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The Tandem Heck–Allylic Substitution Reaction: A Novel Route to Lactams

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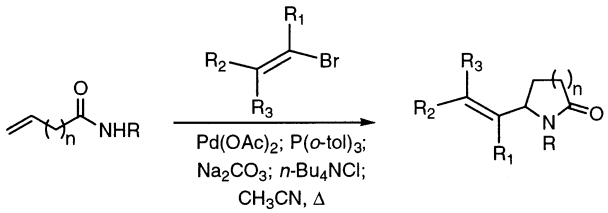
ABSTRACT



A novel route to substituted lactams has been developed using a tandem Heck–allylic substitution reaction. The palladium-catalyzed reaction between ω-olefinic *N*-tosyl amides and vinylic bromides affords in one step the substituted pyrrolidones and piperidones in 49–82% isolated yield. In addition, it is shown that an *N*-phenyl amide can act as a nucleophile in intramolecular allylic substitution reactions.

Palladium-catalyzed tandem reactions have enjoyed considerable interest during the past decade.[1] Several combinations of reactions have been developed both to prepare complex natural products[2] and to provide direct entry into synthetic building blocks.

The observation that the palladium-catalyzed reaction between a vinyl halide and an unactivated olefin often results in the formation of a stable π-allylpalladium species has led to the development of the tandem Heck−allylic substitution reaction.[3] This reaction, elaborated upon extensively by Larock and co-workers,[4] has been carried out in an intramolecular version,[5] as a two-component coupling (either in the Heck reaction step[6] or in the allylic substitution[5c]), or as a three-component coupling.[1a,5c,7] Carbon,[5c,8] oxygen,[9] and nitrogen[10] nucleophiles have been used. In one particular study, an *intermolecular* Heck reaction followed by an *intramolecular* allylic substitution was used to prepare a variety of *N*-tosyl 2-(1-alkenyl)pyrrolidines and -piperidines starting from acyclic olefinic sulfonamides.[6]

We were interested in expanding this coupling−cyclization strategy to acyclic amides to provide the corresponding lactams. Substituted five-membered and six-membered lactams (pyrrolidones and piperidones) are found in innumerable natural products and pharmaceutical compounds.[11] In addition, whereas 2-alkyl[11] and 2-(2-alkenyl) lactams are readily available via *N*-acyliminium ion chemistry,[12] the corresponding 2-(1-alkenyl)-lactams are not easily accessible.

Initially, the olefinic amides **1a**−**c** were reacted with 1-bromopropene[13] and catalytic palladium acetate using the

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(1) (a) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: New York, 1995. (b) Malleron, J.-L.; Fiaud, J.-C.; Legros, J.-Y. *Handbook of Palladium-Catalyzed Organic Reactions*; Academic Press: London, 1997.

(2) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, Germany, 1996; Chapter 31.

(3) (a) Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 3898. (b) Heck, R. F. *Org. React.* **1982**, *27*, 345.

(4) Larock, R. C.; Tu, C. *Tetrahedron* **1995**, *51*, 6635 and references therein.

(5) (a) Harris, G. D., Jr.; Herr, R. J.; Weinreb, S. M. *J. Org. Chem.* **1992**, *57*, 2528. (b) Harris, G. D., Jr.; Herr, R. J.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 5452. (c) Nylund, C. S.; Klopp, J. M.; Weinreb, S. M. *Tetrahedron Lett.* **1994**, *35*, 4287. For an example in which a conjugated diene is used, see: (d) Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423. For an example in which an allene is used, see: (e) Larock, R. C.; Zenner, J. M. *J. Org. Chem.* **1995**, *60*, 482.

(6) Larock, R. C.; Yang, H.; Weinreb, S. M.; Herr, R. J. *J. Org. Chem.* **1994**, *59*, 4172.

(7) Xie, X.; Lu, X. Y. *Tetrahedron Lett.* **1999**, *40*, 8415.

(8) Larock, R. C.; Lu, Y.; Bain, A. C.; Russell, C. E. *J. Org. Chem.* **1991**, *56*, 4589.

(9) Larock, R. C.; Leuck, D. J.; Harrison, L. W. *Tetrahedron Lett.* **1988**, *29*, 6399.

(10) For a comprehensive collection of the literature until 1997, see ref 1b.

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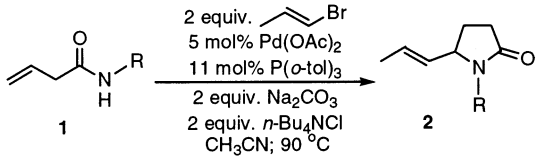
conditions of Larock et al. (Scheme 1 and Figure 1).[6] The reaction with primary amide **1a**[14] and *N*-benzyl amide **1b**[15]

Scheme 1. Tandem Heck Coupling−Allylic Substitution Reaction of Amides



1a,**2a**: R = H; **1b**,**2b**: R = Bn; **1c**,**2c**: R = Ph

did not afford any trace of cyclized products, and analysis of the crude reaction mixture showed only starting material. This is not unexpected because in the cyclization of sulfonamides, the deprotonated species is the nucleophile, while the less acidic amides may not get deprotonated under these conditions. Consequently, the neutral amides would not be sufficiently nucleophilic to attack a π-allylpalladium species.[16]

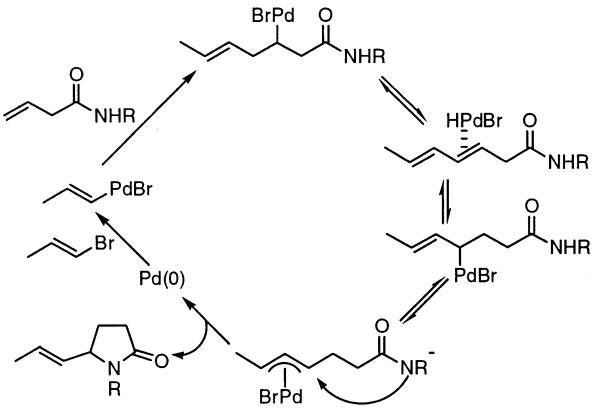


Figure 1. Tandem Heck coupling−cyclization mechanism.[3]

However, encouraging results were obtained when *N*-phenyl amide **1c** was used as a substrate. After 46 h at 90 °C, 97% of the starting material had been converted and **2c** was isolated in 41% yield.[17] This is remarkable, all the more so because a recently described intramolecular aminopalladation of a *p*-nitrophenyl carbamate met with failure.[18] Probably, the pK_a difference between an *N*-phenyl and an *N*-benzyl amide (22.4 and 25.8, respectively)[19] is sufficient to allow deprotonation by Na_2CO_3 in boiling acetonitrile.

For the reaction to succeed, the choice of base and phase-transfer reagent turned out to be very important. The use of organic bases such as Et_3N or Cy_2NMe proved to be inadequate and led to precipitation of Pd-black within the first few minutes of heating. Even the combined use of an organic base with *n*-Bu_4NCl was not successful. Other phase-transfer reagents such as *n*-Bu_4NBr could be used, but the reaction was then considerably slower. It appears that the *n*-Bu_4NCl may have two roles, acting not only as a phase-transfer reagent but also providing chloride as a stabilizing ligand for palladium.[20]

These promising results encouraged the screening of a variety of phosphorus ligands. The ligand turned out to be an important factor in the reaction rate. Shown in Table 1

Table 1. Phosphorus Ligand Effect

entry	P ligand[a]	reaction time (h)	% conversion[b]
1	$P(OEt)_3$	20	54
2	$P(OPh)_3$	16	94
3	$P[O(p\text{-cyanophenyl})]_3$	16	100
4	PPh_3	46	97
5	$P(NMe_2)_3$	24	72
6	$P[O(2,6\text{-dimethylphenyl})]_3$	16	83
7	$P(o\text{-tolyl})_3$	20	92

[a] Metal/ligand ratio = 1/2. [b] Determined by ^1H NMR.

are the results obtained with seven different phosphorus ligands for the conversion of **1c** into **2c**.[21] If the data in this table are analyzed using a Tolman plot,[22] a clear correlation is observed: ligands with larger cone angles and/or poorer electron-donating properties gave rise to faster reactions. An exception is entry 6, although the deviation was found to be due to the lower stability of this ligand. When a slightly larger amount of ligand was used, a higher conversion was obtained.

(11) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 625 and references cited therein.

(12) (a) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1047−1082. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

(13) Used as a mixture of isomers. Due to the reaction mechanism, this leads solely to the trans-substituted product, see ref 6.

(14) This compound was prepared according to the procedure by: Knapp, S.; Levorse, A. T. *J. Org. Chem.* **1988**, *53*, 4006.

(15) This compound was prepared according to the procedure by: Marson, C. M.; Grabowska, U.; Fallah, A. *J. Org. Chem.* **1994**, *59*, 291.

(16) Amides, however, act as nucleophiles in the aminopalladation of a double bond. The addition of a deprotonated amide to a π-allyl palladium intermediate is known; see: Yoshizaki, H.; Satoh, H.; Sato, Y.; Nukui, S.; Shibasaki, M.; Mori, M. *J. Org. Chem.* **1995**, *60*, 2016.

(17) Byproducts could not be identified.

(18) Overman, L. E.; Remarchuk, T. P. *J. Am. Chem. Soc.* **2002**, *124*, 12.

(19) Determined in DMF: Maran, F.; Celadon, D.; Severin, M. G.; Vianello, E. *J. Am. Chem. Soc.* **1991**, *113*, 9320.

(20) Jeffery, T.; David, M. *Tetrahedron Lett.* **1998**, *39*, 5751. Wolf, L. B.; Tjen, K. C. M. F.; Ten Brink, H. T.; Blaauw, R. H.; Hiemstra, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2002**, *1*, 70. It should also be mentioned that it was important to dry the phase-transfer reagent; see Supporting Information. When commercially supplied *n*-Bu_4NCl under otherwise anhydrous conditions was used, the conversion was about one-third during the same reaction period.

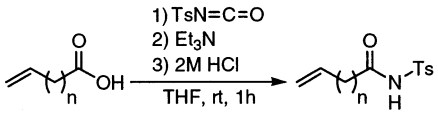
(21) $P[O(p\text{-Cyanophenyl})]_3$ was prepared according to the procedure reported by: Iselin, B.; Rittel, W.; Sieber, P.; Schwyzer, R. *Helv. Chim. Acta* **1957**, *40*, 373. $P[O(2,6\text{-Dimethylphenyl})]_3$ was prepared according to the procedure reported by: Burton, S. D.; Kumara Swamy, K. C.; Holmes, J. M.; Day, R. O.; Holmes, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 6104.

(22) (a) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313. (b) Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*, 2nd ed.; Wiley & Sons: New York, 1994; Chapter 4, p 85.

Although the rate of the reaction could be increased by using phosphite ligands, the isolated yield did not significantly increase. On the basis of ligand stability, reaction times, and conversions, the ligand of choice for these tandem reactions was P(*o*-Tolyl)$_3$.[23]

It is evident that an electron-withdrawing group at nitrogen is important for a successful cyclization. It was therefore anticipated that the use of *N*-tosyl amides might overcome the problems experienced with the *N*-phenyl amides. The pK_a of an *N*-tosyl amide is comparable to that of a carboxylic acid.[24] Starting from commercially available carboxylic acids, the corresponding *N*-tosyl amides **3** and **4** were prepared following a literature procedure[25] in excellent yield (Scheme 2).[26]

Scheme 2. Synthesis of *N*-Tosylamides

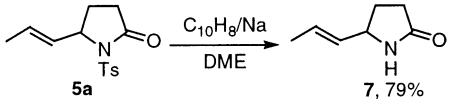


3: n=1, 94%
4: n=2, 96%

Tandem Heck−allylic substitution reactions using **3** and **4** were carried out under similar conditions as for amide **1a**−**c**. Overnight, both substrates afforded the desired lactams with a variety of olefinic side chains[27] in reasonable to good isolated yields. The results are summarized in Table 2. As can be seen from this table, even the use of heavily substituted vinyl bromides results in the corresponding pyrrolidones and piperidones.

To illustrate that the corresponding amides are easily accessible from products **5** and **6**, **5a** was desulfonylated by treatment with sodium naphthalenide in DME[28] to afford the corresponding amide **7** in 79% yield (Scheme 3).[29]

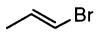
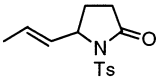
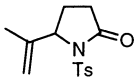
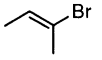
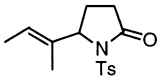
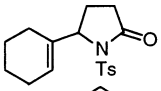
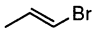
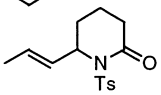
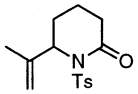
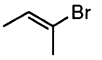
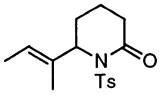
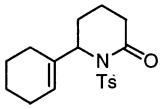
Scheme 3. Desulfonylation of **5a**



5a **7**, 79%

In conclusion, a new application of the tandem Heck−allylic substitution reaction has been developed that provides rapid access to substituted pyrrolidones and piperidones starting from commercially available carboxylic acids. The products can be easily desulfonylated and are valuable building blocks for natural product synthesis. In addition, it has been shown that *N*-phenyl amides are able to act as nucleophiles in intramolecular allylic substitution reactions, a finding that should elicit more research in this field.

Table 2. Tandem Products Using Amides **3** and **4**

N-tosyl amide	vinyl bromide	product,	yield (%)
3			**5a**, 82
			**5b**, 77
			**5c**, 53
			**5d**, 55
4			**6a**, 81
			**6b**, 75
			**6c**, 50
			**6d**, 49

Acknowledgment. The authors thank DSM for financial support.

Supporting Information Available: Experimental details describing the synthesis and characterization of **2c**, **3**, **4**, **5a**−**d**, **6a**−**d**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Preparation of the corresponding six-membered ring (piperidone) required long reaction times, and the reaction never went to completion.

(24) Lei, A.; Lu, X. *Org. Lett.* **2000**, *2*, 2699 and references cited therein. See also: Lei, A.; Liu, G.; Lu, X. *J. Org. Chem.* **2002**, *67*, 974.

(25) Feldman, K. S.; Bruendl, M. M.; Schildknegt, K.; Bohnstedt, A. C. *J. Org. Chem.* **1996**, *61*, 5440.

(26) During this research, Overman and Remarchuk reported the intramolecular aminopalladation of an *N*-tosyl amide in excellent yield and high ee (ref 18). No details about the synthesis of the substrate were disclosed.

(27) 1-Bromocyclohex-1-ene was prepared according to the procedure described by: Billups, W. E.; Lee, G. A.; Arney, B. E.; Whitmire, K. H. *J. Am. Chem. Soc.* **1991**, *113*, 7980.

(28) Greene, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley & Sons: New York, 1999.

(29) This compound has been previously prepared using a multistep route: Vedejs, E.; Meier, G. P. *Tetrahedron Lett.* **1979**, 4185.