Enantioselective Catalysis

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# Copper-Catalyzed Enantioselective Allylic Substitution with Readily Accessible Carbonyl- and Acetal-Containing Vinylboron Reagents**

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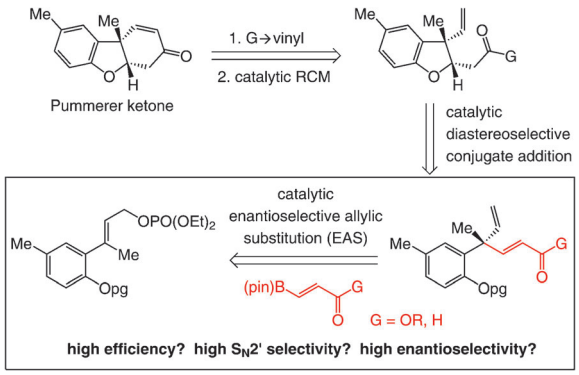
Catalytic enantioselective allylic substitution (EAS) reactions are of prominent utility in chemical synthesis.[1] Such transformations generate a stereogenic center adjacent to an alkene, which can be further functionalized to afford a range of other enantiomerically enriched molecules. Despite noteworthy advances, several issues remain unresolved in this area. Nearly all the existing protocols require nucleophilic metal-based reagents, which, while often the source of high reactivity, are not well suited when certain commonly occurring functional groups are present. Moreover, whereas significant focus has been placed on additions of alkyl groups,[1] reported examples of catalytic processes that lead to incorporation of aryl or heteroaryl,[2] allyl,[3] alkynyl,[4] or allenyl[5] moieties are markedly small in number.

The corresponding reactions resulting in additions of vinyl units have received attention only recently. Efforts in these laboratories have led to the development of catalytic EAS with vinylmetal species, generated through hydroaluminations of alkynes[6] (with di-*iso*-butylaluminum hydride) and used in situ for site- and enantioselective C–C bond formation.[7] Nonetheless, vinylaluminum reagents with a heteroatom substituent at their allylic position cannot be efficiently prepared by hydrometalation.[8] The above shortcoming is underlined by the sequence shown in Scheme 1, regarding a projected enantioselective synthesis of Pummerer ketone,[9] an intermediate in morphine biosynthesis.[10] The key step would ideally involve EAS with a carbonyl-substituted reagent, leading to the formation of an α,β-unsaturated ester that could then be subjected to a diastereoselective intramolecular conjugate addition. The analogous vinylaluminum species are inaccessible. In contrast, the corresponding vinylboron reagents are prepared readily; however, an efficient method for catalytic EAS involving such entities does not exist. Such protocols would notably enhance the general utility of this important class of transformations.




***Scheme 1.*** A route for enantioselective synthesis of Pummerer ketone might involve catalytic allylic substitution with a carbonyl-containing vinyl group, followed by a catalytic diastereoselective intramolecular conjugate addition and catalytic ring-closing metathesis. pg = protecting group, pin = pinacolato.

Herein, we outline a method for catalytic EAS reactions that proceed with vinylboron reagents,[11] including those that contain a carboxylic ester or an acetal unit, which are either purchased or can be prepared by Cu-catalyzed processes.[12] The coupling reactions are promoted by sulfonate-bridged bidentate N-heterocyclic carbene (NHC) complexes of copper and generate all-carbon quaternary stereogenic centers.[13] The desired products, including those with an ester, an aldehyde, or an acetal group, are formed in up to 98% yield, more than 98% $S_N2'$ selectivity and more than 98:2 enantiomeric ratio (e.r.). Utility is demonstrated by concise enantioselective syntheses of Pummerer ketone as well as its hitherto undisclosed *anti* isomer, where diastereoselective intramolecular conjugate additions, controlled by cinchona alkaloid catalysts, and Ru-catalyzed ring-closing metathesis complement the NHC–Cu-catalyzed EAS process.

We initiated our investigations by probing the ability of different NHC–Cu complexes to promote reaction between commercially available *n*-hexyl(pinacolato)vinylboron **9** and *o*-methoxyphenyl-containing allylic phosphate **7a**; the expected product (**8a**) contains an *ortho*-alkoxy-substituted aryl unit, as required in the proposed approach to enantioselective synthesis of Pummerer ketones (see Scheme 1). The presence of NaOMe is to assist the formation of the NHC–Cu-vinyl intermediate (via the methoxy-bearing boronate).[14] Preliminary studies indicated that the transformation is sluggish at ambient temperature (≤30% conversion with various catalysts). Therefore, in contrast to Cu-catalyzed reactions with the related allenylboron reagent,[5] which proceed to completion at 22 °C, it appeared that EAS with the relatively more hindered vinylboron demands more

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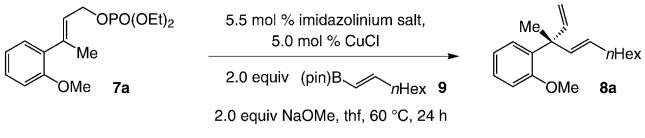
forcing conditions. Whether high site- and enantioselectivity would be achievable under the latter circumstances remained to be established.

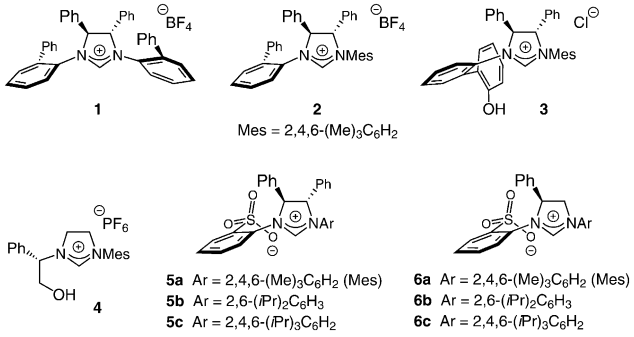
There is reasonable efficiency (58–92% conv., ≤60% yield) and low to appreciable site and enantioselectivity with monodentate and aryloxy- or alkoxy-bridged NHC–Cu complexes (80–93% $S_N2'$ and up to 80:20 e.r.; Table 1, entries 1–4). Conversely, with sulfonate-bridged imidazolinium salts[15] **5a–c** and **6a–c** as catalyst precursors, transformations are efficient, generating divinyl-substituted quaternary carbon stereogenic centers with nearly complete site and enantioselectivity (up to 95% yield, >98% $S_N2'$ and >98:2 e.r.; Table 1, entries 5–10).[16]

***Table 1:*** Initial examination of various chiral NHC–Cu complexes.[a]



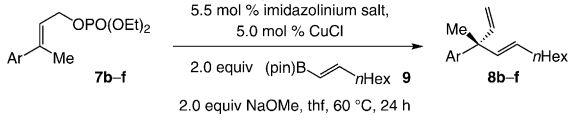

| Entry | Imid. salt | Conv. [%][b] | Yield [%][c] | $S_N2':S_N2$[b] | e.r.[d] |
|---|---|---|---|---|---|
| 1 | **1** | 87 | 51 | 86:14 | 80:20 |
| 2 | **2** | 92 | 59 | 87:13 | 73:27 |
| 3 | **3** | 58 | 12 | 80:20 | n.d.[e] |
| 4 | **4** | 89 | 60 | 93:7 | 52:48 |
| 5 | **5a** | >98 | 95 | 98:2 | 90:10 |
| 6 | **5b** | >98 | 90 | 98:2 | 97:3 |
| 7 | **5c** | >98 | 91 | >98:2 | >98:2 |
| 8 | **6a** | 95 | 87 | >98:2 | 73:27 |
| 9 | **6b** | >98 | 94 | 98:2 | >98:2 |
| 10 | **6c** | >98 | 86 | 98:2 | >98:2 |

[a] Reactions were performed under $N_2$ atmosphere. [b] Determined through analysis of 400 MHz $^1$H NMR spectra of unpurified mixtures. [c] Yield of isolated and purified products. [d] Determined by HPLC analysis (±2%); see the Supporting Information for details. [e] Enantioselectivity not determined because of low yield of isolated product (12%). n.d. = not determined.




Catalytic EAS with vinylboron reagent **9** can be performed with various aryl-substituted allylic phosphates (representative cases in Table 2). Reactions with substrates that contain an *ortho*-aryl group, although somewhat less facile (82–87% conversion in entries 1–3 vs. >98% conversion in entries 4 and 5), are generally more enantioselective (87:13 to >98:2 e.r. vs. 84:16–86:14 e.r.). There is high site selectivity in favor of the branched 1,4-diene isomer in every case (96–98% $S_N2'$).[17]

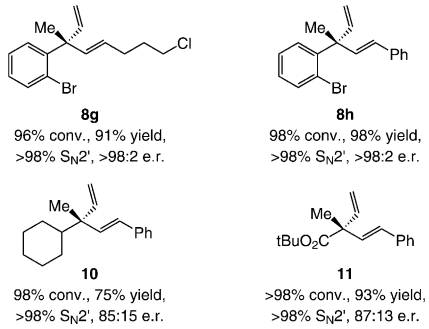
***Table 2:*** Site- and enantioselective NHC–Cu-catalyzed EAS with aryl-substituted substrates and alkenylboron **9**.[a]




| Entry | Substrate (Ar) | Imid. salt | Conv. [%][b] | Yield [%][c] | $S_N2':S_N2$[b] | e.r.[d] |
|---|---|---|---|---|---|---|
| 1 | **7b** (*o*-$MeC_6H_4$) | **6b** | 87 | 82 | 96:4 | 92:8 |
| 2 | **7c** (*o*-$BrC_6H_4$) | **6b** | 87 | 85 | 98:2 | >98:2 |
| 3 | **7d** (*o*-$NO_2C_6H_4$) | **5a** | 82 | 50 | 98:2 | 87:13 |
| 4 | **7e** ($C_6H_5$) | **6c** | >98 | 90 | 98:2 | 86:14 |
| 5 | **7f** (*p*-$ClC_6H_4$) | **6b** | >98 | >98 | 98:2 | 84:16 |

[a] Reactions were performed under $N_2$ atmosphere. [b] Determined through analysis of 400 MHz $^1$H NMR spectra of unpurified mixtures. [c] Yields of isolated purified products (±5%). [d] Determined by HPLC analysis (±2%); see the Supporting Information for details.

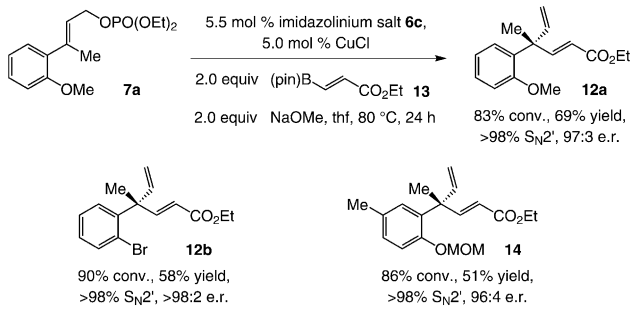
The examples provided in Scheme 2 illustrate that the NHC–Cu-catalyzed EAS can be performed with different robust vinylboron reagents and allylic phosphates, including those that contain an alkyl or a carboxylic ester unit. Thus, (pinacolato)vinylboron species that carry a halogen atom (see **8g**) or an aryl group (see **8h**, **10**, and **11**) can be utilized. As before, high efficiency (75–98% yield) and exceptional site selectivity (>98% $S_N2'$) is observed, and allylic phosphates with *ortho*-substituted aryls are converted to products of higher enantiomeric purity (>98:2 vs. 85:15–87:13 e.r.).




***Scheme 2.*** Products of NHC–Cu-catalyzed EAS of various trisubstituted allylic phosphates and different readily accessible vinylboron reagents. All reactions were performed with 5.5 mol% **6b**; see Table 2 for conditions and the Supporting Information for details.

The transformations discussed up to this point establish the feasibility of using a readily accessible and robust class of boron-based reagents. Next, we turned our attention to examining C–C bond-forming processes in which use of a vinylmetal is not possible. With ester-substituted vinylboron compound **13**, NHC–Cu-catalyzed EAS furnishes the desired product with high selectivity (Scheme 3). Allylic substitutions proceed in more than 98% $S_N2'$ selectivity and 96:4 to more than 98:2 e.r. (Scheme 3)[18] and the desired products are obtained in 51–69% yield. It is possible that slower rate of reaction (80 °C required vs. 60 °C for alkyl-substituted vinylboron reagents) and moderate yields are because the



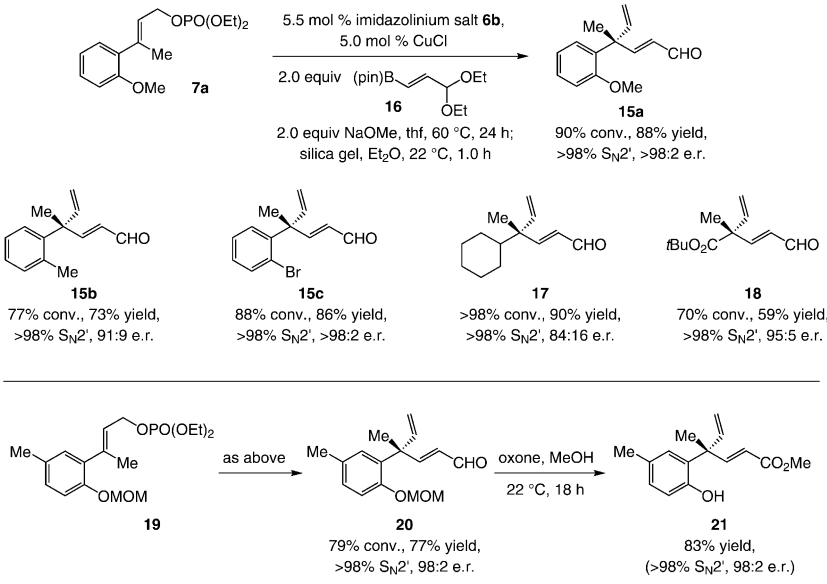

***Scheme 3.*** NHC–Cu-catalyzed EAS with allylic phosphates and carboxylic ester containing vinylboron **13**. MOM = methoxymethyl.

electron-withdrawing ester substituent diminishes the facility of the addition of the vinylcuprate to the allylic phosphate, which is accompanied by the conversion of the $Cu^{I}$ complex to a $Cu^{III}$ intermediate; subsequent reductive elimination generates the C–C bond.[5,7c]

In spite of the appreciable reactivity and exceptional site- and enantioselectivity in the latter processes, we decided to search for a more efficient protocol for obtaining products with carbonyl-containing vinyl units. We were especially interested in identifying a higher yielding approach to the enantioselective preparation of α,β-unsaturated ester **14**, to be incorporated in the projected Pummerer ketones synthesis (see Scheme 1). We accordingly explored the possibility of EAS with another commercially available vinylboron reagent: the acetal-containing **16** (Scheme 4). Based on the above-mentioned electronic effects regarding the slower rate of transformations with vinylboron compound **13**, we envisioned that catalytic EAS with **16**, which carries a less electron-withdrawing substituent, would be more facile and efficient. Reaction of allylic phosphate **7a** with **16** in combination with 5.5 mol% imidazolinium salt **6b**, under otherwise identical conditions (see above), followed by treatment of the mixture with a suspension of silica gel for one hour (22 °C) delivers enal **15a** in 88% yield and more than 98:2 e.r. (< 2% $S_N2$ addition). Other examples in Scheme 4 (**15b–c** and **17–18**) demonstrate the generality of the approach. Use of organoboron **16** offers the attractive combination of furnishing the desired products in higher yields (vs. **13**), while allowing access to the more reactive α,β-unsaturated aldehydes by a simple hydrolytic procedure. The enantiomerically enriched acetals can be accessed through chromatography with silica gel neutralized with $Et_3N$ (3% by volume);[19] for example, the precursor to **15a** is isolated in 86% yield and more than 98:2 e.r. The vinylaluminum species corresponding to **16** or the aldehyde derived from it cannot be prepared by hydroalumination procedures.

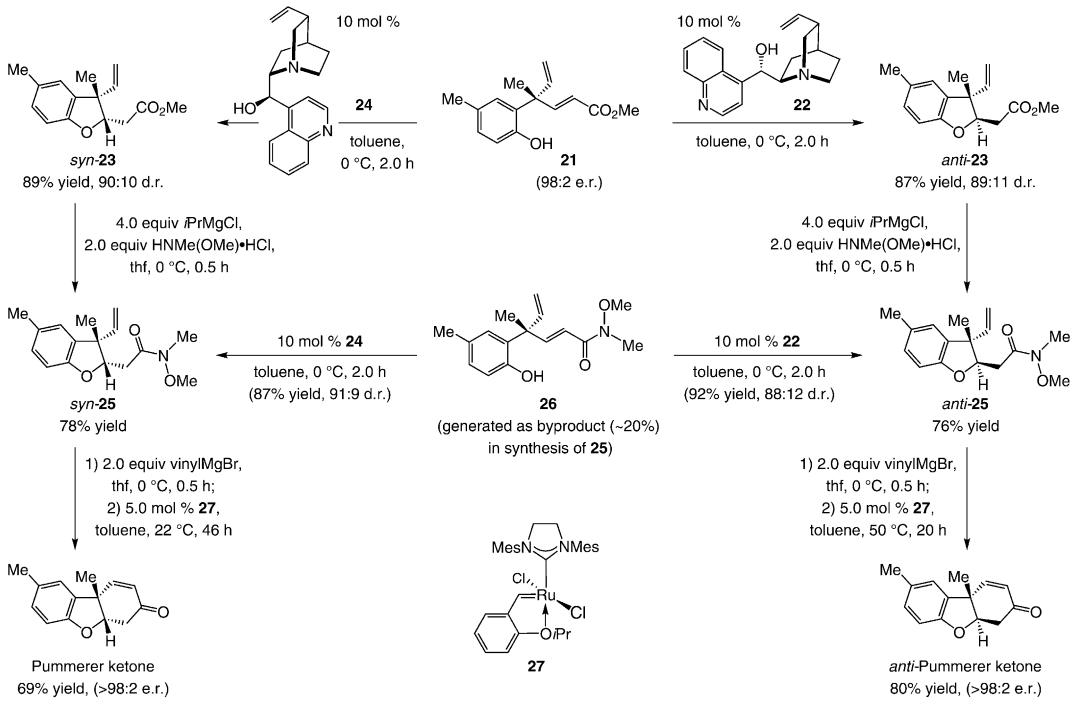
In connection with the synthesis of Pummerer ketones, treatment of allylic phosphate **19** with the aforementioned conditions delivers unsaturated aldehyde **20** in 77% yield, more than 98% $S_N2'$ selectivity, and 98:2 e.r. Subjection of the enal to oxone in MeOH (22 °C, 18 h) delivers the methyl ester concomitant with the removal of the methoxymethyl (MOM) group, affording **21** in 83% yield.[20] The two-step sequence, which commences with allylic phosphate **19** and culminates in unprotected phenol **21** in high enantiomeric purity proceeds in 64% overall yield (vs. 51% yield of methoxymethyl (MOM) ether **14** in Scheme 3).

With an efficient route for enantioselective synthesis of α,β-unsaturated ester **21** outlined, we explored the possibility of converting the EAS-derived product to the desired benzofuran in a diastereoselective manner (see Scheme 1). Because of the similar size of methyl and vinyl substituents at the quaternary carbon center, high diastereoselectivity can only be achieved if an effective chiral catalyst promotes the cyclization. We thus considered the possibility that cinchona alkaloids might catalyze the desired intramolecular phenol conjugate addition[21] efficiently and stereoselectively. We pursued the latter strategy with the knowledge that every extant example thus far is for obtaining a benzopyran.[21] Treatment of **21** with 10 mol% of commercially available and inexpensive cinchonine (**22**) leads to the formation of *anti*-**23** in 87% yield and 89:11 diastereomeric ratio (d.r.; 0 °C, 2.0 h; Scheme 5). Conversion to Weinreb amide *anti*-**25** proceeds efficiently (76% yield). The latter reaction generates approximately 20% of the α,β-unsaturated amide **26** as a by-product; however, the catalytic diastereoselective benzofuran synthesis can be performed with **26** to afford additional amounts of *anti*-**25** with similar efficiency and stereoselectivity (92% yield, 88:12 d.r.; Scheme 5).[22] Subsequent treatment with vinylmagnesium bromide and ring-closing metathesis catalyzed by Ru-based carbene **27**[23] delivers the *anti* isomer of Pummerer ketone in 80% yield (> 98:2 e.r.). Since the stereochemical outcome of the C–O bond generation by the intramolecular conjugate addition can be controlled by a chiral




***Scheme 4.*** NHC–Cu-catalyzed EAS of allylic phosphates with acetal-containing alkenylboron compound **16**.




***Scheme 5.*** Syntheses of Pummerer ketone and its *anti* isomer involving NHC–Cu-catalyzed EAS, cinchona alkaloid catalyzed diastereoselective intramolecular conjugate addition and Ru-catalyzed ring-closing metathesis.

catalyst, the alternative diastereomer can be obtained simply through the use of 10 mol% cinchonidine (**24**, Scheme 5). Benzofuran *syn*-**23** is therefore generated in 89% yield and 90:10 d.r. and can be carried on to complete the enantioselective synthesis of Pummerer ketone.[24]

The possibility of utilizing commercially available and/or easily accessible (pinacolato)vinylboron reagents in Cu-catalyzed enantioselective allylic substitution reactions enhances the value of catalytic EAS reactions. Furthermore, the high site- and enantioselectivities obtained in the transformations detailed above provide further testimony to the unique ability of sulfonate-bridged bidented NHC–Cu complexes to serve as efficient catalysts for this important class of enantioselective C–C bond-forming processes.

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[16] For relevant stereochemical models, see Ref. [5].

[17] Catalysts prepared from **5b**,**c** and **6b**,**c** generate high enantioselectivity for substrates that contain an *ortho*-substituted aryl substituent. However, only NHC–Cu complexes derived from **6b**,**c** reliably deliver high e.r. values with other allylic phosphates.

[18] With the catalyst originating from **6b**, **14** is isolated in 42 % yield (> 98 % $S_N2'$, 96:4 e.r.). The results obtained with **6b** or **6c** are often similar but the outcome can be, at times, slightly different. Currently, we cannot precisely predict the identity of the most optimal complex for a particular application.

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[24] The catalytic RCM that affords Pummerer ketone must be carried out for 46 h at 22 °C (vs. 50 °C and 20 h), because, in contrast to its *anti* isomer, it is prone to racemization. When RCM of enone derived from *syn*-**25** is performed at 50 °C, under otherwise identical conditions, the tricyclic enone is generated with substantial loss of enantiomeric purity ( ≈ 60:40 e.r.; > 98 % conv, 90 % yield). See the Supporting Information for mechanistic rationale and additional details.

  