Enantioselective Catalysis

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Quaternary Carbon Stereogenic Centers through Copper-Catalyzed Enantioselective Allylic Substitutions with Readily Accessible Aryl- or Heteroaryllithium Reagents and Aluminum Chlorides**

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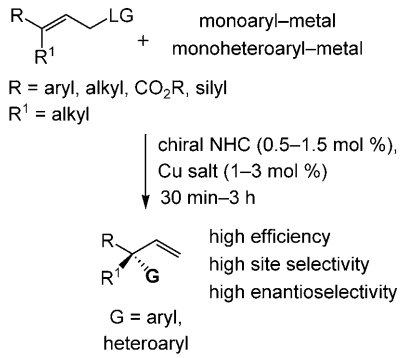
Catalytic enantioselective allylic substitution (EAS) reactions[1] are among the most versatile classes of transformations in organic chemistry: such processes convert readily available achiral substrates to enantiomerically enriched products bearing a stereogenic center adjacent to a readily functionalizable alkene. We have devised chiral amino acid-based[2] and bidentate N-heterocyclic carbene (NHC) Cu complexes[3] that promote EAS processes with dialkylzinc reagents and generate quaternary carbon stereogenic centers[4] with high site- and enantioselectivity. Catalytic enantioselective Cu-free additions of alkylmagnesium halides to allylic halides,[5] as well as dialkylzinc and trialkylaluminum reagents[6] to phosphates, have also been developed. Nonetheless, significant and compelling problems remain unaddressed. Catalytic EAS transformations involving aryl nucleophiles and which deliver quaternary carbon centers are notoriously scarce, and protocols that involve heteroarylmetals do not exist (including those that furnish tertiary C–C bonds). The only reported cases of aryl additions by catalytic EAS that generate quaternary carbons correspond to Si-substituted alkenes and involve diarylzinc reagents,[7] which are relatively difficult to prepare in high purity and offer only one of the two aryl units. Such considerations underline a shortcoming in the state-of-the-art: the absence of EAS methods that deliver quaternary carbon stereogenic centers through reactions with monoaryl–metal reagents, in particular those that are easily accessible and atom-economical.[1]

Herein, we introduce the first set of efficient catalytic EAS processes that involve the use of aryllithium or heteroaryllithium reagents and generate quaternary carbon stereogenic centers (Scheme 1). Reactions proceed with exceptional site- (up to $>98\%$ S_N2') and high enantioselectivity (up to $>98{:}2$ e.r.); transformations are complete within three hours with ≤ 3.0 mol% of a chiral NHC–Cu complex derived from commercially available and air-stable $CuCl_2 \cdot 2H_2O$.



Scheme 1. Practical, site- and enantioselective synthesis of versatile small molecules with an allylic all-carbon quaternary stereogenic center by Cu-catalyzed allylic substitutions through the use of monoaryl- or monoheteroaryl–metal reagents; LG = leaving group.

We began by developing a protocol that only requires aryllithium reagents, and decided to take advantage of the higher propensity of an aryl unit of an (aryl)dialkylaluminum to transfer to copper;[8] reaction of an aryllithium with a commercially available and inexpensive dialkylaluminum halide would deliver the desired reagent.[9] Thus, EAS with phenyl(diethyl)aluminum, synthesized and used in situ from phenyllithium, and allylic phosphate **5** was investigated (Table 1). The ability of four representative chiral NHC–Cu complexes, obtained from bidentate **1** and **2a**[10] and monodentate **3** and **4**,[11] to promote the C–C bond-forming processes was examined. Initial studies indicated that, although all reactions proceed efficiently (Ph/Et transfer $>98{:}2$), the Cu complex derived from sulfonate-bearing **2a** furnishes the highest site- and enantioselectivity.[12] It should be noted that PhMgCl can also be used to access **6** with similar efficiency and selectivity ($>98\%$ conv., $>98\%$ S_N2', 89.5:10.5 e.r.).[13] Reaction of the Grignard reagent with Et_2AlCl is performed in dioxane so that residual magnesium halide ($MgCl_2$·dioxane) can be removed.[14]

An assortment of aryllithium reagents, either purchased or prepared by well-established procedures through metal–halogen exchange with the corresponding bromides, can be used in site-selective ($>98\%$ S_N2'), efficient (81–98% yield) and enantioselective reactions (Table 2).[15] Cu-catalyzed additions with α,β-unsaturated esters (entries 1–4, Table 2) afford the EAS product in up to 91.5:8.5 e.r.; reactions with Si-substituted allylic phosphates deliver the desired allylsilanes in up to 97:3 e.r. (entries 5 and 6, Table 2). All transformations proceed with $>98\%$ S_N2' selectivity. The reactions

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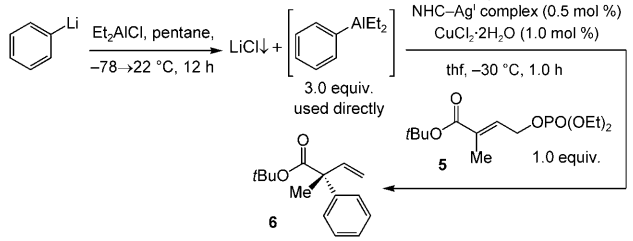
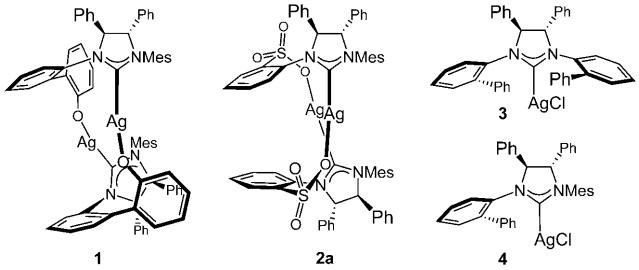
Table 1: Initial examination of various chiral NHC complexes.[a]



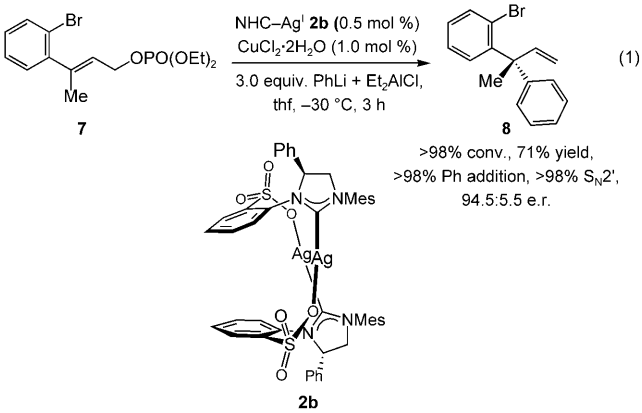
Entry	NHC–Ag^I	Ph/Et addition[b]	S_N2'/S_N2[b]	e.r.[c]
1	**1**	>98:2	>98:2	86:14
2	**2a**	>98:2	>98:2	91:9
3	**3**	>98:2	56:44	89:11
4	**4**	>98:2	83:17	58:42

[a] Reactions were performed under N_2 atmosphere; >98% conversion in all cases. [b] Determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures. [c] Determined by GLC analysis; see the Supporting Information for details.



in entries 5 and 6, affording Si-substituted quaternary carbons, are substantially more efficient than those previously reported involving diarylzincs.[3c] For example, with $(p\text{OMeC}_6\text{H}_4)_2\text{Zn}$, 2.5 mol% **2a** and 24 h of reaction time are needed (vs. 1.0 mol% and 3 h needed in entry 6), and the desired product is isolated in 88:12 e.r. (vs. 97:3 e.r. with the arylaluminum reagent). Furthermore, the $(\text{CuOTf})_2\cdot\text{C}_6\text{H}_6$ salt required for reactions with diarylzincs must be handled under rigorously inert conditions as opposed to the air-stable $\text{CuCl}_2\cdot 2\,\text{H}_2\text{O}$ utilized here.

Although the products obtained through the transformations shown in Table 2 can, in principle, be accessed by reactions of the related aryl-substituted substrates with alkylmetal reagents, such processes remain largely unexplored (the only reported variant involves dialkylzinc reagents[2d]). Regardless of impending future developments, diaryl-substituted products, such as **8** [Eq. (1)], can be most

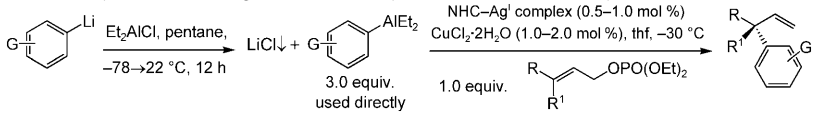


(1)

easily accessed by an effective catalytic arylmetal addition. Another notable feature of the Cu-catalyzed EAS in Equation (1) is that a higher enantiomeric purity is obtained with modified complex **2b**; when **2a** is used in the latter instance, 26% ethyl addition product is observed (vs. <2% with **2b**) and **8** is formed in 90:10 e.r. Similarly, the EAS in entry 4 of Table 2 requires complex **1**, since with **2a**, the desired product is isolated in 78.5:21.5 e.r. (vs. 83:17 e.r.).

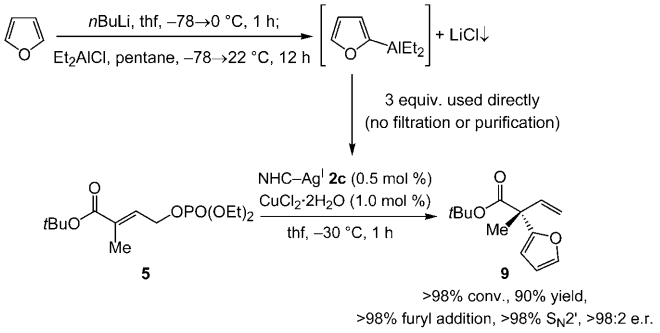
Next, we probed the possibility of catalytic enantioselective additions of heterocyclic units. Efficient and site-selective deprotonation of furan (Scheme 2) can be followed by subjection of the resulting 2-(furyl)lithium to Et_2AlCl to afford (2-furyl)Al(Et)_2. The resulting heteroarylaluminum can be utilized without isolation or purification in a highly group- (<2% Et addition), site- (>98% S_N2') and enantioselective (>98:2 e.r.) process, converting allylic phosphate **5** to α-furyl ester **9** within 1 hour with 0.5 mol% **2c**. When **2a** is utilized in this case, **9** is obtained with equally high efficiency and site-selectivity (>98% conv., >98% S_N2', >98% furyl

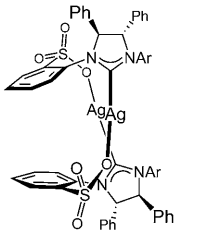
Table 2: Synthesis and in situ use of arylaluminum reagents in Cu-catalyzed enantioselective allylic substitution reactions.[a]



Entry	Aryllithium	Substrate (R; R^1)	NHC–Ag^I [mol%]	t [h]	S_N2'/S_N2[b]	Yield [%][c]	e.r.[d]
1	PhLi	CO_2tBu; Me	**2a**; 0.5	0.5	>98:2	98	91:9
2	PhLi	CO_2tBu; Et	**2a**; 0.5	3.0	>98:2	96	91.5:8.5
3	$p\text{OMeC}_6\text{H}_4\text{Li}$	CO_2tBu; Me	**2a**; 0.5	1.0	>98:2	87	90.5:9.5
4	$p\text{CF}_3\text{C}_6\text{H}_4\text{Li}$	CO_2tBu; Me	**1**; 0.75	1.5	>98:2	88	83:17
5	PhLi	$SiMe_2$Ph; Me	**2a**; 1.0	3.0	>98:2	81	96:4
6	$p\text{OMeC}_6\text{H}_4\text{Li}$	$SiMe_2$Ph; Me	**2a**; 1.0	3.0	>98:2	97	97:3

[a] Reactions were performed under N_2 atmosphere; >98% conversion in all cases. [b] Determined through analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures. [c] Yields of isolated purified products. [d] Determined by GLC or HPLC analysis; see the Supporting Information for details.



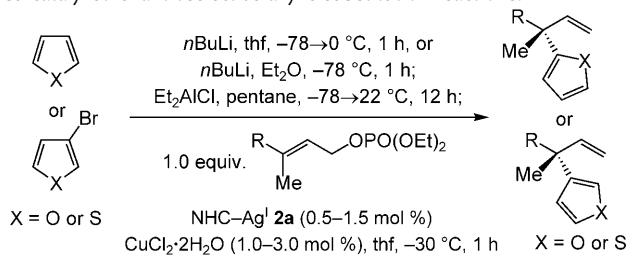


Scheme 2. Synthesis and in situ utilization of (2-furyl)$AlEt_2$ in a highly group-, site- and enantioselective NHC–Cu-catalyzed allylic substitution reaction, affording an all-carbon quaternary stereogenic center.

addition) but with diminished enantiomeric purity (90.5:9.5 vs. >98:2 e.r.).

The data in Table 3 illustrate that furyl- and thienyl(diethyl)aluminum[16] participate in efficient (>98% conv. in 1.0 h with 0.5–1.5 mol% chiral NHC–Ag^I complex) reactions that afford products with high enantioselectivity (86.5:13.5 to >98:2 e.r.) and yield (86–98% after purification). Substrates containing an aryl substituent or those that bear a carboxylic ester (entry 11, Table 3) or a silyl unit (entries 6 and 14, Table 3) undergo notably facile and selective transformations. Reactions with 3-furyl- and 3-thienyl(diethyl)aluminum begin with readily available (bromo)heterocyclic precursors, which are converted to the derived (heteroaryl)aluminum reagents through a simple metal–halogen exchange procedure.[17]

Table 3: Synthesis and in situ use of heterocyclic aluminum reagents in Cu-catalyzed enantioselective allylic substitution reactions.[a]



Entry	Heterocycle	Substrate (R)	mol% **2a**	S_N2'/S_N2[b]	Yield [%][c]	e.r.[d]
1	2-furyl	Ph	0.5	>98:2	93	>98:2
2	2-furyl	$oBrC_6H_4$	0.5	>98:2	86	>98:2
3	2-furyl	$oMeOC_6H_4$	0.5	>98:2	95	>98:2
4	2-furyl	$oMeC_6H_4$	1.0	>98:2	98	98:2
5	2-furyl	$pNO_2C_6H_4$	0.5	>98:2	96	>98:2
6	2-furyl	$SiMe_2Ph$	1.0	>98:2	91	86.5:13.5
7[e]	3-furyl	Ph	1.0	>98:2	90	97:3
8	2-thienyl	Ph	0.5	>98:2	98	96:4
9	2-thienyl	$oBrC_6H_4$	1.5	>98:2	98	98:2
10	2-thienyl	$pNO_2C_6H_4$	0.5	>98:2	96	94:6
11	2-thienyl	CO_2tBu	0.5	>98:2	94	87.5:12.5
12[e]	3-thienyl	Ph	1.0	>98:2	94	94:6
13[e]	3-thienyl	$oBrC_6H_4$	1.0	>98:2	89	97:3
14[e]	3-thienyl	$SiMe_2Ph$	1.0	>98:2	95	94:6

[a–d] See Table 2. [e] The corresponding 3-bromofuran or 3-bromothiophene were used as starting materials (treatment with *n*BuLi in Et_2O); see the Supporting Information for experimental details.

The final stage involved reactions of allylic phosphates with two alkyl substituents, a particularly challenging class of substrates vis-à-vis obtaining exceptionally high enantioselectivities (Scheme 3). Transformations proceed readily to afford the EAS products in 88–97% yield and with >98% site selectivity. Reactions with a methyl and an *n*-alkyl group (cf. sporochnol, **11**, and **12**, 78.5:21.5–91:9 e.r.) are typically less enantioselective than those bearing a larger cyclohexyl unit (cf. **13**–**16**, 91:9–98:2 e.r.). The enantiotopic faces of the alkenes in substrates in Scheme 3 are difficult to differentiate due to similar size and nearly identical electronic attributes of their alkyl substituents. Products are therefore obtained with lower enantioselectivities compared to aryl-, silyl-, and carboxylic ester-substituted alkenes in Scheme 2 or Table 3.

The transformation with allylic phosphate **10** and the aryl(diethyl)aluminum bearing a *p*-methoxyaryl unit affords *R*-(−)-sporochnol. The same natural product was previously synthesized by a process involving an aryl-substituted allylic phosphate with di(2-methyl-2-pentenyl)Zn, promoted by 10 mol% of an amino acid-based chiral Cu complex.[2a] Although the earlier version is more enantioselective (91:9 e.r. vs. 78.5:21.5 e.r.), the EAS depicted in Scheme 3 is superior on several fronts. First, 1.0 mol% of the NHC–Cu complex is required for a reaction that is complete in 1 h at −30 °C versus 10 mol% of the amino acid–Cu complex for 48 h at −78 °C (lower temperature required for maximum enantioselectivity). Second, the combination of an aryllithium and commercially available Et_2AlCl, which is used in situ, is considerably more practical than the preparation, purification and use of the aforementioned dialkylzinc reagent. Third, catalytic EAS with an arylmetal reagent requires allylic phosphate **10**, which is easily accessed in one step from geraniol (vs. Horner–Emmons olefination and reduction of ester, followed by phosphate formation).

In brief, we address a longstanding shortcoming in an important class of enantioselective C–C bond-forming reactions. The present investigations introduce efficient and highly selective Cu-catalyzed EAS reactions that provide access to numerous versatile molecules, containing aryl- or heteroaryl-substituted quaternary carbon stereogenic centers, and which cannot be easily prepared by any alternative protocols.[18] Moreover, the investigations outlined herein offer additional evidence regarding the unique ability of sulfonate-bridged bidentate NHC-based metal complexes to provide an effective solution to difficult problems in catalysis.

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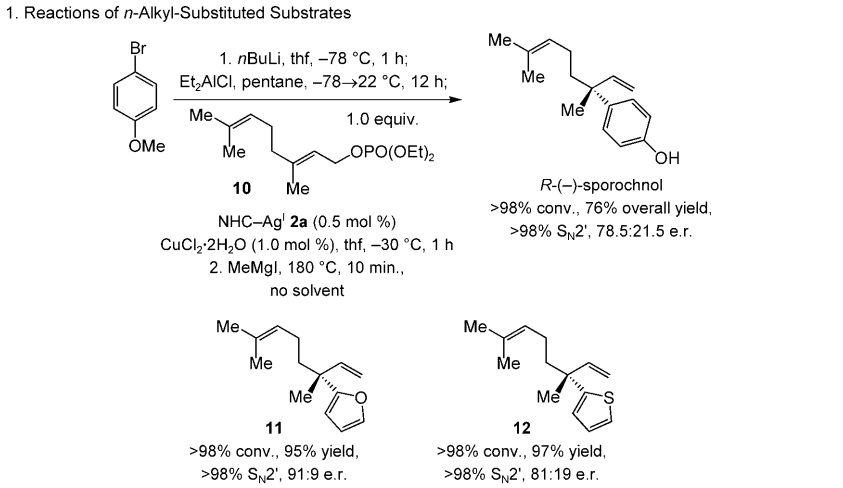
Keywords: allylic substitution · aluminum reagents · enantioselective reactions · N-heterocyclic carbenes · quaternary carbon centers



Scheme 3. NHC–Cu-catalyzed enantioselective additions of aryl and heteroaryl moieties to substrates that bear two alkyl substituents. All reactions performed under the conditions shown for EAS reaction leading to sporochnol, except for **15** and **16**. [a] With 1.0 mol% NHC–Ag^{I} **2a** and 2.0 mol% $CuCl_2 \cdot 2H_2O$. [b] With 1.0 mol% NHC–Ag^{I} **2a** and 2.0 mol% $CuCl_2 \cdot 2H_2O$, −50°C, 3 h.

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[12] When Me_2AlCl or $(iBu)_2AlCl$ are used, alkyl (vs. aryl) transfer products are generated (12% and 10%, respectively) and **6** is formed in 73:27 and 88:12 e.r., respectively.

[13] When PhMgBr is used, site- and enantioselectivity remain the same but efficiency is diminished (68% vs. >98% conv. with PhMgCl).

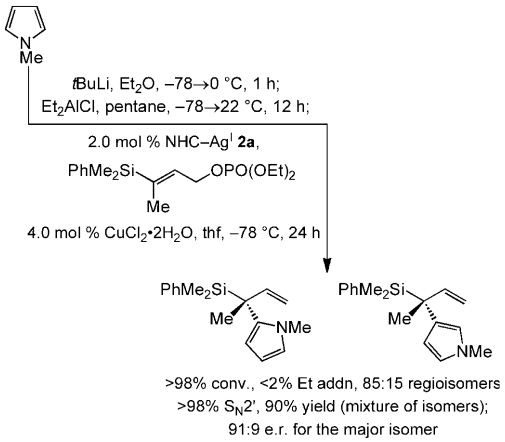
[14] Metal halides can be detrimental to enantioselectivity. For example, when the reaction in entry 2 of Table 1 is performed with an added equivalent of LiCl, the desired product is obtained in ca. 70:30 e.r. Arylaluminum solutions are allowed to stand for

30 min to 1 h to permit precipitation of LiCl to occur prior to the supernatant being utilized. See the Supporting Information for experimental details.

[15] Reactions with *ortho*-substituted arylaluminums are efficient and site-selective (>98% S_N2') but furnish products of lower enantiomeric purity. For example, when (diethyl)*o*-methylphenylaluminum is used with the allylic phosphate in entries 1–4 of Table 2, the EAS product is obtained in 69.5:30.5 e. r. In the corresponding conjugate addition processes, such arylaluminums give rise to improved e.r. values (see Ref. [9a]).

[16] For use of furyl- and thienylaluminum reagents in enantioselective additions to carbonyls, see: a) K-H. Wu, D.-W. Chuang, C.-A. Chen, H.-M. Gau, *Chem. Commun.* **2008**, 2343–2345; b) D. B. Biradar, S. Zhou, H.-M. Gau, *Org. Lett.* **2009**, *11*, 3386–3389.

[17] As the example below indicates, EAS with N-containing heterocyclic substrates proceed readily but are hampered by non-selective initial heteroaryllithium formation, affording a difficult to separate mixture of products. See the Supporting Information for details. Use of the pyridine-containing aluminum reagents leads to <2% conversion. Studies to improve the above transformations are in progress.



[18] Ni-catalyzed reactions of styrenes with ethylene furnish enantiomerically enriched products with a benzylic vinyl unit at an all-carbon quaternary stereogenic center. See: C. R. Smith, H. J. Lim, A. Zhang, T. V. RajanBabu, *Synthesis* **2009**, 2089–2100, and references therein.

