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Copper-Catalysed Cross-Coupling of Alkyl Grignard Reagents and Propargylic Ammonium salts: Stereospecific Synthesis of Allenes.

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Herein we describe a robust and practical method to prepare enantiomerically enriched trisubstituted allenes using alkyl Grignard reagents and bench stable propargylic ammonium salts. Excellent yields as well as regio- and stereoselectivities are observed. Our conditions provide a solution to the allene racemization, which has been a long-standing problem when using Grignard reagents.

Chiral allenes are present in a broad number of natural products and commercialized drugs. They are also important synthetic intermediates due to the unique reactivity of their consecutive π-bonds.[1] One of the most popular and convenient methods for the preparation of allenes is the reaction of organocuprates, generated from organomagnesium or organolithium reagents, with propargylic electrophiles.[2,3] Despite being widely used, this approach still presents several limitations when applied to asymmetric synthesis. The chirality transfer from enantiomerically enriched propargylic electrophiles is not always reliable. Racemization of the allenes when using organocuprates is well documented in the literature.[4] Additionally, stereoselective catalytic approaches do not offer broad structural scope.[5] Small changes in the nature of the nucleophile and the leaving group can significantly modify the regio- and the stereoselectivity of the reaction.[3i,4c] Recently, Sawamura[6] and Lalic[7] overcame some of these limitations using a copper-catalyzed cross-coupling between propargylic phosphates and organoboron compounds as nucleophiles. Although both methods are landmark contributions, the experimental procedures involve the use of a glovebox to prepare the alkylboranes. Additionally, propargylic phosphates often need to be used immediately after preparation to prevent decomposition.

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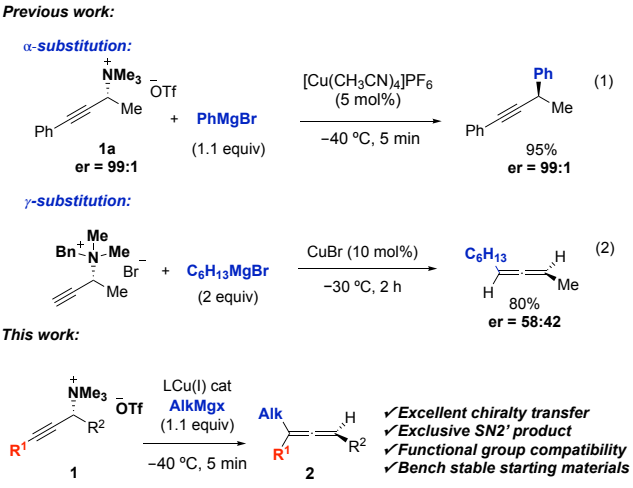
Recently, we have explored the use of enantiomerically enriched propargylic ammonium salts as a novel class of electrophiles for stereospecific copper-catalyzed transformations (Scheme 1, equation 1).[8] They are bench stable solids that are easily prepared in multigram scale with high enantiopurity from secondary propargylic amines.[9] When propargylic ammonium salts such as **1a** were treated with aryl Grignard reagents and a catalytic amount of a copper(I) salt, complete S_N2 regioselectivity and excellent chirality transfer were observed (Scheme 1, equation 1).[8]



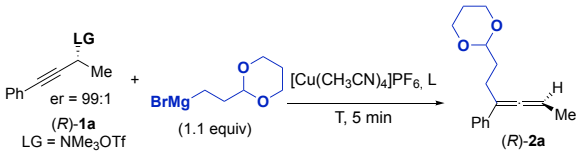
Scheme 1. Stereospecific reactions of propargylic ammonium salts with Grignard reagents.

We then decided to explore the effect of more nucleophilic alkyl Grignard reagents on the regio- and the stereoselectivity of the reaction. Our starting point was an isolated example reported by Claesson showing that an enantiomerically enriched propargylic ammonium bromide reacted with an alkyl Grignard reagent in an S_N2' fashion (Scheme 1, equation 2).[3e] Unfortunately, he observed significant erosion of the chirality transfer. Our previous experience with aryl Grignard reagents has taught us that the copper salt and the nature of the ammonium salt (substituents on nitrogen and counterion) have

a profound effect on the stereospecificity of the process.[8] Therefore, we decided to study the influence of those factors on the alkyl Grignard addition to propargylic ammonium salts, with the goal of avoiding racemization and providing a general method. Herein, we present a robust way to prepare axially chiral allenes from enantioenriched propargylic ammonium triflates. The reaction is very fast (5 min) at –40 °C and only 1.1 equivalents of the Grignard reagent are needed. Our conditions provide a solution to the allene racemization, which has been a long-standing problem when using Grignard reagents and propargylic electrophiles.[5] Additionally, the experimental procedure is simple and convenient: organomagnesium compounds are among the most accessible organometallic species and propargylic ammonium salts are bench stable solids.

We started our study with propargylic ammonium salt **1a** and (1,3-dioxan-2-ylethyl)magnesium bromide (Table 1). Under the conditions previously used with aryl Grignard reagents (10 mol% $[Cu(CH_3CN)_4]PF_6$, –40 °C) only the S_N2'-type product **2a** was formed with high chirality transfer (Table 1, entry 1).[10] Although pleased with this result, we did observe a slight erosion of the enantiomeric ratio (from 99:1 to 94:6). Therefore, we explored the effect of an added ligand in the enantioselectivity of the process (entries 1-5, Table 1). Gratifyingly, using 12 mol% of SPhos the chirality transfer was almost perfect (entry 5, Table 1). Similar results were observed when we reduced the amount of the Cu(I) salt and ligand to 5 and 6 mol% respectively (entry 6, Table 1). CH_2Cl_2 also proved to be an effective solvent to carry out the transformation (entry 7, Table 1). At 0 °C and room temperature (entries 8 and 9), the reaction took place uneventfully with only a slight erosion of the enantiomeric ratio.

Table 1. Optimization of the reaction conditions



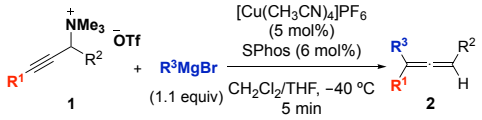
Entry	LG	L	T (°C)	er[e]	Yield[f] (%)
1[a]	NMe_3OTf	none	–40	94:6	95
2[a]	NMe_3OTf	(±)-Binap	–40	97:3	94
3[a]	NMe_3OTf	dppf	–40	96:4	82
4[a]	NMe_3OTf	PCy_3	–40	96:4	70
5[a]	NMe_3OTf	SPhos	–40	98:2	90
6[b]	***NMe_3OTf***	***SPhos***	***–40***	***98:2***	***90***
7[c]	***NMe_3OTf***	***SPhos***	***–40***	***98:2***	***86***
8[b]	NMe_3OTf	SPhos	0	95:5	70
9[b]	NMe_3OTf	SPhos	rt	95:5	77
10[b]	NMe_3OTs	SPhos	–40	65:35	51
11[b]	NMe_3I	SPhos	–40	88:12	51
12[b]	OMs	SPhos	–40	87:13	55
13[d]	NMe_3OTf	—	–40	—	—
14[d]	NMe_3OTf	—	rt	78:22	24

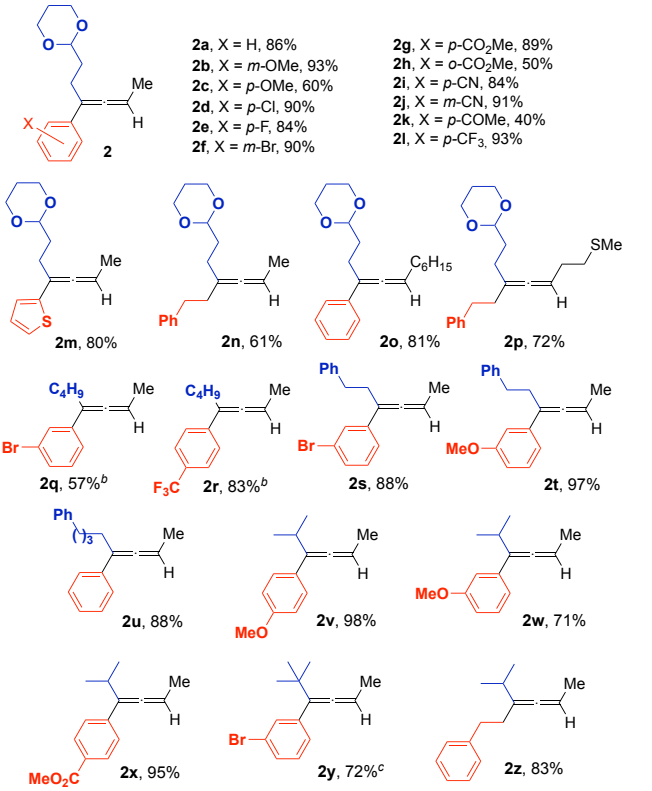
[a]Reaction Conditions: **1a** (0.1 mmol, 1.0 equiv.), RMgX (1.1 equiv.), $Cu(CH_3CN)PF_6$ (10 mol%), L (12 mol%), THF (0.1 M), –40 °C, 5 min. [b]5 mol% of $Cu(CH_3CN)_4PF_6$ and 6 mol% L were used. [c]Using CH_2Cl_2 (0.1 M) as solvent. [d]Reaction run without a Cu(I) salt and ligand. [e]Determined by SFC. [f]Isolated yields.

Interestingly, the counterion on the ammonium salt played a key role in the chirality transfer of the transformation. Tosylate and iodide derivatives showed a significant decrease in the enantiomeric ratio and lower yields, compared to triflate (entries 10 and 11, Table 1). Changing the ammonium leaving group to mesylate was also detrimental for both the yield and the chirality transfer (entry 12, Table 1). In the absence of a copper salt at –40 °C, we did not observe product formation (entry 13, Table 1). At room temperature, however, compound **2a** was obtained in low yield and poor enantiomeric ratio (entry 14, Table 1). These two experiments show the crucial role of the copper salt in the transformation.[11]

With the optimal conditions in hand, we first proceeded to study the structural scope of the transformation with a series of racemic propargylic ammonium salts, with different substituents on the alkyne (R^1) and at the propargylic position (R^2) (Scheme 2). In some cases, we observed low solubility of the ammonium salt in THF, therefore, we decided to carry out the study using CH_2Cl_2 as solvent.

Scheme 2. Structural scope of the allene formation[a]





[a]Reaction Conditions: **1a** (0.2 mmol, 1.0 equiv.), RMgBr (1.1 equiv. in THF), $Cu(CH_3CN)PF_6$ (5 mol%), SPhos (6 mol%), CH_2Cl_2 (0.1 M), –40 °C, 5 min. [b] ^{n}BuMgCl (1.1 equiv. in THF) was used. [c]The reaction was carried out at –20 °

Using (1,3-dioxan-2-ylethyl)magnesium bromide, we prepared a broad range of trisubstituted allenes (compounds **2a**-**2p**). The reaction worked well with aromatic substituents bearing

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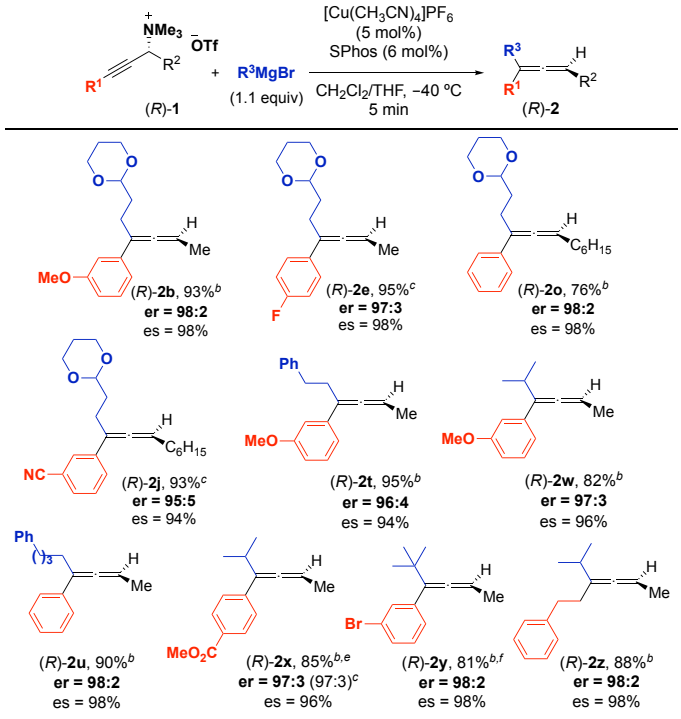
electron donating and electron withdrawing groups at the *ortho*, *meta* and *para* positions. Propargylic ammonium salts with an aryl chloride or bromide (compounds **2d** and **2f**), react only through the C-N bond. Importantly, sensitive functional groups such as esters and cyano (compounds **2g**-**2j**) were compatible with the use of a Grignard reagent. With a more reactive ketone group, we observed formation of the product in 40% yield (compound **2k**) due to lower chemoselectivity. We further modified the substitution on the alkyne with a heteroaromatic ring (compound **2m**) and an alkyl chain (compounds **2n** and **2p**). Introduction of alkyl chains other than methyl at the propargylic position was also feasible (compounds **2o** and **2p**). Other alkyl Grignard reagents, both primary (compounds **2q**-**2u**), secondary (compounds **2v**-**2x** and **2z**) and tertiary (compound **2y**) afforded the desired allenes in good to excellent yields. Unfortunately, silyl substituted alkynes did not react under the optimized conditions.

After exploring the structural scope, we checked if the stereospecificity observed for salt **1a** was general for different ammonium salts (Scheme 3). Excellent chirality transfer with 1,3-*anti* stereospecficity was observed in all cases, without detecting significant allene racemization. Additionally, we checked the effect of the halide in the Grignard reagent with compound (*R*)-**2x**. When we used a solution of ^{i}PrMgCl in THF, instead of ^{i}PrMgBr, allene (*R*)-**2x** was obtained in almost identical yield and enantiomeric ratio (89% yield, er = 97:3).[12]

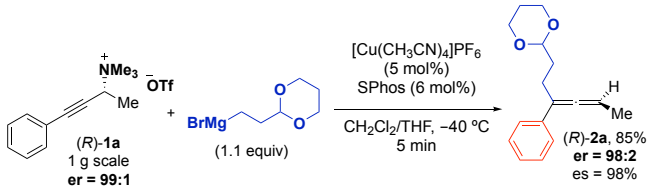
Scheme 3. Stereospecific allene formation[d]



[a]Enantiospecificity (es) = ee-product/ee-starting material X 100%. [b]Starting material er = 99:1. [c]Starting material er = 98:2. [d]Reaction Conditions: **1a** (0.2 mmol, 1.0 equiv.), RMgBr (1.1 equiv. in THF), $Cu(CH_3CN)PF_6$ (5 mol%), CH_2Cl_2 (0.1 M), –40 °C, 5 min. [e]When we used a solution of ^{i}PrMgCl in THF compound (*R*)-**2x** was obtained in 89% yield and er = 97:3. [f]The reaction was carried out at –20 °C.

Moreover, the reaction was carried out at 1 g scale with ammonium salt **1a**, with the same efficiency and levels of chirality transfer (Scheme 4).

Scheme 4. Gram scale synthesis of allene (*R*)-**2a**



We believe the reaction follows the well-accepted mechanism for the copper-catalyzed addition of Grignard reagents to propargylic electrophiles.[3d,3i] Propargylic substrates with good leaving groups are known to afford allenes through a Cu^{III} intermediate **B** (Scheme 5). In our reaction, this intermediate would be formed in an anti S_N2' nucleophilic attack of cuprate **A** to the ammonium salt **1**. From **B**, reductive elimination with retention of the configuration would give the axially chiral allene **2** and organocopper, which would react with a Grignard reagent to regenerate cuprate **A**.

In summary, we have developed a robust and practical method to prepare enantiomerically enriched trisubstituted allenes using alkyl Grignard reagents and bench stable propargylic ammonium salts. Excellent yields as well as regio- and stereoselectivities are observed. The method tolerates functional groups such as esters or cyanides that are not always compatible with the use of Grignard reagents. Importantly, we demonstrate for the first time that the use of an ammonium salt as leaving group allows conditions that prevent racemization of the allene.

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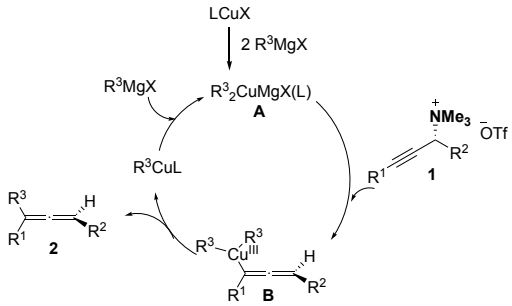
Scheme 5. Proposed mechanism for the stereospecific allene formation



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10 For the stereochemical assignment see Supporting Information.

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12 When we used a solution of ^{i}PrMgCl in Et_2O, compound (*R*)-**2x** was obtained in 26% yield and 90:10 er. We observed low solubility of the ammonium salt in the final CH_2Cl_2/Et_2O solution.

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