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Chiral Diarylmethanes via Copper-Catalyzed Asymmetric Allylic Arylation with Organolithium Compounds

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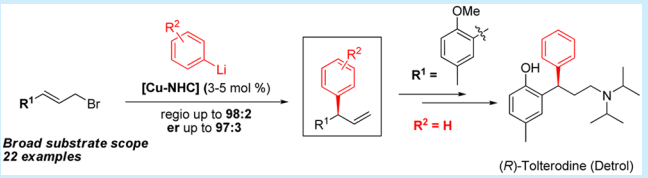
Supporting Information

ABSTRACT: A highly enantioselective copper/*N*-heterocyclic carbene catalyzed allylic arylation with organolithium compounds is presented. The use of commercial or readily prepared aryllithium reagents in the reaction with allyl bromides affords a variety of chiral diarylvinylmethanes, comprising a privileged structural motif in pharmaceuticals, in high yields with good to excellent regio- and enantioselectivities. The versatility of this new transformation is illustrated in the formal synthesis of the marketed drug tolterodine (Detrol).



The enantioselective synthesis of diarylmethane tertiary stereogenic centers, a structural motif that is present in many natural products and pharmaceuticals, has attracted considerable attention in recent years.[1] Examples of compounds bearing this subunit include podofilox (Condylox),[1b] nomifensine, CDP-840,[1c] (+)-sertraline (Zoloft),[1d] and (*R*)-tolterodine,[1e] the latter being a drug with blockbuster status. Catalytic asymmetric synthesis methods to access these compounds comprise both stereospecific and enantioselective transformations.[2−7,10] The first approaches, based on chiral starting materials, include a nickel-catalyzed cross-coupling of 1,1-diaryl ethers described by the group of Jarvo[3a] and a stereoretentive rhodium-catalyzed decarbonylation of enantioenriched *β*,*β*-diarylpropionaldehydes reported by the group of Carreira.[3b] Catalytic enantioselective strategies include Friedel−Crafts reactions,[4a] iridium-catalyzed asymmetric hydrogenation of 1,1-diarylalkenes,[4b,c] a cooperative rhodium/phosphoric acid-catalyzed asymmetric arylation of *α*-aryl-*α*-diazo compounds with aniline derivates,[4d] and a copper-catalyzed enantioselective electrophilic arylation of allylic amides with diaryliodonium salts.[4e] Another attractive approach has been reported by Fu and co-workers, where racemic benzylic alcohols were converted into 1,1-diarylalkanes using an enantioselective nickel-catalyzed cross-coupling protocol.[4f]

Transition-metal-catalyzed 1,4-addition of organoboron compounds to substituted electron-deficient styrenes has also been shown to be effective in accessing this structural motif, in particular using a rhodium-based catalyst.[5] Additionally, the catalytic enantiotopic group selective cross-coupling of achiral geminal bis(pinacolboronates)[6] and the recently developed additions of malonates[7a] or boron reagents[7b,c] to quinone methides provide useful chiral *gem*-diarylmethines and boronic esters derivates.

Diarylmethane stereogenic centers can also be accessed via metal-catalyzed arylation of aryl-substituted allyl electrophiles using organometallic reagents.[2a,8d−g] We envisioned that an asymmetric allylic arylation (AAAr) with highly reactive aryllithium reagents, as presented here, would provide a viable and attractive alternative to access these chiral structures. In the case of copper, the use of the corresponding alkyl nucleophiles has been well established, and AAA reactions of a wide range of alkyl metal reagents and allylic systems have been reported.[8a−e,9] In contrast, the introduction of less reactive aryl groups continues to provide major challenges, and several groups embarked on the development of a general and efficient catalytic system for the formation of chiral diarylmethanes based on this transformation.[10] High regio- and enantioselectivity was demonstrated by Hoveyda and co-workers using chiral bidentate *N*-heterocyclic carbenes (NHC) for the AAAr with aryldialkylaluminum reagents,[10a] derived from the corresponding organolithium compounds. Bidentate NHC have also been employed by the group of Hayashi in the allylic substitution with less reactive arylboronates and allyl phosphates.[10b,c] Additionally, aryl Grignard reagents have been employed by Tomioka and co-workers using chiral monodentate *N*-heterocyclic carbenes.[10d,e]

Recently, we reported that organolithium compounds, among the most widely used reagents in organic synthesis, can be directly used as nucleophiles in copper-catalyzed AAA with a variety of allyl systems.[11] The use of Taniaphos or monodentate phosphoramidites as chiral ligands in dichloromethane and *n*-hexane as solvent and cosolvent, allowed us to control the high reactivity of these compounds and obtain excellent regio- and enantioselectivities in AAA reactions. Disappointingly, the reaction with PhLi under these conditions consistently led to poor regioselectivities.[11a] As aryllithium compounds are commercially available or readily accessible by lithium−halogen exchange[12] and, moreover, they are often employed as precursors

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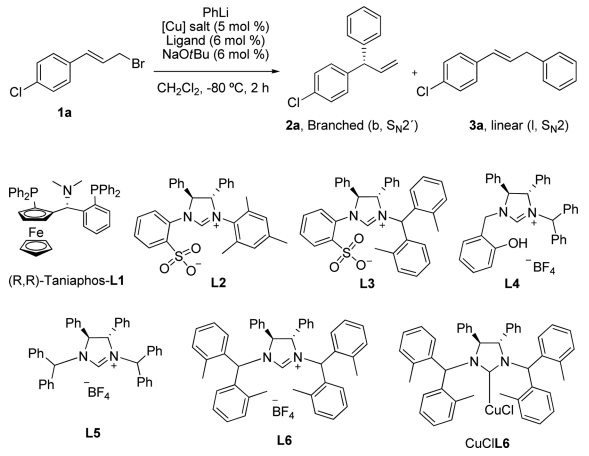
for other organometallic compounds (Al, B, Zn), the development of a general AAAr method using these reagents is highly desirable.

Herein, we report the first regio- and enantioselective method for the copper-catalyzed AAAr with aryllithium compounds to afford optically active diarylvinylmethanes with excellent regio- and enantioselectivities ($S_N2':S_N2$ up to 98:2, er up to 97:3).

The reaction between allyl bromide **1a** and commercially available PhLi, in the presence of catalytic amounts of CuBr·SMe_2 and chiral ligands, was used for the initial optimization (Table 1).[11a] PhLi was diluted with hexane and added over 2 h to a solution of allyl bromide in CH_2Cl_2 at −80 °C. As the use of chiral phosphorus ligands, which provided high selectivity for alkyllithium reagents,[11] did not lead to satisfactory results (entry 1, Table 1 and results not shown), we decided to evaluate a series of strong σ-donating NHCs. The use of chiral bidentate NHC−Cu catalysts, in situ prepared by deprotonating imidazolinium salt **L2**[10a] and structurally related imidazolinium salts **L3** and **L4**, led to low or moderate regioselectivities (entries 2−4, Table 1).[13] We then examined sterically demanding chiral monodentate NHC ligands, and an improved regio- and good enantioselectivity were observed when the catalyst derived from imidazolinium salt **L5**[10d] was used (entry 5, Table 1). To our delight, the catalyst derived from **L6**, having *o*-tolyl moieties, led to a major increase in regioselectivity toward the branched product **2a** (b,l = 97:3) with excellent enantioselectivity (97:3 er, entry 6). A possible rationale is that the use of bulkier aryl substituents on the N atoms enhances the reductive elimination step favoring the S_N2' product.[14] Importantly, the isolated air-stable CuCl−NHC complex derived from **L6** gave the same result, avoiding the use of NaO*t*Bu and simplifying the procedure (entry 7).

Table 1. Screening of Different Ligands[a]

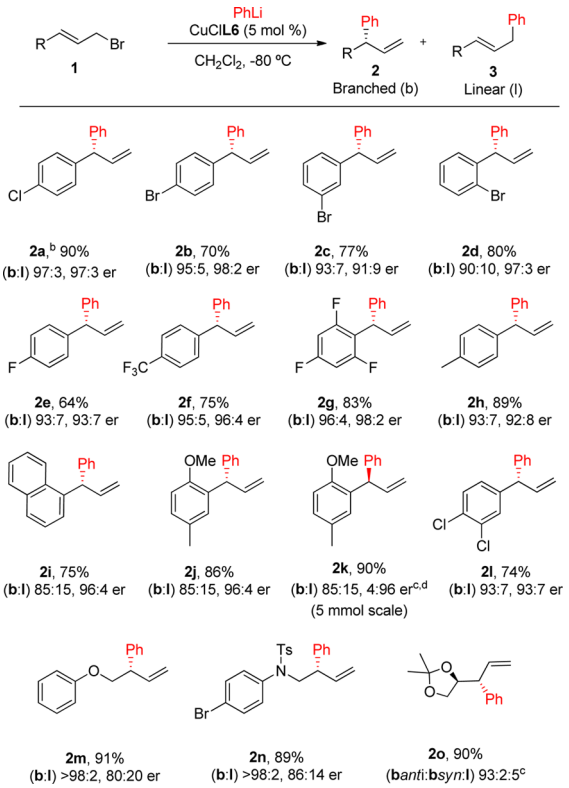


entry	L	[Cu]	2a:3a[b]	2a, er[c]
1	**L1**	CuBr·SMe_2	10:90	n.d.
2	**L2**	CuBr·SMe_2	70:30	n.d.
3	**L3**	CuBr·SMe_2	47:53	n.d.
4	**L4**	CuBr·SMe_2	37:63	n.d.
5	**L5**	CuBr·SMe_2	63:37	94:6
6	**L6**	CuBr·SMe_2	97:3	97:3
7	CuCl**L6**		97:3	97:3

[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 0.4 M) 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 the SI).

Having established optimal conditions, we next investigated the substrate scope and generality of this arylation reaction by using PhLi; the results are summarized in Scheme 1.

Scheme 1. Substrate Scope for the Cu-Catalyzed Enantioselective Allylic Arylation[a]



[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 0.4 M) added over 2 h. All reactions gave full conversion. **2**/**3** ratios and conversions determined by GC−MS and ^{1}H NMR spectroscopy. Er determined by chiral HPLC after conversion to the corresponding primary alcohol using a hydroboration−oxidation procedure (see the SI). [b]The absolute configuration of **2a** was assigned by comparing the sign of the optical rotation with the literature value (ref 10d). [c](4*R*,5*R*)-**L6** was used instead. [d]5 mmol (1.2 g) scale reaction using 3 mol % of catalyst.

The presence of chloro or bromo substituents at the aromatic ring of the substrate were well tolerated, affording the corresponding diarylvinylmethanes in high yields and selectivities and providing synthetically useful functionalities for further transformations (**2a**−**d**). Importantly, no evidence of lithium−halogen exchange was observed, highlighting the high chemoselectivity of the reaction. Trifluoromethylated and fluorinated compounds, which are very important in the agrochemical and pharmaceutical industries,[15] were also suitable substrates furnishing the corresponding *gem*-biaryl products with excellent selectivities (**2e**−**g**). High selectivities were also obtained when electron-donating substituents (**1h**, **1j**, and **1k**) or sterically demanding substrates such as 1-naphthyl-substituted allyl bromide (**1i**) or compounds **1j** and **1k** were used with this Cu−NHC-based catalyst system. Arylation of compound **1l** was accomplished with good regio- and enantioselectivity, providing **2l**, which is an advanced intermediate in the synthesis of

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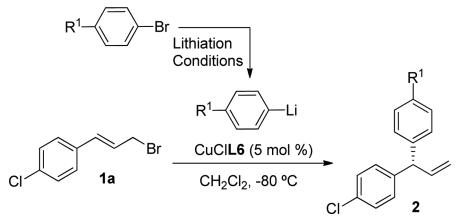
sertraline,[10d] a major pharmaceutical for the treatment of depression. Compound **2k** bearing *m*-methyl and *o*-methoxy substituents at the aryl ring was also prepared with excellent regio- (97:3) and enantioselectivity (96:4) serving as precursor for the synthesis of (*R*)-tolterodine (see below). Importantly, when this reaction was performed on a larger scale (5 mmol, 1.2 g), using a lower catalyst loading (3 mol %), product **2k** was still obtained with the same selectivities without erosion of yield. Allylic bromides bearing a phenol ether or protected amine provided highly functionalized chiral building blocks **2m** and **2n**, with excellent yields and regioselectivity although the enantioselectivity decreased slightly. The use of a dioxolane-containing allylic bromide **1o** led to the diastereoselective formation of valuable 1,2-hydroxyallyl moiety **2o** with excellent stereocontrol for the *anti*-isomer.[16]

We next explored the scope of the reaction with respect to the aryllithium component using **1a** as the electrophilic counterpart. However, to our surprise, no conversion was observed when *p*-tolyllithium or (*p*-methoxyphenyl)lithium solutions, prepared in THF via bromide−lithium exchange using *t*-BuLi, were employed in the reaction under previously optimized conditions (entries 1 and 2, Table 2).

Table 2. Screening of Different Conditions for the Preparation of Reactive Homemade Aryllithium Compounds[a]

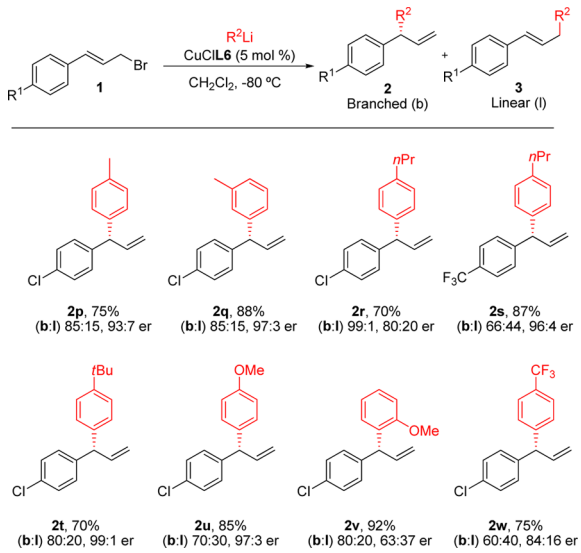


entry	R^1	lithiation cond (final conc, M)	conv (%)/**2**:**3**, **2a** er
1	OMe	*t*-BuLi, −30 °C to rt, 1 h 1:2 THF/pentane (0.57)	0
2	Me	*t*-BuLi, −30 °C to rt, 1 h 1:2 THF/pentane (0.57)	0
3	Me	*t*-BuLi, −30 °C to rt, 1 h 1:2 Et_2O/pentane (0.57)	0
4	Me	Li, Et_2O, rt, 2 h (1.5)	0
5[b]	Me	Li, Et_2O, rt, 2 h (1.5)	47/95:5
6	Me	*n*-BuLi, −30 °C to rt, 1 h 4:3 Et_2O/hexane (0.69)	>99/85:15, **2a** 97:3

[a]Conditions: allyl bromide (0.2 mmol) in CH_2Cl_2 (2 mL). RLi (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 ^{1}H NMR spectroscopy. Er determined by chiral HPLC after conversion to the corresponding primary alcohol using a hydroboration−oxidation procedure (see the SI). [b]1-Chloro-4-methylbenzene was used instead.

Changing THF to less coordinating Et_2O as solvent led to the same result (entry 3, Table 2). As the use of *t*-BuLi to effect lithium−halogen exchange generates 1 equiv of 2-methylpropene, which may coordinatively interfere with the Cu catalyst, we decided to use a different method for the lithiation. Lithium metal[17] in combination with *p*-bromotoluene was still unsatisfactory, although the use of *p*-chlorotoluene allowed us to reach 47% conversion in the corresponding AAAr reaction (entry 5). Finally, we found that the use of *n*-BuLi and Et_2O as solvent, which avoids S_N2 reaction[18] of the resulting ArLi and *n*-BuBr, allowed us to obtain the desired product with full conversion and high regio- and enantioselectivity (entry 6, Table 2, and **2p**, Scheme 2). Under these conditions, aryllithiums bearing

Scheme 2. Scope of Aryllithium Compounds[a]

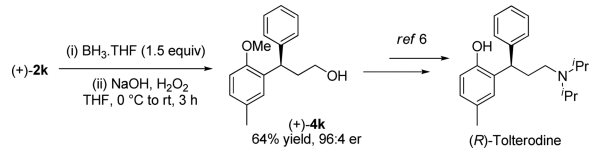


[a]Conditions: allyl bromide (0.2 mmol) in CH_2Cl_2 (2 mL). R^2Li (0.4 mmol) was diluted with hexane to a final concentration of 0.4 M and added over 2 h. All reactions gave full conversion. **2**/**3** ratios and conversions determined by GC−MS and ^{1}H NMR spectroscopy. Er determined by chiral HPLC after conversion to the corresponding primary alcohol using a hydroboration−oxidation procedure (see the SI).

electron-donating methoxy- and alkyl groups as well as electron-withdrawing $-CF_3$ substituents participate in the reactions with allyl bromides **1a**,**f** in good to excellent yields and regio- and enantioselectivities (Scheme 2). A limitation found for this Cu−NHC-based catalytic system is that the use of *o*-methoxy-substituted phenyllithium suffered from diminished enantioselectivity as seen for compound **2v**.

To finally demonstrate the efficiency and applicability of the present methodology, we performed the synthesis of chiral alcohol **4k**,[6] a precursor of (*R*)-tolterodine (Detrol). Here, the catalytic allylic arylation of **2k** with phenyllithium is followed by a one-pot hydroboration−oxidation to afford advanced intermediate **4k** in 64% yield (96:4 er) (Scheme 3). (*R*)-Tolterodine is a potent competitive muscarine receptor antagonist for the treatment of urinary incontinence and cystitis.[1e]

Scheme 3. Conversion of (*R*)-2k into (*R*)-4k, a Synthetic Intermediate of Tolterodine



In summary, the highly enantioselective Cu-catalyzed direct allylic arylation using organolithium compounds has been described. The use of readily available aryllithium reagents in combination with allyl bromides and use of a copper−NHC catalyst are key factors for the success of this reaction. The only stoichiometric waste produced in this novel transformation is LiBr. The use of *n*-BuLi was found to be essential for the

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preparation of aryllithium compounds. The broad substrate and reagent scope and the application of the new method in the formal catalytic enantioselective synthesis of (*R*)-tolterodine illustrates the potential of this allylic arylation for the synthesis of important chiral diarylmethane structures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03396.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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