HHS Public Access

Author manuscript

Nature. Author manuscript; available in PMC 2014 October 17.

Published in final edited form as:

Nature. 2014 April 17; 508(7496): 340–344. doi:10.1038/nature13231.

Enantioselective Construction of Remote Quaternary Stereocenters

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Summary

Molecules containing all-carbon quaternary stereocenters – carbon atoms bonded to four distinct carbon substituents – are prevalent in Nature. However, the construction of such compounds in an enantioselective fashion remains a long-standing challenge to synthetic organic chemists. In particular, methods for forging quaternary stereocenters that are remote from other functional groups are underdeveloped. Herein we report a catalytic and enantioselective intermolecular Heck-type reaction of trisubstituted-alkenyl alcohols with aryl boronic acids. The reported method allows direct access to quaternary all-carbon-substituted β-, γ-, δ-, ε- or ζ aryl carbonyl compounds, as the unsaturation of the alkene is relayed to the alcohol resulting in the formation of a carbonyl group. The scope of the process also includes incorporation of pre-existing stereocenters along the alkyl chain, which links the alkene and the alcohol, wherein the stereocenter is preserved. The described method is flexible, allowing access to diverse building blocks containing an enantiomerically enriched, quaternary center.

The quaternary stereocenter is a common structural motif in many natural products and pharmaceuticals[1-3]. However, the synthesis of these stereocenters in a catalytic and enantioselective manner represents a formidable challenge, especially in acyclic systems[4]. Typically, quaternary stereocenters are prepared from substrates with pre-existing functional groups adjacent to the site of reaction, whereas methods to access quaternary stereocenters distant from such groups present a significant, ongoing synthetic hurdle. The most common enantioselective and catalytic approaches utilize a carbonyl as a functional handle, wherein α-functionalization, via alkylation or aldol reactions[4,5], can be accomplished through the reaction of enolate equivalents (**I** in Fig. 1a)[6-11]. Enantioselective β-functionalization of a carbonyl can be accomplished through 1,4-conjugate addition-type processes using various transition metals and coupling partners (**II** in Fig. 1a)[12-16]. A powerful alternative to the

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

Author Contributions T.-S.M and H.H.P. performed the experiments and analysed the data. T.-S.M and M.S.S. designed the experiments. T.-S.M and M.S.S. prepared this manuscript with feedback from H.H.P..

Data for the crystalized product (a derivative of 2f) are deposited in the Cambridge Crystallographic Data Centre under accession number CCDC 988090.

The authors declare no competing financial interests.

carbonyl as a pre-installed functional group is the allylic electrophile[17-19] or nucleophile[20], which yields a quaternary center adjacent to an alkene (**III**, Fig. 1a)[21-23]. However, in all of these approaches, the location of C–C bond formation relative to the functional group is strictly defined, which does not allow one to directly install a quaternary chiral center at more remote sites.

On the basis of our group's recent success in developing asymmetric redox-relay Heck-type reactions of disubstituted alkenyl alcohols[24,25], we surmised that a site- and enantioselective transformation of trisubstituted alkenes could address this synthetic limitation (Fig. 1b). Applying the proposed method, one could position the alcohol at different chain-lengths from the alkene to obtain a diverse range of functionalized carbonyl products. This is a mechanistic consequence of the process. Specifically, site-selective migratory insertion[26,27] of an alkene into the organometallic intermediate produces a Pd-alkyl **B**, that can migrate toward the alcohol through a sequential β-hydride elimination/reinsertion process (Fig. 1b, **D→E**) to ultimately release the desired carbonyl product **C**[28,29]. Although venerable Heck cyclization reactions have been developed and extensively applied to the formation of quaternary centers by intramolecular reaction of trisubstituted alkenes[30-32], no examples of catalytic, asymmetric, quaternary stereocenters synthesized via intermolecular Heck-type reactions of isolated (non-conjugated) trisubstituted alkenes are known[2].

Several concerns were considered at the outset of this effort including questions regarding reactivity, site-selectivity, and enantioselectivity when using trisubstituted alkenes in intermolecular Heck-type reactions. Acyclic, non-conjugated trisubstituted alkenes are rare substrates in intermolecular Heck-type reactions likely due to either poor binding to the catalyst or slow migratory insertion[33]. If a reaction does occur, the question of site-selectivity is intriguing as the ability to forge a quaternary center relies on addition to the more substituted carbon. In our previous report, we found that subtle electronic variance of the alkenyl carbons, as determined by ^{13}C chemical shift differences, correlates to site-selectivity, with the aryl nucleophile adding to the carbon that is more downfield shifted[24]. Additional support for electronically influenced site-selectivity was revealed by recent density functional theory calculations on the redox-relay Heck reactions of disubstituted alkenes[34,35]. These studies show that site-selectivity is controlled by remote dipole interactions of the attached alcohol. These observations suggested that, in the case of a trisubstituted alkene, insertion should occur preferentially at the more substituted carbon (the hindered and downfield shifted carbon). This also would likely relieve steric strain as the bulky Pd-catalyst is positioned at the less hindered carbon. As the final concern, it is not evident if this process would be highly enantioselective, as *cis* and *trans* disubstituted alkenes have previously yielded enantiomers as products[24,25]. Considering that trisubstituted alkenes contain both of these stereochemical relationships, the outcome is not simply predicted.

We began our investigation by revisiting our previously developed catalytic system[24] for enantioselective oxidative Heck reactions[36-40] of disubstituted alkenes. A trisubstituted homoallylic alcohol (**1**), which displays ethyl and methyl groups at the terminus of the alkene, was selected as a model substrate (Fig 2). Any success with this substrate would bode well for expanding the scope of the reaction to substrates containing other substituents

on the alkene with more pronounced differences. Our initial efforts resulted in poor conversion to the desired product **2a** (40% conversion, 23% yield). Nevertheless, migratory insertion occurred to exclusively install the aryl group at the γ-position (γ/β>15:1) and the product was generated in a high enantiomeric ratio (er) of 97:3 (Table S1, see SI). Encouraged by this initial result, we explored various changes to the reaction conditions, yet these afforded little noticeable improvements in yield. During our previous studies, we observed that the arylboronic acid coupling partner was consumed by various side reactions, such as decomposition of the boronic acid into a phenol and homocoupling of this reagent[41-43]. Indeed, we detected that the arylboronic acid was consumed after 24 h, with corresponding poor conversion of the alkene. We speculated that slow addition of the arylboronic acid would suppress the undesired pathways and favor product formation. Batch-wise addition of the arylboronic acid did improve the yield to 50%. Increasing the catalyst loading led to 65% yield (Fig 2, **2a**), with >15:1 regioselectivity (γ:β) and excellent enantioselectivity (er: 97:3). A series of control experiments verified the importance of the various reaction components: removing either $Cu(OTf)_2$[44] or 3 Å MS[45] substantially reduced the yield, and when the palladium catalyst was excluded, no reaction was observed (Table S1). Both of these additives are frequently used in oxidative Pd-catalysis to facilitate reoxidation of Pd(0) although their precise role in this transformation is not currently understood.

The scope of arylboronic acid coupling partners was investigated with homoallylic alcohol **1** (Fig. 2a). A wide-array of arylboronic acids were found to be compatible, delivering the corresponding all-carbon quaternary γ-aryl aldehyde products with uniformly high enantioselectivity (er up to 99:1) and in moderate to good yields (**2a**–**2n**). High site-selectivity (γ/β ≥ 15:1) is observed with both electron-deficient and electron-rich arylboronic acids. This stands in contrast to our previous reports on enantioselective redox-relay Heck-type reactions of disubstituted alkenes, where only modest site-selectivity was achieved for electron-rich aryl boronic acids[24]. This observed difference suggests that the electronic nature of the alkene dictates site-selectivity. Higher yields are achieved with electron-rich arylboronic acids, as compared to their electron-poor counterparts (compare **2e** with **2k**), which is consistent with their greater nucleophilicity facilitating migratory insertion of the presumed alkene complex. In all cases, excellent enantioselectivity is observed and the reaction can be scaled to 10 mmol yielding >2 grams as demonstrated by example **2f**. Not surprisingly, lower yields are observed when *ortho*-substituted arenes are utilized, as illustrated by **2m** and **2n**, although enantioselectivity remains high. The absolute configuration of a derivative of **2f** was determined to be (*R*) via X-ray crystallography (see supplementary information for details).

The effect of chain length (the distance from the alcohol to alkene) using various racemic trisubstituted alkenyl secondary alcohols was evaluated (Fig. 2b). Of particular note, high site- and enantioselectivity is observed irrespective of the chain length, enabling access to *β*- (**3a**), *δ*- (**3b**, **3c**), or *ε*- (**3d**–**3f**) quaternary functionalized ketone products. Alkenes bearing another oxygen substituent are well-tolerated (**3a**–**3c**) although styrene derived substrates are unreactive under the current reaction conditions. Substrates were also selected to probe the effect of differential size of the alkene aliphatic substituents (**3g**–**3j**, Fig. 2c).

Gratifyingly, excellent site- and enantioselectivity were again observed in all cases. To highlight this, an alkene featuring an ethyl and a butyl group, which have negligible steric differences, performs well, yielding **3i** in 97:3 er.

In analysis of the reaction scope, it appears that the enantioselectivity is essentially independent of the steric and electronic nature of both reaction partners, which is atypical in enantioselective reactions. To further explore this, the effect of alkene geometry on enantioselection was probed by comparing the reaction of *(Z)*-**1a** and *(E)*-**1a** (Fig. 2d). The magnitude of the enantioselectivity is the same for both substrates, again suggesting a robust enantioselective reaction. However, the major enantiomer produced in both cases is different. This is consistent with the binding orientation of the alkene not changing. Specifically, in comparing hypothesized intermediates **A** and **B** (Fig. 2d), the alkenyl carbon closer to the alcohol remains fixed leading to the observed stereochemical outcomes, which is supported by the relative insensitivity of the process to what is displayed on the terminal end of the trisubstituted alkenes. While the precise details of why this catalyst is exceptionally selective is under further investigation, these results support that few synthetic limitations should be encountered in variation of the alkenyl aliphatic substituents.

As hypothesized in the initial mechanistic proposal, the Pd-catalyst presumably migrates along the alkyl chain until the aldehyde is formed. Indeed, computational studies[34,35] of the relay Heck reaction of disubstituted alkenes shows generally low energy barriers for the chain-walking events[46-48]. Therefore, a key question, with implications for the applicability of this method in more complex settings, is whether the catalyst disengages during the "chain-walking" process. To explore this possibility, a natural product derived substrate, (*R*)-**4**, containing a preinstalled stereogenic center in the alkyl chain was evaluated using both enantiomers of catalysts. Preservation of the enantiomeric composition was observed when treating this substrate with either catalyst enantiomer under redox relay Heck conditions to yield (*R*)-**5** (Fig. 3a). This implies that as the catalyst proceeds through the iterative β-hydride elimination/reinsertion events depicted in Fig. 3c, the catalyst remains both ligated to the substrate and on the same face of the alkene throughout the relay process. As a more striking example, alkene (*S*)-**6** was treated with both enantiomers of catalyst to yield the relay products **7** and **8** in high diastereoselectivity (Fig. 3b). Two distinct diasteresomers are produced by the use of different enantiomers of catalyst, since the initial migratory insertion is under catalyst-controlled face selection, but the preset stereogenic center is not altered during the relay process.

To further support the chain walking proposal, an isotopic labeling experiment was carried out (Fig. 3d). A deuterium labeled analog of **4**, alkenol **9**, bearing deuterium atoms at the carbon connecting to the alcohol, was synthesized and submitted to the redox relay Heck reaction. The experiment reveals clean repositioning of one deuterium atom at the site α to the carbonyl group in the product (**13**) (Fig. 3d). This result is consistent with a mechanism whereby the Pd-catalyst migrates through the chain to form intermediate **10**, which undergoes *β*-D elimination followed by reinsertion into **11** to yield intermediate **12** (Fig. 3d).

In this work, we have described a catalytic and enantioselective addition of boronic acid derivatives to trisubstituted alkenes that is highly site-selective for the more hindered

position. The method does not rely on a defined relationship between the site of addition and an adjacent functional group, thus providing a modular method to access quaternary stereocenters in high enantioselectivity. Furthermore, we anticipate that the mechanistic implications of both site-selective addition of an organometallic to a trisubstituted-alkene and the ability of the catalyst to migrate through existing chiral centers will inspire further studies in this area.

METHODS SUMMARY

General procedure for enantioselective Heck reaction

To a dry 100 mL Schlenk flask equipped with a stir bar was added $Pd(CH_3CN)_2(OTs)_2$ (15.9 mg, 0.0300 mmol, 6.00 mol%), $Cu(OTf)_2$ (5.43 mg, 0.0150 mmol, 3.0 mol%), ligand (12.3 mg, 0.0450 mmol, 9.0 mol%), 3 Å MS (75.0 mg, 150 mg/mmol), and DMF (8 mL). To this flask, a three-way adapter fitted with a balloon of O_2 was added, and the flask was evacuated via house vacuum and refilled with O_2 three times while stirring. The resulting mixture was stirred for 10 min. To this, a DMF solution (2 mL) of the alkenyl alcohol (0.5 mmol) and corresponding boronic acid (1.5 mmol, 3 equiv) was added via syringe. The resulting mixture was stirred for 24 h at room temperature. The mixture was diluted with diethyl ether (200 mL) and water (50 mL). The aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with water (3 × 20 mL), brine (1 × 20 mL), and dried over sodium sulfate. The organic extracts were concentrated under reduced pressure, and the resulting residue was purified by silica gel flash chromatography using 2–10% EtOAc in hexanes containing 0.1% triethylamine to yield an aldehyde product. Full experimental details and characterization of new compounds can be found in the Supplementary Information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Institutes of Health (NIGMS GM063540) for their financial support.

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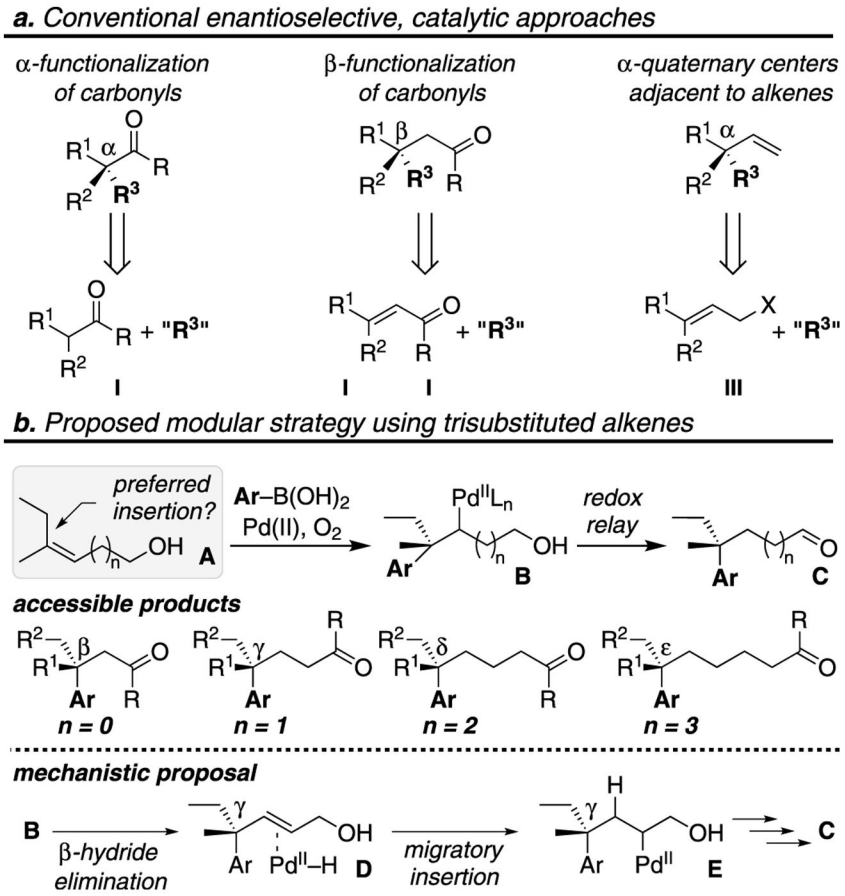

Figure 1. Approaches to constructing acyclic all-carbon quaternary stereocenters

a, Conventional enantioselective, catalytic approaches. α-functionalization of carbonyls (**I**). β-functionalization of carbonyls (**II**). α-quaternary centers adjacent to alkene (**III**). **b**, Proposed modular strategy using a redox relay enantioselective Heck reaction of trisubstituted alkenes and resulting mechanistic analysis.

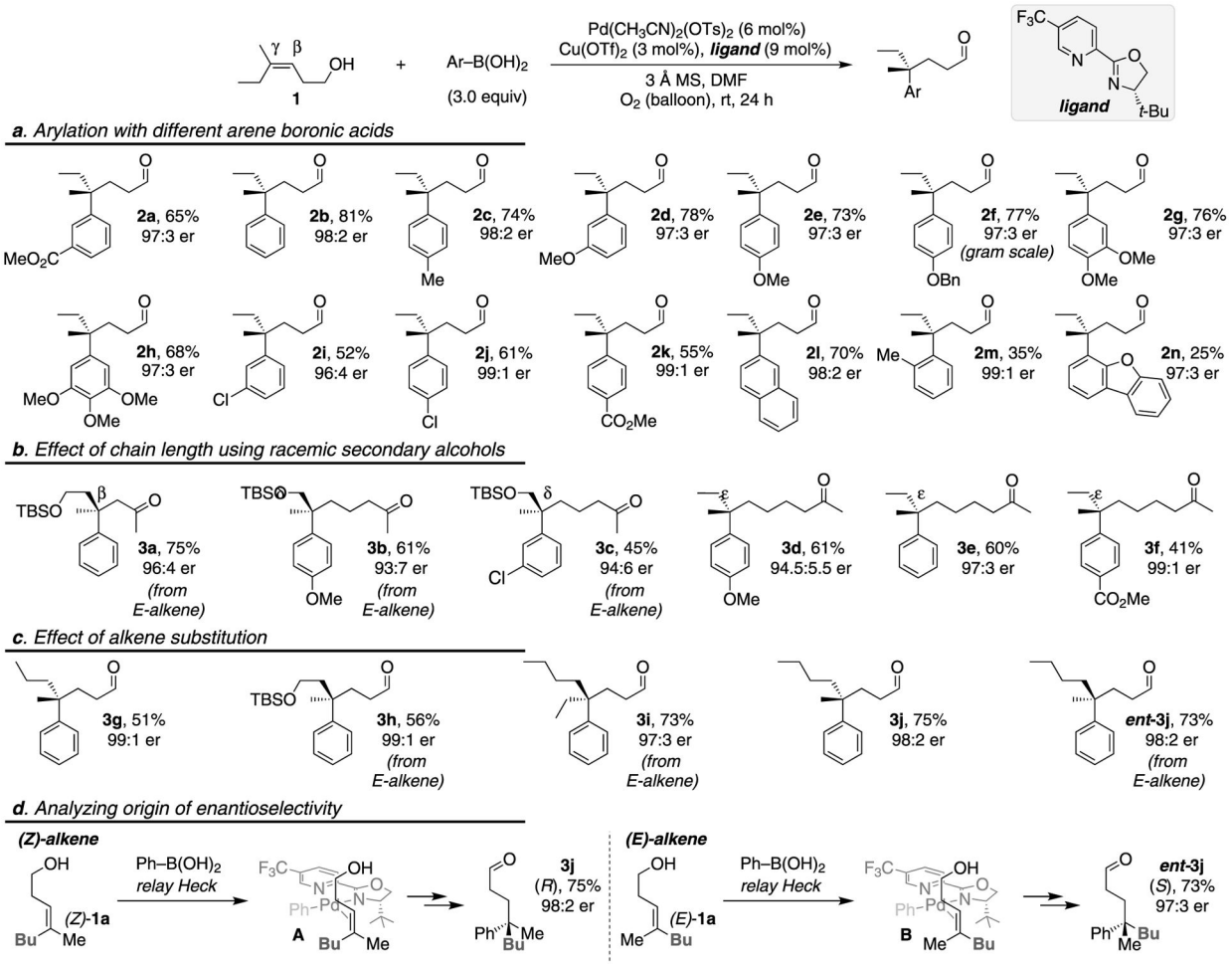

Figure 2. Enantioselective construction of remote quaternary stereocenters

Conditions for **2a**, **2i**–**2n**, **3c**, **3f**, **3i**–**3j**: 10 mol% $Pd(CH_3CN)_2(OTs)_2$, 4 mol% $Cu(OTf)_2$, 14 mol% ligand, 3 equiv $ArB(OH)_2$ (two batch addition, 12 h between additions). **a**, Exploration of scope using various arylboronic acids. **b**, Evaluation of various chain-lengths between the alkene and alcohol on the substrate. **c**, Exploration of the alkene substituents. **d**, Proposed origin of enantioselectivity as a function of alkene geometry. TBS is tert-butyldimethylsilyl.

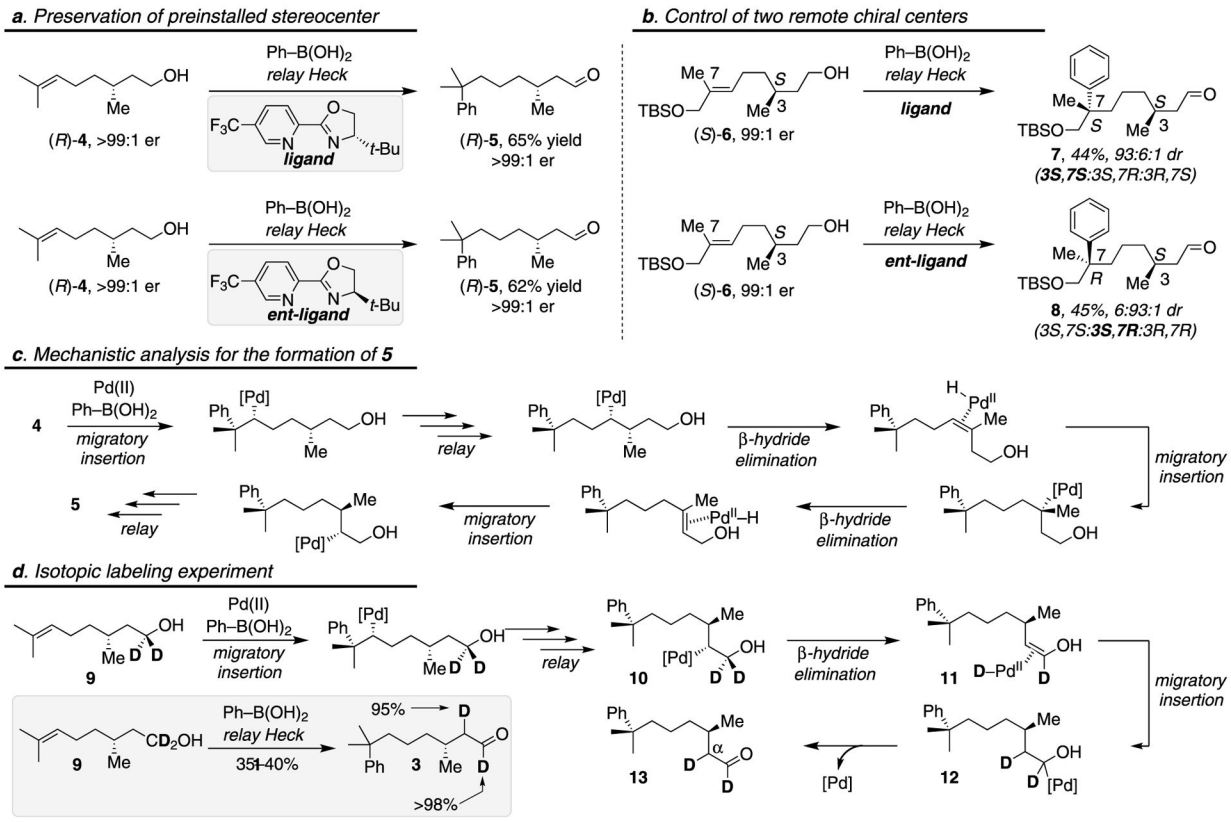

Figure 3. Evaluation of alkene substrates containing a branch point

Conditions: 10 mol% $Pd(CH_3CN)_2(OTs)_2$, 4 mol% $Cu(OTf)_2$, 14 mol% ligand, 3 equiv $PhB(OH)_2$. **a**, Independence of catalyst enantiomer on the conservation of the chiral center during the proposed chain-walking process. **b**, Accessing distinct diasteromers using a combination of catalyst and substrate controlled asymmetric synthesis. **c**, Proposed mechanistic origin for the observed formation of **5** from **4**. **d**, Isotopic labeling experiment and analysis.