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# Highly Site- and Enantioselective Cu-Catalyzed Allylic Alkylation Reactions with Easily Accessible Vinylaluminum Reagents

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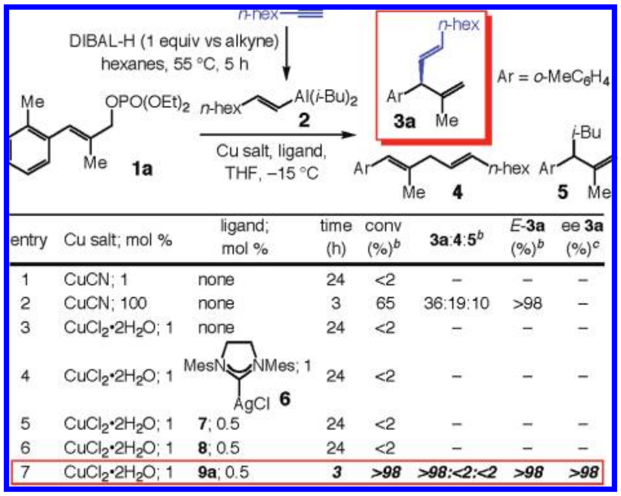
Catalytic enantioselective addition of vinylmetals to activated alkenes is a potentially versatile but underdeveloped class of transformations.[1] Compared to processes with arylmetals[2] and, particularly, alkylmetals,[1a,b] processes with the corresponding vinylic reagents are of higher synthetic utility but remain scarce, and the few reported examples are Rh-catalyzed conjugate additions.[3] We have developed an efficient method for catalytic asymmetric allylic alkylations (AAA) with vinylaluminum reagents that are prepared and used in situ; stereoselective reactions of commercially available DIBAL-H with readily accessible terminal alkynes efficiently deliver the vinylmetals. Alkylations are promoted by 0.5−2.5 mol % chiral N-heterocyclic carbene (NHC)[4] complexes derived from an air stable Cu salt. To the best of our knowledge, this is the first report of catalytic AAA reactions involving vinylmetal reagents.[5]

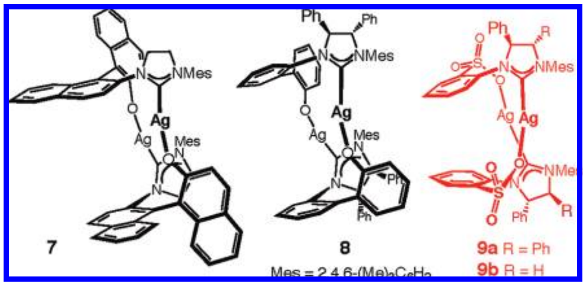
We began by examining reactions of vinylaluminum **2** with allylic phosphate **1a**, which belongs to a less-examined category of substrates for catalytic AAA.[6] Reagent **2** is generated from hydroalumination of 1-octyne with DIBAL-H.[7] When **2** is used to alkylate **1a** in the presence of 1 mol % CuCN, there is no reaction (Table 1, entry 1). Alkylation proceeds to 65% conversion with 100 mol % CuCN in 3 h, but nearly all possible isomers are generated (entry 2); formation of **3a** is accompanied by 19% of 1,4-diene **4** as well as the product from transfer of an *i*-Bu group (**5**, 10%). There is <2% conversion after 24 h with 1 mol % $CuCl_2·2H_2O$ (entry 3), and achiral NHC **6** cannot help promote alkylation (same outcome with $(CuOTf)_2·C_6H_6$ and **6**). Similarly, in the presence of chiral NHC·Ag complexes **7**[4a] or **8**,[4b,8] there is no reaction (entries 5,6). In a remarkable contrast, with only 0.5 mol % **9a**,[9] AAA proceeds to >98% conversion in only 3 h, furnishing **3a** in >98% ee and with >98% $S_N2'$ and *E* selectivity.[10] The high enantioselectivity aside, the data in Table 1 highlight the unique attributes of the Cu complex derived from **9a**, which readily initiates alkylation with exceptional site (>98% $S_N2'$) and group selectivity (<2% **5**). Direct synthesis of vinylaluminums with DIBAL-H is an attractive feature of the method and compares favorably with other protocols. Previous two-step protocols[3b] involve alkyne hydrozirconation with the more costly and sensitive[11] $Cp_2ZrHCl$ (or hydroboration) followed by transmetallation with $Me_2Zn$, which is also relatively expensive.[12]

**Table 1.** Synthesis of Vinylaluminum Reagents and Use in Catalytic Allylic Alkylation[a]



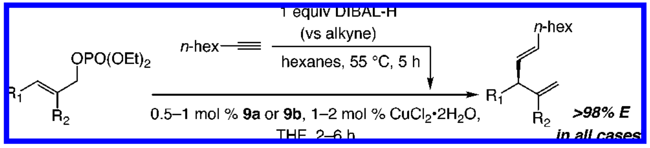
| entry | Cu salt; mol % | ligand; mol % | time (h) | conv (%)[b] | **3a**:**4**:**5**[b] | *E*-**3a** (%)[b] | ee **3a** (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | CuCN; 1 | none | 24 | <2 | – | – | – |
| 2 | CuCN; 100 | none | 3 | 65 | 36:19:10 | >98 | – |
| 3 | $CuCl_2·2H_2O$; 1 | none | 24 | <2 | – | – | – |
| 4 | $CuCl_2·2H_2O$; 1 | MesN NMes; 1<br>AgCl **6** | 24 | <2 | – | – | – |
| 5 | $CuCl_2·2H_2O$; 1 | **7**; 0.5 | 24 | <2 | – | – | – |
| 6 | $CuCl_2·2H_2O$; 1 | **8**; 0.5 | 24 | <2 | – | – | – |
| 7 | $CuCl_2·2H_2O$; 1 | **9a**; 0.5 | ***3*** | ***>98*** | ***>98:<2:<2*** | ***>98*** | ***>98*** |

[a] Conditions: 2.0 equiv of vinyl-Al reagent (vs substrate) under $N_2$. [b] $^1H$ NMR analysis (400 MHz). [c] By chiral HPLC (Supporting Information).



Various allylic phosphates can be used (Table 2); >98% conversion is obtained in 2−6 h with 0.5−1 mol % chiral catalyst. Transformations of trisubstituted olefins bearing an aryl substituent are shown in entries 1−8. Substrates bearing sterically demanding groups (entries 1, 3, 6, and 8), electron-withdrawing aryl units (entries 2−5) or an unsubstituted phenyl (entry 7) undergo AAA in 82−94% yield and 87 to >98% ee. The reaction in entry 9 (88% yield, 77% ee) is an efficient but less selective AAA of a trisubstituted olefin with an *n*-alkyl substituent. The only AAA that affords the undesired chiral $S_N2$ product is one where the aryl substituent contains an electron donating ortho methoxy group (entry 6). As the examples in entries 10−12 indicate, alkylations

**Table 2.** Cu-Catalyzed AAA with Vinylaluminum Reagent **2**[a]



| entry | $R_1$ | $R_2$ | | NHC; mol %; mol % Cu | temp (°C) | product | $S_N2'$ (%)[b] | yield (%)[c] | ee (%)[d] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | *o*-$MeC_6H_4$ | Me | **1a** | **9a**; 0.5; 1 | −15 | **3a** | >98 | 87 | >98 |
| 2 | *o*-$BrC_6H_4$ | Me | **1b** | **9a**; 0.5; 1 | −15 | **3b** | >98 | 84 | 96 |
| 3 | *o*-$NO_2C_6H_4$ | Me | **1c** | **9a**; 0.5; 1 | −15 | **3c** | >98 | 94 | 96 |
| 4 | *p*-$NO_2C_6H_4$ | Me | **1d** | **9a**; 0.5; 1 | −15 | **3d** | >98 | 93 | 89 |
| 5 | *m*-$TsOC_6H_4$ | Me | **1e** | **9a**; 0.5; 1 | −15 | **3e** | >98 | 82 | 87 |
| 6 | *o*-$MeOC_6H_4$ | Me | **1f** | **9a**; 0.5; 1 | −15 | **3f** | 90 | 88[e] | 95 |
| 7 | $C_6H_5$ | Me | **1g** | **9a**; 0.5; 1 | −15 | **3g** | >98 | 84 | 92 |
| 8 | 1-naphthyl | Me | **1h** | **9a**; 0.5; 1 | −15 | **3h** | >98 | 88 | 91 |
| 9 | $Ph(CH_2)_2$ | Me | **1i** | **9b**; 0.5; 1 | −15 | **3i** | >98 | 88 | 77 |
| 10 | $C_6H_5$ | H | **10a** | **9b**; 1; 2 | −50 | **11a** | >98 | 90 | 79 |
| 11 | Cy | H | **10b** | **9b**; 1; 2 | −50 | **11b** | >98 | 92 | 86 |
| 12 | $PhMe_2Si$ | H | **10c** | **9b**; 0.5; 1 | −15 | **11c** | >98 | 91 | 93 |

[a] Conditions: 2 equiv of vinyl-Al reagent (vs substrate); under $N_2$. [b] $^1H$ NMR analysis (400 MHz). [c] Yield after purification; all conversions >98%. [d] By chiral HPLC (Supporting Information). [e] Yield of pure $S_N2'$ product.

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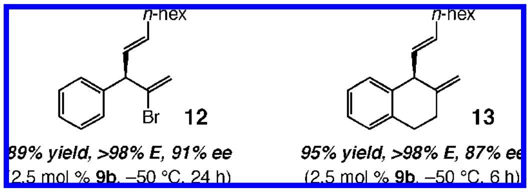
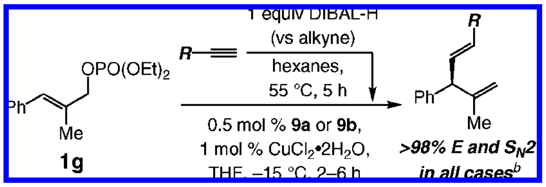
of disubstituted olefins proceed in high yield but are less selective unless a sterically demanding group, such as a silyl substituent, is present (entry 12). The findings in entries 9−12 of Table 2 involve modified complex **9b**, since in such cases, use of **9a** leads to lower selectivities; 1,4-dienes **3i** and **11a**,**b**,**c** are formed in 65%, 56%, 78%, and 90% ee, respectively, when **9a** is employed. Reactions in entries 1−8 proceed with identical degrees of asymmetric induction when **9a** or **9b** are used.



Noteworthy are enantioselective syntheses of acyclic 1,4-diene **12** (91% ee) and bicyclic diene **13** (87% ee; 69% ee with **9a**); these transformations illustrate that catalytic AAA can be used with vinyl bromides and cyclic alkenes. Other alkynes may be employed to access products **14**−**17**, bearing different vinyl groups (Table 3; >98% $S_N2'$ and *E* selectivity). Alkynes with sizable substituents can be utilized: 1,4-diene **17** (entry 4, Table 3) is obtained in 93% yield and 88% ee (82% ee with **9a**).

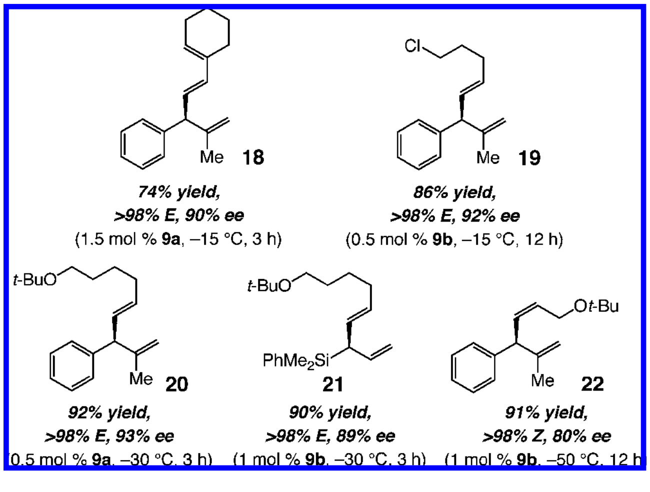
***Table 3.*** Cu-Catalyzed AAA of Vinylaluminum Reagent Derived from Various Terminal Alkynes[a]



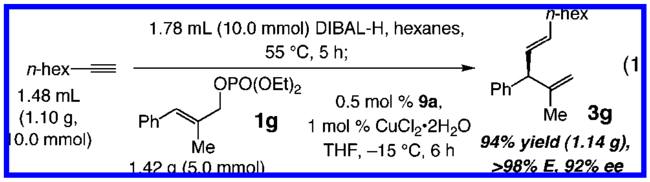
| entry | R | NHC | product | yield (%)[c] | ee (%)[d] |
|---|---|---|---|---|---|
| 1 | $PhCH_2$ | **9b** | **14** | 85 | 91 |
| 2 | (cyclopent)$CH_2$ | **9a** | **15** | 90 | 92 |
| 3 | cyclohex | **9a** | **16** | 91 | 91 |
| 4 | *t*-Bu | **9b** | **17** | 93 | 88 |

[a] Conditions: 2 equiv of vinyl-Al reagent (vs substrate); under $N_2$. [b] $^1H$ NMR analysis (400 MHz). [c] Yield after purification; all conversions >98%. [d] By chiral HPLC (Supporting Information).

Additional attributes of the method are illustrated by preparation of **18**−**22**. Enantioselective synthesis of **18** demonstrates that conjugated enynes can be utilized to access chiral dienes. Products bearing versatile alkyl halide substituents[13] can be synthesized (**19** in 92% ee). Tris(homoallylic) ether **20** and allylsilane **21** are obtained in 93% and 89% ee, respectively, and exclusively as *E* alkene isomers. Allylether **22** is, in contrast, formed with >98% *Z* selectivity (80% ee).[14] In the latter case, the initial hydroalumination is likely directed by the proximal Lewis basic, albeit sterically demanding, *t*-butoxy ether to generate a *cis*-vinylaluminum.



The utility of this method is showcased by the one-pot, gram-scale transformation in eq 1. Treatment of 1-octyne with DIBAL-H, addition of a mixture of **9a** (0.5 mol %) and $CuCl_2{\cdot}2H_2O$ (1 mol %, from a commercial bottle), followed by the addition of 1.42 grams of allylic phosphate **1g**, results in the formation of **3g** in 94% yield and 92% ee (>98% *E*). The Cu-catalyzed three-component enantioselective process was performed on a bench top without the need to resort to glovebox techniques.



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

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(10) When the precursor imidazolinium salt of **9a** is used, 77% conversion is observed (24 h, −15 °C) and **3a** is formed in >98% ee (>98% *E* and $S_N2'$). There is, however, <2% conversion with the $BF_4$·imidazolinium salt of **6**.

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