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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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Abstract

A catalytic enantioselective method for formation of alkyne-substituted all-carbon quaternary carbon 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 % of NHC–Cu complexes derived from air stable and commercially available CuCl₂•2H₂O. The requisite Al-based reagents are prepared through treatment of the corresponding aryl-, heteroaryl-, alkyl-, or alkenyl-substituted terminal alkynes with di-*iso*-butylaluminum hydride in the presence of 5.0 mol % Et₃N 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 due to transformations that are particularly effective with C–C triple bonds.¹ Synthesis of enantiomerically enriched propargyl alcohols or amines through reactions with aldehydes,² ketones² or aldimines³ 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, highly activated substrates, such as Meldrum's acid derivatives or α,β -unsaturated thioamides, are required to counter the low activity of Cu alkynilides. To the best of our knowledge, however, catalytic enantioselective alkynyl additions that generate an all-carbon quaternary stereogenic center⁶ remain undisclosed; nor are we aware of any catalytic allylic substitutions⁷ that deliver enantiomerically enriched products through addition of an alkynyl nucleophile. Herein, we present a catalytic enantioselective protocol for reaction of (*i*-Bu)₂(alkynyl)aluminum reagents to trisubstituted allylic phosphates (eq 1). Additions are promoted by 1.0–5.0 mol % of a copper complex derived from a chiral bidentate sulfonate-based N-heterocyclic carbene (NHC)⁸ and air

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Supporting Information Available: Experimental procedures and spectral, analytical data for all products (PDF). This material is available on the web: <http://www.pubs.acs.org>.

stable $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$; the desired products are formed with exceptional site selectivity (typically, >98% $\text{S}_{\text{N}}2'$), 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.

(1)

Acetylene-based moieties usually serve as relatively robust ligands that are not readily transferred via Cu-based complexes. Accordingly, products from *i*-Bu addition are not observed (<2% by ^1H NMR analysis), and the same class of substrates utilized for NHC–Cu-catalyzed additions of alkyl-, aryl- or vinyl groups⁸ can be employed here as well (i.e., without the need for the use of especially activated alkenes). The utility of the method is illustrated by representative Au-catalyzed transformations that efficiently convert the enantioselective allylic substitution (EAS) products to 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, formed efficiently and selectively by hydrometallation of alkynes with dibal–H, can participate in highly site- and enantioselective Cu-catalyzed EAS reactions⁹ 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 hydrometallation route is inhibited. Towards this end, we took note of the studies by Binger and more recently expanded by Micouin and co-workers, illustrating that by the simple expedience of adding 5.0 mol % Et_3N , terminal alkynes can 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 a 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 % $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, to afford **4a** with complete site selectivity (>98% $\text{S}_{\text{N}}2'$), in 92% yield and 93:7 er.

Use 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 bidentate ligands containing a phenoxy bridge, although appreciably enantioselective (89.5:10.5 er), are significantly less efficient (~30% conv) than those that bear a sulfonate (i.e., **1a–b**). As demonstrated through enantioselective syntheses of **4b–c**, catalytic EAS can be performed with similar facility as observed with **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% $\text{S}_{\text{N}}2'$) is unusual; the reason for such a deviation is unclear at the present time.

Cu-catalyzed EAS reactions with aryl-substituted allylic phosphates have been examined as well; the results of these studies are summarized in Table 1. Reactions proceed with similar or higher enantioselectivity, compared to the aforementioned alkyl-substituted cases (91:9 to >99:1 er vs 92:8–94:6 er), but 2.5 mol % **1a** or **1b** (cf. Scheme 1) is 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 at the aryl group leads to high er values (entries 4–5, Table 1), efficiency suffers greatly with an *o*-Me unit (entry 3). (2) When the aryl ring bears an electron-deficient group, catalytic additions proceed less efficiently (entries 7–8, Table 1); nonetheless, reactions are clean, allowing the desired products to be isolated in useful yields. (3) In one instance, the Cu complex derived from **1b** deliver the desired product in higher enantiomeric purity than **1a** (entry 2; >98% conv, 95% SN2' 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 1–2) as well as alkenyl-substituted (entry 3) alkynylaluminums proceed efficiently to afford the desired 1,4-enynes in 96:4 to >99:1 er and 82–91% yield after purification. The reaction in entry 4 of Table 2, involving an *o*-chlorophenylacetylene, is exceptionally efficient and selective (98% yield, >98% S_N2', >99:1 er). On the other hand, as suggested by the example in entry 5 of Table 2, the presence of a strong electron-withdrawing substituent within the aryl alkyne can be detrimental to the catalytic EAS.

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 allylsilanes bearing a γ -phosphate to afford products of 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 hours upon treatment with 2.0 mol % AuCl₃.¹⁴ The desired heterocycle (*Z*-**17**), the identity of which has been established by X-ray crystallography, is isolated in 95% yield and with 85% *Z*-selectivity.

Another class of Au-catalyzed cyclizations, depicted in Scheme 3, further underlines the versatility of the protocol, and that of the *t*-butyl ester-containing products in particular. Thus, unsaturated γ -lactones **18a-c** are obtained directly, without the need for initial hydrolysis of the carboxylic ester, through Au-catalyzed cyclizations of the enantiomerically enriched 1,4-enynes **13a-c**¹⁵ in 65%–97% yield. It should be noted that treatment of the corresponding methyl esters (e.g., **12**) to the same conditions does 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 present 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. Considering the wealth of transformations that can be performed with the abovementioned functional units, catalytic, stereo- and site selective variants of which continue to emerge, the method described above 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Preliminary Finding: Synthesis and Efficient Cu-Catalyzed Addition with an Alkynylaluminum Reagent^a

Scheme 2.
Cyclic Ether through Au-Catalyzed Cyclization

Scheme 3.
Au-Catalyzed Conversion to Cyclic Lactones

Table 1

NHC–Cu-Catalyzed Enantioselective Allylic Substitutions with Alkynylaluminum Reagent **3a**^a

Entry	substrate (Ar; R)	conv (%) ^b	yield (%) ^c	SN2 (%) ^b	en ^d
1	C ₆ H ₅ ; Me	a >98	98	>98	95:5
2	2-naphthyl; Me ^e	b 98	96	95	91:9
3	<i>o</i> -MeC ₆ H ₄ ; Me	c <5	nd	nd	nd
4	<i>o</i> -BrC ₆ H ₄ ; Me	d >98	97	>98	99:1
5	<i>o</i> -OMeC ₆ H ₄ ; Me	e >98	96	>98	>99:1
6	<i>m</i> -BrC ₆ H ₄ ; Me	f >98	95	98	93:7
7	<i>p</i> -NO ₂ C ₆ H ₄ ; Me ^f	g 82	77	>98	92:8
8	<i>p</i> -CF ₃ C ₆ H ₄ ; Me ^f	h 69	63	>98	92:8
9	C ₆ H ₅ ; Et	i >98	95	>98	91:9

^aReactions performed under N₂ atm.

^bValues determined by analysis of 400 MHz ¹H NMR spectra of unpurified mixtures.

^cYields of isolated products after purification (±5%).

^dValues determined by HPLC analysis; see the Supporting Information for details.

^eReaction performed with NHC–Ag complex **1b**.

^fTime = 30 h. nd = not determined.

Table 2

NHC–Cu-Catalyzed Enantioselective Allylic Substitutions with Aryl-Substituted Allylic Phosphates and Alkynylaluminums^{a-d}

entry	substrate (Ar)	G	product	conv (%) ^{a-d} , yield (%) ^{a-d}	SN2 (%) ^{a-d}	ee ^{a-d}
1	C_6H_5	a <i>n</i> -Hex	7	98; 88	>98	96:4
2	<i>p</i> -ClC ₆ H ₄	j Cy	8	98; 82	>98	96:4
3	<i>o</i> -BrC ₆ H ₄	d Cyclohexenyl	9	>98; 91	>98	>99:1
4	<i>o</i> -OMeC ₆ H ₄	e <i>o</i> -ClC ₆ H ₄	10	>98; 98	>98	>99:1
5	C_6H_5	a <i>p</i> -CF ₃ C ₆ H ₄	11	<2; nd	nd	nd

^{a-d} See Table 1.

nd = not determined