VIP Enantioselective Catalysis

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# Combining NHC–Cu and Brønsted Base Catalysis: Enantioselective Allylic Substitution/Conjugate Additions with Alkynylaluminum Reagents and Stereospecific Isomerization of the Products to Trisubstituted Allenes**

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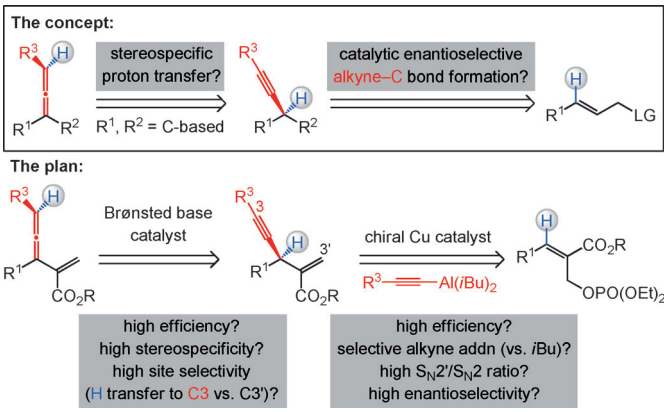
Among different types of unsaturated carbon–carbon bonds, allenes carry significant but relatively unexplored potential in chemical synthesis.[1] Research in more recent years has been focused on the development of catalytic enantioselective protocols that generate allenes[1] or on providing access to molecules that contain them.[2] Various procedures have been introduced for site-, chemo-, and/or stereoselective allene functionalization.[3] Nonetheless, methods of preparation have been largely centered on disubstituted variants;[1] protocols that furnish the trisubstituted allenes, especially those that are catalytic, are less common and typically involve nucleophilic $S_N2'$ additions to enantiomerically enriched alkynyl entities.[4] Among alternative approaches, strategies that deliver trisubstituted allenes through catalytic isomerization of alkyne-containing substrates[5] pose an attractive but somewhat uncharted pathway.[6] We thus envisioned the plan outlined in Scheme 1, involving the feasibility of catalytic and stereospecific isomerization of an enantiomerically enriched alkyne.[7] Bringing such a goal to fruition, however, required a stereoselective catalytic process to effect the desired 1,3-proton shift as well as an efficient, site- and enantioselective method for synthesis of the requisite substrates. Indeed, catalytic enantioselective allylic substitution (EAS) reactions[8] with alkynyl nucleophiles are rare;[9] related catalytic enantioselective processes that generate tertiary stereogenic carbon centers are unknown.[10] Herein, we describe the realization of the plan illustrated in Scheme 1 to address the above-mentioned shortcomings.

We selected trisubstituted allylic phosphates containing a C2 carboxylic ester as substrates (Scheme 1) for several reasons: 1) Preliminary studies indicated that a number of the products from EAS with disubstituted alkenes can be unstable. 2) The presence of a carboxylic ester renders the C–C bond-forming processes equivalent to a catalytic enantioselective conjugate addition of an acetylenic group, of which a relatively limited number of examples exist.[11] 3) Catalytic EAS with alkenes possessing the suggested substitution pattern have been less widely investigated[12] and provide a challenge in reaction efficiency and/or enantioselectivity (vs. variants that afford quaternary carbons or disubstituted olefins[9]). 4) Carboxylic esters and derivatives would allow for exploration of the influence of electronic effects and a chelating Lewis basic group on the catalytic EAS and the subsequent alkyne-to-allene interconversion.




***Scheme 1.*** Strategy for synthesis of enantiomerically enriched trisubstituted allenes by stereospecific transformation of an appropriate alkynyl substrate accessed through catalytic EAS with alkynylaluminum reagents as nucleophiles. LG = Leaving group.

We began by probing transformations that involve the alkynylaluminum reagent generated in situ by reaction of phenylacetylene, diisobutylaluminum hydride (dibal-H), and 5.0 mol% $Et_3N$.[13] Trisubstituted allylic phosphates (**2a–j**, Table 1) undergo reaction to afford the desired enynes (**3a–j**) in 58–98% yield and 90:10–98.5:1.5 e.r.; >98% $S_N2'$ selectivity is observed except for cyclohexyl-substituted **3j** (95:5 $S_N2'/S_N2$, entry 10, Table 1). The bidentate Cu complex derived from **1a** serves as the optimal catalyst.[14] Different aryl-substituted alkenes, including those with a sterically demanding *ortho* group (cf. entries 2–4, Table 1) can be used. Alkyl-substituted allylic phosphates react with high site- and enantioselectivity (entries 9 and 10, Table 1). Reactions in Table 1 proceed at a slower rate than the previously reported EAS with regioisomeric trisubstituted alkenes (24–48 h at −15 °C vs. 6.0 h at −30 °C),[9] although the latter set generates quaternary carbon stereogenic centers; this highlights the aforementioned challenges associated with the present set of substrates.[15]

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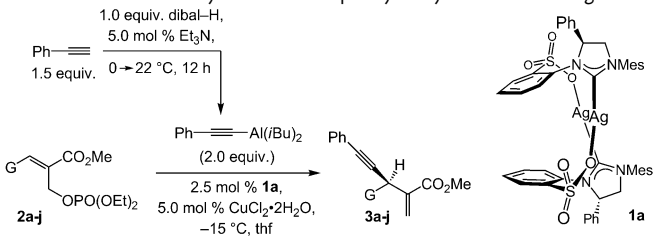
***Table 1:*** NHC–Cu-catalyzed EAS with phenylacetylene-derived reagent.[a]

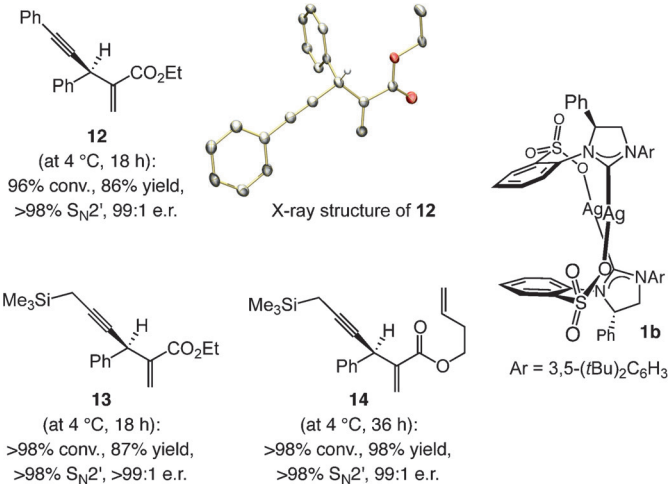



| Entry | G | *t* [h]; Conv. [%][b] | Yield [%][c] | $S_N2'/S_N2$[b] | e.r.[d] |
|---|---|---|---|---|---|
| 1 | $C_6H_5$; **2a** | 36; 98 | 90 | >98:2 | 95:5 |
| 2 | 1-naphthyl; **2b**[e] | 30; 92 | 91 | >98:2 | 92:8 |
| 3 | *o*-$MeOC_6H_4$; **2c**[f] | 48; 69 | 58 | >98:2 | 97:3 |
| 4 | *o*-$FC_6H_4$; **2d** | 36; 95 | 78 | >98:2 | 96:4 |
| 5 | 2-naphthyl; **2e** | 24; 98 | 90 | >98:2 | 94:6 |
| 6 | *m*-$BrC_6H_4$; **2f** | 36; >98 | 98 | >98:2 | 90:10 |
| 7 | *p*-$BrC_6H_4$; **2g** | 24; >98 | 98 | >98:2 | 92:8 |
| 8 | *p*-$F_3CC_6H_4$; **2h** | 36; >98 | 93 | >98:2 | 94:6 |
| 9 | $Ph(CH_2)_2$; **2i** | 24; >98 | 80 | >98:2 | 98.5:1.5 |
| 10 | Cy; **2j** | 24; >98 | 96 | 95:5 | 96:4 |

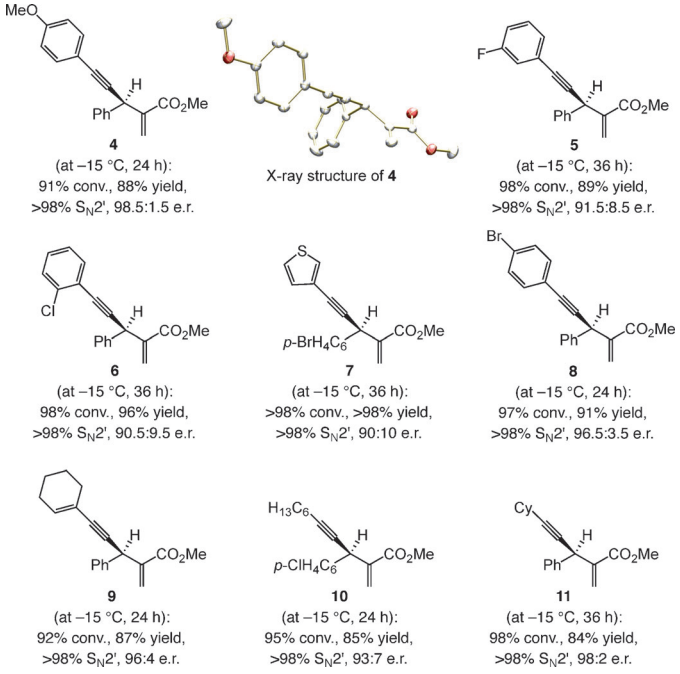
[a] Reactions were performed under $N_2$ atmosphere. [b] Determined through analysis of 400 MHz $^1H$ NMR spectra of unpurified mixtures (±2%). [c] Yield of isolated and purified products. [d] Determined by HPLC analysis (±2%); see the Supporting Information for details. [e] Reaction performed at 4 °C. [f] 5.0 mol% **1a** and 10 mol% Cu salt used. Mes = 2,4,6-$Me_3C_6H_2$, Cy = cyclohexyl.

Catalytic EAS with a range of alkynylaluminums bearing an aryl unit, whether they contain an electron-donating (cf. **4**, Scheme 2), an electron-withdrawing (cf. **6** and **8**), a heteroaryl (cf. **7**), or an alkenyl (cf. **9**) group proceed with similarly high efficiency and selectivity. The X-ray structure of enyne **4** offers support for the stereochemical identity of the major isomers (Scheme 2). Transformations with alkyl-substituted alkynylaluminum species, represented by **10** and **11** (Scheme 2), proceed to ≥95% conversion and deliver products in 84–85% yield, >98:2 $S_N2'/S_N2$, and 93:7–98:2 e.r.

Additions to substrates that contain a larger carboxylic ester unit (vs. $CO_2Me$) proceed with exceptional enantioselectivity (≥99:1 e.r.; Scheme 3), in spite of relatively elevated temperatures (4 vs. −15 °C), when NHC–$Ag^I$ complex **1b** is used (vs. **1a**).[16] The crystal structure for **12** provides additional stereochemical support, and synthesis of silanes **13** and **14** underscore the wide scope of the Cu-catalyzed protocol.




***Scheme 3.*** Additional products of high enantiomeric purity obtained through EAS with alkynylaluminum reagents and the catalyst precursor used to generate them. Reactions were performed under conditions shown in Table 1.



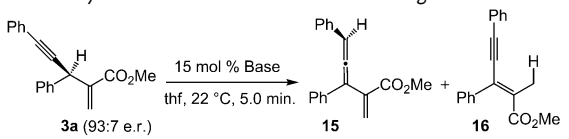

***Scheme 2.*** A range of products can be accessed in high efficiency and site- and enantioselectivity through catalytic EAS. Reactions were performed under the conditions shown in Table 1 (**1a** as catalyst precursor); 0.5 mol% **1a** and 1.0 mol% Cu salt used for EAS affording **7** and **11**.

Cu-catalyzed EAS can be performed on reasonable scale with 0.05–0.25 mol% of the NHC–Cu complex, derived from commercially available and air-stable $CuCl_2 \cdot 2H_2O$. For instance, **3a** (0.4 g **2a**, 0.1 mol% **1a**), **7** (0.2 g, 0.5 mol% **1a**), and **11** (0.2 g, 0.5 mol% **1a**) were obtained in 93%, >98%, and 84% yield and 93:7, 90:10, and 98:2 e.r., respectively (>98% conv. in 36 h at −15 °C; >98% $S_N2'$). The stability of the electrophilic α,β-unsaturated ester products underlines the mildness of the conditions. There is little or no residual dibal-H from the in situ preparation of alkynylaluminums when the catalytic EAS is commenced; there is no 1,2- or conjugate addition to the α,β-unsaturated ester moiety. This is in contrast to the more recently reported diastereoselective Cu-catalyzed transformations involving enantiomerically enriched *Z*-allylic phosphates where stoichiometric amounts of a strong base are present throughout.[10]

We then turned to the possibility of catalytic stereoselective formation of trisubstituted allenes. We screened the ability of some readily available Brønsted bases to effect the desired isomerization (Table 2). Treatment of **3a** (93:7 e.r.) with 15 mol% LiO*t*Bu, NaO*t*Bu, or KO*t*Bu at 22 °C results in

***Table 2:*** Catalytic isomerization to allene: screening of bases.[a]



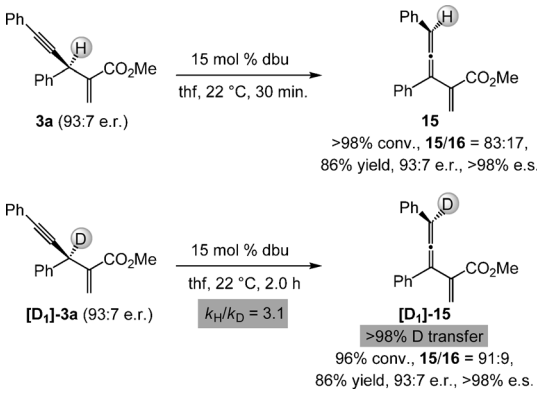

| Entry | Base | Conv. [%][b] | 15/16 | e.r.[c] | e.s. [%][d] |
|---|---|---|---|---|---|
| 1 | LiO*t*Bu | 97 | 72:28 | 58.5:41.5 | 63 |
| 2 | NaO*t*Bu | >98 | 75:25 | 86:14 | 92 |
| 3 | KO*t*Bu | 95 | 51:49 | 60:40 | 64 |
| 4 | dbu | 67 | 86:14 | 92:8 | >98 |
| 5 | tetramethylguanidine | 38 | 97:3 | 92:8 | >98 |
| 6 | tetramethylethylenediamine | <2 | NA | NA | NA |
| 7 | $(i\text{Pr})_2$NEt | <2 | NA | NA | NA |

[a] Reactions were performed under $N_2$ atmosphere. [b] Determined through analysis of 400 MHz $^1$H NMR spectra of unpurified mixtures (±2%). [c] Determined by HPLC analysis (±2%); see the Supporting Information for details. [d] e.s. (enantiospecificity) = product e.r./substrate e.r. ×100. dbu = 1,8-diazabicycloundec-7-ene; NA = not applicable.

≥95% consumption of the starting material in five minutes (entries 1–3, Table 2). Moderate selectivity in favor of allene **15** is observed with the Li and Na salts (72:28–75:25 **15**/**16**), whereas reaction with KO*t*Bu delivers nearly an equal mixture of isomers (entry 3). Moreover, reactions with LiO*t*Bu and KO*t*Bu lead to substantial loss of stereoisomeric purity [63–64% enantiospecificity (e.s.)][17] whereas the derived Na salt promotes isomerization with 92% e.s. Among a number of amines examined (entries 4–7, Table 2),[18] it is the more basic 1,8-diazabicycloundec-7-ene (dbu) and tetramethylguianidine[19] that deliver **15** with >98% e.s. and with higher site selectivity than the metal alkoxides, albeit less efficiently (67% and 38% vs. ≥95% conv.; 86:14 and 97:3 vs. up to 75:25 **15**/**16**). There is no detectable reaction with other amines (entries 6 and 7, Table 2).[18]

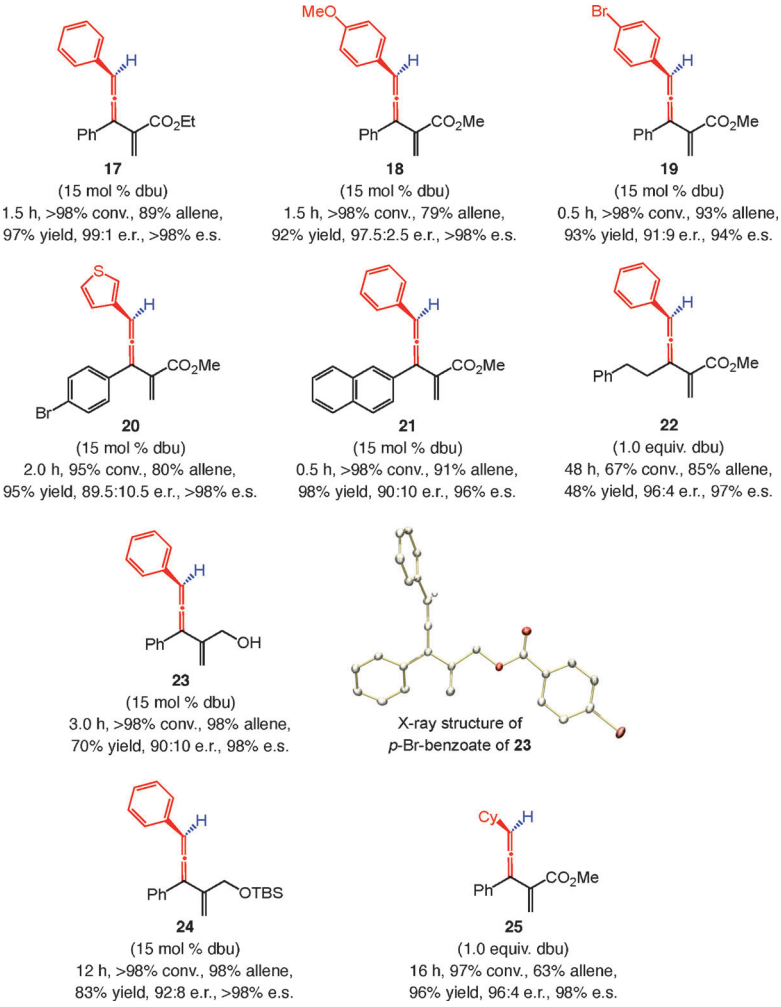
Subsequent optimization studies led us to establish that, as illustrated in Scheme 4, with 15 mol% dbu and when the reaction time is extended to 30 min (vs. 5.0 min.), there is >98% conversion of **3a** to an 83:17 mixture of **15**/**16** in 86% yield and >98% e.s. When [$D_1$]-**3a** is used, complete transfer of deuterium is observed ($k_H/k_D = 3.1$) and [$D_1$]-**15** is formed with >98% e.s.

Various skipped enynes, obtained by NHC–Cu-catalyzed EAS, can be converted to trisubstituted allenes in 63% to 98% site selectivity, 48–98% yield, and 94% to >98% e.s. (Scheme 5). Stereoselective isomerizations promoted by 15 mol% dbu can be carried out with an ethyl ester (cf. **17**, Scheme 5), an alkyne substrate bearing an electron-donating (cf. **18**), electron-withdrawing (cf. **19**), a heteraoryl substituent (cf. **20**), or a sterically demanding naphthyl group (cf. **21**); reactions proceed to




***Scheme 4.*** Alkyne-to-allene isomerization proceeds to completion within 30 min; labeling experiment indicates a significant primary kinetic isotope effect. Yields correspond to mixtures of isomers; see the Supporting Information for details.

≥95% conversion in less than two hours at 22°C. Formation of allene **22** is exceptionally stereoselective (97% e.s.), but requires an equivalent of dbu (vs. 15 mol%) to reach the 67% conversion mark (48% yield) in 48 h (vs. 2.0 h); such a rate



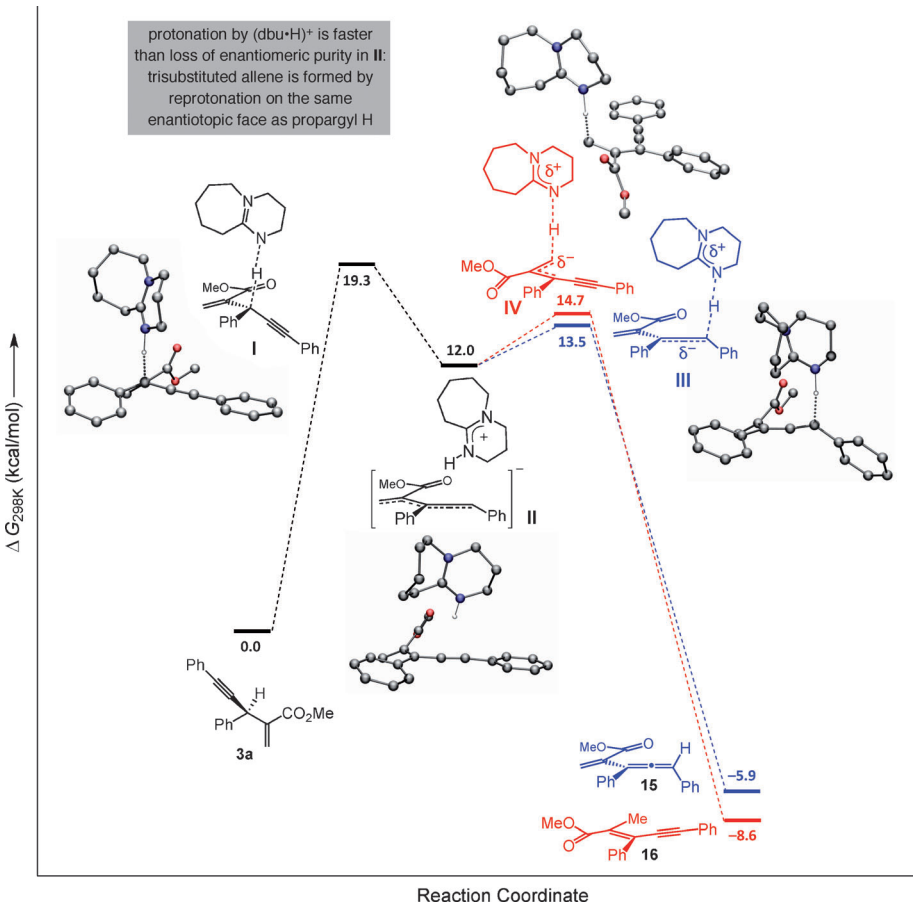

***Scheme 5.*** Trisubstituted allenes can be accessed efficiently in high enantiomeric purity through dbu-catalyzed isomerization; the X-ray structure of a derivative of **23** supports the *syn* mode of proton transfer. Yields correspond to mixtures of isomers.

difference (vs. aryl-substituted variants) is likely because of the lower acidity of the propargylic proton of the corresponding alkyne substrate. Reaction of the allylic alcohol derivative is facile and highly site- and stereoselective, as exemplified by the synthesis of **23**, formed after three hours in 70% yield (>98% conv.), 98:2 allene/alkene, and 98% e.s. The X-ray structure of the *p*-bromobenzoate derived from **23** confirms that the dbu-catalyzed isomerization occurs with retention of stereochemistry (i.e., proton deposited on the same face of allene as the propargyl H). Reaction of the derived silyl ether affords **24** with similarly high site selectivity (98% allene) and with slightly improved stereochemical control (>98% vs. 98% e.s. for alcohol **23**), but is less efficient, presumably due to steric factors (>98% conv. in 12 vs. 3.0 h for **23**). The transformation involving cyclohexyl-containing allene **25** proceeds to 97% conversion and in 98% e.s. in 16 h with 1.0 equivalent of dbu with moderate site selectivity (63% allene).

To gain mechanistic insight regarding the isomerization process, extensive DFT calculations were performed (Scheme 6). Congruent with the kinetic isotope effect shown in Scheme 4, the deprotonation emerges as the most energetically demanding step (**3a**→**I**, Scheme 6). The transition state for protonation to afford the allene (via **III** to give **15**) is lower in energy than that leading to the thermodynamically favored tetrasubstituted alkene (**16** via **IV**). A similar profile is calculated for reactions with NaO*t*Bu.[20] The above considerations suggest that the lower e.s. with the latter alkali metal base as well as the corresponding Li and K salts might be partly the result of erosion of kinetic selectivity by facile equilibration (i.e., deprotonation/reprotonation of allenyl H). Control experiments support the validity of the latter scenario; for example, treatment of a sample of an enantiomerically enriched allene **15** (87:13 e.r.) with 15 mol% NaO*t*Bu leads to substantial loss of enantiomeric purity within 30 min (61:39 e.r.); the same experiment but with 15 mol% dbu does not lead to any detectable change in e.r.[21] It appears that dbu can bring sufficient basicity[19] (vs. other N-containing bases) to promote effective removal of the propargylic proton, generating a conjugate acid that protonates the resulting anion at a sufficiently rapid rate to avoid loss of stereochemical integrity, which can occur through bond rotation.

Theoretical investigations further suggest that the lower selectivity observed with LiO*t*Bu and KO*t*Bu might be partly kinetic in nature (vs. NaO*t*Bu; see entries 1–3, Table 2). The Na counterion is likely of the appropriate Lewis acidity and size to establish a bridge between the carboxylic ester group and the *t*BuOH generated by deprotonation, causing a facile protonation prior to loss of stereochemistry;[20] on the other hand, the less Lewis acidic K ion or the relatively diminutive Li ion are less capable of serving the same function, thereby allowing *t*BuOH to separate from the anionic intermediate to result in racemization before a proton can be deposited to form an allene. In support of the above proposal, when the *tert*-butyldimethylsilyl ether derived from **3a** is subjected to conditions involving NaO*t*Bu (15 mol%, 5.0 min, 22°C), allene **24** is formed in 60:40 e.r. (65% e.s.; >98% conv., 90:10 allene/alkene, 64% yield vs. 86:14 e.r. and 92% e.s. with carboxylic ester **3a**). Nonetheless, the precise origin of site-selective protonation leading to preferential generation of the trisubstituted allenes is unclear; it is plausible that the lower degree of electron density that resides at the site more proximal to a carboxylic ester or its reduced variants (i.e., C3′ in Scheme 1) is less capable of capturing a proton; however, such a possibility is inconsistent with the higher site selectivity in reactions that generate allenes containing a more electron-deficient aryl unit (e.g., compare **18** and **19** in Scheme 5).

Development of additional catalysts for EAS reactions, study of other unexplored modes of functionalization, and




***Scheme 6.*** DFT calculations indicate that, with dbu as base, the deprotonation step might be rate limiting and generation of the allene product is kinetically preferred although the tetrasubstituted alkene is thermodynamically favored. See the Supporting Information for details.

applications of such protocols to the synthesis of biologically active molecules are in progress.

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[13] C. Feuvrie, J. Blanchet, M. Bonin, L. Micouin, *Org. Lett.* **2004**, *6*, 2333.

[14] See the Supporting Information for screening of different complexes.

[15] The precise reason for the observed rate differences has not been determined, but might but might be because reductive elimination of the (alkyne)(alkyl)-$Cu^{III}$ intermediate with the more congested system (release of steric strain) is faster.

[16] For example, with **1a**, reaction to generate **12** proceeds to 73% conversion at −15 °C within 24 h to afford the desired product in 96:4 e.r. (vs. >99:1 e.r. at +4 °C with **1b**). The modification in catalyst structure points to a somewhat sensitive nature of catalyst–substrate interactions. Enhanced reactivity and selectivity is likely due to the availability of sufficient space for the relatively more congested substrates provided by the 3,5-disubstituted NAr unit of the chiral Cu complex in the vicinity of the transition metal center (vs. 2,4,6-trisubstituted moiety of **1a**).

[17] S. E. Denmark, T. Vogel, *Chem. Eur. J.* **2009**, *15*, 11737.

[18] See the Supporting Information for the complete list of Brønsted base amines investigated.

[19] A p$K_a$ value of 18.0 has been measured for dbu in thf (vs. 17.0 for tetramethylguanidine and 13.4 for tetramethylethylenedia-

  

mine); see: I. Kaljurand, T. Rodima, A. Pihl, V. Mäemets, I. Leito, I. A. Koppel, M. Mishima, *J. Org. Chem.* **2003**, *68*, 9988.
[20] See the Supporting Information for energetics of isomerization with NaO*t*Bu.
[21] When lower substrate acidity demands the use of stoichiometric amounts of dbu, adventitious isomerization to the trisubstituted alkene occurs. For example, treatment of **25** with 1.0 equiv dbu leads to significant isomerization (78% in 12 h at 22 °C in thf).

  