Published in final edited form as:

Angew Chem Int Ed Engl. 2019 February 25; 58(9): 2685–2691. doi:10.1002/anie.201812535.

Racemic Vinylallenes in Catalytic Enantioselective Multicomponent Processes. Rapid Generation of Complexity through 1,6-Conjugate Additions

Youming Huang, Sebastian Torker, Xinghan Li, Juan del Pozo, and Amir H. Hoveyda

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, MA 02467 (USA)

Abstract

Racemic vinylallenes are shown to be attractive substrates for catalytic multicomponent diastereo-, and enantioselective 1,6-conjugate addition of multifunctional allyl moieties to easily accessible $\alpha,\beta,\gamma,\delta$ -unsaturated diesters. Reactions may be catalyzed by 5.0 mol % of a readily accessible NHC–Cu complex at ambient temperature, and other than a vinylallene, involve $B_2(\text{pin})_2$, and an $\alpha,\beta,\gamma,\delta$ -unsaturated diester. By just one operation, a variety of vinylallenes were converted to products bearing a *Z*-trisubstituted alkenyl–B(pin) moiety, a vinyl group, a β,γ -unsaturated diester unit, and vicinal stereogenic centers in up to 67% yield, 87:13 *Z*:*E* ratio, >98:2 d.r., and 98:2 e.r. A variety of chemoselective modifications involving the alkenyl–B(pin), vinyl, or the 1,2-disubstituted olefin moieties were carried out to demonstrate versatility and utility. Stereochemical models, based on mechanistic and DFT studies, demonstrate the dynamic behavior of intermediated Cu–allyl species and account for various selectivity profiles. These studies foreshadow the use of vinylallenes as starting materials in a wide range of multicomponent reactions, those catalyzed by Cu–H or Cu–B(pin) complexes.

Graphical Abstract

No longer ignored: Readily accessible racemic vinylallenes are shown to be attractive substrates for catalytic multicomponent diastereo-, and enantioselective 1,6-conjugate additions. In just one step, highly complex structures containing a *Z*-trisubstituted alkenyl–B(pin) moiety, a vinyl group, a β,γ -unsaturated diester unit, and vicinal stereogenic centers are generated in up to 67% yield, 87:13 *Z*:*E* selectivity, >98:2 d.r., and 98:2 e.r.

Keywords

boron; 1,6-conjugate additions; copper; enantioselective catalysis; vinylallenes

Various methods have emerged for catalytic enantioselective union of an unsaturated organic molecule, bis(pinacolato)diboron [B₂(pin)₂], and an electrophile,^[1,2,3,4,5] which afford difficult-to-access multifunctional entities. Early advances involved achiral monosubstituted^[1] or 1,1-disubstituted allenes,^[1g] where an initial regio- and stereoselective addition of an in situ generated Cu–B(pin) complex to the less substituted C=C bond afforded a boryl-substituted Cu–allyl species; this was followed by an α - or γ -selective addition to an electrophile. With a 1,3-diene,^[2] different Cu–allyl regioisomers may be generated. With 1,3-enynes,^[3] the Cu–B(pin) complex was also shown to add first to the less substituted vinyl moiety, and, depending on the process, the energetically more favorable Cu–allenyl intermediate^[6] (vs. Cu–propargyl) may react with an electrophile to furnish the α - or the γ -addition isomer.

Vinylallenes are readily accessible^[7] but have not been previously utilized in catalytic multicomponent processes. The expected products would be of high value, as they would contain a versatile vinyl and a stereochemically defined trisubstituted alkenyl–B(pin) units (Scheme 1), and thus, such entities represent an attractive possibility. Nonetheless, two key questions must be addressed: 1) Would Cu–B addition occur selectively at the allene or the vinyl site? 2) As 1,3-disubstituted allenes are chiral, would enantiomerically enriched substrates be needed?

We selected catalytic multicomponent 1,6-conjugate additions with vinylallene as our initial foray for several reasons. Unlike catalytic 1,4-conjugate additions, for which there are many enantioselective methods,^[8] 1,6-conjugate additions involving carbon-based nucleophiles are rare,^[9] especially with C4 not fully substituted. The only known instances are those of Feringa,^[10] Hayashi,^[11–12] Alexakis.^[13] These advances, while notable, were confined to magnesium-,^[10] Al-, or Zn-based^[13] entities containing a simple alkyl unit. Reactions with a silyl-protected alkyne^[11] or an aryl moiety broadened the scope, but just one aryl group in a (ArBO)₃ compound could be transferred.^[12]

We surmised that the Cu–B(pin) complex would add regioselectively to a vinylallene to generate **II** via **I** (Scheme 1). Although the vinyl site is less hindered, interaction between an allene bond, bearing an sp- and an sp²-hybridized carbon (vs. two sp²-hybridized vinyl carbons), and the Cu–B(pin) bond, where probably the HOMO is centered,^[14] would be preferred. The Cu–allyl species **II** could isomerize to **III**, the reaction of which with an $\alpha,\beta,\gamma,\delta$ -unsaturated diester would afford **IV**. The intermediacy of **III** would mean that racemic vinylallene may be used (i.e., enantioselective synthesis vs. kinetic resolution).

We began by probing reactions involving **1a**, B₂(pin)₂ and vinylallene **2a** (Scheme 2). With chiral phosphine ligands there was complete consumption of **1a** but no **3a** was detected.^[15] With **imid-1a**,^[16] optimal for previously reported reactions with monosubstituted allenes,^[1e] 1,4-conjugate boryl addition was the main competing pathway;^[17] **3a** was isolated in just 21% yield and with 75:25 *Z:E* selectivity, >98:2 diastereomeric ratio (d.r.), and 83:17

enantiomeric ratio (e.r.). These early findings underscored the distinct nature of the processes with a vinyl-containing 1,3-disubstituted allene (vs. monosubstituted variants ^[1e]).

Reactions with other imidazolinium salts were evaluated (Scheme 2).^[15] With **imid-1b**, d.r. remained high (>98:2), and efficiency (56% yield) and e.r. (94:6) were enhanced considerably, but there was little change in the *Z:E* ratio (75:25). We then examined N-adamantyl-substituted **imid-1c**, a lesser-known member of this ligand class,^[18] the use of which had led to relatively low e.r. (~80:20) in the NHC–Cu-catalyzed 1,6-conjugate additions with monosubstituted allenes (Scheme 1a).^[1e] Here, somewhat surprisingly, while the reaction was slightly less efficient (52% yield), d.r. and e.r. remained high (>98:2 and 95:5, respectively), and the *Z:E* ratio improved (85:15).

After further optimization [i.e., 1.1 equiv. B₂(pin)₂ and NaOtBu], we explored the scope of aryl-substituted dienates (Table 1). 1,6-Addition was exclusive throughout, and a single disubstituted alkene isomer and diastereomer was detected in every case (>98% β,γ-alkene and >98:2 d.r., respectively). Reactions of bulky *o*-tolyl-substituted **1b** and 1-naphthyl-containing **1c**, which afforded **3b** and **3c** in 58% and 59% yield, 87:13 *Z:E* selectivity, and 96:4 and 95:5 e.r., respectively, (entries 2–3). Additions to electron-rich (entries 4–6) or electron-deficient (entry 7–8) dienates were efficient and selective, as were the heterocyclic variants (entries 9–10).

Alkyl-substituted dienates (Scheme 3a) were converted **5a-c** with similar efficiency and selectivity; 1,6:1,4, and γ selectivity remained exceptional. However, diastereoselectivity levels do depend on the size of the alkyl group: **5a**, containing a smaller methyl group, was generated in 81:19 d.r., increasing with a larger alkyl moiety (**5b-c**, 87:13 and >98:2 d.r., respectively). With inylallenes that contain a relatively hindered substituent, transformations proceeded with similar efficiency, d.r., *Z:E* ratio, and e.r. (**6c-d** vs. **6a-b**). We were unable to identify conditions that would allow the isolation of the expected products from the corresponding reaction with an aryl-substituted vinylallene (unidentifiable mixtures).

A general point regarding the present approach merits note. A transformation that delivers products in 50–70% yield, as is the case here, while useful in chemical synthesis, is typically not considered as highly efficient. Nonetheless, multicomponent processes may be performed with readily accessible catalysts and starting materials, entail formation of multiple bonds, and address more than one selectivity issue, and should therefore be considered in a different light. The greater amount of waste notwithstanding, an alternative multi-step route, were it feasible, and if each step were higher yielding, may still not be as high yielding overall.

For the present approach to achieve its maximum potential, it is imperative that the different functional units within a product structure can be modified with high site-, regio-, and/or stereoselectivity. In this context, we were able to transform **3a** (Scheme 4a) to *E*-trisubstituted ester **7** (>98% *E*), which retains its *Z*-trisubstituted alkenyl boronate in two steps and 51% overall yield (Scheme 4a). This is a more direct and milder approach compared to a reported two-step procedure (68% vs. 70% yield for 2 steps).^[19]

Nonetheless, the sterically congested trisubstituted alkenyl-B(pin) compounds exposes an existing deficiency in the state-of-the-art in catalytic cross-coupling, as repeated attempts to effect such a transformation resulted in <5% conversion to the desired product (see below for an alternative (non-catalytic) set of conditions). Furthermore, we carried out the sequence of transformations leading to **12** (Scheme 4b), formerly used to synthesize vitamin D₃.^[20] We prepared 2.1 g of **6e** in similar yield and selectivity as the smaller scale reactions (Scheme 3b). Conversion to **8** under mild basic conditions^[1e] was followed by cross-metathesis involving the vinyl moiety and readily available *Z*-alkene **9**. After Wittig reaction, the disubstituted alkenes were site selectively reduced to afford **10**. To obtain *E*-trisubstituted olefin **11**, we used a one-vessel operation entailing treatment with MeLi, followed by PhSeCl^[21] and trifluoroethanol. Removal of the silyl group afforded alcohol **11** in 49% overall yield (for 2 steps) and 96:4 *Z:E* ratio. Formation of the derived tosyl ester, removal of the methoxymethyl (MOM) group, and base-induced tosylate elimination afforded **12** in 38% overall yield (for 3 steps).

The above findings pose several key mechanistic issues. One question is: why does the catalyst derived from **imid-1c** deliver higher *Z:E* selectivity (vs. **imid-1a-b**; Scheme 2)? This is likely because the boryl moiety of a Cu-B(pin) complex can be deposited at the sp²-hybridized carbon by two different modes of addition, namely, those leading to intermediates **V** and **VI** (Scheme 5a). The latter organocopper entities can then be transformed to **Z**_{prod} via **VII**, wherein the sizeable Cu(NHC) is attached to the least hindered primary carbon. However, **E**_{prod} can also be formed through **VI** via higher energy **VIII** and **IX**. There are therefore two ways by which *Z:E* selectivity might be influenced. Either the kinetic selectivity established by the initial Cu-B addition is maintained and is reflected in the final *Z:E* ratio, requiring relatively slow *Z*-to-*E* interconversion, or there is a certain degree of stereoisomerization and the selectivity is determined by the relative rates of reactions with the dienophile (i.e., Curtin-Hammett kinetics). To gain insight, we carried out the following experiments.

We monitored the reaction with stoichiometric amounts of **NHC-Cu-1**, B₂(pin)₂ and *rac*-**2a** (¹H NMR, thf-*d*₈, -40→22 °C; Scheme 5b), observing two sets of peaks. These signals which exchanged rapidly at 22 °C but resolved at -40 °C (94:6 ratio), probably originate from (*E,Z*)-**Cu-allyl-1** and (*E,E*)-**Cu-allyl-1** (Scheme 5b).^[15] An X-ray structure for (*E,Z*)-**Cu-allyl-1** was secured (CCDC number, 1874716).

For insight regarding the dynamic behavior of such Cu-allyl species, we carried out protoboryl additions with the NHC-Cu complex derived from **imid-1d** with MeOH or *t*BuOH (Scheme 5c). Whereas **13** was formed in >98:2 *Z:E* ratio with MeOH, selectivity decreased to 94:6 with *t*BuOH. These data suggest the following: 1) Initially, a *Z*-allyl-Cu isomer (**VII**, Scheme 5a) is generated exclusively, as, otherwise, the *E* product isomer (**E**_{prod}) would be formed by fast trapping with MeOH. 2) There is probably some *Z*-to-*E* isomerization prior to trapping of the kinetically formed *Z*-allyl-Cu when the slower reacting *t*BuOH is involved. In another set of experiments, we carried out a pair of reactions with enantiomerically enriched **2a** (81:19 e.r.) in the presence of Cu complexes derived from (*R*)- and (*S*)-**imid-1d** (Scheme 5d). In both instances **3a** was formed with identical *Z:E* selectivity (85:15), suggesting that the organocopper intermediate is in equilibrium and trapping with

1a is slower. Finally, DFT calculations involving a model NHC (Scheme 5e) indicate that π -allyl isomerization is facile ($G_{\text{rel}} = 3.5$ kcal/mol; only the highest of two sequential transition states shown), and that single bond rotation that lead to *s-cis*→*s-trans* isomerization, while slower ($G_{\text{rel}} = 12.7$ kcal/mol), are energetically feasible.

Other questions relate to the origin of higher *Z* selectivity with **imid-1d**, and the reason for high e.r. and the lower d.r. with dienoates that bear a smaller substituent (cf. Scheme 3). Considering that Curtin-Hammett kinetics is likely (cf. Scheme 5b), DFT studies (MN15/def2-TZVPP/M06-L/def2-SVP level)^[15] point to two coordination geometries involving a Na⁺ bridge (**A-D**, Scheme 6a); **A** and **B** lead to the *Z* isomer, whereas the *E* isomer would result from **C** and **D**.^[22] In **A** and **C**, in which alkoxide oxygen O¹ points to the right, there is steric repulsion between the bound dienoate and the NHC substituent G; there is no such interaction in **B** and **D**, wherein O¹ is oriented in the opposite direction. The smaller energy difference separating **A** and **C** (vs. **B** and **D**) means that reaction via these complexes favors an *E* trisubstituted alkene (namely, lower *Z:E* ratios), probably because G and Me are more proximal in **A** than in **B** (i.e., $k_{\text{C}}/k_{\text{A}} > k_{\text{D}}/k_{\text{B}}$). It is worth noting that a larger N-Ar unit is involved in the actual system (vs. N-Me group). Moreover, with an N-Ad moiety (i.e., with **imid-1d**), there is a wider energy gap between **A/C** and **B/D** (E_{rel} between **A** and **B** = 6.4 ± 2.0 kcal/mol), rendering **A/C** significantly less accessible. In contrast, in the case of complexes with an NAr-substituted NHC (i.e., derived from **imid-1b**), **A/C** and **B/D** probably contribute more similarly (E_{rel} between **A** and **B** = 1.8 ± 2.0 kcal/mol), and more of the *E* isomer is formed with **imid-1b** (vs. when **imid-1d** is used). In line with the experimental results is the relatively large energy difference between the transition states leading to the major (**B**) and minor enantiomer (**E**, Scheme 6b, $E_{\text{rel}} = 4.4$ kcal/mol). This difference arises from repulsion between the N-Ad and the B(pin) moieties in **E**. As noted,^[1e] such steric pressure weakens Na⁺-substrate coordination, resulting in longer average Na·····O distance (2.204 Å in **B** to 2.223 Å in **E**). Diastereoselectivity is lower with dienoates with a smaller substituent probably due to reduced steric pressure in **F** (Scheme 6c), which leads to the formation of the minor isomer, when **4a** (R = Me) is involved ($E_{\text{rel}} = 2.8$ kcal/mol); in comparison, d.r. is higher with **1a** (R = Ph) as the substrate ($E_{\text{rel}} = 4.5$ kcal/mol).

In brief, we show that vinylallenes are promising substrates for catalytic multicomponent processes (with Cu-H^[23] or Cu-B(pin) complexes) and can provide direct access to structurally complex compounds. The above findings are a notable addition to two important and under-developed areas: broadly applicable catalytic enantioselective conjugate additions of allyl moieties,^[24] and catalytic regio-, diastereo- and enantioselective 1,6-conjugate additions of C-based nucleophiles.^[1e,9]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements.

This research was funded by the NIH (GM-47480). Y.H. was partially supported by a postdoctoral fellowship from the Shanghai Institute of Organic Chemistry and Zhejiang Medicine Co., Pharmaron. J. d. P. was supported in the

form of a postdoctoral fellowship by Alfonso Martin Escudero Foundation. We are grateful to Dr. Bo Li for his invaluable assistance in securing the X-ray structure for compound (*E,Z*)-Cu-allyl-1.

References & Footnotes

- [1]. a)For selected reports involving enantioselective multicomponent reactions that involve an achiral allene and are catalyzed by a chiral Cu–B(pin) complex, see: with carbonyl- or imine-containing compounds, Meng F, Jang H, Jung B, Hoveyda AH, *Angew. Chem. Int. Ed* 2013, 52, 5046–5051;b)Yeung K, Ruscoe RE, Rae J, Pulis AP, Procter DJ, *Angew. Chem. Int. Ed* 2016, 55, 11912–11916;c)Jang H, Romiti F, Torker S, Hoveyda AH, *Nat. Chem* 2017, 9, 1269–1275. [PubMed: 29168479] d)With allylic electrophiles: Meng F, McGrath KP, Hoveyda AH, *Nature* 2014, 513, 367–374. [PubMed: 25230659] e)With α,β -unsaturated carbonyl compounds: Meng F, Li X, Torker S, Shi Y, Shen X, Hoveyda AH, *Nature* 2016, 537, 387–393; [PubMed: 27479320] f)Zhou Y, Shi Y, Torker S, Hoveyda AH, *J. Am. Chem. Soc* 2018, 140, 16842–16854. For reactions involving 1,1-disubstituted allenes with an alcohol serving as the electrophile, see: [PubMed: 30444358] g)Jang H, Jung B, Hoveyda AH, *Org. Lett* 2014, 16, 4658–4661. [PubMed: 25153792]
- [2]. a)For selected reports involving enantioselective multicomponent reactions that involve a 1,3-diene and are catalyzed by a chiral Cu–B(pin) complex, see: Sasaki Y, Zhong C, Sawamura M, Ito H, *J. Am. Chem. Soc* 2010, 132, 1226–1227; [PubMed: 20063883] b)Li X, Meng F, Torker S, Shi Y, Hoveyda AH, *Angew. Chem. Int. Ed* 2016, 55, 9997–10002;c)Jiang L, Cao P, Wang M, Chen B, Wang B, Liao J, *Angew. Chem. Int. Ed* 2016, 55, 13854–13858;d)Jia T, He Q, Ruscoe RE, Pulis AP, Procter DJ, *Angew. Chem. Int. Ed* 2018, 57, 11305–11309.
- [3]. a)For selected reports involving enantioselective multicomponent reactions that involve a 1,3-enyne and are catalyzed by a chiral Cu–B(pin) complex, see: Sasaki Y, Horita Y, Zhong C, Sawamura M, Ito H, *Angew. Chem. Int. Ed* 2011, 50, 2778–2782;b)Meng F, Haefner F, Hoveyda AH, *J. Am. Chem. Soc* 2014, 136, 11304–11307; [PubMed: 25089917] c)Gan X-C; Zhang Q; Jia X-S; Yin L *Org. Lett* 2018, 20, 1070–1073. [PubMed: 29419304]
- [4]. a)For selected reports involving enantioselective multicomponent reactions that involve an alkene and are catalyzed by a chiral Cu–B(pin) complex, see: Lee Y, Hoveyda AH, *J. Am. Chem. Soc* 2009, 131, 3160–3161; [PubMed: 19256564] b)Han JT, Jang WJ, Kim N, Yun J, *J. Am. Chem. Soc* 2016, 138, 15146–15149; [PubMed: 27808507] c)Lee J, Torker S, Hoveyda AH, *Angew. Chem. Int. Ed* 2017, 56, 821–826;d)Radomkit S, Liu Z, Closs A, Mikus MS, Hoveyda AH, *Tetrahedron* 2017, 73, 5011–5017; [PubMed: 29973744] e)Lee J, Radomkit S, Torker S, del Pozo J, Hoveyda AH, *Nat. Chem* 2018, 10, 99–108.f)For instances where a Pd-based co-catalyst is used, see: Jia T, Cao P, Wang B, Lou Y, Yin X, Wang M, Liao J, *J. Am. Chem. Soc* 2015, 137, 13760–13763. [PubMed: 26458555] f)For a recent overview of this general class of transformations, see: Pulis AP, Yeung K, Procter DJ, *Chem. Sci* 2017, 8, 5240–5247. [PubMed: 28959423]
- [5]. a)For recent overviews of this general class of catalytic multicomponent reactions catalyzed by Cu-based complexes, see: Semba K, Fujihara T, Terao J, Tsuji Y, *Tetrahedron* 2015, 71, 2183–2197;b)Pulis AP, Yeung K, Procter DJ, *Chem. Sci* 2017, 8, 5240–5247; [PubMed: 28959423] c)Hemming D, Fritzmeier R, Westcott SA, Santos WL, Steel PG, *Chem. Soc. Rev* 2018, 47, 7477–7494. [PubMed: 30206614]
- [6]. Mszar NW, Haefner F, Hoveyda AH, *J. Am. Chem. Soc* 2014, 136, 3362–3365. [PubMed: 24555471]
- [7]. Vinylallenes were prepared in two steps and ~70% overall yield according to the procedure by Ready; see: Pu X, Ready JM, *J. Am. Chem. Soc* 2008, 130, 10874–10875. See the Supporting Information for details. [PubMed: 18652467]
- [8]. Alexakis A, Krause N, Woodward S in *Copper-Catalyzed Asymmetric Synthesis* (Alexakis A, Krause N, Woodward S, Eds), Wiley–VCH, Weinheim, 2014, pp. 33–68.
- [9]. Tissot M, Li H, Alexakis A, in *Copper-Catalyzed Asymmetric Synthesis* (Alexakis A, Krause N, Woodward S, Eds), Wiley–VCH, Weinheim, 2014, pp. 69–84.
- [10]. a) den Hartog T, Harutyunyan SR, Font D, Minnaard AJ, Feringa BL, *Angew. Chem. Int. Ed* 2008, 47, 398–401;b) den Hartog T, van Dijken DJ, Minnaard AJ, Feringa BL, *Tetrahedron: Asymmetry* 2010, 21, 1574–1584.

- [11]. Sawano T, Ashouri A, Nishimura T, Hayashi T, J. Am. Chem. Soc 2012, 134, 18936–18939. [PubMed: 23131028]
- [12]. a) Nishimura T, Yasuhara Y, Sawano T, Hayashi T, J. Am. Chem. Soc 2010, 132, 7872–7873; [PubMed: 20481533] b) Nishimura T, Noishiki A, Hayashi T, Chem. Commun 2010, 48, 973–975.
- [13]. a) Tissot M, Alexakis A, Chem. Eur. J 2013, 19, 11352–11363; [PubMed: 23852566] b) Magrez-Chiquet M, Morin MST, Wencel-Delord J, Amraoui SD, Baslé O, Alexakis A, Crévisy C, Mauduit M, Chem. Eur. J 2013, 19, 13663–13667. [PubMed: 24038460]
- [14]. a) Zhao H, Lin Z, Marder TB, Organometallics 2006, 25, 15637–15643; b) Kubota K, Jin M, Ito H, Organometallics 2016, 35, 1376–1383; c) Borner C, Anders L, Brandhorst K, Kleeberg C, Organometallics 2017, 36, 4687–4690.
- [15]. See the Supporting Information for details.
- [16]. a) Clavier H, Coutable L, Toupet L, Guillemin J-C, Mauduit M, J. Organomet. Chem 2005, 690, 5237–5254; b) Germain N, Magrez M, Kehrli S, Mauduit M, Alexakis A, Chem. Eur. J 2012, 18, 5301–5306; c) Nawaz F, Zaghouni M, Bonne D, Chuzel O, Rodriguez J, Coquerel Y, Eur. J. Org. Chem 2013, 8253–8264.
- [17]. a) Conjugate boryl additions have been promoted by NHC–Cu complexes as well as with NHCs as catalysts. For examples, see: Catalyzed by an NHC–Cu complex: Park JK, Lackey HH, Rexford MD, Kovnir K, Shatruk M, McQuade DT, Org. Lett 2010, 12, 5008–5011; [PubMed: 20919706] b) Takatsu K, Shintani R, Hayashi T, Angew. Chem. Int. Ed 2011, 50, 5548–5552. Catalyzed by an NHC: c) Wu H, Radomkit S, O'Brien JM, Hoveyda AH, J. Am. Chem. Soc 2012, 134, 8277–8285; [PubMed: 22559866] d) Wu H, Garcia JM, Haeflner F, Radomkit S, Zhugralin AR, Hoveyda AH, J. Am. Chem. Soc 2015, 137, 10585–10602. [PubMed: 26263513]
- [18]. Salt Imid-Id, although a member of a relatively large class of chiral ligand precursors (Ref. [9]), to the best of our knowledge, has not been previously identified as optimal for any catalytic enantioselective processes.
- [19]. Trost BM, Lee CB, J. Am. Chem. Soc 2001, 123, 3687–3696. [PubMed: 11457100]
- [20]. a) Clasby MC, Craig D, Marsh A, Angew. Chem. Int. Ed. Engl 1993, 32, 1444–1446; b) Nemoto H, Kurobe H, Fukumoto K, Kametani T, J. Org. Chem 1986, 51, 5311–5320.
- [21]. a) Armstrong RJ, García-Ruiz C, Myers EL, Aggarwal VK, Angew. Chem. Int. Ed 2017, 56, 786–790; b) Armstrong RJ, Aggarwal VK, Synthesis 2017, 49, 3323–3336. c) When I₂ was used, there was significant loss in alkene stereoisomeric purity; see: Xu S, Lee C-T, Rao H, Negishi E.-i., Adv. Synth. Catal 2011, 353, 2981–2987. [PubMed: 24072993]
- [22]. Only the most energetically competitive modes of reaction are shown in Figure 1. For complete DFT analysis and further discussion, see the Supporting Information.
- [23]. a) For selected reports involving enantioselective multicomponent reactions catalyzed by a chiral Cu–H complex, see: with mono- and 1,1-disubstituted allenes: Liu RY, Yang Y, Buchwald SL, Angew. Chem. Int. Ed 2016, 55, 14077–14080; b) Tsai EY, Liu RY, Yang Y, Buchwald SL, J. Am. Chem. Soc 2018, 140, 2007–2011; [PubMed: 29376366] c) Tan Y-X, Tang X-Q, Liu P, Kong D-S, Chen Y-L, Tian P, Lin G-Q, Org. Lett 2018, 20, 248–251. [PubMed: 29244512] d) With 1,3-enynes: Yang Y, Parry IB, Lu G, Liu P, Buchwald SL, Science 2016, 353, 144–150; [PubMed: 27284169] e) Huang Y, del Pozo J, Torker S, Hoveyda AH, J. Am. Chem. Soc 2018, 140, 2643–2655. [PubMed: 29417810]
- [24]. a) Sieber JD, Morken JP, J. Am. Chem. Soc 2008, 130, 4978–4983; [PubMed: 18338891] b) Shizuka M, Snapper ML, Angew. Chem. Int. Ed 2008, 47, 5049–5051; c) Kuang Y, Liu X, Chang L, Wang M, Lin L, Feng X, Org. Lett 2011, 13, 3814–3817; [PubMed: 21688863] d) Yanagida Y, Yazaki R, Kumagai N, Shibasaki M, Angew. Chem. Int. Ed 2011, 50, 7910–7914; e)

Scheme 2.

Identification of an effective NHC–Cu complex. [a] Conv. ($\pm 2\%$; loss of **1a**), *Z:E* ratio, and d.r. ($\pm 2\%$) determined by analysis of ^1H NMR spectra of unpurified mixtures. [b] Yield ($\pm 5\%$, average of at least three runs) is for purified product (*ZE* mixture). [c] E.r. determined by HPLC analysis. See the Supporting Information for details.

a. Products from reactions with different dienoates:

5a

>98% conv., 55% yield,
84:16 *Z:E*, 81:19 d.r., 97:3 e.r.

5b

>98% conv., 60% yield,
85:15 *Z:E*, 87:13 d.r., 97:3 e.r.

5c

85% conv., 58% yield,
80:20 *Z:E*, >98:2 d.r., 98:2 e.r.

b. Products from reactions with different vinylallenes:

6a

>98% conv., 50% yield,
86:14 *Z:E*, >98:2 d.r., 95:5 e.r.

6b

>98% conv., 51% yield,
84:16 *Z:E*, >98:2 d.r., 96:4 e.r.

6c

>98% conv., 51% yield,
85:15 *Z:E*, 83:17 d.r., 96:4 e.r.

6d

>98% conv., 55% yield,
86:14 *Z:E*, >98:2 d.r., 94:6 e.r.

Scheme 3.

Transformations with different alkyl-substituted dienoates and vinylallenes. See the Supporting Information for details.

Scheme 4.

Exploration of the utility of the catalytic multicomponent method. See the Supporting Information for details. dbu, 1,8-diazabicyclo[5.4.0]undec-7-ene; TBS, *t*-butyldimethyl silyl; MOM, methoxymethyl.

a. Pathways leading to formation of *Z*- and *E*-alkenyl-B(pin) products via Cu-allyl intermediates:

b. Spectroscopic experiment illustrating that Cu-B(pin) addition to a vinylallene occurs with high kinetic *Z* selectivity

c. *Z*:*E* ratio can vary based on the rate of electrophile trapping:

d. Identical stereocontrol with enantio-enriched catalysts and vinylallene 2a:

e. Calculated values for barriers of π -allyl isomerization and single bond rotation (*s-cis* to *s-trans* conversion):

Scheme 5.

Studies regarding pathways that cause lower *Z*:*E* selectivity. Abbreviations: ts = transition state.

Scheme 6.

Stereochemical models accounting for the various stereoselectivity issues.

Table 1:

Multicomponent processes involving racemic vinylallene **2a** and aryl-substituted dienates.^[a]

Entry	Ar	Yield (%) ^[b]	Z:E (Alkenyl-B(pin)) ^[c]	e.r. ^[d]
1	C ₆ H ₅ (1a)	62	86:14	95:5
2	<i>o</i> -MeC ₆ H ₄ (1b)	58	87:13	96:4
3	1-naphthyl (1c)	59	87:13	95:5
4	<i>o</i> -MeOC ₆ H ₄ (1d)	64	88:12	96:4
5	<i>m</i> -MeC ₆ H ₄ (1e)	56	86:14	95:5
6	<i>p</i> -MeOC ₆ H ₄ (1f)	67	87:13	95:5
7	<i>p</i> -BrC ₆ H ₄ (1g)	53	85:15	95:5
8	<i>p</i> -F ₃ CC ₆ H ₄ (1d)	63	83:17	94:6
9	3-furyl (1i)	65	85:15	97:3
10	3-thienyl (3j)	65	86:14	97:3

^[a] Reactions were performed under N₂ atm. Conv. was >98% in all cases (±2%; loss of allene).

^[b] Yield (±5%, average of at least three runs) corresponds to purified products (Z:E mixture).

^[c] Z:E ratios and d.r. (±2%) were determined by analysis of ¹H NMR spectra of unpurified mixtures.

^[d] E.r. was determined by HPLC analysis. See the Supporting Information for details.