Catalytic enantioselective 1,6-conjugate additions of propargyl and allyl groups

Fanke Meng, **Xiben Li**, **Sebastian Torker**, **Ying Shi**, **Xiao Shen**, and **Amir H. Hoveyda**[1]

[1]Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts, 02467, USA

Abstract

Conjugate (or 1,4-) additions of carbanionic species to α,β-unsaturated carbonyl compounds are vital to research in organic and medicinal chemistry, and there are several known chiral catalysts that facilitate the catalytic enantioselective additions of nucleophiles to enoates[1]. However, catalytic enantioselective 1,6-conjugate additions are uncommon, and ones that are able to incorporate readily functionalizable moieties, such as propargyl or allyl groups, into acyclic $\alpha,\beta,\gamma,\delta$-doubly unsaturated acceptors are unknown[2]. Chemical transformations that could generate a new bond at the C6 position of a dienoate are particularly desirable, as the resulting products would be subjected to further modifications; such reactions, especially when dienoates contain two equally substituted olefins, are scarce[3] and are confined to reactions promoted by a phosphine–copper (with alkyl Grignard[4,5], dialkylzinc or trialkylaluminum compounds[6,7]), a diene–iridium (with arylboroxines)[8,9], and a bisphosphine–cobalt catalyst (with monosilyl-acetylenes)[10]. 1,6-conjugate additions are otherwise limited to substrates where there is full substitution at C4[11]. It is not clear why certain catalysts favor bond formation at C6, and – while there are a small number of catalytic enantioselective conjugate allyl additions[12,13,14,15] – related 1,6-additions and processes involving a propargyl unit are non-existent. In this manuscript, we show that an easily accessible organocopper catalyst can promote 1,6-conjugate additions of propargyl and 2-boryl-substituted allyl groups to acyclic dienoates with high selectivity. A commercially available allenylboron compound or a monosubstituted allene may be used. Products can be obtained in up to 83 percent yield, >98 percent diastereo- (for allyl additions) and 99:1 enantiomeric ratio. Mechanistic details, including the origins of high site- (1,6- versus 1,4-) and enantioselectivity as a function of the catalyst structure and reaction type, have been elucidated by means of density functional theory (DFT) calculations.

Designing an efficient 1,6-conjugate addition is difficult is that the largest coefficient of the lowest unoccupied molecular orbital (LUMO; see **i**, Fig. 1a) is at C4 and consequently this is where the bond is preferentially generated. We surmised that any conjugate addition should begin by interaction of the nucleophilic allenylcopper species with dienoate C4 by an oxidative addition to give **ii** or π-complexation[16] to afford **iii** (Fig. 1a). 1,6-Addition could then be favorable if certain alternative processes were faster than the 1,1′-reductive elimination that affords 1,4-allenyl addition compound **iv** (Route A, Fig. 1a). We envisioned two possible scenarios in this regard: 1) Compound **ii** might undergo a 1,3-shift followed by 1,1′-reductive elimination to deliver 1,6-allenyl addition product **vi** via **v** by forming a bond between dienoate's C6 and the Cα of the allenylmetal system (Route B); this type of π-allyl isomerization has been previously suggested[5] but experimental or computational support was not provided. 2) Organocopper complex **iii** might be directly transformed to the 1,6-propargyl-addition product **vii** by a creation of a bond between the dienoate C6 and the Cγ of the allenyl–copper moiety (Route C, Fig. 1a). That is, the allenylcopper complex in its bent form (see Fig. 1c) may interact with the C3–C4 π cloud, placing the nucleophilic Cγ near the dienoate C6. This pathway would be reminiscent of a 3,3′-reductive elimination proposed vis-à-vis enantioselective allyl–allyl coupling with Ni- and Pd complexes[17,18]. A similar reaction mode with an organocopper species has been mentioned in just one instance (again, without experimental or computational support)[19].

We first carried out a model transformation involving dienoate **1a** and commercially available allenyl–B(pin) **2** with a Cu complex derived from imidazolinium salt **3a** and CuCl. We opted for NaOPh versus an alkoxide as the stroichiometric base (e.g., NaO*t*-Bu) because the residual CuOPh is less Lewis basic and would not interfere with the function of a chiral catalyst; small amounts of either may however be used to deprotonate the imidazolinium salt to generate the NHC–Cu complex. In the event, at ambient temperature and after 16 hours **4a** was isolated in 64% yield as a single alkene isomer (>98% β,γ-enoate); the 1,6-allenyl, 1,4-propargyl or 1,4-allenyl addition products were not detected (**5a**–**7a**). The exclusive formation of **4a** implies that the pathway involving a π-allyl shift is not operative (Route B); otherwise, allenyl compound **6a** would be formed. The catalytic cycle in Fig. 1c is probably the most relevant. Under the same conditions but with the corresponding α,β,γ,δ-unsaturated mono-ester there was minimal conversion (<5%).

Next, we examined the effect of chiral phosphorous-based ligands. In certain cases either a complicated mixture of compounds was generated (**8a** and **8d**, Fig. 2a) or, unlike the aforementioned N-heterocyclic carbene (NHC) copper species, appreciable amounts of the 1,4-addition product (**5a**) were formed (mechanistic analysis below). Enantioselectivity was uniformly low. Matters improved with NHC–Cu complexes (**9a-e**, Fig. 2a): **4a** was generated exclusively (>98:2 1,6-:1,4-propargyl addition), and the complex derived from phenylglycine-derived **9b** delivered it in 74% yield and 97.5:2.5 enantiomeric ratio (e.r.). Nevertheless, some of the screening data were unexpected. Whereas reaction with the larger **9c** afforded substantially reduced selectivity (67.5:32.5 e.r.), with imidazolinium salt **9d**, which contains a less imposing 3,5-dimethylphenyl moiety, **4a** was formed in 92:8 e.r. Further, unlike the related catalytic allylic substitution processes[20], protection of the NHC

hydroxy group was detrimental to enantioselectivity: reaction with silyl protected **9e** gave nearly racemic product.

The enantioselective protocol has considerable scope (Fig. 2b). Dienoates withan aryl unit (**4b**-**g**), whether it is electron donating (**4e**) or electron withdrawing (**4g**), react efficiently to give products in >98:2 propargyl:allenyl and 1,6-:1,4 selectivity and 94:6–97:3 e.r. A bromoaryl group is tolerated (**4f**), which is notable since an unhindered aryl–bromine bond can be prone to undergoing oxidative insertion with a copper(I) complex. High efficiency and selectivity was observed with heterocyclic substrates (**4h,i**) or those that bear an alkenyl (**4j**), a linear or a branched aliphatic group (**4k,l**). The sterically congested *tert*-butyl-substituted **4m** was isolated in 74% yield and 98:2 e.r. (>98% propargyl and 1,6-addition); the ease with which this C–C bond is formed corroborates the initial addition occurring at C4, distally from the quaternary site at C6, followed by an intramolecular event that is less susceptible to steric pressure. All-carbon quaternary stereogenic centers[21] were formed efficiently and with exceptional group-, site- and enantioselectivity (**10a**-**c**, Fig. 2b). Again, none of the allenyl- or 1,4-addition byproducts were generated and a single olefin isomer (>98% *E*) was detected (400 MHz ^{1}H NMR analysis; see the Supplementary Information for details.)

We then evaluated the possibility of a multicomponent enantioselective 1,6-addition by which a dienoate, a monosubstituted allene and B$_2$(pin)$_2$ may be combined (Fig. 3a). We envisioned association of allylcopper species **VI** with a substrate to yield **VII**, which could rearrange to give **VIII**. Electronic modification of one of the reacting alkenes by a B(pin) moiety could counter γ-addition. The other concern was that diastereomeric mixtures could form.

Reaction of dienoate **1a**, allene **11** and B$_2$(pin)$_2$ with 5.0 mol % imidazolinium salt **3a** and CuCl afforded **12a** exclusively and with exceptionally high 1,6-:1,4- and diastereomeric ratios (d.r.; Fig. 3b). The low yield of **12a** arises from a breakdown in chemoselectivity, namely by competitive boryl 1,4-addition. The optimal catalyst would therefore have to deliver high enantioselectivity and favor Cu–B addition to the allene over its reaction with a dienoate. Examination of different chiral imidazolinium salts led to encouraging results, as **12a** was generated more efficiently (57–74% yield). The Cu complex derived from imidazolinium salt **9d** proved optimal, affording **12a** in 62% yield, >98:2 d.r. and 95:5 e.r. However, the trends in enantioselectivity were again puzzling. It was not a surprise that the transformations with catalysts derived from imidazolinium salts **9b,c** gave **12a** in 89:11 and 75:25 e.r., respectively, as there was a similar trend (albeit with a larger difference) with the propargyl additions (cf. Fig. 2a). What was perplexing was that enantioselectivity was higher with the less sterically congested **9d** (95:5 e.r.).

Use of a diboryl compound such as **13**[22] (Fig. 3c) is a less attractive option. The need for the initial synthesis of an allylboron compound notwithstanding, the two-stage alternative, although highly γ-, site- and diastereoselective, proceeds with diminished enantioselectivity (Fig. 3c): with **13** as the reagent, **12a** was obtained in 81:19 e.r. (vs. 95:5 through the multicomponent process). Control experiments indicate that lower e.r. originates from efficient addition of an achiral allylcopper species, generated from allyl(PhO)CuNa with **13**,

to the dienoate to give racemic product; the background reaction produces the 1,6-addition isomers exclusively (see below for further discussion the Supplementary Information for mechanistic/computational analysis). In the multicomponent processes, on the other hand, only an NHC–Cu(OPh) complex can efficiently activate the B–B bond in $B_2(pin)_2$.

The multicomponent process has ample range as well (Fig. 3e). Aryl- (**12b-f**), heteroaryl-(**12g,h**), or alkyl-substituted (**12i**) dienoates can be converted to the desired products with >98% γ-, site-, and diastereoselectivity and 93:7–99:1 e.r. Compounds containing an alkene (**12j**), an alkyne (**12k**) or a Weinreb amide (**12l**) were synthesized in 58–74% yield and 88:12–95:5 e.r., and unsubstituted allene may be used (**12m**). Unlike with allenylboronate **2** (cf. Fig. 2b), reactions with the more highly substituted enoates that would afford quaternary carbon centers were inefficient (<10% conv.); this is probably because of the increased steric repulsion caused by the sizeable B(pin) moiety.

Several key mechanistic questions needed to be addressed at this point: Why does the identity of the optimal chiral Cu complex vary significantly, and why is it that, unlike multicomponent allylic substitutions[20], the unprotected hydroxyl group within the catalyst structure is needed for high enantioselectivity? To shed light on these issues, DFT calculations were performed at ωB97XD/Def2TZVPP//ωB97XD/Def2SVP$_{THF(PCM)}$ level of theory (see the Supplementary Information for details). Computational studies (Fig. 4) indicate that the linear Cu(I)–allenyl species derived from imidazolinium salts **9b** and **9d** associate with the C3–C4 bond, furnishing a square planar-type π-complex[16] (**A–D**, Fig. 4a), precursors to 1,6-propargyl addition products (Fig. 2). The propensity of NHC–Cu complexes to afford an η^2 complex at the C3–C4 site may be attributed to the stronger electron donating ability of the heterocyclic ligands (vs. phosphine), which raises the energy of copper's d-orbitals, causing stronger binding with the corresponding π* orbital[16,23]. 1,6-Addition products can be formed once an NHC–Cu-π complex is formed. A relevant experimental finding is that, similar to NHC–Cu but unlike phosphine Cu complexes, reactions with allenyl(*t*-BuO)CuNa (generated without a ligand) proceed with exceptional 1,6-:1,4-selectivity (>98:2). This might be because, as with an NHC–Cu system, the strongly π-basic in situ-formed (allenyl)$_2$cuprate species [from allenyl(*t*-BuO)CuNa] can establish a complex with the C3–C4 alkene (see **viii→ix**, Fig. 4b), resulting in 1,6-propargyl addition. With the less Lewis basic phosphines, back-bonding is less favored. Additionally, DFT calculations indicate that with a weaker σ-donating phosphine unit, the highest occupied molecular orbital (HOMO; dz^2, Fig. 1c) in a linear allenyl–Cu–phosphine complex is lower in energy (–7.43 eV for L = PPh$_3$ vs. –7.14 eV for L = NHC). Consequently, aryloxide–Cu complexation can be stronger (less "filled–filled" electronic repulsion) during **x→xi** (Fig. 4b), leading to 1,4-propargyl addition. It follows that transformations proceeding via these conformationally more flexible transition structures are less enantioselective (vs. NHC–Cu systems; cf. Fig. 2a).

DFT calculations reveal that high enantioselectivity originates from the structural organization caused by a cationic sodium interacting with the catalyst's hydroxyl unit, in turn H-bonded with the phenoxy counterion and the dienoate carbonyl groups. In the more favorable pathway with **9b** (via **A**; Fig. 4a, left panel) there is less steric strain between the N-aryl's methyl group and the allenyl hydrogen H$_a$ than in **B** (Me·····H$_a$ distance of 2.80 vs.

2.34 Å, respectively). Steric pressure in **B** can be alleviated by rotation of the NHC ligand around the Cu–C^{NHC} bond but this weakens the interaction between the hydroxy and the sodium cation (i.e., Na····O^1, 3.81 vs. 2.53 Å in **B** and **A**, respectively). With the complex derived from 3,5-dimethyl-substituted **9d** (Fig. 4a, right panel) a smaller energy gap separates the two modes of reaction (**C** vs. **D**; 1.1 vs. 4.4 kcal/mol for **A** and **B**); this might be because there is less difference in steric repulsion between the allenyl hydrogen and the *ortho* hydrogen of the N-aryl group in **D** (H_N····H_a, 3.10 and 2.89 Å in **C** and **D**, respectively).

With the more sizeable pinacolatoboron-substituted allylcopper species (**E-H**, Fig. 4c) a similar complexation involving the catalyst's hydoxyl unit and a sodium cation takes hold. The smaller NHC–Cu system (from 3,5-dimethyl-phenyl- substituted **9d**) can differentiate better between the two orientations of the allylic nucleophile compared to when **9b** is involved (Fig. 4b, right panel). Specifically, in the transition state leading to the major enantiomer **G** the allylcopper moiety's Cγ is oriented such that there is optimal overlap with C6 of the dienoate. In complex **H**, alignment of the latter two components engenders distortion of the C4–C3–Cu–C^{NHC} dihedral angle (–19.4° vs. +10.3° for **H** and **G**, respectively). The N-aryl methyl unit in **H** sits closer to the bulky pinacolato moiety (2.22 Å) and a methoxy group (2.30 Å) than in **G** when it is at a more favorable distance from the allylic methyl and ester substituents (2.71 and 2.44 Å, respectively). With the less selective catalyst derived from **9b**, which contains an N-2,6-dimethylphenyl group (Fig. 4b, left panel), the steric repulsion involving the N-aryl methyl and the methylene unit of the allylcopper moiety is the dominant interaction in **F** as well as **E** (Me····CH_2, 2.26 and 2.36 Å in **E** and **F**, respectively). Hence, overall, the calculated energy difference between **E** and **F** amounts to just 0.4 kcal/mol (vs. 2.5 kcal/mol for **H** vs. **G**; Fig. 4c).

The enantiomerically enriched products can be converted to otherwise difficult-to-access molecules (Fig. 5). Synthesis of enyne **14** (95% yield, Fig. 5a) shows that the kinetically generated β,γ-alkene can be equilibrated to the lower energy, conjugated isomer. In contrast, with an amine base and water, the corresponding β-substituted aldehydes were formed exclusively: **15a-c** and **16**, containing a quaternary carbon stereogenic center, were obtained in 49–58% yield. These transformations offer an attractive entry for synthesis of β-substituted enantiomerically enriched aldehydes that cannot be prepared easily by alternative protocols; as already mentioned, there are no catalytic enantioselective 1,4-propargyl additions[1]. Synthesis of this type of enantiomerically enriched aldehydes by conjugate addition of an aryl- or alkyl-metal reagent (e.g., PhMgCl or Me_2Zn) to an unsaturated ester followed by oxidation state adjustment would be problematic due to sensitivity of the methylene unit in the α,β,δ,ω- dienoate (or the corresponding enyne). The diester moiety offers additional opportunities; for example, through an alkylation/enzymatic desymmetrization[24] sequence, **4a** was converted to alcohol-ester **18** (Fig. 5b), which bears a quaternary carbon stereogenic center. As represented by **19** (Fig. 5c), oxidation of the alkenyl–B(pin) moiety affords γ,δ-unsaturated ketones with vicinal stereogenic centers; these fragments have been utilized in total synthesis of biologically active compounds and might be prepared by Claisen rearrangement[25] (see the Supplementary Information for

additional bibliography) but are difficult to access directly, especially in a catalytic and enantioselective manner[26].

Preparation of triene **24**, employed in an intramolecular Diels-Alder reaction en route to anti-HIV agent (–)-equisetin[27], highlights utility (Fig. 5c). Enyne **4n** was secured with >98% propargyl and 1,6-selectivity in 72% yield and 92:8 e.r. This transformation was performed on ~0.5 gram scale (15 times) and with unpurified commercially available organoboron reagent **2**, underscoring the ease with which significant quantities of the ligand precursor can be synthesized, the scalability of the catalytic processes and the their high degree of reliability/reproducibility. NHC–Cu-catalyzed site- and stereoselective proto-boryl addition[28] to the alkyne [(<2% addition to alkene, <2% Z alkenyl–B(pin)] afforded **20** in 91% yield (~4.6 g). Oxidation of the C–B bond, Wittig reaction (>98% E), followed by cleavage of the β,γ-unsaturated diester moiety to the derived aldehyde (cf. Fig. 5a), afforded **21** in 67% overall yield (~1.7 g). E-Alkenyl–B(pin) **22** was then prepared in 89% yield (~2.6 g) by a Cr(II)-based reagent (oxidation state with low toxicity)[29]. Phosphine–Pd-catalyzed cross-coupling with alkenyl iodide **23**[30] delivered ~1.7 grams of the desired triene **24** (94% yield; >98% E). Although a pathway of similar length may be envisioned starting from readily available enantiomerically pure starting materials (e.g., citronellol), this strategy has the advantage of being more easily amenable to preparation of various other analogues of the biologically active agent.

We thus introduce an approach for efficient catalytic enantioselective 1,6-conjugate addition of two types of valuable unsaturated organic moieties to dienoates. The mechanistic details regarding various features of an effective catalyst should help pave the way for achieving such important objectives. Considering that other readily available unsaturated organoboron and/or organocopper systems may be used, the low cost and ease with which the catalysts can be accessed, the reliably high selectivity values, and the versatility of the resulting products, the strategies delineated above adumbrate considerable impact on future advances in stereoselective catalysis and chemical synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Alexakis, A.; Krause, N.; Woodward, S. Copper-Catalyzed Asymmetric Synthesis. Alexakis, A.; Krause, N.; Woodward, S., editors. VCH–Wiley; 2014. p. 33-68.

2. Silva EMP, Silva AMS. 1,6-Conjugate addition of nucleophiles to α,β,γ,δ-diunsaturated systems. Synthesis. 2012; 44:3109–3128.

3. Tissot, M.; Li, H.; Alexakis, A. Copper-Catalyzed Asymmetric Synthesis. Alexakis, A.; Krause, N.; Woodward, S., editors. VCH–Wiley; 2014. p. 69-84.

4. den Hartog T, Harutyunyan SR, Font D, Minnaard AJ, Feringa BL. Catalytic enantioselective 1,6-conjugate addition of Grignard reagents to linear dienoates. Angew Chem Int Edn. 2008; 47:398–401.

5. den Hartog T, van Dijken DJ, Minnaard AJ, Feringa BL. An enantioselective approach to *syn* deoxypropionate units combining Cu-catalyzed 1,6- and 1,4-conjugate addition. Tetrahedron:Asymmetry. 2010; 21:1574–1584.

6. Tissot M, Alexakis A. Enantio- and regioselective conjugate addition of organometallic reagents to linear polyconjugated nitroolefins. Chem Eur J. 2013; 19:11352–11363. [PubMed: 23852566]

7. Magrez-Chiquet M, et al. Enantioselective 1,-6-conjugate addition of dialkylzinc reagents to acyclic dienones catalyzed by Cu-DiPPAM complex – extension to asymmetric sequential 1,6/1,4-conjugate addition. Chem Eur J. 2013; 19:13663–13667. [PubMed: 24038460]

8. Nishimura T, Yasuhara Y, Sawano T, Hayashi T. Iridium/chiral diene-catalyzed asymmetric 1,6-addition of arylboroxines to α,β,γ,δ-unsaturated carbonyl compounds. J Am Chem Soc. 2010; 132:7872–7873. [PubMed: 20481533]

9. Nishimura T, Noishiki A, Hayashi T. Electronic tuning of chiral diene ligands in iridium-catalyzed asymmetric 1,6-addition of arylboroxines to γ-aryl-α,β,γ,δ-unsaturated ketones. Chem Commun. 2012; 48:973–975.

10. Sawano T, Ashouri A, Nishimura T, Hayashi T. Cobalt-catalyzed asymmetric 1,6-addition of (triisopropylsilyl)-acetylene to α,β,γ,δ-unsaturated carbonyl compounds. J Am Chem Soc. 2012; 134:18936–18939. [PubMed: 23131028]

11. Hénon H, Mauduit M, Alexakis A. Regiodivergent 1,4 versus 1,6 asymmetric copper-catalyzed conjugate addition. Angew Chem Int Edn. 2008; 47:9122–9124.

12. Sieber JD, Morken JP. Asymmetric Ni-catalyzed allylation of activated enones. J Am Chem Soc. 2008; 130:4978–4983. [PubMed: 18338891]

13. Shizuka M, Snapper ML. Catalytic enantioselective Hosomi–Sakurai conjugate allylation of cyclic unsaturated ketoesters. Angew Chem Int Edn. 2008; 47:5049–5051.

14. Kuang Y, Liu X, Chang L, Wang M, Lin L, Feng X. Catalytic asymmetric conjugate allylation of coumarins. Org Lett. 2011; 13:3814–3817. [PubMed: 21688863]

15. Yanagida Y, Yazaki R, Kumagai N, Shibasaki M. Asymmetric synthesis of isothiazoles through Cu catalysis: Direct catalytic asymmetric conjugate addition of allyl cyanide to α,β-unsaturated thioamides. Angew Chem Int Edn. 2011; 50:7910–7914.

16. Yoshikai N, Nakamura E. Mechanisms of nucleophilic organocopper(I) reactions. Chem Rev. 2012; 112:2339–2372. [PubMed: 22111574]

17. Keith JA, Behenna DC, Mohr JT, Ma S, Marinescu SC, Oxgaard J, Stoltz BM, Goddard WA. The inner-sphere process in the enantioselective Tsuji allylation reaction with (*S*)-*t*-Bu-phosphinooxazoline ligands. J Am Chem Soc. 2007; 129:11876–11877. [PubMed: 17824701]

18. Ardolino MJ, Morken JP. Congested C–C bonds by Pd-catalyzed enantioselective allyl–allyl cross-coupling, a mechanism-guided solution. J Am Chem Soc. 2014; 136:7092–7100. [PubMed: 24720611]

19. Hornillos V, Pérez M, Fañanás-Mastral M, Feringa BL. Copper-catalyzed enantioselective allyl–allyl cross-coupling. J Am Chem Soc. 2013; 135:2140–2143. [PubMed: 23350620]

20. Meng F, McGrath KP, Hoveyda AH. Multifunctional organoboron compounds for natural product synthesis. Nature. 2014; 513:367–374. [PubMed: 25230659]

21. Quasdorf KE, Overman LE. Catalytic enantioselective synthesis of quaternary carbon stereocenters. Nature. 2014; 516:181–191. [PubMed: 25503231]

22. Pelz NF, Woodward AR, Burks HE, Sieber JD, Morken JP. Palladium-catalyzed enantioselective diboration of prochiral allenes. J Am Chem Soc. 2004; 126:16328–16329. [PubMed: 15600327]

23. Denmark SE, Beutner GL. Lewis base catalysis in organic synthesis. Angew Chem Int Edn. 2008; 47:1560–1638.

24. Domíngues de María P, García-Burgos CA, Bargeman G, van Gemert RW. Pig liver esterase (PLE) as biocatalyst in organic synthesis: From nature to cloning and to practical applications. Synthesis. 2007:1439–1452.

25. Becker J, Butt L, von Kiedrowski V, Mischler E, Quentin F, Hiersemann M. Total synthesis of (–)-ecklonialactone B. Org Lett. 2013; 15:5982–5985. [PubMed: 24215353]

26. Krautwald S, Schafroth MA, Sarlah D, Carreira EM. Stereodivergent α-allylation of linear aldehydes with dual iridium and amine catalysis. J Am Chem Soc. 2014; 136:3020–3023. [PubMed: 24506196]

27. Yuki K, Shindo M, Shishido K. Enantioselective total synthesis of (–)-equisetin using a Me$_3$Al-mediated intramolecular Diels–Alder reaction. Tetrahedron Lett. 2001; 42:2517–2519.

28. Jang H, Zhugralin AR, Lee Y, Hoveyda AH. Highly selective methods for synthesis of internal (α-) vinylboronates through efficient NHC–Cu-catalyzed hydroboration of terminal alkynes. Utility in chemical synthesis and mechanistic basis for selectivity. J Am Chem Soc. 2011; 133:7859–7871. [PubMed: 21526827]

29. Takai K, Shinomiya M, Kaihara H, Yoshida N, Moriwake T, Utimoto K. Transformation of aldehydes into (*E*)-1-alkenylboronic esters with a geminal dichromium reagent derived from a dichloromethylboronic ester and CrCl$_2$. Synlett. 1995:963–964.

30. Johansson Seechurn CCC, Kitching MO, Colacot TJ, Sniekus V. Palladium-catalyzed cross-coupling: A historical contextual perspective to the 2010 Nobel Prize. Angew Chem Int Edn. 2012; 51:5062–5085.
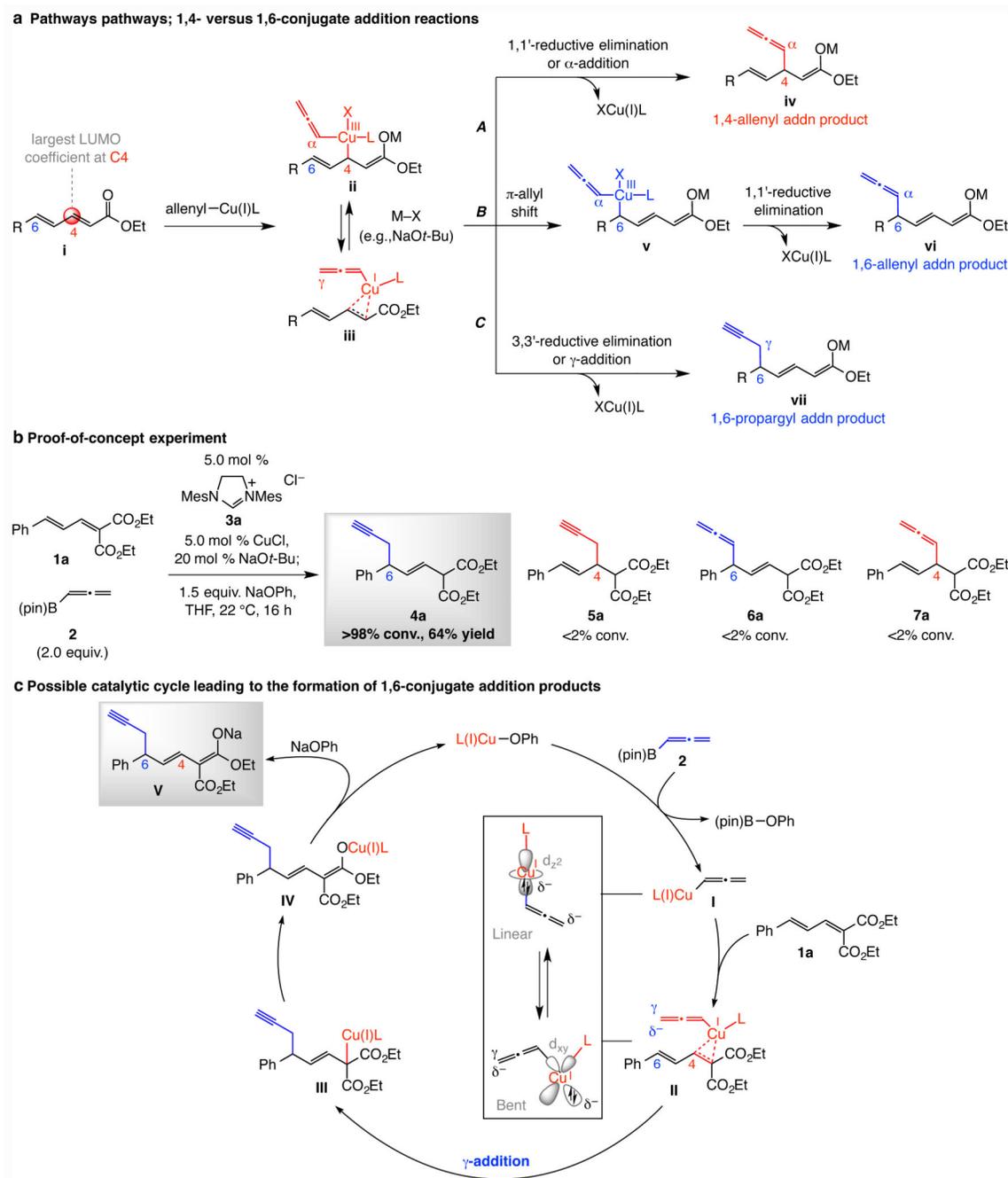
Figure 1. Possible conjugate addition pathways, the initial experiment and a plausible catalytic cycle

a, In a conjugate reaction, addition to the C4 site is kinetically favored (→**ii** or **iii**); subsequent 1,1′-reductive elimination (or α-addition) could afford product **iv** (Route A), or a 1,3—π-allyl shift (→**v**) may precede reductive elimination, affording 1,6-allenyl addition product **vi** (Route B). Alternatively, **ii/iii** may be directly converted to **vii** by a γ-addition (3,3′-reductive elimination type) process (Route C). **b,** Proof-of-principle experiment indicates that with an allenyl–copper intermediate, Route C predominates. **c,** Plausible

catalytic cycle for the preferential formation of the 1,6-propargyl addition product. Abbreviations: R, or G, various organic functional groups; LUMO, lowest unoccupied molecular orbital; M, metal; pin, pinacolato; Mes, 2,4,6-trimethylphenyl.
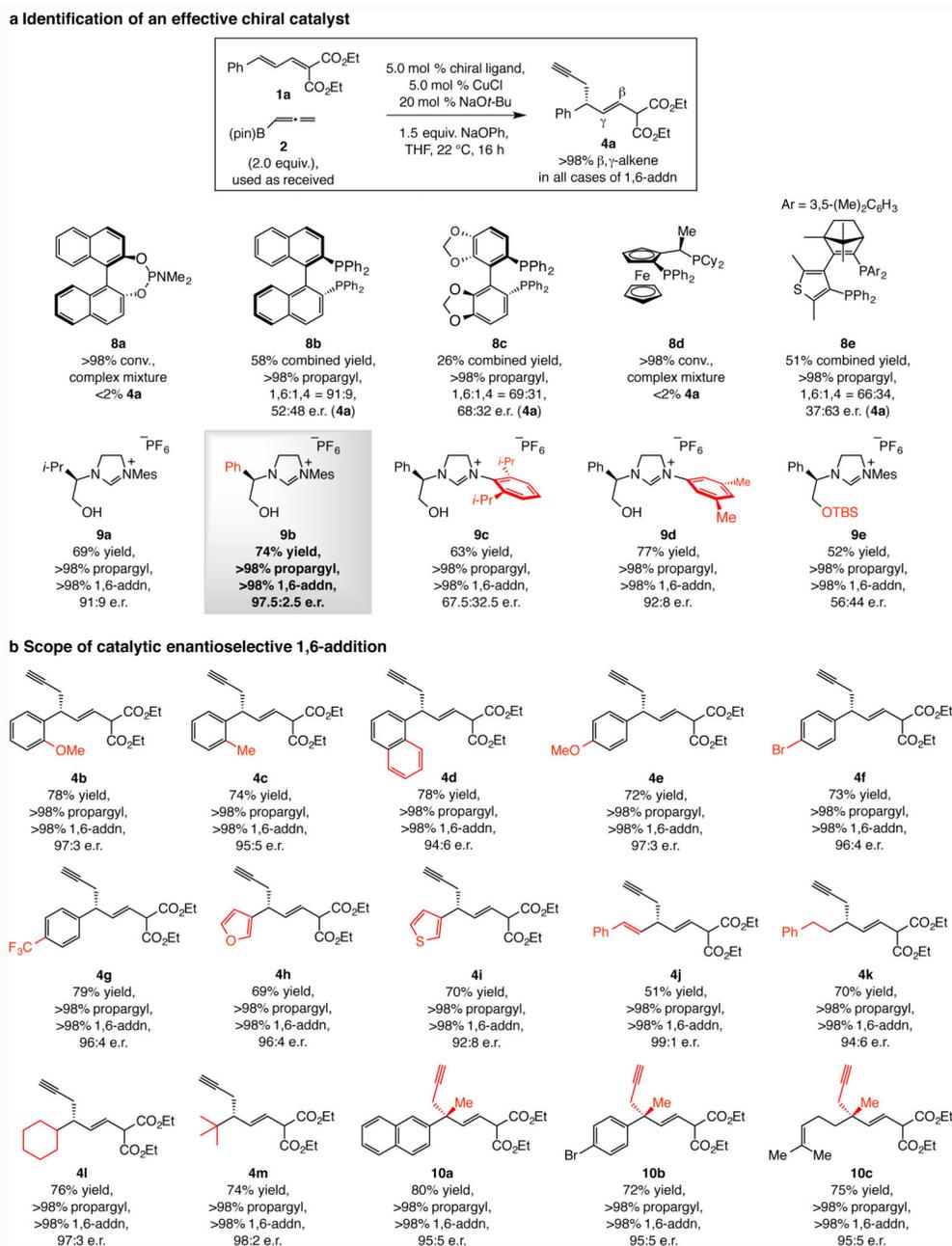
Figure 2. Catalytic enantioselective 1,6-propargyl conjugate additions

a, Screening of a variety of chiral phosphine and NHC ligands indicated that the chiral copper catalysts derived from the latter series are significantly more effective, and that corresponding to imidazolinium salt **9b** is optimal. **b,** The catalytic process is broadly applicable, affording products uniformly with >98% propargyl and 1,6-addition selectivity and in up to 80% yield and 98:2 e.r. Products containing a tertiary or an all-carbon quaternary carbon stereogenic center can be accessed. Abbreviations: pin, pinacolato; TBS, *tert*-butyldimethylsilyl, Mes, 2,4,6-trimethylphenyl; Mes, 2,4,6-trimethylphenyl.

Reactions were performed under N_2 under the conditions shown in the box for **4a**, except for **10a-c**, where 10 mol % **9b** and CuCl were used and mixture was allowed to stir for 24 h. Conversions, propargyl:allenyl and 1,6-:1,4-addition ratios were measured by analysis of ^{1}H NMR spectra of unpurified mixtures; the variance of values estimated to be <±2%. Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). See the Supplementary Information for experimental details and spectroscopic analyses.
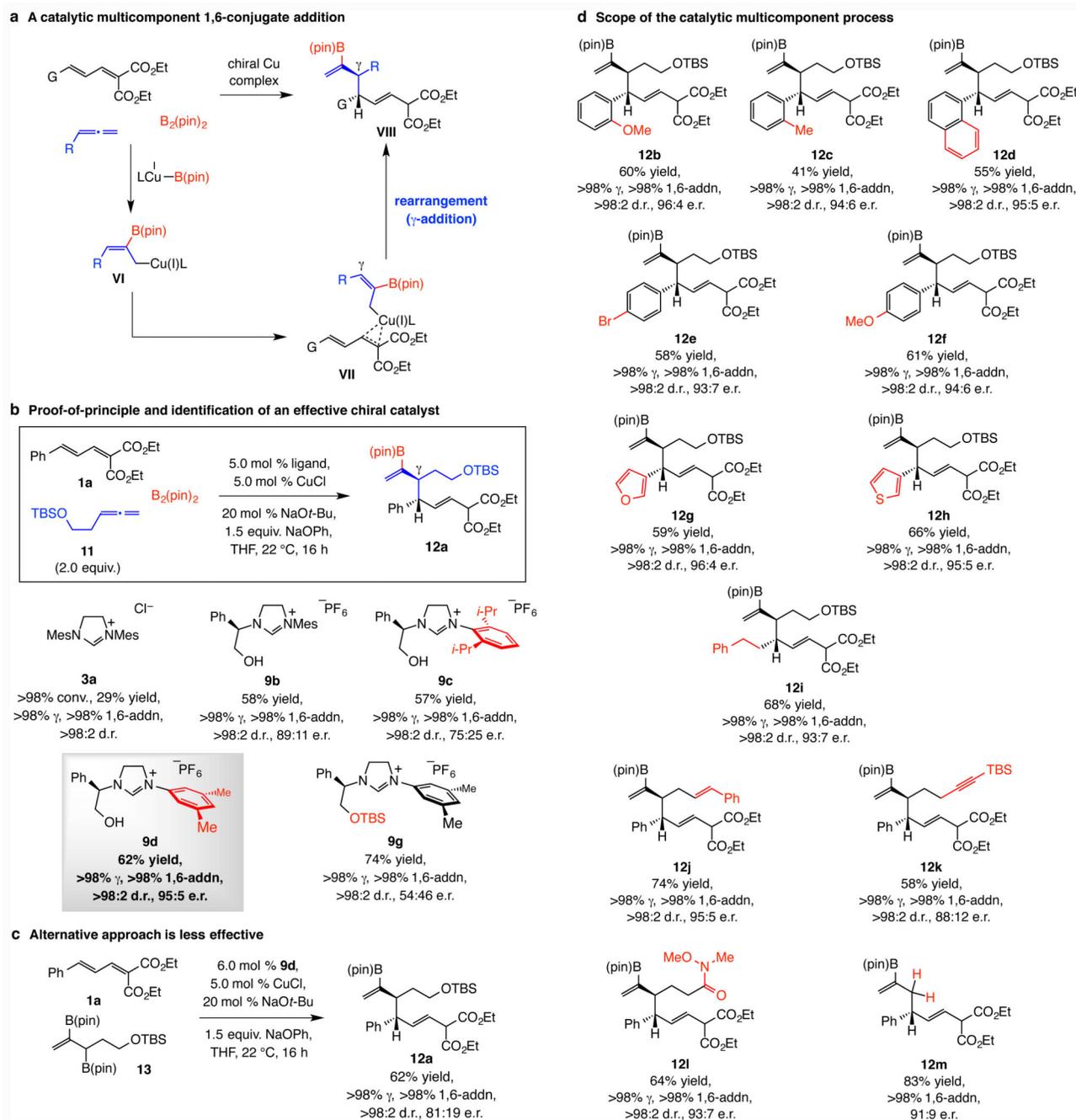
Figure 3. Catalytic diastereo- and enantioselective multicomponent 1,6-conjugate addition of 2-B(pin)-substituted allyl moieties

a, The pathway through which 1,6-addition products may be generated by a multicomponent process involving a dienoate, an allene and $B_2(pin)_2$. **b,** Preliminary experiment with an achiral NHC–Cu complex demonstrates that, although inefficient, reactions are exceptionally γ-, group- and 1,6-selective. Screening studies to identify an effective chiral catalyst indicates that a different NHC ligand is optimal for these transformations (vs. propargyl additions). **c,** The alternative approach entailing initial synthesis of a diboryl

reagent leads to lower enantioselectivity. **d,** The catalytic protocol has considerable scope. Abbreviations: pin, pinacolato; TBS, *tert*-butyldimethylsilyl.

Reactions were performed under N_2 under the conditions shown for synthesis of *rac*-**12a** (Fig. 3b). Conversions, propargyl:allenyl, 1,6-:1,4-addition and diastereomeric ratios (d.r.) were measured by analysis of ^{1}H NMR spectra of unpurified mixtures; the variance of values estimated to be $<\pm2\%$. Yields correspond to isolated and purified products and represent an average of at least three runs ($\pm5\%$). Ketone **12k** was obtained after oxidative work-up. See the Supplementary Information for experimental details and spectroscopic analyses.
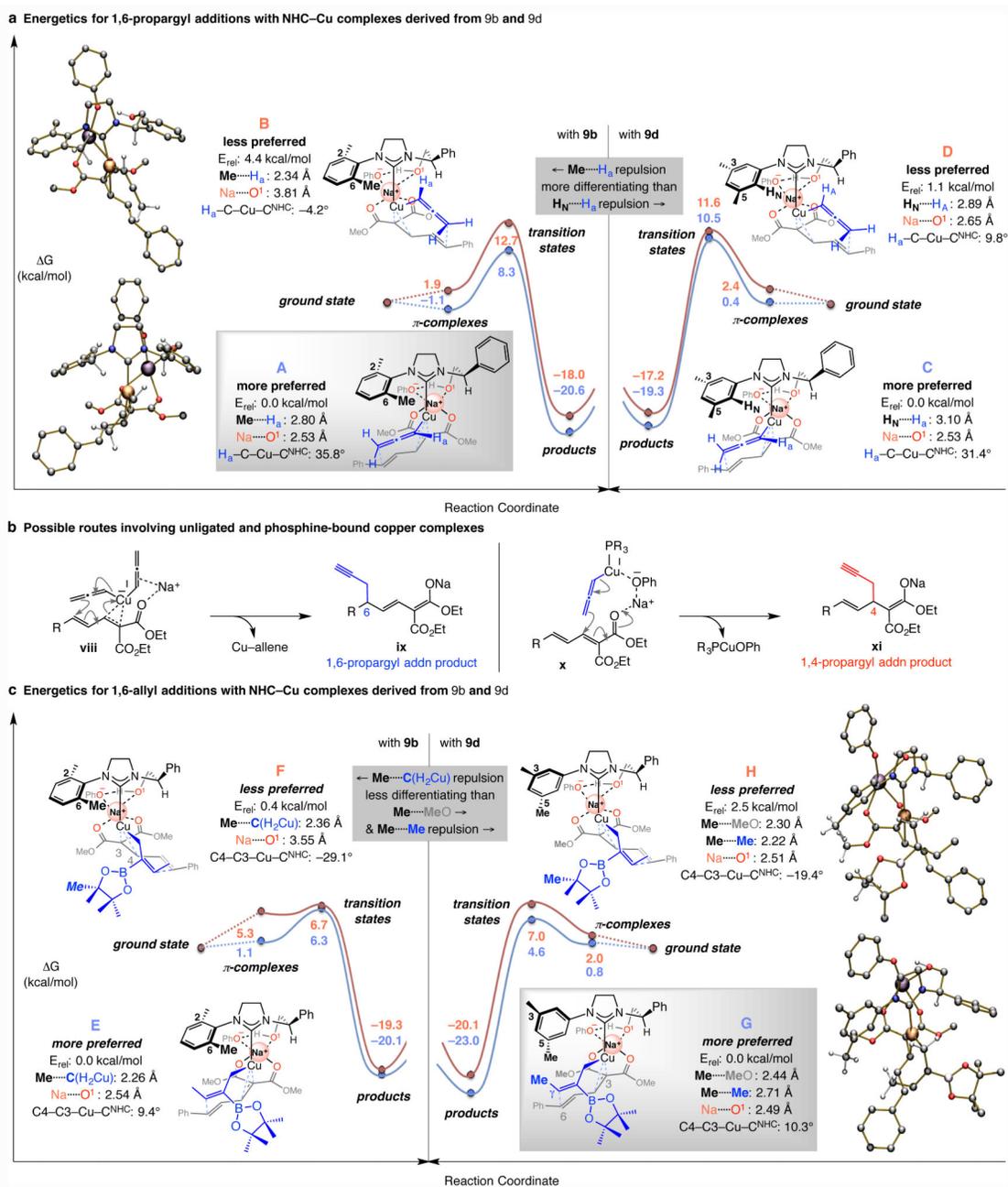
Figure 4. Mechanistic considerations

a, Based on DFT calculations [ωB97XD/Def2TZVPP//ωB97XD/Def2SVP level of theory (THF)] stereochemical models were developed for NHC–Cu-catalyzed 1,6-propargyl additions with catalysts bearing an N-mesityl moiety (from **9b**). The issue is the larger energetic differentiation arising from steric repulsion between an *o*-methyl unit of the N-aryl group and the allenylcopper moiety (i.e., Me····H_a, **9b**) versus one involving an aryl proton (i.e., H_N····H_a, **9d**). **b,** Routes by which a phosphine–based and non-ligated Cu complex might generate products, respectively. **c,** Transition state energies for enantioselective allyl additions are consistent with the observation that the catalyst derived from **9d** is optimal (vs.

9b). Steric repulsion involving a *meta*-methyl group of the NHC ligand with the carboxylic ester and the allylcopper substituents are the distinguishing elements. See the Supplementary Information for details of calculations. Abbreviations: NHC, N-heterocyclic carbene; E_{rel}, relative energy.
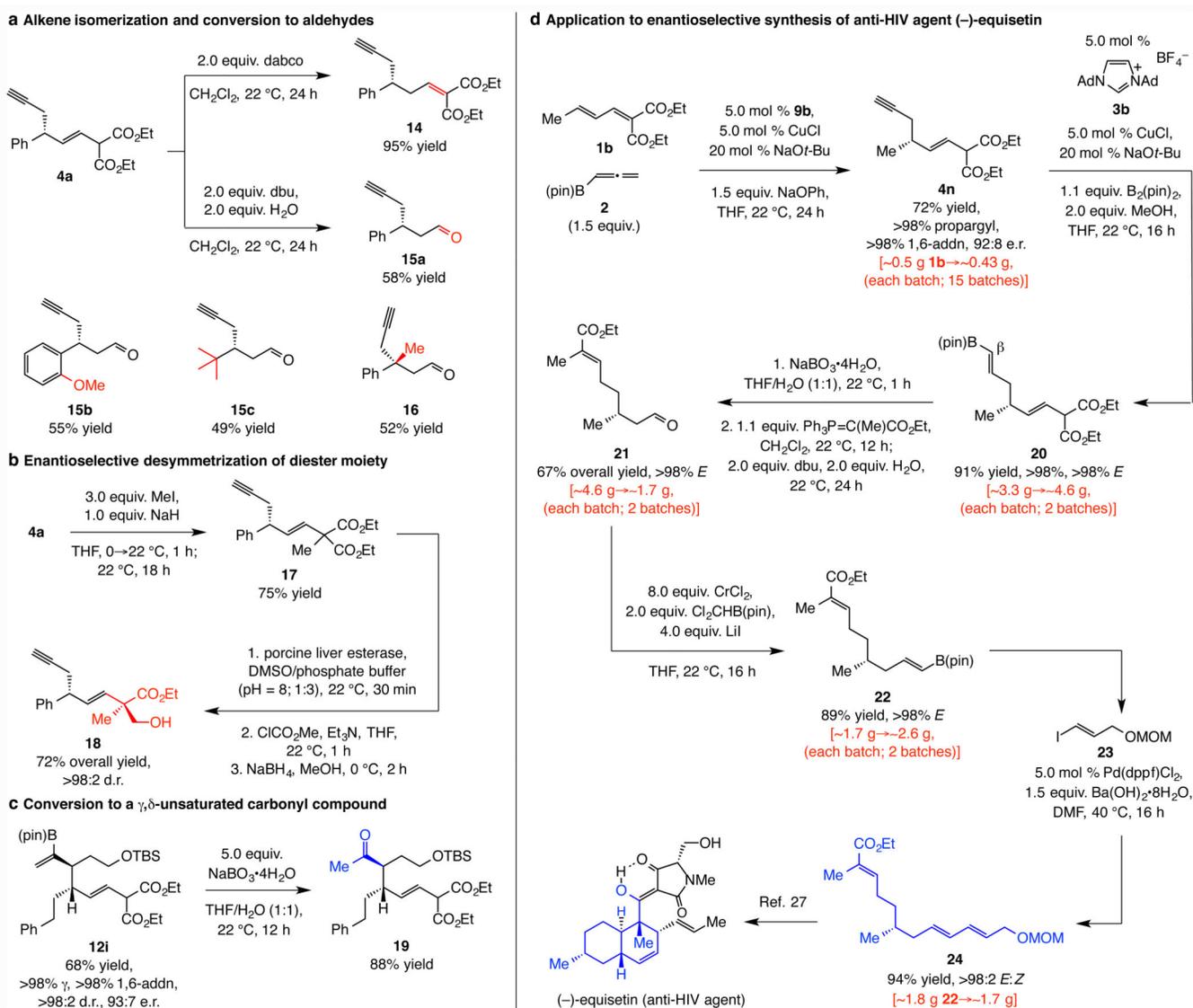
Figure 5. Functionalizations and demonstration of utility
a, The kinetically favored alkene can be readily isomerized to the thermodynamically preferred isomer under one set of basic conditions, while with water present, cleavage of the diester moiety leads to the formation of β-substituted aldehydes. **b,** Alkylation followed by enzymatic desymmetrization of the diester unit proceeds with excellent stereochemical control. **c,** Oxidation of the alkenyl–B(pin) moiety affords otherwise difficult-to-access γ,δ-unsaturated ketones with vicinal stereogenic centers at the α- and β-carbon sites. **d,** Application to synthesis of gram quantities of enantiomerically enriched triene **24**, previously used in the total synthesis of anti-HIV agent (–)-equisetin showcases utility of the catalytic approach. Abbreviations: dabco, 1,4-diazabicyclo[2.2.2]octane; dbu, 1,8-diazabicyclo[5.4.0]undec-7-ene ; DMSO, dimethylsulfoxide; Ad, adamantyl; dppf, 1,1′-bis(diphenylphosphino)ferrocene; MOM, methoxymethyl; pin, pinacolato.