Asymmetric Catalysis

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Enantioselective Palladium-Catalyzed Direct Alkylation and Olefination Reaction of Simple Arenes**

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Over the past decade significant advances have been made in transition-metal-catalyzed arene functionalization reactions through C–H activation. This topic is not only just of academic interest but also attractive for industrial applications, owing to features such as cheap starting materials, reduced wastes, and increased atom economy.[1] Despite impressive progress to date, one of the challenges remaining in the arene C–H activation is control of the selectivity.[2] This is a pervasive problem in C–H activation that is generally due to the fact that a single molecule typically possesses many indistinctive C–H bonds and because of the high energy barrier for cleavage of a C–H bond.[3] Consequently, it is particularly challenging to develop enantioselective arene C–H activation processes because the regioselectivity must also simultaneously be controlled. Although the asymmetric Friedel–Crafts reaction can be viewed as an efficient strategy for stereocontrolled direct arene functionalization, the substrates are generally limited to electron-rich arenes.[4] Prior to 2008, the only examples of asymmetric C–H activation reactions concerned C–H activation/enantioselective olefination[5a,b] and atropselective olefin hydroarylation.[5c] Very recently, breakthrough results in both intermolecular and intramolecular enantioselective palladium-catalyzed arene C–H activation were reported by Yu and co-workers[6] as well as Albicker and Cramer, respectively.[7] With proper choice of chiral ligands, the enantioselective direct C–H activation of simple arenes was realized with practical *ee* values. In this Highlight, the significance of their results is summarized.

Despite numerous efforts to realize enantioselective C–H bond activation using chiral palladium catalysts, up to now, there are only limited reports mainly focusing on the allylic C–H and indole C–H systems.[8] The major issue that must be overcome is the development of the appropriate ligands that both enable the C–H activation process and effect stereoinduction during C–H insertion.

Continuing with their pioneering work on palladium-catalyzed C–H bond activation, Yu and co-workers have succeeded in diastereoselective control over C–H activation.[9] To develop a catalytic enantioselective C–H activation process, they recently utilized a prochiral substrate, triarylmethane **1a** with a 2-pyridyl group (Scheme 1).[6a] After the identification of a dinuclear palladium complex, formed from **1b** and $Pd(OAc)_2$, they proposed that chiral induction might be achieved with a chiral carboxylate.

After screening various chiral carboxylates, Boc-proline (**L1**) afforded the C–C coupling product **2** in 20% *ee*. Cyclopropyl amino acid **L2**, which is structurally more rigid, performed better and afforded **2** in 46% *ee*. The finding that the products were obtained with almost identical *ee* values but opposite configuration from ligands **L2** and **L3** and racemic product was obtained with **L4** indicated that the α-carbon chiral center plays a key role for the stereoinduction. A coordination model **3** was proposed and is depicted in Scheme 2. The conformation **4** is unfavorable for cyclopalladation owing to the steric hindrance between the *o*-Tol group and the carbamate group as they are on the same side of the catalyst. This model was well supported by the fact that the bulkier menthoxycarbonyl-protected amino acid **L5** was revealed as the optimal ligand (96% yield, 88% *ee*). The enantioselective C–H activation of a $C(sp^3)$–H bond was also demonstrated, albeit in lower enantiomeric excess.

Yu and co-workers recently succeeded in carrying out the direct olefination of arenes through carboxy-induced C–H bond activation.[10] In this elegant study, amino acids were found to be efficient ligands to both increase the conversion and modulate the regioselectivity for multisubstituted phenylacetic acids [Scheme 3, Eq. (1)]. Soon thereafter, they developed an enantioselective C–H olefination of diphenylacetic acids.[6b] The carboxylate group was used as the directing group in **7** and Boc-Ile-OH (**L6**) was found to be an efficient ligand [Scheme 3, Eq. (2)]. The reaction of substrate **7** and styrene derivatives led to olefination products **9** in reasonable yields and up to 97% *ee*. In addition, these enantioenriched products could be readily converted into aldehydes or lactones without loss of the optical purity. In Yu's protocol, the use of readily available and air-stable amino acids as efficient ligands makes the procedure simple and practical.

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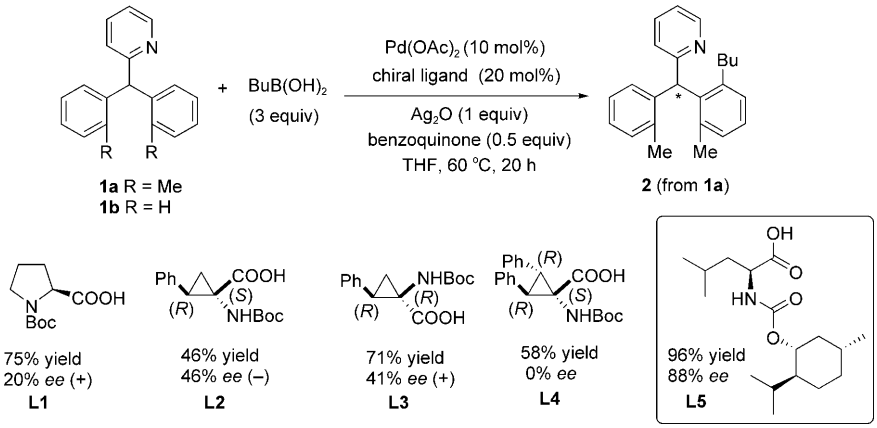
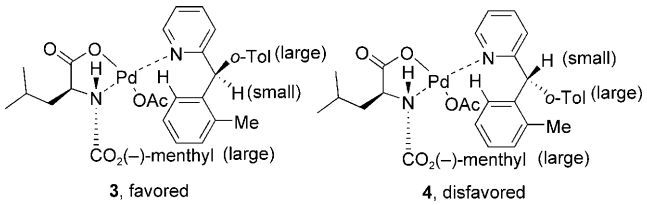


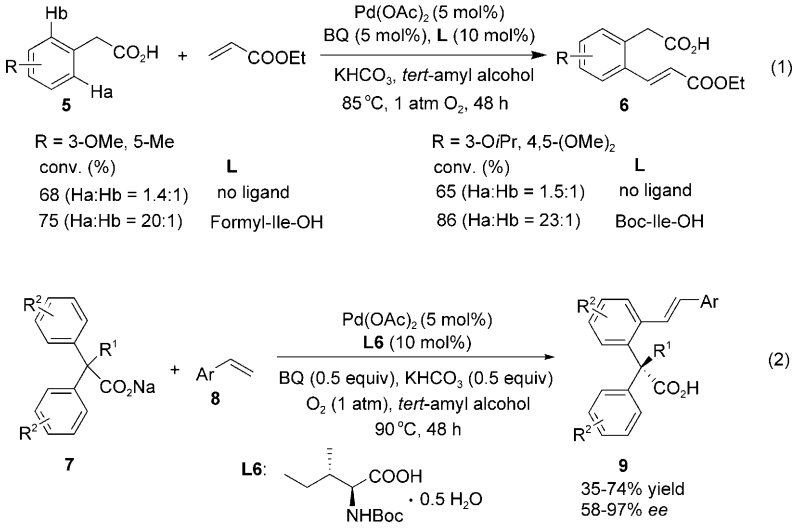
Scheme 1. Palladium-catalyzed alkylation of **1a** with an alkyl boronic acid. Boc = *tert*-butoxycarbonyl.



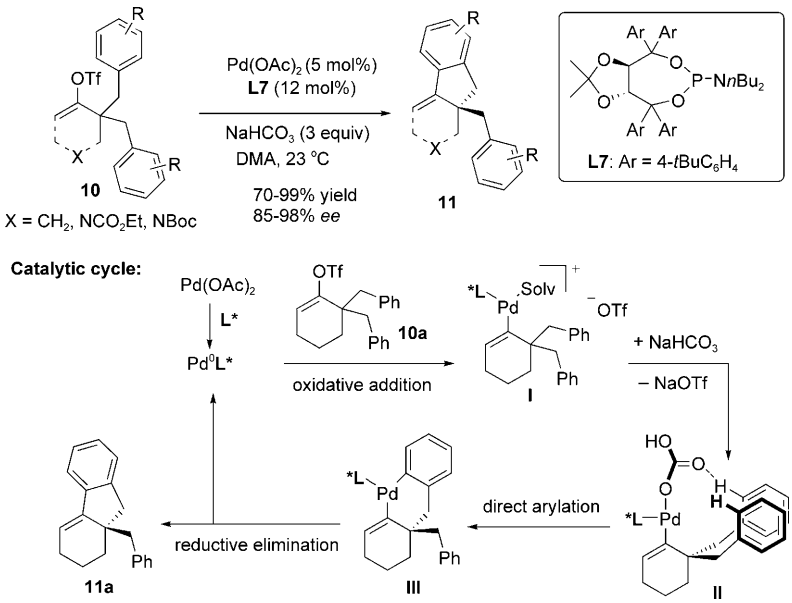
Scheme 2. Working model for enantioselective arene C–H activation. Tol = tolyl.

Albicker and Cramer also reported an excellent study on enantioselective palladium-catalyzed intramolecular arylation reactions, which allow the facile access to indanes with quaternary stereocenters.[7] Notably, the reaction starts with a Pd^0 catalyst, which first undergoes oxidative addition. The resulting Pd^{II} intermediate performs bicarbonate-assisted proton abstraction to activate one of the two prochiral arene C–H bonds. Stereoinduction is achieved through the presence of the chiral ligand on the palladium center. The arylation product was obtained after reductive elimination, thus releasing the Pd^0 catalyst to finish the catalytic cycle (Scheme 4). One advantage of targeting Pd^0/Pd^{II} catalysis is the compatibility with phosphorus ligands, of which a large pool of chiral backbones already exists. After screening a set of chiral phosphorus ligands, with **L7** in DMA, the intramolecular arylation of vinyl triflates could be performed smoothly with excellent enantiomeric excess. Under the optimized reaction conditions, various substrates were well tolerated. Notably, the reaction proceeds well at room temperature, which is advantageous in enhancing stereoinduction.

In summary, the research groups of Yu and Cramer have demonstrated highly enantioselective palladium-catalyzed direct functionalization of simple arenes which has been a longstanding challenge in asymmetric synthesis. These chiral induction tactics represent a great breakthrough for the development of enantioselective C–H activation, which will gain further attention in future investigations. Extending the



Scheme 3. Palladium-catalyzed arene C–H olefination. BQ = benzoquinone, Ile-OH = isoleucine.



Scheme 4. Palladium-catalyzed direct arylation of vinyl triflates. DMA = *N*,*N*-dimethylacetamide, Solv = solvent, Tf = trifluoromethanesulfonyl.

substrate scope and searching for efficient chiral ligands are likely to be the most important tasks remaining in this field.

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