Cross-Coupling

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Cobalt-Catalyzed Negishi Cross-Coupling Reactions of (Hetero)Arylzinc Reagents with Primary and Secondary Alkyl Bromides and Iodides**

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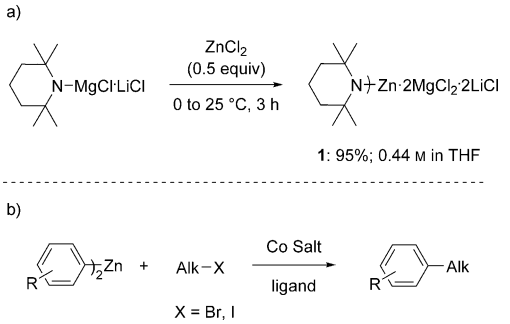
Abstract: *We report a cobalt-catalyzed cross-coupling of di(hetero)arylzinc reagents with primary and secondary alkyl iodides or bromides using THF-soluble $CoCl_2$·2 LiCl and TMEDA as a ligand, which leads to the corresponding alkylated products in up to 88% yield. A range of functional groups (e.g. COOR, CN, CF_3, F) are tolerated in these substitution reactions. Remarkably, we do not observe rearrangement of secondary alkyl iodides to unbranched products. Additionally, the use of cyclic TBS-protected iodohydrins leads to trans-2-arylcyclohexanol derivatives in excellent diastereoselectivities (up to d.r. = 99:1).*

Transition-metal-catalyzed cross-coupling reactions are valuable tools for C–C bond-forming reactions and have found many applications for the synthesis of biologically active molecules.[1] Pd- or Ni-catalyzed cross-coupling reactions dominate this field, but have several drawbacks, for example, the toxicity[2] and high price of the metal, as well as the requirement of sophisticated ligands to achieve a broad reaction scope.[3] Recently, cross-coupling reactions with cobalt catalysts were found to be a valuable alternative.[4] However, despite the spectacular advances of Co-catalyzed coupling reactions between $C(sp^2)$ and $C(sp^3)$ centers by using magnesium reagents,[5] no Co-catalyzed Negishi-type[6] coupling reactions using arylzinc reagents have been described.[7]

Recently, we have reported a range of synthetic methods for preparing polyfunctional unsaturated zinc reagents.[8] In particular, the directed metalation[9] of polyfunctional heterocycles and aromatic substrates has a broad reaction scope, and sterically hindered bases,[10] such as TMPZnCl·LiCl[11] and TMP_2Zn·2 $MgCl_2$·2 LiCl[12] (**1**; TMP = 2,2,6,6-tetramethylpiperidyl) have given a straightforward entry to a range of unsaturated diorganozinc compounds.

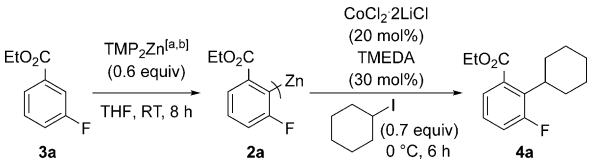
Herein, we report a Co-catalyzed Negishi-type cross-coupling reaction of primary and secondary alkyl iodides and bromides[13] with diarylzinc reagents prepared by a directed C–H zincation using TMP_2Zn·2 $MgCl_2$·2 LiCl (**1**; Scheme 1).[14]



Scheme 1. a) Preparation of TMP_2Zn·2 $MgCl_2$·2 LiCl (**1**). b) Cobalt-catalyzed cross-coupling reactions.

In preliminary experiments, we have examined the cross-coupling of the diarylzinc reagent (**2a**), which was generated by a directed metalation of ethyl 3-fluorobenzoate (**3a**)[15] using TMP_2Zn·2 $MgCl_2$·2 LiCl[10] (**1**, 0.6 equiv), with *c*Hex-I in the presence of various metal catalysts (Table 1). The addition of the zinc species to *c*Hex-I in the presence of $[Co(acac)_2]$ or $FeCl_2$[16] resulted in the exclusive formation of the protonated

Table 1: Optimization of the conditions for the Co-catalyzed cross-coupling.



Entry	Catalyst (mol%)	Ligand (mol%)	Yield[c] [%]
1	$FeCl_2$ (20)	4-fluorostyrene (50)	0
2	$FeCl_2$ (20)	TMEDA (30)	13
3	$[Co(acac)_2]$ (20)	4-fluorostyrene (50)	0
4	$[Co(acac)_2]$ (20)	TMEDA (30)	18
5	$CoCl_2$ (20)	4-fluorostyrene (50)	42
6	$CoCl_2$ (20)	TMEDA (30)	84
7	$CoCl_2$·2 LiCl (20)	TMEDA (30)	94 (87)[d]
8	$CoCl_2$·2 LiCl (20)	4-fluorostyrene (50)	38
9	$CoCl_2$·2 LiCl (20)	**L1** (30)	40
10	$CoCl_2$·2 LiCl (10)	TMEDA (30)	33

[a] $MgCl_2$ and LiCl are omitted for the sake of clarity. [b] The use of TMPZnCl·LiCl did not lead to a satisfactory conversion into the desired product. [c] Determined by GC with undecane ($C_{11}H_{24}$) used as an internal standard. [d] Yield of isolated product. acac = acetylacetonate. **L1** = *trans-N,N,N′,N′*-tetramethylcyclohexane-1,2-diamine.

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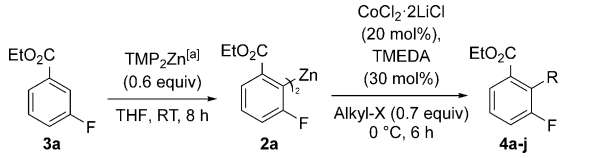
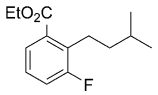
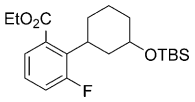
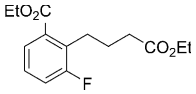
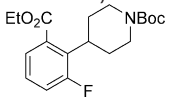
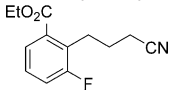
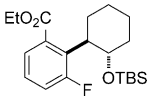
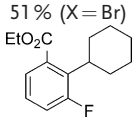
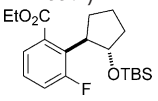
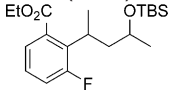
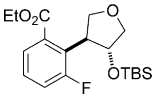
zinc species when using 4-fluorostyrene (50 mol%).[17] Moderate yields of **4a** (13–18%) were obtained using *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA, 30 mol%) as a ligand (entries 1–4). Switching to cobalt(II) chloride (20 mol%) and 4-fluorostyrene (50 mol%) or TMEDA (30 mol%) in THF at 0°C furnished the desired cross-coupling product **4a** in 42% and 84% yield, respectively (entries 5 and 6). Significant improvements were achieved by using the THF-soluble $CoCl_2$·2LiCl (20 mol%)[18] and TMEDA (30 mol%),[19] which afforded the coupling product **4a** in 87% yield of the isolated product (entry 7). Further variation of the ligand[5b] or lowering the amount of the cobalt catalyst from 20 mol% to 10 mol% led only to a decrease in the yield (entries 7–10).

With these optimized reaction conditions in hand, we have performed a range of alkylations using primary alkyl iodides, which led to the polyfunctional alkylated benzoates (**4b–d**) in 58–77% yield (Table 2, entries 1–3). Remarkably, the *ortho*,*ortho*′ substituents present in the diarylzinc species (**2a**) did not disturb the cross-coupling and most of the reactions were complete within 6 h at 0°C. Primary alkyl bromides have also been used successfully coupled, but with somewhat lower yields (entries 2–4). Functional groups such as an ester or a nitrile are well-tolerated in such cross-coupling reactions. Interestingly, secondary alkyl iodides reacted smoothly to provide the alkylation products **4a** and **4e–j** in 55–79% yield (entries 4–10). In no case did we observe rearrangement products (branched to unbranched; see entry 5 and Table 3).[20] When an oxygen substituent was present in position 2 to the carbon–iodine bond, excellent diastereoselectivities were observed (up to d.r. = 99:1, see entries 8–10) and the products were isolated in 55–69% yield. Additionally, this cross-coupling can also be performed with heterocyclic alkyl iodides, thereby leading to the expected products **4g** and **4j** in 79% and 55% yield, respectively (see entries 7 and 10).

Table 2: Scope of various primary and secondary alkyl iodides or bromides.



Entry	Product/yield [%]	Entry	Product/yield [%]
1	 **4b**: 63% (X = I)	6	 **4f**: 79% (X = I, d.r. = 50:50)[d]
2	 **4c**: 58% (X = I) 38% (X = Br)	7	 **4g**: 79% (X = I)
3	 **4d**: 71% (X = I) 51% (X = Br)	8	 **4h**: 68% (X = I, d.r. = 99:1)[e]
4	 **4a**: 61% (X = Br) 2% (X = Cl)[b]	9	 **4i**: 69% (X = I, d.r. = 99:1)[f]
5	 **4e**: 70% (X = I, d.r. = 50:50)[c]	10	 **4j**: 55% (X = I, d.r. = 99:1)[g]

[a] $MgCl_2$ and LiCl are omitted for the sake of clarity. [b] The yield was determined by GC. [c] The starting material was 99:1 *syn*/*anti*. [d] The starting material was 75:25 *cis*/*trans*. [e] The starting material was 75:25 *cis*/*trans*. [f] The starting material was 99:1 *trans*/*cis*. [g] The starting material was 99:1 *trans*/*cis*. TBS = *tert*-butyldimethylsilyl.

The reaction scope of this Co-catalyzed alkylation is quite broad and a range of diarylzinc reagents prepared by a directed deprotonation using TMP_2Zn·2$MgCl_2$·2LiCl (**1**, 0.6 equiv) provided the isolated alkylated products **5a–o** in 51–88% yield (Table 3). Thus, this sequential one-pot metalation/cross-coupling procedure could be extended to various 1,2- and 1,3-disubstituted aromatic compounds. The zincation of 2-fluorobenzonitrile or 3-fluorobenzonitrile using **1** (0.6 equiv) proceeds within 12 h at 25°C, and the subsequent coupling reactions with secondary alkyl iodides provides the desired products **5a–e** in 52–86% yield (entries 1–4). Remarkably, diheteroarylzinc reagents generated by directed zincation using **1** undergo the alkylation reactions in good yields to afford the expected products **5a–o** (51–88% yield, entries 6–14). Thus, zincated benzofurans or benzothiophenes reacted with secondary alkyl iodides such as *c*Hex-I, *i*Pr-I, or *n*Bu-I to furnish the corresponding cross-coupling products **5f–i** in 61–76% yield (entries 6–9). The metalation of benzofuran with TMP_2Zn·2$MgCl_2$·2LiCl (**1**, 0.6 equiv) was complete within in 12 h at 25°C, thereby providing the corresponding zinc reagent. This species undergoes the Co-catalyzed cross-coupling with *n*Bu-I to afford the substituted benzofuran **5h** in 63% yield (entry 8). This alkylated benzofuran (**5h**) is a key intermediate for the synthesis of amiodarone, an active antiarrhythmic agent.[21,22] Similarly, 3,6-dimethoxypyridazine was zincated using **1** (0.6 equiv, 4 h, RT), and the cross-coupling with 2-iodopropane or *c*Hex-I afforded the desired polyfunctional hetereocycles **5j**, **k** in 69 and 61% yield, respectively (entries 10 and 11). Coumarin is also an excellent substrate, with its zincation complete within 1 h at 25°C. After alkylation with various primary and secondary alkyl iodides, the substituted coumarins **5l–n** were obtained in up to 88% yield (entries 12–14) Similarly, the regioselective zincation of thiochromone (−40°C, 1 h)[23] at the α-position to sulfur followed by a Co-catalyzed alkylation with 2-iodobutane led to the desired product **5o** in 51% yield (entry 15).

In summary, we have reported a new Co-catalyzed cross-coupling of polyfunctional diaryl- and diheteroarylzinc reagents with primary and secondary alkyl iodides (or bromides) using the highly soluble cobalt salt $CoCl_2$·2LiCl.

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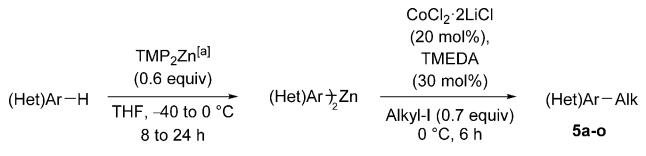
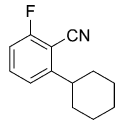
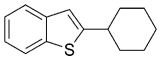
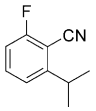
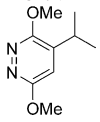
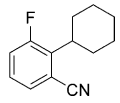
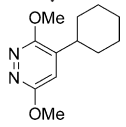
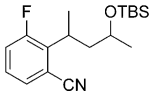
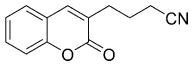
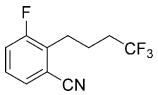
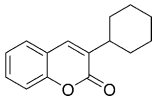
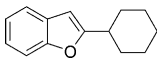
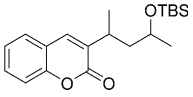
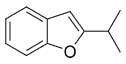
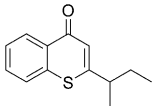
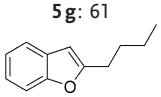
Table 3: Scope of various diaryl- and diheteroarylzinc reagents.



Entry	Product/yield [%]	Entry	Product/yield [%]
1	 **5a**: 84	9	 **5i**: 72
2	 **5b**: 81	10	 **5j**: 69
3	 **5c**: 84	11	 **5k**: 61
4	 **5d**: 63[b]	12	 **5l**: 76
5	 **5e**: 52	13	 **5m**: 66
6	 **5f**: 71	14	 **5n**: 88[b]
7	 **5g**: 61	15	 **5o**: 51
8	 **5h**: 63		

[a] $MgCl_2$ and LiCl are omitted for the sake of clarity. [b] The starting material was 99:1 *syn*/*anti*, the product 50:50 *syn*/*anti*.

Remarkably, no rearrangement of the secondary alkyl group is observed. This cross-coupling is also compatible with various functional groups and hetereocyclic scaffolds. Further applications to the synthesis of natural products are underway.

Keywords: cobalt · cross-coupling · heterocycles · metalation · zinc

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Angew. Chem. **2015**, *127*, 4560–4563

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