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Regio- and Stereospecific Copper-Catalyzed Substitution Reaction of Propargylic Ammonium Salts with Aryl Grignard Reagents.

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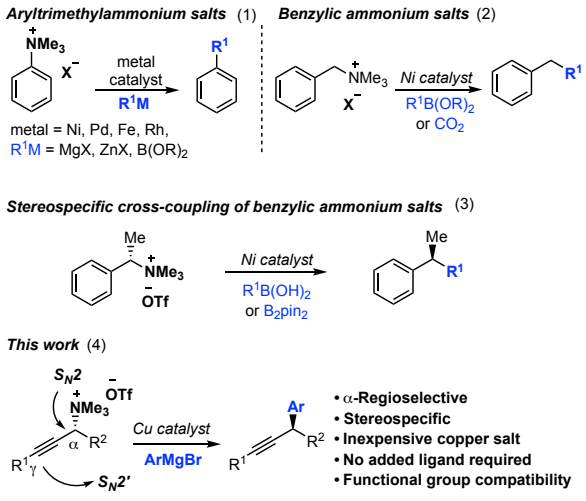
Supporting Information Placeholder

ABSTRACT: We have developed a copper-catalyzed substitution reaction of propargylic ammonium salts with aryl Grignard reagents. The reaction is stereospecific, α-regioselective and proceeds with exceptional functional group tolerance. Conveniently, a stable, inexpensive and commercially available copper salt is used and no added ligand is required.

Transition-metal catalyzed reactions have emerged as one of the most powerful tools for the formation of carbon-carbon bonds. Recently, significant efforts have been made in this field to look for more stable and easily available electrophiles. Different approaches for the activation of C-H,[1] C-C[2] and C-O[3] bonds have been developed, providing chemists with a broad range of new tools that is changing the design of synthetic strategies. In this field, transition-metal catalyzed cleavage of C-N bonds is less explored and still remains a challenge.[4] This is not surprising considering the high bond dissociation energy of the C-N bond.[5] An attractive approach to bypass this problem is the transformation of simple amines into ammonium salts, which are air and thermally stable solids. Ammonium salts are readily prepared from amine precursors, so they benefit from the large variety of methods available to prepare nitrogen containing molecules.[6]

Following the pioneering work of Wenkert,[7] several groups have successfully used aryl and benzylic ammonium salts in Kumada,[8] Negishi,[9] Suzuki,[10] Buchwald-Hartwig,[11] and cross-electrophile[12] couplings (Scheme 1, eq. 1-2).[13] However, despite their availability and stability, the use of ammonium salts in metal-catalyzed reactions is still relatively restricted, especially in stereoselective transformations. In this context, Watson has reported the stereospecific Suzuki-Miyaura coupling of chiral secondary benzylic ammonium salts,[14] but other secondary chiral salts remain unexplored (Scheme 1, eq. 3). Additionally, most of the reported examples require the use of the air-sensitive and thermally unstable $Ni(cod)_2$. Surprisingly, the use of copper-catalysis is virtually unexplored.[15] Therefore, finding new catalytic systems based on stable and non-precious metals, and expanding the structural scope of the ammonium salts, are still unmet challenges. Progress in this area would definitely expand the field of metal-catalyzed cleavage of C-N bonds.

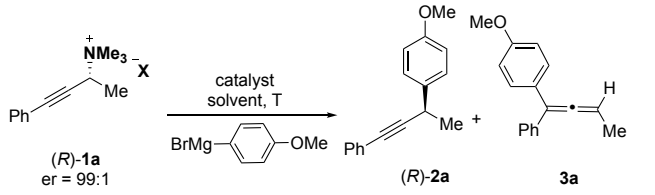
Scheme 1. Cross Coupling of Trimethylammonium Salts



Motivated by these challenges, we looked at secondary propargylic ammonium salts as potential electrophiles for stereospecific metal-catalyzed transformations (Scheme 1, eq. 4). They are readily available from the amine precursors providing an alternative to the use of highly reactive and often unstable propargylic bromides and phosphates. Importantly, secondary propargylic amines are stable precursors that can be prepared in high enantiopurity from the corresponding alcohols or through a variety of asymmetric catalytic methods.[16] As a drawback, secondary propargylic ammonium salts

present two possible reactive sites (the α and the γ positions) that could lead to mixtures of formal S_N2 or S_N2' products. Therefore, a successful catalytic system should be able to control both the regio- and the stereoselectivity. In this communication, we describe our efforts toward this goal using a copper salt and aryl Grignard reagents. The reaction is stereospecific and completely α-regioselective, which is striking for copper-catalyzed transformations of propargylic electrophiles. The reaction proceeds well with a commercially available and inexpensive copper salt and without the need of an added ligand.[17]

Table 1. Optimization of the Reaction Conditions



Entry	Catalyst	LG	T (ºC)	er[a]	yield **2a** (%)[b]
1[c]	$Pd(PPh_3)_2Cl_2$	NMe_3OTf	rt	n.d.	12[d]
2[e]	$[Ni(dppe)]Cl_2$	NMe_3OTf	rt	n.d.	22[f]
3[g]	CuCl	NMe_3OTf	–40	85:15	80
4[g]	$Cu(CH_3CN)_4PF_6$	NMe_3OTf	–40	99:1	98
5[g]	$Cu(CH_3CN)_4PF_6$	NMe_3OTf	–20	95:5	96
6[g]	$Cu(CH_3CN)_4PF_6$	NMe_3OTf	0	94:6	94
7[h]	$Cu(CH_3CN)_4PF_6$	NMe_3OTf	–40	99:1	95
8[h,i]	**$Cu(CH_3CN)_4PF_6$**	NMe_3OTf	**–40**	**99:1**	**98**
9	$Cu(CH_3CN)_4PF_6$	NMe_3OMs	–40	94:6	58
10	$Cu(CH_3CN)_4PF_6$	NMe_3BF_4	–40	94:6	68
11	$Cu(CH_3CN)_4PF_6$	NMe_3I	–40	94:6	58
12	$Cu(CH_3CN)_4PF_6$	NMe_3OTs	–40	98:2	56
13	—	NMe_3OTf	–40	—	—
14	—	NMe_3OTf	rt	54:46	22

[a]Determined by chiral SFC. [b]Isolated yields. [c]Conditions with Pd: **1a** (0.1 mmol, 1.0 equiv.), ArMgX (1.1 equiv.), $Pd(PPh_3)_2Cl_2$ (10 mol%), THF (0.1 M), 4 h. [d]40:60 mixture of **2a** and **3a**. [e]Conditions with Ni: **1a** (0.1 mmol, 1.0 equiv), ArMgX (1.1 equiv.), $[Ni(dppe)]Cl_2$ (10 mol%), THF (0.1 M), 4 h. [f]**2a** was isolated with the corresponding propargylic bromide as a 82:18 mixture. [g]Conditions with Cu: **1a** (0.1 mmol, 1.0 equiv.), ArMgX (1.1 equiv.), CuX (10 mol%), THF (0.1 M), –40 ºC, 5 min, unless otherwise noted. [h]5 mol% of $Cu(CH_3CN)_4PF_6$ was used. [i]CH_2Cl_2 was used instead of THF.

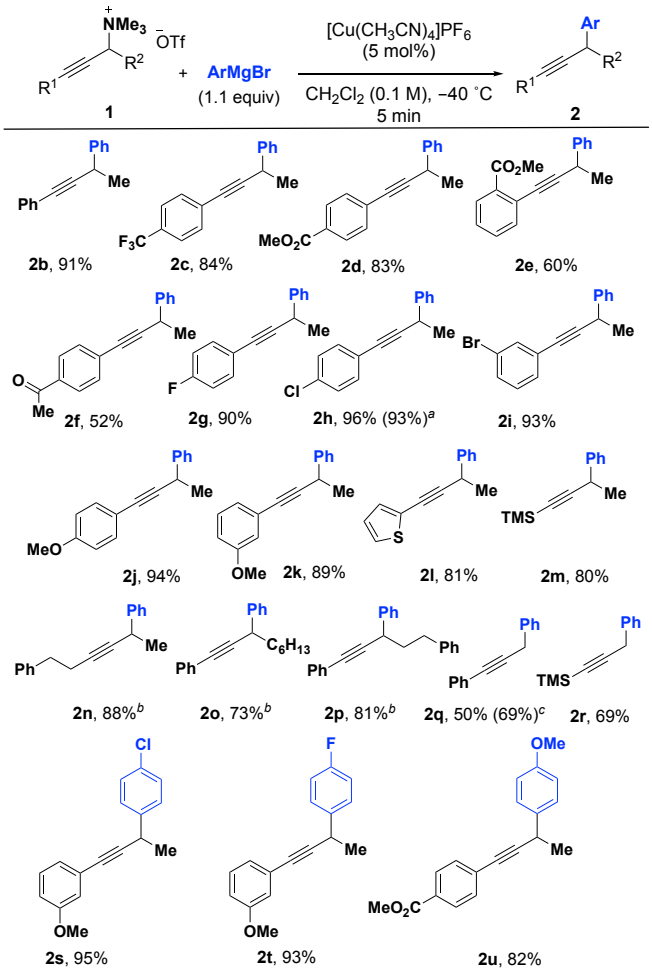
Propargylic ammonium salt (*R*)-**1a** was easily prepared from the corresponding (*S*) propargylic alcohol through a one-pot mesylation/amination with dimethylamine, followed by treatment with methyl triflate.[18] To explore the reactivity of these novel electrophiles, we first chose highly reactive nucleophiles such as aryl Grignard reagents. When we tried palladium catalyzed Kumada conditions, previously reported for aryltrimethylammonium salts, we observed the formation of a 40:60 mixture of propargylic derivative **2a** and allene **3a** in low yield (Table 1, entry 1). Changing to $[Ni(dppe)]Cl_2$ eliminated formation of allene **3a**, and compound **2a** was isolated in low yield along with the corresponding propargylic bromide (Table 1, entry 2). Based on our previous experience in copper-catalyzed transformations,[19] we decided to test the use of copper catalysis. Using CuCl (10 mol%) in THF at –40 ºC we observed the immediate formation of the α-product (*R*)-**2a** in high yield and moderate enantiomeric ratio (Table 1, entry 3). The reaction was extremely fast (5 min) at –40 ºC and only 1.1 equivalents of the Grignard reagent were needed. Therefore, it was reasonable to predict a broad functional group compatibility, despite the high reactivity of the nucleophiles. Importantly, allene **3a** was not detected in the ^1H NMR of the crude product, an unusual result in copper-catalyzed reactions of propargylic electrophiles.[20,21]

We were pleased to find that switching to $Cu(CH_3CN)_4PF_6$ (10 mol%) significantly improved both the yield and the enantioselectivity, affording (*R*)-**2a** with complete inversion of the configuration (Table 1, entry 4).[22] When the reaction was run at higher temperatures (0 and –20 ºC), we observed a slight erosion of the enantiomeric ratio (Table 1, entries 5 and 6). The catalyst loading was reduced to 5 mol% without affecting the yield or the stereoselectivity (Table 1, entry 7). The reaction also worked well in CH_2Cl_2, which improved the solubility of the ammonium salt (Table 1, entry 8). Interestingly, the counterion on the ammonium salt was not an innocent witness (Table 1, entries 8-12). Our results show that the triflate anion plays a key role in tuning the yield and enantioselectivity. In the absence of a copper salt at –40 ºC, no product formation was observed (Table 1, entry 13). At room temperature, however, **2a** was obtained in low yield and poor enantiomeric ratio (Table 1, entry 14). These two experiments show the crucial role of the copper-salt in the reaction.[23]

Encouraged by these results, we prepared a series of racemic secondary propargylic ammonium salts to determine first the structural scope of the transformation (Scheme 2). Using the optimized conditions with phenyl magnesium bromide, we obtained compound **2b** in excellent yield. Our conditions allowed a wide variety of functional groups on the aromatic ring (R^1) of the ammonium salt, at the *ortho*, *meta* and *para* positions (compounds **2c**-**2k**). High yields were observed for substrates with electron withdrawing groups (compounds **2c-2i**). Remarkably, even sensitive groups like esters (compounds **2d** and **2e**) and ketones (compound **2f**) were tolerated. In particular, the chemoselectivity observed with compound **2f** (while not complete) demonstrates the functional group compatibility.[24] Importantly, aryl chloride and bromide derivatives react exclusively

through the C-N bond under copper-catalysis (compounds **2h** and **2i**). We also carried out the reaction at gram scale with compound **2h** without affecting the yield.

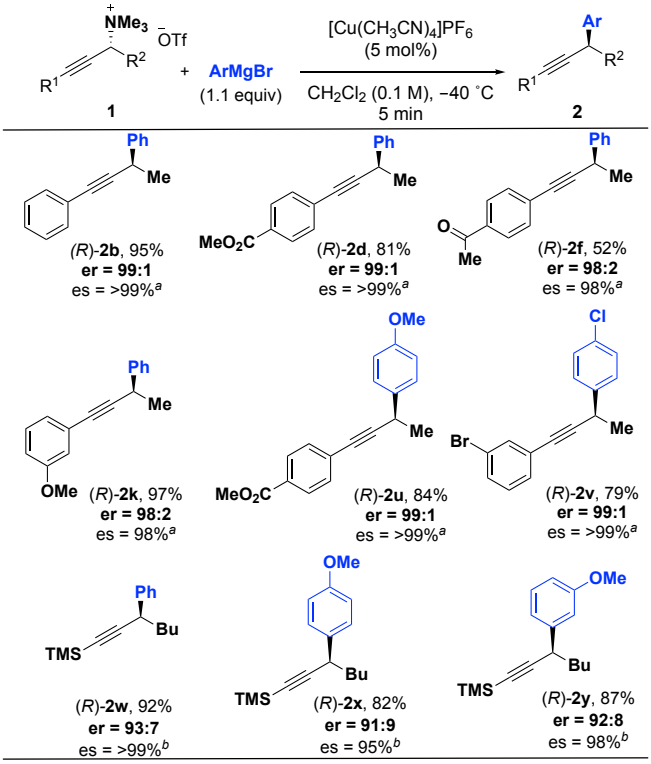
Scheme 2. Scope of the Substitution Reaction of Propargylic Ammonium Salts



[a]Reaction performed with 1 gram of ammonium salt. [b] General conditions were used except for $Cu(CH_3CN)_4PF_6$ (10 mol%) and CH_2Cl_2 (0.03 M). [c]The reaction was carried out at 23 ºC.

Similarly, compounds with electron donating groups (compound **2j**) and heterocycles (compound **2l**) were prepared in excellent yield. Further structural modifications in the ammonium salt such as silyl and alkyl substitution in the alkyne (compounds **2m** and **2n**) and different alkyl chains at the propargylic position (compounds **2o** and **2p**) are also allowed. For compounds **2n**, **2o** and **2p**, we had to increase the amount of solvent and catalyst loading (10 mol%) to achieve good conversion. This lower reactivity could be due to stereoelectronic effects of the substituents on the alkyne (**2n**) and propargylic carbon (**2o**, **2p**). Surprisingly, primary ammonium salts gave only moderate yields (compounds **2q** and **2r**) at –40 ºC. A competition experiment between ammonium salts **1a** (1 equiv.) and **1q** (1 equiv.) with 1 equiv. of Grignard reagent, under standard reaction conditions, afforded 61% of **2b** and only 5% yield of **2q** (see Supporting Information). This experiment suggests that secondary substrates are more reactive than primary ammonium salts in the copper-catalyzed reaction. The yield for compound **2q** was improved to 69% when the reaction was carried out at room temperature. The coupling also worked with a variety of aryl Grignard reagents with electron-withdrawing (compounds **2s**, **2t**) and electron-donating groups (compound **2u**). In all cases, we observed exclusive substitution at the α-position.

Scheme 3. Stereospecific Substitution Reactions[d]



[a]Starting material er = 99:1. [b]Starting material er = 93:7. [c]Enantiospecificity (es)= $ee_{product}/ee_{starting\ material}$x100%.

Next, we checked if the stereospecificity observed for (*R*)-**1a** (Table 1) was general for different ammonium salts and Grignard reagents (Scheme 3). Ammonium salts with aryl and silyl substitution on the alkyne and different alkyl chains at the propargylic position afforded the desired compounds in high yield and with excellent chirality transfer. Interestingly, the method allows for the preparation of enantiomerically enriched bifunctional compounds such as **2v**, with two orthogonal halide substituents which would be difficult to prepare using other transition metals.

Although further mechanistic studies need to be implemented, our results support an S_N2 mechanism involving addition of a catalytically generated aryl cuprate to the ammonium salt. The lower reactivity observed for primary ammonium salts compared to secondary derivatives (compounds **2q** and **2r**), could suggest a substantial

amount of carbon-nitrogen bond rupture in the transition state.[25]

In summary, we have developed a stereospecific method for the catalytic Kumada type coupling of secondary propargylic ammonium salts with aryl Grignard reagents. We show for the first time that propargylic ammonium salts are suitable partners in metal-catalyzed reactions. Conveniently, a stable, inexpensive and commercially available copper salt is used and no added ligand is required. Surprisingly, only the α-regioisomer is formed, which is striking for copper-catalyzed transformations. Additional studies on stereospecific copper-catalyzed coupling reactions of ammonium salts are underway.

ASSOCIATED CONTENT

Experimental procedures, compound characterization data, analytic details for all enantiomerically enriched products and crystal structural data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

No competing financial interests have been declared.

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(22) See Supporting Information for details on the determination of the absolute configuration of the products.

(23) The corresponding propargylic mesylate afforded **2a** with lower yield and reduced enantioselectivity. The propargylic phosphate gave an inseparable 95:5 mixture of **2a** and allene **3a**. Both, mesylate and phosphate derivatives decomposed quickly and could not be stored. These results highlight the benefit of using an ammonium salt as leaving group. See Supporting Information for details.

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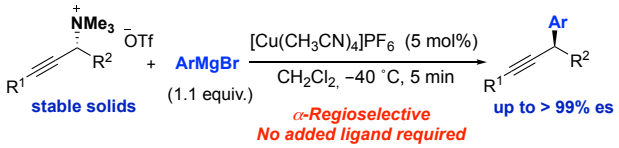
NMe3
OTf
R1
R2
stable solids
+
ArMgBr
(1.1 equiv.)
[Cu(CH3CN)4]PF6 (5 mol%)
CH2Cl2, −40 °C, 5 min
α-Regioselective
No added ligand required
Ar
R1
R2
up to > 99% es