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Direct Aminoalkylation of Arenes and Hetarenes via Ni-Catalyzed Negishi Cross-Coupling Reactions

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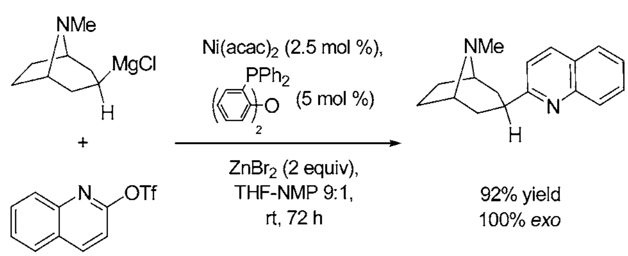
ABSTRACT



A direct room-temperature Ni-catalyzed cross-coupling of aminoalkylzinc halides, readily available from the corresponding aminoalkyl chlorides via Grignard reagents, with aryl and hetaryl electrophiles, allows a convenient one-step preparation of aminoalkyl (het)arenes, bearing a basic tertiary nitrogen in the side chain, including piperidine and tropane derivatives. Such aminoalkylarene scaffolds are widely present in various biologically active molecules.

The aminoalkyl moiety is one of the most frequently occurring functionalities in biologically active molecules.[1] Basic trialkylamine groups are one of the most important pharmacophores.[2] Of great interest would be a method allowing a simple and direct introduction of an aminoalkyl moiety into a molecule.[3] For aryl and hetaryl compounds this task can be accomplished by using cross-coupling chemistry. While many reports dealing with cross-coupling of alkylmetal derivatives bearing an amide or sulfonamide nitrogen have been published,[4] no coupling reaction of an aminoalkyl organometallic species (except boron) possessing a *basic* nitrogen is known so far. Very recently, Molander described a direct coupling of aminoalkyl groups to arenes and hetarenes by a Pd-catalyzed cross-coupling reaction of potassium aminoalkyltrifluoroborates. He demonstrated the high potential of this method for the synthesis of biologically active molecules.[5] Those reagents, however, often require a multistep preparation, and the reaction is so far limited to primary alkylamines. Herein, we report a novel aminoalkylation protocol, based on a Ni-catalyzed cross-coupling reaction between aminoalkylzinc compounds

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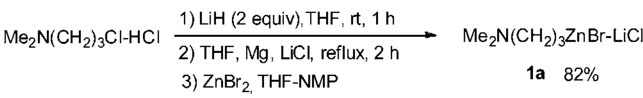
and various aryl and heteroaryl bromides, chlorides, and triflates. This method allows a direct introduction of both primary and secondary aminoalkyl groups possessing a basic nitrogen.

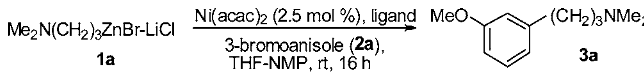
Treatment of commercial 3-dimethylaminopropyl chloride hydrochloride with an excess of LiH in THF followed by filtration gave a dry solution of the corresponding base, suitable for the preparation of a Grignard reagent. The insertion of magnesium metal in the presence of LiCl[6] (2 equiv) and DIBAL-H[7] (3 mol %) in THF afforded the corresponding organomagnesium compound in 82% yield, as was determined by the iodometric titration.[8] A transmetalation using $ZnBr_2$ (2.0 M $ZnBr_2$ in THF−NMP)[9] gave 3-dimethylaminopropylzinc halide **1a** (Scheme 1).

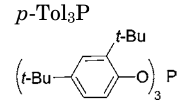
Scheme 1. Preparation of 3-Dimethylaminopropylzinc Halide



Initial attempts to employ Pd-catalysts, previously used to perform sp^3-sp^2 Negishi cross-couplings,[10−13] were not very promising. Only traces of the cross-coupling product were detected using $Pd(dba)_2$ (3 mol %) and PPh_3, o-Tol_3P,[10] t-Bu_3P,[11] or tri-(2-furyl)phosphine[12] in the model reaction of the zinc reagent **1a** with *m*-bromoanisole (**2a**), while Pd(dppf)Cl_2[13] gave **3a** in 37% yield at 25 °C after 16 h. Bearing in mind the high activity of Ni-catalysts in the Negishi cross-coupling,[9,14] we have screened several common phosphine ligands in the presence of $Ni(acac)_2$ (2.5 mol %). Among the ligands screened, *bis*-(2-diphenylphosphinophenyl)ether (DPE-Phos) gave the best results, affording the cross-coupling product **3a** in almost quantitative yield (Table 1). Further optimization revealed that the optimal ratio of the ligand to nickel was 2:1, and the optimal amount of $ZnBr_2$ was 2 mol per mol of the Grignard reagent. Having established the optimized conditions for the cross-coupling reaction, we investigated the behavior of other primary and secondary aminoalkylzinc reagents. Following the same protocol, aminoalkylzinc reagents **1a**−**1d** were prepared starting from commercially available hydrochlorides (for **1b**−**1d**), and from tropanol (for **1e**). Noteworthy, the solutions of the corresponding aminoalkylmagnesium chlorides in THF are relatively stable and can be stored at 0 °C (titration after 6 months revealed loss of the active magnesium species less than 20%).

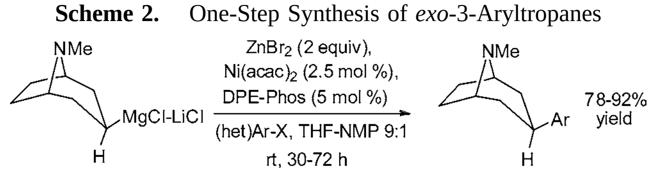
Table 1. Ligand Screening in the Cross-Coupling Reaction of 3-Dimethylaminopropylzinc Halide with 3-Bromoanisole



entry	ligand	ratio Ni to ligand	yield of **2** (%)
1	dppp	1:1	33
2	IPr−HCl	1:1	17
3	n-$BuPAd_2$	1:2	50
4	P(Oi-Pr)$_3$	1:3	73
5	Ph_3P	1:3	79
6	p-Tol_3P	1:4	87
7		1:3	88
8	t-Bu_3P	1:2	12
9	DPE-Phos	1:1	93
10	**DPE-Phos**	**1:2**	**97**

Cross-coupling of the prepared aminoalkylzinc derivatives under the optimized conditions proceeded smoothly with a broad range of aryl and heteroaryl bromides, chlorides, and triflates. In most cases, the reaction was completed within 1−3 h at 25 °C, giving the products of type **3** in 78−98% yield (Table 2). The isolation of the aminoalkyl arenes is very facile and usually consists of an acid−base extraction with ether, affording pure compounds by NMR and GC−MS analysis. To our delight, the reaction with secondary aminoalkyl zinc species proceeded equally well and furnished only slightly lower yields (Table 2, entries 12−17). Noteworthy, triflates are also suitable substrates for this coupling reaction (entries 14 and 17), making possible the transformation of a phenol function into an aminoalkyl group. The reaction conditions tolerate various functionalities such as an ester, a nitrile, and a keto group. Interestingly, the cross-coupling of 8-methyl-8-azabicyclo[3.2.1]octylzinc species gives exclusively *exo*-3-aryltropanes, as was confirmed by NOESY experiments[15] (Scheme 2, Table 2, entries 15−17).

Scheme 2. One-Step Synthesis of *exo*-3-Aryltropanes



This selectivity originates from the stereospecific formation of the corresponding Grignard reagent, as the cross-coupling reaction proceeds with retention of configuration.[16]

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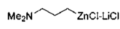
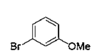
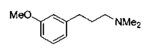
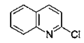
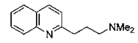
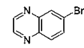
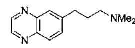
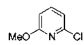
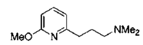
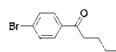
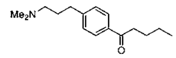
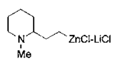
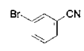
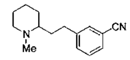
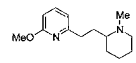
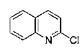
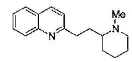
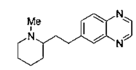
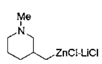
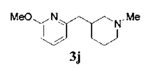
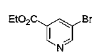
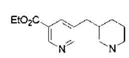
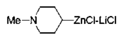
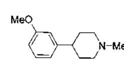
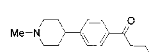
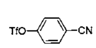
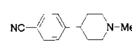
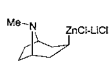
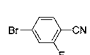
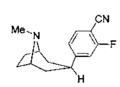
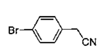
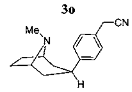
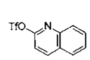
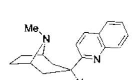
(15) Mu, L.; Drandarov, K.; Bisson, W. H.; Schibig, A.; Wirz, C.; Schubiger, P. A.; Westera, G. *Eur. J. Med. Chem.* **2006**, *41*, 640.
(16) For a recent discussion on the configurational stability of Grignard reagents during their preparation and reactions, see: Beckmann, J.; Dakternieks, D.; Draeger, M.; Duthie, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6509. Secondary alkylzinc compounds are known to undergo cross-coupling with retention of configuration: Boudier, A.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 687.

Table 2. Ni-Catalyzed Cross-coupling Reaction of Aminoalkylzinc Reagents (**1**) with Aryl and Heteroaryl Electrophiles (**2**)

entry	aminoalkylzinc compound of type **1**	(het)aryl halide or triflate of type **2**	product of type **3**	reaction time, h	yield of **3**, %[a]
1	 **1a**[b]	 **2a**	 **3a**	3	97
2	**1a**	 **2b**	 **3b**	3	88
3	**1a**	 **2c**	 **3c**	1	98
4	**1a**	 **2d**	 **3d**	1	85
5	**1a**	 **2e**	 **3e**	1	90
6	 **1b**[b]	 **2f**	 **3f**	0.5	96
7	**1b**	**2d**	 **3g**	0.5	94
8	**1b**	 **2b**	 **3h**	1	95
9	**1b**	**2c**	 **3i**	3	91[c]
10	 **1c**[b]	**2d**	 **3j**	20	90
11	**1c**	 **2g**	 **3k**	20	78[c]
12	 **1d**[b]	**2a**	 **3l**	6	92
13	**1d**	**2e**	 **3m**	2	84
14	**1d**	 **2h**	 **3n**	8	95
15	 **1e**	 **2i**	 **3o**	30	78[c,d]
16	**1e**[b]	 **2j**	 **3p**	72	92[c,d]
17	**1e**	 **2k**	 **3q**	72	80[c,d]

[a] Reagents and conditions: **2a**−**k** (1.0 mmol), **1a**−**e** (1.2 equiv), $ZnBr_2$ (2.0 M in THF, 2 equiv), $Ni(acac)_2$ (2.5 mol %), DPE-Phos (5 mol %), THF−NMP (9:1), 25 °C, followed by the acid−base extractive workup. The yields are given for the isolated compounds of >97% purity by NMR and GC. [b] For the preparation of aminoalkylzinc halides, see Supporting Information. [c] Yield after a chromatographical purification. [d] Only *exo*-product isolated.

In summary, we have developed a general method for the one-pot installation of aminoalkyl groups, including cyclic derivatives like piperidine and tropane, into an arene or hetarene, using a Ni-catalyzed Negishi cross-coupling reaction of aminoalkylzinc reagents, which are easily available from the corresponding aminoalkyl chlorides. This approach allows a fast and convenient construction of “drug-like” molecules, possessing an aromatic system and a basic tertiary nitrogen, using a simple one-pot protocol. Further development of this method is currently underway in our laboratories.

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Supporting Information Available: Experimental procedures and characterization of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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