CN, OPiv, NMe_2, CO_2NEt_2, SF_5, and OTBS were tolerated in the Grignard reagents (entries 1−9). Additionally, a heterocyclic magnesium halide was coupled successfully, leading to the indole derivative **4j** in high diastereoselectivity with 75% isolated yield and dr = 99:1 (entry 10).

Additionally, we have applied this Co-mediated cross-coupling to various substituted cycloalkyl iodides such as **1c** (dr 1:99) or **1d** (dr 1:99). To our delight, the *trans*-coupling products **5a**,**b** (Scheme 2A) and **6a**,**b** (Scheme 2B) were obtained in a dr up to 99:1. Thus, the reaction of (3-((*tert*-butyldimethylsilyl)oxy)-phenyl)magnesium bromide, (4-(trifluoromethyl)phenyl)-magnesium bromide, or (4-methoxyphenyl)magnesium bromide with the cycloalkyl iodides **1c** or **1d**, using $CoCl_2$·2LiCl (50 mol %) and neocuproine (20 mol %), furnished the arylated derivatives **5a**,**b** and **6a**,**b** in up to 81% yield and with a dr of 99:1.

The diastereoselective cross-coupling products of type **6** are synthetically very useful and can easily be converted to the corresponding ketones. Thus, the coupling of **1d** with *p*-$MeOC_6H_4MgBr$ gave the desired product **6c** in 99:1 dr and 85% yield. The alkene moiety in **6c** was transformed via ozonolysis to ketone **7**, without loss of the stereoselectivity and in 61% isolated yield (Scheme 3).

Remarkably, this cross-coupling can also be performed with heterocyclic alkyl iodides of type **1e**, leading to *trans*-3,4-disubstituted tetrahydrofurans (**8a**−**d**, entries 1−4) and pyrrolidines (**8e**,**f**, entries 5 and 6) as single diastereomers (Table 4).

Although the mechanism of this cross-coupling was not studied in detail, experiments have shown that RMgX and $CoCl_2$ readily react with each other, leading to the homocoupling products quantitatively. However, under the reaction conditions (slow addition of RMgX), the desired cross-coupling is much faster than the homocoupling. The stereoconvergence of the reaction may also be the result of a radical reaction pathway, as proposed by Oshima for similar reactions.[5h]

In conclusion, we have reported a highly diastereoselective coupling reaction using the highly soluble cobalt salt $CoCl_2$·2LiCl, leading to *trans*-1,2-substituted products with high diastereoselectivity (up to >99:1 dr). Additionally, this cross-coupling is compatible with various functional groups and hetereocyclic scaffolds. Further extension of this method, as well as mechanistic studies, is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02119.

Full experimental details; ^{1}H, ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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