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Preparation of Enamides via Palladium-Catalyzed Amidation of Enol Tosylates

Artis Klapars,* Kevin R. Campos, Cheng-yi Chen, and Ralph P. Volante

Department of Process Research, Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065

artis_klapars@merck.com

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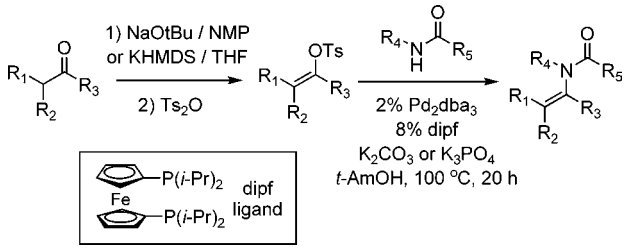
ABSTRACT



A Pd-catalyzed coupling of enol tosylates and amides has been developed. Ligand screening revealed dipf as the most general ligand for this transformation. A variety of enol tosylates were coupled to an array of enamides in 58–97% yield.

Enamides are valuable synthetic intermediates, particularly in conjunction with asymmetric hydrogenation, which provides an efficient route to chiral amines.[1] Regrettably, methods for the preparation of enamides are relatively scarce.[2] While successful in a limited number of cases, direct condensation of a ketone with an amide to provide an enamide is not a general transformation.[3] Transition-metal-catalyzed coupling reactions offer a more reliable approach to the stereoselective preparation of enamides. For example, the copper-catalyzed coupling of amides with vinyl iodides or bromides is an attractive method provided that the vinyl iodide or bromide is available.[4] In many cases, however, preparation of the vinyl halides may be inconvenient. Therefore, the use of enol sulfonates, readily available from the corresponding ketones, may be preferred.

Our group recently reported a palladium-catalyzed amidation of enol triflates using the Pd_2dba_3/Xantphos catalyst system.[5] We sought to extend this transformation to enol tosylates, which offers two important advantages. First, tosylating agents are generally less expensive and more readily available than *N*-phenyltriflimide,[6] the reagent used to prepare enol triflates. Second, from a process development perspective the crystallinity associated with enol tosylates would provide a convenient means for isolation and purification of the product.

Surprisingly few enol tosylates have been documented in the literature, and no general procedure for their preparation has been reported.[7] We found that the best conditions for the generation of enol tosylates involved enolization of a ketone (using NaOtBu[8] in NMP or alternatively KHMDS in

(1) Review: Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103.

(2) (a) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084. (b) Neugnot, B.; Cintrat, J.-C.; Rousseau, B. *Tetrahedron* **2004**, *60*, 3575. (c) Brice, J. L.; Meerdink, J. E.; Stahl, S. S. *Org. Lett.* **2004**, *6*, 1845. (d) Harrison, P.; Meek, G. *Tetrahedron Lett.* **2004**, *45*, 9277.

(3) (a) Tschaen, D. M.; Abramson, L.; Cai, D.; Desmond, R.; Dolling, U.-H.; Frey, L.; Karady, S.; Shi, Y.-J.; Verhoeven, R. *J. Org. Chem.* **1995**, *60*, 4324. (b) Dupau, P.; Le Gendre, P.; Bruneau, C.; Dixneuf, P. H. *Synlett* **1999**, 1832.

(4) (a) Coleman, R. S.; Liu, P.-H. *Org. Lett.* **2004**, *6*, 577. (b) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667. (c) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333. (d) Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* **1991**, 1443.

(5) Wallace, D. J.; Klauber, D. J.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749.

(6) $PhNTf_2$ is not available in bulk and produces PhNHTf as a byproduct which may be difficult to remove.

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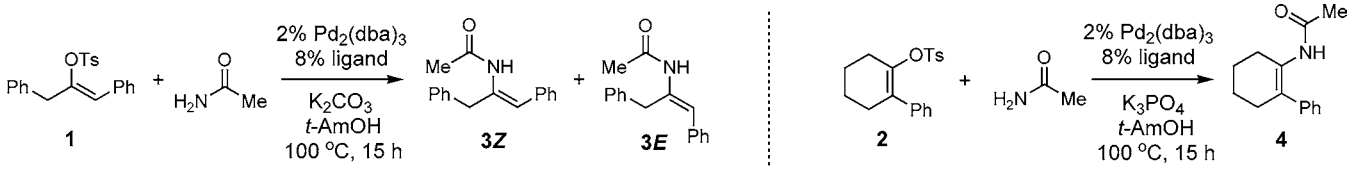
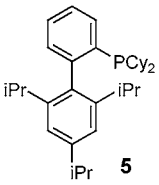
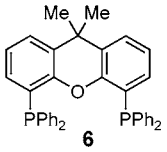
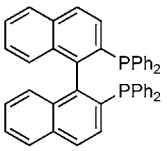
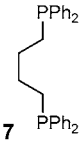
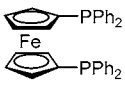
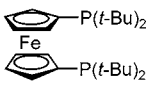
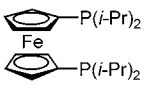
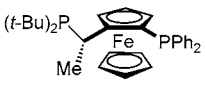
Table 1. Ligand Screening for the Pd-Catalyzed Amidation of Two Different Enol Tosylates

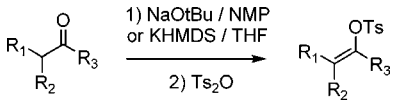


Ligands:	no ligand	Ph_3P	$(o\text{-Tol})_3P$	$(t\text{-Bu})_3PH^+BF_4^-$	 5	 6	
*Conv. of Tosylate **1**:*	2%	95%	5%	10%	73%	79%	>99%
*HPLC Yield of **3Z+3E**:*	<0.1%	7%	<0.1%	1%	45%	78%	99%
***3Z/3E** Ratio:*	N/A	2.0 : 1	N/A	N/A	1.4 : 1	17 : 1	2.1 : 1
*Conv. of Tosylate **2**:*	16%	43%	10%	16%	34%	17%	35%
*HPLC Yield of **4**:*	<0.1%	1%	<0.1%	<0.1%	16%	<0.1%	30%

Ligands:		 7		 8	 9	
*Conv. of Tosylate **1**:*	39%	98%	>99%	99.7%	>99%	>99%
*HPLC Yield of **3Z+3E**:*	1%	91%	98%	24%	99%	86%
***3Z/3E** Ratio:*	N/A	1.8 : 1	2.7 : 1	2.0 : 1	5.2 : 1	1.8 : 1
*Conv. of Tosylate **2**:*	15%	40%	76%	54%	99%	97%
*HPLC Yield of **4**:*	<0.1%	21%	72%	17%	94%	95%

THF for the more acidic ketones) followed by addition of *p*-toluenesulfonic anhydride (Scheme 1).[9] The enol tosylates were crystalline solids in all cases except for tosylate **10**.

Scheme 1. Preparation of Enol Tosylates



The Pd-catalyzed coupling reaction was addressed next. To the best of our knowledge, no examples of the amidation of enol tosylates had been reported when we set out to explore this challenging transformation. This was not totally unexpected considering, by analogy, that aryl tosylates are substantially less reactive than the corresponding aryl triflates. Hence, amination of aryl tosylates typically requires the most active ligands such as electron-rich biarylphosphines,[10] or ferrocenylphosphines of the Josiphos family.[11]

In search for a competent catalyst system, a diverse set of phosphine ligands was examined for the amidation of two different vinyl tosylates, **1** and **2** (Table 1). Unexpectedly, some of the most universal monodentate phosphine ligands such as $t\text{-Bu}_3PH^+BF_4^-$ and XPhos (**5**)[12] provided poor to moderate yields. It was soon discovered that loosely chelating bidentate phosphines provided the best results.[13] Although XantPhos (**6**) failed to catalyze the amidation of the tosylate

(7) Examples: (a) Frydman, N.; Bixon, R.; Sprecher, M.; Mazur, Y. *Chem. Commun.* **1969**, 1044. (b) Cox, R. A.; McAllister, M.; Roberts, K. A.; Stang, P. J.; Tidwell, T. T. *J. Org. Chem.* **1989**, *54*, 4899. (c) Huffman, M. A.; Yasuda, N. *Synlett* **1999**, 471. (d) Baxter, J. M.; Steinhuebel, D.; Palucki, M.; Davies, I. W. *Org. Lett.* **2005**, *7*, 215.

(8) Presumably, the thermodynamic enolates were generated.

(9) TsCl caused α-chlorination of the enolates.

(10) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.

(11) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 8704.

(12) No attempt was made to use the alternative procedures involving the inconveniently air-sensitive free phosphine in the case of *t*-Bu_3P, or involving the cumbersome prereduction of $Pd(OAc)_2$ in the case of Xphos. It is conceivable that the activity of these catalysts suffered as the result.

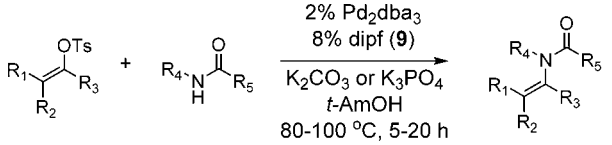
2, it performed well in the case of the less hindered enol tosylate **1**. Even simple and inexpensive diphosphines such as dppb (**7**) provided satisfactory results in a number of cases. In general, dipf (**9**) proved to be the most universal ligand and was chosen for further explorations (Table 2). It is interesting to note that this is the first application of the dipf ligand (**9**) to a Pd-catalyzed C−N coupling reaction.[14]

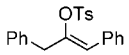
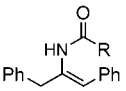
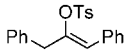
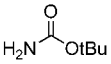
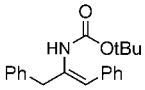
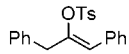
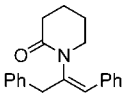
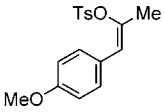
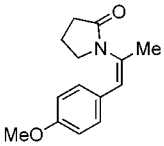
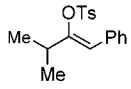
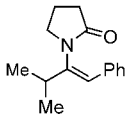
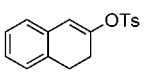
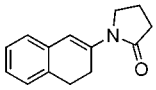
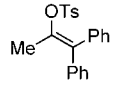
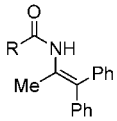
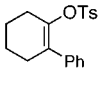
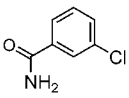
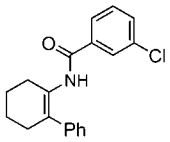
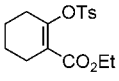
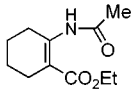
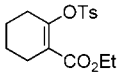
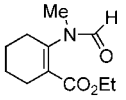
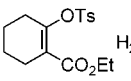
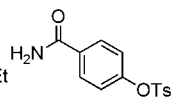
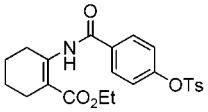
In accord with the observations by Buchwald and co-workers,[10] *tert*-amyl alcohol was identified as the best solvent. The reactions were typically run at 0.5 M (about 5 mL/g) because the fastest rates were observed at a relatively high concentration. A screening of bases revealed that K_2CO_3 was preferred for the less hindered vinyl tosylates while K_3PO_4 performed best for the more hindered tosylates (Table 2, entries 6, 8, 9, and 10). Regarding the Pd source, Pd_2dba_3 provided slightly faster reactions than $Pd(dba)_2$ and much cleaner conversions than $Pd(OAc)_2$. Although 4 mol % Pd was used for most of the reactions, some of the reactions could also be performed with as little as 1 mol % Pd and 2 mol % of the dipf ligand.

In some cases, isomerization of the enamide product was observed. In fact, further isomerization took place under the reaction conditions after the coupling reaction was complete. Thus, the isomerization could be minimized using shorter reaction times. A bulkier amide coupling partner such as pivalamide (Table 2, entry 2) generally decreased the extent of isomerization. Furthermore, the rate of isomerization was also dependent on the ligand used in the coupling reaction (Table 1). This observation indicates that the isomerization process probably involves coordination of the enamide to the Pd catalyst.

The scope of the coupling reaction is currently limited to enol tosylates featuring an aryl substituent (Table 2, entries 1−10) or an electron-withdrawing group (Table 2, entries 11−13)[15] in the β-position of the enol tosylate.[16] In contrast, an aryl group at the α-position of the enol tosylate has a negative effect on the reaction as exemplified by the lack of reactivity of substrates **11** and **12** (Figure 1). The positive effect of a β-phenyl group is completely offset by the negative effect of the α-phenyl substituent in substrate **13**, which provides <10% of the enamide product under the reaction conditions. At the same time, an electron-donating *p*-MeO group in an enol tosylate (Table 2, entry 5) does not appear to deteriorate the reactivity. Despite these intricate electronic effects, the coupling reaction is quite tolerant of steric hindrance in the enol tosylates allowing the preparation of a variety of tetrasubstitued enamides (Table 2, entries 8−13).

Table 2. Coupling of Amides and Enol Tosylates



Entry	Tosylate	Amide	Enamide Product	Isolated Yield (Isomer Ratio)
1				R = Me, 92% (10:1 Z/E)
2				R = tBu, 88% (>50:1 Z/E)
3				96% (30:1 Z/E)
4				58% (>50:1 Z/E)
5				94% (>50:1 Z/E)
6				97% (>50:1 Z/E)
7				83%
8				R = Me, 96%
9				R = H, 91%
10				88%
11				87%
12				80%
13				95%

The coupling reaction was successful with most primary amides investigated. However, only the least sterically demanding secondary amides performed well (Table 2,

(13) Use of the BINAP ligand for aryl amination: (a) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. Use of the dppf ligand for aryl amination: (b) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217.

(14) The dipf ligand has been used for a Pd-catalyzed α-arylation of a nitrile: (a) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330. For the use of the DtBPF ligand (**8**) in a C−N coupling reaction, see: (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369.

(15) A control experiment was performed for the example in Table 2, entry 11. If Pd_2bda_3 and the ligand were omitted, <0.1% yield of the desired enamide product was observed.

(16) Interestingly, enol triflates exhibit a similar reactivity pattern in the Pd-catalyzed amidation reaction (see ref 5).

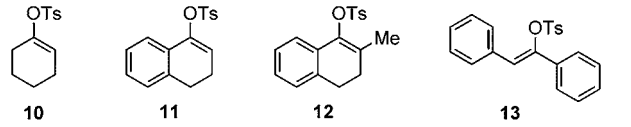


Figure 1. Enol tosylates that are poor substrates for the coupling reaction.

entries 5−7 and 12). A similar reactivity trend is also typical for the Pd-catalyzed[17] and Cu-catalyzed[18] amidations of aryl halides. Formamide (entry 9) and a carbamate (entry 3) were good coupling partners. Although aryl bromides were found to inhibit the coupling reaction,[19] aryl chlorides (entry 10) and aryl tosylates (entry 13) were tolerated under the reaction conditions.

In summary, we have developed a method for stereoselective coupling of enol tosylates and amides using the Pd_2dba_3/dipf(**9**) catalyst system.[20] This procedure is applicable to enol tosylates bearing an aryl substituent or an electron withdrawing group in the β-position of the double bond. A significant degree of steric hindrance is tolerated in the enol tosylate providing a convenient method for the synthesis of functionalized trisubstituted and tetrasubstituted enamides.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043.

(18) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

(19) If 1 equiv of 5-bromo-*m*-xylene was added to the coupling reaction of enol tosylate **1** shown in Table 1 (using ligand **9**), only 35% conversion of enol tosylate and 32% conversion of aryl bromide was observed. For comparison, >99% conversion of enol tosylate was obtained in the absence of the aryl bromide.

(20) **General Procedure.** A Schlenk tube was charged with Pd_2dba_3 (18.3 mg, 0.020 mmol, 4.0 mol % Pd), dipf ligand (Strem Chemicals, 33.5 mg, 0.0800 mmol, 8.0 mol %), enol tosylate (1.0 mmol), amide (1.2 mmol), and K_2CO_3 or K_3PO_4 (2.0 mmol). The Schlenk tube was evacuated and then backfilled with N_2. *tert*-Amyl alcohol (2.0 mL) was added via syringe, the Schlenk tube was sealed, and the reaction mixture was stirred at 80−100 °C for 5−20 h. The resulting suspension was filtered through a plug of silica gel, the filtrate was concentrated, and the residue was purified by flash chromatography on silica gel to provide the desired enamide product.