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Nickel-catalyzed cross-coupling of primary alkyl halides with phenylethynyl- and trimethylsilyethynyllithium reagents

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ABSTRACT

A highly efficient alkyl–alkynyl coupling system is described which is promoted by a well-defined and moisture-stable pincer complex [NiCl{C_6H_3-2,6-($OPPh_2$)$_2$}] (**1**). Non-activated alkyl halides could be efficiently coupled with phenylethynyl- and trimethylsilylethynyllithium reagents at room temperature. Compared to the alkylation of primary alkyl halides with alkynyllithium reagents in literatures, this method requires milder conditions (room temperature) and proceeds quickly. This research will make these readily available alkynyllithium reagents much more useful for organic synthesis.

1. Introduction

Over the past few decades, the alkynylation of $C_{sp}{}^2$-halides, conducted either with alkynylmetal reagents or directly with terminal alkynes, has emerged as an extremely powerful method for the synthesis of alkynes [1–3]. However, for a long time, the corresponding application of non-activated alkyl halides has been a challenge due to a more difficult oxidative addition step and the tendency of alkylmetal intermediates to undergo side reactions like β-H elimination. Recently, much effort has been made to conduct metal-catalyzed cross-coupling reactions with alkyl halides as electrophilic couplings partners [4–8] and notable advances have been described for the Kumada [9–17] and Negishi [18–20] type coupling reactions. Early investigations showed the application of Ni, Co, Fe and Pd complexes in the activation of alkyl halides, which follow a radical pathway (single-electron transfer mechanism) [21], and in some cases the radical may undergo a ring closure in the presence of remote double bond [12,20]. To date, most of the investigations have focused on the use of alkyl and aryl metal nucleophiles. In contrast, reports of coupling reactions with alkynyl nucleophiles are rare. Oshima reported that Co(acac)$_3$ (acac: acetylacetonate) promoted cross-coupling of alkyl halides with 2-trimethylsilylethynylmagnesium bromide [12]. Luh described a Pd-catalyzed cross-coupling reaction of alkyl bromides and iodides with substituted alkyllithium and suggested this coupling reaction may be a reductive elimination-controlled process because of the better performance of triphenylphosphine than that of trialkylphosphine [11]. For the Sonogashira coupling reaction of such substrates, in addition to only two prior examples using Pd-NHC catalysts [22,23], Hu recently [24] demonstrated a Ni system with a pincer amidobis(amine) ligand [24–28]. Nitrogen based tridentate ligands are believed to stabilize alkylmetal intermediates [21,24–28]. Very recently, Cahiez released a new general procedure for coupling aliphatic and aromatic Grignard reagents with alkynyl halides under copper catalysis [29].

In our investigation of the strong bond activation using first row platinum group metals (Fe, Co, Ni) with phosphite PCP-pincer ligands [30], we reasoned that the PCP-Ni complex might be able to promote the coupling of alkyl halides with nucleophiles. We herein report our initial studies on the coupling reactions between un-activated alkyl halides and alkynyllithium reagents at room temperature. The (pre) catalyst is a well-defined PCP-Ni^{II}-Cl compound [NiCl{C_6H_3-2,6-($OPPh_2$)$_2$}] (**1**) [31]. Alkynyllithiums are easily prepared and at least as reactive as the corresponding alkynylzinc reagents. However, cross-coupling reactions using these nucleophiles were generally unsatisfactory and few examples have been reported [1,11].

2. Experimental methods

2.1. General remarks

All reactions were carried out under N_2 atmosphere and all solvents were freshly distilled before use. Alkyl halides were

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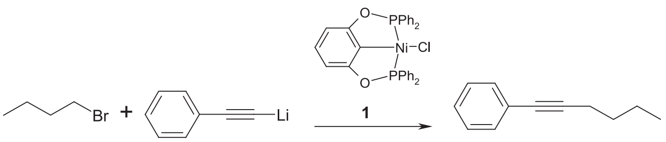
Table 1
Catalytic coupling of 1-bromobutane with phenylethynyllithium.[a]



Entry	Solvent	Cat (mol%)	t (h)	T (°C)	PhCCLi (equiv)	Yields (%)[b]
1	THF	2.0	1.5	r.t.	1.3	5
2	THF	2.0	12	r.t.	1.3	7
3	THF	2.0	1.5	60	1.3	60
4	Toluene	2.0	1.5	r.t.	1.3	3
5	TMEDA	2.0	1.5	r.t.	1.3	8
6	DMF	2.0	1.5	r.t.	1.3	97
7	THF-NMP (2:1)	2.0	1.5	r.t.	1.3	90
8	NMP	2.0	1.5	r.t.	1.3	96
9	NMP	0.5	1.5	r.t.	1.3	99
10	NMP	0.5	0.75	r.t.	1.3	90
11	NMP	0.1	1.5	r.t.	1.3	94
12	NMP	0.5	12	r.t.	1.3	72
13	NMP	0.5	1.5	r.t.	1.0	88
14	NMP	0.5	12	r.t.	1.0	78
15	NMP	0.5	1.5	r.t.	2.0	90
16	NMP	0.5	12	r.t.	2.0	50
17	NMP	0	1.5	r.t.	1.3	50

[a] Typical reaction conditions: 1-bromobutane (1 mmol), Ni catalyst and internal standard (n-dodecane) were mixed in the solvent (4 ml), phenylethynyllithium in THF (1 ml) was added dropwise within 1 min according to the conditions specified in Table 1.

[b] GC yield relative to 1-bromobutane against internal standard.

purchased from commercial sources or prepared from the corresponding alcohol with HBr. PCP-Ni-Cl compound [$\mathrm{NiCl\{C_6H_3\text{-}2,6\text{-}(OPPh_2)_2\}}$] (1) was prepared according to literature procedure [31]. NMR spectra were recorded on a Bruker 300 AV spectrometer. GC–MS was performed on Thermo Trace GC Ultra-DSQ.

2.2. Representative procedure for the coupling reactions of alkyl halides

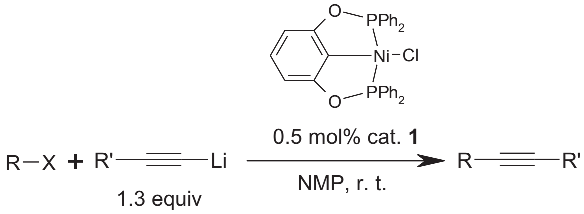
Under N_2 atmosphere at room temperature, to a NMP (30 ml) solution of PCP-Ni-Cl compound 1 (0.5 mol%) and alkyl halides (10 mmol) was added dropwise a THF solution (10 ml) of phenylethynyl- or trimethylsilyethynyllithium reagent prepared from the corresponding alkyne (13 mmol) and n-BuLi (13 mmol, 2.5 M in hexane solution). After reaction the mixture was quenched with H_2O, extracted with Et_2O, and again washed with water to remove NMP, finally dried with $MgSO_4$. After filtration and evaporation, the residue was chromatographed on silica gel (hexane or petroleum ether:ethyl acetate = 40:1).

3. Results and discussion

Initial tests were carried out for the coupling of 1-bromobutane with phenylethynyllithium. Screening results are listed in Table 1. We were delighted to find the cross-coupling occurred in good to excellent yields in polar amide solvents NMP (1-methyl-2-pyrrolidinone) and DMF (dimethylformamide) (Table 1, entries 6–8). Further examination revealed the effect of NMP to provide good yields, similar to earlier reports [18,19,32–34]. The choice of solvent had a significant impact on the yield (Table 1, entry 17). The usage of the PCP-Ni^{II}-Cl catalyst (0.5 mol%) made the increment of the yield from 50% to 99% (Table 1, from entry 17 to entry 9). This control experiment proves that nickel-catalyzed coupling is the dominent reaction pathway. Without the participation of the nickel catalyst the possible reaction would be a carbometalation-elimination sequence [35,36]. Other combinations of solvents and additives, such as toluene, THF, TMEDA (*N,N,N′,N′*-tetramethylethylenediamine) and KI, led to lower coupling yields (Table 1, entries 1–5, and see supporting information). Only 0.1 mol - 0.5 mol% catalyst loading and a slight excess of phenylethynyllithium (1.3 equiv) were required to afford excellent yields (Table 1, entries 9–11). Further addition of phenylethynyllithium up to 2 equiv or prolonged the reaction times (12 h) gave lower yields (Table 1, entries 12 and 15). As the addition of organometallics (RM) to alkynes constitutes a known method for the preparation of alkenylmetal reagents [37,38], it appears likely that some alkynyllithium adds to the alkyne coupling product in a competitive pathway.

To evaluate the scope of this cross-coupling system, phenylethynyllithium and trimethylsilylethynyllithium reagents were reacted with alkyl halides under the optimized conditions with slight modification of the reaction times. A variety of substrates were coupled in good yields at room temperature (Table 2). Even non-activated 1-chlorobutane gave 70% yield (Table 2, entry 1). For secondary alkyl halides, the increasing steric hindrance makes

Table 2
Catalytic cross-coupling of alkyl halides with alkynyllithium reagents.



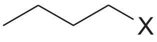
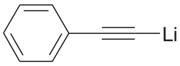
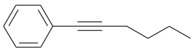
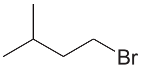
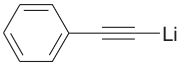
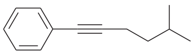
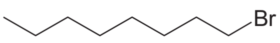
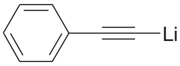
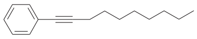
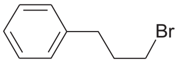
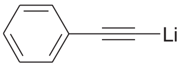
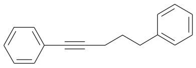
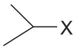
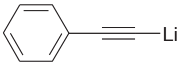
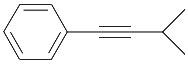
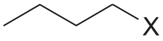
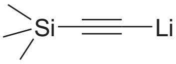
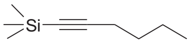
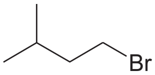
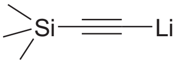
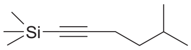
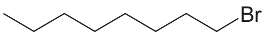
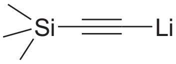
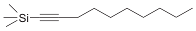
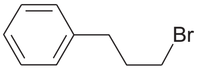
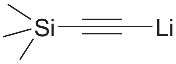
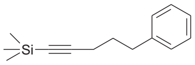
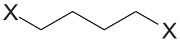
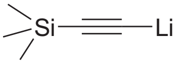
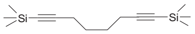
Entry	R–X	R'≡Li	R'≡R	t (h)	Yield (%)[a]
1				0.75 1.5 1.5	99 (X = I)[b] 90 (X = Br) 70 (X = Cl)[b]
2				1.5	91

Table 2 (*continued*)

Entry	R—X	R'—≡—Li	R'—≡—R	t (h)	Yield (%)[a]
3				2.0	74
4				1.5	85
5				1.5	30 (X = Br) trace (X = Cl)
6				0.75	70 (X = I) 61 (X = Br) 40 (X = Cl)
7				0.75	56
8				0.75	55
9				0.75	60
10				0.75	38 (X = Cl)[c] 57 (X = Br)[c]

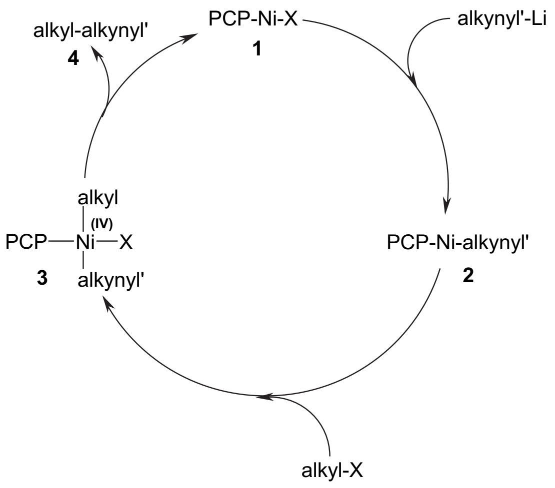
[a] Isolated yield.

[b] GC yield relative to alkyl halides against internal standard (n-dodacane).

[c] 2.5 equiv of 2-trimethylsilylethynyllithium were used.

metal-catalyzed processes much more difficult [8]. Even under optimized conditions, secondary alkyl halides gave unsatisfactory results. 2-Bromopropane could be coupled only in 30% yield (Table 2, entry 5). The reaction of 2-chloropropane (Table 2, entry 5) and cyclic alkyl halides (data not shown) resulted in failure, only minor amounts of coupling products were observed by GC–MS. Modification of the reaction conditions, including solvent, catalyst loading and temperature had no significant impact (see supporting information). Under the conditions (20 or 40 mol% Co(acac)$_3$, 4 equiv 2-trimethylsilylethynylmagnesium bromides) previously reported by Oshima, secondary alkyl bromides could be coupled in good yields, but employing phenylethynyl Grignard reagent also gave yields below 20% [12].

For trimethylsilylethynyllithium, the coupling reactions proceeded faster and the yields did not improve at longer reaction time (see supporting information), but generally the reactions gave yields 20–30% lower compared with phenylethynyllithium. Reactions of dihalides with trimethylsilylethynyllithium were also studied. Treatment of 1,4-dichlorobutane and 1,4-dibromobutane with 2.5 equiv of 2-trimethylsilylethynyllithium in the presence of complex **1** gave bis-alkynylation product in moderate yields (Table 2, entry 10).



Scheme 1. Proposed mechanism for Ni-catalyzed alkyl–alkynyl coupling reaction.

Similar to Kumada and Negishi type coupling reactions using alkyl or arylmetal nucleophiles, we propose that in this system the PCP-Ni^{II}-Cl complex **1** reacts first to form an alkynyl nickel species **2** (Scheme 1). Zargarian proved that a closely related PCP-Ni^{II}-alkynyl complex could be prepared by reacting {(i-Pr$_2$PCH$_2$CH$_2$)$_2$CH}NiBr with LiC≡CPh [39], while it could not be isolated in pure form. Oxidative addition of alkyl halides delivers a formal nickel(IV) intermediate **3**, which gives rise to the coupling product **4** via reductive elimination. It was suggested that the coupling of aryl halides with bis(1,5-cyclooctadiene)nickel(0) implicates a transient bis(aryl)nickel(IV) dihalide [40–44]. It is considered that the pincer PCP-ligand plays a role in the formation of nickel(IV) species [44]. The self-coupling of alkylnyllithiums to 1,3-diynes by reaction with NiCl$_2$(PPh$_3$)$_2$ in the presence of triphenylphosphine under stoichiometric conditions indicates that the 1,3-diynes are produced by reductive elimination from intermediate dialkynylnickel species [45]. Lithium acetylenides react with 2-chloro-2-nitropropane to form the cross-coupling product by a process which does not involve a free radical chain mechanism [46].

Alternative pathways (such as radical mechanism or direct bimolecular reaction of an arylnickel halide with an aryl halide) might exist and more detailed studies will be necessary.

4. Conclusions

We have demonstrated a highly efficient alkyl–alkynyl coupling system promoted by PCP-Ni^{II}-Cl complex **1** with alkynyllithium reagents. The usage of the PCP-Ni^{II}-Cl catalyst made the increment of the yield from 50% to 99%. Compared to the alkylation of primary alkyl halides with alkynyllithium reagents in THF in the presence of 10% NaI or Bu_4NI [47] and the Sonogashia protocols [24], this method requires milder conditions (room temperature) and proceeds quickly. And in comparison with the traditional ways in preparing the corresponding substituted alkynes, which were carried out in liquid ammonia [48,49], this simple system shows much advantage. The scope of C,C-coupling reactions were remarkably expanded using alkynyl nucleophiles. This research will make these readily available alkynyllithium reagents much more useful for organic synthesis. We are currently trying to expand this catalytic system to secondary and functionalized alkyl haildes and other kind of coupling reactions.

Acknowledgments

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Appendix. Supplementary material

Supplementary data associated with this article can be found, in the online version, at: doi:10.1016/j.jorganchem.2011.05.017.

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