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Palladium-Catalyzed Amidation of Enol Triflates: A New Synthesis of Enamides

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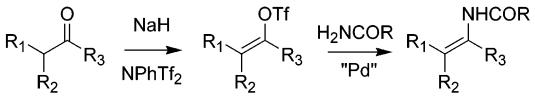
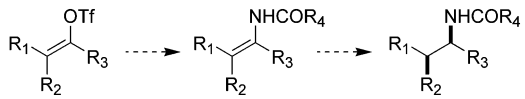
ABSTRACT



The palladium-catalyzed coupling of a range of enol triflates with amides, carbamates, and sulfonamides has been developed. This offers a simple and widely applicable synthesis of enamides, which may not be readily available by other means.

In recent years there has been a surge of interest in the palladium-catalyzed C−N bond-forming reactions of aryl halides with amines and amides.[1−3] These reactions can proceed under mild conditions and are compatible with a range of substrates, offering improvements over traditional methods. For many palladium-catalyzed reactions, enol triflates can also function as reactive coupling partners;[4] however, this has only recently been extended to C−N bond-forming reactions with the amination of a simple enol triflate to afford an enamine.[5] The related amidation of an enol triflate would constitute a straightforward synthesis of enamides, which are valuable substrates for asymmetric hydrogenation reactions and hence for the synthesis of optically pure amines (Scheme 1).

Scheme 1



With regard to a recent drug discovery program at Merck, a stereodefined trisubstituted enamide was required for hydrogenation studies. While 1,1-disubstituted enamides can be prepared,[6] the synthesis of highly substituted enamides in an efficient and stereoselective manner is more challenging.[7] The palladium- or copper-mediated amidation of a vinyl halide appeared attractive;[8] however, the controlled production of these substrates would also present a challenge. In contrast, the selective formation of a single enol triflate from a ketone may rely on simple kinetic vs thermodynamic control in the enolate formation step and can be tuned by judicious choice of base and solvent combinations. To the best of our knowledge, no amidations of enol triflates have been reported, and in this paper we describe our initial studies on this useful reaction.

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(2) (a) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609. (b) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc*. **1996**, *118*, 7217**.** (c) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (d) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746.

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(4) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl*. **1986**, *25*, 508. (b) Scott, W. J.; McMurray, J. E. *Acc. Chem. Res*. **1988**, *21*, 47.

(5) Willis, M. C.; Brace, G. N. *Tetrahedron Lett*. **2002**, *43*, 9085. See also Hicks, F. A.; Brookhardt, M. *Org. Lett*. **2000**, *2*, 219.

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(7) For stereocontrolled synthesis of 1,2-disubstituted enamides, see: (a) Furstner, A.; Brehm, C.; Cancho-Grande, Y. *Org. Lett*. **2001**, *3*, 3955. (b) Snider, B. B.; Song, F. *Org. Lett*. **2000**, *2*, 407 and references therein. For stereoselective preparation of trisubstituted enamides, see: Tanaka, R.; Hirano, S.; Urabe, H.; Sato, F. *Org. Lett*. **2003**, *5*, 67 and references therein.

(8) For copper-catalyzed amidations of vinyl halides, see: (a) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L *Org. Lett*. **2003**, *5*, 3667. (b) Shen, R.; Porco, J. A. Jr. *Org. Lett*. **2000**, *2*, 1333. (c) Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett*. **1991**, 1443. For a palladium-catalyzed *intramolecular* reaction, see: Kozawa, Y.; Mori, M. *Tetrahedron Lett*. **2002**, *43*, 111.

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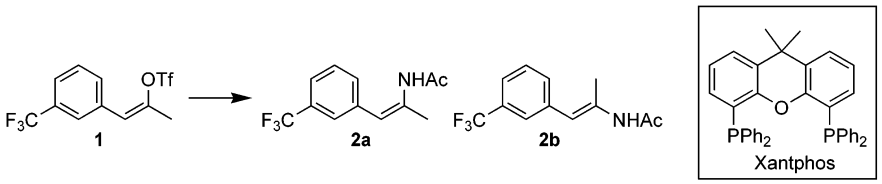
Table 1. Optimization of Coupling Conditions



ligand	palladium	solvent	base	temp	time	conversion	ratio[a]
Xantphos	$Pd(OAc)_2$	dioxane	Cs_2CO_3	80 °C	16 h	>95	45:55
Xantphos	$Pd(OAc)_2$	dioxane	Cs_2CO_3	rt	6 h	75	92:8
Xantphos	$Pd_2(dba)_3$	dioxane	Cs_2CO^3	rt	8 h	85	94:6
Xantphos	$Pd_2(dba)_3$	dioxane	Cs_2CO_3	rt	20 h	>95	45:55
PCy_3	$Pd_2(dba)_3$	dioxane	Cs_2CO_3	rt	16 h	0	
BINAP	$Pd_2(dba)_3$	dioxane	Cs_2CO_3	35 °C	16 h	16	46:54
dppf	$Pd_2(dba)_3$	dioxane	Cs_2CO_3	35 °C	16 h	0	
Xantphos	$Pd_2(dba)_3$	THF	Cs_2CO_3	rt	6 h	67	93:7
Xantphos	$Pd_2(dba)_3$	dioxane	KO*t*Bu	rt	3 h	0[b]	
Xantphos	$Pd_2(dba)_3$	dioxane	$^iPr_2NEt$	35 °C	16 h	0	

[a] HPLC ratio of **2a**:**2b**. [b] Starting material converted to alkyne

The readily accessible enol triflate **1**, along with acetamide, was chosen to screen reaction conditions, and initially the procedure developed by Buchwald[1f] for the amidation of aryl halides was examined [$Pd(OAc)_2$, Xantphos,[9] and Cs_2CO_3 in 1,4-dioxane at 80 °C]. After 8 h, complete conversion of the enol triflate to a 1:1 mixture of two new products was observed, and after chromatographic separation, these were identified as the two isomeric enamides **2a** and **2b**.[10] This indicated that the coupling was indeed a viable process but also suggested that isomerization of the enol triflate or product had taken place during the reaction. Indeed, resubjection of either of the purified enamides to the reaction conditions afforded a 1:1 mixture of isomers. Lowering the temperature to 40−50 °C led to slower isomerization, and at room temperature the enamides were relatively stable to the reaction conditions. Hence, for successful implementation, amidation at room temperature would be required. On the basis of this, a number of palladium sources, ligands, bases, and solvents were screened for this reaction

As can be seen from Table 1, running the reaction at room-temperature allowed for moderate conversion with minimal isomerization and a change of palladium source to $Pd_2(dba)_3$ gave a 94:6 ratio of enamide isomers with high conversion after 8 h. Even at these temperatures product equilibration still occurred after prolonged reaction times. The use of ligands other than Xantphos (PCy_3, BINAP, dppf) was not successful, with only BINAP providing any of the desired product. Changing the solvent had only a minor effect; however, Cs_2CO_3 was found to be the optimal base. Amine bases did not promote the reaction, and the use of KO*t*Bu afforded solely the corresponding alkyne.

With a viable coupling procedure in hand, attention was turned to the generality of the process and the couplings of a range of structurally diverse enol triflates with different amides were studied (Table 2). Where enamide equilibration was not possible, reactions were run at 50 °C and, as anticipated, this higher reaction temperature allowed for complete consumption of starting material without detrimental side reactions.

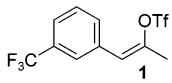
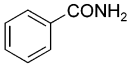
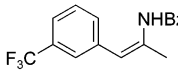
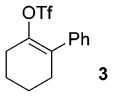
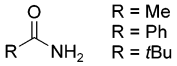
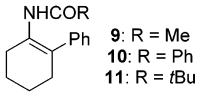
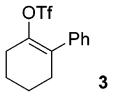
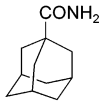
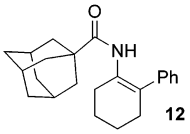
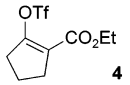
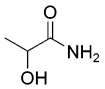
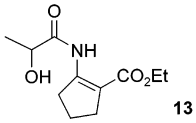
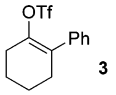
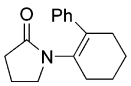
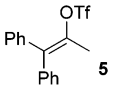
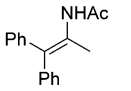
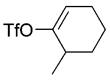
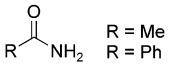
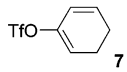
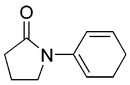
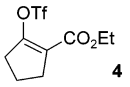
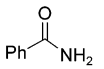
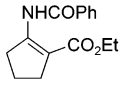
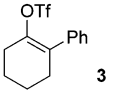
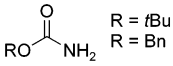
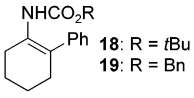
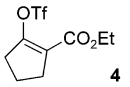
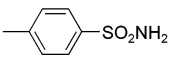
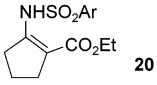
The coupling was found to be compatible with primary aliphatic and aromatic amides, including the hindered trimethylacetamide and adamantanecarboxamide (entries 4 and 5), and also with functionalized amides (entry 6).[11] In the case of secondary amides, good yields were obtained with the cyclic 2-pyrrolidinone (entry 7), but *N*-methylbenzamide did not react with either enol triflate **3** or **4**. This may be due to steric constraints, as a similar lack of reactivity for secondary amides has been observed in related reactions.[1f] The high yields obtained for the couplings of primary amides can also be attributed to the lack of reactivity of the secondary amide product to further coupling. The hindered enol triflate **5** required higher reaction temperatures, reaching only 80% conversion after 20 h at 80 °C (entry 8). Some form of enol triflate activation by electron-withdrawing substituents or conjugation appeared to be necessary, as enol

(9) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081.

(10) New compounds were fully characterized by ^1H, ^{13}C, IR, and HRMS and/or elemental analysis.

(11) General Procedure for Palladium-Catalyzed Amidation Reaction: Synthesis of Enamide **11**. To a solution of enol triflate **3** (255 mg, 0.832 mmol) in dioxane (5.0 mL) at room temperature was added Cs_2CO_3 (379 mg, 1.16 mmol), trimethylacetamide (109 mg, 1.08 mmol), Xantphos (43.6 mg, 0.075 mmol), and $Pd_2(dba)_3$ (23.0 mg, 0.025 mmol). The mixture was degassed and stirred at 50 °C for 9 h after which time complete conversion was obtained. The mixture was filtered, concentrated, and purified by flash column chromatography (toluene) to give the desired enamide (214 mg, 96%): mp = 96−98 °C; IR ($CHCl_3$ solution) 3252, 2920, 1650, 1645, 1510, cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.37 (dd, J = 7.9, 1.4 Hz, 2H), 7.27 (tt, J = 7.9, 1.4 Hz, 1H) 7.19 (dd, J = 7.9, 1.4 Hz, 2H), 6.73 (s, 1H), 2.64 (m, 2H), 2.35 (m, 2H), 1.76 (m, 4H), 1.00 (s, 9H); ^{13}C (100.6 MHz, $CDCl_3$) δ 176.3, 140.8, 130.9, 128.6, 128.1, 127.0, 125.6, 39.0, 30.7, 27.6, 27.3, 22.8, 22.7; LCMS 258 (MH^+, 80), 174 (80), 157 (100); HRMS $C_{17}H_{23}NO$ (MH^+) theory 258.1858, measured 258.1851.

Table 2. Coupling of Various Enol Triflates and Amides[a]

entry	enol triflate	amide	product	yield[b]
1[c]	 **1**		 **8**	71% (+ 5% isomer)
2 3 4	 **3**	 R = Me R = Ph R = *t*Bu	 **9**: R = Me **10**: R = Ph **11**: R = *t*Bu	**9**: 88% **10**: 84%[d] **11**: 96%
5	 **3**		 **12**	97%
6	 **4**		 **13**	89%
7	 **3**		 **14**	97%
8[e]	 **5**		 **15**	76%
9	 **6**	 R = Me R = Ph	No reaction	
10	 **7**		 **16**	10%
11	 **4**		 **17**	47%[d]
12 13	 **3**	 R = *t*Bu R = Bn	 **18**: R = *t*Bu **19**: R = Bn	**18**: 80% **19**: 95%
14	 **4**		 **20**	87%

[a] Reagents and conditions: enol triflate 1.0 equiv, amide 1.2 equiv, Cs_2CO_3 1.4 equiv, $Pd_2(dba)_3$ 3 mol %, Xantphos 9 mol %, 0.2 M in dioxane, 50 °C, 8−14 h. [b] Isolated yield after chromatography. [c] At room temperature. [d] Using KO*t*Bu. [e] At 80 °C.

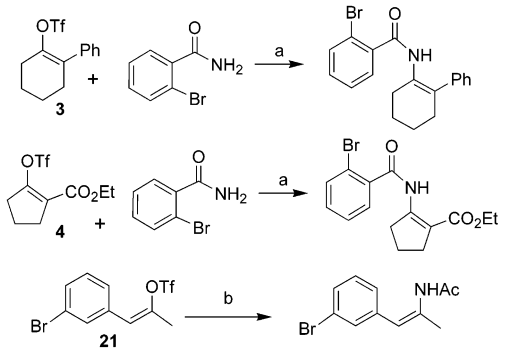
triflate **6** did not react with acetamide or benzamide (entry 9) and only trace amounts of product were isolated from the reaction of enol triflate **7** with 2-pyrolidinone (entry 10). In substrates where elimination to alkynes or allenes was not possible, KO*t*Bu could be employed as an alternative base. With enol triflate **3**, shorter reaction times were required with the soluble base compared to Cs_2CO_3 (entry 3); however, competing hydrolysis to the starting ketone lowered yields with enol triflate **4** (entry 11).

While amides are the most commonly employed nitrogen protecting group for enamide hydrogenation reactions, the harsh conditions required to remove these groups can limit substrate compatibility. With this in mind, C−N bond-forming reactions were studied with other readily available nitrogen compounds. Both *tert*-butyl and benzyl carbamate underwent coupling reactions with enol triflate **3** in high yield (entries 12 and 13); however, the less nucleophilic *p*-toluenesulfonamide could only be coupled with the highly reactive enol triflate **4** (entry 14).[12]

The presence of an aryl bromide in either coupling partner did not interfere with the desired reaction under the above conditions. For example, the coupling of enol triflate **3** or **4** with 2-bromobenzamide at 50 °C afforded solely the product resulting from amidation of the enol triflate with no polym-

(12) While a conjugate addition/elimination pathway could operate for this enol triflate, we feel that this is unlikely due to the lack of reactivity in the absence of palladium (<5% conversion after 24 h). We thank a referee for alerting us to this possibility.

Scheme 2[a]



[a] Reagents and conditions: (a) Cs_2CO_3 1.4 equiv, $Pd_2(dba)_3$ 3 mol %, Xantphos 9 mol %, dioxane, 50 °C, 16 h. [b] Acetamide 1.3 equiv, Cs_2CO_3 1.4 equiv, $Pd_2(dba)_3$ 3 mol %, Xantphos 9 mol %, dioxane, 23 °C, 9 h.

erization of the bromobenzamide or subsequent Heck reaction of the product (Scheme 2). Coupling of acetamide with enol triflate **21** at room temperature gave an 83% yield of the product from reaction of the enol triflate. Increasing the reaction temperature to 50 °C resulted in some alkene isomerization, but no coupling with the aryl bromide group was observed at this temperature.

In conclusion, we have demonstrated that the palladium-catalyzed amidation of activated enol triflates to afford enamides is a viable procedure for the synthesis of a range of cyclic and acyclic enamides. The reactions proceed under mild conditions that would be compatible with a range of functionality. Selective coupling of an enol triflate in the presence of aryl bromides can be achieved. Carbamates, and in some cases sulfonamides, can also be coupled efficiently. Where enamide equilibration can occur, control of reaction temperature allowed for stereoselective synthesis of the required enamides.

Acknowledgment. We thank Tom Novak for the high-resolution mass spectral data, Brenda Pipik for elemental analysis, and Jingjun Yin for preparation of Xantphos.

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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