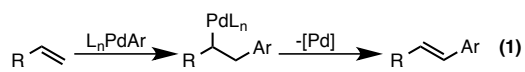


THE ASYMMETRIC CONSTRUCTION OF C–C BONDS VIA REDOX-RELAY CATALYSIS

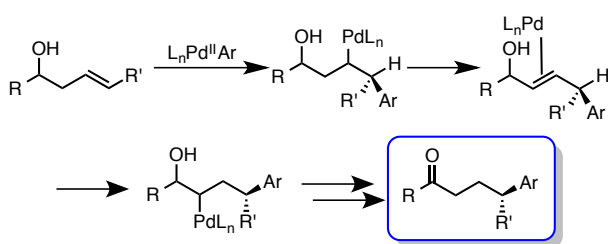
Reported by Jennifer L. Kennemur

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General platforms toward the asymmetric construction of remote C–C bonds can potentially shift paradigms in retrosynthetic analyses for both target- and diversity-oriented synthesis. The Heck reaction is a powerful tool used to formally functionalize vinylic C–H bonds with unsaturated oxidants to form C–C bonds.¹ However, the classic oxidative Heck reaction has seemingly no role in the realm of asymmetric C–C bond formation as the intermediate sp^3 center is reconverted to an sp^2 center upon β -hydride elimination (eq.1). Further, the synthetic utility of the Heck reaction is inherently limited to the use of electronically- and structurally-biased olefins.



In 2012, the Sigman group manipulated two inherent limitations of the classic Heck reaction to work in unity. In particular, the authors capitalized on accessible β -hydrogens to prevent reconversion of



Scheme 1: Redox-Relay Catalysis

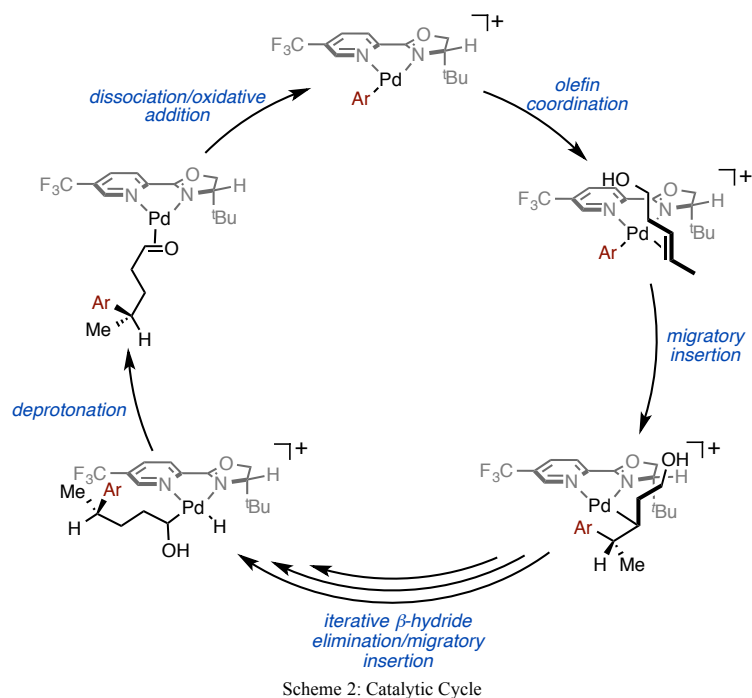
the olefin at the newly formed C–C bond to affect an asymmetric Heck reaction between an alkenyl alcohol and aryl boronic acid.² Following a syn-arylpalladation, iterative β -hydride elimination/migratory insertion occurs *toward* the alcohol to afford a thermodynamically favored carbonyl remote to the

newly formed chiral center (Scheme 1). Sigman *et al.* constructed a variety of β -, γ -, and δ -substituted carbonyl compounds from allyl, homoallyl and bis-homoallyl alcohols, respectively, in moderate to good yields and regioselectivities with excellent enantioselectivity.

Following the seminal report, the Sigman group extended this methodology to a wide variety of ubiquitous boronic acid coupling partners.³ The authors also observed reactivity with longer chained alkenyl alcohols to produce asymmetric ϵ -, ζ -, η -substituted carbonyls, functionalities otherwise difficult to access.

In 2014, Wang *et al.* and Wiest *et al.* independently proposed a catalytic cycle (Scheme 2) and probed key mechanistic features; namely, (1) the orientation of olefin coordination during the rate-limiting migratory insertion and (2) the preferred directionality and/or reversibility of Pd chain walking.⁴

With a rapidly isomerizing starting complex (cis,trans isomerization), the migratory insertion step is under Curtin-Hammett control and thus, the relative energies associated with olefin coordination in the transition states solely dictate the regio- and enantioselectivity of the Heck coupling. According to both empirical observation and computational studies, the olefin preferentially coordinates trans to the pyridine ring with the alcohol moiety above the plane and proximal to the ligand, minimizing steric repulsion while maximizing attractive Columbic forces (e.g. π -H coordination) (Figure 1).



The modes of olefin coordination for (E)- and (Z)-alkenyl alcohols lead to enantiomeric products, prompting Sigman *et al.* to question the enantioselectivity of reactions with tri-substituted

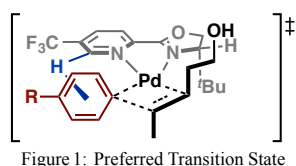


Figure 1: Preferred Transition State

alkenyl alcohols as they contain both an (E)- and (Z)-relationship. Excitingly, they were able to expand the redox-relay platform to tri-substituted alkenyl alcohols to form quaternary centers with excellent site selectivity and enantioselectivity.⁵

Another key mechanistic feature is the directionality of the iterative olefin isomerization. To probe the directionality of chain walking; however, a lack of deuterium scrambling has supported a unidirectional chain walking to form the carbonyl product.⁶ With this in mind, Sigman *et al.* recently extended the redox-relay methodology to alkenyl triflate coupling partners, as the electrophilic catalyst is able to differentiate between β -hydrogens and avoid a π -allyl complex and subsequent catalyst arrest.⁷

This pioneering work by Sigman and others has demonstrated the sensitive tunability of organometallic species to control regio- and enantioselectivity and to subsequently relay functionality to remote sites. Future work in this area should concentrate on expanding the scope of the oxidative coupling partner and applying this platform to various olefin functionalization reactions.

¹ Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5531. ² Werner, E. W.; Mei, T.-S.; Burckle, A. J.; Sigman, M. S. *Science* **2012**, *338*, 1455. ³ Mei, T.-S.; Werner, E. W.; Burckle, A. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 6830. ⁴ (a) Dang, Y.; Qu, S.; Wang, Z.-X.; Wang, X. *J. Am. Chem. Soc.* **2014**, *136*, 986. (b) Xu, L.; Hilton, M. J.; Zhang, X.; Norrby, P.-O.; Wu, Y.-D.; Sigman, M. S.; Wiest, O. *J. Am. Chem. Soc.* **2014**, *136*, 1960. ⁵ Mei, T.-S.; Patel, H. H.; Sigman, M. S. *Nature* **2014**, *508*, 340. ⁶ Hilton, M. J.; Xu, L.-P.; Norrby, P.-O.; Wu, Y.-D.; Wiest, O.; Sigman, M. S. *J. Org. Chem.* **2014**, *79*, 11841. ⁷ Patel, H. H.; Sigman, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 3462.