Homogeneous Catalysis

DOI: 10.1002/anie.201300785

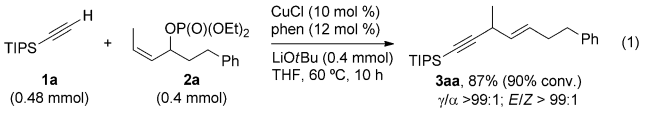
Copper-Catalyzed γ-Selective and Stereospecific Direct Allylic Alkylation of Terminal Alkynes: Synthesis of Skipped Enynes**

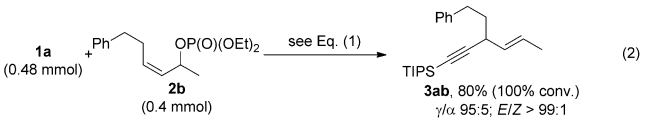
Yusuke Makida, Yurie Takayama, Hirohisa Ohmiya, and Masaya Sawamura**

Skipped enynes, that is, 1,4-enynes, are versatile building blocks which can be further derivatized through various stereoselective transformations.[1,2] The development of facile and efficient methods for the synthesis of skipped enynes is thus important. In particular, stereoselective synthesis of chiral 1,4-enynes with a stereogenic center at the propargylic/allylic position is highly desirable.[3] Among the routes to skipped enynes, allylic alkylation of alkynyl nucleophiles is particularly efficient and versatile because the substrates and the reagents are readily available and the reactions are highly reliable in terms of regio- and stereoselectivities. Kobayashi and co-workers reported a γ-selective allylic alkylation of stoichiometric alkynylcopper(I) reagents with excellent 1,3-*anti* stereoselectivity.[4] More recently, Hoveyda and co-workers developed copper-catalyzed enantioselective allylic alkylation with highly reactive alkynylaluminum reagents, which were prepared by metalation of terminal alkynes with DIBAL-H, thus giving chiral skipped enynes having a terminal alkene moiety.[5] These methods are useful for the preparation of chiral skipped enynes, but require prefunctionalization of the alkyne substrate and are problematic regarding functional-group compatibility. In this regard, the direct use of terminal alkynes for selective synthesis of enantioenriched skipped enynes is a desirable strategy.[6]

Herein, we report a copper-catalyzed direct allylic alkylation of terminal alkynes with internal secondary allylic phosphates, and it proceedes with excellent γ regioselectivity and *E* stereoselectivity.[7] The reaction of enantioenriched secondary allylic phosphates proceeded with 1,3-*anti* stereochemistry to afford the corresponding chiral 1,4-enynes with a controlled stereogenic center at the propargylic/allylic position. The protocols are versatile and useful for the synthesis of functionalized skipped enynes because various terminal alkynes such as silyl, aromatic, or aliphatic alkynes can be used without prefunctionalization. This method is particularly useful for the synthesis of skipped enynes with an internal alkene moiety. The chiral skipped enynes can be used for various derivatizations such as heterocyclic annulations as demonstrated by a formal total synthesis of a gonadotropin releasing hormone (GnRH) antagonist.

Specifically, the reaction of triisopropylsilylacetylene (**1a**; 0.48 mmol) with the *Z*-allylic phosphate **2a** (0.4 mmol) in the presence of CuCl (10 mol%), 1,10-phenanthroline (phen; 12 mol%), and LiO*t*Bu (0.4 mmol) in THF (0.8 mL) at 60°C for 10 hours afforded the allylated alkyne product (skipped enyne) **3aa** in 87% yield (90% conv.) with excellent regio- (γ/α > 99:1) and stereoselectivity (*E*/*Z* > 99:1) [Eq. (1); TIPS = triisopropylsilyl]. The reaction of the constitutional isomer **2b** proceeded with slightly decreased but still high γ selectivity (95:5) to afford **3ab** along with the corresponding α-substitution product [Eq. (2)]. The slight difference in the regioselectivities of the reaction with the isomeric substrates suggests that relative steric demands of the α and γ substituents perturb the regioselectivity to some extent. These results, however, indicate that a useful level of γ selectivity is attainable against this unfavorable steric effect.





Several observations concerning the optimum reaction conditions for the reaction between **1a** and **2a** [Eq. (1)] are to be noted. No reaction occurred in the absence of CuCl or when KO*t*Bu was used instead of LiO*t*Bu. The reaction proceeded in the absence of 1,10-phenanthroline, but with lower efficiency (77% yield).[8] The use of **2a** with an *E* configuration resulted in decreased yield and regioselectivity (54%, 61:39). Allylic substrates with carbonate or chloride leaving groups were not reactive or afforded complicated mixtures.

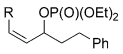
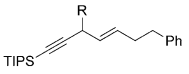
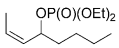
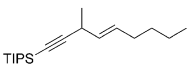
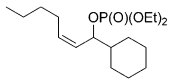
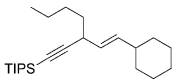
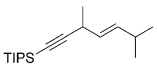
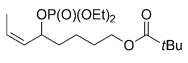
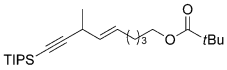
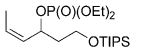
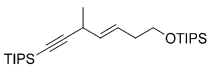
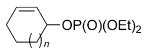
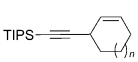
The steric effects of the α and γ substituents of allylic phosphates (**2**) on the reactivity and regioselectivity were further evaluated (Table 1, entries 1–6). The allylic phosphates possessing bulkier substituents (*n*Bu or *i*Bu), in place of the γ-Me substituent of **2a**, also proceed with the excellent regioselectivity (entries 1 and 2). The allylic phosphate **2e** bearing an even bulkier *c*Hex substituent at the γ position was efficiently coupled with **1a**, albeit with decreased γ selectivity (entry 3). The 2-phenylethyl group at the α position of **2a** could be replaced with *n*Bu (**2f**), *c*Hex (**2g**), and *i*Pr (**2h**) groups without a change in the regioselectivity (entries 4–6).

[*] Y. Makida, Y. Takayama, Prof. Dr. H. Ohmiya, Prof. Dr. M. Sawamura
Department of Chemistry, Faculty of Science, Hokkaido University
Sapporo, 060-0810 (Japan)
E-mail: ohmiya@sci.hokudai.ac.jp
sawamura@sci.hokudai.ac.jp
Homepage: http://barato.sci.hokudai.ac.jp/~orgmet/index-Eng1.html

[**] This work was supported by the Grants-in-Aid for Young Scientists (A), JSPS to H.O. and by CREST and ACT-C, JST to M.S. Y.M. thanks the JSPS for their scholarship support.

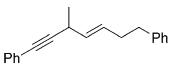
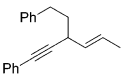
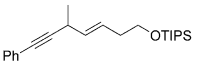
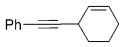
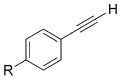
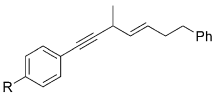
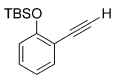
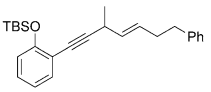
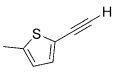
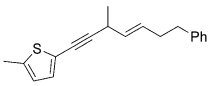
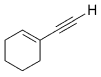
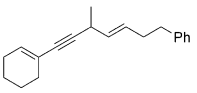
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201300785.

Table 1: Copper-catalyzed allylic alkylation with **1a**.[a]

Entry	Phosphate	Product[b] Yield[c] (γ/α[d])
1	 **2c** (R = *n*Bu)	 **3ac** 70% (>99:1)
2	**2d** (R = *i*Bu)	**3ad** 88% (>99:1)
3	**2e** (R = *c*Hex)	**3ae** 84% (89:11)
4	 **2f**	 **3a** 99% (>99:1)
5[e]	 **2g**	 **3ag** 74% (>99:1)
6	 **2h**	 **3ah** 68% (>99:1)
7	 **2i**	 **3ai** 81% (>99:1)
8	 **2j**	 **3aj** 76% (>99:1)
9	 **2k** (*n* = 1)	 **3ak** 89% (–)
10	**2l** (*n* = 2)	**3al** 74% (–)

[a] The reaction was carried out with **1a** (0.48 mmol), **2** (0.4 mmol), CuCl (10 mol%), phen (12 mol%), and LiO*t*Bu (0.4 mmol) in THF (0.8 mL) at 60°C for 10 h. [b] Isomeric ratio $E/Z > 99:1$ (except for entries 9 and 10). [c] Yield of isolated product. [d] Determined by ^{1}H NMR or GC analysis of the crude reaction mixture. [e] The reaction was carried out on a 1.0 mmol scale.

Table 2: Copper-catalyzed allylic alkylation with various aromatic alkynes.[a]

Entry	Alkyne	Phosphate	Product[b] Yield[c] (γ/α[d])
1	 **1b**	**2a**	 **3ba** 79% (96:4)
2	**1b**	**2b**	 **3bb** 81% (94:6)
3	**1b**	**2j**	 **3bj** 72% (99:1)
4	**1b**	**2k**	 **3bk** 99% (–)
5	 **1c** (R = OMe)	**2a**	 **3ca** 88% (>99:1)
6	**1d** (R = CF_3)	**2a**	**3da** 82% (>99:1)
7	**1e** (R = CO_2Me)	**2a**	**3ea** 87% (96:4)
8	 **1f**	**2a**	 **3fa** 88% (92:8)
9	 **1g**	**2a**	 **3ga** 71% (91:9)
10	 **1h**	**2a**	 **3ha** 73% (96:4)

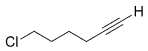
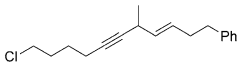
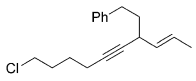
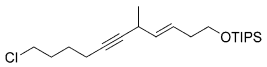
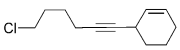
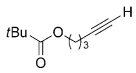
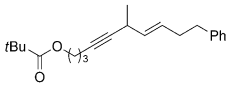
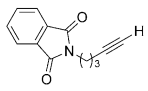
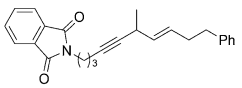
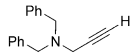
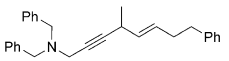
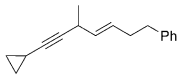
[a] The reaction was carried out with **1** (0.24 mmol), **2** (0.2 mmol), CuCl (10 mol%), phen (12 mol%), and LiO*t*Bu (0.2 mmol) in THF (0.4 mL) at 60°C for 15 h. [b] Isomeric ratio $E/Z > 99:1$ (except for entry 4). [c] Yield of isolated product. [d] Determined by ^{1}H NMR or GC analysis of the crude reaction mixture. TBS = *tert*-butyldimethylsilyl.

The compatibility of various functional groups on the allylic phosphates **2** was also investigated. Triisopropylsilylacetylene (**1a**) reacted with phosphates bearing ester (**2i**) and silyl ether (**2j**) substituents to afford the products in 81% and 76% yields, respectively (entries 7 and 8). The protocol was also applicable to six- or seven-membered ring allylic phosphates (**2k**,**l**; entries 9 and 10).

Aromatic alkynes are also suitable substrates for this copper catalysis (Table 2).[9] Phenylacetylene (**1b**) reacted with various allylic phosphates in high yields with high γ selectivities (entries 1–4). The reactions of phenylacetylene derivatives with electronically and positionally diverse substituents including *p*-MeO, *p*-CF_3, *p*-CO_2Me, and *o*-TBSO groups (**1c**, **1d**, **1e** and **1f**) were compatible with the reaction conditions and afforded the corresponding products in high yields with high regioselectivities (entries 5–8). A sulfur-containing heteroaromatic alkyne, 2-ethynyl-5-methylthiophene (**1g**), was also a suitable substrate (entry 9). The 1,3-enyne derivative **1h** underwent the reaction with **2a** to afford the corresponding dienyne (**3ha**) with 96% γ-selectivity (entry 10).

The applicability toward aliphatic alkynes is shown in Table 3. In this case, CH_3CN was the appropriate solvent

Table 3: Copper-catalyzed allylic alkylation with various aliphatic alkynes.[a]

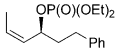
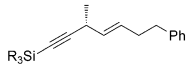
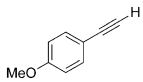
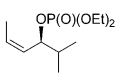
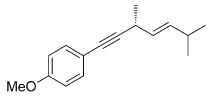
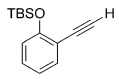
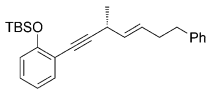
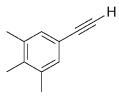
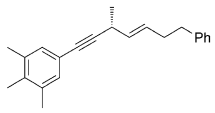
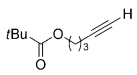
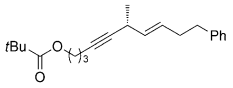
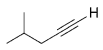
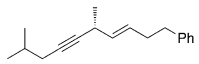
Entry	Arene	Phosphate	Product[b] Yield[c] (γ/α[d])
1	 **1i**	**2a**	 **3ia** 81% (>99:1)
2	**1i**	**2b**	 **3ib** 89% (92:8)
3	**1i**	**2j**	 **3ij** 62% (>99:1)
4	**1i**	**2k**	 **3ik** 77% (–)
5	**1j**	**2a**	  **3ja** 78% (96:4)
6	**1k**	**2a**	  **3ka** 87% (96:4)
7	**1l**	**2a**	  **3la** 72% (96:4)
8	**1m**	**2a**	  **3ma** 88% (93:7)

[a] The reaction was carried out with **1** (0.24 mmol), **2** (0.2 mmol), CuCl (10 mol%), phen (12 mol%), and Li*O*t*Bu (0.2 mmol) in CH_3CN (0.4 mL) at 60°C for 15 h. [b] Isomeric ratio $E/Z > 99:1$ (except for entry 4). [c] Yield of isolated product. [d] Determined by ^{1}H NMR or GC analysis of the crude reaction mixture.

instead of THF. Specifically, the reactions between 6-chloro-1-hexyne (**1i**) and **2a** gave the chlorinated product (**3ia**) in high yield (81%) with excellent regioselectivity (entry 1). The alkyne **1i** also showed good reactivity toward other allylic phosphates (**2b**,**j**,**k**,; entries 2–4). Functionalized aliphatic alkynes with a pivalate ester (**1j**), phthalimide (**1k**), or dibenzylamine (**1l**) substituent at their chain termini reacted in high yields with high γ selectivities (entries 5–7). Cyclopropylacetylene (**1m**) reacted with **2a** albeit with slightly decreased γ selectivity (entry 8).

The direct allylic alkylation of terminal alkynes with enantioenriched allylic phosphates proceeded with 1,3-*anti* stereochemistry, thus allowing the stereocontrolled construc-

Table 4: Reactions with 1,3-*anti* stereochemistry.[a]

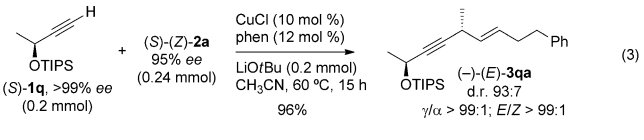
Entry	Alkyne	Phosphate	Product[b] Yield[c] (*ee* [%][d]; *anti*/*syn*)
1	 **1a** (R = *i*Pr)	 (*S*)-(*Z*)-**2a** 95% *ee*	 (−)-(*E*)-**3aa** 92% (90; 97:3)
2	**1n** (R = Me)	(*S*)-(*Z*)-**2a** 95% *ee*	(*R*)-(*E*)-**3na** 64% (88; 96:4)
3	 **1c**	 (*S*)-(*Z*)-**2h** 99% *ee*	 (−)-(*E*)-**3ch** 44% (93; 97:3)
4	 **1f**	(*S*)-(*Z*)-**2a** 95% *ee*	 (−)-(*E*)-**3fa** 88% (91; 98:2)
5	 **1o**	(*S*)-(*Z*)-**2a** 95% *ee*	 (−)-(*E*)-**3oa** 75% (91; 98:2)
6	 **1j**	(*S*)-(*Z*)-**2a** 95% *ee**	 (−)-(*E*)-**3ja** 78% (79; 92:8)
7	 **1p**	(*S*)-(*Z*)-**2a** 95% *ee*	 (−)-(*E*)-**3pa** 52% (94; 99:1)

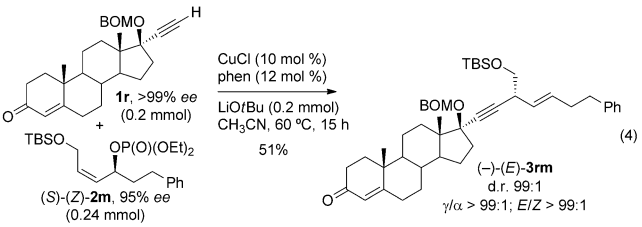
[a] The reaction was carried out with **1** (0.24 mmol), **2** (0.2 mmol), CuCl (10 mol%), phen (12 mol%), and Li*O*t*Bu (0.2 mmol) in THF (entries 1–5) or CH_3CN (entries 6 and 7) (0.4 mL) at 40°C for 15–24 h. [b] Isomeric ratio (entries 1–6, $\gamma/\alpha > 99:1$, $E/Z > 99:1$; entry 7, γ/α 97:3, $E/Z > 99:1$). Determined by ^{1}H NMR or GC analysis of the crude reaction mixture. [c] Yield of isolated product. [d] The *ee* values were determined by HPLC analysis using a chiral stationary phase.

tion of 3-branched 1,4-enyne structures (Table 4). Specifically, the alkylation of the silylacetylenes **1a** and **1n** with (*S*)-(*Z*)-**2a** (95% *ee*) at 40°C (24 h) proceeded with high *anti* stereoselectivities, thus affording (−)-(*E*)-**3aa** and (*R*)-(*E*)-**3na**, respectively (entries 1 and 2). The reaction of arylacetylenes with *p*-MeO, *o*-TBSO, and 3,4,5-trimethyl groups (**1c**,**f**,**o**) also proceeded with high 1,3-*anti* stereoselectivities (entries 3–5). In addition, the aliphatic alkynes **1j** and **1p** were successfully utilized for this protocol to furnish (−)-(*E*)-**3ja** and (−)-(*E*)-**3pa**, respectively, with useful levels of stereoselectivities (*anti*/*syn* 92:8, entry 6; 99:1, entry 7).

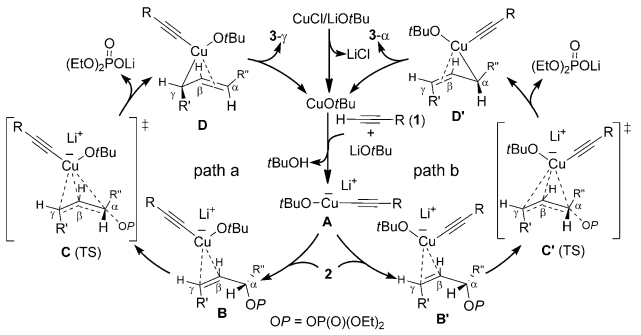
As shown in Equations (3) and (4) (BOM = benzyloxymethyl), the reactions of chiral propargylic alcohol derivatives with enantioenriched allylic phosphates produced controlled stereogenic centers at both the propargylic positions. Specifically, the reaction of (*S*)-2-triisopropylsilyloxy-3-butyne ((*S*)-**1q**) with (*S*)-(*Z*)-**2a** (95% *ee*) afforded (−)-(*E*)-**3qa** in an excellent yield (96%) with high stereoselectivity

(*anti*/*syn* 95:5, product d.r. 93:7) [Eq. (3)]. Furthermore, the chiral ethisterone derivative **1r** reacted with (*S*)-(*Z*)-**2m** (95% *ee*) to afford (−)-(*E*)-**3rm**, thus allowing stereocontrolled elongation of the steroidal side chain (d.r. 99:1) with the α,β-unsaturated carbonyl moiety remaining untouched [Eq. (4)].



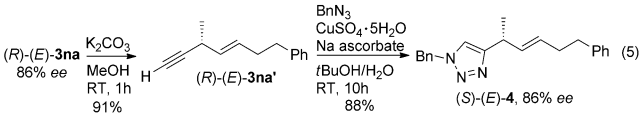


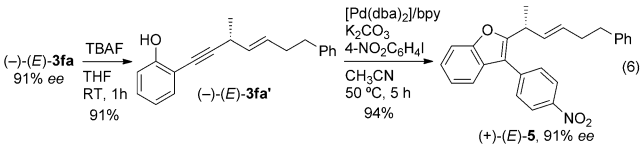
In considering a reaction mechanism, it is noted that the present copper-catalyzed allylic alkylation of terminal alkynes has some common features with the copper-catalyzed allylic alkylation of electron-deficient heteroarenes, work we previously reported. These features include comparable pK_a values of the pronucleophiles, reaction conditions using a stoichiometric LiO*t*Bu base, and the γ-selectivity pattern which is dependent on steric effects of the substituents.[10] Accordingly, the active organocopper species is likely in the form of a monoorganoalkoxycuprate ([alkynyl-Cu-O*t*Bu]$^-$) rather than a neutral organocopper(I) species. As shown in Scheme 1, the reaction would proceed through oxidative addition of a heterocuprate (**A**) to an allylic phosphate to form allylcopper(III) intermediates.[11] The γ selectivity should be determined at the oxidative addition step as a consequence of the asymmetric nature of **B** and **B′**.



Scheme 1. Possible mechanism.

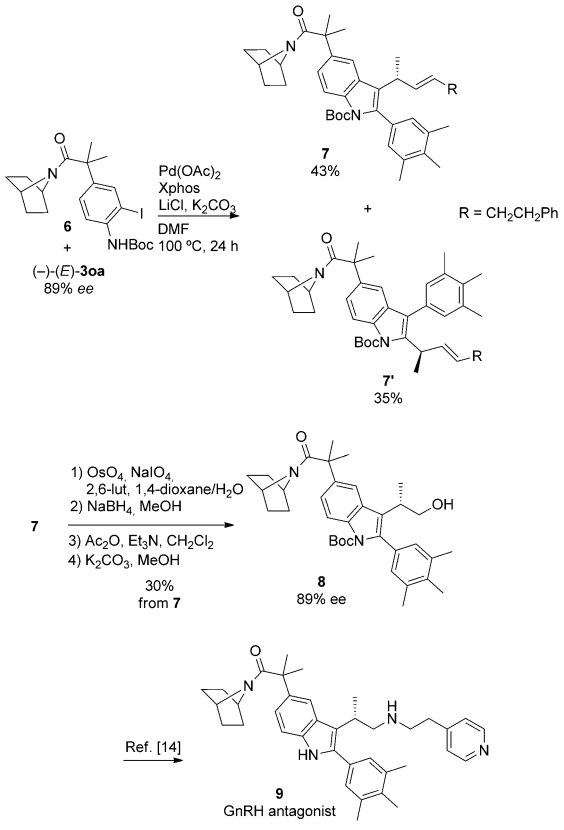
Facile conversion of the alkyne moieties in the enantioenriched enyne derivatives into heterocyclic scaffolds was achieved by desilylation and subsequent copper-catalyzed [3+2] cycloaddition or palladium-catalyzed hereroannulation, thus affording the triazole (*S*)-(*E*)-**4** (86% *ee*)[12] and benzofuran (+)-(*E*)-**5** (91% *ee*),[13] respectively [Eqs. (5) and (6); bpy = 2,2′-bipyridine, dba = dibenzylideneacetone, TBAF = tetra-*n*-butylammonium fluoride]. These transformations demonstrate the usefulness of branched skipped enynes as precursors to various heteroarenes with a controlled stereogenic center located α to the aromatic rings.





We then used this skipped enyne strategy for a formal total synthesis of the GnRH (Gonadotropin Releasing Hormone) antagonist **9** (Scheme 2).[14] Thus, Larock indole synthesis between (−)-(*E*)-**3oa** (89% *ee*)[15] and the iodoaniline derivative **6** afforded **7** (43%) along with the isomer **7′** (35%).[16] The major isomer was treated with OsO_4/$NaIO_4$/2,6-lutidine. Reductive acetylation and subsequent deacetylation produced the alcohol **8** with 89% *ee*. The synthesis of **9** from **8** was reported previously.[14] Thus, a formal total synthesis of GnRH antagonist was achieved.

In summary, we have developed a copper-catalyzed protocol for direct allylic alkylation of terminal alkynes with



Scheme 2. Formal total synthesis of a GnRH antagonist.

internal secondary allylic phosphates, which proceeded with excellent γ and *E* selectivities. The protocol was applicable to various alkynes including silyl, aromatic, and aliphatic alkynes. The reaction of enantioenriched allylic phosphates showed excellent 1,3-*anti* stereoselectivity to generate a secondary stereogenic center at the allylic and propargylic position. As a result, the copper-catalyzed protocol allows straightforward access to enantioenriched chiral skipped enynes, which are useful precursors for various derivatizations.

Received: January 29, 2013
Published online: April 9, 2013

Keywords: alkynes · allylic compounds · copper · homogeneous catalysis · synthetic methods

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