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Multifunctional organoboron compounds for scalable natural product synthesis

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Abstract

Efficient catalytic reactions that generate C–C bonds enantioselectively and those that produce trisubstituted alkenes diastereoselectively are central to research in chemistry. Transformations that accomplish these two tasks simultaneously in a single operation are prized, particularly if the catalysts, substrates and reagents are easily accessed at low cost and reaction conditions are mild. Here, we report a facile multicomponent catalytic process that begins with a chemo-, site- and diastereoselective copper–boron addition to a mon-substituted allene; the resulting boron-substituted organocopper intermediates then participate in a chemo-, site- and enantioselective allylic substitution. Products, which contain a stereogenic carbon center, a mono-substituted alkene and an easily modifiable *Z*-trisubstituted alkenylboron group, are obtained in up to 89% yield, with >98% branch- and stereoselectivity and >99:1 enantiomeric ratio. The copper-based catalyst is derived from a robust heterocyclic salt that can be prepared in multi-gram quantities from inexpensive starting materials and without costly purification procedures. Utility of the approach is showcased through enantioselective synthesis of gram quantities of natural products rottnestol (member of an antibiotic family) and herboxidiene/GEX1A (anti-tumor).

Enantioselective processes where a catalyst unites a pair of starting materials and then induces the resulting species to react with a third substrate are sought-after in chemistry[1,2]. Pathways that involve difficult-to-access intermediates and products then become feasible, and wasteful and costly procedures for isolation and/or purification of sensitive reagents are obviated[3]. Uncommon instances of such multicomponent processes can be found in phosphine–Ir or Ru-catalyzed enantioselective reductive fusion of hydrogen, unsaturated hydrocarbons and carbonyl or imine compounds[4,5]. An unprecedented degree of complexity would result if a multi-tasking catalyst were to promote several transformations that are each selective on multiple levels with the final product bearing the marks of every single discriminatory event; a representative pathway is shown in Fig. 1a.

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Author Contributions F. M. performed the catalyst and method development studies as well as the total syntheses of rottnestol and herboxidiene/GEX1A. K. P. M. carried out the computational studies. A. H. H. and F. M. conceived the project. A. H. H. designed and directed the investigations and composed the manuscript with revisions provided by the other authors.

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Multicomponent Synthesis of Complex Alkenylboron Fragments

Boron-substituted alkenes are widely used multipurpose functional groups. Single-catalyst/multi-substrate transformations that deliver multifunctional unsaturated organoboron compounds are therefore of great interest. In the first phase of our studies (Fig. 1b), we found that chemoselective addition of (phosphine)Cu–B(pin) [B(pin) = (pinacolato)boron], derived from reaction of an in situ-generated (phosphine)Cu–alkoxide with $B_2(pin)_2$, to a mono-substituted allene (vs. aldehyde) affords 2-B(pin)-substituted allylcopper complex **I**, which then reacts with an aldehyde (vs. allene) to afford homoallylic alkoxide **iii**. An assortment of aldol-type products were obtained after oxidative treatment in up to >99:1 diastereomeric (d.r.) and 97:3 enantiomeric ratio (e.r.).[6] Transformations with N-heterocyclic carbene (NHC) complexes of copper, while efficient, generated racemic products.

The above reactions give 1,1-disubstituted alkenylboron units because of a second-stage γ addition (cf. **ii**), which causes the loss of a treasured attribute of the initially formed intermediate (**i**): a stereochemically defined and modifiable trisubstituted olefin. A multicomponent catalytic enantioselective process that preserves the trisubstituted alkenylboron group would have higher value. We thus envisioned a transformation involving chemo-, site- and stereoselective Cu–B(pin) addition to an allenyl substrate followed by chemo- and site-selective (branched vs. linear) cross-coupling of the resulting allylcopper species through enantioselective allylic substitution (EAS). The envisioned catalytic sequence would furnish multi-functional organoboron products **v** by a single operation; this would be in contrast to the existing strategies where each functional unit must be installed individually through extended and less efficient sequences[7,8] (for complete bibliography, see the Supplementary Information). Such a process would be a significant addition to an important but limited group of catalytic allyl–allyl reactions. Site- and enantioselective incorporation of allyl groups through catalytic EAS has been confined to simple fragments introduced via allylboron[9], allylmagnesium[10], or allylic alcohol[11] compounds (see the Supplementary Information for complete bibliography).

The expected organoboron products (**v**, Fig. 1b) are rich in adaptable moieties. A stereogenic center would be formed in the homoallylic position of a stereochemically defined trisubstituted alkenylboron unit that may be converted to other *E*- or *Z*-trisubstituted olefins. For instance, conversion of the C–B(pin) of **v** to a C–C bond with inversion of stereochemistry would deliver **vi**, which is a functional group found in numerous biologically active molecules; a notable case corresponds to a segment of immunosuppressive agent FK-506[12] (cf. highlighted fragment in Fig. 1c). Efficient and stereoselective synthesis of such trisubstituted olefin-containing fragments remains a difficult problem. In previous efforts either the undesired *Z* olefin was removed from a near equal mixture of isomers[13,14], or modification of a terminal alkyne by relatively lengthy routes were required[15]. The terminal olefin of the products is an asset as well: it would provide the opportunity for many types of modifications. One example entails conversion to an *E*,*E*-diene by sequential catalytic cross-metathesis with vinyl–B(pin)[16] and cross-coupling (cf. Fig. 1c),[17] generating a fragment that is common to several biologically active natural products. The highlighted segments in nafuredin (NADH-fumarate reductase

inhibitor[18,19]), milbemycin β_3 (insecticidal[20]), rottnestol (member of a family of antibiotics[21]) and herboxidiene/GEX1A (phytotoxic, anti-tumor[22]) are representative.

Identification of an Effective Catalyst and Method Development

Successful implementation of the aforementioned plan demands high chemoselectivity despite the involvement of two C–C π bonds [i.e., Cu–B(pin) addition to allene vs. allylic phosphate]. Mono-substituted allenes[23] as well as allylic carbonates[24] have indeed been shown to undergo efficient reactions with copper–boron complexes. Allenes are comparatively unhindered and might react with a Cu–B(pin) complex more readily, but the Lewis basic phosphate can associate with a transition metal to set off an undesirable sequence of events. Another strategic element is that reaction of the allylcopper intermediate with the allylic phosphate must be followed by a facile reductive elimination (cf. **iv**, Fig. 1b); this way, the trisubstituted alkenylboron unit would be retained and the chiral, branched product isomers would be formed preferentially (i.e., **3a** favored vs. **4**–**6**; cf. Table 1).

To identify conditions that would deliver **3a** in favor of 1,1-disubstituted alkenyl–B(pin) **4**, achiral **5** or diene **6** (Table 1), we selected the reaction involving allene **1a** and allylic phosphate **2a**. We soon found that, distinct from reactions with aldehydes[6] (Fig. 1b), a phosphine–Cu complex is ineffective (e.g., with PCy_3 and **7**[25], entries 1–2, Table 1), and bis-phosphine-derived catalysts cause only the allylic phosphate to be consumed (e.g., with complex derived from **8**, entry 3). That is, unlike the reactions involving aldehydes, mono-substituted allenes fail to compete with allylic phosphates when bis-phosphines serve as ligands. These observations substantiated our unease regarding the presence of two types of electrophilic olefins.

We then made the unexpected discovery that, in further contrast to carbonyl additions, an NHC–Cu complex can guide the catalytic cycle along the desired path (Table 1). The NHC–Cu species derived from aryl-substituted heterocyclic salt **9a** (entry 4) afforded **3a** as the major component (81% yield); the alternative alkenylboron-containing products **4**, **5** or **6** were not detected (<2%); the complete site (branch) selectivity was equally surprising. Conversely, with enantiomerically pure **9b** (entry 5), **3a** was isolated in trace amounts, and reactions involving chiral salts **10**[26] and **11**[27] either produced **3a** in low yield (cf. phenol **10**, entry 6) or none at all (cf. sulfonate **11**, entry 7). Investigation of enantiomerically pure NHC precursors bearing an N-aryl and an N-alkyl group led us to establish that reaction with aminoalcohol-derived **12a**[28] (entry 8, Table 1) affords **3a** in 67% yield, >98% S_N2' selectivity and 89:11 e.r. Follow-up studies revealed that enantioselectivity can be sensitive to the substituent at the stereogenic center of the chiral catalyst (entries 8–10, Table 1). Additional modification revealed that **12d** is precursor to a more efficient (80% yield; entry 11) and enantioselective catalyst (94:6 e.r.). Incorporation of larger N-aryl substituents did not lead to any improvement (cf. **12e**, entry 12).

The method can be used to prepare a range of multifunctional organoboron compounds in high selectivity (Fig. 2a). The requisite imidazolinium salt **12d**, an air stable solid, can be prepared in multi-gram quantities by a modified version of a reported procedure;[28] the necessary reagents, including either enantiomeric form of phenylglycinol, can be bought at

low cost. Allylic phosphates bearing sterically hindered substituents (cf. **3b**–**c**), halogenated aryl groups (cf. **3d**–**e**) or an alkyl unit (cf. **13**) are suitable substrates. Although NHC–Cu–B(pin) complexes react readily with β-alkylstyrenes,[29] additions to an allene/EAS occur more readily (cf. **14**). Allenes that contain other modifiable groups, such as an alkyne (cf. **15**), an amine (cf. **16**), or an amide (cf. **17** or **19**) may be used. As the outcomes of the transformations expected to generate amides **17**–**19** indicate, a Lewis basic group, depending on its distance from the allene site, can alter reaction rates. Unsubstituted allene was used to access 1,1-disubstituted alkenyl–B(pin) **20** in 89% yield, >98% branch selectivity and 97:3 e.r. Catalytic cross-coupling reactions with readily accessible aryl halides proceed with retention of stereochemistry to generate trisubstituted alkenes (cf. **21**–**23**, Fig. 2b).

Origins of High Efficiency, Branch- and Enantioselectivity

The challenge of designing a multicomponent process is in identifying a catalyst that can clear several efficiency and selectivity hurdles before reaching the finish line and starting over. Key attributes of the optimal NHC–Cu complex (derived from **12d**) are discussed below.

Chemoselectivity and efficiency

The difference between percent conversion and yield of **3a** with certain Cu complexes (Table 1) signals a breakdown in chemoselectivity: competitive Cu–B addition to **2a** (vs. allene **1a**) leads to formation of byproducts. Hence, it appears that the less Lewis basic and sterically demanding phosphine-based systems (e.g., **8**, Table 1), which are distinct from those of NHC ligands[30,31], allow the phosphate to associate and react more readily. The pathway that hampers the transformations of the less effective NHC–Cu complexes is more tractable. Allylic substitution of a B(pin) group with **2a** produces a branched allylboron intermediate (**24**, Fig. 3a) that can be converted to the corresponding allylcopper species (**25**), which then reacts with another molecule of allylic phosphate **2a** to form 1,5-diene **26**. Indeed, without the allene, the NHC–Cu complexes catalyze the formation of diene **26** efficiently (e.g., 53% yield for **9a**, 76% yield for **11** and 50% yield for **12d**). Similar generation of an allylcopper might be inefficient with the Cu center of a bis-phosphine complex, which is likely less Lewis acidic as a result of its weaker two-electron donor ligand (vs. an NHC)[32], causing the allylboronate compound to react in other ways.

Comparison of the transformations performed with NHC–Cu complexes derived from **9c**–**f** (Fig. 3b) indicates that the proper balance between electronic attributes and size of the heterocyclic ligand is needed if high efficiency and chemoselectivity are to be achieved. The catalyst arising from **9d** is too large to promote transformation, whereas the ligands derived from the smaller **9c** and **9f** contain N-alkyl units (vs. N-aryl) and are therefore too nucleophilic to facilitate the desired succession of events. Imidazolinium salt **9e** delivers an NHC–Cu complex that is small enough to promote reaction without being too diminutive or overly nucleophilic to promote Cu–B(pin) addition to the allylic phosphate. The complex resulting from **10** (>98% conv., 36% yield of **3a**; entry 6, Table 1) in all probability serves as a monodentate ligand that contains an N-mesityl and a smaller *ortho*-substituted N-aryl moiety, rendering it less selective (see below). The bidentate Cu catalyst arising from **11** is

likely the only instance of a bidentate complex formed in the screening studies (detailed below); the cuprate species possesses higher energy Cu d-electrons that are more compatible to interact with the lower lying π* orbital of an allylic phosphate (vs. an allene)[33], facilitating the undesired allylic substitution of a B(pin) unit (low chemoselectivity).

Branch- and enantioselectivity

Chiral heterocyclic ligands (e.g., **10**, **11**, **12a**–**e**) with a chelating group commonly serve as precursors to bidentate NHC–Cu systems (i.e., cuprate complexes). However, the resulting Cu–O tether can rupture through reaction with $B_2(pin)_2$, revealing a monodentate complex that carries a neutral metal center[34]. For two reasons we did not initially think that such a cleavage takes place with Cu complexes resulting from **12a**–**e**. Firstly, usually exceptional S_N2' selectivity is observed with reactions of organoboron compounds that are promoted by bidentate NHC–Cu catalysts[34–35]; this preference may be attributed to rapid reductive elimination of the Cu(III) intermediate[33] so that substantial steric hindrance can be relieved (cf. the top pathway available to **II** in Fig. 3d). The less sterically demanding monodentate complexes, on the other hand, generate achiral linear isomers either preferentially[34] or to a significant degree[35]. Secondly, high enantioselectivities have been observed with catalysts that contain a chiral NHC ligand that is either bidentate (e.g., **11** in Table 1),[28] or monodentate (e.g., **9b**) but with conformationally constraining stereogenic centers,[36,37] or both[24,34–35]. High enantioselectivity without bidentate ligation and/or conformationally restricting substituents is unusual, since it must originate from a single stereogenic center within the conformationally flexible arm of a C_1-symmetric NHC ligand. Nevertheless, such a scenario became irrefutable when we found that reaction with silyl ether **12f** (Fig. 3c) proceeds with nearly identical efficiency and selectivity as when **12d** is used. (We were unable to prepare and examine an authentic sample of the boronate derivative; similar results were obtained with the corresponding *tert*-butyldiphenylsilyl ether analogue of **12f**.) Additionally, with methyl ether **12g** (Fig. 3c), enantioselectivity was all but completely eroded. Stereoselectivity is thus likely induced by the large B(pin)-substituted chiral appendage, formed through reaction of $B_2(pin)_2$ with the Cu–O bond and emulated by the silyl ether in **12f**.

DFT calculations point to transition structure **I** as the source of the major product enantiomer (Fig. 3d; see the Supplementary Information for details of all calculations). The allylic phosphate occupies two sites of the tetrahedral Cu(I) complex to generate a square planar Cu(III) species that undergoes reductive elimination via **II** to give **viii** (vs. **ix**). The P=O→Cu coordination facilitates the association of the allylic phosphate with the sterically demanding NHC–Cu–allyl complex; this picture is supported by the variations in reaction efficiency observed for the transformations involving products **17**–**19** (cf. Fig. 2a). In the case of **18** (<2% conv.), the Lewis basic amide carbonyl is properly situated to chelate with the Cu center in the first intermediate to prevent phosphate chelation (cf. **x**, Fig. 3e). The ring size in the bidentate complex **xi** is similar to that found in the oxidative addition precursor **V** (Fig. 3e).

The two-point catalyst/substrate binding enhances the organization of the stereochemistry-determining transition state, generating high stereochemical induction via **II**. The minor

isomer is probably produced via **III**, wherein the sizeable boronate group can swerve into close contact with the protruding allylic phosphate substituent. The B(pin) moiety of the allyl ligand must either collide with the ethyl substituents of the NHC's N-aryl moiety (shown) or induce steric repulsion due to propinquity of the B(pin) unit and the NHC side chain. There must therefore be a feature of the catalyst structure that is responsible for C–C bond formation occurring proximal to the chiral arm of the NHC ligand. Molecular models suggest that, because of steric factors, the ortho (ethyl) substituents of the ligand's N-aryl moiety discourage placement of the allyl fragments in their proximity. The complete loss of enantioselectivity that results from placement of the groups at the N-aryl moiety's C3 and C5 positions corroborates the proposed scenario (i.e., the derived boronate of NHC precursor **12h**, Fig. 3c).

Finally, there are the exceptional $S_N2':S_N2$ ratios despite involvement of a monodentate–Cu complex[35,38]. This almost certainly originates from the sizeable B(pin) unit of the allyl ligand of the Cu(III) complex; the boronate moiety is absent in the formerly examined EAS reactions with organoboron compounds[34,35]. The steric repulsion engendered by the sizeable B(pin) group elevates the ground state energy of the Cu(III) intermediate species **II** (major) and **IV** (minor), accelerating reductive elimination (to give **viii** in Fig. 3d) before it can collapse to the π-allyl species (cf. **ix** in Fig. 3d). DFT calculations support the contention that the presence of the large B(pin) group lowers the activation barrier to reductive elimination (strain release).

Gram Scale Total Synthesis of Rottnestol

Synthesis of a complex organic molecule with catalytic multicomponent processes as the its central feature would be a clear indicator of their utility, particularly if meaningful quantities of a target molecule were to be secured. We first designed a route to prepare gram quantities of pure rottnestol where every issue of stereochemical control would be addressed by a catalytic transformation. We envisioned using the NHC–Cu-catalyzed enantioselective process involving an allylic phosphate for synthesis of the polyene segment, while the carbohydrate moiety would be accessed through a catalytic $B_2(pin)_2$/allene/aldehyde fusion (Fig. 4).

The synthesis route commenced with the Cu–B(pin) addition/EAS sequence (Fig. 4a). Treatment of mono-substituted allene **1b** and methyl-substituted allylic phosphate **2b** with 3.0 mol % *S*-**12d** and CuCl (cf. Fig. 2) afforded trisubstituted alkenyl–B(pin) **27** in 79% yield, with complete branch and *Z* selectivity and in 92:8 e.r.; the reaction was performed on two batches of ca. 1.7 g of **1b**, delivering a total of ca. 4.2 g of the product. Conversion of the C–B(pin) to a C–Me bond was accomplished with complete inversion of stereochemistry (>98% *E*) through reaction with methyllithium and iodine[39], delivering trisubstituted alkene **28** in 91% yield (3.4 g). NHC–Ru-catalyzed *E*-selective cross-metathesis with commercially available vinyl–B(pin)[16] in the presence of 5.0 mol % Ru carbene **29**[40] and formation of the corresponding alkenyl–iodide[16] proceeded in 80% overall yield, furnishing ca. 3.6 g of **30**, which was transformed to 1.4 g of triene **31** in three straightforward steps (73% overall yield).

To prepare the carbohydrate fragment (Fig. 4b), we adopted an enantioselective reaction involving aldehyde **32**, which can be prepared in one step from a commercially available alcohol and four other entities that can also be purchased: methylallene **1c**, $B_2(pin)_2$, bis-phosphine **33** and CuCl. Silyl protection of the β-hydroxyketone afforded **34** in 75% overall yield (3.4 g through two batches) with complete control of stereoselectivity (>98:2 d.r. and e.r.). Ketone **34** was converted to carbohydrate **35** after four steps in 67% overall yield (1.18 g). NHC–Cu-catalyzed protoboration of the terminal alkyne in **35** furnished β-alkenyl–B(pin) **36** in 97:3 β:α ratio, >98% *E* selectivity and 93% yield (1.8 g).[41] More than one gram of stereoisomerically pure rottnestol was obtained after catalytic cross-coupling[42] of alkenyl–iodide **31** and alkenyl–B(pin) **36** followed by generation of the cyclic hemiacetal by acid treatment. The route in Fig. 4 is more efficient than those disclosed previously (21.5% vs. 3.7% overall yield)[43] and which resulted in no more than milligram quantities of the target molecule.

Gram Scale Total Synthesis of Herboxidiene/GEX1A

Devising a route leading to anti-tumor agent herboxidiene/GEX1A was next. Here, we explored a different aspect of the NHC–Cu-catalyzed transformation (Fig. 5). In the case of rottnestol the multicomponent process was employed early on (cf. **27**, Fig. 4); in contrast, with herboxidiene/GEX1A, the process would be implemented at a later stage with a more complex allene. In the event, ca. seven grams of substrate **37** were obtained by a seven-step procedure in 29% overall yield, >98:2 d.r. and e.r.; the central reaction in the sequence was phosphine–Cu-catalyzed multicomponent reaction of $B_2(pin)_2$, methylallene **1c** and an aldehyde derived from (*R*)-methyl lactate (cf. synthesis of **34**). Considerable structural complexity, including the appropriate 1,5-relative stereochemistry, was thus generated in short order: 1,5-diene **38** (ca. 1.5 g for each run) was obtained in ca. 76% yield with complete site-, *Z*- and diastereoselectivity. Trisubstituted alkene **39** was accessed through alkylation and catalytic cross-metathesis with vinyl–B(pin), yielding ca. 3.3 g of the desired product; both alkenes were formed with >98% *E* selectivity. Phosphine–Pd-catalyzed cross-coupling of alkenyl–B(pin) **39** with alkenyl-iodide **40**, synthesized through a diastereo- and enantioselective eight-step process starting from β-(+)-citronellene (see the Supplementary Information), afforded 2.55 grams of triene **41**. After three operations,[44,45] 1.03 gram of the anti-tumor agent was secured; this represents nearly twice the overall yield as the most concise of the previously reported syntheses[45] (5.5% vs. 3.4%; see the Supplementary Information for bibliography).

Conclusions and Discussions

The advances outlined here demonstrate that two simple unsaturated organic molecules and a commercially available diboron reagent can be combined to generate multifunctional alkenylboron fragments that are marked by several advantageous attributes. The requisite catalyst is assembled in situ by the reaction of an abundant and inexpensive CuCl and a chiral ligand that is easily synthesized in multi-gram quantities readily and cost-effectively. Due to the above features, and because the NHC–Cu-catalyzed process is robust, gram quantities of a variety of complex organic molecules become reliably available.

This advance foreshadows the development of protocols involving additional difficult-to-access alkenylboron containing organocopper compounds. What emerges is the possibility of utilizing other abundantly available poly-unsaturated hydrocarbons, such as dienes[46] or enynes[47], for efficient preparation of high-value products. Such a strategy obviates the need for succumbing to one-at-a-time installment of each functional unit, resulting in pathways that are unnecessarily time consuming, costly and waste generating.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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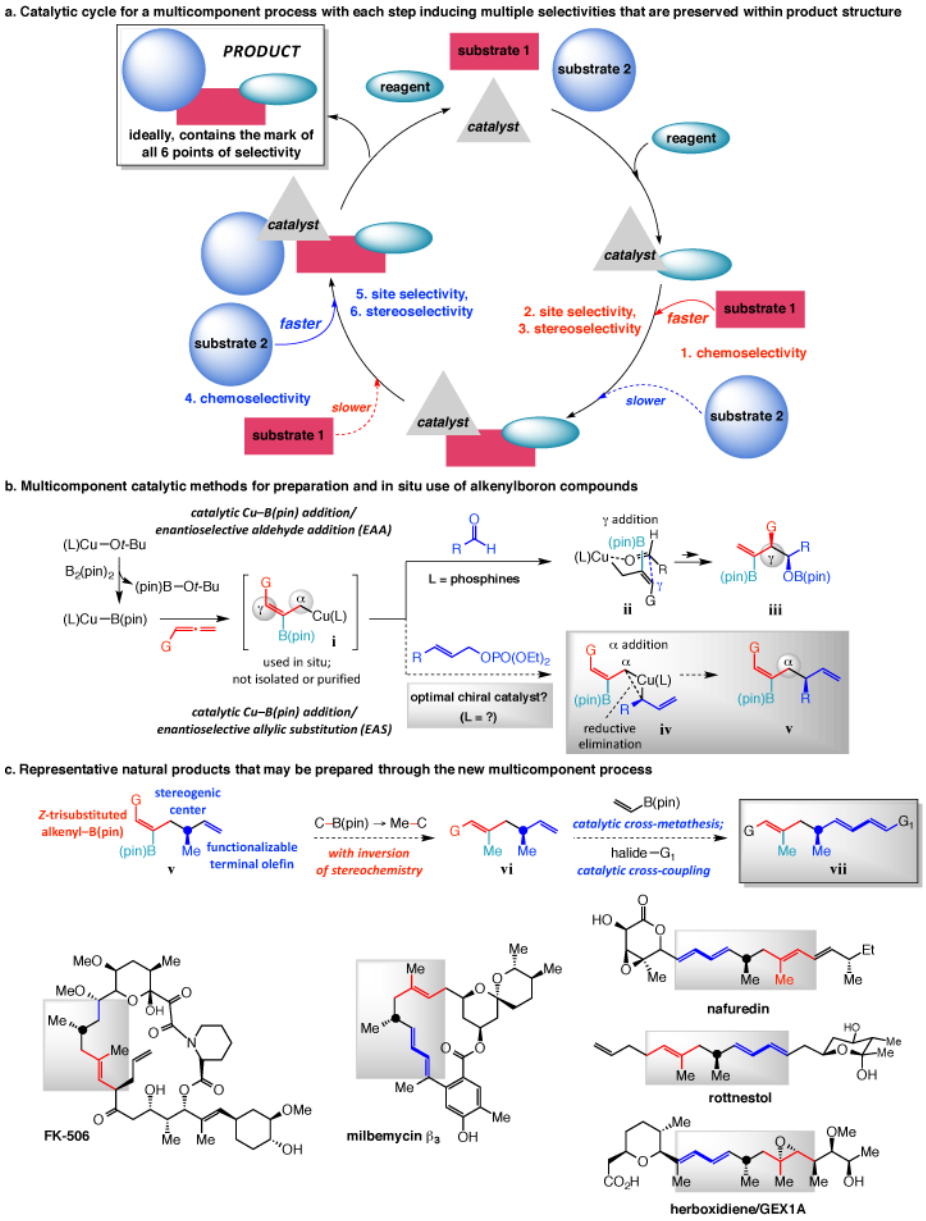

Figure 1. Multicomponent catalytic enantioselective generation of alkenylboron compounds

a, The general scheme for a multicomponent catalytic cycle involving a reagent and two substrates might be envisioned to proceed by a sequence entailing multiple selectivity issues. Ideally, all points of selectivity would be retained. **b,** Catalytic stereoselective generation of an alkenyl–B(pin) intermediate (**i**), which might react in situ site-, diastereo- and enantioselectively with an aldehyde or an allylic phosphate to generate valuable multifunctional products. In the second proposed sequence, each point of selectivity, especially the trisubstituted alkene, would be preserved within the final structure. **c,** Sequential catalytic Cu–B(pin) addition/enantioselective allylic substitution, affording products represented by **v**, constitutes an attractive strategy for synthesis of biologically active compounds. NHC = N-heterocyclic carbene, B(pin) = (pinacolato)boron, G = functional group, LG = leaving group.

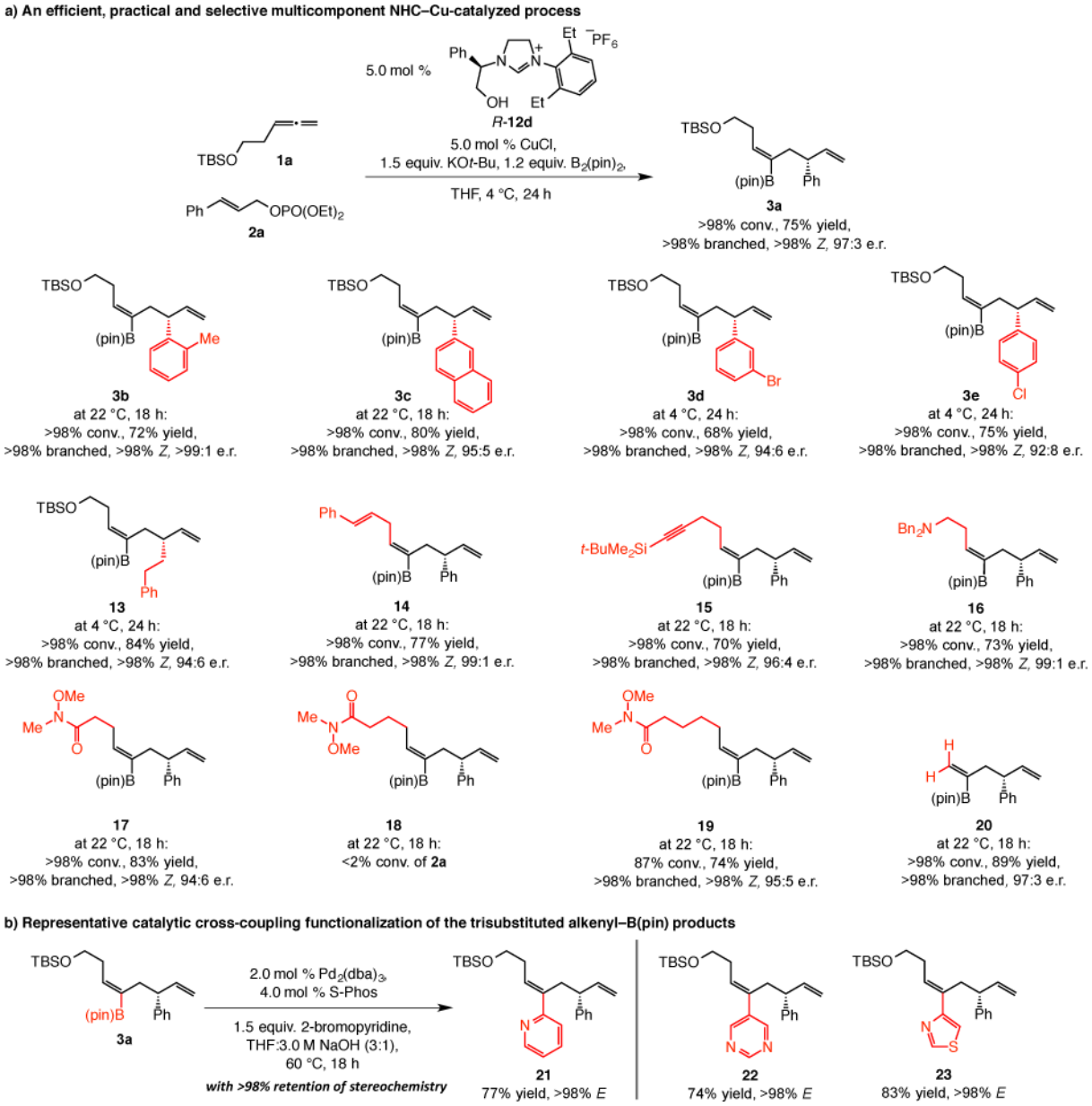

Figure 2. Catalytic chemo-, site- and enantioselective multicomponent reactions

a, Transformations are promoted by NHC–Cu complexes generated in situ from **12d**, which can be easily prepared from inexpensive starting materials on multi-gram scale in ca. 50% overall yield. Transformations proceed with 5.0 mol % catalyst at 4 °C–22 °C and are complete in 18–24 h to deliver the desired products in >98% *Z*, S_N2', and chemoselectivity and 92:8 to >99:1 e.r. **b,** The trisubstituted alkenyl–B(pin) obtained with complete *Z* selectivity can be converted to a variety of coveted trisubstituted *E* alkenes through catalytic cross-coupling with readily available aryl bromides; all reactions proceed with complete retention of stereochemistry. Abbreviations: TBS = *t*-butyldimethylsilyl, dba = dibenzylideneacetone, S-Phos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl.

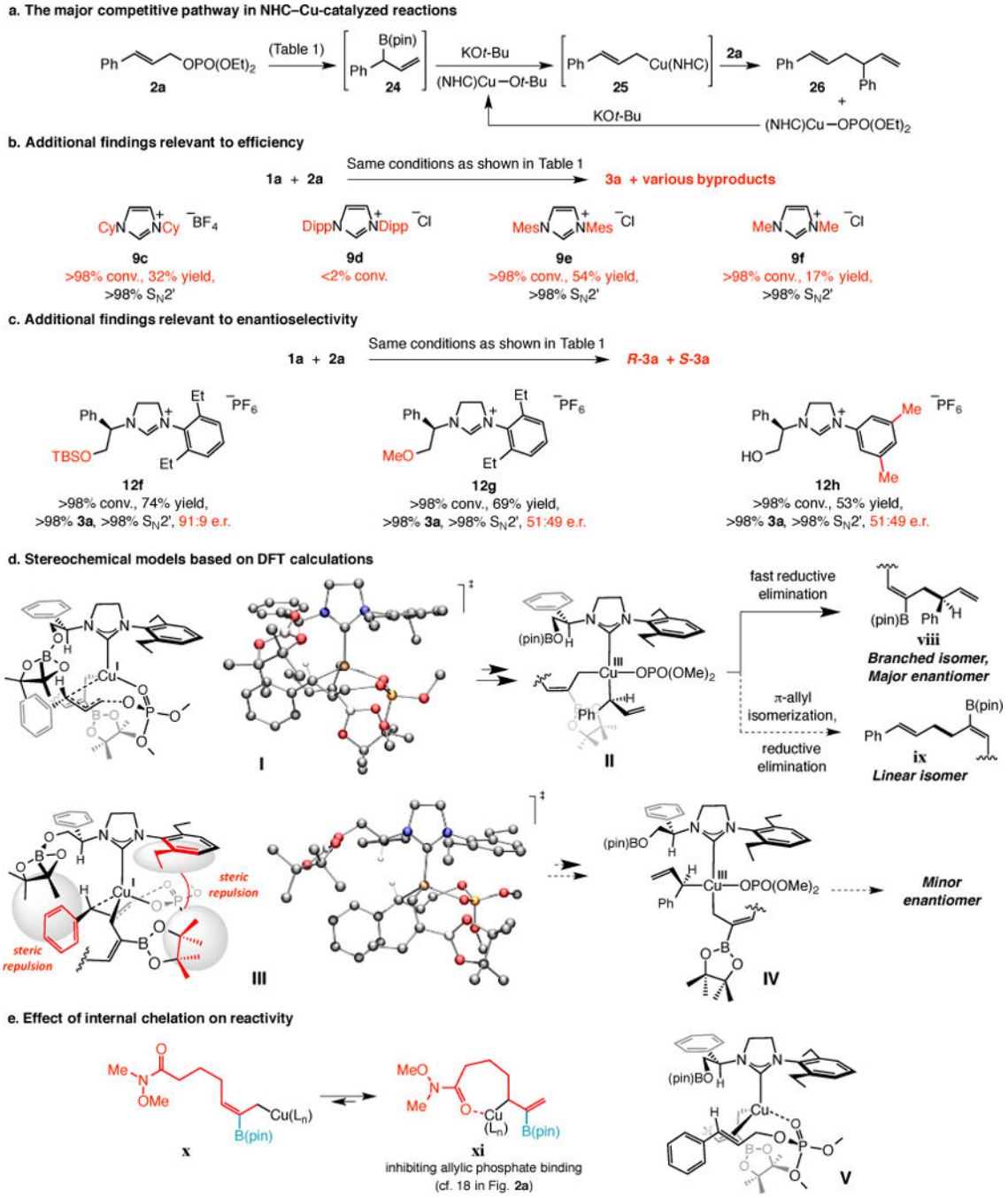

Figure 3. Origins of high efficiency and selectivity

a, Low efficiency with some NHC–Cu-catalyzed reactions is due to a competitive pathway arising from undesirable chemoselectivity. **b**, The efficiency of the multicomponent process hinges on the catalyst possessing the appropriate steric and electronic attributes. **c,** Modification of the chiral NHC ligand indicates that the optimal Cu-based catalyst is likely a monodentate complex with an N-alkyl side chain containing the sole stereogenic center. **d,** DFT calculations point to a mode of transformation **I** leading to the major enantiomer (vs. **III**). The uniformly exceptional branch or S_N2' selectivity (vs. linear or S_N2), despite the

involvement of a neutral monodentate NHC–Cu catalyst, might be due to steric facilitation of the reductive elimination step (vs. π-allyl formation) via **II** and **IV. e**, Evidence for the importance of Cu–phosphate chelation to reaction efficiency. Abbreviation: Dipp = 2,6-(*i*-Pr)$_2$C$_6$H$_3$, TBS = (*t*-Bu)Me$_2$Si.

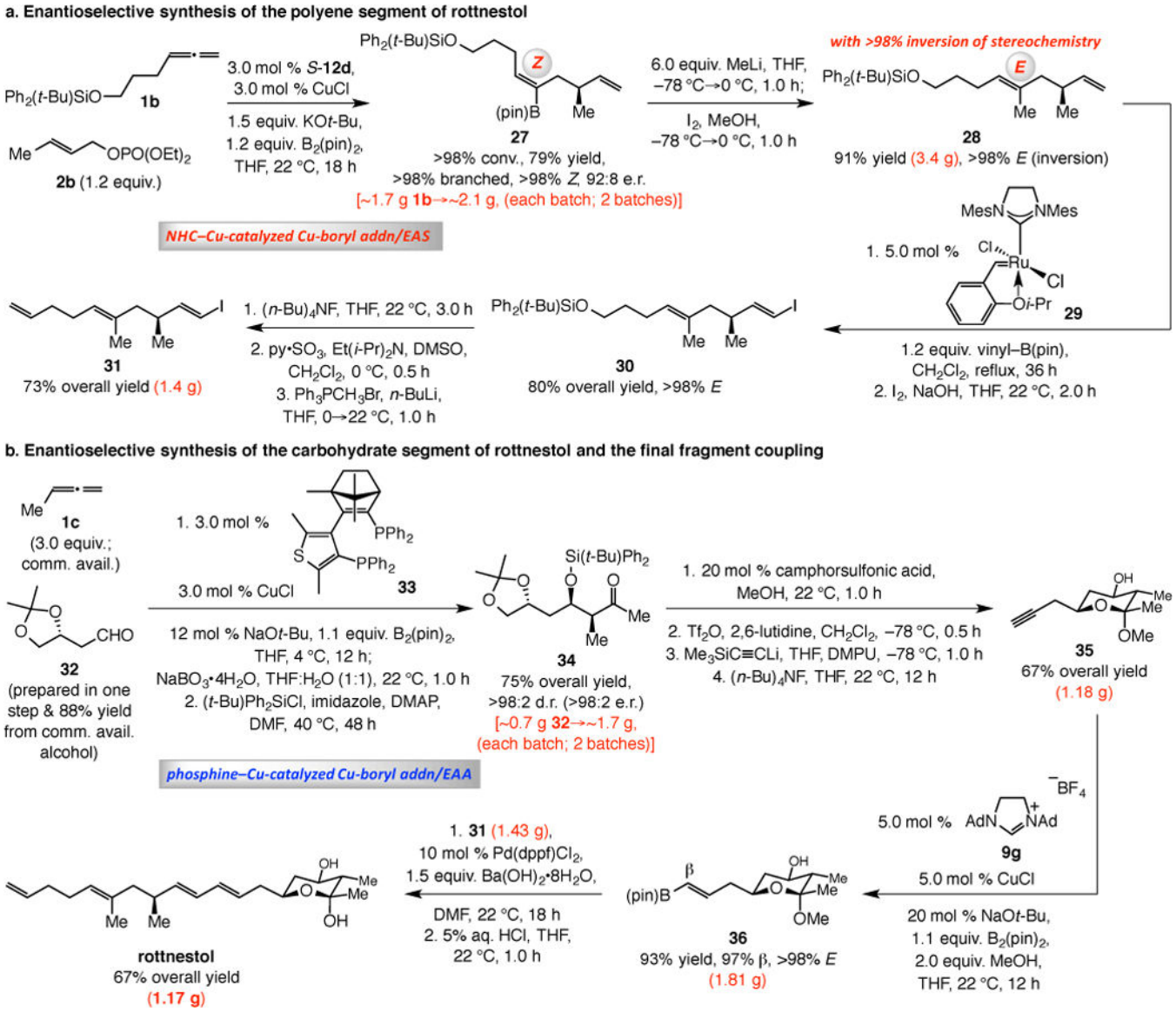

Figure 4. Enantioselective gram-scale synthesis of rottnestol

Every stereochemical issue route is addressed by a catalytic process that involves an organoboron compound; this is highlighted by two multicomponent chemo-, site-, diastereo- and enantioselective assemblies. **a,** Site- and enantioselective NHC–Cu-catalyzed $B_2(pin)_2$/allene/allylic phosphate and NHC–Ru-catalyzed catalytic cross-metathesis (CM) reactions are combined to access the acyclic fragment. **b,** A phosphine–Cu-catalyzed multicomponent process involving an allene and an aldehyde is used to access the carbohydrate moiety. The final fragment coupling is achieved by phosphine–Pd-catalyzed coupling, generating nearly 1.2 g of the natural product. Abbreviations: DMAP = 4-dimethylaminopyridine, DMPU = N,N'-dimethyl-N,N'-trimethyleneurea, dppf = 1,1′-bis(diphenylphosphino)ferrocene.

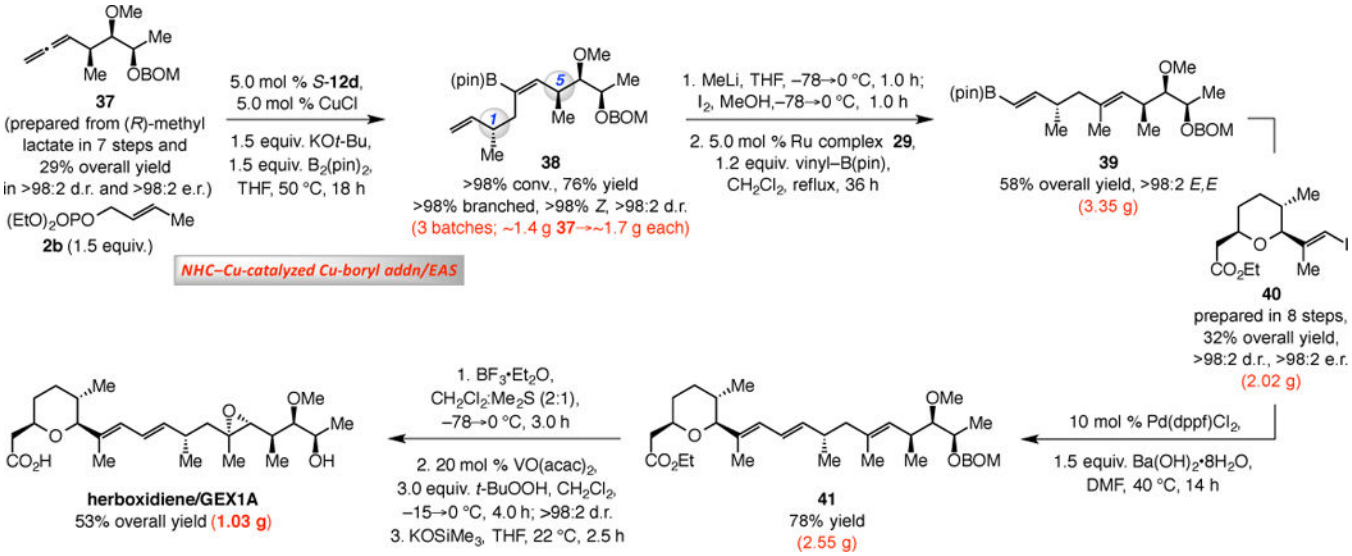

Figure 5. Enantioselective gram-scale synthesis of herboxidiene/GEX1A

The key step, taking place mid-point in the multi-step route involves a relatively complex enantiomerically pure mono-substituted (**37**). The reaction can be performed on gram scale batches to obtain ca. 1.7 g of 1,5-diene **38** for each run (ca. 76% yield), with >98% site-, *Z*- and diastereoselectivity. Subsequent conversion to *E*,*E*-diene **39** proceeds with complete stereochemical control as well. Catalytic cross-coupling generates triene **41**, which is then transformed to 1.03 g of the natural product. It is noteworthy that every transformation shown above that involves a stereochemical issue proceeds with complete selectivity (i.e., catalytic multi-component process, alkylation of the alkenylboron intermediate, catalytic cross-metathesis, catalytic cross-coupling and directed epoxidation). Abbreviation: acac = acetylacetone.

Table 1

Examination of copper complexes as catalysts for sequential Cu–B(pin) addition/EAS

Entry number	Ligand or Ligand precursor	Conversion (%)*; Yield of 3a (%)†	Site Selectivity (3a:4:5:6)*	*Z:E**	Enantiomeric ratio for 3b§
1	PCy_3	<2; NA	NA	NA	NA
2	**7**	<2; NA	NA	NA	NA
3	**8**	>98; <2	NA	NA	NA
4	**9a**	<98; 81	>98:<2:<2:<2	>98:2	NA
5	**9b**	40:<2	NA	NA	NA
6	**10**	>98; 36	>98:<2:<2:<2	>98:2	22:78 (*R:S*)
7	**11**	>98; <2	NA	NA	NA
8	**12a**	>98; 67	>98:<2:<2:<2	>98:2	89:11 (*R:S*)
9	**12b**	>98; 74	>98:<2:<2:<2	>98:2	93:7 (*R:S*)
10	**12c**	>98; 72	>98:<2:<2:<2	>98:2	85:15 (*R:S*)
11	**12d**	>98; 80	>98:<2:<2:<2	>98:2	94:6 (*R:S*)
12	**12e**	>98; 77	>98:<2:<2:<2	>98:2	92:8 (*R:S*)

Reactions were carried out under N_2 atm.; see the Supplementary Information for details. NA = not applicable.

*Conversion (conv.), site selectivity and *Z:E* ratios were determined by analysis of 400 MHz ^{1}H NMR spectra; variance of values is estimated to be <±2%.

†Yield of purified products.

§Enantiomeric ratio (e.r.) values were determined by HPLC analysis; variance of values is estimated to be <±1%. See the Supplementary Information for details.

Abbreviation: Mes = 2,4,6-Me_3-C_6H_2.