Multicomponent Reactions

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Cu-Catalyzed Chemoselective Preparation of 2-(Pinacolato)boron-Substituted Allylcopper Complexes and their In Situ Site-, Diastereo-, and Enantioselective Additions to Aldehydes and Ketones**

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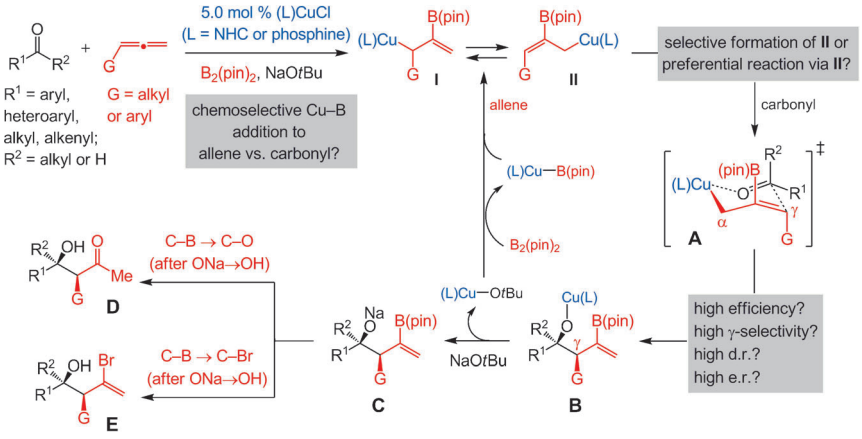
Transformations that entail catalytic generation of reactive entities for in situ use in stereoselective synthesis are in high demand;[1] such processes are more efficient and operationally simpler than when a priori preparation and purification of stoichiometric quantities of sensitive intermediates are required.[2] Successful design of multicomponent pathways hinges on high chemoselectivity: A starting material and a reagent must first be catalytically transformed into a new species, which then has to undergo reaction with another substrate. If the catalyst structure is incorporated within the intermediate molecule, reactivity and selectivity can be further controlled. When one or both partners carry several potentially reactive sites, other issues of selectivity must be addressed. Matters of efficiency and site- and/or stereoselectivity need to be resolved at every stage, and conditions must be found to ensure facile catalyst turnover.



Scheme 1. Chemoselective Cu–B addition to an allene, followed by site-, diastereo-, and enantioselective addition of the resulting 2-(pinacolato)boron-substituted allylcopper species to aldehydes and ketones can lead to a range of valuable organic molecules by a catalytic multicomponent operation. B(pin) = (pinacolato)boron, L = ligand.

Herein, we present a sustainable, three-component, single-vessel catalytic protocol for the chemo-, diastereo- and enantioselective conversion of bis(pinacolato)diboron [$B_2(pin)_2$], monosubstituted allenes, and aldehydes or ketones into 2-B(pin)-substituted homoallylic alkoxides (Scheme 1). Transformations commence by catalytic generation of 2-B(pin)-allylcopper complexes through chemoselective reactions of Cu–B species with allenes, followed by in situ additions to carbonyl substrates.[3] When α,β-unsaturated carbonyls are used, efficient 1,2-allylations remain favored versus boryl or allyl conjugate additions. Catalysts are derived from abundant Cu salts and commercially available precursors of N-heterocyclic carbene (NHC) or phosphine ligands, each offering advantages in chemo- and/or stereoselectivity; allenes are purchased or prepared by high-yielding processes.[4] High-value products are formed in no more than 18 h at 4–22 °C with > 98 % γ-selectivity and 88:12 to > 98:2 d.r. (in 68–92 % yield after oxidation); enantioselectivity can be achieved in up to 97:3 enantiomeric ratio (e.r.). To the best of our knowledge, direct catalytic additions of 2-boryl-allyl units to aldehydes are unknown; in cases where 2-boron-substituted allylboron species are prepared separately, alternative modes of site selectivity are observed (more below). There are also no catalytic methods for nucleophilic additions of 2-boryl-allyl units to ketones.[3]

We have shown that 2-B(pin)-substituted allylcopper complexes may be accessed by site-selective Cu–B(pin) addition to allenes (Scheme 1).[5a] As reactions were performed in the presence of MeOH, in situ protonation of the (pin)B-substituted allylcopper complex resulted in net protoboration and regeneration of a catalytically active Cu–B(pin) complex (via a Cu–OMe intermediate). We wondered if Cu–B additions to allenes could proceed chemoselectively with an aldehyde also present (Scheme 1), and whether, without MeOH, the resulting B(pin)-substituted allylcopper complex would react with the carbonyl substrate to generate **B** with high γ- and diastereoselectivity. Such a sequence could proceed via **A** and involve the less congested Cu center of **II**; reaction through **I** (Scheme 1), which might be in equilibrium with **II**,[6] would afford isomeric products with one stereogenic center.[7,8] Another question related to Cu

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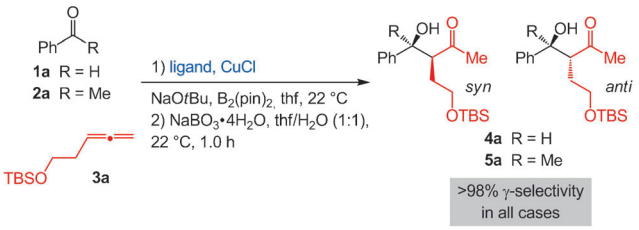
complexes adding efficiently to less-reactive ketones and whether d.r. values would be high. Oxidation of the C–B bond (after **C**→**D**) would render allylcopper complex **II** a metal enolate equivalent, delivering products of value for stereoselective synthesis of biologically active polyketides.[9,10]

We began by evaluating different Cu-based catalysts (Table 1). Treatment of aldehyde **1a** and allene **3a** with 5.0 mol% of CuCl and either **6** or **7** affords, after oxidative workup,[11] β-hydroxyketone **4a** with complete γ-selectivity and 92:8 and 94:6 d.r. but in 36% and 41% yield, respectively (Table 1, entries 1 and 2).[12] Control experiments show that the moderate efficiency arises from competitive NHC/Cu-catalyzed Cu–B addition to the aldehyde (approximately 90% conversion in 8.0 h without the allene). With the less Lewis basic *rac*-binap (Table 1, entry 3), chemoselectivity improves in favor of Cu–B addition to the allene, delivering **4a** in 80% yield, >98% γ-selectivity and 95:5 d.r. (<2% B(pin) addition to **1a**).[13] In contrast, NHC- and *rac*-binap-based catalysts promote efficient allylation of ketone **2a** (Table 1, entries 4–6),[14] consistent with a sluggish 1,2-addition of NHC–Cu–B to the carbonyl group.[15] Complete γ-selectivity is observed and diastereoselectivity is high in spite of the diminished size difference between the ketone substituents (versus those of an aldehyde); unfavorable diaxial interactions in **A** are likely less severe owing to relatively long incipient bonds.[16]

Various aryl-substituted aldehydes can be used (**4b–f**, Scheme 2); efficiency, γ-, and diastereoselectivities are high.

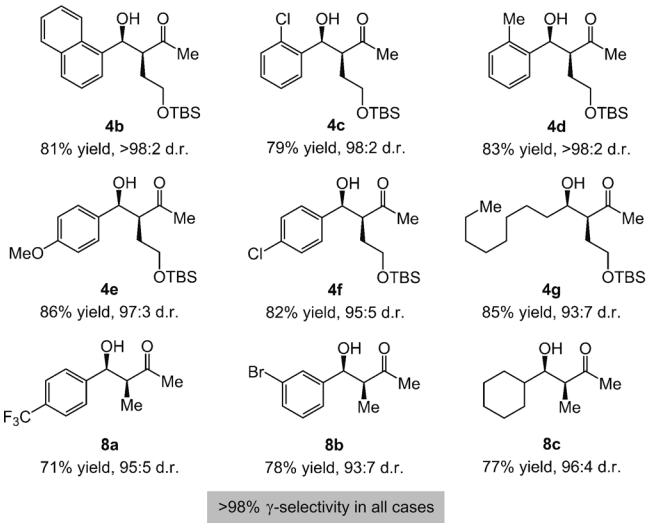
Table 1: Screening of representative catalyst types.[a]



Entry	Substrate	Ligand	Conv. [%][b]	d.r.[b]	Yield [%][c]
1	**1a**	**6**	47	92:8	36
2	**1a**	**7**	58	94:6	41
3	**1a**	*rac*-binap	>98	95:5	80
4	**2a**	**6**	>98	91:9	76
5	**2a**	**7**	>98	93:7	83
6	**2a**	*rac*-binap	>98	94:6	85

[a] Reaction conditions: 1) substrate (1.1 equiv), ligand (5.0 mol%), CuCl (5.0 mol%), NaO*t*Bu (20 mol% for **1a** or 1.5 equiv for **2a**), $B_2(pin)_2$ (1.1 equiv), thf, 22 °C, 8.0 h (**1a**) or 18 h (**2a**) under N_2 atm; 2) $NaBO_3 \cdot 4H_2O$, thf/H_2O (1:1), 22 °C, 1.0 h (for **1a** and **2a**) under N_2 atm. [b] Determined by analysis of 400 MHz ^1H NMR spectra of unpurified mixtures (±2%). [c] Yields of isolated and purified products (±5%; major isomer for entries 1–3 and both isomers for entries 4–6). See the Supporting Information for details. binap = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, TBS = *tert*-butyldimethylsilyl.

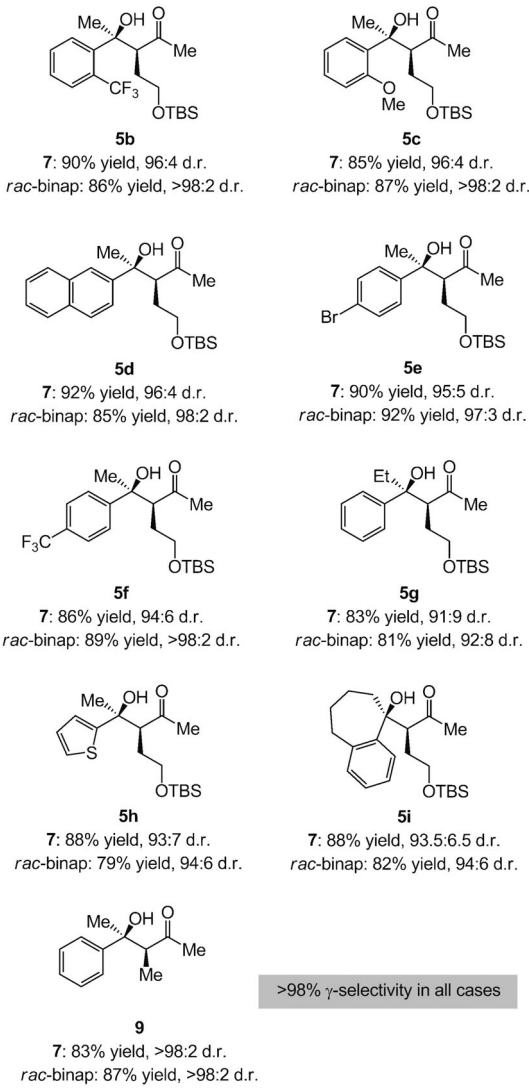
6 Mes = 2,4,6-$(Me)_3C_6H_2$ **7** Ad = adamantyl



Scheme 2. Products from sequential 2-B(pin)-substituted allylcopper formation/aldehyde addition/oxidation reactions catalyzed by *rac*-binap/Cu complex. Reactions performed with 4.0 mol% of *rac*-binap, 4.0 mol% of CuCl, and 16 mol% of NaO*t*Bu under otherwise the same conditions as shown in Table 1, except 5.0 equivalents of allene used for **8a** and **8b** and 2.0 equivalents of allene used for **8c**. >98% conv. in all cases. See the Supporting Information for details.

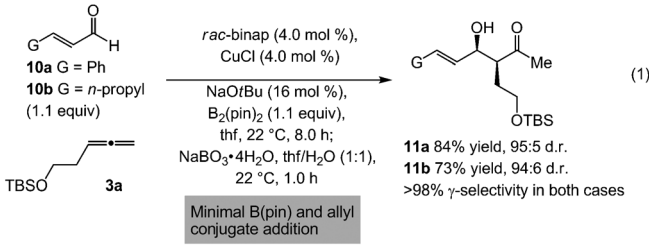
Methyl-substituted allenes are effective substrates (see **8a–c**). Aldehydes with aryl groups of diverse electronic and steric attributes are suitable as well (see **4b–f**, **8a**, and **8b**); those with an electron-deficient substituent (see **8a** and **8b**) require excess allene (5.0 equiv) as, otherwise, B(pin)-addition predominates. Reactions with alkyl-substituted aldehydes are equally facile and selective (see **4g** and **8c**).

Aryl ketones are converted into products bearing tertiary hydroxy groups in ≥79% yield, >98% γ-selectivity, and ≥91:9 d.r. with NHC/Cu or *rac*-binap/Cu complexes (Scheme 3). Sterically congested ketones (see **5b–d**), those that contain electron-withdrawing (see **5b**, **5e**, and **5f**) or -donating substituents (see **5c**) react with high efficiency and selectivity. The transformation with an ethyl ketone (see **5g**) is facile but slightly less diastereoselective, presumably owing to the diminished size difference between the carbonyl substituents (see **A**, Scheme 1). Heterocyclic substituents are tolerated (e.g., **5h** in ≥93:7 d.r.)[17] and cyclic ketones are effective substrates: **5i** is isolated in 82–88% yield and up to 94:6 d.r. (Scheme 3). Efficient and selective formation of **9** (83–87% yield, >98:2 d.r.) is notable: it offers an attractive alternative to a propionate ketone aldol process, where, as would be true in all cases, access to the trisubstituted enolate in high selectivity would be difficult. Unlike reactions with aldehydes, however, use of alkyl-substituted ketones leads to a preponderance of side reactions; it is plausible that the lower electrophilicity of aliphatic ketones renders enolization by NaO*t*Bu and the ensuing undesired reactions more competitive. Products expected from additions to aliphatic ketones could be synthesized by catalytic hydrogenation of the corresponding tertiary allylic alcohols derived from transformations with α,β-unsaturated carbonyls.



Scheme 3. Products from sequential catalytic allylcopper formation/aryl ketone addition/C–B oxidation reactions catalyzed by either a **7**/Cu complex or *rac*-binap/Cu complex. >98% conv. in all cases. See Table 1 for conditions and the Supporting Information for experimental and analytical details.

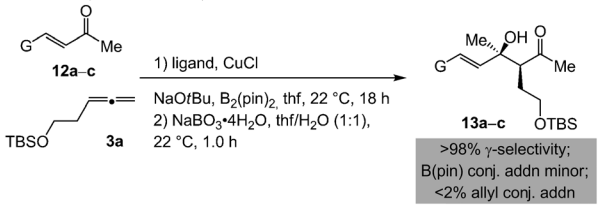
Reactions with unsaturated carbonyls bear the extra complication of possible competitive B(pin) or allyl conjugate addition.[18] Nonetheless, we find that subjection of enals **10a** and **10b** to the reaction conditions with **3a** and 4.0 mol% of *rac*-binap/Cu complex leads to complete allene consumption, furnishing allylic alcohols **11a** and **11b** in ≥73% yield and up to 95:5 d.r. [Eq. (1)]. The challenge of such catalytic transformations is underlined by the finding that without allene **3a**, under otherwise identical reaction conditions, there is complete consumption of **10a** in only 4.0 h (versus >98% conv. for the synthesis of **11a** and **11b** in 8.0 h).[19]

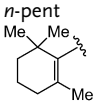


(1)

High diastereoselectivities are observed with α,β-unsaturated ketones in spite of the diminished size difference between the carbonyl substituents (versus aryl ketones; Table 2). With either 5.0 mol% of **7** or *rac*-binap, enones

Table 2: Sequential catalytic reactions with α,β-unsaturated ketones.[a]



Entry	Substrate	G	Ligand	d.r.[b]	Yield [%][c]
1	**12a**	Ph	**7**	>98:2	64
2	**12a**	Ph	*rac*-binap	91:9	68
3	**12b**	*n*-pent	**7**	>98:2	53
4	**12b**	*n*-pent	*rac*-binap	91.5:8.5	77
5	**12c**		**7**	90:10	86
6	**12c**		*rac*-binap	87:13	81

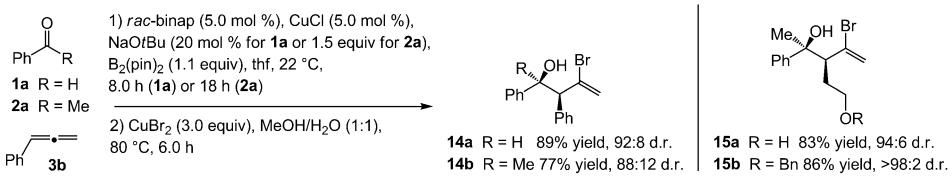
[a] Reaction conditions: with **7**: 1) substrate (1.5 equiv), **7** (5.0 mol%), CuCl (5.0 mol%), NaO*t*Bu (1.5 equiv), $B_2(pin)_2$ (1.5 equiv), thf, 22 °C, 18 h under N_2 atm; 2) $NaBO_3{\cdot}4H_2O$, thf/H_2O (1:1), 22 °C, 1.0 h under N_2 atm. With *rac*-binap: 1) substrate (1.2 equiv), *rac*-binap (5.0 mol%), CuCl (5.0 mol%), NaO*t*Bu (1.5 equiv), $B_2(pin)_2$ (1.2 equiv), thf, 22 °C, 18 h under N_2 atm; 2) $NaBO_3{\cdot}4H_2O$, thf/H_2O (1:1), 22 °C, 1.0 under N_2 atm. [b] Determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures (±2%). [c] Yields of isolated and purified products (±5%; both isomers). See the Supporting Information for details.

12a and **12b** are converted into tertiary allylic alcohols in 53–77% yield (Table 2, entries 1–4); the remainder of the material is consumed by conjugate addition of adventitious B(pin) (^{1}H NMR analysis).[20] Dienones are appropriate substrates (Table 2, entries 5 and 6); the increased efficiency in the formation of **13c** (81–86% yield) is likely because the hindered cyclic moiety discourages conjugate addition. Diastereoselectivities are higher with the NHC-based catalysts; the larger size of the P-based ligand might destabilize the chair-type transition state for the carbonyl addition (see Scheme 1, **A**). Reactions shown in Scheme 3 do not exhibit such a trend, as the more sizeable aryl units of the ketone better enforce a chair-like transition structure.

Several matters of efficiency and selectivity underscore the distinguishing advantages of the present approach. Pd-catalyzed diboron additions to allenes deliver 2-B(pin)-substituted allylborons, which, unlike in the processes described above, react with aldehydes to generate acetate aldol products (after oxidation; Scheme 4a);[21] related transformations with ketones would require an additional catalyst (not reported). Our attempts to utilize the same B(pin)-substituted set of allylboron species as precursors to allylcopper inter-

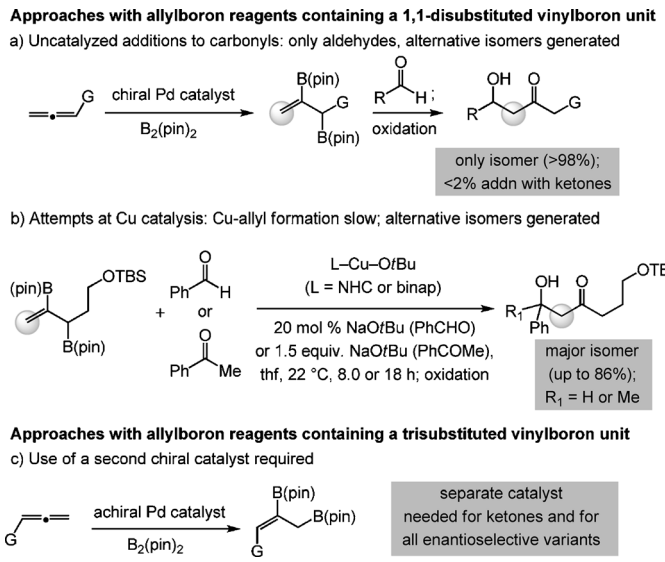
mediates, as summarized in Scheme 4b, led to predominance of the same mode of site selectivity as mentioned above (see Scheme 4a); this is largely because the requisite 2-B(pin)-allylcopper species cannot be generated efficiently through such a pathway.[22] A different type of Pd-catalyzed diboron addition to allenes furnishes achiral B-(pin)-substituted allyboron isomers bearing a trisubstituted vinylboron moiety[23] (Scheme 4c versus Scheme 4a). These latter entities, similar to allylcopper **II** in Scheme 1, can react with aldehydes to yield product isomers represented by **B** (R_2 = H, Scheme 1); however, enantioselective reactions with aldehydes as well as any additions to ketones, would require the use of a second catalyst. It is unlikely that allylcopper species are converted into allylboron intermediates that then undergo addition; otherwise, two equivalents of $B_2(pin)_2$ would be required for complete conversion (versus 1.1–1.5 equiv used), additions to aldehydes would likely not be subject to enantioselective catalysis (see below), and there would be minimal reaction with ketones.

Vinyl halides (Scheme 5) are another set of useful isolable derivatives that can be accessed.[11] By subjection of the initial product mixtures to $CuBr_2$ various vinyl bromides are obtained including: **14a** (89% yield and 92:8 d.r.) and **14b** (77% yield and 88:12 d.r), originating from the reaction of phenyl-substituted allene **3b**, **15a** (83% yield and 94:6 d.r.), from a process involving **3a**, and **15b** (86% yield and >98:2 d.r.), generated through the use of the benzyl derivative of **3a**.[24] As far as we are aware, methods for stereoselective synthesis of this type of vinyl halide-containing tertiary alcohols by direct allyl additions to ketones are unavailable.[25,26]

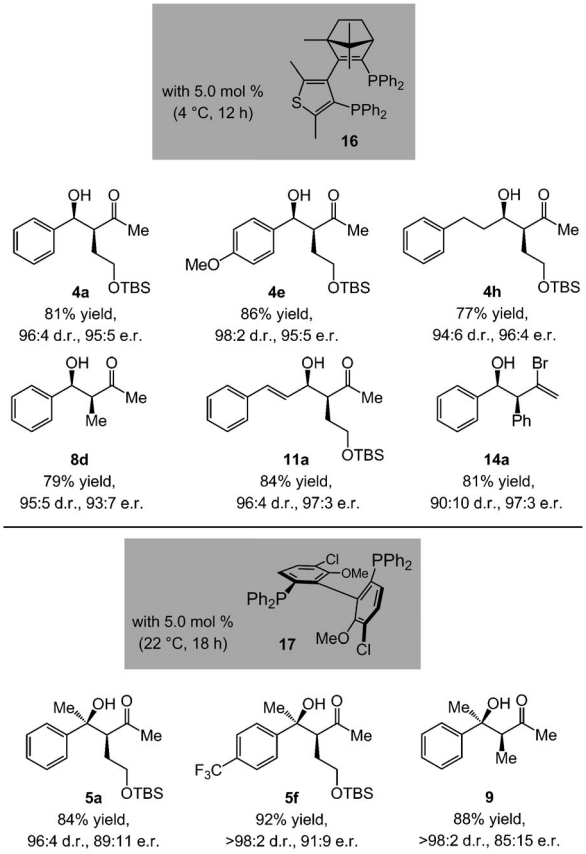


Scheme 5. The Cu-catalyzed protocol can be used to obtain valuable vinylbromides with high efficiency. The reaction conditions for the formation of **14a** and **14b** are shown. Compound **15a** is formed under the same conditions from substrates **2a** and **3a** and **15b** from **2a** and the benzyl derivative of **3a**.

Phosphine/Cu complexes promote the catalytic process in up to 97:3 enantiomeric ratio (e.r.);[27] reactions with aryl-, alkenyl-, or alkyl-substituted carbonyls afford products that are not readily accessible in high selectivity by catalytic enantioselective aldol additions (Scheme 6).[28] With various chiral NHC-based complexes, enantioselectivities do not exceed 60:40 e.r.[4] The use of two commercially available chiral bisphosphines (**16** and **17**) provide optimal enantioselectivities for additions to aldehydes and ketones;[29] the precise origin of such variations is the subject of current studies.



Scheme 4. Strategies involving initial preparation and use of 2-B(pin)-substituted allylboron reagents lead to alternative product isomers or demand the identification and use of a second catalyst, in contrast to the present Cu-catalyzed approach.



Scheme 6. Cu-catalyzed γ- and diastereoselective coupling of allenes with carbonyls can be performed enantioselectively through the use of chiral bisphosphine ligands. >98% conv. in all cases. For exact reaction conditions, see Table 1 and Scheme 5.

Design of more effective chiral catalysts for reactions with ketones as well as applications to natural product synthesis are in progress.

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[4] See the Supporting Information for details.
[5] a) B. Jung, A. H. Hoveyda, *J. Am. Chem. Soc.* **2012**, *134*, 1490; b) F. Meng, B. Jang, F. Haeffner, A. H. Hoveyda, *Org. Lett.*, DOI:10.1021/ol4004178; for a related study, see: c) W. Yuan, S. Ma, *Adv. Synth. Catal.* **2012**, *354*, 1867.
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[10] For a review on polyketide natural products, see: D. O'Hagan, *The Polyketide Metabolites*, Ellis Horwood, Chichester, UK, **1991**.
[11] The vinylboron products are unstable to silica gel; such instability might originate from boron chelation with the neighboring alcohol.
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[14] Excess NaO*t*Bu is needed for reactions with ketones, presumably because L–Cu–B(pin) regeneration by reaction of the more sterically congested Cu–alkoxide **B** with $B_2(pin)_2$ is slower via σ-bond metathesis and must proceed by alkoxide-assisted ligand exchange (versus 16 mol% base needed with an aldehyde), see: F. Gao, J. L. Carr, A. H. Hoveyda, *Angew. Chem.* **2012**, *124*, 6717; *Angew. Chem. Int. Ed.* **2012**, *51*, 6613.
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[17] Reactions with pyridyl aldehydes or ketones lead to <2% conversion.
[18] For Cu-catalyzed B(pin) conjugate additions to unsaturated carbonyls, see: E. Hartmann, D. J. Vyas, M. Oestreich, *Chem. Commun.* **2011**, *47*, 7917.
[19] High chemoselectivity in favor of reaction initiating with addition to the allene in spite of a slower rate of transformation with an enal might be due to a substantially faster rate of Cu–allene coordination, see Ref. [5b] for further discussion.
[20] As with aldehydes (Table 1), the initial Cu–B(pin) additions are more chemoselective with the P-based complex. As 1,2-addition of B(pin) to ketones is slow, excess enone is used with **7** to maximize efficiency.
[21] A. R. Woodward, H. E. Burks, L. M. Chan, J. P. Morken, *Org. Lett.* **2005**, *7*, 5505.
[22] Because C–B to C–Cu transmetallation is inefficient, uncatalyzed allylboration of aldehydes and metal-alkoxide-catalyzed addition of the same reagents to ketones predominate (NaO*t*Bu is needed for C–Cu formation).
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[24] For references regarding synthesis of 2-halogen-substituted products, see the Supporting Information.
[25] For catalytic diastereoselective allyl additions to ketones (not 2-B(pin) substituted), see: a) H. Ren, G. Dunet, P. Mayer, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 5376; b) Z. Peng, T. D. Blümke, P. Mayer, P. Knochel, *Angew. Chem.* **2010**, *122*, 8695; *Angew. Chem. Int. Ed.* **2010**, *49*, 8516; c) T. Takeda, M. Yamamoto, S. Yoshida, A. Tsubouchi, *Angew. Chem.* **2012**, *124*, 7375; *Angew. Chem. Int. Ed.* **2012**, *51*, 7263; for reactions of ketones and stoichiometric amounts of allylboronic acids (not 2-B substituted), isolated from allylic alcohols by a Pd-catalyzed process, see: d) M. Raducan, R. Alam, K. J. Szabó, *Angew. Chem.* **2012**, *124*, 13227; *Angew. Chem. Int. Ed.* **2012**, *51*, 13050. See the Supporting Information for additional references.
[26] For use of enantiomerically pure reagents for additions of substituted allyl units to carbonyls (no 2-B(pin) group), see the Supporting Information.
[27] For catalytic enantioselective allyl additions to ketones (not 2-B(pin)-substituted), see: a) R. Wada, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 8910; b) M. Wadamoto, H. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 14556; c) S. Lou, P. N. Moquist, S. E. Schaus, *J. Am. Chem. Soc.* **2006**, *128*, 12660; d) X. Jiang, Y. Cao, Y. Wang, L. Liu, F. Shen, R. Wang, *J. Am. Chem. Soc.* **2010**, *132*, 15328.
[28] Direct enantioselective catalytic aldol additions with aldehydes have been reported (none with ketones). Reactions with cyclic ketones (enol precursors) are more common and the large majority of acyclic cases involve transformations with strongly electron-deficient aryl aldehydes and generate products that bear a methyl or an alkoxy unit adjacent to the carbonyl (higher reactivity of the enol); low to moderate regioselectivity is typically observed (propionate versus acetate aldol). For example, see: a) S. Luo, H. Xu, J. Li, L. Zhang, J.-P. Cheng, *J. Am. Chem. Soc.* **2007**, *129*, 3074; b) S. Aratake, T. Itoh, T. Okano, N.

Nagae, T. Sumiya, M. Shoji, Y. Hayashi, *Chem. Eur. J.* **2007**, *13*, 10246. Reactions with aliphatic aldehydes are scarce (none with enals); one reported example requires > 140 h; see: c) G. Ma, A. Bartoszewicz, I. Ibrahem, A. Córdova, *Adv. Synth. Catal.* **2011**, *353*, 3114.

[29] For example, **4a** is generated in 95:5 d.r. and 90:10 e.r. (87% yield) when **17** is used, whereas **5a** is formed in 92:8 d.r. and 76:24 e.r. (82% yield) with **16**.

