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Enantio- and Regioselective Heck-Type Reaction of Arylboronic Acids with 2,3-Dihydrofuran

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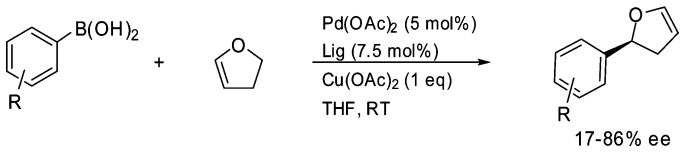

Reported herein is a protocol for the enantioselective Pd(II)-catalyzed Heck-type reaction between arylboronic acids and 2,3-dihydrofuran. The highest chemical and optical yields were obtained when a $Pd(OAc)_2$/(*R*)-MeO(biphenylphosphine) or a $Pd(OAc)_2$/(*R*)-(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) catalyst and a $Cu(OAc)_2$ reoxidant were employed.

Introduction

Nowadays, the asymmetric palladium-catalyzed Mizoroki−Heck (MH) reaction is a well-established and powerful method for the construction of tertiary and quaternary chiral centers.[1] Although both the intramolecular and intermolecular transformations are often used as key strategic steps in the syntheses of complex polycyclic molecules[2] and valuable synthetic intermediates such as dihydrofurans,[3] dihydropyrroles,[4] and cycloalkenes,[5] there is still room for further improvements. First, extremely prolonged reaction times are normally required to obtain satisfactory results (up to 9 days in some cases).[6] Second, enantioselectivity erosion is often observed when substrates other than aryl/vinyl trifluoromethansulfonates (triflates) or iodides are employed;[7] when considering that efficient enantiodifferentiation (at the olefin coordination and migratory insertion steps) apparently requires a simultaneous coordination of the palladium center to both the chiral diphosphine and the prochiral olefin, a partial loss of enantioselectivity is the result of the competition between cationic and neutral reaction pathways (Scheme 1).[8] As a consequence, the scope of asymmetric MH reactions is mainly limited to aryl/vinyl triflates and iodides, which tend to react according to the cationic mechanism.[7,9]

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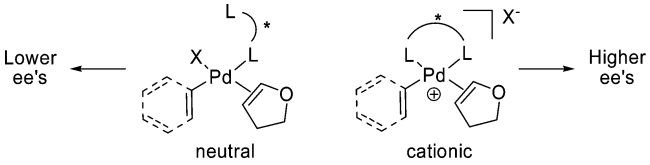
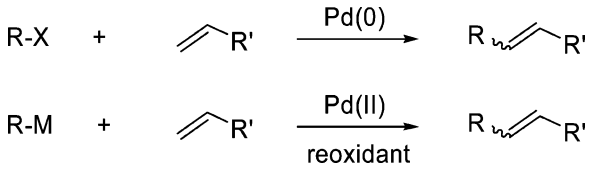
SCHEME 1. Cationic vs Neutral Pathway in an Asymmetric MH Reaction



SCHEME 2. Electrophile-Mediated Pd(0)-Catalyzed vs Nucleophile-Mediated Pd(II)-Catalyzed MH-Type Reaction



The related transformation, namely, the nucleophile-mediated Pd(II)-catalyzed MH reaction, appears as an attractive alternative to its classical counterpart (Scheme 2).

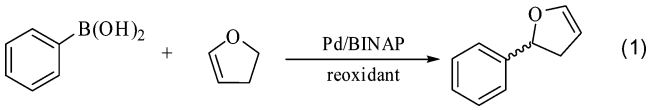
Performing transmetallation as the initial step (instead of oxidative addition) and then performing reoxidation of the palladium catalyst (following reductive elimination) as the final step of the catalytic cycle distinguish between the two methods. Indeed, a number of protocols utilizing silanols,[10] organostannates,[11] and organoboron nucleophiles[12] in the MH-type reaction have been recently described. A priori, if a suitable catalytic system for the asymmetric version of this transformation (Scheme 3) is found, then one can expect the above-mentioned limitations to be eliminated. First, because no halogen−palladium species are involved in the catalytic cycle, the reaction is likely to proceed via the cationic pathway, which improves the optical yield. Second, the "bottleneck" oxidative addition step (at least for catalysts bearing bidentate ligands)[13] is replaced by a simple transmetallation step.[14] Therefore, the reaction times may be reasonably shortened without making the reaction conditions more harsh.

Some time ago, we initiated a research program that aimed to explore the reaction. However, "the proof of concept" came from an independent report by Mikami.[15] Mikami and coworkers demonstrated for the first time that an enantioselective Pd(II)/Chiraphos-catalyzed organoboron-mediated Heck-type reaction is, indeed, possible. Unfortunately, the reported transformation was limited to 4-trifluorometyl-phenylboronic acid and alkyl 1-cyclopentene-1-carboxylates.

Herein, we describe our catalytic system that demonstrates a higher enantioselectivity and a wider reaction scope.

Results and Discussion

A set of optimization experiments was carried out to discover suitable reaction conditions. Initially, we examined the arylation of 2,3-dihydrofuran by phenylboronic acid in the presence of $Pd(OAc)_2$/*rac*-(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) (*rac*-BINAP) catalyst (eq 1). We found that the thermodynamically more stable 2-phenyl-2,3-dihydrofuran could be obtained almost exclusively at room temperature, in a THF medium, in the presence of a stoichiometric amount of $Cu(OAc)_2$ reoxidant, and without a base applied. Remarkably, the regioselectivity of the reaction was affected neither by the presence of inorganic bases (K_3PO_4, K_2CO_3, and Na_2CO_3) nor by air as a re- or co-oxidant, and comparable results in terms of regioselectivity were obtained. In addition, the formation of biphenyl (a likely byproduct) was negligible.



It is also noteworthy that phenylboronic acid had to be used as a limiting reagent under our reaction conditions. When we used an inverted phenylboronic acid/2,3-dihydrofuran (2,3-DHF) ratio, we observed the formation of a significant amount of 4-hydroxy-1,4-diphenylbutan-1-one. Apparently, this product is a result of the double arylation of 2,3-DHF that is followed by isomerization and ring-opening of the intermediate (Scheme 4).[16]

A possible weak point of the initial protocol is the use of oxidizable phosphine ligands under oxidative conditions. To our surprise, the oxidation of BINAP was not extensive; the blank experiment performed under similar reaction conditions, but in the absence of 2,3-DHF, led to only ca. 10% BINAPO (based on GC analysis). Unfortunately, this oxidation process was not the only catalyst deactivation pathway. The formation of triphenylphosphine was also observed, mainly, when the reaction was carried out in the presence of air. This less expected byproduct likely originates from a Pd-Phenyl/P-$Phenyl_2$ exchange, which is a common and well-documented decomposition path for $(PAr_3)_2Pd(Ar)X$ complexes (a Novak-type reaction).[17] However, this process was not extensive under airfree conditions; thus, only a slight excess of the ligand (1.5:1) was necessary for a successful transformation.

Having these results in hand, experiments with the best combinations of reagents were repeated in the presence of (*R*)-BINAP. The representative results (Table 1) clearly show that the presence of dioxygen either as a co-oxidant (entries **1**−**4**, Table 1) or as the only reoxidant (entry **5**, Table 1) always led to reduced chemical and optical yields; apparently, this is

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(13) Although kinetics might change depending on the catalyst/reactants combination (See for example Rosner, T.; Le Bars, J.; Pfaltz, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 1848.), oxidative addition is very often a rate-limiting step for catalysts bearing bidentate ligands. (a) Jutand, A.; Mosleh, A. *Organometallics* **1995**, *14*, 1810. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

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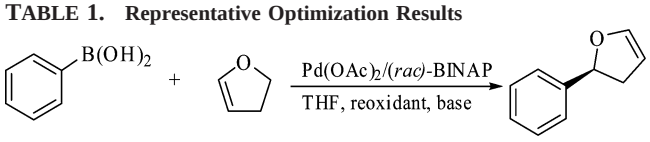
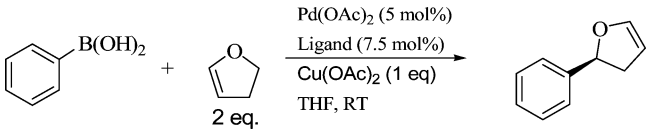
TABLE 1. Representative Optimization Results



entry	conditions	yield, %[a]	ee, %[b]
1	$Cu(OAc)_2$, K_2CO_3, air, RT	34	41
2	$Cu(OAc)_2$, Na_2CO_3, air, RT	29	45
3	$Cu(OAc)_2$, K_3PO_4, air, RT	31	41
4	$Cu(OAc)_2$, no base, air, RT	33	43
5	K_2CO_3, air, RT	17	n/d[c]
6	$Cu(OAc)_2$, K_2CO_3, no air, RT	46	57
7	$Cu(OAc)_2$, no base, no air, RT	69	57
8[d]	$Cu(OAc)_2$, no base, no air, 15 °C	63	61

[a] Yield based on ^{1}H NMR. [b] The ee was determined by chiral GC chromatography (Chiraldex G-TA). [c] None detected. [d] The reaction was carried out at 5 °C.

TABLE 2. Chiral Ligands for Enantioselective Heck-Type Reaction



entry	ligand	yield, %[a]	ee, %[b]
1	*(R)*-BINAP	69	57
2	*(R)*-3,5-xyl-BINAP	36	28
3	*(R)*-MeOBiphep	63	83
4	*(S,S)*-chiraphos	trace	n/d[c]
5	*(R,R)*-DIOP	trace	n/d[c]
6	2,2′-Bis[(*4S*)-4-benzyl-2-oxazoline]	trace	n/d[c]

[a] Yield based on ^{1}H NMR. [b] The ee was determined by chiral GC-chromatography (Chiraldex G-TA). [c] None detected.

because of the enhanced ligand destruction. However, the use of inorganic bases did not affect the enantioselectivity but only affected the efficacy of the reaction (entry **6** vs **7**, Table 1). It is possible that excessive acetate ions can efficiently facilitate the initial transmetallation step.[18] Thus, strong basic and airfree conditions were beneficial in terms of chemical and optical yields (entry **7**, Table 1). Further, a very slight improvement can be achieved by performing the reaction at a lower temperature; the desired product was obtained in 63% yield and 61% enantiomeric excess (ee, entry **8**, Table 1).

Other chiral ligands were examined as well (Table 2). It is noteworthy that only the use of biphenyl-based diphosphines was advantageous (entries **1**−**3**, Table 2). The best result was obtained with commercially available (*R*)-MeO(biphenylphosphine) (biphenylphosphine = Biphep), which showed a superior enantioselectivity without a notable difference in chemical yield. Nonoxidizable nitrogen-based ligands such as oxazolines (entry **6**, Table 2) and flexible diphosphines (DIOP and Chiraphos) did not work well under our reaction conditions.

The scope and limitations of the suggested transformation were studied at this point. The results of the study are tabulated in Table 3. All of the reactions were performed using both (*R*)-BINAP and (*R*)-MeOBiphep/$Pd(OAc)_2$ catalysts.

In general, we found that the reaction is highly sensitive to the steric properties of the starting materials and that high ee may be achieved only when para- or meta- substituted arylboronic acids are used (with one exception). At the same time, the electronic nature of the substituent does not appear to affect the reaction outcome. Thus, both electron-rich (entries **1**, **7**, and **8**, Table 3) and electron-poor (entries **3**−**5** and **10**, Table 3) starting materials result in the formation of enantioenriched 2-aryl-2,3-dihydrofurans in comparable yields and with 63−85% ee. In all of these cases, (*R*)-MeOBiphep demonstrates a clear superiority over the (*R*)-BINAP ligand (42−57% ee for the last).

Unfortunately, enantioselectivity drops significantly when an ortho substituent is present. For instance, *o*-tolylboronic and 1-naphthylboronic acids led to the formation of essentially racemic products in the presence of (*R*)-MeOBiphep. Remarkably, the previously less efficient (*R*)-BINAP was slightly superior in these cases (entries **2** and **9**, Table 3). However, the reaction of 2-chlorophenylboronic acid (entry **6**, Table 3) was again enantioselective, but it demonstrated an inconsiderable superiority of BINAP for ortho-substituted starting materials (86 vs 82%). The last result appears to indicate that electronic factors may also play a role in some cases.

It is not yet clear if relatively high enantioselectivities under our reaction conditions are achieved because of the efficient enantiodifferentiation at the migratory-insertion step or because of a possible kinetic resolution that may take place during the

SCHEME 3. Nucleophile-Mediated Pd(II)-Catalyzed Pathway (blue) vs Nucleophile-Mediated Pd(0)-Catalyzed Pathway (red) in the Asymmetric MH-Type Reaction

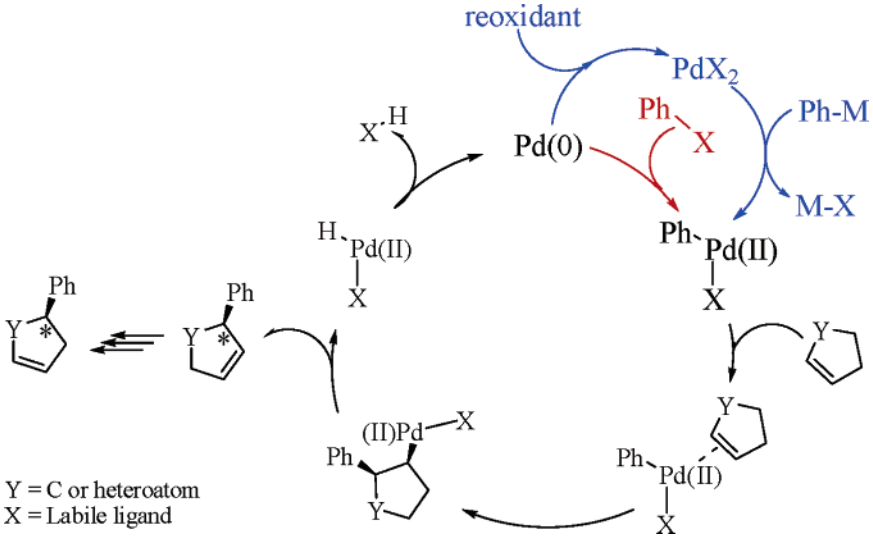
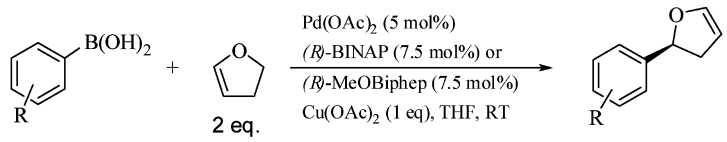
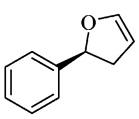
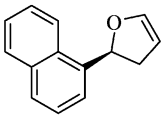
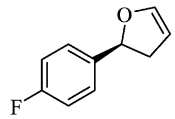
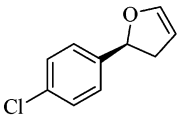
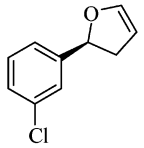
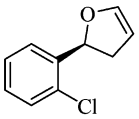
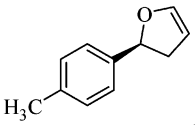
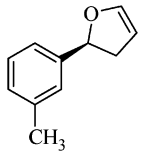
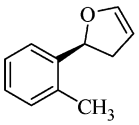
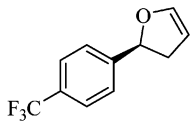


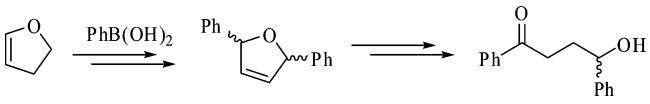
TABLE 3. Scope of the Enantioselective Heck-Type Reaction



Product			
(*R*)-BINAP (*R*)-MeOBiphep	**1-(*S*)a:** 71%,[a] 57% ee[b] **1-(*S*)b:** 67%,[a] 82% ee[b]	**2-(*S*)a:** 78%,[a] 21% ee[b] **2-(*S*)b:** 74%,[a] 4% ee[b]	**3-(*S*)a:** 47%,[a] 42% ee[b] **3-(*S*)b:** 46%,[a] 75% ee[b]
Product			
(*R*)-BINAP (*R*)-MeOBiphep	**4-(*S*)a:** 42%,[a] 48% ee[c] **4-(*S*)b:** 31%,[a] 77% ee[c]	**5-(*S*)a:** 51%,[a] 54% ee[c] **5-(*S*)b:** 51%,[a] 85% ee[c]	**6-(*S*)a:** 33%,[a] 86% ee[b] **6-(*S*)b:** 38%,[a] 82% ee[b]
Product			
(*R*)-BINAP (*R*)-MeOBiphep	**7-(*S*)a:** 51%,[a] 43% ee[b] **7-(*S*)b:** 48%,[a] 63% ee[b]	**8-(*S*)a:** 42%,[a] 60% ee[b] **8-(*S*)b:** 47%,[a] 76% ee[b]	**9-(*S*)a:** 35%,[a] 17% ee[b] **9-(*S*)b:** 36%,[a] <1% ee[b]
Product			
(*R*)-BINAP (*R*)-MeOBiphep	**10-(*S*)a:** 32%,[a] 56% ee[c] **10-(*S*)b:** 37%,[a] 78% ee[c]		

[a] Isolated yield (average of two runs). [b] The ee was determined by HPLC using a Chiralpack AD column. [c] The ee was determined by ^{1}H NMR using (+)-Pr(hfc)$_3$ as a reagent.

SCHEME 4



isomerization of the kinetic 2-phenyl-2,5-dihydrofuran into the thermodynamic 2-phenyl-2,3-dihydrofuran (Scheme 3).[3b] On the basis of the fact that we do not observe the accumulation of the kinetic product at any stage of the reaction, we can speculate that the isomerization is fast and, therefore, has little effect if any on enantioselectivity. However, a deeper insight into the mechanism of the enantioselection process might be obtained after detailed kinetic studies.

In conclusion, we demonstrated for the first time that the Mizoroki−Heck type reaction of arylboronic acids with isomerizable olefins can be performed in a highly enantio- and regioselective fashion. Further investigation of this reaction with other olefins and attempts to improve the chemical yield and to possibly apply the method to the synthesis of more complex molecules are in progress.

Experimental Section

Representative Procedure for the Enantioselective Organoboron-Mediated Heck-Type Reaction. Both (*R*)-MeOBiphep (29 mg, 0.05 mmol) and Cu(OAc)$_2$ (120 mg, 0.66 mmol) were added to a solution of Pd(OAc)$_2$ (7.4 mg, 0.033 mmol) in a single-use screw-capped tube that was equipped with a stir bar. Air was replaced with 99.999% N_2 by means of three evacuation/refill cycles. A solution of 2,3-DHF (100 μL, 1.32 mmol) in THF (1 mL) was added to the mixture, and the blue suspension was stirred for 20 min. Phenylboronic acid (80 mg, 0.66 mmol) in 3 mL of

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THF was injected, and the reaction mixture was allowed to stir for 12 h at room temperature. Following the end of the mixing time, the mixture was diluted with EtOAc, filtered through a pad of Celite, washed with water and brine, and dried with $MgSO_4$. The solution was evaporated under reduced pressure, and the residue was purified by column chromatography to give (*S*)-2,3-dihydro-2-phenylfuran (64 mg, 67%). HPLC (Chiralpack AD, hexane: *i*-PrOH 99.9:0.1, 1.0 mL/min): (*S*)-isomer $t_R = 9.06$ min, (*R*)-isomer $t_R = 7.8$ min; 82% ee; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.41-7.29$ (5H, m), 6.51−6.48 (1H, m), 5.53 (1H, dd, $J = 10.7$, 8.4 Hz), 5.01−4.98 (1H, m), 3.17−3.06 (1H, m), 2.69−2.60 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.3, 143.0, 128,5, 127.6, 125.6, 99.0, 82.3, 37.8; MS (70 eV, EL) m/z: 145 [M^+], 117, 115, 91.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra and enantiomeric purity determination for all compounds listed in Table 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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