Nickel-catalyzed cross-coupling reactions of benzylic zinc reagents with aromatic bromides, chlorides and tosylates†

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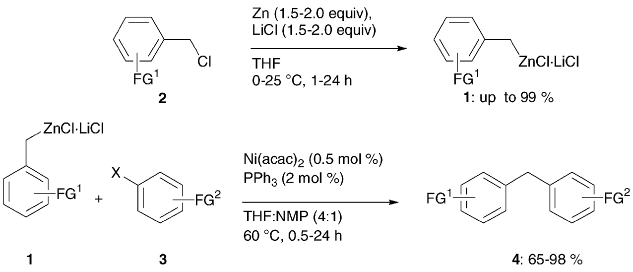
Benzylic zinc reagents prepared by direct insertion of zinc to benzylic chlorides in the presence of LiCl undergo smooth cross-coupling reactions with aromatic chlorides, bromides and tosylates using Ni(acac)$_2$ and PPh$_3$ as a catalyst system.

Diarylmethanes are an important class of compounds with pharmacological activity.[1] So far, the most popular route to diarylmethanes is the addition of organometallic reagents to benzaldehydes and subsequent reduction.[2] Recently, we have developed a general method for the preparation of highly functionalized benzylic zinc reagents (**1**) derived from benzylic chlorides (**2**) using zinc dust and LiCl (Scheme 1). Remarkably, this method tolerates the presence of important functional groups such as an ester, a ketone and a cyanide.[3] Herein, we wish to describe a new practical Ni-catalyzed cross-coupling reaction[4] of polyfunctionalized benzylic zinc of type **1** with aryl halides (**3**) leading to functionalized diarylmethanes of type **4** in good to excellent yields (Scheme 1 and Table 1). Although, many ligands have been tested, we have found as a highly efficient, cheap and convenient catalytic system PPh$_3$ (2 mol%) combined with Ni(acac)$_2$ (0.5 mol%)[5] in a mixture of THF and NMP. Under these conditions, a broad range of aromatic and heteroaromatic halides (bromides and chlorides) and tosylates undergo a smooth cross-coupling leading to polyfunctional diarylmethanes of type **4**.

Thus, the reaction of 3-cyanobenzylzinc chloride (**1a**, 1.2 equiv.) with 4-bromoacetophenone (**3a**) at 60 °C (0.5 h) using Ni(acac)$_2$ (0.5 mol%) and PPh$_3$ (2 mol%) in THF : NMP (4 : 1 mixture) afforded the desired diarylmethane **4a** in 75% yield (entry 1). Also, aromatic chlorides such as **3b** and 2-chloropyrimidine (**3c**), react readily within 30 min to the corresponding diarylmethanes (**4b**: 89%, **4c**: 69%, entries 2 and 3).

The reaction of the secondary benzylic zinc chloride **1b** with 4-bromo-benzoic acid ethyl ester (**3d**) affords within 12 h at 60 °C the 1,1-bisarylethane (**4d**, 95%, entry 4).

The cross-coupling of an electron rich benzylic zinc chloride such as 3,4,5-trimethoxybenzylzinc chloride (**1c**) with the protected uracil **3e** affords the uracile derivative **4e**, a precursor of Trimethoprim,[6] in 86% yield (entry 5). The isomeric uracil derivative **4f** was also prepared by the cross-coupling of **1c** with 4-chloro-2,6-dimethoxypyrimidine (**3f**) in 98% yield (entry 6).



Scheme 1

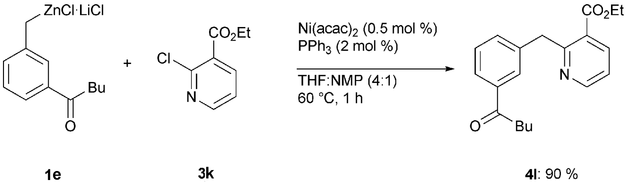
Moreover, an electron poor benzylic zinc chloride bearing a carbethoxy function (**1d**) in *meta* position undergoes a smooth reaction with the protected uracil **3e** to afford **4g** in 84% yield (entry 7). Its cross-coupling with 4-chlorobenzonitrile (**3g**) leads to the diarylmethane **4h** (60 °C, 30 min) in 91% yield (entry 8). Various aromatic and heteroaromatic tosylates, which are easily available from the corresponding phenoles,[7] are efficient cross-coupling partners. Thus, the aryl tosylates **3h–j** react with 3-carbethoxybenzylzinc chloride **1d** to the corresponding diarylmethanes **4i–k** in yields up to 85% (entries 9–11).

Remarkably, benzylzinc chlorides bearing keto groups in *meta* position react as well. Thus, the reaction of 3-pentanoylbenzylzinc chloride (**1e**) with the chloropyridine **3k** leads to the nicotinic acid derivative **4l** in 90% yield (Scheme 2, entry 12).

Also, the quinolyl tosylate **3l** and the pyridyl tosylate **3m** undergo cross-coupling reactions with **1e**, leading to the desired products **4m** and **4n** (92% and 84%, entry 13 and 14).

Even the sensitive acetyl-substituted benzylic zinc reagent **1f**, added over 30 min *via* a syringe pump, reacts with the pyridyl chloride (**3k**) without significant enolization to the nicotinic acid derivative **4o** in 68% yield (entry 15).

In summary, we have reported a highly efficient Ni-catalyzed cross-coupling for preparing polyfunctionalized diarylmethanes. Remarkably, a broad range of polyfunctionalized benzylic zinc reagents can be used, including keto substituted



Scheme 2

Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstr. 5-13, Haus F, 81377 München, Germany.
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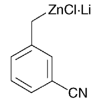
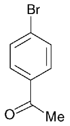
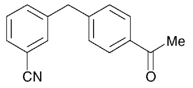
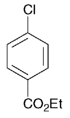
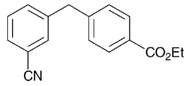
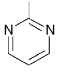
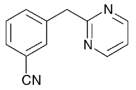
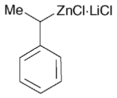
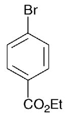
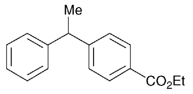
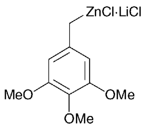
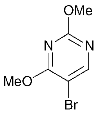
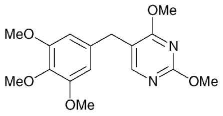
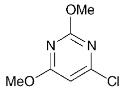
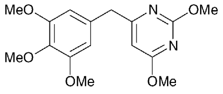
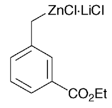
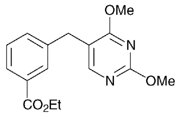
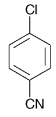
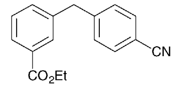
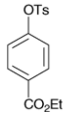
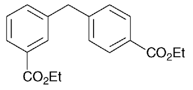
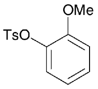
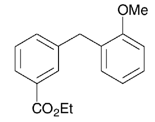
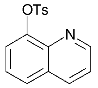
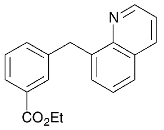
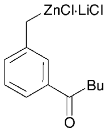
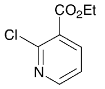
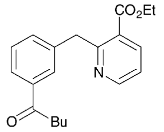
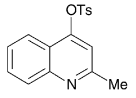
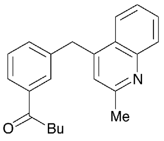
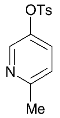
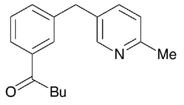
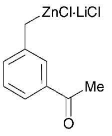
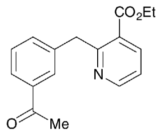
Table 1 Ni(acac)$_2$ and PPh$_3$ catalyzed cross-coupling reactions between functionalized benzylic zinc reagents and aryl chlorides, bromides and tosylates

Entry	Zinc reagent[a]	Electrophile	Diarylmethane reaction time/h	Yield (%)[b]
1	 **1a**	 **3a**	 **4a** (0.5)	75
2	**1a**	 **3b**	 **4b** (0.5)	89
3	**1a**	 **3c**	 **4c** (0.5)	69
4	 **1b**	 **3d**	 **4d** (12)	95
5	 **1c**	 **3e**	 **4e** (2)	86
6	**1c**	 **3f**	 **4f** (2)	98
7	 **1d**	**3e**	 **4g** (1.5)	84
8	**1d**	 **3g**	 **4h** (0.5)	91
9	**1d**	 **3h**	 **4i** (2)	65
10	**1d**	 **3i**	 **4j** (24)	85
11	**1d**	 **3j**	 **4k** (3)	69
12	 **1e**	 **3k**	 **4l** (1)	90
13	**1e**	 **3l**	 **4m** (16)	92
14	**1e**	 **3m**	 **4n** (16)	84
15	 **1f**	**3k**	 **4o** (2)	68[c]

[a] For the cross-coupling reaction, 1.2 equiv. of the zinc reagent is used. [b] Isolated yield of analytically pure product. [c] The zinc reagent was added over 30 min *via* syringe pump.

organometallics. Further extension of this method is under way in our laboratories.

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