

Palladium-Catalyzed α -Vinylolation of Carbonyl Compounds

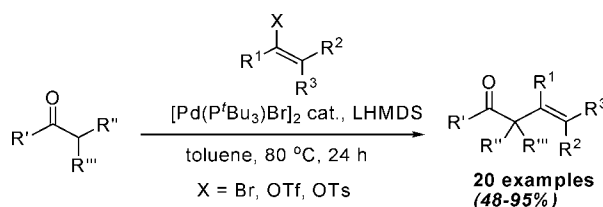
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ABSTRACT



A mild, general, catalytic system for the α -vinylolation of carbonyl compounds has been developed. By employing $[\text{Pd}(\text{P}^t\text{Bu}_3)\text{Br}]_2$ as catalyst and LHMDS as base, vinyl bromides, vinyl triflates, and vinyl tosylates couple with 3-methyloxindole in satisfactory yields. The same catalytic system is extended to the α -vinylolation of ketones and esters.

In 1997, Buchwald,¹ Hartwig,² and Miura³ concurrently reported the palladium-catalyzed α -arylation of ketones that opened a new avenue for simple and useful construction of molecules that were traditionally difficult to synthesize.⁴ In parallel with advancements in transition metal mediated C–C, C–N, C–O, C–S, and C–P bond formations in the past decade, the α -arylation reaction has been expanded to a variety of nucleophilic coupling partners such as ketones,⁵ esters,⁶ amides,⁷ nitriles,⁸ aldehydes,⁹ nitroalkanes,¹⁰ sul-

phones,¹¹ and lactones.¹² In this process, an enolate or a related anion generated under basic conditions undergoes coupling with an aryl halide in the presence of a palladium or nickel catalyst. In the development of these α -arylation reactions, it was found that the ligand plays a critical role in the success of the coupling reaction and a great deal of effort has been placed in tuning the electronic and steric properties of the ligand bound to the transition metal centers. While many reports have appeared detailing substrate scope expansion of the enolate coupling partner, the electrophilic component is generally limited to aryl halides or aryl triflates. Expansion of the electrophilic coupling partner to include olefinic halides and triflates would allow ready access to the corresponding vinyl carbonyl compounds. Buchwald has recently reported an elegant asymmetric α -vinylolation of ketone enolates; however, the substrate scope is limited.¹³ Other examples for this useful transformation are scarce.^{12b} The importance of a general α -vinylolation reaction of enolates stems not only from the frequent appearance of C–C double bonds in natural products and biologically active compounds,

- (1) Paluki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108.
(2) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382.
(3) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1740.
(4) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.
(5) (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473.
(b) Satoh, T.; Kametani, Y.; Terao, Y.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1999**, *40*, 5345. (c) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.
(6) (a) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996. (b) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410. (c) Gaertzen, O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465.
(d) Jørgensen, M.; Lee, S.; Wolkowski, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 12557.
(7) (a) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546. (b) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402.
(8) (a) Satoh, T.; Inoh, J.-I.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239. (b) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330.
(9) Terao, Y.; Fukuoka, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2002**, *43*, 101.
(10) Vogl, E. M.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 106.

- (11) Kashin, A. N.; Mitin, A. V.; Beletskaya, I. P.; Wile, R. *Tetrahedron Lett.* **2002**, *43*, 2539.
(12) (a) Spielvogel, D. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 3500. (b) Liu, X.; Hartwig, J. F. *Org. Lett.* **2003**, *5*, 1915.
(13) Chieffi, A.; Kamikawa, K.; Ahman, A.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897.

but also from the rich and well-studied chemistry of olefins that enables efficient synthesis of complex structures. Therefore the development of α -vinylation reactions is very attractive, as an addition to the related transition metal-catalyzed reactions such as Heck, Suzuki, Negishi, and Stille couplings, where use of vinyl coupling partners has been broadly used in the synthesis of natural products.¹⁴

In conjunction with one of our programs, development of an effective α -vinylation reaction of carbonyl compounds was desirable as a synthetic strategy. Herein, we report our results on the successful α -vinylation of 3-methyloxindole and the related ketones and esters.

Oxindole **1** was selected as the model substrate due to the presence of the structural motif in many biologically important compounds.¹⁵ To our surprise, direct arylation of **1** has not been studied, although indirect synthesis of *N*-methyloxindole has been reported via intramolecular or stepwise intermolecular arylation.¹⁶ To develop a useful α -vinylation reaction, we examined the coupling of **1** with 1-cyclohexenyl triflate **2** under various conditions. Two features of this reaction were notable: (i) Although vinyl triflates are easily prepared from the corresponding ketones,¹⁷ use of vinyl triflates in α -vinylation of enolates has not been reported. (ii) Substrate **1** contains both C and N nucleophiles which may result in the formation of mixed C–C and C–N vinylation products when subjected to the reaction conditions. To the best of our knowledge, there is no literature precedent for α -arylation of an amide with a free N–H bond.

Initially, the model reaction was screened at 80 °C in toluene with either Pd₂(dba)₃/ligand combination or a preformed palladium complex¹⁸ as the catalyst, with lithium hexamethyldisilazane (LHMDS) as base to generate the enolate in situ.

A few sterically hindered and electron-rich mono- and bis-phosphines (Figure 1 and Table 1) were found effective,

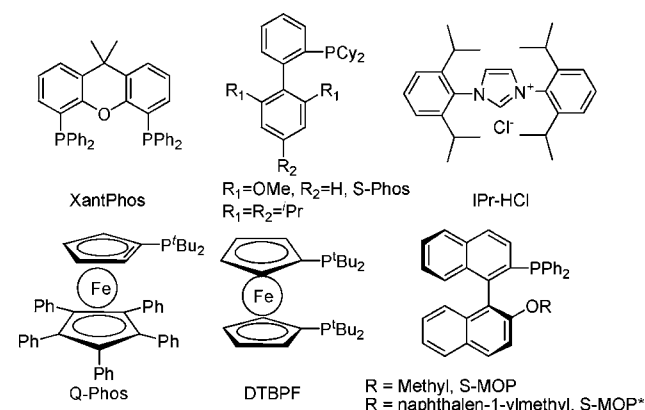


Figure 1. Selected ligand structures.

providing 55–94% yields of the coupled product **3** (Table 1, entries 1, 2, 3, and 7).¹⁹ The reaction catalyzed by the dimeric Pd(I) complex [Pd(P^tBu₃)Br]₂ afforded the highest yield of 94% (Table 1, entry 1). Other ligands that have been

Table 1. Catalyst Evaluation

entry	Pd-source	ligand	yield (%) ^{a,b}
1	[P ^t Bu ₃ PdBr] ₂	n/a	94
2	(PhP ^t Bu ₂) ₂ PdCl ₂	n/a	55
3	(DTBPF) ₂ PdCl ₂	n/a	72
4	Pd ₂ (dba) ₃	XantPhos	<5
5	Pd ₂ (dba) ₃	S-Phos	<5
6	Pd ₂ (dba) ₃	X-Phos	<5
7	Pd ₂ (dba) ₃	Q-Phos	83
8	Pd ₂ (dba) ₃	IPr-HCl	9
9	Pd ₂ (dba) ₃	BINAP	20
10	Pd ₂ (dba) ₃	S-MOP	34
11	Pd ₂ (dba) ₃	S-MOP*	32

^a HPLC assay yield. ^b Reaction conditions: To a mixture of **1** (1.0 equiv), Pd source (5 mol % Pd), and ligand (5–10 mol %) in toluene was added LHMDS (2.5 equiv). The mixture was stirred for 5 min followed by addition of **2** (1.5 equiv). The dark solution was heated to 80 °C for 24 h and analyzed by HPLC.

successfully used in related palladium-catalyzed couplings, including α -arylations, were less effective for the α -vinylation of **1**. Interestingly, no instances of C–N coupling product were observed.²¹

Having identified [Pd(P^tBu₃)Br]₂ as the optimal catalyst, the effects of solvent and base were next examined. With LHMDS as base, reactions in toluene or xylene proceeded smoothly, but those performed in dioxane, THF, DME, or DMF occurred with lower yields. With toluene as solvent, reactions carried out with LHMDS or NaHMDS as a base gave the best yields, while those with Cs₂CO₃, K₂CO₃,

(14) For a review of palladium-catalyzed couplings of vinyl compounds, see: Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; Wiley-VCH: Weinheim, Germany, 1996; pp 565–631.

(15) (a) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2003**, *20*, 216. (b) Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2002**, *19*, 148. (c) Tang, Y.-Q.; Sattler, I.; Thiericke, R.; Grabley, S.; Feng, S.-Z. *Eur. J. Org. Chem.* **2001**, 261. (d) Suzuki, H.; Morita, H.; Shiro, M.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 2489. (e) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353.

(16) Lee, S.; Hartwig, J. *J. Org. Chem.* **2001**, *66*, 3402.

(17) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Synthesis* **2005**, 3229.

(18) The chosen catalysts have been shown successful in other coupling reactions, see: (a) Hamada, T.; Chieffi, A.; Ahman, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261. (b) Guram, A. S.; King, A. O.; Allen, J. G.; Wang, X.; Schenkel, L. B.; Chan, J.; Bunel, E. B.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J.; Reider, P. J. *Org. Lett.* **2006**, *8*, 1787. (c) Vicini, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053. (d) Hama, T.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 4976. (e) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043. (f) Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824.

(19) For experimental/characterization details, see the Supporting Information.

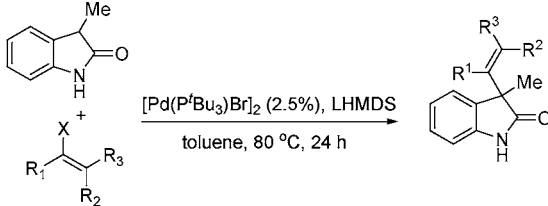
(20) (a) Dura-Vila, V.; Mingos, D. M. P.; Vilar, R.; White, A. J. P.; Williams, D. J. *J. Organomet. Chem.* **2000**, *600*, 198. (b) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746. (c) Commercially available from Johnson Matthey.

(21) For examples of N-vinylation, see: (a) Movassaghi, M.; Ondrus, A. E. *J. Org. Chem.* **2005**, *70*, 8638. (b) Klapars, A.; Campos, K. R.; Chen, C.-Y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185.

K₃PO₄, NaO^tBu, or KO^tBu showed lower or negligible conversions.

With the optimal conditions in hand, we examined the scope of this reaction by coupling of a variety of vinyl bromides and triflates with **1** (Table 2). Reaction of vinyl

Table 2. Substrate Scope for α -Vinylation of **1**

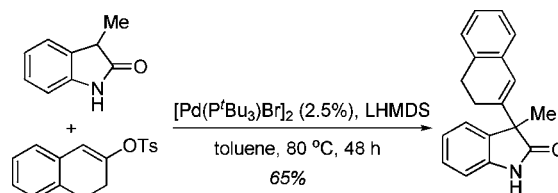
			
entry	olefin	product	yield (%) ^{a, b}
1			89
2			85
3			84
4			70
5			56
6			74
7			85

^a Isolated yield. ^b Reaction conditions: To a mixture of **1** (1.0 equiv) and [P^tBu₃PdBr]₂ (2.5 mol %) in toluene was added LHMDS (2.5 equiv). The resulting mixture was stirred for 5 min followed by addition of vinyl bromide, triflate, or tosylate (1.5 equiv).

bromides or triflates gave 56–89% yields (Table 2, entries 1–7), while terminal vinyl bromides coupled with **1** afforded an 84–85% yield of product with complete retention of olefin geometry (Table 2, entries 2 and 3). Hindered tri- or tetrasubstituted vinyl bromides or triflates also coupled smoothly to give the desired product in 70–85% yield (Table 2, entries 4, 6, and 7). Coupling of 1-trifluoromethyl-2-bromopropene with **1** proceeded smoothly to afford 56% yield of the desired vinylation product (Table 2, entry 5).²²

Recently, vinyl tosylates have been used in coupling reactions as organic halide equivalents due to the fact that they are easy to prepare and generally are stable crystalline compounds. However, they are also difficult coupling partners and few studies have been reported with these compounds.^{21b} To our delight, the current conditions provided a 65% yield for the reaction of 1,2-dihydro-3-naphthyl tosylate with 3-methoxyindole **1** (Scheme 1).

Scheme 1



To explore the generality of the current process, we extended the α -vinylation reaction to other related carbonyl compounds (Table 3). With use of the optimized reaction conditions described above, both cyclic and acyclic ketone enolates were shown to react with vinyl bromides and triflates, providing β,γ -unsaturated ketones in 48–95% yield. Again the electron-deficient vinyl trifluoromethyl group was introduced in 62–65% yield (Table 3, entry 2). Tetrasubstituted vinyl triflate or bromide was effective in this coupling, though lower yields of 48% and 66%, respectively, were obtained (Table 3, entries 3b, 6a, and 7). α -Vinylations of methylene and methyl groups were moderate (56–81%) in the cases studied (Table 3, entries 5, 6, and 7). The α -vinylation reaction of the ethyl ester of *N*-Boc-piperidine-4-carboxylic acid was also successful under these conditions (Table 3, entries 8 and 9).

Although asymmetric catalysis has been emerging as an important tool in modern organic synthesis, enantioselective α -arylation has yet to be established as a general method. The reported asymmetric protocols are highly substrate-dependent with little generality.^{13,19a,23}

We screened a range of chiral ligands under our optimal conditions for α -vinylation of **1** with 1-cyclohexenyl triflate **2**. Preliminary results showed that some chiral ligands mediated the asymmetric coupling reaction albeit in low yield of product **3**. One of the promising ligands was MOP*²⁴ (Figure 1 and Table 1), which gave 31% ee at 80 °C (48 h,

(22) Fluorinated organic compounds constitute important targets in many research fields due to the electronic and biological properties of fluoride compounds, and introduction of a trifluoromethyl group in a mild manner is often challenging. Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, UK, 2006.

(23) For more examples, see: (a) Åhman, A.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918. (b) Spielvogel, D. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 3500. (c) Hartwig also disclosed the palladium-catalyzed arylation of amides using Evans' auxiliary and moderate to excellent diastereoselectivities were obtained: Liu, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5182.

(24) Provided by Prof. Stephen L. Buchwald. Also see ref 13.

Table 3. Vinylation of Ketones and Esters

entry	ketone/ester	olefin	product	isolated yield (%) ^{a, b}
1				(a) n = 1, 75 (b) n = 2, 95
2				(a) n = 1, 62 (b) n = 2, 65
3				(a) R ₁ = H, 85 (b) R ₁ = CO ₂ Me, 48
4				87
5				81
6				66
7				56
8				76
9				80

^a Isolated yield. ^b Reaction conditions: To a mixture of ketone or ester (1.0 equiv) and [P^tBu₃PdBr]₂ (2.5 mol %) in toluene was added LHMDS (2.5 equiv). The resulting mixture was stirred for 5 min followed by addition of vinyl bromide or triflate (1.5 equiv).

yield 35%) and 40% ee at 40 °C (96 h, yield 38%), respectively.²⁵

In conclusion, we have developed a mild catalytic system for the α -vinylation of 3-methyloxindole **1**, as well as a variety of ketones and esters with exclusive C–C bond formation. The reaction affords good yields of products with use of commercially available reagents, making this an attractive method to introduce the C=C double bond into organic molecules. Further mechanistic studies are required to optimize the asymmetric α -vinylation reaction

(25) The parent MOP gave similar yield but no enantioselectivity. Hayashi, T. *Acc. Chem. Res.* **2000**, 33, 354.

Acknowledgment. We thank Professor Stephen Buchwald at MIT for his helpful discussion and a sample of S-MOP* and Drs. Eric Bercot and Xiang Wang for their valuable comments during the preparation of this manuscript. J.H. thanks Troy Soukup and Jenny Chen for analytical support.

Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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