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Palladium(0)-Catalyzed Coupling Reactions of an *N*-Tosylpyrrolidinone-Derived Enamine Triflate

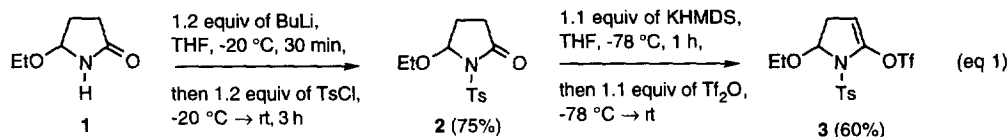
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Abstract: The synthetic utility of a 5-membered lactam-derived vinyl triflate has been evaluated. This vinyl triflate was used in several types of Pd(0)-mediated coupling reactions like Stille type couplings and CO-insertion reactions. Copyright © 1996 Elsevier Science Ltd

The synthetic potential of vinyl triflates derived from aldehydes and ketones has been well established over the last decade.¹ Such vinyl triflates have shown to be suitable substrates in various types of coupling reactions *e.g.* Stille couplings,² Heck reactions,³ cuprate additions,⁴ and Nozaki-Hiyama couplings.⁵ In contrast with the numerous examples of reactions with simple vinyl triflates, there are only limited examples of similar reactions with lactone-derived vinyl triflates.⁶ Recently, (non-aromatic) 6- and 7-membered lactam-derived vinyl triflates were also employed in various Pd-catalyzed coupling reactions.⁷ As an extension of our earlier work on synthetic applications of pyrrolidinone systems,⁸ we became interested in methods involving vinyl triflate chemistry since the remaining double bond allows further functionalization of the 5-membered heterocyclic ring. In this letter we disclose some preliminary results on Stille type couplings and CO-insertion reactions of the butyrolactam-derived vinyl triflate **3**.

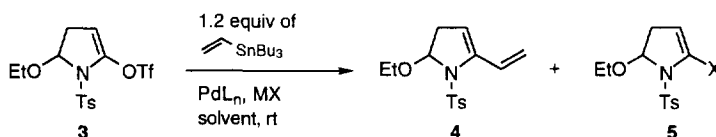
The tosylated α -ethoxypyrrolidinone **2** was chosen as a precursor for vinyl triflate chemistry because it is readily available from succinimide and also because the presence of the ethoxy and the *N*-tosyl function renders the corresponding triflate more stable.⁹ Moreover, after formation of the vinyl triflate and coupling with an appropriate side chain, the pyrroline ring can either be further functionalized *via N*-acyliminium ion type chemistry,⁸ or *via* reaction of the double bond that remains after vinyl triflate coupling. Last but not least, the possibility of using enantiopure ethoxy lactams could also be invoked.^{8a} The synthesis of vinyl triflate **3** commenced with the known ethoxy lactam **1** (eq 1),⁸ which was tosylated upon treatment with *n*-BuLi and TsCl to afford **2** in 75% yield.



Deprotonation of lactam **2** with KHMDS at low temperature followed by trapping of the enolate with triflic anhydride led to the desired vinyl triflate **3** in 60% yield.¹⁰ Use of different triflating agents like *N*-phenyltriflimide¹¹ or *N*-(5-chloro-2-pyridyl)triflimide¹² gave significantly lower yields. The vinyl triflate **3** was obtained as a colorless oil after aqueous work-up and further purification by column chromatography. Although the triflate was prone to decomposition if minor impurities were present, the pure compound could be stored at -20°C for a week.

The vinyl triflate **3** was first subjected to Stille type coupling reactions. Treatment of **3** with vinyltributyltin under typical Stille conditions ($\text{Pd}(\text{PPh}_3)_4$, DMF, heat)² led only to decomposition of starting material (see Table 1). Therefore mild conditions were sought that would lead to the desired product at room temperature. Moderate yields of the desired coupling product **4** were found upon addition of LiCl (1.1 equiv), which is known to enhance reactions of vinyl triflates *via* displacement of the triflate in the intermediate Pd-complex.^{13,14} It is noteworthy that when a slight excess of LiCl was added (1.1 equiv), a mixture of diene **4** (29%) and chloride **5**¹⁵ (34%) was obtained, while an excess of LiCl (10 equiv) exclusively led to **5**. A similar result was observed when triflate **3** and LiCl (10 equiv) were stirred in DMF in the absence of any catalyst, which demonstrates that palladium plays no role in this transformation.¹⁶ Treatment of triflate **3** with KBr in DMF solely led to the corresponding vinyl bromide (isolated in 28% yield due to its instability), while LiI gave a complex product mixture.

Table 1

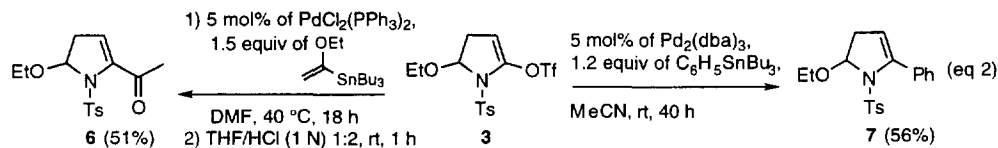


PdL_n (mol%)	MX (equiv)	Solvent	4 (%) ^a	5 (%) ^a
$\text{Pd}(\text{PPh}_3)_4$ (5)		DMF	-	-
$\text{Pd}(\text{PPh}_3)_4$ (5)	LiCl (1.1)	DMF	29	34 (X = Cl)
$\text{Pd}(\text{PPh}_3)_4$ (5)	LiCl (10)	DMF	-	60
none	LiCl (10)	DMF	-	97 (X = Cl)
none	KBr	DMF	-	28 (X = Br)
$\text{Pd}(\text{PPh}_3)_4$ (5)	CuI (0.1)	DMF	56	-
$\text{Pd}(\text{AsPh}_3)_4$ (4) ^b		DMF	50	-
$\text{Pd}(\text{AsPh}_3)_4$ (4) ^b		NMP	77	-

^a isolated yields; ^b prepared *in situ* from $\text{Pd}_2(\text{dba})_3$ and AsPh_3 .

Upon using a catalytic amount of CuI (0.1 equiv) as co-catalyst,¹⁷ however, the diene **4** was obtained in 56% yield. After these attempts we turned to conditions reported by Farina *et al.*¹⁸ (4 mol% of $\text{Pd}(\text{AsPh}_3)_4$ (formed *in situ* from $\text{Pd}_2(\text{dba})_3$ and AsPh_3) in DMF or *N*-methylpyrrolidinone (NMP)) that provided the desired coupling product **4** in a satisfactory 77% yield.¹⁹

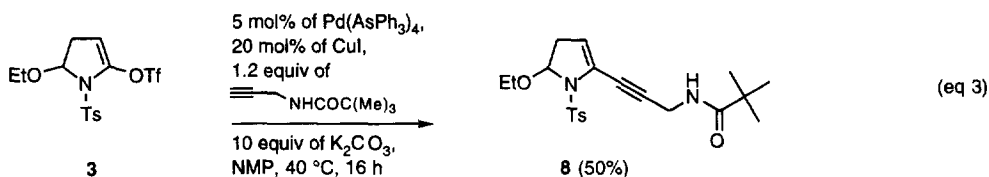
Reactions with other stannanes are shown in eq 2. Unfortunately, the aforementioned reaction conditions did not give satisfactory results in these cases, so that further searching for suitable reaction conditions was needed. Thus, coupling of vinyl triflate **3** with (1-ethoxyvinyl)tributyltin was best achieved when $\text{PdCl}_2(\text{PPh}_3)_2$ was used as the catalyst in DMF at 40 °C,²⁰ after which acid-mediated hydrolysis led to the α,β -unsaturated ketone **6** in 51% overall yield.



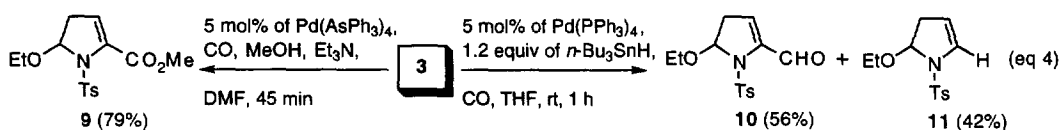
Cross-coupling of vinyl triflate **3** with phenyltributyltin was shown to proceed in an acceptable yield when "ligandless" conditions were applied *i.e.* $\text{Pd}_2(\text{dba})_3$ in MeCN at room temperature (56% yield).²¹

Following reactions with stannanes, a coupling of vinyl triflate **3** with an acetylene was studied (eq 3).^{7a} Thus, reaction of triflate **3** with Piv-protected propargylamine in the presence of $\text{Pd}(\text{AsPh}_3)_4$ and K_2CO_3 in NMP at 40 °C afforded enyne **8** in 50% isolated yield. Use of organic bases was less successful, as Et_3N

gave no reaction and the use of Et_2NH quickly led to the corresponding pyrrole, which did not couple to the propargylamine under these reaction conditions.



Examples that involve insertion of CO are depicted in eq 4. Treatment of vinyl triflate **3** with $\text{Pd(AsPh}_3)_4$ in DMF under a CO-atmosphere in the presence of methanol and triethylamine at room temperature, rapidly produced the corresponding α,β -unsaturated ester **9** in 79% yield.²² When similar conditions were applied using diisopropylamine instead of methanol, amide formation indeed took place (according to TLC), but was followed immediately by loss of ethanol to give the corresponding pyrrole in 58% yield.



Conversion of the triflate into an aldehyde functionality was achieved by using $\text{Pd(PPh}_3)_4$ and $n\text{-Bu}_3\text{SnH}$ as a hydride donor in THF (eq 4).²³ In this case, CO-insertion was accompanied by coordination of $n\text{-Bu}_3\text{SnH}$ to the intermediate Pd-complex, so that a mixture of aldehyde **10** and pyrroline **11** was obtained. Changing to CH_2Cl_2 as the solvent resulted in exclusive formation of the pyrroline **11**. The starting material was recovered unchanged when tris(trimethylsilyl)silane or triethylsilane was used as hydride donor under identical conditions ($\text{Pd(PPh}_3)_4$, CO, THF).

In summary, a novel butyrolactam-derived vinyl triflate has been shown to be a synthetically useful intermediate in various types of coupling reactions. While relatively harsh conditions have to be avoided due to the tendency of the system to form pyrroles, moderate to good yields are obtained of pyrroline systems that can be further functionalized in several ways. Other types of coupling reactions and synthetic applications of this and other 5-membered lactam-derived vinyl triflates are currently under investigation.

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References and Notes:

- For a review on vinyl triflate chemistry, see: Ritter, K. *Synthesis* **1993**, 735.
- (a) Stille, J.K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508; (b) Scott, W.J.; Stille, J.K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.
- De Meijere, A.; Meyer, F.E. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2379.
- See e.g.: Lipshutz, B.H.; Elworthy, T.R. *J. Org. Chem.* **1990**, *55*, 1695.
- Cintas, P. *Synthesis* **1992**, 248.
- For cuprate additions, see e.g. (a) Tsushima, K.; Murai, A. *Chem. Lett.* **1990**, 761. (b) Nicolaou, K.C.; Reddy, K.R.; Skokotas, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.-K. *J. Am. Chem. Soc.* **1993**, *115*, 3558. For cuprate additions to thiolactone-derived vinyl triflates, see: (c) O'Neil, I.A.; Hamilton, K.M.; Miller, J.A.; Youmg, R.J. *Synlett* **1995**, 151; For Nozaki-Hiyama couplings, see: (d) Nicolaou, K.C.; Theodorakis, E.A.; Rutjes, F.P.J.T.; Sato, M.; Tiebes, J.; Xiao, X.-Y.; Hwang, C.-K.; Duggan, M.E.; Yang, Z.; Couladouros, E.A.; Sato, F.; Shin, J.; He, H.-M.; Bleckman, T. *J. Am. Chem. Soc.* **1995**, *117*, 10239.

- 7) (a) Okita, T.; Isobe, M. *Tetrahedron* **1995**, 3737; (b) Foti, C.J.; Comins, D.L. *J. Org. Chem.* **1995**, 60, 2656.
- 8) See e.g.: (a) Romagnoli, R.; Roos, E.C.; Hiemstra, H.; Moolenaar, M.J.; Speckamp, W.N.; Kaptein, B.; Schoemaker, H.E. *Tetrahedron Lett.* **1994**, 35, 1087; (b) Hopman, J.C.P.; Hiemstra, H.; Speckamp, W.N. *J. Chem. Soc. Chem. Commun.* **1995**, 617; (c) Moolenaar, M.J.; Speckamp, W.N.; Hiemstra, H.; Poetsch, E.; Casutt, M. *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 2391.
- 9) This is complementary with observations of Isobe^{7a} and Comins,^{7b} who state that the unsubstituted *N*-benzoyl-2-pyrrolidinone-derived vinyl triflate is highly unstable.
- 10) Spectral data of **3**: IR (CHCl₃) ν_{\max} 3020, 2975, 1650, 1430, 1365, 1230, 1170, 1135, 1085, 980 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.74 (d, *J* = 8.4 Hz, 2 H, ArH), 7.34 (d, *J* = 8.4 Hz, 2 H, ArH), 5.35 (dd, *J* = 4.2, 0.9 Hz, 1 H, OCH), 5.21-5.19 (m, 1 H, =CH), 3.95 (dq, *J* = 9.6, 7.0 Hz, 1 H, OCHH), 3.65 (dq, *J* = 9.6, 7.0 Hz, 1 H, OCHH), 2.44 (s, 3 H, ArCH₃), 2.26-2.22 (m, 2 H, CH₂), 1.22 (t, *J* = 7.0 Hz, CH₃CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 145.1, 140.6, 134.1, 130.0, 127.6, 118.5 (q, *J* = 321.5 Hz, CF₃), 103.5, 91.4, 63.1, 33.7, 21.6, 14.6; HRMS: found for (M⁺ - EtOH): 368.9971, calcd. for C₁₂H₁₀NO₅F₃S₂: 368.9953.
- 11) McMurry, J.E.; Scott, W.J. *Tetrahedron Lett.* **1983**, 24, 979.
- 12) Comins, D.L.; Dehghani, A. *Tetrahedron Lett.* **1992**, 33, 6299.
- 13) Scott, W.J.; Crisp, G.P.; Stille, J.K. *J. Am. Chem. Soc.* **1984**, 106, 4630.
- 14) All new materials were obtained as pure compounds and appropriately characterized by spectroscopic methods (IR, ¹H NMR, ¹³C NMR, high resolution mass spectral data).
- 15) Spectral data of **5**: ¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, *J* = 8.3 Hz, 2 H, ArH), 7.31 (d, *J* = 8.0 Hz, 2 H, ArH), 5.51 (d, *J* = 6.1 Hz, 1 H, CHO), 5.29-5.27 (m, 1 H, =CH), 3.98 (dq, *J* = 9.7, 7.1 Hz, 1 H, OCHH), 3.65 (dq, *J* = 9.7, 7.0 Hz, 1 H, OCHH), 2.42 (s, 3 H, ArCH₃), 2.27 (ddd, 17.4, 6.1, 2.0 Hz, 1 H, CHH), 2.16 (ddd, *J* = 17.4, 3.5, 0.7 Hz, 1 H, CHH), 1.22 (t, *J* = 7.0 Hz, CH₃CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 144.4, 134.8, 139.7, 128.0, 127.5, 113.8, 92.7, 63.1, 35.6, 21.6, 14.8; HRMS: found for (M⁺ - EtOH): 255.0097, calcd. for C₁₁H₁₀ClNO₂S: 255.0097.
- 16) A similar example in which a triflate is replaced by a cyanide has been reported: Sisti, N.J.; Fowler, F.W.; Grierson, D.S. *Synlett* **1991**, 816.
- 17) Farina, V.; Kapodia, S.; Krishnan, B.; Wang, C.; Liebeskind, L.S. *J. Org. Chem.* **1994**, 59, 5905.
- 18) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, 113, 9585.
- 19) A solution of vinyl triflate **3** (65 mg, 0.16 mmol) in dry NMP (1.6 mL) under a N₂-atmosphere was treated with Pd₂(dba)₃ (2.9 mg, 3.1 μ mol) and triphenylarsine (7.7 mg, 25 μ mol) and the resulting solution was stirred for 10 min at rt. Vinyltributyltin (55 μ L, 0.19 mmol) was added and after stirring for 1 h at rt, the reaction mixture was diluted with EtOAc (25 mL) and washed with water (3 x 10 mL) and brine (10 mL). The resulting organic layer was dried (Na₂SO₄), concentrated and chromatographed (silica, 30% ethyl acetate in petroleum ether) to give the diene **4** (35 mg, 77%) as a colorless oil. **4**: IR (CHCl₃) ν_{\max} 3275, 2060, 1595, 1360, 1350, 1170, 1090 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.61 (d, *J* = 8.3 Hz, 2 H, ArH), 7.25 (d, *J* = 8.3 Hz, 2 H, ArH), 6.53 (ddd, *J* = 17.5, 11.0, 0.9 Hz, 1 H, CH₂=CH), 5.56 (d, *J* = 17.5 Hz, 1 H, CHH=CH), 5.45-5.44 (m, 1 H, C=CH), 5.36 (d, *J* = 5.2 Hz, 1 H, OCH), 5.24 (d, *J* = 11.0 Hz, 1 H, CHH=CH), 4.00 (dq, *J* = 9.7, 7.1 Hz, 1 H, OCHH), 3.65 (dq, *J* = 9.7, 7.1 Hz, 1 H, OCHH), 2.41 (s, 3 H, ArCH₃), 2.14-2.06 (m, 2 H, CH₂), 1.22 (t, *J* = 7.1 Hz, 3 H, CH₃CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 143.7, 141.0, 135.2, 129.4, 129.1, 127.3, 117.0, 113.5, 92.4, 62.8, 35.9, 21.5, 14.8. HRMS: 247 (M⁺ - EtOH, 31%), 182 (17%), 91 (100%). HRMS: found for (M⁺ - EtOH): 247.0648, calcd. for C₁₃H₁₃NO₂S: 247.0667.
- 20) Solberg, J.; Undheim, K. *Acta Chem. Scand. Ser. B.* **1989**, 43, 62.
- 21) Farina, V.; Krishnan, B.; Marshall, D.R.; Roth, G.P. *J. Org. Chem.* **1993**, 58, 5434.
- 22) Cacchi, S.; Morera, E.; Ortari, G. *Tetrahedron Lett.* **1985**, 26, 1109.
- 23) Scott, W.J.; McMurray, J.E. *Acc. Chem. Res.* **1988**, 21, 47.