

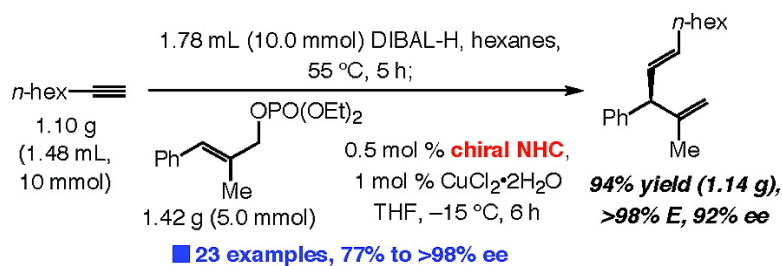
Communication

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

Yunmi Lee, Katsuhiko Akiyama, Dennis G. Gillingham, M. Kevin Brown, and Amir H. Hoveyda\*

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467

Received October 26, 2007; E-mail: amir.hoveyda@bc.edu

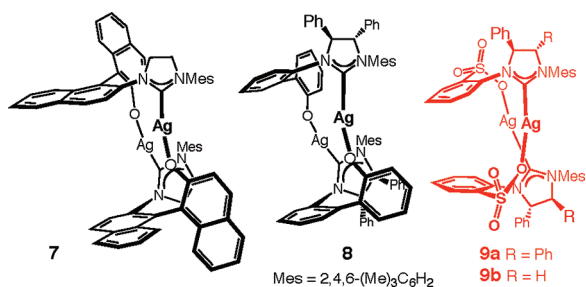
Catalytic enantioselective addition of vinylmetals to activated alkenes is a potentially versatile but underdeveloped class of transformations.<sup>1</sup> Compared to processes with arylmetals<sup>2</sup> and, particularly, alkylmetals,<sup>1a,b</sup> processes with the corresponding vinylic reagents are of higher synthetic utility but remain scarce, and the few reported examples are Rh-catalyzed conjugate additions.<sup>3</sup> 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)<sup>4</sup> 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.<sup>5</sup>

We began by examining reactions of vinylaluminum **2** with allylic phosphate **1a**, which belongs to a less-examined category of substrates for catalytic AAA.<sup>6</sup> Reagent **2** is generated from hydroalumination of 1-octyne with DIBAL-H.<sup>7</sup> 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

**Table 1.** Synthesis of Vinylaluminum Reagents and Use in Catalytic Allylic Alkylation<sup>a</sup>

entry	Cu salt; mol %	ligand; mol %	time (h)	conv (%) <sup>b</sup>	3a:4:5 <sup>b</sup>	E-3a (%) <sup>b</sup>	ee 3a (%) <sup>c</sup>
1	CuCN; 1	none	24	<2	—	—	—
2	CuCN; 100	none	3	65	36:19:10	>98	—
3	CuCl <sub>2</sub> ·2H <sub>2</sub> O; 1	none	24	<2	—	—	—
4	CuCl <sub>2</sub> ·2H <sub>2</sub> O; 1	MesN(AgCl)NMe <sub>2</sub> ; 1	24	<2	—	—	—
5	CuCl <sub>2</sub> ·2H <sub>2</sub> O; 1	<b>7</b> ; 0.5	24	<2	—	—	—
6	CuCl <sub>2</sub> ·2H <sub>2</sub> O; 1	<b>8</b> ; 0.5	24	<2	—	—	—
7	CuCl <sub>2</sub> ·2H <sub>2</sub> O; 1	<b>9a</b> ; 0.5	<b>3</b>	>98	>98:<2:<2	>98	>98

<sup>a</sup> Conditions: 2.0 equiv of vinyl-Al reagent (vs substrate) under N<sub>2</sub>. <sup>b</sup> <sup>1</sup>H NMR analysis (400 MHz). <sup>c</sup> By chiral HPLC (Supporting Information).



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<sub>2</sub>·2H<sub>2</sub>O (entry 3), and achiral NHC **6** cannot help promote alkylation (same outcome with (CuOTf)<sub>2</sub>·C<sub>6</sub>H<sub>6</sub> and **6**). Similarly, in the presence of chiral NHC·Ag complexes **7**<sup>4a</sup> or **8**,<sup>4b,8</sup> there is no reaction (entries 5,6). In a remarkable contrast, with only 0.5 mol % **9a**,<sup>9</sup> AAA proceeds to >98% conversion in only 3 h, furnishing **3a** in >98% ee and with >98% S<sub>N</sub>2' and *E* selectivity.<sup>10</sup> 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<sub>N</sub>2') 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<sup>3b</sup> involve alkyne hydrozirconation with the more costly and sensitive<sup>11</sup> Cp<sub>2</sub>ZrHCl (or hydroboration) followed by transmetalation with Me<sub>2</sub>Zn, which is also relatively expensive.<sup>12</sup>

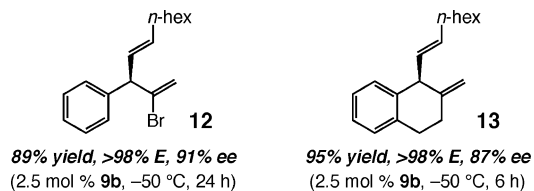
Various allylic phosphates can be used (Table 2); >98% conversion is obtained in 2–6 h with 0.5–1 mol % chiral catalyst. Transformations of trisubstituted olefins bearing an aryl substituent are shown in entries 1–8. Substrates bearing sterically demanding groups (entries 1, 3, 6, and 8), electron-withdrawing 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<sub>N</sub>2 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**<sup>a</sup>

entry	R <sub>1</sub>	R <sub>2</sub>	NHC; mol %; mol % Cu	temp (°C)	product	S <sub>N</sub> 2' (%) <sup>b</sup>	yield (%) <sup>c</sup>	ee (%) <sup>d</sup>
1	<i>o</i> -MeC <sub>6</sub> H <sub>4</sub>	Me	<b>9a</b> ; 0.5; 1	-15	<b>3a</b>	>98	87	>98
2	<i>o</i> -BrC <sub>6</sub> H <sub>4</sub>	Me	<b>9a</b> ; 0.5; 1	-15	<b>3b</b>	>98	84	96
3	<i>o</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Me	<b>9a</b> ; 0.5; 1	-15	<b>3c</b>	>98	94	96
4	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Me	<b>9a</b> ; 0.5; 1	-15	<b>3d</b>	>98	93	89
5	<i>m</i> -TsOC <sub>6</sub> H <sub>4</sub>	Me	<b>9a</b> ; 0.5; 1	-15	<b>3e</b>	>98	82	87
6	<i>o</i> -MeOC <sub>6</sub> H <sub>4</sub>	Me	<b>9a</b> ; 0.5; 1	-15	<b>3f</b>	90	88 <sup>e</sup>	95
7	C <sub>6</sub> H <sub>5</sub>	Me	<b>9a</b> ; 0.5; 1	-15	<b>3g</b>	>98	84	92
8	1-naphthyl	Me	<b>9a</b> ; 0.5; 1	-15	<b>3h</b>	>98	88	91
9	Ph(CH <sub>2</sub> ) <sub>2</sub>	Me	<b>9b</b> ; 0.5; 1	-15	<b>3i</b>	>98	88	77
10	C <sub>6</sub> H <sub>5</sub>	H	<b>10a</b> <b>9b</b> ; 1; 2	-50	<b>11a</b>	>98	90	79
11	Cy	H	<b>10b</b> <b>9b</b> ; 1; 2	-50	<b>11b</b>	>98	92	86
12	PhMe <sub>2</sub> Si	H	<b>10c</b> <b>9b</b> ; 0.5; 1	-15	<b>11c</b>	>98	91	93

<sup>a</sup> Conditions: 2 equiv of vinyl-Al reagent (vs substrate); under N<sub>2</sub>. <sup>b</sup> <sup>1</sup>H NMR analysis (400 MHz). <sup>c</sup> Yield after purification; all conversions >98%. <sup>d</sup> By chiral HPLC (Supporting Information). <sup>e</sup> Yield of pure S<sub>N</sub>2' product.

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**).

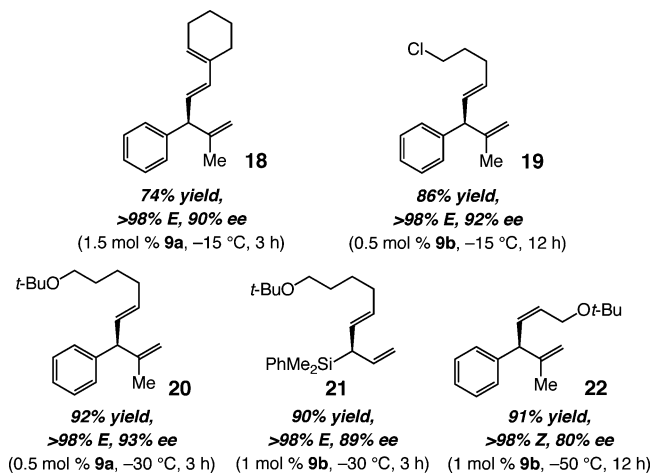
**Table 3.** Cu-Catalyzed AAA of Vinylaluminum Reagent Derived from Various Terminal Alkynes<sup>a</sup>

1 equiv DIBAL-H (vs alkyne)  
hexanes, 55 °C, 5 h  
0.5 mol % **9a** or **9b**,  
1 mol %  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ ,  
THF, -15 °C, 2–6 h  
>98% *E* and  $S_N2'$   
in all cases<sup>b</sup>

entry	R	NHC	product	yield (%) <sup>c</sup>	ee (%) <sup>d</sup>
1	PhCH <sub>2</sub>	<b>9b</b>	<b>14</b>	85	91
2	(cyclopent)CH <sub>2</sub>	<b>9a</b>	<b>15</b>	90	92
3	cyclohex	<b>9a</b>	<b>16</b>	91	91
4	<i>t</i> -Bu	<b>9b</b>	<b>17</b>	93	88

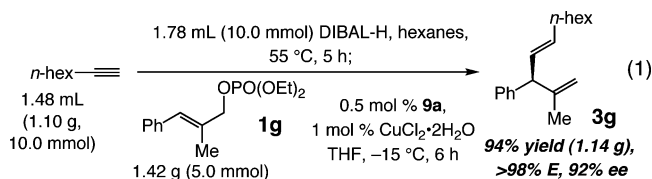
<sup>a</sup> Conditions: 2 equiv of vinyl-Al reagent (vs substrate); under  $\text{N}_2$ . <sup>b</sup> <sup>1</sup>H NMR analysis (400 MHz). <sup>c</sup> Yield after purification; all conversions >98%. <sup>d</sup> By chiral HPLC (Supporting Information).

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<sup>13</sup> 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).<sup>14</sup> 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  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (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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