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Pyridine Ligands as Promoters in $Pd^{II/0}$-Catalyzed C–H Olefination Reactions

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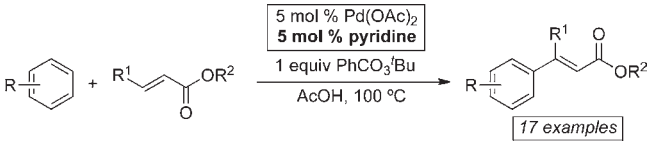
ABSTRACT



Commercially available pyridine ligands can significantly enhance the rate, yield, substrate scope, and site selectivity of arene C–H olefination (Fujiwara–Moritani) reactions. The use of a 1:1 ratio of Pd/pyridine proved critical to maximize reaction rates and yields.

The Pd-mediated C–H olefination of benzene was first reported in 1967 by Fujiwara and Moritani.[1] Since this initial publication, numerous catalytic versions of this transformation have been developed. The vast majority of these catalytic protocols proceed under "ligandless" conditions (with Pd^{II} salts such as $Pd(OAc)_2$ as catalysts) and use oxidants such as peroxides, peroxyesters, dioxygen, polyoxometalates, Cu^{II}, or Ag^{I} to achieve catalytic turnover.[2] A variety of aromatic compounds can be employed as arene substrates,[2] and high levels of site selectivity are possible using substrates that contain directing groups.[2−5]

Despite the above illustrated advances, several significant problems remain unsolved.[6,7] First, the substrate scope for simple aromatics that do not contain directing groups remains primarily limited to electron-rich and -neutral derivatives; in general, electron-deficient arenes exhibit sluggish reactivity.[7e,h] Second, most substituted aromatic substrates react to afford mixtures of isomeric products.[6,7e] While there has been some success in the use of solvent and/or oxidant to control site selectivity in the C–H olefination of heterocycles (e.g., indole, pyrrole),[8] catalyst controlled selectivity remains challenging for most other classes of arene substrates. Third, the vast majority of catalytic Fujiwara–Moritani (F–M) reactions require

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(2) (a) Moritani, I.; Fujiwara, Y. *Synthesis* **1973**, 524. (b) Karimi, B.; Behzadnia, H.; Elhamifar, D.; Akhavan, P. F.; Esfahani, F. K.; Zamani, A. *Synthesis* **2010**, 1399. (c) Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170.

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(4) For sp^3-C–H olefination, see: (a) Zhang, Y. H.; Shi, B. F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072. (b) Stowers, K. J.; Fortner, K. C.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 6541. (c) Wang, C.; Ge, H. *Synthesis* **2011**, 2590.

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(7) (a) Fujiwara, Y.; Moritani, I.; Matsuda, M.; Teranishi, S. *Tetrahedron Lett.* **1968**, 3863. (b) Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166. (c) Shue, R. S. *J. Chem. Soc. D* **1971**, 1510. (d) Shue, R. S. *J. Catal.* **1972**, *26*, 112. (e) Fujiwara, Y.; Asano, R.; Moritani, I.; Teranishi, S. *J. Org. Chem.* **1976**, *41*, 1681. (f) Zhang, X.; Fan, S.; He, C. Y.; Wan, X.; Min, Q. Q.; Yang, J.; Jiang, Z. X. *J. Am. Chem. Soc.* **2010**, *132*, 4506. (g) Li, Z.; Zhang, Y.; Liu, Z. Q. *Org. Lett.* **2012**, *14*, 74. (h) Zhang, Y.; Li, Z.; Liu, Z. Q. *Org. Lett.* **2012**, *14*, 226.

(8) (a) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125. (b) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528. (c) Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3004. (d) Potavathri, S.; Dumas, A. S.; Dwight, T. A.; Naumiec, G. R.; Hammann, J. M.; DeBoef, B. *Tetrahedron Lett.* **2008**, *49*, 4050.

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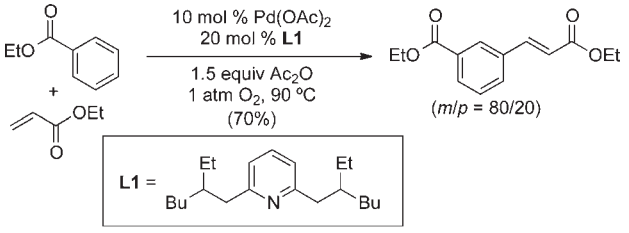
α,β-unsaturated olefins as the alkene substrate. While some examples with styrene and ethylene have been reported,[7] the use of α-olefins remains problematic in most cases.[7f−h]

An attractive strategy to address all three of these challenges would be to develop supporting ligands that enhance the reactivity and selectivity of the Pd^{II} catalyst,[9] as has been demonstrated in related biaryl coupling reactions.[10] Recently Yu et al. demonstrated promising preliminary success toward this goal. As shown in Scheme 1, the use of 2,6-dialkylpyridine ligand **L1** enabled the coupling of several electron-deficient aromatic substrates with α,β-unsaturated olefins using O_2 as the terminal oxidant.[11] Notably, the monoligand complex (**L1**)$Pd(OAc)_2$ was proposed as the catalytically active species in this system on the basis of NMR analysis.

While the results in Scheme 1 are exciting, much room for improvement remains. For example, high catalyst loadings of $Pd(OAc)_2$/**L1** (10 mol %/20 mol %) were required, site selectivity was modest for most substrates, and **L1** is not commercially available. Notably, Yu reported that the use of commercial ligands such as pyridine and lutidine under his optimized aerobic conditions (1:2 ratio of Pd/monodentate ligand) completely inhibited catalytic turnover.

Scheme 1. $Pd(OAc)_2$/**L1**-Catalyzed C−H Olefination Reactions with O_2 as the Terminal Oxidant[11a]



A recent report from our group suggested that it might be possible to utilize much simpler pyridine ligands than **L1** to enhance reactivity and modulate site selectivity in Pd-catalyzed F−M reactions.[12] Our studies showed that the use of a 1:1 ratio of $Pd(OAc)_2$/pyridine (pyr) leads to a dramatic acceleration of the $Pd^{II/IV}$-catalyzed C−H acetoxylation of benzene derivatives. The observed effect was proposed to result from an increased rate of C−H activation at the coordinatively unsaturated catalyst $(pyr)Pd(OAc)_2$.[12] Since a similar arene C−H activation step is proposed in the F−M reaction, we hypothesized that the use of an equimolar ratio

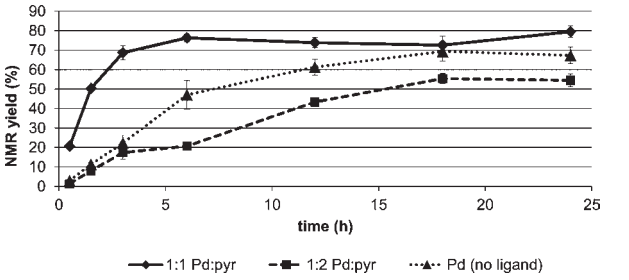


Figure 1. Formation of **1** over 24 h as a function of catalyst [1:1 $Pd(OAc)_2$/py (◆),1:2 $Pd(OAc)_2$/py(■), $Pd(OAc)_2$ (▲)].

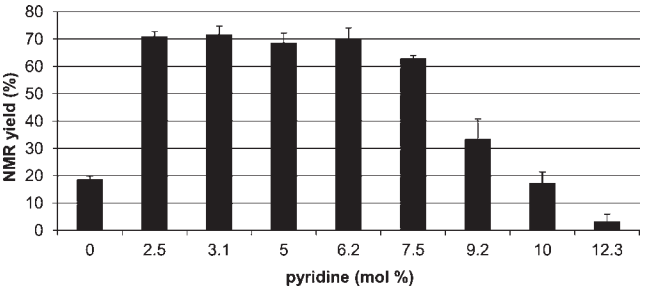


Figure 2. Yield of **1** after 3 h as a function of mol % pyridine.

of $Pd(OAc)_2$ to pyridine would have an analogous accelerating effect on this transformation.

Our initial studies to test this hypothesis focused on the $Pd(OAc)_2$/pyridine-catalyzed C−H olefination of benzene with ethyl cinnamate to afford ethyl 3,3-diphenylacrylate (**1**). The reaction was first examined using 1 atm of O_2 as the oxidant (in analogy to Scheme 1). However, in our hands, these conditions provided irreproducible rates and reaction yields. This might be due to challenges associated with controlling the concentration of O_2 (g) and due to slow oxidation of Pd(0) (which could lead to catalyst decomposition). We were pleased to find that substitution of O_2 with *tert*-butylperoxybenzoate as the terminal oxidant resulted in reproducible rates and yields and enabled us to assess the influence of pyridine on this transformation.[8a,b,9b,9c,13]

The time study shown in Figure 1 revealed that $Pd(OAc)_2$ with no added ligand was a moderately effective catalyst. For example, 5 mol % of $Pd(OAc)_2$ provided complete conversion (and ∼70% yield of **1**) after 18 h at 100 °C. The addition of 2 equiv of pyridine per Pd (10 mol % pyridine) slowed the rate, affording an ∼55% yield of **1** after 18 h. However, the use of a 1:1 ratio of $Pd(OAc)_2$ to pyridine resulted in a 76% yield of **1** after just 6 h at 100 °C.[14]

(9) For intermolecular reactions, see: (a) Mikami, K.; Hatano, M.; Terada, M. *Chem. Lett.* **1999**, 55. For intramolecular reaction, see: (b) Schiffner, J. A.; Machotta, A. B.; Oestreich, M. *Synlett* **2008**, 2271. (c) Schiffner, J. A.; Woste, T. H.; Oestreich, M. *Eur. J. Org. Chem.* **2010**, 174.

(10) For recent examples, see: (a) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (b) Izawa, Y.; Stahl, S. S. *Adv. Synth. Catal.* **2010**, *352*, 3223. (c) Campbell, A. N.; Meyer, E. B.; Stahl, S. S. *Chem. Commun.* **2011**, *47*, 10257.

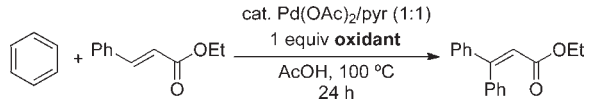
(11) (a) Zhang, Y. H.; Shi, B. F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072. (b) Zhang, S.; Shi, L.; Ding, Y. *J. Am. Chem. Soc.* **2011**, *133*, 20218.

(12) Emmert, M. H.; Cook, A. K.; Xie, Y. J.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 9409.

(13) Tsuji, J.; Nagashima, H. *Tetrahedron* **1984**, *40*, 2699.

(14) Notably, under these conditions, ligand **L1** performed much more poorly than simple pyridine; furthermore, the ratio of **L1**:Pd (1:1 versus 2:1) had minimal influence on the rate or final yield of the reaction (Figures S1 and S3).

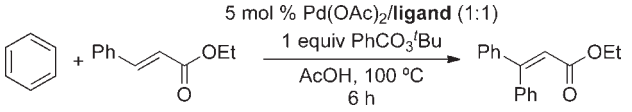
Table 1. Optimization of C−H Olefination Reaction



entry	Pd/pyr (mol %)	oxidant	% yield[a]
1	Pd (5)/pyr (5)	$PhCO_3{}^tBu$	78
2	Pd (2.5)/pyr (2.5)	$PhCO_3{}^tBu$	73
3	Pd(1)/pyr(1)	$PhCO_3{}^tBu$	58
4	Pd (5)/pyr (5)	Benzoquinone	8
5	Pd (5)/pyr (5)	^{t}BuOOH	41
6	Pd (5)/pyr (5)	AgOAc	49
7	Pd (5)/pyr (5)	$K_2S_2O_8$	57

[a] NMR average yields based on 1,3-dinitrobenzene standard. Reported yields represent averages of at least two reactions.

Table 2. Ligand Effects on C−H Olefination



entry	ligand	% yield[a]
1	pyridine	76
2	2-picoline	69
3	4-methoxypyridine	69
4	3-nitropyridine	78
5	acridine	80
6	3,5-dichloropyridine (**L2**)	81
7	**L1**	61

[a] NMR average yields based on 1,3-dinitrobenzene standard. Reported yields represent averages of at least two reactions.

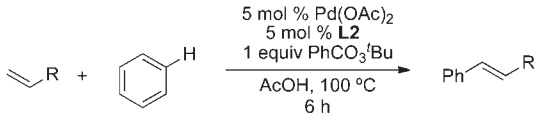
We next conducted a more detailed assessment of the influence of the Pd to pyridine ratio on this reaction by determining reaction yields for various Pd/pyr ratios after 3 h. As shown in Figure 2, significantly higher yields were observed with 2.5−6.2 mol % of pyridine (corresponding to Pd/pyr between 1:0.5 and ~1:1).

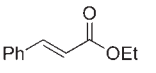
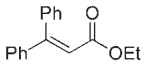
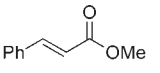
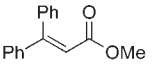
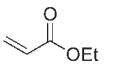
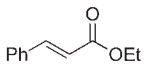
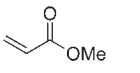
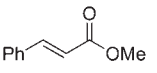
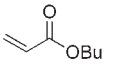
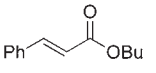
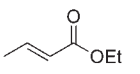
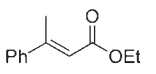
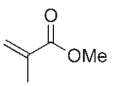
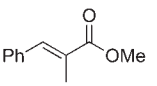
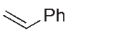
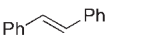
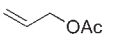
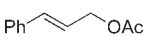
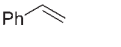
Additional optimization of this transformation is summarized in Table 1. As shown in entries 1−3, the $Pd(OAc)_2$/pyr loading could be lowered to 2.5 mol % without a major drop in reaction yield. Even just 1 mol % of $Pd(OAc)_2$/pyr provided synthetically useful yields of **1**. Other terminal oxidants were effective; most notably, $K_2S_2O_8$ afforded a 57% yield of the C−H olefination product (entry 7). Overall, $PhCO_3{}^tBu$ provided the best results of the oxidants examined.[15]

Other pyridine ligands were also evaluated for this transformation. Many commercially available mono- and disubstituted pyridines afforded comparable results to pyridine (Tables 2 and S8). Furthermore, yields could be improved

(15) For a complete list of oxidants examined, see Table S7.

Table 3. C−H Olefination of Benzene with Different Alkenes



entry	olefin	product	equiv C_6H_6	yield (%)
1			40 equiv 11 equiv	88[a] 76[a]
2			40 equiv 11 equiv	95[b] 75[a]
3			40 equiv 11 equiv	94[b] 62[a]
4			40 equiv 11 equiv	89[b] 64[a]
5			40 equiv 11 equiv	85[b] 65[a]
6			40 equiv	58[a]
7			40 equiv	34[a,c]
8			40 equiv	43[a]
9			40 equiv	57[a,d]
10			40 equiv	33[b,e]

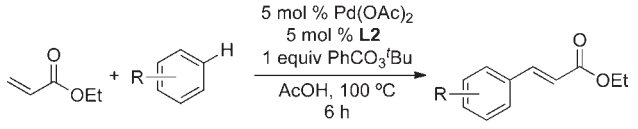
[a] Isolated yield. [b] Yield determined by ^{1}H NMR analysis of crude reaction mixture. [c] Isolated as a mixture with the byproduct phenylated at the α-methyl. [d] Isolated as a mixture with the corresponding diphenylated product. [e] Oxidant used as the limiting reagent with an excess of ethylene.

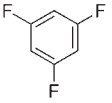
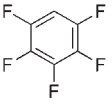
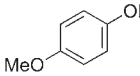
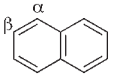
using 3-nitropyridine, acridine, and 3,5-dichloropyridine (Table 2, entries 4−6). Of all the investigated ligands, 3,5-dichloropyridine (**L2**) afforded the highest yield (81%); therefore, **L2** was used in further studies to assess the substrate scope of this transformation. Interestingly, **L1** (entry 7) gave slower rates and lower yields of the product than pyridine (Table 2, entry 1; Figure S3) under our conditions. This is particularly remarkable because **L1** was reported to be uniquely effective for the aerobic reaction in Scheme 1.[11] These results suggest that ligand effects on the reactivity of Pd catalysts in F−M reactions can be highly oxidant-dependent.[16]

A variety of alkenes participate in the $Pd(OAc)_2$/**L2**-catalyzed C−H olefination, with α,β-unsaturated olefins serving as particularly effective substrates. For example, the reactions of benzene (40 equiv) with acrylate derivatives proceeded in 34−95% yield (Table 3, entries 1−7).

(16) Ligand **L1** may be susceptible to benzylic oxidation in the presence of oxidants like $PhCO_3{}^tBu$, which could account for the differences in reactivity with O_2 vs $PhCO_3{}^tBu$ as the terminal oxidant.

Table 4. C−H Olefination of Different Arenes with Ethyl Acrylate



entry	arene	isolated yield (%)	entry	arene	isolated yield (%)
1[a]		73 1/1.2/1.3[b]	6[a]		93
2[a]		69 4.1/1/7.4[b]	7[c]		67
3[a]		69 1/3.0[b]	8[c]		65 1/1.6[b]
4[a]		75	9[c]		42 1/5.6/1.5[b]
5[a]		79 1.1/1[b]	10[c]		32 1/15.8/4.2[b]

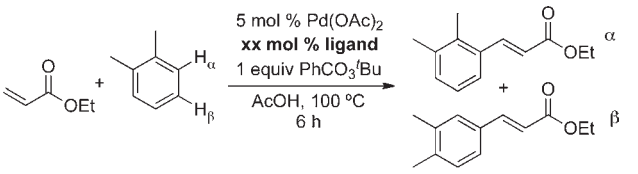
[a] [arene] = 1 M. [b] Product ratios determined from isolated mixtures. Ratio reported as *o*/*m*/*p* or α/*β*. [c] [arene] = 0.28 M.

Moderate yields (62−76%) were obtained even upon lowering the equivalents of benzene from 40 to 11 equiv for many of these substrates. Styrene, allyl acetate, and ethylene (entries 8−10) also afforded olefinated products in moderate yields under these conditions.

As shown in Table 4, many different arene substrates participate in $Pd(OAc)_2$/**L2**-catalyzed C−H olefination with ethyl acrylate. Electron-rich arenes such as toluene, anisole, and *o*-xylenes afforded good yields (69−75%) of mono-olefinated products (entries 1−4). Naphthalene also provided good results, affording a 1:1 ratio of the α and *β* isomeric products in 79% yield (entry 5). Finally, electron-deficient aromatics (which have traditionally proven to be challenging substrates for C−H olefination)[7e,h] reacted in moderate to good yields (32−93%, entries 6−10). Notably, ethyl benzoate and trifluorotoluene preferentially afforded the *meta*-olefinated product, with selectivities very similar to those reported by Yu for related aerobic reactions using ligand **L1** (entries 9−10).[11]

Preliminary results show that the pyridine ligand can influence not only the reaction rate and yield but also the site selectivity of C−H olefination. For example, as shown in Table 5, with *o*-xylene as the substrate the ratio of *β*/α isomeric products changed from 2.8:1 to 4.2:1 upon moving from $Pd(OAc)_2$ to $Pd(OAc)_2$/acridine (1:1) as the catalyst. Furthermore, increasing the Pd/acridine ratio to 1:3 further enhanced the selectivity to 4.7:1. While this selectivity remains modest, the results provide promising support for the viability of catalyst control over site selectivity in these and related C−H functionalization reactions.

Table 5. Ligand Effects on Site Selectivity



entry	ligand (mol %)	% yield[a]	*β*/α
1	none	61	2.8 ± 0.1
2	**L1** (5)	61	2.6 ± 0.1
3	**L2** (5)	81	2.9 ± 0.1
4	acridine (5)	62	4.2 ± 0.5
5	acridine (15)	63	4.7 ± 0.3

[a] Yield and isomer ratio determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture based on 1,3-dinitrobenzene standard. Reported yields represent averages of three reactions.

In conclusion, this report demonstrates that simple pyridine ligands serve as efficient promoters for the $Pd^{II/0}$-catalyzed Fujiwara−Moritani reaction. Ongoing efforts are focused on identifying ligands to further improve both the reactivity and selectivity in these systems.

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Supporting Information Available. Complete experimental details, characterization data for all new compounds, and additional optimization tables. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.