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Asymmetric Intermolecular Heck-Type Reaction of Acyclic Alkenes via Oxidative Palladium(II) Catalysis

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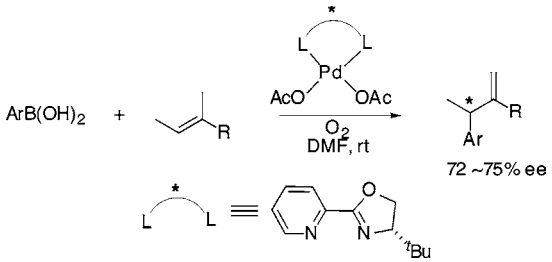
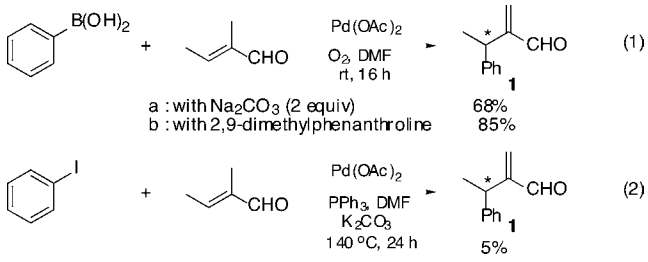
ABSTRACT



Herein, we report an asymmetric intermolecular Heck-type reaction of acyclic alkenes by using a palladium–pyridinyl oxazoline diacetate complex under oxidative palladium(II) catalysis conditions. A premade palladium–ligand complex afforded higher enantioselectivities than a corresponding premixed palladium–ligand system, while offering enhanced asymmetric induction when compared to known intermolecular Heck-type protocols.

In recent years, one of the major objectives in synthetic organic chemistry has been asymmetric catalyses for C−C bond formations including asymmetric Heck-type reactions,[1] which have rarely been used in practice due to their limitations and harsh conditions. Although high enantioselectivities were observed in a number of intramolecular Heck-type cyclizations, intermolecular reactions have given poor enantioselectivities, except with cyclic olefins such as dihydrofuran and dihydropyrrole.[2−4] For instance, Uemura and co-workers reported the first example of an enantioselective intermolecular arylation of prochiral acyclic alkenes; however, the observed enantioselectivity was only 17% ee.[5] In an effort to mitigate these shortcomings, we applied our oxidative Pd(II) method to an intermolecular coupling of acyclic alkenes, presumably the most challenging substrates for this type of asymmetric conversion.



While extensively researching C−C bond formation using oxidative Pd(II) catalysis, we found that the coupling of

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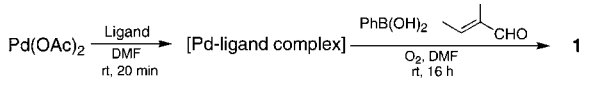
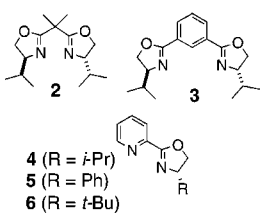
phenylboronic acid and *trans*-2-methyl-2-butenal produced exclusively the rearrangement compound **1**, generating a new stereogenic center (eq 1-a). In addition, with a bidentate amine ligand, such as 2,9-dimethylphenanthroline (eq 1-b), the coupling reaction provided the desired product in a high yield even at room temperature without a base.[6,7] Notably, the corresponding Heck reaction proceeded poorly (5%) even at high temperatures (eq 2). These results prompted us to investigate asymmetric Heck-type reaction by employing various chiral ligands.

As summarized in Table 1, we screened well-known bidentate *N*,*N*-ligands for possible asymmetric Heck-type reactions, while phosphine-based ligands turned out to be inefficient due to side reactions, including homocoupling and phenol formation.[8] During the course of our study, Mikami et al. reported their results,[3] conforming to our data. To avoid redundancy, we are not reporting these results, which are slightly better perhaps due to better handling of oxidative Pd(II) catalysis we have developed. Included in this study were bisoxazoline ligands (**2**[9c] and **3**[9a]) and pyridinyl oxazoline ligands (**4**,[9a] **5**,[9b] and **6**[9b]). Prior to the addition of the boron compound and alkene, $Pd(OAc)_2$ and a ligand were premixed in DMF at room temperature for 20 min, and the reaction mixture was then stirred for 16 h under a molecular oxygen atmosphere.

Table 1. Effect of Various Ligands Premixed with $Pd(OAc)_2$



entry	ligand[a]	yield (%)[b]	ee(%)[c]
1	**2**	71	16
2	**3**	66	9
3	**4**	71	25
4	**5**	69	21
5	**6**	76	42

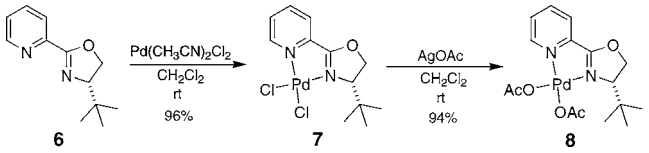


[a] The reaction was carried out premixing 5 mol % of $Pd(OAc)_2$ and 5.5 mol % of ligand before the addition of coupling substrates. [b] Isolated yield. [c] Determined by chiral HPLC analysis (Daicel Chiracel OD) (Mobile phase: ^{i}PrOH/hexanes = 5:95 v/v %, rate = 1 mL/min).

Utilizing ligands **2** and **3**, phenylboronic acid underwent the rearranged arylation of *trans*-2-methyl-2-butenal to afford **1** in 71 and 66% yields, respectively, with low enantioselectivities (9−16% ee; entries 1 and 2). Unsymmetrical oxazoline ligands **4** and **5** induced higher enantioselectivities than symmetrical ones **2** and **3** (entries 3 and 4). However, chiral induction was still disappointing (21−25% ee). By increasing the size of the oxazoline substituent, enantioselectivity was improved to 42% ee (entry 5). Although these were significant improvements over other asymmetric Heck reactions, our results did not meet our expectations.

We suspected that moderate enantioselectivities were due to incomplete formation of palladium−ligand complexes and/or relatively easy disassociation of palladium and ligands. For instance, the coupling reaction gave lower enantioselectivity (31% ee) when all the reagents were added at once without premixing $Pd(OAc)_2$ and the ligand **6**. Lower asymmetric induction was presumably ascribed to the background reaction with a free palladium catalyst, which would be more efficient than the ligand-chelated catalyst. Hence, we sought to employ a pure palladium−ligand catalyst such as **8** derived from oxazoline ligand **6** (Scheme 1). When pyridinyl−oxazoline ligand **6** was treated with $Pd(CH_3CN)_2Cl_2$ in dichloromethane at room temperature, a palladium−ligand dichloride complex **7** was produced cleanly in a high yield, and its structure was unambiguously confirmed by ^{1}H NMR and X-ray crystallography analysis.[10] Subsequently, construction of the Pd−pyridinyl−oxazoline acetate complex **8** was accomplished by treating the dichloride adduct **7** with 2 equiv of silver acetate in dichloromethane. Although the diacetate complex **8** was relatively stable, it started decomposing in a few days. Therefore, we usually used freshly prepared catalytic complex for the couplings.

Scheme 1



As shown in Table 2, our hypothesis was validated by using the complex **8**. For example, the asymmetric reaction with phenylboronic acid and *trans*-2-methyl-2-butenal afforded **1** (Ar = Ph) in a dramatically improved enantioselectivity compared to the premixed conditions (entry 1). In addition, the reaction of *p*-methoxyphenylboronic acid and *p*-*N*,*N*-dimethylaminophenyl boronic acid possessing electron-donating groups took place smoothly to provide the desired

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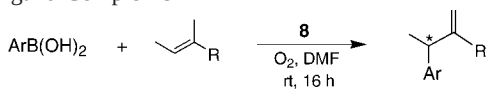
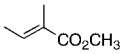
(10) For X-ray crystallography analysis data, see the Supporting Information.

Table 2. Asymmetric Oxidative Heck Reaction Using Premade Pd−Ligand Complex **8**



entry[a]	$ArB(OH)_2$	alkene	product (yield)[b,c]	conf.[d]
1	Ar = C_6H_5		**1** (74%, 75% *ee*)	(R)
2	*p*-$MeOC_6H_4$		**9** (67%, 73% *ee*)	(R)
3	*p*-$Me_2NC_6H_4$		**10** (79%, 75% *ee*)	-
4	2-Naphthyl		**11** (73%, 72% *ee*)	-
5	6-MeO-2-Naphthyl		**12** (68%, 68% *ee*)	(R)
6	Ar = C_6H_5		**13** (67%, 69% *ee*)	(R)
7	*p*-$MeOC_6H_4$		**14** (76%, 75% *ee*)	(R)
8	6-MeO-2-Naphthyl		**15** (75%, 62% *ee*)[e]	(R)

[a] The reaction was carried out using 1.1 equiv of arylboronic acids with 5 mol % of **8**. [b] Isolated yield. [c] Determined by chiral HPLC analysis (Daicel Chiracel OD) (Mobile phase: ^{i}PrOH/hexanes = 5:95 v/v % rate = 1 mL/min). [d] Absolute configuration. [e] Enantioselectivity was determined by NMR analysis with a chiral Eu reagent.

products, and enantioselectivities were comparable (entries 2 and 3). In the case of 2-naphthalenylboronic acid and 6-methoxy-2-naphthalenylboronic acid, the desired rearrangement product was obtained with 72 and 68% ee (entries 4 and 5), respectively. The ester analogue reacted smoothly to furnish similar enantioselectivities (62−75% ee; entries 6−8). The absolute configurations of **1**, **9**, **12**, **13**, **14**, and **15** were determined as *R*-enriched by transforming[11] the products to the corresponding phenyl propionic esters[12a] and comparing them with authentic samples.[12b−e]

On the basis of these results, we suggest a plausible olefin-coordinated structure in the migratory insertion step to determine enantioselectivity (Figure 1). Based on the X-ray crystallographic data for the structure of Pd−pyridinyl−oxazoline complex **7**, the pyridine ring and the oxazoline ring are placed in the same plane. After the transmetalation step of arylboronic acid, *trans*-2-methyl-2-butenal would be coordinated at right angles to the planar pyridinyl−oxazoline ring.[4] The carbonyl group and the α-methyl moiety then would be located near the oxazoline ring to establish

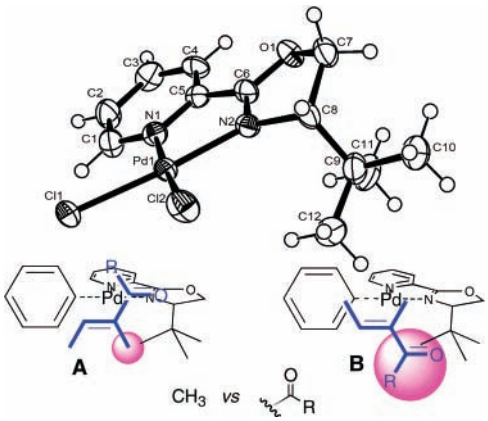


Figure 1. ORTEP representation (include H) of the molecular structure of **7** and proposed transition structures for the oxidative Heck reaction using Pd−ligand complex **8**.

migratory insertion into the Pd−Ph bond. Therefore, the olefin can be envisioned to coordinate the catalyst in two different conformations, **A** or **B**, which differ in the extent of steric repulsion between the olefin substituents and the *tert*-butyl group on the oxazoline ring. Consequently, the reaction would proceed through the coordination model **A**, which would lead to the observed enantioselectivity.

In conclusion, our asymmetric Heck-type catalysis represents a novel proof-of-concept, and we address three important features in this paper: (a) Compared to conventional Heck-type conditions, our oxidative Pd(II) catalysis exhibited higher efficiency under milder conditions in cross-coupling of highly substituted olefins. As a consequence, this oxidative Heck facilitated the preparation of scalemic coupling products. (b) We observed that the nonchelated free palladium catalysis played an important role in couplings, yielding low enantioselectivities under premixed conditions which one would normally use. (c) Oxidative boron Heck demonstrated significant improvements over existing methods in asymmetric catalysis (i.e., 17−75% ee). Keeping those conditions in mind, we embarked on further studies in more effective chiral Pd(II) complexes and coupling conditions, which will be reported in due course.

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Supporting Information Available: Representative experimental procedures with spectral data and X-ray crystallography data for compound **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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