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Enantioselective Synthesis of Alkyne-Substituted Quaternary Carbon Stereogenic Centers through NHC−Cu-Catalyzed Allylic Substitution Reactions with (*i*-Bu)$_2$(Alkynyl)aluminum Reagents

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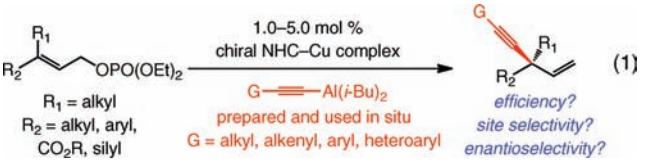
Supporting Information

ABSTRACT: A catalytic enantioselective method for the formation of alkyne-substituted all-carbon quaternary stereogenic centers is reported. Additions of alkynylaluminums to alkyl-, aryl-, carboxylic ester-, or silyl-substituted allylic phosphates are promoted by 1.0−5.0 mol % loadings of NHC−Cu complexes derived from air-stable and commercially available $CuCl_2 \cdot 2H_2O$. The requisite Al-based reagents are prepared through treatment of the corresponding aryl-, heteroaryl-, alkyl-, or alkenyl-substituted terminal alkynes with diisobutylaluminum hydride in the presence of 5.0 mol % Et_3N at ambient temperature. The desired 1,4-enynes are obtained in up to 98% yield and >99:1 enantiomeric ratio. Selected Au-catalyzed cyclizations involving the alkyne unit of the enantiomerically enriched products are presented as a demonstration of the method's utility in chemical synthesis.

In spite of significant recent advances in enantioselective catalysis, the number of protocols that promote the addition of an alkyne group to a C-based electrophile remains relatively small. Such methods are of value because there are transformations that are particularly effective with C−C triple bonds.[1] Synthesis of enantiomerically enriched propargyl alcohols or amines through reactions with aldehydes,[2] ketones,[2] or aldimines[3] has been disclosed. However, catalytic processes involving additions of alkynyl nucleophiles to alkene-based substrates are less common. Several approaches have been outlined regarding catalytic enantioselective conjugate additions of alkynylmetal reagents to unsaturated carbonyls, leading to the formation of alkyne-substituted tertiary carbon stereogenic centers.[4,5] In instances where a chiral Cu complex is used,[4d,e] highly activated substrates, such as Meldrum's acid derivatives or α,β-unsaturated thioamides, must be used to counter the low activity of Cu alkynilides. To the best of our knowledge, catalytic enantioselective alkynyl additions that generate an all-carbon quaternary stereogenic center[6] remain undisclosed; nor are we aware of any catalytic allylic substitutions[7] that deliver enantiomerically enriched products through addition of an alkyne. Herein, we present a catalytic enantioselective protocol for the reaction of (*i*-Bu)$_2$(alkynyl)aluminum reagents to trisubstituted allylic phosphates (eq 1). These additions are promoted by a 1.0−5.0 mol % loading of a copper complex derived from a chiral bidentate sulfonate-based N-heterocyclic carbene (NHC)[8] and air-stable $CuCl_2 \cdot 2H_2O$; the desired products are formed with exceptional site selectivity (typically, >98% S_N2') in 63−98% yield and up to >99:1 enantiomeric ratio (er). One of the most noteworthy features of the present studies is that the bidentate NHC complexes efficiently promote transfer of the alkyne groups. Acetylene-based moieties usually serve as relatively robust ligands that are not readily transferred via Cu-based complexes. In contrast, in the reactions described here, products from *i*-Bu addition are not observed (<2% by ^{1}H NMR analysis), and the same class of substrates utilized for NHC−Cu-catalyzed additions of alkyl-, aryl-, or vinyl groups[8] can be employed (i.e., without the need to use especially activated alkenes). The utility of the method is illustrated by representative Au-catalyzed transformations that efficiently convert the enantioselective allylic substitution (EAS) products into heterocyclic structures bearing a quaternary carbon stereogenic center.



One of the most attractive features of Al-based nucleophilic reagents is the ease with which they can be synthesized from readily accessible starting materials and used in situ. We have shown that *vinyl*aluminums, which can be formed efficiently and selectively by hydrometalation of alkynes with dibal−H, can participate in highly site- and enantioselective Cu-catalyzed EAS reactions[9] or conjugate additions;[10] such vinylmetals might also be accessed through Ni-catalyzed hydroaluminations of alkynes and utilized in a similar fashion.[11] To access alkynylaluminums, we decided to continue using the commercially available and inexpensive dibal−H; such a strategy, however, would require facilitation of the desired alkyne deprotonation while the competitive hydrometalation route is inhibited. Toward this end, we took note of the studies by Binger and the more recently expanded ones by Micouin and co-workers illustrating that the simple expedience of adding 5.0 mol % Et_3N allows terminal alkynes to be converted to alkynylaluminums in the presence of dibal−H.[12] Accordingly, as illustrated in Scheme 1, we were able to establish that alkynylaluminum **3a** derived from phenylacetylene undergoes highly efficient (>98% conv in 4.0 h) EAS with allylic phosphate **2** in the presence of 0.5 mol % NHC−Ag complex **1a** and 1.0 mol % $CuCl_2 \cdot 2H_2O$, affording **4a** with complete site selectivity (>98% S_N2') in 92% yield and 93:7 er.

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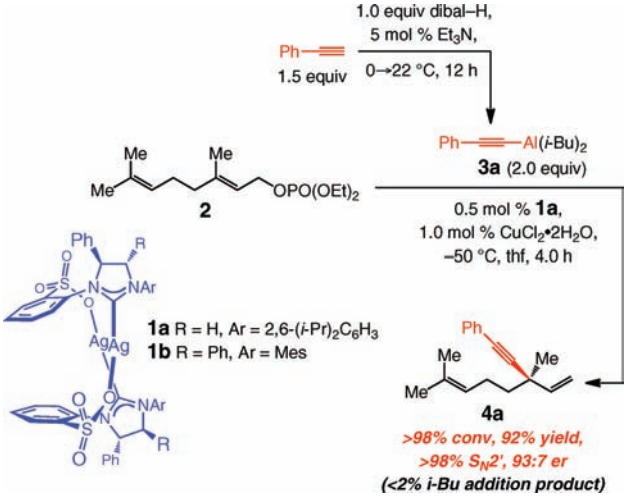
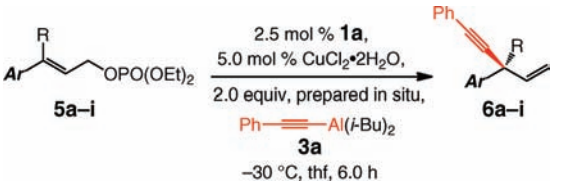
Scheme 1. Preliminary Finding: Synthesis and Efficient Cu-Catalyzed Addition with an Alkynylaluminum Reagent[a]



[a] Reactions were performed under a N_2 atmosphere (see the Supporting Information for details). Mes = 2,4,6-$Me_3C_6H_2$.

Table 1. NHC−Cu-Catalyzed Enantioselective Allylic Substitutions with Alkynylaluminum Reagent 3a[a]

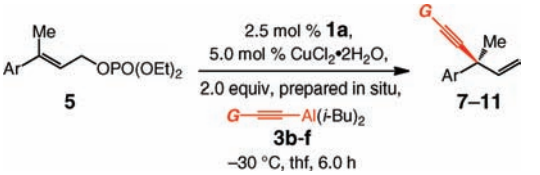


entry	substrate (*Ar*; R)		conv (%)[b]	yield (%)[c]	S_N2' (%)[b]	er[d]
1	C_6H_5; Me	**a**	>98	98	>98	95:5
2	2-naphthyl; Me[e]	**b**	98	96	95	91:9
3	*o*-MeC_6H_4; Me	**c**	<5	nd	nd	nd
4	*o*-BrC_6H_4; Me	**d**	>98	97	>98	99:1
5	*o*-$OMeC_6H_4$; Me	**e**	>98	96	>98	>99:1
6	*m*-BrC_6H_4; Me	**f**	>98	95	98	93:7
7	*p*-$NO_2C_6H_4$; Me[f]	**g**	82	77	>98	92:8
8	*p*-$CF_3C_6H_4$; Me[f]	**h**	69	63	>98	92:8
9	C_6H_5; Et	**i**	>98	95	>98	91:9

[a] Reactions were performed under a N_2 atmosphere. nd = not determined. [b] Determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures. [c] Yields of isolated products after purification (±5%). [d] Determined by HPLC analysis (see the Supporting Information for details). [e] Reaction was performed with NHC−Ag complex **1b**. [f] Time = 30 h.

The selection of NHC−Ag complex **1a** as the precursor to the Cu catalyst was based on the preliminary examination of various chiral carbene ligands.[13] Catalyst screening studies indicated that use of a bidentate NHC complex is critical, as the monodentate variants proved to be ineffective (<10% conv). Reactions promoted by the ligands containing a phenoxy bridge, although appreciably

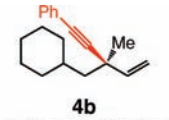
Table 2. NHC−Cu-Catalyzed Enantioselective Allylic Substitutions with Aryl-Substituted Allylic Phosphates and Alkynylaluminums[a]

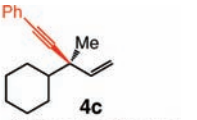


entry	substrate (Ar)		*G*	product	conv (%);[b] yield (%)[c]	S_N2' (%)[b]	er[d]
1	C_6H_5	**a**	*n*-Hex	**7**	98; 88	>98	96:4
2	*p*-ClC_6H_4	**j**	Cy	**8**	98; 82	>98	96:4
3	*o*-BrC_6H_4	**d**	Cyclohexenyl	**9**	>98; 91	>98	>99:1
4	*o*-$OMeC_6H_4$	**e**	*o*-ClC_6H_4	**10**	>98; 98	>98	>99:1
5	C_6H_5	**a**	*p*-$CF_3C_6H_4$	**11**	<2; nd	nd	nd

[a−d] See footnotes *a*−*d* of Table 1.

enantioselective (89.5:10.5 er), are significantly less efficient (~30% conv) than those bearing a sulfonate (i.e., **1a** and **1b**). As demonstrated through the enantioselective syntheses of **4b** and **4c**, catalytic EAS can be performed with facility similar to that observed for **4a** with substrates bearing a more sterically demanding branched alkyl side chain. The less than complete site selectivity observed in the case of **4b** (90% S_N2') is unusual; the reason for such a deviation is unclear at the present time.





Cu-catalyzed EAS reactions with aryl-substituted allylic phosphates were examined as well; the results of these studies are summarized in Table 1. The reactions proceeded with similar or higher enantioselectivity than for the aforementioned alkyl-substituted cases (91:9 to >99:1 er vs 92:8 to 94:6 er), but 2.5 mol % **1a** or **1b** (cf. Scheme 1) was required for >98% conversion (vs 0.5 mol % for **4a**−**c**). Several additional points regarding the data in Table 1 merit mention: (1) Although ortho substitution on the aryl group led to high er values (entries 4 and 5), the efficiency suffered greatly with an *o*-Me unit (entry 3). (2) For aryl rings bearing an electron-deficient group, the catalytic additions proceeded less efficiently (entries 7 and 8); nonetheless, the reactions were clean, allowing the desired products to be isolated in useful yields. (3) In one instance, the Cu complex derived from **1b** delivered the desired product in higher enantiomeric purity than **1a** (entry 2; >98% conv, 95% S_N2', and 63:37 er with **1a**).

As the findings shown in Table 2 indicate, a variety of terminal alkynes can be easily and efficiently deprotonated and used in the NHC−Cu-catalyzed EAS process. Reactions with alkyl- (entries 1 and 2) as well as alkenyl-substituted (entry 3) alkynylaluminums proceeded efficiently to afford the desired 1,4-enynes in 96:4 to >99:1 er and 82−91% yield after purification. The reaction

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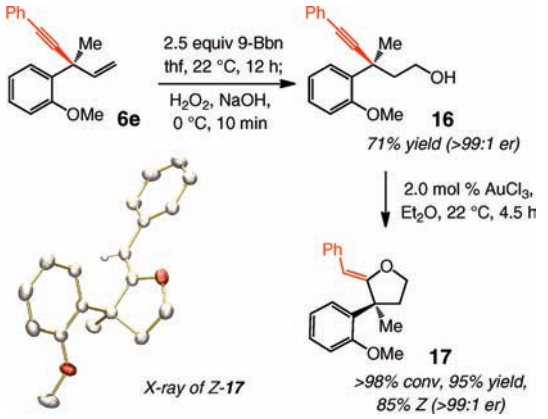
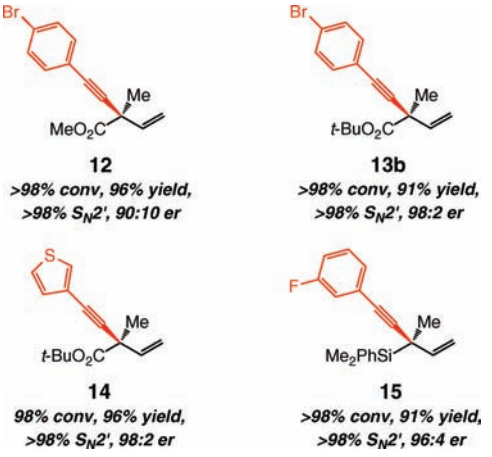
Scheme 2. Cyclic Ether through Au-Catalyzed Cyclization



involving an *o*-chlorophenylacetylene (entry 4) was exceptionally efficient and selective (98% yield, >98% S_N2', >99:1 er). On the other hand, as suggested by the example in entry 5, the presence of a strongly electron-withdrawing substituent within the aryl alkyne can be detrimental to the catalytic EAS.

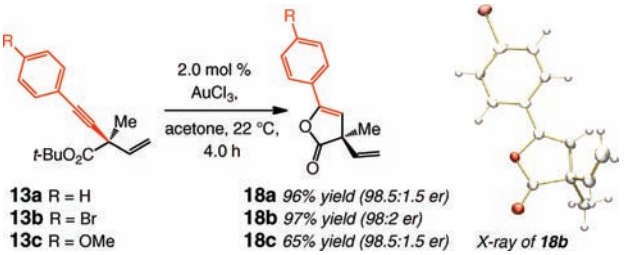
The enantioselective syntheses of enynes **12**, **13b**, **14**, and **15** underline three additional noteworthy aspects of the method: (1) Reactions can be performed with α,β-unsaturated esters or vinylsilane bearing a γ-phosphate to afford products with high enantiomeric purity wherein the quaternary carbon stereogenic center is positioned adjacent to a carbonyl group or silyl unit. (2) There is little or no adventitious reduction of the carboxyl ester group by residual dibal−H used in the preparation of the alkynylaluminum. (3) Catalytic EAS can be used with alkynylmetal reagents that carry a heterocyclic substituent (cf. **14**).



The potential of the products obtained through NHC−Cu-catalyzed additions of alkynylaluminums for application in chemical synthesis is underlined by the transformations shown in Scheme 2. Primary carbinol **16**, obtained through site-selective hydroboration of enyne **6e**, is readily converted to the derived cyclic enol ether within 4.5 h upon treatment with 2.0 mol % $AuCl_3$.[14] The desired heterocycle (*Z*-**17**), the identity of which was established by X-ray crystallography, was isolated in 95% yield with 85% *Z*-selectivity.

Another class of Au-catalyzed cyclizations, depicted in Scheme 3, further underlines the versatility of the protocol and of the *tert*-butyl

Scheme 3. Au-Catalyzed Conversion to Cyclic Lactones



ester-containing products in particular. Thus, unsaturated γ-lactones **18a**−**c** were obtained directly in 65%−97% yield, without the need for initial hydrolysis of the carboxylic ester, through Au-catalyzed cyclizations of the enantiomerically enriched 1,4-enynes **13a**−**c**.[15] It should be noted that treatment of the corresponding methyl esters (e.g., **12**) to the same conditions did not result in any detectable cyclization.[16] The above procedures are unique to alkyne-containing molecules and cannot be performed on products from previously reported catalytic EAS reactions (such as those obtained through vinylmetal additions).[8]

In summary, we have presented a method for enantioselective synthesis of small organic molecules containing readily differentiable alkyne and alkene groups; a carboxyl ester unit can be present in such enantiomerically enriched products as well. In view of the wealth of transformations that can be performed with the above-mentioned functional units, catalytic, stereo- and site-selective variants of which continue to emerge, the method described herein should prove to be of value in the preparation of enantiomerically enriched organic molecules. Studies regarding site- and enantioselective NHC−Cu-catalyzed alkyne additions to other substrate classes, including those that contain a disubstituted olefin, are in progress and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectral and analytical data for all products, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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