C–H Functionalization

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Enantioselective Palladium(II) Phosphate Catalyzed Three-Component Reactions of Pyrrole, Diazoesters, and Imines**

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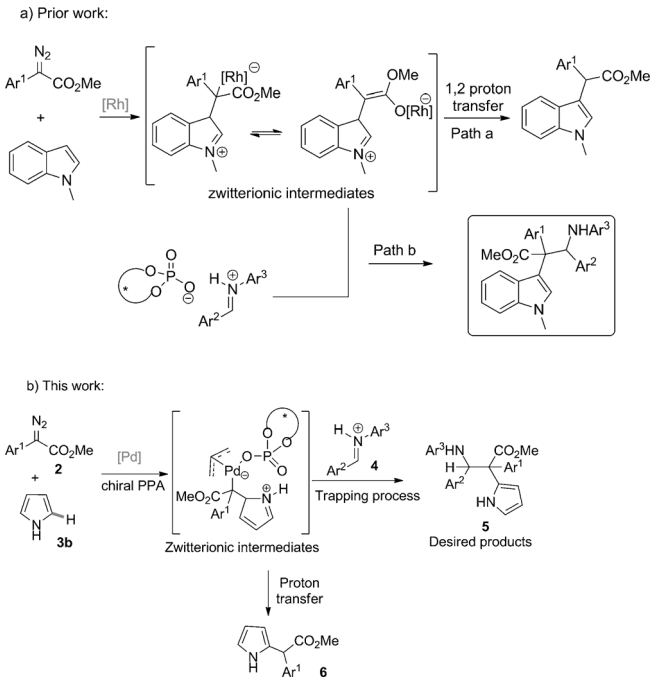
Transition-metal-catalyzed carbene transformations are one of the most powerful reactions in organic chemistry.[1] Transition-metal catalysts have played a crucial role in modulating the reactivity for diazo decomposition as well as the reactivity of the resulting metal carbenoid intermediates.[2] Dirhodium and copper complexes have been reported to be efficient catalysts for diazo decomposition reactions, including cyclopropanation,[3] C–H insertion,[4] and ylide formation.[5] Other transition-metal catalysts, such as silver[6] or gold[7] catalysts have been reported in some carbenoid-mediated transformations, thus demonstrating different reactivity compared to that of the rhodium and copper catalysts. Palladium complexes have attracted growing interest in carbenoid chemistry.[8] For example, Wang and co-workers have made significant contributions to palladium-catalyzed cross-coupling reactions involving diazo decomposition.[8f–h] Despite ongoing progress, to the best of our knowledge, highly enantioselective palladium-carbenoid-mediated reactions have not yet been reported.[9]

Pyrroles are abundant in natural products and pharmaceutical agents[10] and are valuable synthons in organic synthesis.[11] Direct C–H functionalization of unprotected pyrrole is considered to be the most convenient approach to obtain pyrrole derivatives. However, compared to the functionalization of indoles, such an approach with pyrrole is rather difficult owing to its instability under acidic reaction conditions and the tendency of difunctionalization at both the 2- and 5-positions.[12] In addition, stereoselective control of pyrrole functionalization is also challenging because of weak steric interactions with chiral catalysts resulting from its smaller molecular size. So far, only a few successful examples of enantioselective Friedel–Crafts reactions of pyrroles have been reported.[13] Except for one racemic example of ruthenium-catalyzed functionalization of unprotected pyrroles from diazo compounds,[14] there is no report regarding an enantioselective C–H functionalization of an unprotected pyrrole through metal carbenoids, and it is likely due to the lack of suitable and compatible catalytic systems. We report herein an effective catalytic system, palladium(II) with chiral Brønsted acids, to catalyze an enantioselective three-component reaction of unprotected pyrroles, diazoesters, and imines. In this reaction, highly enantioselective C–H functionalization of an unprotected pyrrole is realized, through palladium carbenoid activation, to produce pyrrole derivatives bearing two stereogenic centers in a diastereoselectively tuneable fashion.

Recently, our group reported rhodium-catalyzed trapping of a zwitterionic intermediate for C–H functionalization of indole, thus affording functionalized indole derivatives with excellent chemo-, diastereo-, and enantioselectivity (Scheme 1 a).[15] We wished to extend this novel trapping process to include pyrrole, and envisioned the use of imines to trap the proposed zwitterionic intermediates derived from pyrrole and diazo compounds (Scheme 1 b).



Scheme 1. Trapping of zwitterionic intermediates with imines. PPA = phosphoric acid.

In our initial investigation of dirhodium or dirhodium/phosphoric acid-catalyzed three-component reactions with *N*-methyl pyrrole, we were disappointed to find that attempts to trap the proposed zwitterionic intermediates from *N*-methyl pyrrole with imines were unsuccessful (see Table S1 in the Supporting Information and Table 1, entry 1). Under these

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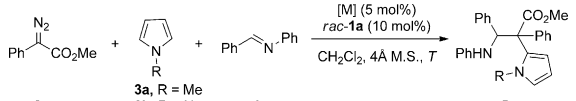
Table 1: Catalyst screening for the three-component reaction of pyrrole, methyl phenyldiazoacetate, and **4a**.[a]



2a **4a** **5a**

Entry	3	[M]	T [°C]	5a Yield [%][b]	d.r.[c] (syn/anti)
1	**3a**	$[Rh_2(OAc)_4]$	25	–[d]	–
2	**3b**	$[Rh_2(OAc)_4]$	25	trace	–
3	**3a**	$[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$	25	trace[d]	–
4	**3b**	$[Pd_2(dba)_3]\cdot CHCl_3$	25	5	–
5	**3b**	$[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$	25	12	–
6	**3b**	$[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$	0	48	85:15
7[e]	**3b**	$[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$	0	65	86:14
8[f]	**3b**	$[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$	0	trace	–
9[g]	**3b**	–	0	n.r.	–

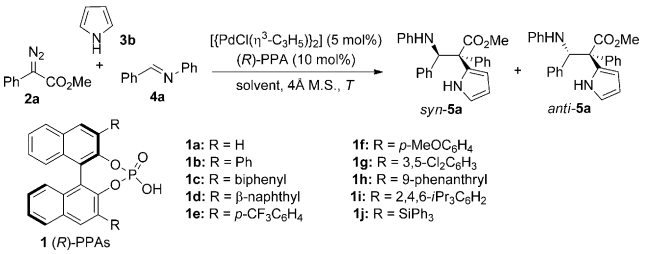
[a] General reaction conditions: [M]:*rac*-**1a**/**2a**/**3a**/**4a** = 0.05:0.1:2:2:1. A solution of **2a** in CH_2Cl_2 was added to a suspension of metal catalyst, *rac*-**1a**, **3**, **4a** and 4 Å M.S. in CH_2Cl_2 over 1 h by a syringe pump. [b] Yields of isolated products. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] Mainly N–H insertion product. [e] **2a** and **3b** were introduced together to the reaction solution. [f] Run in the absence of *rac*-**1a**. [g] Used only 10 mol% of *rac*-**1a** as catalyst. dba = dibenzylideneacetone, M.S. = molecular sieves, n.r. = no reaction.

reaction conditions, exclusive formation of the pyrrole C–H insertion product was observed. When unprotected pyrrole was employed as a substrate, the rhodium catalyst was poisoned, thus leading to slow diazo decomposition (Table 1, entry 2). We then decided to explore other transition-metal catalysts to promote the three-component reaction.

A number of transition-metal catalysts including $CuSO_4$, AgOTf, $[Pd(PPh_3)_4]$, $[Pd_2(dba)_3]\cdot CHCl_3$, $Pd(OAc)_2$, $[PdCl_2(PPh_3)_2]$, and $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$ were initially investigated in the three-component reaction of *N*-methyl pyrrole (**3a**), methyl phenyldiazoacetate (**2a**), and the imine **4a**. Racemic phosphoric acid (PPA; *rac*-**1a**; 10 mol%) was used as a cocatalyst to activate the imine substrate.[16] It was found that $Pd(OAc)_2$ and $[Pd(PPh_3)_4]$ failed to decompose **2a**. $CuSO_4$, AgOTf, and $[Pd_2(dba)_3]\cdot CHCl_3$ decomposed **2a** slowly, and gave trace amounts of the C–H insertion product (see Table S1). It was intriguing that $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$ decomposed **2a** rapidly, but only afforded the C–H insertion product (Table 1, entry 3). When the unprotected pyrrole **3b** was employed as a substrate instead of **3a**, $CuSO_4$, AgOTf, $[Pd(PPh_3)_4]$, $Pd(OAc)_2$, and $[PdCl_2(PPh_3)_2]$ all failed to decompose **2a** (Table S1). $[Pd_2(dba)_3]\cdot CHCl_3$ was effective, but only gave the desired three-component reaction product **5a** in 5% yield (Table 1, entry 4). To our delight, in the presence of 5 mol% $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$ and at 0 °C the desired three-component product **5a** was obtained in 48% yield with 85:15 d.r. (Table 1, entry 6). Products derived from the addition of **3b** to **4a** were observed. To minimize this side reaction, a solution of **3b** and **2a** were introduced to the CH_2Cl_2 slurry of **4a** and the catalysts. This addition sequence helped to suppress the side reaction, and enhanced the product yield to 65% (Table 1, entry 7). Control reactions with either PPA or $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$ as the catalyst showed the necessity of both $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$ and PPA for the success of the reaction (Table 1, entries 8 and 9). Pioneering work by List and co-authors reported a synergistic catalytic system of palladium complexes and chiral phosphoric acids in enantioselective allylic alkylation reactions,[17a] and similar catalytic systems were reported in other enantioselective allylic alkylation reations,[17b–d] as well as transformations involving a proposed π-allylpalladium intermediate.[17e] To the best of our knowledge, synergistic catalytic systems of palladium complexes and chiral phosphoric acids has never been employed in palladium-carbenoid-mediated chemistry.

Encouraged by the initial result, a series of 3,3′-substituted chiral binol PPAs[16d–e] were evaluated (Table 2, entries 2–10).

Table 2: Optimization of reaction conditions for the enantioselective three-component reaction of **2a**, **3b**, and **4a**.[a]



Entry	Solvent	T [°C]	(R)-PPA	Yield [%][b]	d.r.[c] (syn/anti)	ee [%][d]
1	CH_2Cl_2	0	**1a**	56	58:42	6
2	CH_2Cl_2	0	**1b**	40	44:56	−40
3	CH_2Cl_2	0	**1c**	32	30:70	29
4	CH_2Cl_2	0	**1d**	53	40:60	−46
5	CH_2Cl_2	0	**1e**	40	26:74	62
6	CH_2Cl_2	0	**1f**	50	49:51	17
7	CH_2Cl_2	0	**1g**	55	23:77	8
8	CH_2Cl_2	0	**1h**	40	19:81	52
9	CH_2Cl_2	0	**1i**	62	80:20	91
10	CH_2Cl_2	0	**1j**	32	32:68	89
11	THF	0	**1i**	51	80:20	97
12	THF	−20	**1j**	33	< 5:95	99
13[e]	THF	−20	**1j**	54	5:95	98
14[e]	THF	0	**1i**	53	80:20	96

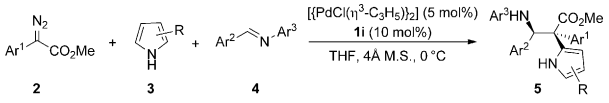
[a] $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$/**1**/**2a**/**3b**/**4a** = 0.05:0.1:2:2:1. [b] Yields of isolated products. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis using a chiral stationary phase. Value is that of the major isomer. [e] In the presence of 5 mol% of L-tartaric acid. THF = tetrahydrofuran.

When the chiral TRIP-PPA **1i** was used an *ee* value of 91% was achieved with an 80:20 d.r. favoring the *syn* diastereomer (Table 2, entry 9). Another extremely bulky PPA (**1j**) afforded **5a** with a d.r. of 32:68 favoring the *anti* diastereomer in 89% *ee* (Table 2, entry 10). To obtain the *syn*-diastereomer, **1i** was employed, and the solvent effect was investigated (see Table S2). THF was found to be the best solvent to give **5a** with an 80:20 d.r. and 97% *ee* for the major *syn* diastereomer (Table 2, entry 11). In contrast, to obtain the *anti* diastereomer, screening solvents and temperature were carried out (Table S2). THF was found to improve the d.r. to less than 5:95 with a 99% *ee*, but the yield was still low (Table 2,

entry 12). With L-tartaric acid as an acidic additive (see Table S3),[18] the product yield increased to 54% yield while maintaining the high stereoselective control (Table 2, entry 13). In the absence of a chiral PPA, the reaction in the presence of 5 mol% L-tartaric acid and $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$ resulted in negligible enantioselectivity (<4% *ee*) in 45% yield with an 86:14 d.r. favoring the *syn* diastereomer (Table S3), thus indicating the critical role of the chiral PPA to control the reaction selectivity. In addition, adding 5 mol% L-tartaric acid to the *syn*-selective reaction with **1i** led to subtle change in terms of chemical yield and reaction selectivity (Table 2, entry 14 versus 11).

Under the optimized reaction conditions, various aromatic imines and diazoesters were evaluated with **1i** to make *syn*-**5**, and the results are summarized in Table 3. Except for

Table 3: Substrate scope of *syn*-selective enantioselective three-component reaction of **2**, **3**, and **4a**.[a]



2 3 4 5

2a: Ar^1 = Ph; **2b**: Ar^1= *p*-BrC_6H_4; **2c**: Ar^1= *p*-ClC_6H_4;
2d: Ar^1 = *p*-Tol; **2e**: Ar^1 = *p*-$MeOC_6H_4$; **2f**: Ar^1 = *m*-$MeOC_6H_4$

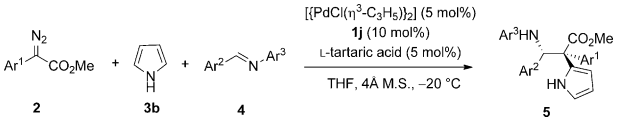
3b: R = H; **3c**: R = 2-ethyl; **3d**: R = 2,4-dimethyl

Entry	**2**/**3**	**4**: Ar^2, Ar^3	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**2a**/**3b**	**4a**: Ph, Ph	**5a**: 51	80:20	97[e]
2	**2a**/**3b**	**4b**: *p*-$MeOC_6H_4$, Ph	**5b**: 58	89:11	99
3	**2a**/**3b**	**4c**: *m*-$MeOC_6H_4$, Ph	**5c**: 53	87:13	97
4	**2a**/**3b**	**4d**: *p*-$CF_3C_6H_4$, Ph	**5d**: 42	74:26	58
5	**2a**/**3b**	**4e**: *p*-ClC_6H_4, Ph	**5e**: 53	78:22	94
6	**2a**/**3b**	**4f**: *m*-ClC_6H_4,Ph	**5f**: 55	88:12	82
7	**2a**/**3b**	**4g**: *p*-BrC_6H_4, Ph	**5g**: 41	78:22	93
8	**2a**/**3b**	**4h**: Ph, *m*-BrC_6H_4	**5h**: 56	89:11	90
9	**2a**/**3b**	**4i**: Ph, *p*-ClC_6H_4	**5i**: 49	62:38	91
10	**2a**/**3b**	**4j**: *p*-BrC_6H_4, *p*-Tol	**5j**: 60	86:14	96[f]
11	**2a**/**3b**	**4k**: *p*-Tol, *p*-BrC_6H_4	**5k**: 61	72:28	97
12	**2a**/**3b**	**4l**: 2-thienyl,*p*-BrC_6H_4	**5l**: 73	95:5	96
13	**2a**/**3b**	**4m**: 2-furyl, *p*-BrC_6H_4	**5m**: 69	95:5	81
14	**2b**/**3b**	**4g**	**5n**: 52	86:14	93[g]
15	**2c**/**3b**	**4g**	**5o**: 55	87:13	94
16	**2d**/**3b**	**4g**	**5p**: 63	86:14	94
17	**2e**/**3b**	**4g**	**5q**: 48	86:14	86
18	**2f**/**3b**	**4g**	**5r**: 50	82:18	94
19	**2a**/**3c**	**4g**	**5s**: 58	89:11	96
20	**2a**/**3d**	**4g**	trace	–	–

[a] $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$/**1i**/**2**/**3**/**4** = 0.05:0.1:2:2:1. [b] Yields of isolated products. [c] *syn*/*anti*, determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis using a chiral stationary phase. Value is that of the *syn* isomers. [e] 84% *ee* for *anti* isomer. [f] 86% *ee* for *anti* isomer. [g] 77% *ee* for *anti* isomer.

the electron-withdrawing imine **4d** (**4**, Ar^2 = *p*-$CF_3C_6H_4$), which resulted in decreased stereoselective control (74:26 d.r., 58% *ee*), other substrates including some aromatic heterocyclic imines (entries 12 and 13) were well tolerated and demonstrated high to excellent stereoselective control (entries 1–18). The reaction with substituted pyrroles was explored, and 2-ethyl pyrrole (**3c**) gave the corresponding product **5s** in 58% yield with an 89:11 d.r. and 96% *ee*

Table 4: Selected examples of *anti*-selective enantioselective three-component reactions of **2**, **3b**, and **4**.[a]



2 3b 4 5

Entry	**2**	**4**	Yield [%][b]	d.r.[c] (*syn*/*anti*)	*ee* [%][d]
1	**2a**	**4a**	**5a**: 54	5:95	98 (12[e])
2	**2a**	**4i**	**5i**: 42	10:90	98 (25[e])
3	**2a**	**4j**	**5j**: 55	9:91	98 (40[e])
4	**2a**	**4k**	**5k**: 63	4:96	98
5	**2b**	**4g**	**5n**: 48	11:89	96 (9[e])
6	**2d**	**4g**	**5p**: 44	7:93	>99

[a] $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$/**1j**/L-tartaric acid/ **2**/**3b**/**4** = 0.05:0.1:0.05:2:2:1. [b] Yields of isolated products. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis using a chiral stationary phase. Value is that for the *anti* isomer. [e] The *ee* values for the *syn* isomers.

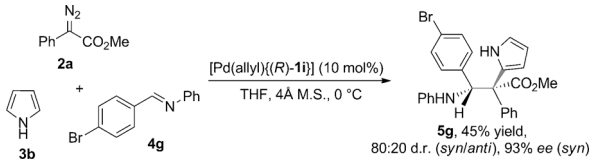
(entry 19). However, 2,4-dimethyl pyrrole gave only trace amounts of the desired coupling product (entry 20).

Representative results with the use of **1j** under the optimal reaction conditions to afford *anti*-**5** are summarized in Table 4. All the reactions gave high diastereoselectivity (11:89–4:96 d.r.) and excellent enantioselectivity (96–99% *ee*) for the major isomers.

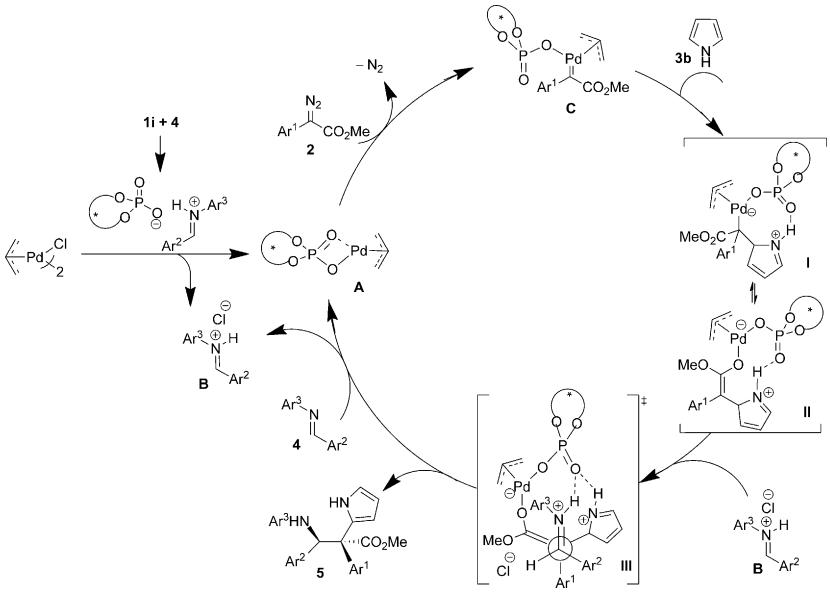
The absolute configuration of *syn*-**5n** and *anti*-**5k** were unambiguously determined to be 2*R*,3*R* and 2*R*,3*S* (see the Supporting Information), respectively, by single-crystal X-ray diffraction analysis. The stereochemistry of other products within each series was tentatively assigned by analogy. These data show that the switch of diastereoselectivity in **5** occurred at the C3-position although the corresponding PPAs (*R*)-**1i** and (*R*)-**1j** have the same absolute configuration.

Control reactions (see Scheme S1 in the Supporting Information) exclude the possibility that the desired product **5a** was formed either from the addition of the C–H insertion product to **4a** or the aziridine ring-opening reactions with pyrrole by a stepwise reaction. In the current three-component reaction, the desired products **5** can only be formed when the three substrates are combined in the presence of the two catalysts. To get insight into structures of active palladium species in the catalytic cycle, the progress of the reaction was monitored by high-resolution mass spectrometry (HRMS) analysis. A palladium/phosphate complex [Pd(allyl){(*R*)-**1i**}] was detected in the crude reaction mixture before and after the reaction, thus indicating that ligand exchange occurred during the reaction. To further prove the catalytic activity of the palladium-phosphate complex, [Pd(allyl){(*R*)-**1i**}] was made and isolated from the reaction of $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$ and the silver salt of (*R*)-**1i**.[19] The purified [Pd(allyl){(*R*)-**1i**}] was employed alone in the three-component reaction of **2a**, **3b**, and **4g** in the absence of additional amounts of the PPA, and the desired product **5g** was obtained in comparable yield with essentially the same selectivity (Scheme 2 versus Table 3, entry 7).[20]

Although the exact reaction mechanism warrants further detailed study, a plausible reaction pathway is proposed in



Scheme 2. Three-component reaction catalyzed by a palladium/phosphate complex.



Scheme 3. Plausible reaction mechanism.

Scheme 3. Ligand exchange generates the chiral palladium/phosphate complex **A** and iminium **B**. Diazo decomposition of the aryl diazoacetates **2** catalyzed by the palladium(II) catalyst **A** forms the palladium carbenoid **C** by extrusion of dinitrogen. Subsequently, nucleophilic attack of the pyrrole **3b** onto **C** affords the proposed zwitterionic intermediates (**I** or enolate **II**[21]), which are trapped by **B** through the proposed transition-state **III**. Then proton transfer occurs to produce **5** and regenerate **A**. In the zwitterionic intermediates, an intramolecular hydrogen bond between the phosphoryl oxygen atom and the pyrrole N–H is proposed to be essential. Previous studies on the functionalization of indole[22a] and pyrrole,[13d,22b] as well as the failure with *N*-methyl pyrrole in the current three-component reaction support the necessity and significance of a free pyrrole NH functionality.

In conclusion, we have discovered a chiral palladium(II) phosphate catalyzed stereodivergent asymmetric three-component reaction of unprotected pyrroles, diazoesters, and imines. This catalytic mode is different from that of dirhodium/chiral phosphoric acid cocatalysis. The reaction can produce all four possible stereoisomers of chiral pyrrole derivatives in moderate yield with high control of diastereo- and enantioselectivity. The palladium/chiral PPA catalytic system was first used in the zwitterionic intermediate trapping process. This study also represents the first highly enantioselective reaction in palladium-carbenoid-mediated transformations. Chiral palladium(II) phosphate systems should have wide application in other palladium-catalyzed enantioselective transformations.

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