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 is a formidable challenge, especially in acyclic systems. 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 alkylolation or aldol reactions, can be accomplished through the reaction of enolate equivalents (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 (II in Fig. 1a). A powerful alternative to the carbonyl as a pre-installed functional group is the allylic electrophile (I 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 carbonyls, 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 (R2 = 0) 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.

Although well-known Heck cyclization reactions have been developed and extensively applied to the formation of quaternary centres by intramolecular reaction of trisubstituted alkenes, no examples of catalytic, asymmetric quaternary stereocentres synthesized through intermolecular Heck-type reactions of isolated (non-conjugated) trisubstituted alkenes are known.

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...
intermolecular Heck-type reactions, probably because of poor binding to the catalyst or slow migratory insertion. 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. This would possibly also relieve steric strain that occurs preferentially at the more substituted carbon (the hindered and downfield-shifted carbon). This was possibly also relief steric strain because the bulky Pd catalyst is positioned at the less hindered carbon. Nevertheless, migratory insertion occurred to install the aryl group predominantly at the $\gamma$-position (>15 times more likely than at the $\beta$-position) and the product was generated in a high enantioselective 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. Nevertheless, 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

**Reaction optimization and scope**

We began our investigation by revising our previously developed catalytic system for enantioselective oxidative Heck reactions 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 $\gamma$-position (>15 times more likely than at the $\beta$-position) and the product was generated in a high enantioselective ratio (e.r.) of 97:3. 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. 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

![Chemical structure](image-url)
pathways and favour product formation. Batchwise addition of the aryloboronic 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 aryloboronic-acid coupling partners was investigated with homoallylic alcohol 1 (Fig. 2a). A wide array of aryloboronic 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 aryloboronic 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 aryloboronic acids$^{24}$. This observed difference suggests that the electronic nature of the alkene dictates site selectivity. Higher selectivity is observed and the reaction can be scaled to 10 mmol, yielding 3i in 97:3 e.r.

Mechanistic experiments

From analysis of the scope of the reaction, it seems that the enantioslectivity 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, the major enantiomer produced in the two cases differ. This is consistent with the binding orientation of the alkene not changing.

Figure 3 | Evaluation of alkene substrates containing a branch point.

Conditions: 10 mol% Pd(CH$_3$CN)$_2$(OTs)$_2$, 4 mol% Cu(OTf)$_2$, 14 mol% ligand, 3 equiv. PhB(OH)$_2$.

a. Preservation of preinstalled stereocentre.

b. Control of two remote chiral centres.

c. Mechanistic analysis for the formation of 5.

d. Isotopic labelling experiment.

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Conditions: 10 mol% Pd(CH$_3$CN)$_2$(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 of the redox-relay Heck reaction of disubstituted alkenes shows generally lower energy barriers for the ‘chain-walking’ events. 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 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, alkene 9, bearing deuterium atoms at the carbon connecting to the alkene, 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 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 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(CH3CN)(OTf)2 (15.9 mg, 0.030 mmol, 6.0 mol%), Cu(OTf)2 (5.4 mg, 0.015 mmol, 3.0 mol%), ligand A, and n-pentane (2 ml). To a trisubstituted alkene and the ability of the catalyst to migrate through existing chiral centres will inspire further studies in this area.

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41. Werner, E. W. & Sigman, M. S. A highly selective and general palladium catalyst for the oxidative Heck reaction of electronically nonbiased olefins. J. Am. Chem. Soc. 132, 13981–13983 (2010).

42. Yoo, K. S., Yoon, C. H. & Jung, K. W. Oxidative palladium(II) catalysis: a highly efficient and chemoselective cross-coupling method for carbon–carbon bond formation under base-free and nitrogenous-ligand conditions. J. Am. Chem. Soc. 128, 16394–16393 (2006).

43. Du, X. et al. Mizoroki–Heck type reaction of organoboron reagents with alkenes and alkynes. A Pd(II)-catalyzed pathway with Cu(OAc)2 as an oxidant. Org. Lett. 3, 3313–3316 (2001).

44. Gligorich, K. M. & Sigman, M. S. Recent advancements and challenges of palladium(II)-catalyzed oxidation reactions with molecular oxygen as the sole oxidant. Chem. Commun. 3854–3867 (2009).

45. Steinhoff, B. A., King, A. E. & Stahl, S. S. Unexpected roles of molecular sieves in palladium-catalyzed aerobic alcohol oxidation. J. Org. Chem. 71, 1861–1868 (2006).

46. Kochi, T., Hamasaki, T., Aoyama, Y., Kawasaki, J. & Kakiuchi, F. Chain-walking strategy for organic synthesis: catalytic cycloisomerization of 1,4-dienes. J. Am. Chem. Soc. 134, 16544–16547 (2012).

47. Johnson, L. K., Killian, C. M. & Brookhart, M. New Pd(II)- and Ni(II)-based catalysts for polymerization of ethylene and α-olefins. J. Am. Chem. Soc. 117, 6414–6415 (1995).

48. Larock, R. C., Leung, W.-Y. & Stolz-Dunn, S. Synthesis of aryl-substituted aldehydes and ketones via palladium-catalyzed coupling of aryl halides and non-allylic unsaturated alcohols. Tetrahedr. Lett. 30, 6629–6632 (1989).

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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).

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