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Simple and efficient nickel-catalyzed cross-coupling reaction of alkynylalanes with benzylic and aryl bromides†

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Highly efficient and simple coupling reactions of benzylic and aryl bromides with aluminium acetylide catalyzed by $NiCl_2(PPh_3)_2$ are reported. The coupling reactions proceed at room temperature employing 4 mol% catalyst, affording coupling products in excellent yields of up to 95% in short reaction times. The system worked efficiently with aryl and heterocyclic bromides as well.

In the last decade much effort has been paid to the construction of organic frameworks bearing alkynyl moieties since these are found in a wide range of natural and unnatural organic materials.[1] The carbon–carbon bond-forming reaction with terminal alkynes and a variety of carbon electrophiles has attracted considerable attention.[2] Among these, Sonogashira reaction has become one of the most widely used methods for the incorporation of alkynyl functionality into organic compounds.[3] It enables the coupling of an organic halide or pseudohalide with a terminal alkyne, normally using a Pd catalyst along with a Cu cocatalyst at high temperatures. A variety of organometallic reagents containing metals, such as Zn,[4] Mg,[5] B,[6] Sn,[7] Cu,[8] have been used in palladium or nickel cross-coupling reactions and the synthetic scope of this kind of reaction has been continuously expanded by the use of new organic electrophiles, catalysts, or organometallic reagents.

In recent years, numerous metal catalyzed cross coupling reactions of aryl[9] and vinyl halides[10] with terminal alkynes have been studied. There are few reports of benzyl halides which undergo oxidative addition with palladium and the resultant benzylpalladium derivatives involve in cross-coupling reactions with aryl and alkenylmetals containing metals, such as Zn,[11] B,[12] and Sn.[13] However, it is somewhat surprising that coupling between benzylic halide and alkynyl metals had remained virtually unknown until Sarandeses and coworkers[14] reported the reaction of indium acetylide reagents with benzyl bromide in excellent yield catalyzed by Pd(dppf). Later, Qian and Nigishi[15] reported palladium catalyzed cross coupling of akynylzincs with benzylic electrophiles and Okamoto *et al.*[16] reported cobalt-catalyzed benzyl–alkynyl coupling using alkynyl Grignard reagent. Although, almost all such kind of reactions are catalyzed by either expensive Pd metal or at higher temperature and the scope of substituted benzylic halides is still limited. Therefore, the efficient and practical synthetic methodology of the alkyne coupling is of considerable importance.

Despite having the high reactivity and greater Lewis acidity of the aluminium center, organoalanes are less studied in cross coupling reactions. Recently, several groups[17] including us[18] have successfully used them in catalytic reactions. Furthermore, the organoalanes have been proven to be highly efficient coupling reagents with aryl bromide and chlorides.[19] In order to continue our efforts in developing the organoalane compounds for cross coupling reactions, herein, we report the efficient, simple and inexpensive Ni catalyzed cross coupling reactions of organic electrophiles with aluminium acetylide.

We first surveyed several Ni sources as a catalyst (scheme in Table 1). The reactions were optimized at room temperature on benzyl bromide (**1a**) and aluminium phenyl acetylide, and the results are summarized in Table 1. In the absence of Ni catalyst, the reaction did not take place at all over 1 h (entry 1). While the reactions employing 4 mol% of Ni salts like $NiCl_2$, $Ni(acac)_2$, $Ni(OAc)_2$, and $Ni(ClO_4)_2$ also gave the disappointing results (entries 2–5). However, the reaction in the presence of 4 mol% $NiCl_2(PPh_3)_2$ in toluene yielded 84% of coupling product (entry 6). It is known that coordinating solvents like THF, DME, or ether can stabilize and help to control the reactivity and selectivity of the aluminium reagents.[20] Solvents were then screened. The reactions in stronger coordinating solvents such as THF or DME were slower, affording **2a** in lower yields (entries 7 and 10). In this study, the weaker coordinating ether was turned to be the best solvent for the reaction, which gave more than 99% of the desired product with less than 1% of dibenzyl as by-product in 1 h (entry 11) as well as in 30 min (entry 12). When the amount of $NiCl_2(PPh_3)_2$ was reduced to 2 mol%, the reaction afforded **2a** in 82% yield (entry 13).

We explored the generality of this reaction and screened a number of substituted benzyl bromides and terminal alkynes (Table 2). The catalytic system works excellently to benzylic bromides bearing either electron-donating or electron-withdrawing substituents. For example, substituted benzyl bromides containing electron-donating substituents on the aromatic ring (entries 2–7) with 4 mol% of catalyst loading were effective enough to produce the coupling product in excellent yields of ≧90% in

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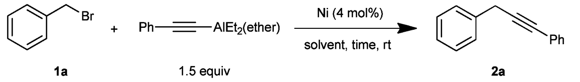
† Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR data, spectra and HRMS of coupling products. See DOI: 10.1039/c1cc14206b

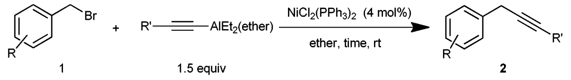
Table 1 Optimizations of coupling reactions of benzyl bromide with aluminium acetylide catalyzed by Ni salts[a]

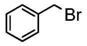
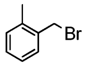
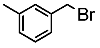
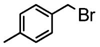
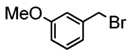
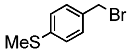
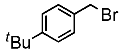
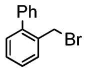
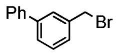
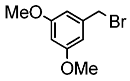
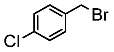
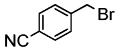
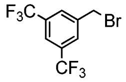
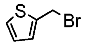
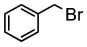
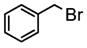
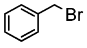
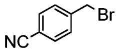
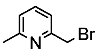


Entry	Ni	Solvent	Time/h	Conv.[b] (%)
1	—	Toluene	1	NR
2	$NiCl_2$	Toluene	1	NR
3	$Ni(acac)_2$	Toluene	1	06
4	$Ni(OAc)_2$	Toluene	1	04
5	$Ni(ClO_4)_2$	Toluene	1	NR
6	$NiCl_2(PPh_3)_2$	Toluene	1	84
7	$NiCl_2(PPh_3)_2$	THF	1	54
8	$NiCl_2(PPh_3)_2$	Hexane	1	07
9	$NiCl_2(PPh_3)_2$	CH_2Cl_2	1	22
10	$NiCl_2(PPh_3)_2$	DME	1	65
11	$NiCl_2(PPh_3)_2$	Ether	1	99
12	$NiCl_2(PPh_3)_2$	Ether	0.5	99
13[c]	$NiCl_2(PPh_3)_2$	Ether	0.5	82

[a] Benzyl bromide/Al reagent = 1.0/1.5 mmol. [b] Conversions are based on ^1H NMR spectra. [c] $NiCl_2(PPh_3)_2$ = 2 mol%.

Table 2 Couplings of substituted benzyl halides and aluminium acetylide catalyzed by $NiCl_2(PPh_3)_2$[a]



Entry	Substrate	1	R′	Time/h	2	Yield[b] (%)
1		**(1a)**	Ph	0.5	**2a**	93
2		**(1b)**	Ph	1	**2b**	90
3		**(1c)**	Ph	1	**2c**	91
4		**(1d)**	Ph	1	**2d**	92
5		**(1e)**	Ph	1	**2e**	93
6		**(1f)**	Ph	1	**2f**	93
7		**(1g)**	Ph	1	**2g**	92
8		**(1h)**	Ph	1	**2h**	88
9		**(1i)**	Ph	1	**2i**	91
10		**(1j)**	Ph	1	**2j**	94
11		**(1k)**	Ph	1	**2k**	95
12		**(1l)**	Ph	0.5	**2l**	92
13		**(1m)**	Ph	0.5	**2m**	93
14		**(1n)**	Ph	0.5	**2n**	88
15		**(1o)**	*n*-C_4H_9	0.5	**2o**	91
16		**(1p)**	$ClCH_2(CH_2)_2CH_2$	0.5	**2p**	90
17		**(1q)**	$PhCH_2$	1	**2q**	90
18		**(1r)**	$SiMe_3$	0.5	**2r**	91
19		**(1s)**	$SiMe_3$	8	**2s**	91

[a] Benzyl bromide/Al reagent = 1.0/1.5 mmol; diethylether, 3 mL. [b] Isolated yields of products.

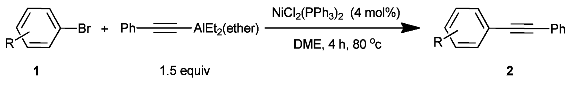
1 h. As well as 2- and 3-phenylbenzyl bromides and 3,5-dimethoxybenzyl bromide also afforded the coupling product in 88%, 91% and 94% yields (entries 8–10) respectively. A same catalyst loading of 4 mol% was good enough for the substituted benzyl bromides containing electron-withdrawing substituents on the aromatic ring such as 4-chlorobenzyl bromide, 4-cyanobenzyl bromide or 3,5-bis(trifluoromethyl)benzyl bromide to afford the coupling product in 95%, 94% and 94% yields (entries 11–13), respectively. Interestingly, 2-bromomethyl thiophene as one of the reaction partners under the same reaction conditions afforded 85% yield in 30 min (entry 14).

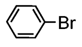
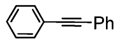
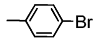
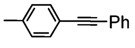
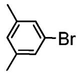
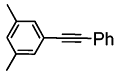
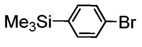
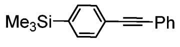
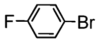
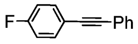
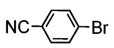
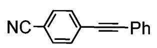
To extend the reaction scope, coupling reactions of benzyl halides with functionalized aluminium acetylide reagents were then studied. Catalyst loading of 4 mol% were employed for the coupling reactions of benzyl bromide with the aluminium reagent prepared by using 1-hexyne, 6-chloro-1-hexyne, and 3-phenyl-1-propyne affording products in 91%, 90% and 90% yields (entries 15–17) at room temperature in 30 min, respectively. We then carried out the coupling reaction of strong electron-withdrawing substituents on benzyl bromide such as 4-cyano benzyl bromide with the aluminium reagent prepared using TMS acetylene, which afforded the product in 94% yield as well (entry 18). To our delight, the optimal conditions were found to be compatible with the coupling of 2-(bromomethyl)-6-methylpyridine and the aluminium reagent prepared using TMS acetylene afforded the coupling product in 91% yield at room temperature in 8 h (entry 19).

To broaden the reaction scope, we subsequently examined coupling reactions of aryl bromides (Table 3). We initially chose bromobenzene and aluminium phenyl acetylide as coupling partners, and found that the reaction took place effectively at 80 °C in the presence of 4 mol% of $NiCl_2(PPh_3)_2$ in 4 h which afforded the coupling product in 93% yield (entry 1). Moreover, the coupling reaction worked efficiently with substituted aryl bromides either having the electron-donating or electron-withdrawing substituents on it (entries 2–6).

In conclusion, we have developed extremely efficient, simple and inexpensive Ni-catalyzed cross coupling reactions of

Table 3 Couplings of substituted aryl halides and aluminium acetylide catalyzed by $NiCl_2(PPh_3)_2$[a]



Entry	Substrate	1	Product	2	Yield[b] (%)
1		(**1t**)		**2t**	90
2		(**1u**)		**2u**	85
3		(**1v**)		**2v**	93
4		(**1w**)		**2w**	91
5		(**1x**)		**2x**	92
6		(**1y**)		**2y**	85

[a] Aryl bromide/Al reagent = 1.0/1.5 mmol; solvent, DME (3 mL). [b] Isolated yields of products.

benzylic or aryl bromides involving alkynylalane compounds. The reactions proceeded effectively at room temperature in a short reaction time of ≦1 h in the case of substituted benzylic bromides. The low catalyst loadings of 4 mol% are good enough to achieve coupling products in excellent yields for substrates containing strong electron-withdrawing or electron-donating substituents on the aromatic ring. Furthermore, the coupling reaction worked efficiently with heterocyclic compound as well.

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