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Enantioselective construction of remote quaternary stereocentres

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Small molecules that contain all-carbon quaternary stereocentres—carbon atoms bonded to four distinct carbon substituents—are found in many secondary metabolites and some pharmaceutical agents. The construction of such compounds in an enantioselective fashion remains a long-standing challenge to synthetic organic chemists. In particular, methods for synthesizing quaternary stereocentres that are remote from other functional groups are underdeveloped. Here we report a catalytic and enantioselective intermolecular Heck-type reaction of trisubstituted-alkenyl alcohols with aryl boronic acids. This method provides direct access to quaternary all-carbon-substituted β-, γ-, δ-, ε- or ζ-aryl carbonyl compounds, because 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 stereocentres along the alkyl chain, which links the alkene and the alcohol, in which the stereocentre is preserved. The method described allows access to diverse molecular building blocks containing an enantiomerically enriched quaternary centre.

The quaternary stereocentre is a common structural motif in many natural products and pharmaceuticals[1–3]. However, the synthesis of these stereocentres in a catalytic and enantioselective manner is a formidable challenge, especially in acyclic systems[4]. Typically, quaternary stereocentres are prepared from substrates with pre-existing functional groups adjacent to the site of reaction, whereas methods to access quaternary stereocentres distant from such groups present a considerable, ongoing synthetic hurdle. The most common enantioselective and catalytic approaches use a carbonyl as a functional handle, wherein α-functionalization, by means of alkylation or aldol reactions[4,5], can be accomplished through the reaction of enolate equivalents[6–11] (**I** in Fig. 1a). Enantioselective β-functionalization of a carbonyl can be accomplished through 1,4-conjugate-addition-type processes using various transition metals and coupling partners[12–16] (**II** in Fig. 1a). A powerful alternative to the carbonyl as a pre-installed functional group is the allylic electrophile[17–19] or nucleophile[20], which yields a quaternary centre adjacent to an alkene[21–23] (**III** in Fig. 1a). However, in all of these approaches, the location of C–C bond formation relative to the functional group is strictly defined, which makes it difficult to install a quaternary chiral centre 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-selective and enantioselective transformation of trisubstituted alkenes could address this synthetic limitation (Fig. 1b). By applying the proposed method, it is possible to 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 towards the alcohol through a sequential β-hydride elimination/migratory-insertion process (Fig. 1b, **D** → **E**) ultimately to release the desired carbonyl product, **C**[28,29]. Although well-known Heck cyclization reactions have been developed and extensively applied to the formation of quaternary centres by intramolecular reaction of trisubstituted alkenes[30–32], no examples of catalytic, asymmetric, quaternary stereocentres synthesized through intermolecular Heck-type reactions of isolated (non-conjugated) trisubstituted alkenes are known[2].

We had several concerns at the outset of this work, 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

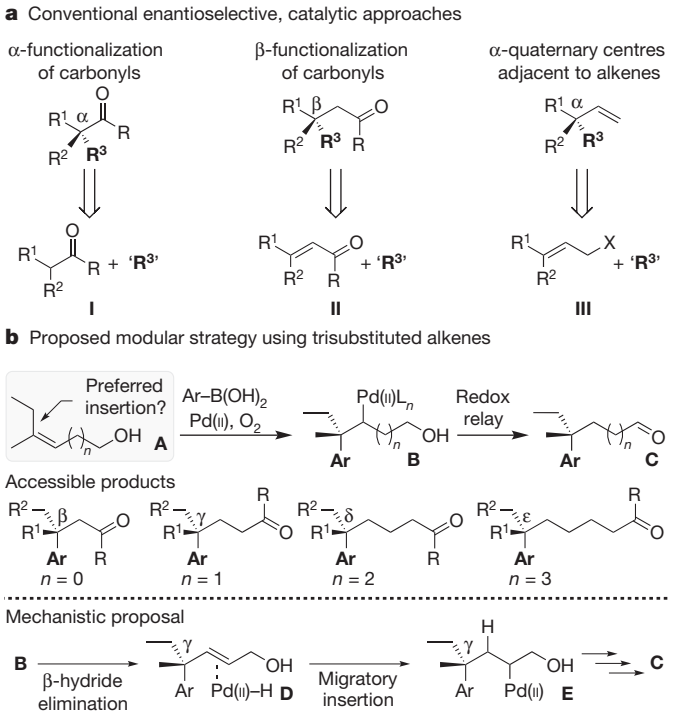

Figure 1 | Approaches to constructing acyclic all-carbon quaternary stereocentres. a, Conventional enantioselective, catalytic approaches: α-functionalization of carbonyls (**I**); β-functionalization of carbonyls (**II**); α-quaternary centres adjacent to alkenes (**III**). **b**, Proposed modular strategy using a redox-relay enantioselective Heck reaction of trisubstituted alkenes and resulting mechanistic analysis. Ar, aryl.

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intermolecular Heck-type reactions, probably because of poor binding to the catalyst or slow migratory insertion[33]. If a reaction does occur, the question of site selectivity is intriguing because the ability to forge a quaternary centre relies on addition to the more substituted carbon. In our study of the redox-relay Heck reaction of disubstituted alkenes, subtle electronic variance of the alkenyl carbons, as determined by ^{13}C chemical shift differences, correlates with 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 this reaction[34,35]. These studies show that site selectivity is controlled by remote dipole interactions of the attached alcohol. Taken together, 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 would possibly also relieve steric strain because the bulky Pd catalyst is positioned at the less hindered carbon. Our final concern was whether this process would be highly enantioselective, given that *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 easily predicted.

Reaction optimization and scope

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 has 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 install the aryl group predominantly at the γ-position (>15 times more likely than at the β-position) and the product was generated in a high enantiomeric ratio (e.r.) of 97:3 (Supplementary Table 1). 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

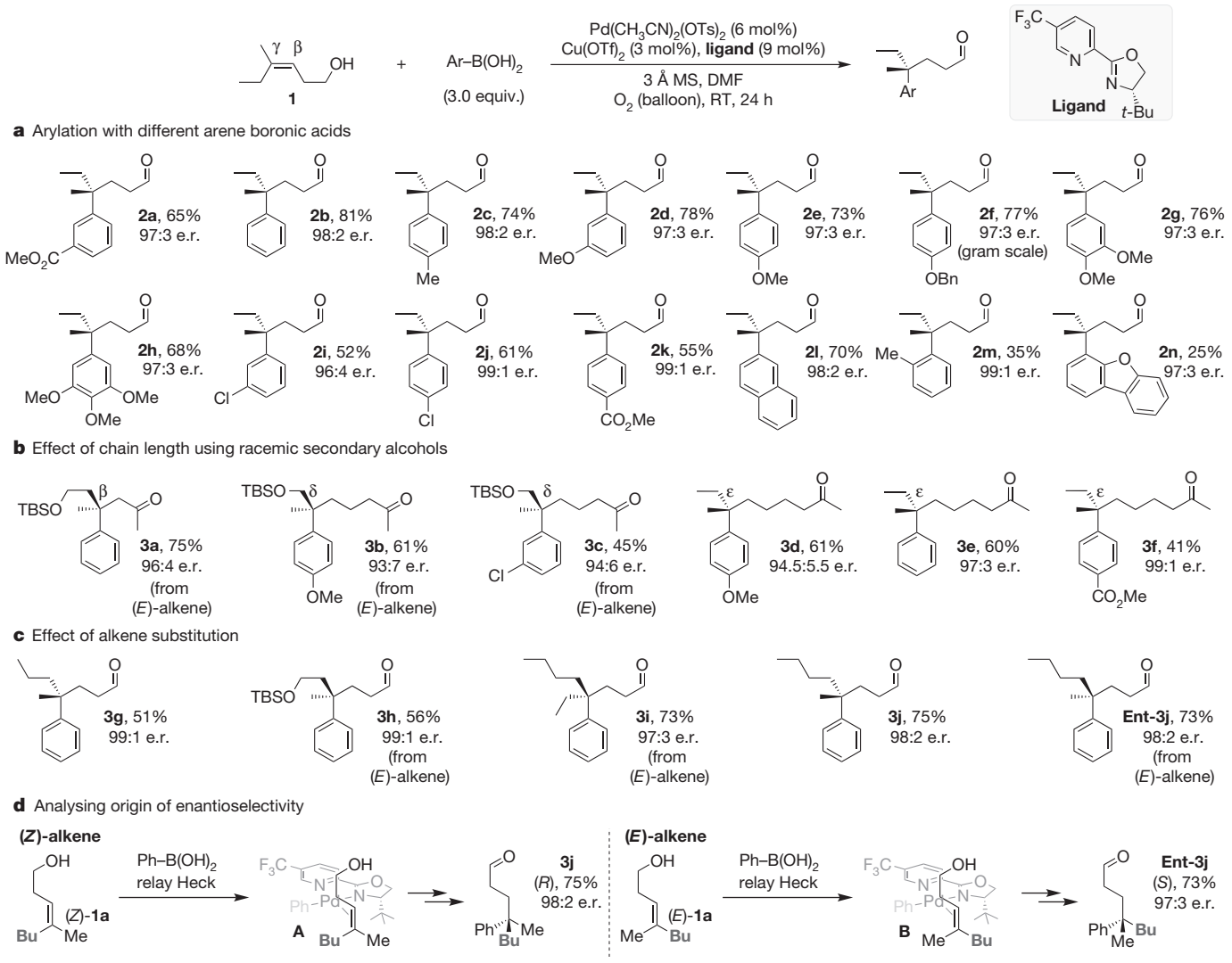

Figure 2 | Enantioselective construction of remote quaternary stereocentres. Conditions for **2a**, **2i**–**2n**, **3c**, **3f**, **3i**–**3j**: 10 mol% $Pd(CH_3CN)_2(OTs)_2$, 4 mol% $Cu(OTf)_2$, 14 mol% ligand, 3 equiv. $ArB(OH)_2$ (two-batch addition, 12 h between additions). *t*-Bu, *t*-butyl; OTs, tosylate; OTf, trifluoromethanesulphonate; MS, molecular sieves; RT, room temperature. Reported yield and e.r. values are an average of at least two experiments. **a**, Exploration of scope of process using various arylboronic acids. Me, methyl. **b**, Evaluation of various chain lengths between the alkene and the alcohol on the substrate. TBS, *t*-butyldimethylsilyl. **c**, Exploration of the alkene substituents. **d**, Proposed origin of enantioselectivity as a function of alkene geometry. Ph, phenyl.

pathways and favour product formation. Batchwise addition of the arylboronic acid did improve the yield to 50%. Increasing the catalyst loading led to 65% yield (**2a** in Fig. 2a), with >15:1 site selectivity (γ/β) and excellent enantioselectivity (e.r. 97:3). A series of control experiments verified the importance of the various reaction components: the absence of either $Cu(OTf)_2$ (ref. 44) or 3 Å molecular sieves[45] substantially reduced the yield, and when the palladium catalyst was excluded, no reaction was observed (Supplementary Table 1). 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 (e.r. 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 with 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 g as demonstrated by example **2f**. Not surprisingly, lower yields are observed when *ortho*-substituted arenes are used, as illustrated by **2m** and **2n**, although enantioselectivity remains high. The absolute configuration of a derivative of **2f** was determined to be (*R*) by X-ray crystallography (Supplementary Information).

The effect of chain length (the distance from the alcohol to the alkene) using various racemic, trisubstituted alkenyl secondary alcohols was evaluated (Fig. 2b). Of particular note, high site selectivity and enantioselectivity is observed irrespective of the chain length, enabling access to *β*- (**3a**), *δ*- (**3b**, **3c**) and *ε*-quaternary (**3d**−**3f**) functionalized ketone products. Alkenes bearing another oxygen substituent are well tolerated (**3a**−**3c**), although substrates with a styrene unit are unreactive under the present reaction conditions. Substrates were also selected to probe the effect of differential size of the alkene aliphatic substituents (**3g**−**3j** in Fig. 2c). Excellent site selectivity and enantioselectivity is again observed in all cases. To highlight this, an alkene featuring an ethyl group and a butyl group, which have negligible steric differences, performs well, yielding **3i** in 97:3 e.r.

Mechanistic experiments

From analysis of the scope of the reaction, it seems that the enantioselectivity is essentially independent of the steric and electronic nature of both reaction partners, which is atypical in enantioselective reactions. To explore this further, we probed the effect of alkene geometry on enantioselection 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 the two cases differ. This is consistent with the binding orientation of the alkene not changing. Specifically,

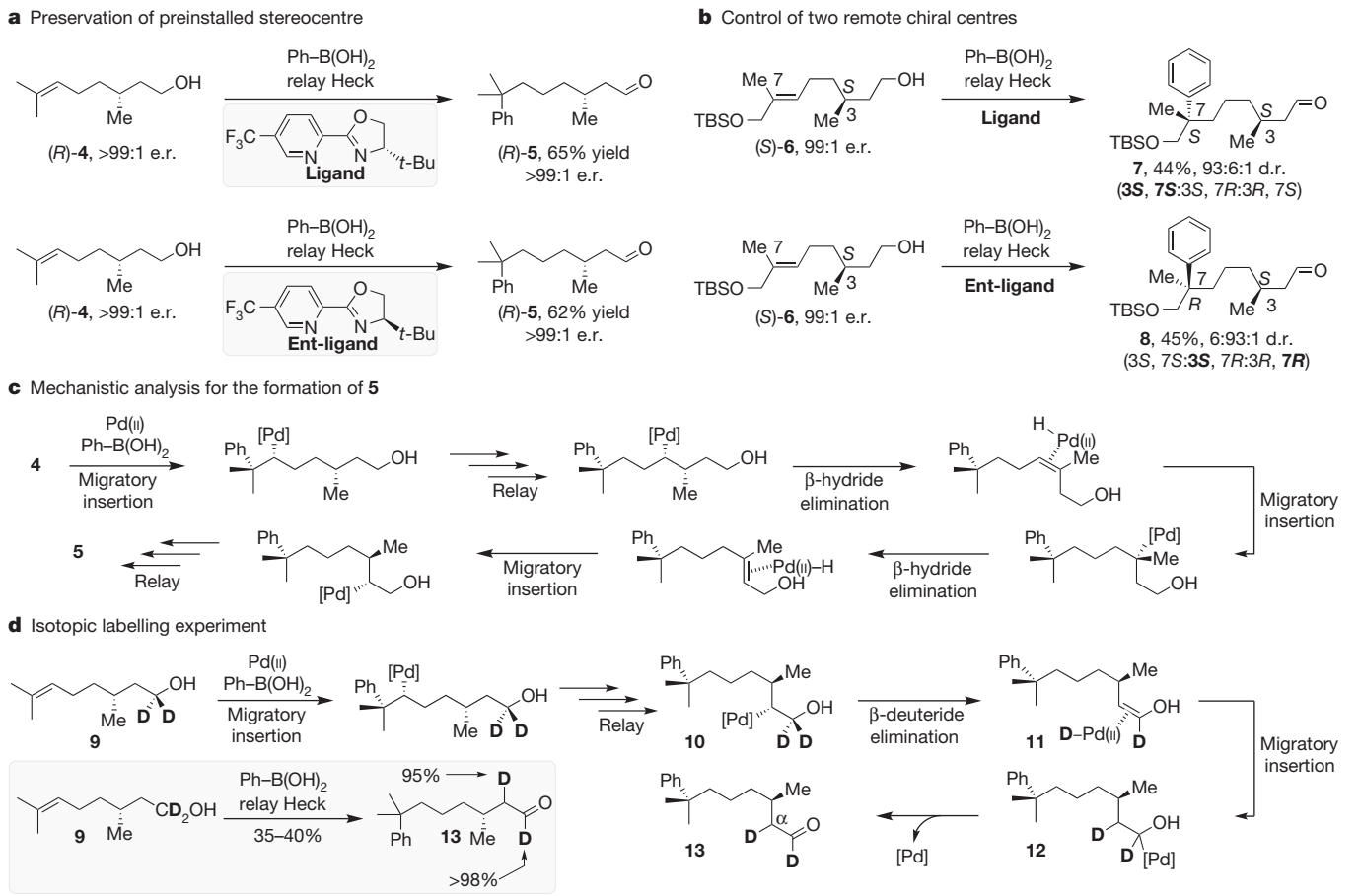

Figure 3 | Evaluation of alkene substrates containing a branch point. Conditions: 10 mol% $Pd(CH_3CN)_2(OTs)_2$, 4 mol% $Cu(OTf)_2$, 14 mol% ligand, 3 equiv. $PhB(OH)_2$. **a**, Independence of catalyst enantiomer on the conservation of the chiral centre during the proposed chain-walking process. **b**, Accessing distinct diastereomers using a combination of catalyst- and substrate-controlled asymmetric synthesis. d.r., diastereomeric ratio. **c**, Proposed mechanistic origin for the observed formation of **5** from **4**. **d**, Isotopic labelling experiment and analysis.

comparison of the proposed intermediates **A** and **B** (Fig. 2d) shows that the alkenyl carbon closer to the alcohol remains fixed, leading to the observed stereochemical outcomes. This conclusion is supported by the relative insensitivity of the process to the group that appears on the terminal end of the trisubstituted alkenes. Although the precise details of why this catalyst is exceptionally selective are under further investigation, these results indicate that few synthetic limitations should be encountered in variation of the alkenyl aliphatic substituents.

As suggested 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 redox-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 pre-installed stereogenic centre in the alkyl chain was evaluated using both enantiomers of the catalyst. 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/migratory-insertion 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 diastereomers are produced by the use of different enantiomers of catalyst, because the initial migratory insertion is under catalyst-controlled face selection, but the preset stereogenic centre is not altered during the relay process.

To support the chain walking proposal further, we carried out an isotopic labelling experiment (Fig. 3d). A deuterium-labelled analogue 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*-deuteride elimination followed by reinsertion to yield intermediate **12** (Fig. 3d).

Conclusion

We have described a catalytic and enantioselective addition of arylboronic acids 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, and thus provides a modular method to access quaternary stereocentres 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 centres will inspire further studies in this area.

METHODS SUMMARY

To a dry, 100-ml Schlenk flask equipped with a stir bar, we added $Pd(CH_3CN)_2(OTs)_2$ (15.9 mg, 0.030 mmol, 6.0 mol%), $Cu(OTf)_2$ (5.4 mg, 0.015 mmol, 3.0 mol%), ligand (12.3 mg, 0.045 mmol, 9.0 mol%), 3 Å molecular sieves (75.0 mg, 150 mg $mmol^{-1}$) and dimethylformamide (DMF; 8 ml). To this flask, a three-way adaptor 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 by syringe. The resulting mixture was stirred for 24 h at room temperature (23–25 °C). 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) and brine (20 ml) and dried over sodium sulphate. The organic extracts were concentrated under reduced pressure, and the resulting residue was purified by silica gel flash chromatography using 2–10% ethyl acetate 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.

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Author Information Data for the crystallized product (a derivative of **2f**) have been deposited in the Cambridge Crystallographic Data Centre under accession number CCDC 988090. Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to M.S.S. (sigman@chem.utah.edu).