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Oxidative Coupling

Copper(I)-Mediated Oxidative Cross-Coupling between Functionalized Alkynyl Lithium and Aryl Magnesium Reagents**

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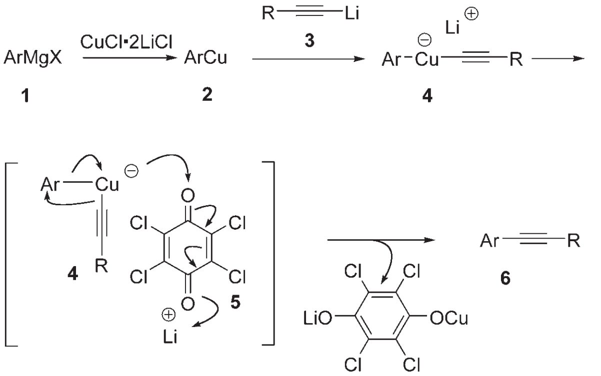
Dedicated to Professor Dieter Seebach on the occasion of his 70th birthday

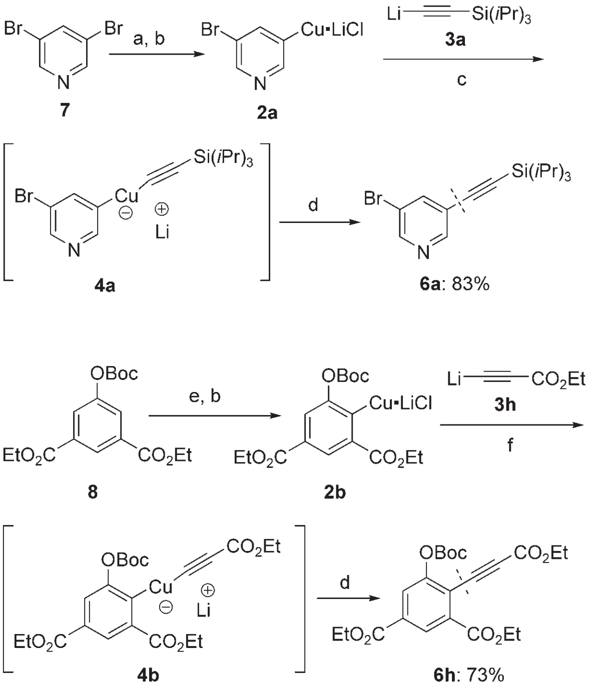
Polyfunctional alkynes are important intermediates for the preparation of natural products, pharmaceuticals, and organic materials[1] such as molecular wires.[2] The Sonogashira reaction[3] and the Negishi cross-coupling[4] are very powerful methods for preparing polyfunctional alkynes through the formation of a C(sp^2)–C(sp) bond. However, the Sonogashira coupling fails for the selective monocoupling of dihaloarenes and dihaloalkenes as well as for the coupling of sterically shielded haloarenes.[3k]

Recently, we reported an oxidative homocoupling of unsaturated magnesium or zinc reagents using a diphenoquinone or chloranil (**5**) as oxidation agents.[5] Soon after, we described a related oxidative amination procedure providing a general synthesis of polyfunctional amines.[6] Herein, we report a new type of oxidative coupling[7] for the preparation of polyfunctional alkynes. Aryl or heteroaryl magnesium halides (ArMgX, **1**) are transmetalated to the corresponding copper reagents (ArCu, **2**) using the THF-soluble salt $CuCl\cdot 2\,LiCl$.[8] Subsequent reaction with an alkynyl lithium compound of type **3** results in the formation of a mixed lithium aryl(alkynyl) cuprate **4**.[9] Its treatment with chloranil (**5**) provides polyfunctional alkynes of type **6** by an oxidative cross-coupling reaction (Scheme 1).



Scheme 1. Proposed mechanism for the oxidative cross-coupling of arylcopper reagents **2** with alkynyl lithium compounds **3** using chloranil (**5**).

The scope and the functional-group compatibility of this reaction proved to be broad. We first examined the coupling using a range of alkynyl lithium compounds with a typical heteroaryl magnesium compound. Thus, 3,5-dibromopyridine (**7**) was converted to 5-bromo-3-pyridylmagnesium chloride by a Br–Mg exchange using *i*PrMgCl·LiCl[10] (1.1 equiv, 0 °C, 0.5 h; then 25 °C, 0.5 h) and subsequent transmetalation to the corresponding organocopper species **2a** ($CuCl\cdot 2\,LiCl$[8] (1.1 equiv), −50 °C, 25 min). After the addition of **3a** (2.0 equiv, −50 °C, 1 h), the resulting mixed cuprate **4a** was treated with chloranil (1.3 equiv, −78 °C→−50 °C, 3 h), thus providing the alkynylated pyridine derivative **6a** in 83 % yield (Scheme 2). Various alkynyl lithium compounds[11] bearing aliphatic substituents (entries 1 and 2, Table 1), an alkenyl



Scheme 2. Oxidative cross-coupling of polyfunctional copper reagents. Reaction conditions: a) *i*PrMgCl·LiCl (1.1 equiv, 0 °C, 0.5 h; then 25 °C, 0.5 h); b) CuCl·2 LiCl (1.1 equiv, −50 °C, 25 min); c) **3a** (2.0 equiv, −50 °C, 1 h); d) **5**, 1.3 equiv, −78 °C→−50 °C, 3 h); e) TMPMgCl·LiCl (1.1 equiv, 0 °C, 1 h); f) **3h** (2.0 equiv, −78 °C, 1 h). TMP = 2,2,6,6-tetramethylpiperidyl, Boc = *tert*-butoxycarbonyl.

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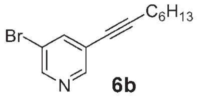
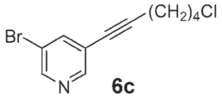
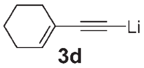
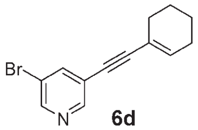
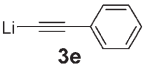
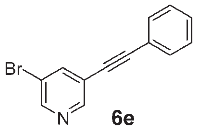
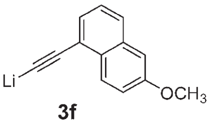
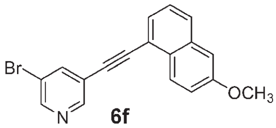
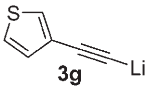
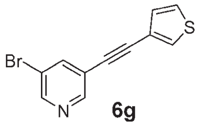
Table 1: Oxidative coupling of organocopper reagent **2a** with various alkynyl lithium compounds (**3b**–**3g**) using chloranil as oxidant.

Entry	Alkynyl lithium compound	Alkyne	Yield [%][a]
1	$Li{-}{\equiv}{-}C_6H_{13}$ **3b**	 **6b**	75[b]
2	$Li{-}{\equiv}{-}(CH_2)_4Cl$ **3c**	 **6c**	70[b]
3	 **3d**	 **6d**	70[b]
4	 **3e**	 **6e**	72[b]
5	 **3f**	 **6f**	68[b]
6	 **3g**	 **6g**	65[b]

[a] Yield of isolated, analytically pure product. [b] The aryl magnesium reagent was prepared by a bromine–magnesium exchange reaction with *i*PrMgCl·LiCl.

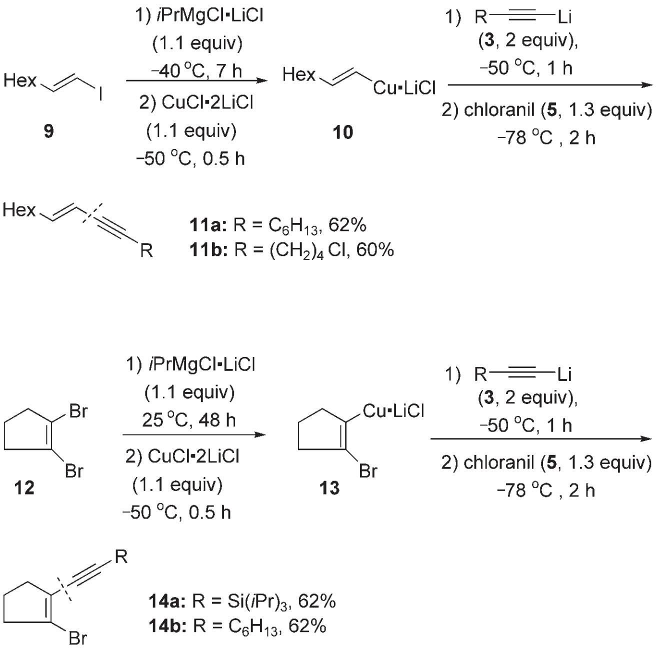
group (entry 3, Table 1), or various aryl or heteroaryl substituents (entries 4–6, Table 1) provide the desired polyfunctional alkynes **6b**–**6g** in 68–75 % yields. In general, an excess of alkynyl lithium compound (**3**, 1.5–2.0 equiv) is necessary to avoid homocoupling reactions.

This cross-coupling is compatible with various aryl and heteroaryl magnesium reagents. Thus, the direct magnesiation of the diester **8** with TMPMgCl·LiCl[12] (1.1 equiv, 0 °C, 1 h) provides the aryl magnesium chloride **1b**, which after transmetalation with CuCl·2 LiCl[8] (1.1 equiv, −50 °C, 25 min) furnishes the copper species **2b**. Its reaction with ethyllithium propiolate **3h**[13] affords the mixed copper organometallic compound **4b**, which by treatment with chloranil (1.3 equiv, −78 °C, 1 h, −78 °C→−50 °C, 3 h) leads to the unsaturated triester **6h** in 73 % yield (Scheme 2). A range of sterically hindered aryl magnesium reagents[12b] (**1b**–**e**) were found to undergo oxidative couplings with alkynyl lithium compounds (**3a**–**c**, **e**), thus leading to the polyfunctional alkynes **6i**–**p** in 65–74 % yield (entries 1–8, Table 2). Typical substituted aryl magnesium reagents bearing various substituents (entries 9–13, Table 2) react under our conditions with alkynyl lithium compounds (**3a**,**b**) to provide the expected alkynes **6q**–**6u** in 68–77 % yield. Reaction of 1-naphthylmagnesium bromide with the alkynyl lithium compounds **3e** and **3a** furnishes the 1-alkynyl naphthalene derivatives **6v** and **6w** in 70 % yield (entries 14–15, Table 2).[14] The heterocyclic copper derivatives prepared from **1k**[12a] and **1l** also react with **3a** and **3b** to afford the corresponding 2-alkynylpyridine and 3-alkynylbenzofuran derivatives **6x** and **6y** in 62–66 % yield (entries 16–17, Table 2).

This oxidative coupling has been extended to a stereoselective preparation of enynes.[4] Thus, (*E*)-octenyl iodide (**9**, $E/Z > 99{:}1$)[15] was converted into the corresponding alkenyl magnesium reagent by treatment with *i*PrMgCl·LiCl[15] (−40 °C, 7 h). Addition of CuCl·2 LiCl provides the copper reagent **10**, which after the addition of first an alkynyl lithium compound (**3b** or **3c**) and then chloranil (**5**, 1.3 equiv, −78 °C, 2 h) furnishes the *E*-enynes ($E/Z > 99{:}1$) **11a** ($R = C_6H_{13}$, 62 %) and **11b** ($R = (CH_2)_4Cl$, 60 %). Similarly, the reaction of 1,2-dibromocyclopentene (**12**) with *i*PrMgCl·LiCl (1.1 equiv, 25 °C, 48 h) provides 2-bromocyclopentenylmagnesium bromide, which was subsequently transmetalated to the corresponding copper reagent **13**. Addition of first an alkynyl lithium compound (**3a** or **3b**, 2 equiv, −50 °C, 1 h) and then chloranil (**5**, 1.3 equiv, −78 °C, 2 h) affords the bromoenynes **14a** ($R = Si(iPr)_3$) and **14b** ($R = C_6H_{13}$) in 62 % yield (Scheme 3).

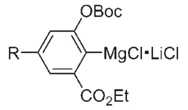
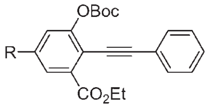
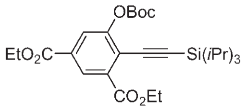
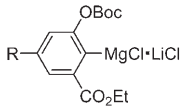
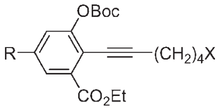
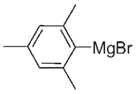
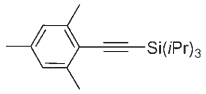
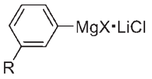
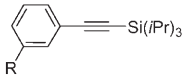
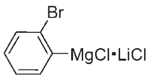
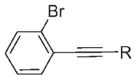
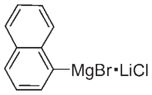
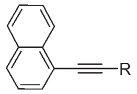
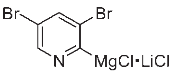
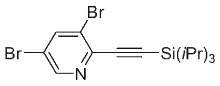
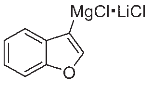
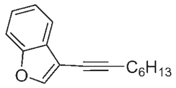
The unsaturated bromine-substituted alkynes **14b**, **6u**, and **6y** (Scheme 4) are well-suited for the preparation of new annulated pyridines.[16] The reaction of unsaturated and saturated bromides **14b** and **6u** with *t*BuLi (2 equiv, −78 °C, 1 h) provides the corresponding lithium intermediates **15** and **16**, which readily react with *p*-tolylnitrile[17] (*p*-TolCN, 1.3 equiv, −78 °C, 1 h).

In the case of **15**, the resulting lithium intermediate undergoes a remarkable 6-*endo-dig* ring closure[18] leading to the 4-lithiated pyridine derivative **17**. After iodolysis or protonation, the polyfunctional annulated pyridines **19a** and **19b** are obtained in 64 and 60 % yield, respectively (Scheme 4). In the case of the aryl lithium compound **16**, the resulting lithiated imine undergoes a ring closure only

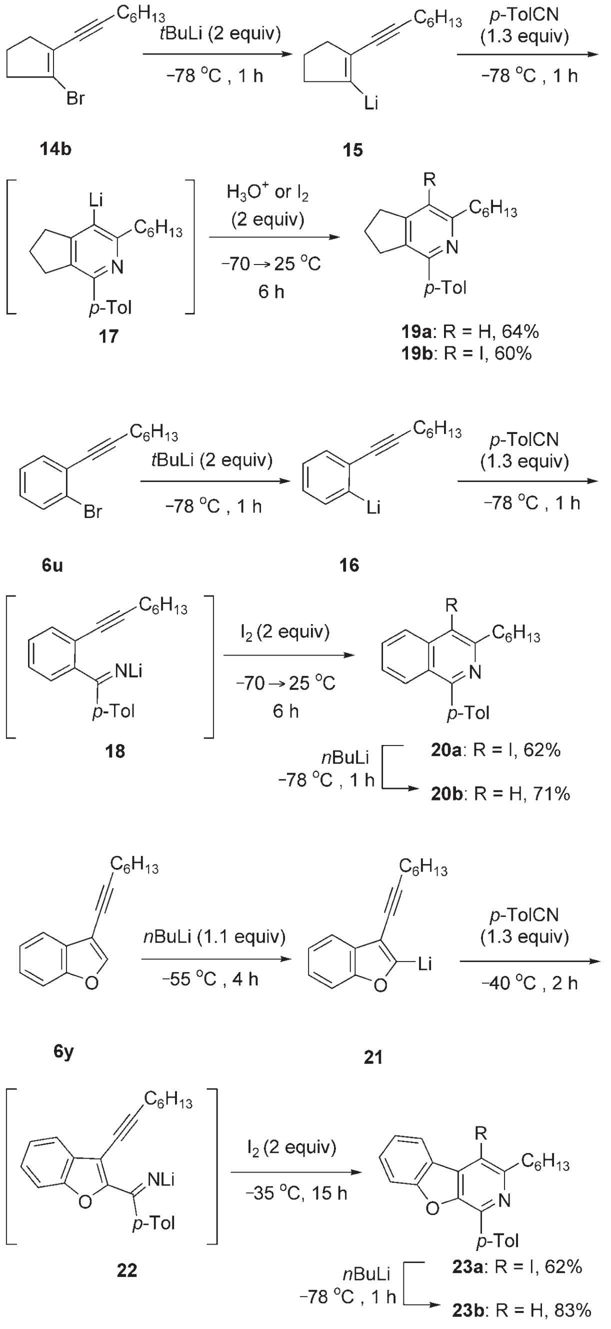


Scheme 3. Oxidative cross-coupling of acylic and cyclic alkenylcopper compounds **10**, **13** with alkynyl lithium compounds **3** using chloranil (**5**).

Table 2: Synthesis of polyfunctional disubstituted alkynes by the oxidative coupling of polyfunctional aryl and heteroaryl mixed cuprates using chloranil.

Entry	Grignard reagent	3	Alkyne	Yield [%][a]
				
1	**1b**: R=$\mathrm{CO_2Et}$	**3e**	**6i**: R=$\mathrm{CO_2Et}$	65[b]
2	**1c**: R=H	**3e**	**6j**: R=H	70[b]
3	**1d**: R=OBoc	**3e**	**6k**: R=OBoc	63[b]
				
4	**1b**	**3a**	**6l**	74[b]
				
5	**1c**: R=H	**3b**	**6m**: R=H, X=$\mathrm{C_2H_5}$	69[b]
6	**1c**: R=H	**3c**	**6n**: R=H, X=Cl	70[b]
7	**1b**: R=$\mathrm{CO_2Et}$	**3c**	**6o**: R=$\mathrm{CO_2Et}$, X=Cl	68[b]
				
8	**1e**	**3a**	**6p**	73[c]
				
9	**1f**: R=OMe	**3a**	**6q**: R=OMe	68[c]
10	**1g**: R=I	**3a**	**6r**: R=I	77[d]
11	**1h**: R=CN	**3a**	**6s**: R=CN	72[d]
				
12	**1i**	**3a**	**6t**: R=Si(*i*Pr)$_3$	70[d]
13	**1i**	**3b**	**6u**: R=$\mathrm{C_6H_{13}}$	68[d]
				
14	**1j**	**3e**	**6v**: R=Ph	70[c]
15	**1j**	**3a**	**6w**: R=Si(*i*Pr)$_3$	70[c]
				
16	**1k**	**3a**	**6x**	66[b]
				
17	**1l**	**3b**	**6y**	62[d]

[a] Yield of isolated, analytically pure product. [b] The aryl magnesium reagent was prepared through deprotonation using TMPMgCl·LiCl (1.1 equiv). [c] The aryl magnesium reagent was prepared by magnesium insertion into the bromoarene. [d] The aryl magnesium reagent was prepared by a bromine–magnesium exchange reaction with *i*PrMgCl·LiCl.



Scheme 4. Reaction of 1-lithio-1,3-enynes with nitriles to give pyridine derivatives **19a,b**, **20a,b**, and **23a,b**.

after addition of iodine (−70 °C→25 °C, 6 h; Scheme 4). This method can be extended to other heterocyclic systems. Thus, the lithiation of the 3-alkynylbenzofuran **6y** in the 2-position (*n*BuLi (1.1 equiv), −55 °C, 4 h) and subsequent addition of *p*-TolCN (1.3 equiv, −40 °C, 2 h) furnishes the lithiated imine **22**, which after the addition of iodine provides the iodoisoquinoline **23a** in 62 % yield (Scheme 4). To test the reversibility of this cyclization, we treated iodoisoquinoline **20a** with *n*BuLi (−78 °C, 1 h), and after protonation we observed no ring-opening products but only the isoquinoline **20b**. Similarly, the reaction of **23a** with *n*BuLi (−78 °C, 1 h) provided only the isoquinoline **23b** after protonation, thus showing that the ring closure of **18** and **22** is not reversible.

In summary, we have reported a new oxidative coupling of lithium aryl(alkynyl) cuprates, which provides polyfunctional alkynes or enynes in good yields. Several new bromoalkynes prepared by this method are currently being used for the preparation of valuable annulated pyridines and isoquinolines. Further applications of this reaction are currently underway.

Experimental Section

Typical procedure: Synthesis of **6a** (Scheme 2): A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with **7** (237 mg, 1.0 mmol). After cooling to 0 °C, *i*PrMgCl·LiCl (0.92 mL, 1.20 M in THF, 1.1 mmol) was added dropwise. The mixture was stirred for 0.5 h and then for further 0.5 h at 25 °C to afford the Grignard reagent **1a**. CuCl·2LiCl (1.2 mL, 1.0 M in THF, 1.2 mmol) was added dropwise to **1a** at −50 °C, and the mixture was stirred for 25 min. Compound **3a** (2.0 mmol; prepared by adding *n*BuLi (2 mmol) to a 0.5 M solution of triisopropylsilylacetylene in THF (365 mg, 2 mmol) at 0 °C and stirring for 30 min) was added dropwise to the resulting cuprate **2a**, and the mixture was stirred for 1 h at −50 °C. The reaction mixture was cooled to −78 °C, and a solution of **5** (320 mg, 1.3 mmol) in anhydrous THF (7 mL) was added slowly over a period of 45 min. The reaction mixture was then warmed to −50 °C and stirred for 3 h. $\mathrm{Et_2O}$ (10 mL) was poured into the crude reaction mixture, and the reaction mixture was then filtered through celite and the residue washed with $\mathrm{Et_2O}$ (ca. 100 mL). The organic phase was washed with 2×10 mL $\mathrm{NH_4OH}$(aq) (2.0 M) and extracted with $\mathrm{Et_2O}$. The combined organic layers were dried ($\mathrm{MgSO_4}$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/$\mathrm{Et_2O}$ 20:1) yielded the alkyne **6a** (281 mg, 83 %) as a pale yellow viscous oil.

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Keywords: alkynes · cross-coupling · cuprates · nitrogen heterocycles

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