



Homogeneous Catalysis

Cobalt-Catalyzed Cross-Coupling of Functionalized Alkylzinc Reagents with (Hetero)Aryl Halides

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Abstract: A combination of 10% CoCl₂ and 20% 2,2'bipyridine ligands enables cross-coupling of functionalized primary and secondary alkylzinc reagents with various (hetero)aryl halides. Couplings with 1,3- and 1,4-substituted cycloalkylzinc reagents proceeded diastereoselectively leading to functionalized heterocycles with high diastereoselectivities of up to 98:2. Furthermore, alkynyl bromides react with primary and secondary alkylzinc reagents providing the alkylated alkynes.

The transition-metal catalyzed construction of new C-C bonds is of utmost importance in modern organic chemistry, and finds wide application in academic and industrial processes.^[1] Especially, Negishi cross-couplings are among the most versatile methods for the formation of carbon bonds to create highly functionalized scaffolds.^[2] Organozinc reagents represent an attractive class of organometallic reagents for cross-couplings, combining both, the low toxicity of zinc salts as well as a high functional group tolerance. Albeit, various examples of palladium-^[2,3] or nickel-catalyzed^[2,3e,4] C(sp²)-C(sp³) cross-couplings using alkylzinc reagents have been reported, the search for cheaper and more abundant alternative catalytic systems is highly desirable. Cobalt-salts have been found to display several beneficial characteristics.^[5] In comparison to palladium, cobalt is a cost-effective metal and for many transformations no sophisticated ligands are required for efficient catalysis.^[5] Additionally, several reported protocols showed that cobalt salts are especially well suited catalysts for various types of reactions utilizing organozinc reagents as nucleophilic coupling partners,^[5] including acylations,^[6] cross-coupling reactions,^[7] or aminations.^[8]

Using this beneficial combination, we herein report a cobalt-catalyzed cross-coupling of functionalized primary

and secondary alkylzinc reagents with a variety of aryl, heteroaryl and alkynyl halides.

In a preliminary experiment, 6-chloronicotinonitrile (1a) was treated with (2-(1,3-dioxan-2-yl)ethyl)zinc chloride (2a) under various conditions (Table 1). In the absence of a cata-

Table 1: Optimization of the reaction conditions for the cross-coupling of **1 a** with alkylzinc reagent **2 a**.



Entry	Catalyst	Ligand	Yield of 3 a [%] ^[a]
1	-	-	0
2	MnCl ₂	-	0
3	CuCl ₂	-	0
4	$FeCl_2$	-	0
5	CrCl ₂	-	0
6	NiCl ₂	-	51
7	CoCl ₂	-	52
8	CoCl ₂	bipy ^[b]	66
9	CoCl ₂	dtbbpy ^[c]	63
10	CoCl ₂	neocuproine	65
11	CoCl ₂	TMEDA	39
12 ^[d]	CoCl ₂	bipy ^[b]	80 (75) ^[e]
13 ^[d]	CoCl ₂ ^[f]	bipy ^[b]	82

[a] Reactions were performed on a 0.25 mmol scale. Yields were determined by GC-analysis. Tetradecane ($C_{14}H_{30}$) was used as internal standard. [b] 2,2'-Bipyridine. [c] 4,4'-Di-*tert*-butyl-2,2'-dipyridyl. [d] 20 mol% of bipy was used. [e] Isolated yield of the reaction performed on a 1.00 mmol scale. [f] CoCl₂ (99.99% purity) was used.

lyst, the desired coupling product **3a** could not be detected (entry 1). Various metal halides such as MnCl₂, CuCl₂, FeCl₂ or CrCl₂ were tested. However, no catalytic activity was observed for this cross-coupling (entries 2–5). As expected, NiCl₂ was able to catalyze the reaction leading to **3a** in 51 % yield (entry 6). However, CoCl₂ also proved to be a suitable catalyst for this transformation affording the desired alkylated heterocycle **3a** in 52 % yield (entry 7). Various ligands were tested to further improve the reaction outcome (entries 8–12). Thus, using the unsubstituted 2,2'-bipyridine led to the best coupling yield of 66 % (entry 8). Increasing the amount of ligand furnished **3a** in 75 % isolated yield (entry 12). Variation of the reaction solvent, the amount of the zinc reagent or the catalyst loading did not further improve the yield.^[9] At this point we verified that no other

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metal contaminants are responsible for this catalytic reaction. Using CoCl_2 (99.99 % purity) in combination with a new stir bar^[10] and reaction vessel afforded the pyridine derivative **3a** in 82 % yield (entry 13). With these results in hand, the scope of this cross-coupling reaction was examined.

N-heterocyclic halides of type **1** were coupled with various functionalized alkylzinc reagents of type **2** (Scheme 1). Thus, the reaction of **1a** with (3-phenylpropyl)zinc chloride afforded **3b** in 73% yield. Also, the corresponding bromopyridine was used leading to coupling products **3c** and **3d** in 62–75% yield. Several alkylzinc reagents bearing various



Scheme 1. Compounds of type **3** obtained by Co-catalyzed reaction of N-heterocyclic halides of type **1** with primary alkylzinc reagents of type **2**. Reactions were performed on a 0.5 mmol scale. Yields were determined from the purified and analytical pure product. [a] 20% CoCl₂, 40% dtbbpy and 1.9 equiv of the corresponding alkylzinc reagent were used.

functional groups were excellent substrates for this crosscoupling. Zinc organometallics containing nitrile groups, masked amines, and acetates were successfully coupled furnishing the alkylated pyridines 3e-3g in 66–87 % yield.

The reactions of zinc species derived from natural products such as (1R)-(-)-nopol and (S)-citronellol with ethyl 6-chloronicotinate afforded **3h** and **3i** in 76–83 % yield. Also, using 2-halonicotinic esters in combination with zinc reagents bearing a heterocyclic or an alkyne moiety coupled smoothly leading to **3j** and **3k** in 78–83 % yield. Furthermore, other N-heterocyclic halides, such as quinoline, isoquinoline, quinazoline, and pyrimidine derivatives were successfully cross-coupled with various functionalized alkylzinc reagents furnishing products **3l–3s** in 58–95 % yield. However, the reaction with less activated heterocyclic halides led to poor coupling results.^[11]

Next, this cobalt catalyzed cross-coupling was extended to various electron-deficient aryl halides as electrophilic coupling partners (Scheme 2). Thus, (2-(1,3-dioxan-2-yl)ethyl)-zinc chloride (**2a**) was coupled with 4-bromo-2-fluorobenzo-



Scheme 2. Compounds of type **3** obtained by the Co-catalyzed reaction of aryl halides of type **1** with alkylzinc reagents of type **2**. Reactions were performed on a 0.5 mmol scale. Yields were determined from the purified and analytical pure product. [a] 20% $CoCl_2$, 40% dtbbpy and 1.9 equiv of the corresponding alkylzinc reagent were used. [b] Dtbbpy was used instead of bipy. The reaction was performed at rt.

nitrile and ethyl 4-iodobenzoate furnishing 3t,u in 66–82% yield. Benzophenone was successfully alkylated in *ortho*- and *para*-position, respectively, starting from the corresponding halide, leading to 3v and 3w in 70–85% yield. Cross-coupling of a zinc reagent containing an ester moiety with a functionalized chlorobenzophenone led to 3x in 73% yield. Also, cyclopropylzinc chloride was used in this procedure, affording the benzophenones 3y and 3z in 70–71% yield.

Encouraged by the results with the secondary cyclopropylzinc reagent, we examined the cross-coupling of various substituted six-membered cycloalkylzinc reagents. In the past, several diastereoselective $C(sp^3)$ - $C(sp^2)$ Negishitype cross-couplings using palladium^[12] and nickel salts^[13]

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have been reported. Also, a cobalt-catalyzed version applying bis-arylzinc reagents is known.^[7e] However, this methodology only allows the coupling of 1,2-substituted cycloalkyl iodides with (hetero)aryl zinc reagents in a diastereoselective manner. To overcome this limitation, we approached the problem by using substituted cycloalkylzinc species with heteroaryl halides as coupling partners. Previous studies have shown that the carbon-zinc bond is prone for an easy epimerization in the presence of metal salts.^[12a,b] Thus, a highly diastereoselective cross-coupling is only enabled by a fast transmetalation of the thermodynamically more stable alkylzinc species to the transition-metal catalyst.^[12a]

To evaluate the scope of a diastereoselective crosscoupling using substituted cyclohexylzinc reagents, 2-methylcyclohexylzinc iodide was coupled with 6-bromonicotinonitrile. A short screening revealed that a catalytic system of 10% CoCl₂ and 20% 4,4'-di-*tert*-butyl-2,2'-dipyridyl in acetonitrile led to the best yield and diastereomeric ratio.^[9] Hence, the coupling of various 1,3-, and 1,4-functionalized cycloalkylzinc reagents with N-heterocyclic bromides was examined (Scheme 3).

The reaction of 6-bromonicotinonitrile with 3-methylcyclohexylzinc iodide led to the thermodynamically more stable cis-1,3-disubstituted cyclohexane **3aa** in 80% yield and d.r. = 91:9. However, using the corresponding zinc reagent bearing the bulkier *iso*-propyl residue led to **3ab** in 63% yield and an improved diastereomeric ratio of 96:4. Additionally, this zinc reagent was coupled with 2-bromopyrimidine furnishing **3ac** (52% yield, d.r. = 94:6^[14]). Also, 1,4-substituted cyclohexyl-zinc reagents could be used in this protocol. Thus, the cross-coupling of zinc reagents bearing an ester or a pyrrole substituent with a trifluoromethylated bromopyridine led to the corresponding *trans*-1,4-bifunctionalized cyclohexanes **3ad** and **3ae** in 51–54% yield (d.r. = 80:20–98:2^[15]). Bromopyrimidine derivatives were coupled with functionalized cyclohexyl reagents affording **3af–3ah** in 64–73% yield and diastereomeric ratios of up to 98:2.

Remarkably, 2-bromopyrimidine could be coupled with complex alkylzinc reagents prepared from steroid and sesquiterpene derivatives (Scheme 4). The reaction of cholesterylzinc chloride **2b** furnished **3ai** in 78% yield and a diastereomeric ratio of 98:2. Also, the corresponding coupling using zinc reagent **2c** derived from a reduced nootkaton derivative proceeded in a highly diastereoselective fashion leading to **3aj** in 52% yield (d.r. = 98:2).



Scheme 3. Diastereoselective cobalt-catalyzed cross-coupling of heteroaromatic bromides of type 1 with 1,3- and 1,4-substituted secondary alkylzinc reagents of type 2 leading to products of type 3. Reactions were performed on a 0.5 mmol scale. Yields were determined from the purified and analytical pure product. The diastereomeric ratio (d.r.) was determined by GC analysis. The major diastereomer is shown.



Scheme 4. Diastereoselective cobalt-catalyzed cross-coupling of 2-bromopyridine with zinc organometallics **2b** and **2c** derived from cholesterol and nootkatone derivatives. Reactions were performed on a 0.5 mmol scale. Yields were determined from the purified and analytical pure product. The diastereomeric ratio (d.r.) was determined by GC analysis. The major diastereomer is shown.

Finally, this cobalt-catalyzed cross-coupling was further extended to alkynyl bromides (Scheme 5). (Bromoethynyl)benzene (**4a**) reacted smoothly with (2-(1,3-dioxan-2-yl)ethyl)zinc chloride (**2a**) affording the alkylated alkyne **5a** in 55% yield. Interestingly, the coupling of the TIPS protected alkyne **4b** with the 1,4 phenyl substituted cyclohexylzinc reagent **2d** furnished the 1,4-*trans*-alkynylated cyclohexane derivative **5b** in 54% yield and d.r. = 99:1.

To gain an insight into the reaction mechanism, radicaltrapping experiments using (2,2,6,6-tetramethylpiperidin-1yl)oxyl (TEMPO) were performed. Previous studies showed



Scheme 5. Cobalt-catalyzed cross-coupling of alkynyl bromides with primary and secondary alkylzinc reagents. Reactions were performed on a 0.5 mmol scale. Yields were determined from the purified and analytical pure product. The diastereomeric ratio (d.r.) was determined by GC analysis. The major diastereomer is shown.

that TEMPO is able to significantly inhibit cobalt-catalyzed reactions, which might indicate an involvement of radical intermediates within the course of these reactions.^[6e,16] Thus, to a standard coupling setup of 6-chloronicotinonitrile (**1a**) with (2-(1,3-dioxan-2-yl)ethyl)zinc chloride (**2a**), 2.0 equiv of TEMPO were added.^[9] However, the coupling product **3a** was afforded in similar yield, compared to the standard conditions without the radical trapping agent. This indicates that this new cobalt-catalyzed cross-coupling might not proceed via radical intermediates.

In conclusion, we have reported a cobalt-catalyzed crosscoupling of various substituted primary and secondary alkylzinc reagents with aryl and heteroaryl halides. Couplings using 1,3- and 1,4-functionalized cyclohexylzinc reagents proceeded with high diastereoselectivities of up to 98:2. Furthermore, this procedure allowed the coupling of primary and secondary alkylzinc reagents with alkynyl bromides. Further mechanistic investigations are currently underway in our laboratories.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: catalysis · cobalt catalysis · cross-coupling · diastereoselectivity · alkylzinc reagents

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