Angewandte
Highlights

Asymmetric Heck Reaction

DOI: 10.1002/anie.201310585

Breaking News on the Enantioselective Intermolecular Heck Reaction**

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asymmetric catalysis · Heck–Matsuda reaction ·
hemilabile ligands · Mizoroki–Heck reaction

The Heck reaction is one of the fundamental palladium(0)-catalyzed C–C bond-forming reactions, and its impact on the way molecules are built today was recognized with the Nobel Prize in Chemistry. The breadth and depth of research dedicated to its various facets over the past decades[1] leaves the erroneous impression that Heck chemistry is now a mature area. The mechanistic understanding of how the countless parameters of a Heck reaction affect its outcome is still premature, and that includes the subtle factors that govern the regioselectivity of the migratory insertion as well as the β-hydride elimination. These issues are particularly evident in intermolecular scenarios with internal (sterically and electronically nonbiased) alkenes. The inability to control these steps in a predictable manner is likely to account for the limited progress in the asymmetric variant. Enantioselective intermolecular Heck reactions usually require cyclic alkenes where conformational rigidity and, hence, restricted rotation around C–C bonds steers β-hydride elimination away from the newly formed C–C bond (Figure 1, left). This clear limitation was recently overcome by Sigman and co-workers by the design of ligands that make it possible to distinguish between almost identical C–H bonds in the β-hydride elimination event (Figure 1, right).[2] This Highlight summarizes the exciting development of the enantioselective intermolecular Heck reaction of acyclic alkenes.[2,3] Also, we include here another discovery that profoundly expanded the synthetic utility of enantioselective intermolecular couplings of cyclic alkenes: the use of hemilabile mixed phosphine/phosphine oxide ligands.[4–7]

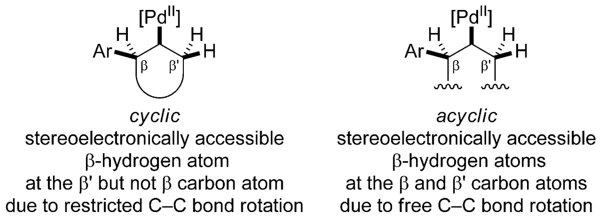
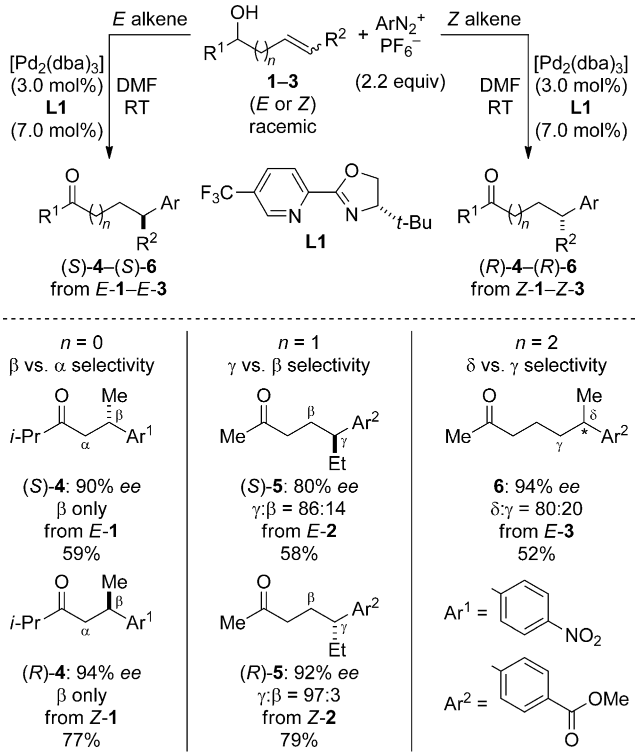


Figure 1. β-Hydride elimination in cyclic (left) and acyclic (right) systems.

Sigman and co-workers accomplished a remarkable intermolecular Heck reaction of allylic and homoallylic alcohols (Scheme 1).[2] The site selectivity of the migratory insertion is not totally unexpected in the proximity of the hydroxy group[8,9] but the regioselective β-hydride elimination that reestablishes the alkene away from the newly formed C–C bond is spectacular. Pyridine-based **L1** from a family of chiral ligands unprecedented in asymmetric Heck chemistry is believed to account for this exceptional result. Also, **L1**



Scheme 1. Enantioselective intermolecular Matsuda–Heck reaction of internal alkenes tethered to a hydroxy group.[2] dba = dibenzylideneacetone.

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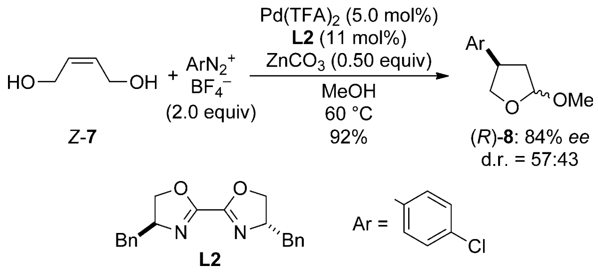
[**] M.O. is indebted to the Einstein Foundation (Berlin) for an endowed professorship.

renders the palladium(II) hydride sufficiently electrophilic that it reinserts the alkene after β-hydride elimination rather than dissociating from it. The recurring sequence of β-hydride elimination and reinsertion with opposite regioselectivity moves the alkene through the carbon chain, eventually transforming the tethered hydroxy group into a carbonyl functionality. This alkene zipper corresponds to a redox isomerization termed "redox-relay strategy" by the authors. As a result, not only the allylic alcohol but also the homoallylic alcohol and a higher homologue are converted into the carbonyl compounds.

Ligand **L1** fulfills another role, namely enantioinduction. The level of enantiocontrol is uniformly high for a broad range of hydroxy-group-containing alkenes but the fact that the double-bond geometry determines the absolute configuration which is unaffected by the existing stereocenter is even more notable ($E \rightarrow S$ and $Z \rightarrow R$, Scheme 1). Heck arylations of *E* and *Z* pairs of racemic allylic and homoallylic alcohols **1** and **2** afforded carbonyl compounds **4** and **5** with high enantioselectivity and reasonable regioselectivity. The latter is not optimal for homoallylic *E*-**2** (γ:β = 86:14), and that trend continues for *E*-**3** with an additional methylene group (δ:γ = 80:20). Still, these numbers are impressive in light of the previous state-of-the-art.

There is yet another aspect that deserves particular emphasis. The work of Sigman and co-workers discloses an enantioselective Heck–Matsuda reaction, in other words, a Heck reaction that employs diazonium salts as coupling partners.[10,11] Examples of asymmetric variants had been elusive until Sigman's breakthrough and independent work of Correia and co-workers.[3] The latter team had also realized that phosphine-free ligands such as bis(oxazoline)-type scaffolds are compatible with diazoniums salts. Intermolecular arylations of several substituted cyclopentenes using ligand **L2** had already been promising, reaching a maximum of 84 % *ee* (not shown).[3a] Moreover, enantiomeric excesses were also good for allylic alcohols but, in constrast to Sigman's findings, there was no site selectivity in the migratory insertion. However, symmetric *Z*-**7** reacted smoothly with high enantioselectivity to yield acetal (*R*)-**8** (Scheme 2).[3b] The absolute configuration was independent of the alkene geometry (stereoconvergent reactions of *Z*-**7** and *E*-**7**), and that also distinguishes Correia's from Sigman's catalytic system.

The development of the enantioselective Heck–Matsuda reaction occurred simultaneously with another fundamental discovery. It was found that chiral mixed phosphine/phosphine oxides[12] are excellent supporting ligands in the asymmetric intermolecular Heck reaction. These hemilabile ligands indeed surpass their nonoxidized counterparts, i.e., conventional diphosphines. Monooxidized BINAP **L3** (Figure 2) which is generated in the palladium(II)-to-palladium(0) reduction in catalyses employing $Pd(OAc)_2$ as precatalyst,[13] emerged as particularly effective (cf. Scheme 3 and Scheme 5, top).[4,6] Moreover, Zhou and co-workers demonstrated the outstanding performance of spirocyclic ligand **L4** in several representative intermolecular Heck reactions (cf. Schemes 4–6).[5–7]



Scheme 2. Enantioselective intermolecular Heck–Matsuda reaction of a symmetric allylic alcohol.[3b] Bn = benzyl, TFA = trifluoroacetate.

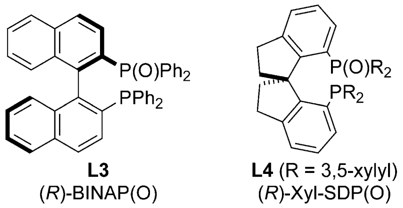
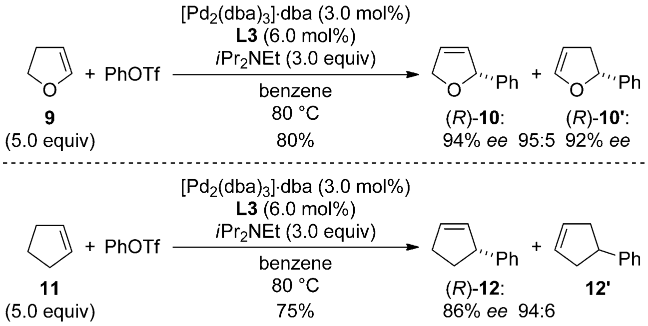
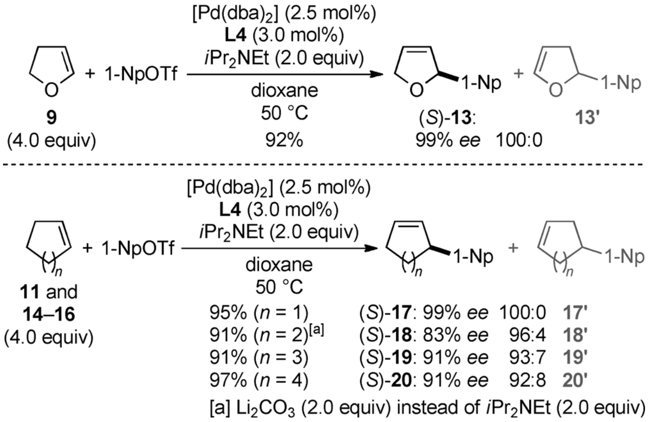


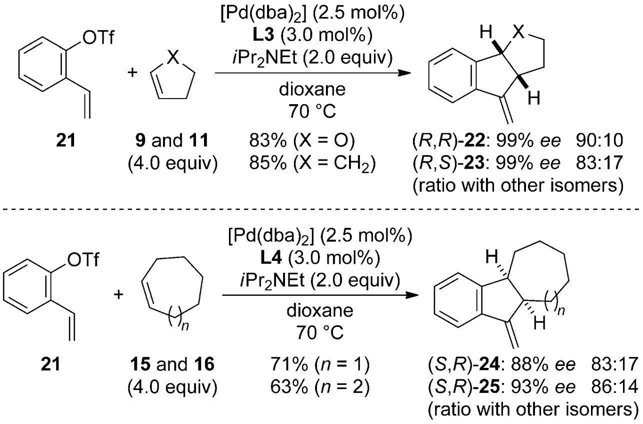
Figure 2. Hemilabile mixed phosphine/phosphine oxides as ligands for enantioselective intermolecular Heck reactions. BINAP = 2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl and Xyl-SDP = 7,7′-bis[di(3,5-dimethylphenyl)phosphino]-1,1′-spirobiindane.



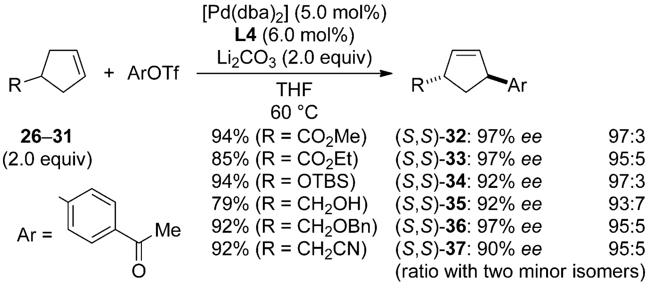
Scheme 3. BINAP(O) as a superior ligand in enantioselective Heck reactions of cyclic alkenes.[4] Tf = trifluoromethanesulfonyl.



Scheme 4. General approach to the enantioselective intermolecular Heck reaction.[5] 1-Np = 1-naphthyl.



Scheme 5. Enantioselective domino reaction involving a highly enantioselective intermolecular Heck reaction.[6]



Scheme 6. Enantioselective desymmetrization by an intermolecular Heck reaction.[7]

Wöste and Oestreich realized that BINAP and BINAP(O) produce different results in the typical arylation of 2,3-dihydrofuran (**9**→**10** and **10′**, Scheme 3, top).[4] With BINAP, thermodynamically more stable **10′** is predominantly formed, and (*S*)-**10** (67 % *ee*) and (*R*)-**10′** (93 % *ee*) are of opposite absolute configuration (not shown).[14] With **L3**, little alkene migration is observed, and (*S*)-**10** and (*S*)-**10′** are formed in equally high enantiomeric excesses with the same sense of asymmetric induction. Likewise, the difficult arylation of cyclopentene proceeds smoothly with good selectivities (**11**→(*R*)-**12** and **12′**, Scheme 3, bottom).[4] Similarly, Zhou and co-workers introduced **L4** to these and related enantioselective Heck reactions (Scheme 4).[5] Enantiomeric excesses were exceedingly high, and alkene migration was almost completely suppressed. The generality of the catalyst system is exceptional, and the challenging arylations of cyclic alkenes **14**–**16** and other typical substrates (not shown) are absolutely remarkable.

A beautiful application of Zhou's catalytic setup is an asymmetric version of a domino reaction initially devised by de Meijere and co-workers.[15] The annulation of triflate **21** with cyclic alkenes commences with an enantioselective intermolecular Heck reaction followed by a diastereoselective Heck cyclization (**21**→**22**–**25**, Scheme 5).[6] The level of enantioselection is excellent with **L3** (top) and certainly good with **L4** (bottom), and the formation of noncyclized isomers is acceptable in view of the molecular complexity generated in a single synthetic operation.

The success with unsubstituted cyclic alkenes, **11** in particular, must have prompted Zhou and co-workers to extend their methodology to functionalized but achiral cyclopentenes (**26**–**31**→**32**–**37**, Scheme 6).[7] That transforms the enantioselective arylation into a desymmetrization where diastereoselectivity must be controlled as well. The selectivities obtained were again superb, once more underscoring the broad applicability of the combination of a palladium(0) precatalyst and a mixed phosphine/phosphine oxide ligand.

The asymmetric intermolecular Heck reaction had always been outshone by the intramolecular variant, mainly due the issues discussed in the introduction of this article. The tremendous progress summarized here is likely to bring the former on par with the latter. The enantioselective arylation of terminally substituted allylic and homoallylic alcohols with such levels of site selectivity and regiocontrol is clearly a major step forward. That alone would have been spectacular but it is remarkable that this was achieved by a Heck–Matsuda reaction. No asymmetric version had been known before. The work of Sigman and also Correia really opens new avenues for an old reaction. Moreover, mixed phosphine/phosphine oxides had been disregarded as (chiral) ligands for Heck chemistry for decades, and the contributions particularly by Zhou illustrate the power of this class of ligands. Nearly all reported examples of enantioselective intermolecular Heck reactions were improved and novel asymmetric transformations were disclosed, all of that with a general catalyst system.[16]

Received: December 6, 2013

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[16] While this manuscript was in press, Zhou and Wu solved another long-standing problem in asymmetric intermolecular Heck chemistry with a modified catalytic setup using ligand **L4**. Aryl halides[14] now also afford excellent enantiomeric excesses in the enantioselective Heck arylation of cyclic alkenes: C. Wu, J. Zhou, *J. Am. Chem. Soc.* **2014**, *136*, 650 – 652.