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Enantioselective Synthesis of Di- and Tri-Arylated All-Carbon Quaternary Stereocenters via Copper-Catalyzed Allylic Arylations with Organolithium Compounds

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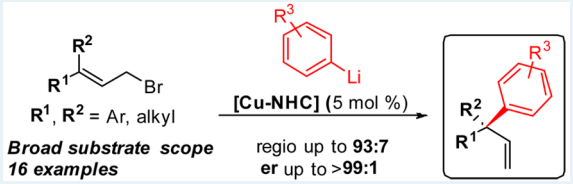
Supporting Information

ABSTRACT: The highly enantioselective copper(I)/N-heterocyclic carbene (NHC) catalyzed synthesis of di- and triarylated all-carbon quaternary stereocenters via asymmetric allylic arylation (AAAr) with aryl organolithium compounds is demonstrated. The use of readily available or easily accessible aryl organolithium reagents in combination with trisubstituted allyl bromides, in the presence of a copper/NHC catalyst, affords important di- and triarylated all-carbon quaternary stereocenters in good yields and enantioselectivities. This method tolerates a wide range of alkyl and substituted aryl groups in the starting allyl bromides, including less common biaryl moieties, which, in combination with diverse organolithium reagents, delivers a broad scope of products in an operationally straightforward and efficient manner.



KEYWORDS: *allylic substitution, enantioselective, copper, N-heterocyclic carbene, quaternary stereocenter, triarylmethane, organolithium*

Catalytic methodologies to form congested all-carbon quaternary stereogenic centers are among the most challenging transformations in organic synthesis.[1] Despite major progress in recent years,[2] new and effective procedures to achieve this transformation are particularly warranted. This holds especially for sterically highly demanding di- and triaryl-substituted quaternary stereocenters, which are important structural units in bioactive compounds such as haplophytine[3a] and diazonamide A.[3b] In particular, triaryl methane structures[4] serve as fluorescent molecules which have applications in cell imaging,[5] selective sensors for metal ions,[6] anticancer agents,[7] and potassium ion channel blockers.[8] Among the protocols reported recently, asymmetric allylic substitution (AAS) reactions have drawn major attention for the construction of these quaternary stereocenters due to the versatility and flexibility of the method.[9] Pioneered by Bäckvall and van Koten in 1995,[10] the AAS with organometallic reagents, catalyzed by copper[11] or other transition metals,[12] has proven to be incredibly effective in its capacity to deliver S_N2'-products with tertiary carbon stereocenters in high yields and enantioselectivities. Via these methods, several useful synthons can be prepared which have been applied in the total synthesis of many natural products or biologically active compounds.[13] However, despite the existence of well-established methods for the construction of tertiary carbon stereocenters, there are remarkably few methods based on AAS for the construction of all-carbon quaternary stereocenters. To the best of our knowledge, only a limited number of reports exist on the use of alkyl organometallic reagents as nucleophiles in allylic substitution forming quaternary stereocenters; these include the use of dialkyl zinc,[14] boron,[15] aluminum,[16] and Grignard reagents.[17] Furthermore, methods using aryl organometallic reagents to prepare all-carbon quaternary stereocenters are scarce despite the fact that chiral diarylmethanes are highly relevant for the synthesis of natural products and pharmaceuticals.[3,18] Importantly, Hoveyda and co-workers succeeded using diaryl zinc[19] and aryl aluminum reagents,[20] derived from the corresponding organolithium reagents, whereas Hayashi and co-workers[21] achieved this transformation using aryl boronic esters, and Sawamura and co-workers[22] very recently applied azoles as nucleophiles (Figure 1a).

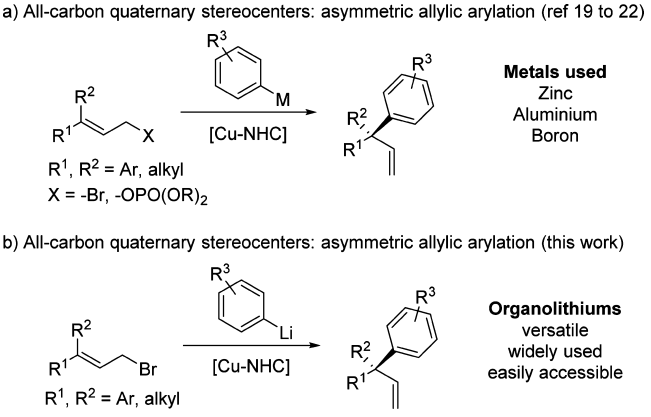


Figure 1. Formation of all-carbon quaternary stereocenters with AAAr.

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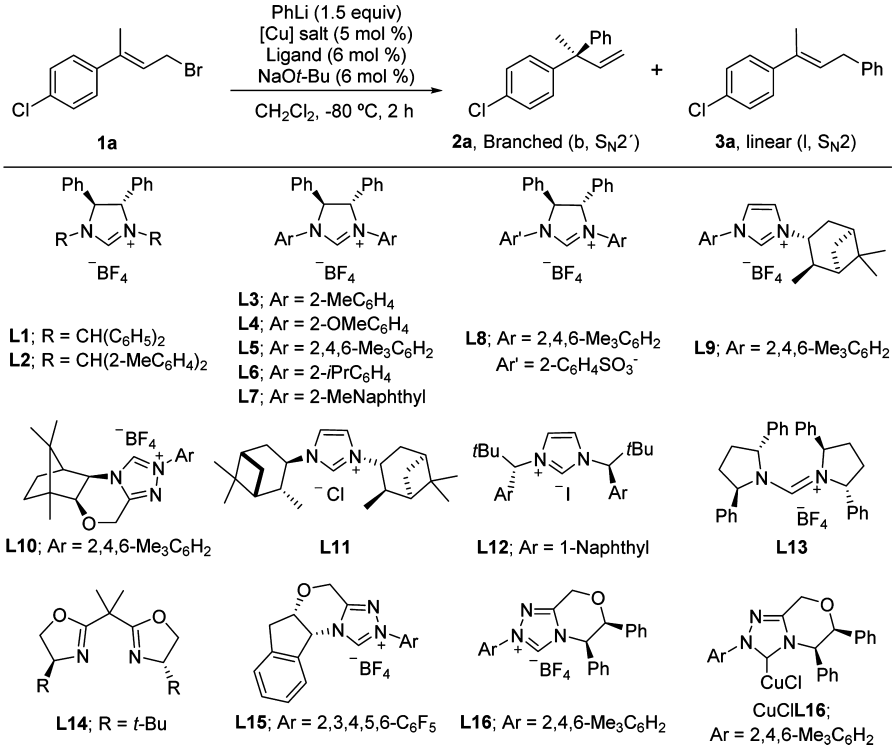
Table 1. Screening of Chiral Ligands[a]



entry	ligand	[Cu]	2a:3a[b]	2a, er[c]
1	**L1**	$CuBr{\cdot}SMe_2$	40:60	50:50
2	**L2**	$CuBr{\cdot}SMe_2$	60:40	50:50
3	**L3**	$CuBr{\cdot}SMe_2$	94:6	58:42
4	**L4**	$CuBr{\cdot}SMe_2$	85:15	54:46
5	**L5**	$CuBr{\cdot}SMe_2$	98:2	62:38
6	**L6**	$CuBr{\cdot}SMe_2$	87:13	67:33
7	**L7**	$CuBr{\cdot}SMe_2$	96:4	55:45
8	**L8**	$CuBr{\cdot}SMe_2$	44:56	n.d.
9	**L9**	$CuBr{\cdot}SMe_2$	87:13	75:25
10	**L10**	$CuBr{\cdot}SMe_2$	80:20	72:28
11	**L11**	$CuBr{\cdot}SMe_2$	44:56	55:45
12	**L12**	$CuBr{\cdot}SMe_2$	37:63	n.d.
13	**L13**	$CuBr{\cdot}SMe_2$	28:72	n.d.
14	**L14**	$CuBr{\cdot}SMe_2$	10:90	n.d.
15	**L15**	$CuBr{\cdot}SMe_2$	15:85	n.d.
16	**L16**	$CuBr{\cdot}SMe_2$	75:25 (62%)[d]	97:3
17	CuCl**L16**		72:28 (61%)[d]	97:3

[a]Conditions: Allyl bromide (0.2 mmol) in CH_2Cl_2 (2 mL). PhLi (0.3 mmol, 1.8 M solution in dibutyl ether diluted with hexane to a final concentration of 0.3 M) was added over 2 h. All reactions gave full conversion. [b]**2a**/**3a** ratios and conversions determined by GC−MS and ^{1}H NMR spectroscopy. [c]Determined by chiral HPLC after conversion to the corresponding primary alcohol using a hydroboration−oxidation procedure (see SI). [d]Isolated yield of **2a**.

In recent years, our group has reported a number of alternative AAS reactions combining highly reactive alkyl organolithium reagents as nucleophiles with allyl bromides or allyl ethers as electrophiles in the presence of a Cu(I)L catalytic system (L = Taniaphos or phosphoramidite) to achieve the formation of tertiary carbon stereocenters with excellent regio- and enantioselectivites.[13j,23] We extended this protocol, again with alkyl organolithium reagents, to synthesize quaternary all-carbon stereocenters with good to high regio- and enantioselectivites.[24] Early this year, we reported that the stereoselective formation of tertiary stereocenters via AAS could also be achieved with usually less-reactive aryl organolithium reagents in high regio- and very high enantioselectivities by switching to a Cu(I)-NHC catalytic system.[18e] Aryl lithium reagents have the important advantage, compared to many other organometallic species, of being either commercially available or very easy to prepare, even more so than their alkyl counterparts. They can be readily accessed in various ways such as metal−halogen exchange, direct metalation, or ortho-metalation.[25] Due to the advantage of their ready availability, these lithium reagents often serve as precursors for other commonly used organometallic reagents.

Here, we report the first regio- and enantioselective Cu(I)-catalyzed asymmetric allylic arylation (Cu-AAAr) of trisub-

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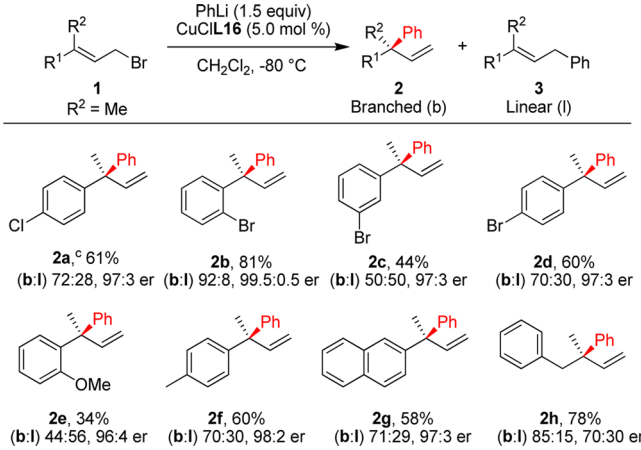
stituted allyl bromides using aryl organolithium compounds as nucleophiles to yield di- and triarylated quaternary all-carbon stereocenters with high regio- and very high enantioselectivities (S_N2': S_N2 up to 93:7, up to >99:1 er).

We started our investigation of this transformation with trisubstituted allyl bromide **1a** as model electrophile and commercially available PhLi as nucleophile in the presence of a catalytic amount of CuBr·SMe_2 and chiral imidazolium salts (Table 1).[18e] When a solution of PhLi diluted in *n*-hexane was added over 2 h to an in situ-generated Cu(I)-NHC complex (**L1** or **L2**, 5 mol %) and allyl bromide in dry CH_2Cl_2 at −80 °C, we observed the chemoselective formation of desired S_N2'-product **2a** as a roughly equimolar mixture with the corresponding regioisomeric S_N2-product **3a**. While imidazolium salts **L1** and **L2** had proven to be most suitable in the Cu-AAAr reaction to synthesize tertiary carbon stereocenters with aryl organolithium reagents,[18e] these chiral ligands did not lead to satisfactory results for quaternary centers as both branched and linear products were observed (entries 1 and 2, Table 1). We therefore pursued our investigation by screening for a more suitable carbene ligand. Salts **L3** and **L4** bearing *o*-tolyl or *o*-anisole groups on the two carbene nitrogens gave high regioselectivity (94:6 and 85:15) but almost no enantioselectivity (entries 3 and 4). Imidazolium salts bearing even bulkier substituents such as 2,4,6-$Me_3C_6H_2$ (**L5**) or 2-*i*-PrC_6H_4 (**L6**) led to even higher regioselectivites (98:2 and 87:13), but only slightly better enantioselectivities (up to 67:33 er, entries 5 and 6). Similarly bulky substituent 2-MeNaphthyl **L7** also gave high regio- and poor enantioselectivity (entry 7). In order to improve the enantioselectivity, we turned our attention to bifunctional ligands such as **L8**. However, this led to a drop in regioselectivity, which was attributed to the addition of PhLi to the sulfonate group (entry 8). Moving from saturated imidazolium salts to unsaturated salts such as **L9** and **L10** led to a significant improvement in enantioselectivity (up to 75:25 er) while retaining good regioselectivity (up to 87:13, entries 9 and 10). Building on this promising regio- and enantioselectivity, we continued to screen different unsaturated chiral imidazolium salts. Disappointingly, increasing sterics like in bulky ligand precursors **L11** and **L12** resulted in very poor regio- and enantioselectivities (entries 11 and 12) while noncyclic carbene precursor **L13** or C_2-symmetric chiral bisoxazoline **L14** led to reversals in branched to linear selectivity (entries 13 and 14). It was decided to switch carbene backbones altogether and test the activity of triazolium salts. While **L15** again did not lead to satisfying results (entry 15), we were pleased to find that triazolium salt **L16** gave **2a** in 62% isolated yield with not only improved regioselectivity (75:25) but also excellent enantioselectivity of 97:3 er (entry 16). In order to simplify the protocol, we tested the in principle equivalent preformed copper complex **CuClL16** in the reaction which gave identical results to the in situ-formed catalyst (entry 17).

Having optimized conditions in hand, we investigated the substrate scope of the reaction of allyl bromides **1** with PhLi using chiral N-heterocyclic carbene complex **CuClL16** as catalyst. First, the substitution at the aryl R^1 position was varied while maintaining the alkyl R^2 moiety as a methyl substituent in combination with PhLi as a nucleophile (Table 2). Substrates **1b**, **1c**, and **1d**, bearing a bromide at the ortho, meta, or para positions of the aromatic ring, respectively, gave the desired products **2b**, **2c**, and **2d** (Table 2) with excellent enantioselectivites (97:3 to >99:1 er) and, with a few

Table 2. Substrate Scope[a,b]



[a]Conditions: Allyl bromide **1** (0.2 mmol) in CH_2Cl_2 (2 mL). PhLi (0.3 mmol, 1.8 M solution in dibutyl ether diluted with hexane to a final concentration of 0.3 M) was added over 2 h. All reactions gave full conversion. **2**/**3** ratios and conversions determined by GC−MS and ^{1}H NMR spectroscopy. The er was determined by chiral HPLC after conversion to the corresponding primary alcohol using a hydroboration−oxidation procedure (see SI). [b]Isolated yield of S_N2' product. [c]The absolute configuration of **2a** was assigned by comparing the sign of the optical rotation with the literature value (ref 21).

exceptions, moderate to good regioselectivities (70:30 to 92:8). The catalytic conversion also displayed high chemoselectivity, with no competing side reactions such as substitution or lithium−halogen exchange observed. Notably, exceptionally high regio- and enantioselectivity was obtained when using ortho-bromo substituted **1b** (99.5:0.5 er); this may be due to further halogen bonding interaction with the catalyst. In contrast, substrate **1e** bearing an *o*-methoxy substituent led to product **2e** with high enantioselectivity but with decreased regioselectivity. Substrates having either a *p*-methyl substituent (**1f**) or an extended conjugated system (**1g**) also gave the corresponding products **2f** and **2g** with good regio- and high enantioselectivity. Moving from cinnamyl type substrates to non cinnamyl allyl bromide **1h** led to **2h** (Table 2) with good regio- but moderate enantioselectivity.

We examined the substituent effect of the group R on the γ-position of the allyl bromide **1** using *p*-MeC_6H_4Li as a nucleophile on four different substrates (Table 3). Substrates **1i** and**1j** bearing methyl and ethyl substituents at the γ-position led to the desired products **2i** and **2j** (Table 3) with almost similar results in terms of regio- and enantioselectivity to model substrate **1a**. Substrate **1k** bearing a more sterically demanding *i*-propyl substituent at the γ-position gave the product **2k** with similar regioselectivity to **2i** and **2j** but with moderate enantioselectivity (68:32 er). Having a phenyl substituent at the γ-position of the substrate (**1l**) allowed us to synthesize a rare chiral triaryl methane product **2l** with three different aromatic groups and a synthetically flexible vinyl group in 34% isolated yield with good enantioselectivity (Table 3). Chiral all-carbon quaternary triarylmethane moieties are highly valuable, but as far as we know, very few methods exist for their synthesis.[4]

Finally, we studied the scope of the reaction in terms of the aryl lithium partner under our standard conditions. These were readily prepared by adapting previously reported procedures[18e] and were tested on substrate **1b** (Table 4). Fully deuterated

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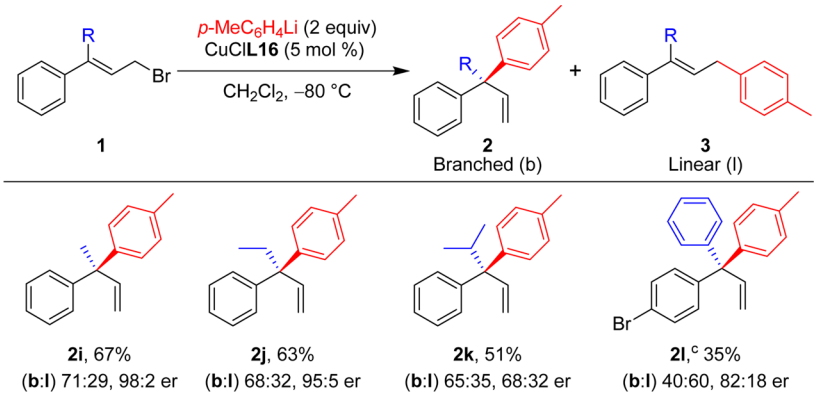
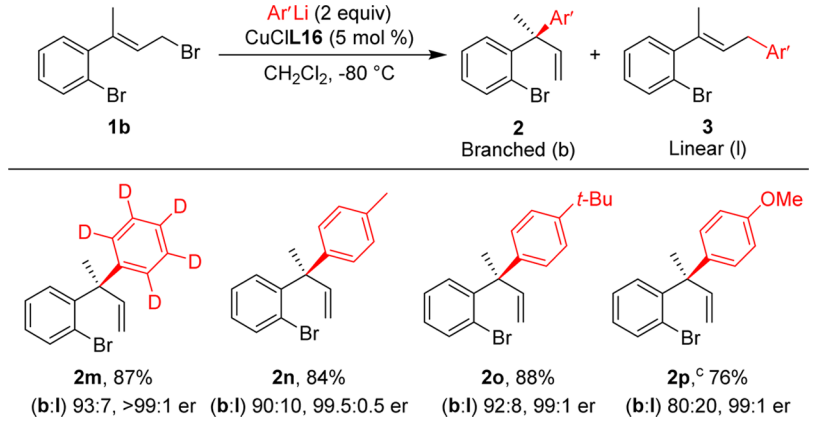
Table 3. Effect of γ-Substituent[a,b]



[a]Conditions: Allyl bromide (0.2 mmol) in CH_2Cl_2 (2 mL). *p*-MeC_6H_4Li (0.4 mmol) was diluted with hexane to a final concentration of 0.4 M and was added over 2 h. **2a**/**3a** ratios and conversions determined by GC–MS and ^1H NMR spectroscopy. The er was determined by chiral HPLC after conversion to the corresponding primary alcohol using a hydroboration–oxidation procedure (see SI). [b]Isolated yield of S_N2' product. [c]10 mol % of CuClL**16** was used.

Table 4. Scope of Aryl lithium Compounds[a,b]



[a]Conditions: Allyl bromide (0.2 mmol) in CH_2Cl_2 (2 mL). Ar′Li (0.4 mmol) was diluted with hexane to a final concentration of 0.4 M and was added over 2 h. All reactions gave full conversion. **2**/**3** ratios and conversions determined by GC–MS and ^1H NMR spectroscopy. The er was determined by chiral HPLC after conversion to the corresponding primary alcohol using a hydroboration–oxidation procedure (see SI). [b]Isolated yield of S_N2' product. [c]10 mol % of CuClL**16** was used and *p*-$OMeC_6H_4Li$ was diluted in toluene.

PhLi gave the desired product **2m** with high regio- (93:7) and excellent enantioselectivity (>99:1 er). Adding diverse alkyl substituents at the para position of the aryl lithium did not affect the outcome of the reaction and gave products **2n** and **2o** with very high regio- and enantioselectivities. Electron-rich *p*-methoxy substituted aryl lithium gave product **2p** without any decrease in enantioselectivity but with slightly lower regioselectivity.

In summary, a highly enantioselective synthesis of quaternary all-carbon stereocenters via Cu-catalyzed direct allylic arylation using organolithium compounds is reported. A Cu(I)-NHC catalytic system proved to be essential for this transformation and allowed the preparation of a wide range of di- and triarylated vinyl methane compounds with good to excellent enantioselectivites. This transformation is also highly atom economical as LiBr is the only stoichiometric waste during this transformation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b01681.

Experimental details and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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