Palladium-Catalyzed Allylic Alkylation of α-Sulfinyl Carbanions under Biphasic Conditions

Guillaume Maitro, Guillaume Prestat, David Madec,* Giovanni Poli*

Université Pierre et Marie Curie – Paris 6, Laboratoire de Chimie Organique (UMR CNRS 7611), Institut de Chimie Moléculaire (FR 2769), case 183, 4 place Jussieu, 75252 Paris cedex 05, France
Fax +33(1)44277567; E-mail: giovanni.poli@upmc.fr; E-mail: madec@ccr.jussieu.fr

Received 23 January 2006

Dedicated to the memory of Professor Marcial Moreno Mañas.

Abstract: Palladium-catalyzed allylic alkylation of α-sulfinyl carbanions can take place under biphasic conditions. These new conditions provide a simple, mild and efficient route to allylated sulfoxides in good yields. The reaction tolerates a wide variety of EWG groups as additional carbanion stabilizing groups such as ester, acetyl, cyano, amide, sulfonyl and sulfinyl functions.

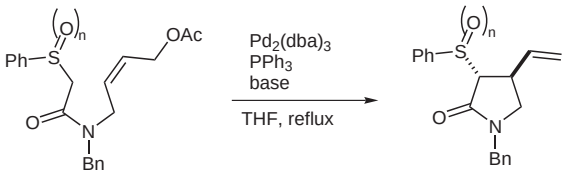
Key words: palladium, sulfoxides, carbanions, catalysis, allylic alkylation

Transition-metal-catalyzed allylic substitutions have proven to be a fundamental tool for carbon–carbon bond formation.[1] In this context, whereas the palladium-catalyzed allylic alkylation of stabilized α-sulfenyl- and α-sulfonyl carbanions has been amply described,[2] the corresponding reaction involving α-sulfinyl carbanions, despite the stereogenic character of the sulfur atom, has been so far virtually neglected.[3] Such a fact is probably due to the high coordination power of the sulfoxide function toward palladium,[4] which prevents the direct transposition of classical reaction conditions from α-sulfenyl- or α-sulfonyl-activated carbanions to the corresponding α-sulfinyl analogues. For example, in the course of our previous studies on the palladium-catalyzed intramolecular allylic alkylation of unsaturated amides,[5] the expected vinylpyrrolidones could be satisfactorily obtained when a sulfenyl- or a sulfonyl-based additional carbanion stabilizing group (ACSG) was present, whereas under the same conditions the corresponding sulfinyl-based derivative refused to cyclize (Table 1).[6]

We recently reported that the palladium-catalyzed intramolecular allylic alkylation of unsaturated amides could be efficiently run under phase-transfer conditions (Equation 1).[7] These conditions were milder and higher yielding than those previously reported in a homogenous medium.

Given the remarkable efficiency of these reaction conditions, we decided to test this new system in the so far elusive palladium-catalyzed allylation of sulfinyl-based carbanions. The allylic alkylation of *tert*-butyl benzenesulfinyl acetate (**1**)[8] with allyl acetate was first studied as a model reaction. The reaction was very sluggish using the classical system $[Pd(C_3H_5)Cl]_2$ (5 mol%), dppe (12.5 mol%), NaH (1.1 equiv), in THF at room temperature. After five days, the desired allylated product was isolated in a poor (≤15%) yield (Table 2, entry 1). Thermal treatment led to the degradation of the starting material after two hours at reflux (entry 2). To our satisfaction, switch to the above-mentioned biphasic conditions resulted in substantial improvement.[9]

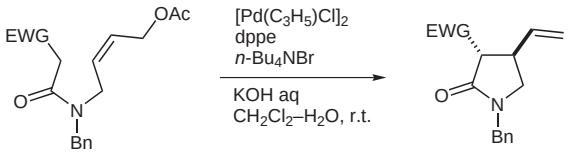
Table 1 Palladium-Catalyzed Intramolecular Allylic Alkylation of Sulfur Stabilized Amides[a]



Entry	n	Base	Yield (%)[b]
1	2	BSA/AcOK	78
2	0	NaH	58
3	1	NaH	0

[a] Reagents and conditions: substrate, $Pd_2(dba)_3$ (5 mol%), PPh_3 (50 mol%), base (BSA, 1.2 equiv and AcOK, 10 mol% or NaH, 1.1 equiv) in THF, reflux, 12 h.
[b] Yields are given for isolated products.

Indeed, the use of *n*-Bu_4NBr (10 mol%) as the phase transfer agent, $[Pd(C_3H_5)Cl]_2$ (2 mol%) as the palladium source, dppe (5 mol%) as the ligand, and KOH (2.0 equiv) as the base, in a biphasic CH_2Cl_2–H_2O (1:1; v/v) system led after 30 minutes to the desired allylation product **2** (1:1 diastereomeric ratio) in 44% yield at room temperature

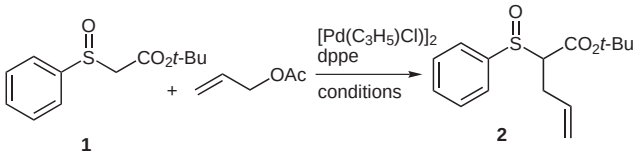


EWG = CO_2Me, COMe, CN, SPh, SO_2Ph

Equation 1 Palladium-catalyzed intramolecular allylic alkylation under phase-transfer conditions

SYNLETT 2006, No. 7, pp 1055–1058
Advanced online publication: 24.04.2006
DOI: 10.1055/s-2006-939702; Art ID: G01606ST

Table 2 Palladium-Catalyzed Allylation of *tert*-Butyl Benzenesulfinyl Acetate: Optimization of the Reaction Conditions[a]



1 2

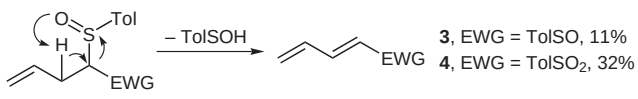
Entry	Conditions	Time	Yield (%)[b]
1	NaH, THF, r.t.	120 h	≤15
2	NaH, THF, reflux	2 h	0
3	KOH, H_2O–CH_2Cl_2, *n*-Bu_4NBr, r.t.	30 min	44
4	KOH, H_2O–CH_2Cl_2, r.t.	5 min	62

[a] Reagents and conditions: allyl acetate (1 equiv), substrate (1.1 equiv), $[Pd(C_3H_5)Cl]_2$ (2 mol%), dppe (5 mol%) and base.
[b] Yields are given for isolated product. The allylated product was isolated as a 1:1 mixture of diastereomers.

(entry 3). Interesting to note, the yield could be sizeably improved (62%) by simply omitting *n*-Bu_4NBr (entry 4). It thus appears that the phase-transfer agent is not only unnecessary to the allylation reaction, but also somehow detrimental.[10] In a second set of experiments, the influence of the nature of the ACSG was studied. Table 3 illustrates our results.[11] Methyl benzenesulfinyl acetate did not afford the corresponding allylation product owing to competitive saponification of the starting material (entry 1). Although this result was not completely unexpected, it is worth noting that such a problem was not met in the previously reported methyl ester stabilized intramolecular allylation under identical conditions (Equation 1).

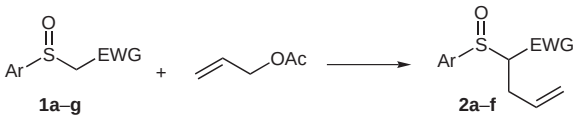
Acetyl-,[12] cyano-,[13] amide-,[14] and sulfinyl-[15] ACSGs allowed also formation of the corresponding allylated products **2b**–**f** in good to excellent yields (Table 3, entries 3–6), the sulfonyl group[16] being the only ACSG affording a poor yield of the corresponding product **2g** (entry 7).

In experiments of entries 6 and 7, the α,β–γ,δ-unsaturated sulfoxide **3**[17] and sulfone **4**,[18] resulting from sulfenic acid elimination,[19] were isolated in 32% and 11% yield, respectively (Equation 2). Noteworthy, **1f** required 21 hours to afford the desired product, whereas the sulfenyl-substituted precursor **1h** was completely inert under the reaction conditions (entry 8). These results might be related to the comparatively low acidity of **1f** and **1h**.[20] To further explore the scope of this new process, we investigated next the palladium-catalyzed allylic alkylation of acetyl-, *tert*-butoxycarbonyl-, cyano- and diphenylaminocarbonyl-stabilized precursors **1b**–**e** with 3-acetoxy-cyclopentene.



Equation 2 Formation of dienic compounds via elimination.

Table 3 Influence of the Nature of the ACSG[a]



1a–g 2a–f

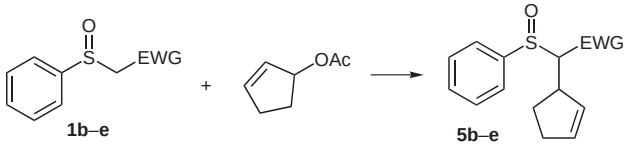
Entry	Ar	EWG	Product	Time	Yield (%)[b]
1	Ph	CO_2Me	**2a**	–	0
2	Ph	CO_2t-Bu	**2b**	5 min	62
3	Ph	COMe	**2c**	15 min	86
4	Ph	CN	**2d**	1 min	96
5	Ph	$CONPh_2$	**2e**	1 h	52[c]
6	Tol	SOTol[d]	**2f**	21 h	46[e]
7	Tol	SO_2Tol	**2g**	3 h	24[f]
8	Tol	STol	**2h**	24 h	nr

[a] Reagents and reaction conditions: allyl acetate (1 equiv), α-sulfinyl activated substrate (1.1 equiv), $[Pd(C_3H_5)Cl]_2$ (2 mol%), dppe (5 mol%), KOH (50% aq solution, 2.0 equiv), CH_2Cl_2–H_2O (1:1), r.t.
[b] Yields are given for isolated products. Unless otherwise stated, the allylated products were isolated as a 1:1 mixture of diastereomers.
[c] A 70:30 diastereomeric ratio was obtained.
[d] A 1:1 mixture of diastereomers was used as starting material.
[e] The allylated product was isolated as a mixture of three diastereomers.
[f] The allylated product was isolated as a single diastereomer.

Gratifyingly, the optimized conditions converted these substrates into the corresponding allylated products **5b**–**e** in good to excellent yields (Table 4).

Since **2b**–**e** and **5b**–**e** were obtained as mixtures of two and four isomers, respectively, oxidation of the allylated sulfoxides into the corresponding sulfones was con-

Table 4 Scope of the Reaction Using 3-Acetoxy Cyclopentene[a]



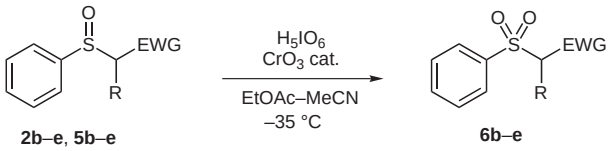
1b–e 5b–e

Entry	EWG	Product	Time	Yield (%)[b]
1	COMe	**5b**	5 min	86
2	CO_2t-Bu	**5c**	5 min	93
3	CN	**5d**	5 min	95
4	$CONPh_2$	**5e**	3 h	52

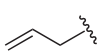
[a] Reagents and reaction conditions: 3-acetoxy-cyclopentene (1 equiv), α-sulfinyl-activated substrate (1.1 equiv), $[Pd(C_3H_5)Cl]_2$ (2 mol%), dppe (5 mol%), KOH (50% aq solution, 2.0 equiv), CH_2Cl_2–H_2O (1:1), r.t.
[b] Yields are given for isolated products. The allylated products were isolated as a mixture of four isomers.

sidered, so as to reduce the number of diastereomers in the adducts. Such an oxidation turned out to be rather delicate since the starting sulfoxides tend to suffer easy sulfenic acid elimination to the corresponding 1,3-dienes. After some experimentation we eventually found that the CrO_3-catalyzed oxidation, according to Trudell et al.,[21] allowed isolation of the desired sulfones **6e–h** in satisfactory yields (Table 5).

Table 5 Oxidation of the Allylated Sulfoxides to the Corresponding Sulfones[a]



2b–e, **5b–e** **6b–e**

Entry	Substrate	EWG	R	Product	Yield (%)[b]
1	**2b**	CO_2t-Bu		**6b**	96
2	**2c**	COMe		**6c**	75
3	**2d**	CN		**6d**	99
4	**2e**	$CONPh_2$		**6e**	91
5	**5b**	CO_2t-Bu		**6′b**	57[c]
6	**5c**	COMe		**6′c**	43[c]
7	**5d**	CN		**6′d**	40[c]
8	**5e**	$CONPh_2$		**6′e**	50[c]

[a] Reagents and conditions: substrate (1 equiv), H_5IO_6 (2.1 equiv), CrO_3 (10 mol%), EtOAc–CH_3CN (2:1), –35 °C.
[b] Yields are given for isolated products.
[c] The oxidized products were isolated as a 1:1 mixture of diastereomers.

In summary, we have reported a new and operationally very simple protocol for the palladium-catalyzed allylic alkylation of α-sulfinyl carbanions, a transformation not satisfactorily achievable under classical conditions. The new reaction conditions allow the allylation of the tested precursors in good yields and with milder reaction conditions than previously reported. Extension to intramolecular and/or asymmetric variants of the present method is currently under investigation.

Acknowledgment

The support and sponsorship concerted by CNRS and COST Action D24 ‘Sustainable Chemical Processes: Stereoselective Transition Metal-Catalyzed Reactions’ are kindly acknowledged.

References and Notes

(1) For reviews, see: (a) Tsuji, J. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; John Wiley and Sons: New York, **2002**, 1669. (b) Trost, B. M.; Vranken, D. L. V. *Chem. Rev.* **1996**, *96*, 395. (c) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Book: Mill Valley, **1994**.

(2) For palladium-catalyzed allylic alkylation of α-sulfonyl activated carbanions, see: (a) Giambastiani, G.; Poli, G. *J. Org. Chem.* **1998**, *63*, 9608. (b) Cuvigny, T.; Julia, M.; Rolando, C. *J. Organomet. Chem.* **1985**, *285*, 395. (c) Colobert, F.; Genêt, J.-P. *Tetrahedron Lett.* **1985**, *26*, 2779. For palladium-catalyzed allylic alkylation of α-sulfenyl activated carbanions, see: (d) Hiroi, K.; Hidaka, A.; Sezaki, R.; Imamura, Y. *Chem. Pharm. Bull.* **1997**, *45*, 769. (e) Hiroi, K.; Koyama, T.; Anzai, K. *Chem. Lett.* **1990**, 235.

(3) To our knowledge, only two examples in the literature report the use of α-sulfinyl carbanions as nucleophilic partners in Pd-mediated allylic alkylation. For a stoichiometric example see: (a) Trost, B. M.; Weber, L.; Strege, P.; Fullerton, T. J.; Dietsche, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3426. (b) For a catalytic example see: Hiroi, K.; Suzuki, Y.; Kato, F.; Kyo, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 37.

(4) For reviews concerning the use of sulfoxide ligands in palladiumcatalysis, see: (a) Fernandez, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651. (b) Hanquet, G.; Colobert, F.; Lanners, S.; Solladié, G. *ARKIVOC* **2003**, *(vii)*, 328.

(5) Poli, G.; Giambastiani, G.; Pacini, B.; Porcelloni, M. *J. Org. Chem.* **1998**, *63*, 804.

(6) Giambastiani, G. *PhD Thesis*; University Pierre et Marie Curie: Paris, **2001**.

(7) Madec, D.; Prestat, G.; Martini, E.; Fristrup, P.; Poli, G.; Norrby, P.-O. *Org. Lett.* **2005**, *7*, 995.

(8) (a) This substrate was prepared by oxidation of the corresponding thioether (see ref. 8b) with Oxone® and wet alumina (see ref. 8c). (b) Babin, D.; Demassey, J.; Demoute, J.-P.; Dutheil, P.; Terrie, I.; Tessier, J. *J. Org. Chem.* **1992**, *57*, 584. (c) Greenhalgh, R. P. *Synlett* **1992**, 235.

(9) For generalities on phase transfer catalysis, see: (a) Demlow, E. V.; Demlow, S. S. *Phase Transfer Catalysis*, 3rd ed.; VCH: Weinheim, **1993**. (b) Goldberg, Y. *Phase Transfer Catalysis: Selected Problems and Applications*; Gordon and Breach Science Publ.: Reading, **1992**. (c) Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase Transfer Catalysis: Fundamentals, Applications, and Industrial Perspectives*; Chapman and Hall: New York, **1994**.

(10) For a review on the effect of halides in transition-metal catalysis see: Fagnou, K.; Lautens, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 26.

(11) **General Procedure for Palladium-Catalyzed Allylic Allylation of α-Sulfinyl Activated Carbanions under Biphasic Conditions.**
To a solution of $[Pd(C_3H_5)Cl]_2$ (2 mol%) in CH_2Cl_2 (500 μL) dppe (5 mol%) was added. After 5 min stirring at r.t., the allyl acetate (1 mmol), a CH_2Cl_2 (4.5 mL) solution of the sulfoxide (1.1 mmol), H_2O (5 mL), and KOH (50% aq solution, 2 mmol) were successively added. The resulting biphasic system was vigorously stirred at r.t. for the indicated reaction time. The aqueous phase was extracted three times with CH_2Cl_2. The collected organic phases were dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified by flash chromatography.

(12) Nokami, J.; Kataoka, K.; Shiraishi, K.; Osafune, M.; Hussain, I.; Sumida, S.-I. *J. Org. Chem.* **2001**, *66*, 1228.

(13) Ono, T.; Tamaoka, T.; Yuasa, Y.; Matsuda, T.; Nokami, J.; Wakabayashi, S. *J. Am. Chem. Soc.* **1984**, *106*, 7890.
(14) This substrate has been prepared by oxidation of the corresponding thioether with Oxone® and wet alumina (see ref. 8).
(15) Brebion, F. *PhD Thesis*; Université Pierre et Marie Curie: Paris, **2004**.
(16) (a) Jarvis, B. B.; Fried, H. E. *J. Org. Chem.* **1975**, *40*, 1278. (b) Kunieda, N.; Nokami, J.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 256.
(17) Barluenga, J.; Martinez-Gallo, J. M.; Najera, C.; Frananas, F. J.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2605.
(18) Mikolajczyk, M.; Perlikowska, W.; Omelanczuk, J.; Cristau, H.-J.; Perraud-Darcy, A. *J. Org. Chem.* **1998**, *63*, 9716.
(19) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.
(20) For pK_a values of compounds strictly related to **1f** and **1h** see: http://www.chem.wisc.edu/areas/reich/pkatable/.
(21) Xu, L.; Cheng, J.; Trudell, M. L. *J. Org. Chem.* **2003**, *68*, 5388.