ORGANIC LETTERS

2005
Vol. 7, No. 25
5585−5587

Regioselective Heck Couplings of α,*β*-Unsaturated Tosylates and Mesylates with Electron-Rich Olefins

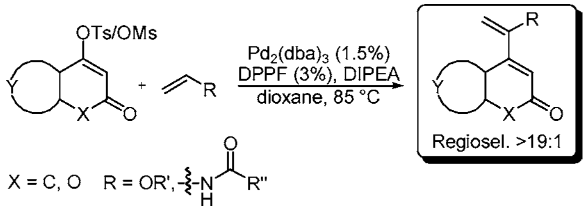
Anders Lindhardt Hansen and Troels Skrydstrup*

Department of Chemistry and the Interdisciplinary Nanoscience Center, University of Aarhus, Langelandsgade 140, 8000 Aarhus C, Denmark

ts@chem.au.dk

Received September 5, 2005

ABSTRACT



Highly regioselective Heck couplings of α,*β*-unsaturated tosylate and mesylate derivatives with *N*-acyl *N*-vinylamines and vinyl ethers were achieved. Several 2-alkoxy-1,3-dienes and 2-acylamino-1,3-butadienes were synthesized in good yields using 1.5 mol % of $Pd_2(dba)_3$, 3 mol % of DPPF, and diisopropylethylamine in dioxane. When working with α,*β*-unsaturated ketones and esters, this method provides a less costly alternative to similar couplings using a triflate electrophile.

Formation of new sp^2 C−C bonds using the palladium(0)-catalyzed Heck reaction is a well-known and widely used technique.[1] The degree of regioselectivity in the reaction is strongly dependent on the substrates and the reaction conditions used. Electron-deficient olefins, such as acrylates or acrylamides, usually provide *β*-substituted products, whereas with electron-rich olefins (vinyl ethers and amides), substitution occurs mainly at the α-position. Obtaining exclusive α-substitution on electron-rich alkenes often requires the use of bidentate ligands, polar solvents, and aryl/alkenyl triflates as the electrophile.[2] Considerable work has been devoted to the development of new catalytic systems to facilitate couplings with the less reactive but also less expensive and more readily available aryl chlorides instead of aryl bromides/iodides.[1f,g] Aryl/alkenyl electrophiles carrying halogens preferentially follow a neutral Heck mechanism leading to a higher degree of the *β*-substituted product. Unfortunately, this complicates the use of these compounds regarding couplings with electron-rich alkenes, which often leads to a mixture of regioisomeric products. Additives such as silver triflate remove the halogen from the solution and facilitate pure α-substitution but increase the cost of the reaction.[3] Palladium-catalyzed Heck couplings with alkenyl tosylates

---

(1) For some relevant reviews, see: (a) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: Orlando, FL, 1985. (b) Tsuji, J. *Palladium Reagents and Catalysts: Innovation in Organic Synthesis*; Wiley: Chichester, U.K., 1995. (c) Brase, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 3. (d) Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 6. (e) *Transition Metal Catalyzed Reactions*; Davis, S. G., Murahashi, S.-I., Eds.; Blackwell Science: Oxford, 1999. (f) Beletskaya, I.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (g) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002. (h) Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449. (i) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed.; University Science Books: Sausalito, CA, 1999; Chapter 4.6. (j) Beller, M.; Riermeier, T. H.; Stark, G. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Vol. 1, p 208. (k) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427.

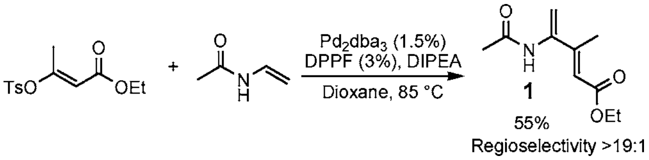
(2) For a few papers on the topic of insertion and regioselectivity, see: (a) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417. (b) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (c) Ludwig, M.; Stromberg, S.; Svensson, M.; Akermark, B. *Organometallics* **1999**, *18*, 970. (d) Larhed, M.; Hallberg, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002. (e) Mo, J.; Xu, L.; Xiao, J. *J. Am. Chem. Soc.* **2005**, *127*, 751. (f) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1992**, *57*, 3558.

10.1021/ol052136d CCC: $30.25

have previously been reported, but all the examples were performed with electron-deficient alkenes.[4,5] Developing new catalytic systems replacing the toxic and expensive triflate-substituted electrophiles would be of interest not only from an academic point of view but also from an industrial one.

Previously, we reported a catalytic system facilitating the coupling of an α,*β*-unsaturated tosylate to *N*-vinyl acetamide affording 2-acylamino-1,3-butadiene **1** in 55% isolated yield and with >19:1 α-regioselectivity (Scheme 1).[6–8]

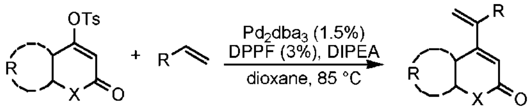
Scheme 1. Heck Couplings of α,*β*-Unsaturated Tosylates with *N*-Vinyl Acetamide

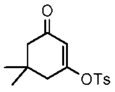
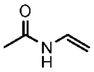
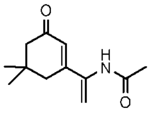
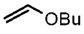
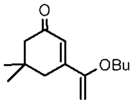
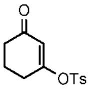
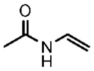
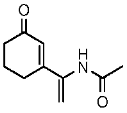
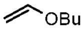
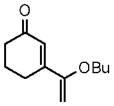
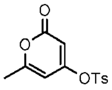
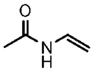
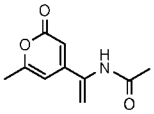
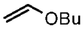
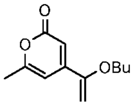
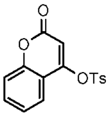
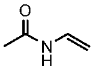
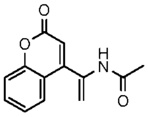
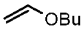
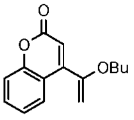
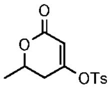
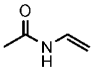
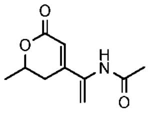
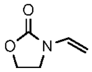


Herein, we report general reaction conditions for the palladium(0)-catalyzed coupling of α,*β*-unsaturated tosylates to vinyl ethers and enamides with high regioselectivity and good yields providing 2-alkoxy-1,3-dienes and 2-acylamino-1,3-butadienes. Both types are useful compounds in the synthesis of functionalized cyclohexenes by cycloaddition reactions.[9] Further expansion of this catalytic system to include α,*β*-unsaturated mesylates was also successful, providing similar reactivities and regioselectivities in certain cases.

All tosylate and mesylate derivatives, **2**−**6** (Table 1) and **16**−**18** (Table 2), respectively, were synthesized according to known literature procedures from commercially available starting materials.[10] The Heck reactions were performed with Pd_2dba_3 as the palladium source, DPPF as the bidentate ligand, and DIPEA as the stoichiometric base.[8] Cross-couplings with the tosylate derivatives and *N*-vinyl acetamide[11] generally went to completion within 6 h (Table 1, entries 1, 3, 5, 7, and 9), but reaction times as short as 1 h were observed for the synthesis of compound **7** (entry 1). An excess of the tosyl substrate (1.5 equiv) was applied to

Table 1. Heck Couplings of α,*β*-Unsaturated Tosylates with Enamides and Butyl Vinyl Ether[a]



Entry	Tosylate	Olefin	Product	Yield
1	 **2**		 **7**	83%
2	**2**		 **8**	75%
3	 **3**		 **9**	79%
4	**3**		 **10**	82%
5	 **4**		 **11**	91%
6	**4**		 **12**	84%
7	 **5**		 **13**	73%
8	**5**		 **14**	91%
9	 **6**		 **15**	55%
10	**2**		No rxn	-

[a] Conditions for enamides: Enamide (1 equiv), tosylate (1.5 equiv), DIPEA (2 equiv). Conditions for vinyl ether: Vinyl butyl ether (4 equiv), DIPEA (3 equiv), tosylate (1 equiv). For reaction times, see Supporting Information. Regioselectivity >19:1 branched:linear, measured by ^1H NMR. All yields are isolated yields.

---

(3) Cabri, W.; Candiani, I,; Bedeschi, A.; Roberto, S. *Tetrahedron Lett.* **1991**, *32*, 1753.

(4) Fu, X.; Zhang, S.; Yin, J.; McAllister, T. L.; Jiang, S. A.; Chou-Hong, T.; Thiruvengadam, K.; Zhang, F. *Tetrahedron Lett.* **2002**, *43*, 573.

(5) For examples on the use of vinyl/aryl tosylates in palladium(0)-catalyzed coupling reactions, as well as oxidative addition studies, see: (a) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369. (b) Fu, X.; Thiruvengadam, T. K.; Zhang, F. *Tetrahedron Lett.* **2002**, *43*, 573. (c) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 8704. (d) Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 194. (e) Klapars, A.; Campos, K. R.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185. (f) Fu, X.; Zhang, S.; Yin, J.; Schumacher, D. P. *Tetrahedron Lett.* **2002**, *43*, 6673.

(6) Hansen, A. L.; Skrydstrup, T. *J. Org. Chem.* **2005**, *70*, 5997.

(7) For recent Heck coupling with enamides, see: (a) Andappan, M. M. S.; Nilsson, P.; von Schenck, H.; Larhed, M. *J. Org. Chem.* **2004**, *69*, 5212. (b) Vallin, K. S. A.; Zhang, Q.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **2003**, *68*, 6639. (c) Harrison, P.; Meek, G. *Tetrahedron Lett.* **2004**, *45*, 9277.

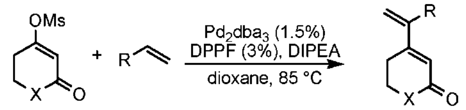
(8) DIPEA = diisopropylethylamine, DPPF = 1,1′-bis(diphenylphosphino)ferrocene.

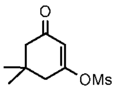
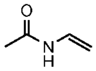
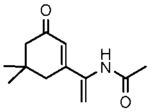
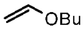
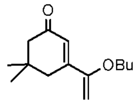
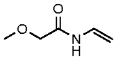
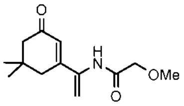
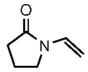
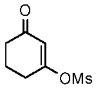
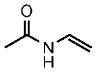
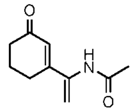
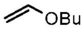
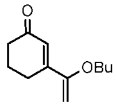
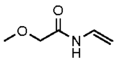
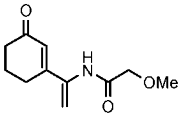
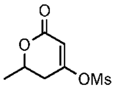
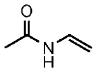
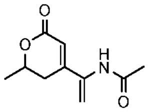
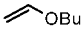
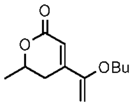
(9) (a) Andersson, C.-M.; Hallberg, A. *J. Org. Chem.* **1989**, *54*, 1502. (b) Krohn, K.; Micheel, J.; Zukowski, M. *Tetrahedron* **2000**, *56*, 4753.

(10) See Supporting Information.

(11) *N*-Vinyl acetamide is commercially available.

Table 2. Heck Couplings of α,β-Unsaturated Mesylates with Enamides and Butyl Vinyl Ether[a]



Entry	Mesylate	Olefin	Product	Yield
1	 **16**		 **7**	82%
2	**16**		 **8**	67%
3	**16**		 **19**	57%
4	**16**		No Rxn	-
5	 **17**		 **9**	61%
6	**17**		 **10**	58%
7	**17**		 **20**	45%
8	 **18**		 **15**	28%
9	**18**		 **21**	42%

[a] Conditions for enamides: Enamide (1 equiv), tosylate (1.5 equiv), DIPEA (2 equiv). Conditions for vinyl ether: Vinyl butyl ether (4 equiv), DIPEA (3 equiv), tosylate (1 equiv). For reaction times, see Supporting Information. Regioselectivity >19:1 branched:linear, measured by ^{1}H NMR. All yields are isolated yields.

ensure complete conversion of *N*-vinyl acetamide, which otherwise complicated purification of the coupling product. Vinyl butyl ether was less reactive, and longer reaction times were needed (entries 2, 4, 6, and 8) in most cases ranging from 2.5 h for **8** (entry 2) to 23 h for **10** (entry 4). Regioselectivities were determined by ^{1}H NMR spectral analysis of the crude reaction mixture and, in all cases, proved better than >19:1 (branched:linear). Compounds **7**−**15** were purified by column chromatography, affording yields as high as 91%. Surprisingly, no reaction occurred when the *N*-vinyl oxazolidinone was examined (entry 10).

Next we tested the possibility of using the mesylate derivatives **16**−**18** (Table 2) as such derivatives represent an even less expensive class of electrophiles than the tosylates.[12] Subjecting **16** to the reaction conditions used for the tosylates and *N*-vinyl acetamide with a reaction time of 5 h resulted in formation of **7** in a similar yield and with a >19:1 (branched:linear) regioselectivity (entry 1). Other coupling attempts between mesylates and enamides were also performed (entries 3, 5, 7, and 8), although the latter two proved more sluggish and hence led to lower coupling yields. Butyl vinyl ether was also successfully coupled to the mesylates (entries 2, 6, and 9), although typically longer reaction times were required compared to the enamides (from 11 to 24 h). In contrast to the tosylates, no coupling between the enamides and butyl vinyl ether and the mesylated derivatives of coumarin and 4-hydroxy-6-methyl-2-pyrone were observed with complete isolation of the starting substrates. This implies that the mesylate derivatives are less reactive as electrophiles than the corresponding tosylates, requiring a strong electron-withdrawing group in the starting materials. Alternatively, a catalytic system with more electron-donating ligands that possibly facilitate the oxidative addition step could be explored. Reacting **16** with *N*-vinyl pyrrolidone, an *N*,*N*-disubstituted enamide, resulted in no reaction, suggesting that the monosubstituted amide functionality might play an important role in the reaction mechanism.

In summary, we have prepared several 2-alkoxy-1,3-dienes and 2-acylamino-1,3-butadienes starting from inexpensive tosylate and mesylate derivatives. The couplings proceed in good yields and with regioselectivities attaining >19:1. This proves that alternatives to the expensive and toxic triflating agents exist when working with α,β-unsaturated systems. The high degree of regioselectivity obtained implies that a cationic reaction mechanism is operating for these couplings. Further work is now ongoing to optimize the coupling with electron-deficient olefins, as well as broadening the perspective of applying the mesyl electrophiles to other known Pd(0)- and Ni(0)-catalyzed reactions.

Acknowledgment. We are indebted to the Danish National Science Research Council and the University of Aarhus for generous financial support.

Supporting Information Available: Experimental procedures for (a) the synthesis of the tosylate and mesylate derivatives, and (b) the Heck coupling reactions. ^{1}H NMR and ^{13}C NMR spectra for the tosylate and mesylate compounds and coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052136D

---

[12] Aldrich prices on reagent grade compounds in euro/mol: mesyl chloride = 15.38, tosyl chloride = 27.16, triflic anhydride = 460.88.