Synthetic Methods

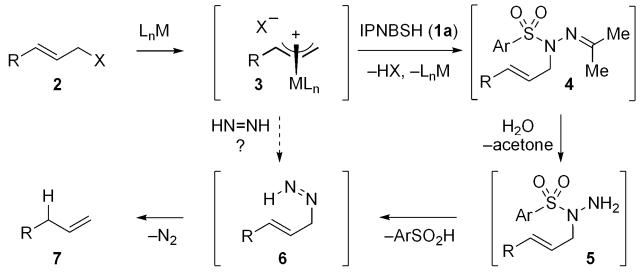
DOI: 10.1002/anie.200802921

# A Stereospecific Palladium-Catalyzed Route to Monoalkyl Diazenes for Mild Allylic Reduction**

*Mohammad Movassaghi* and Omar K. Ahmad*

Transition-metal-catalyzed allylic alkylation reactions have been utilized extensively in synthetic organic chemistry.[1] These reactions include many powerful transformations that focus on carbon–heteroatom bond formation, including reports concerning the use of nitrogen nucleophiles.[2] Herein we report the first example of a stereospecific transition-metal-catalyzed conversion of allylic electrophiles into the corresponding monoalkyl diazenes for a mild and highly stereoselective reduction in a single operation. This palladium-catalyzed diazene synthesis offers opportunities for asymmetric synthesis by the stereospecific reduction of optically active substrates or the use of chiral catalyst systems, using vinyl epoxide and allylic carbonate substrates, respectively.

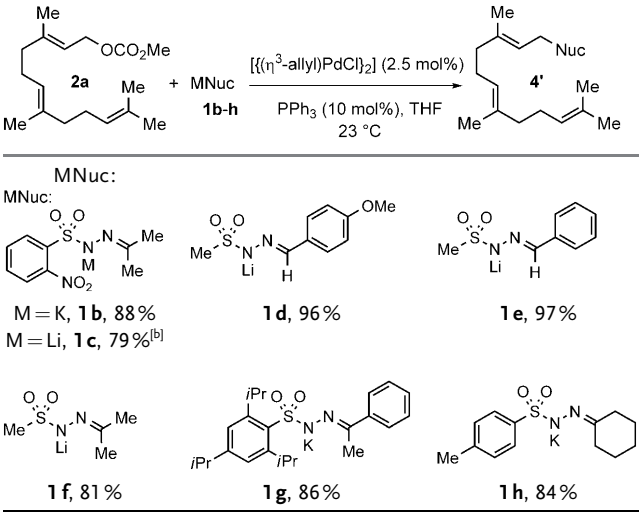
We recently reported the use of *N*-isopropylidene-*N*′-2-nitrobenzenesulfonylhydrazide (IPNBSH, **1a**) for the conversion of alcohols into the corresponding monoalkyl diazenes by the Mitsunobu reaction.[3,4] Our findings regarding the chemistry of **1a** led us to investigate its use as a diimide surrogate in the transition-metal-catalyzed synthesis of monoalkyl diazenes (Scheme 1). We envisioned the reaction of the π-allyl complex **3** with sulfonylhydrazone **1a** to give hydrazone **4**.[5] In situ hydrolysis and fragmentation of **4**[3,6] would give the allylic diazene **6** and, upon sigmatropic loss of dinitrogen, afford the desired product **7**. The use of **1a** in place of diimide enables the conversion of **3** into diazene **6** without isolation of intermediates.




***Scheme 1.*** Metal-catalyzed synthesis of allylic diazenes and subsequent loss of $N_2$. IPNBSH = *N*-isopropylidene-*N*′-2-nitrobenzenesulfonylhydrazide; Ar = 2-$NO_2C_6H_4$.

We initially focused on the development of efficient conditions for the Pd-catalyzed allylation of sulfonylhydrazones (Table 1). Allylic carbonates, such as **2a**, were found to be superior substrates to allylic bromides or allylic acetates.[7] The use of sulfonamide salts enhanced the rate of the desired palladium-catalyzed allylic alkylation.[7] The optimal conditions for this transformation involved the treatment of allylic carbonate **2a** with [{($\eta^3$-allyl)PdCl}$_2$] (2.5 mol%), triphenylphosphine (10 mol%), and potassium sulfonylhydrazide **1b** (1.0 equiv)[7,8] at 23 °C for 24 h, affording the desired adduct **4′** in 88% yield (Table 1). These reaction conditions are effective with both aldehyde- and ketone-derived sulfonylhydrazone salts as nucleophiles. Methanesulfonyl- and arenesulfonylhydrazones derived from both saturated and unsaturated carbonyl precursors were successfully converted into the desired hydrazone adducts.[9] Whereas the potassium derivative **1b** proved a more effective reagent than the analogous lithium derivative **1c**, where possible, the greater solubility of the lithium sulfonylhydrazides was advantageous in leading to faster reactions and higher conversions.

***Table 1:*** Sulfonylhydrazone nucleophiles.[a]




[a] Yields given are for the isolated corresponding adducts **4′**; average of two experiments. [b] [12]Crown-4 (10 mol%) was added to the reaction mixture.

We next explored the applicability of these conditions to the palladium-catalyzed displacement of a range of allylic

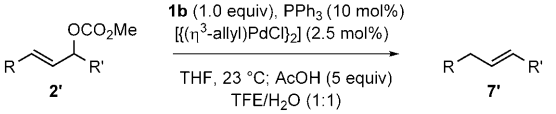
[*] Prof. Dr. M. Movassaghi, O. K. Ahmad
Department of Chemistry, Massachusetts Institute of Technology
Cambridge, Massachusetts 02139 (USA)
E-mail: movassag@mit.edu
Homepage: http://web.mit.edu/movassag/www/index.htm

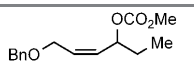
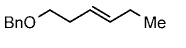
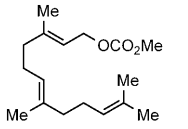
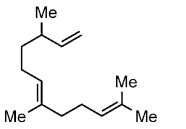
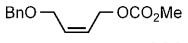
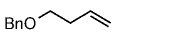
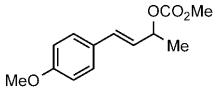
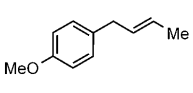
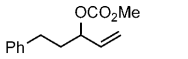
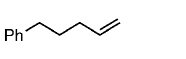
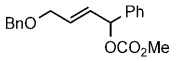
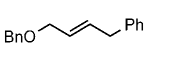
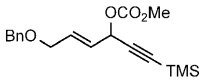
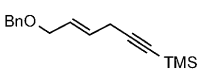
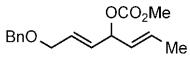
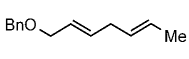
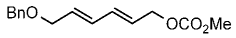
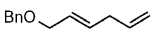
[**] M.M. is a Beckman Young Investigator and a Sloan Research Fellow. O.K.A is grateful for a Merck graduate fellowship. We acknowledge financial support by the NSF (547905), AstraZeneca, Amgen, Eli Lilly, GlaxoSmithKline, Merck Research Laboratories, and Boehringer Ingelheim Pharmaceutical Inc.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200802921.

carbonates (**2′**) with the reagent **1b** (Table 2). Gratifyingly, the desired palladium-catalyzed displacement chemistry followed by mild in situ hydrolysis[3] proved effective for a wide range of both primary and secondary allylic carbonate

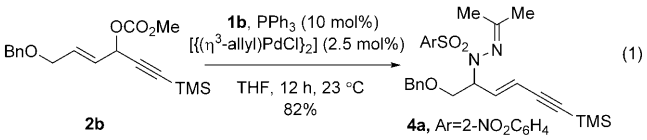
***Table 2:*** Reduction of allylic carbonates.




| Entry | Substrate | Product | Yield [%][a] |
|---|---|---|---|
| 1 |  |  | 76[b] |
| 2 |  |  | 86 |
| 3 |  |  | 91 |
| 4 |  |  | 59[b,c] |
| 5 |  |  | 75 |
| 6 |  |  | 82[d] |
| 7 |  |  | 54[d] |
| 8 |  |  | 73[e] |
| 9 |  |  | 68 |

[a] Yield of the isolated reduction product; average of two experiments. [b] *E*:*Z*, 95:5. [c] Modified conditions: **1a** (1 equiv) and $Na_2CO_3$ (10 mol%) used in place of **1b** in $CH_2Cl_2$. [d] *E*:*Z*, 96:4. [e] C2 *E*:*Z*, 96:4; C5 *E*:*Z*, 95:5. TFE = trifluoroethanol, AcOH = acetic acid.

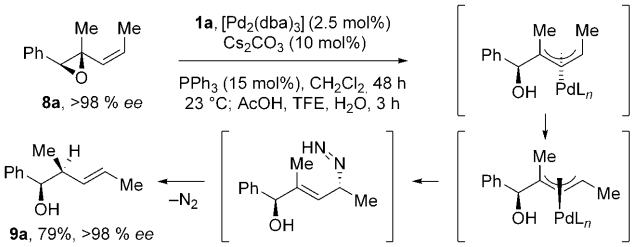
substrates. Even highly sensitive substrates, such as the doubly activated carbonates (Table 2, entries 6–8), were successfully converted into the corresponding adducts (**4**, Scheme 1) and hydrolyzed to give the desired reduction products. Significantly, the use of analogous doubly activated alcohol substrates under Mitsunobu reaction conditions or metal hydride reduction of the corresponding carbonate derivative resulted in significant decomposition and elimination.[7,10] For example, treatment of carbonate **2b** with tris(dibenzylideneacetone)dipalladium, tri-*n*-butylphosphine, and ammonium formate in 1,4-dioxane led to significant decomposition of the starting material and afforded < 15% of the desired unconjugated product (compare to Table 2, entry 7).[7,10] Furthermore, the regioselective reduction of substrates (Table 2, entries 4–9) demonstrates the versatility of this method in comparison to alternative free-radical-based reductions,[7,11] which lead to complex mixtures of products. Whereas the high level of stereoselectivity for *E*-alkene products is due to the sigmatropic loss of dinitrogen from an allylic diazene intermediate,[4b,12] the regiochemical preference in the reduction reflects the initial adduct formation favoring conjugated products, as illustrated by the exclusive isolation of adduct **4a** [Eq. (1)] from carbonate **2b** if no water is added to the reaction mixture (Table 2, entry 7).




(1)

Entries 6–8 of Table 2 are consistent with net $S_N2'$ displacement of carbonates with reagent **1b** to give conjugated sulfonylhydrazones that are ultimately subject to sigmatropic loss of dinitrogen, affording the unconjugated products. For comparison, treatment of methyl 5-phenylpent-1-en-3-yl carbonate with **1b** under the optimal conditions gives 5-phenylpent-1-ene (Table 2, entry 5), whereas treatment of the corresponding alcohol, 5-phenylpent-1-en-3-ol, with **1a** under Mitsunobu conditions affords the isomeric (*E*)-5-phenylpent-2-ene as a result of direct $S_N2$ displacement with **1a**, followed by loss of dinitrogen.[3,7]

Vinyl epoxides also serve as substrates[13] for this palladium-catalyzed synthesis of allylic diazenes. The use of $[Pd_2(dba)_3]$ in conjunction with **1a** and cesium carbonate as the base additive efficiently provided the desired reduction product (Scheme 2). This chemistry provides a mild and



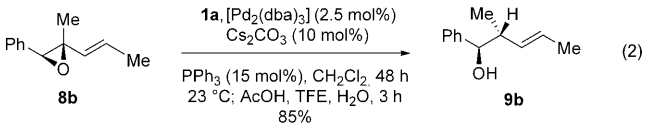

***Scheme 2.*** Palladium-catalyzed conversion of allylic epoxides into allylic diazenes and subsequent loss of $N_2$. dba = dibenzylideneacetone.

highly stereoselective conversion of allylic epoxides into the corresponding homoallylic alcohol products. As shown in Scheme 2, reduction of optically active *Z*-allylic epoxide **8a** (> 98% *ee*) under the aforementioned reaction conditions gave the desired *syn*-homoallylic alcohol **9a** (> 98% *ee*) in 79% yield.[7] The product is isolated as the *E* alkene (> 98:2, *E*:*Z*), as expected for fragmentation of allylic diazene intermediates.[4b,12]

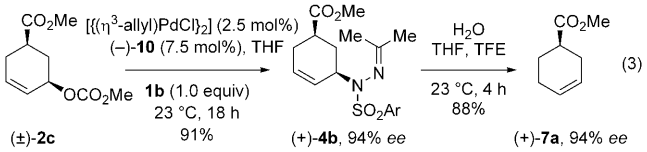
Additionally, treatment of the isomeric *E*-allylic epoxide **8b** resulted in the stereoselective synthesis of the *anti*-homoallylic alcohol derivative **9b** [Eq. (2)].[7] It should be noted that the use of formic acid as the reducing agent in the palladium-catalyzed reduction of **8a** affords the *anti*-diastereoisomer **9b**,[14] highlighting the distinction between the reduction described herein and other related processes.

The aforementioned transformations highlight the potential development of catalytic asymmetric variants of this

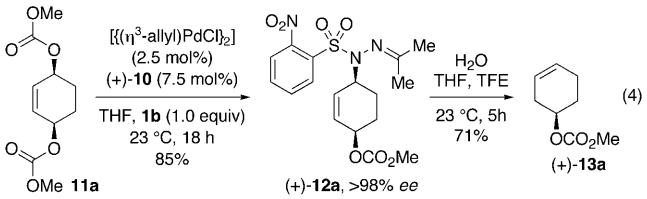
  

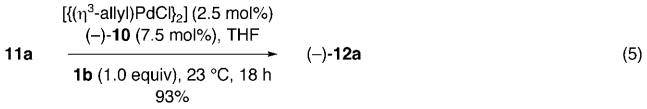


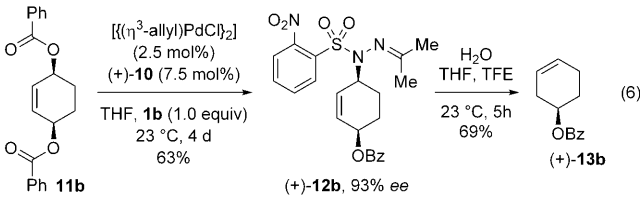

reduction chemistry.[1] The treatment of carbonate (±)-**2c** and reagent **1b** with a catalyst system comprised of Trost's[15] (*1S*,*2S*)-(−)-1,2-diaminocyclohexane-*N*,*N*′-bis(2′-diphenylphosphinobenzoyl) ligand ((−)-**10**, 7.5 mol%) and [($\eta^3$-allyl)PdCl]$_2$ (2.5 mol%) gave the sulfonylhydrazone adduct (+)-**4b** in 91% yield and 94% *ee* [Eq. (3)]. Mild hydrolysis of hydrazone (+)-**4b** afforded the optically active ester (+)-**7a** in 88% yield and 94% *ee*. The absolute configuration of adduct (+)-**4b** was established by comparison of the optical rotation of the product (+)-**7a** with literature values.[7] Notably, the conversion of (±)-**2c** into (+)-**7a** can be effected, without isolation of hydrazone intermediate (+)-**4b**, by direct hydrolysis after complete consumption of (±)-**2c**, affording (+)-**7a** in 71% yield.[7]




Furthermore, treatment of the *meso*-dicarbonate **11a** with reagent **1b**, under the optimized reaction conditions with ligand (+)-**10**, afforded the adduct (+)-**12a** in > 85% yield and 98% *ee* [Eq. (4)].[16] The ready availability of both enantiomers of the ligand **10** gives easy access to either enantiomer of the desired adduct and the corresponding reduction product [Eq. (5)]. Notably, this chemistry is also amenable to the use of allylic benzoate electrophiles. The catalytic asymmetric synthesis of the adduct (+)-**12b** proceeded with a good level of enantioselection (93% *ee*), albeit with a slower reaction rate as compared to allylic carbonates or epoxides [Eq. (6)]. The mild hydrolysis of the hydrazone adducts **12a** and **12b** provided the corresponding reductively transposed products (+)-**13a** and (+)-**13b** [Eqs. (4) and (6)].[16,17]




In summary, a mild and highly stereoselective reduction of allylic carbonates and vinyl epoxide substrates is described. Palladium-catalyzed activation of allylic electrophiles efficiently provided a range of N-alkylated sulfonylhydrazones. N-allylated derivatives of IPNBSH (**1a**) were prepared using this method and their in situ hydrolysis provided access to the corresponding reduction products. This chemistry offers a unique solution to stereospecific synthesis of monoalkyl diazene intermediates from allylic electrophiles under mild reaction conditions. Sensitive substrates that are incompatible with other methods were reduced in a highly stereoselective and regioselective manner. The catalytic asymmetric activation of electrophiles coupled with this new route to allylic monoalkyl diazenes offers additional opportunities for asymmetric synthesis.

Received: June 18, 2008
Revised: September 5, 2008
Published online: October 16, 2008

**Keywords:** allylic compounds · asymmetric synthesis · homogeneous catalysis · hydrazones · reduction

[1] B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921.
[2] a) B. M. Trost, A. Aponick, *J. Am. Chem. Soc.* **2006**, *128*, 3931; b) R. Weihofen, O. Tverskoy, G. Helmchen, *Angew. Chem.* **2006**, *118*, 5673; *Angew. Chem. Int. Ed.* **2006**, *45*, 5546; c) C. Defieber, M. A. Ariger, P. Moriel, E. M. Carreira, *Angew. Chem.* **2007**, *119*, 3200; *Angew. Chem. Int. Ed.* **2007**, *46*, 3139; d) A. M. Johns, Z. Liu, J. F. Hartwig, *Angew. Chem.* **2007**, *119*, 7397; *Angew. Chem. Int. Ed.* **2007**, *46*, 7259; e) I. Dubovyk, I. D. G. Watson, A. K. Yudin, *J. Am. Chem. Soc.* **2007**, *129*, 14172; f) also, see L. E. Overman, *J. Am. Chem. Soc.* **1976**, *98*, 2901.
[3] M. Movassaghi, O. K. Ahmad, *J. Org. Chem.* **2007**, *72*, 1838.
[4] a) A. G. Myers, B. Zheng, *J. Am. Chem. Soc.* **1996**, *118*, 4492; b) A. G. Myers, B. Zheng, *Tetrahedron Lett.* **1996**, *37*, 4841.
[5] a) For a review on N nucleophiles, see M. Johannsen, K. A. Jorgensen, *Chem. Rev.* **1998**, *98*, 1689; b) For an example of Pd-catalyzed N-allylation of benzophenone hydrazones, see Ref. [2d]; c) for an example of Ir-catalyzed N-allylation of a tosylhydrazone, see R. Matunas, A. J. Lai, C. Lee, *Tetrahedron* **2005**, *61*, 6298; d) for an example of carbonium ion trapping by a sulfonylhydrazide leading to an allylic reduction, see J. L. Wood, J. A. Porco, Jr., J. Taunton, A. Y. Lee, J. Clardy, S. L. Schreiber, *J. Am. Chem. Soc.* **1992**, *114*, 5898.
[6] a) S. Hünig, H. R. Müller, W. Thier, *Angew. Chem.* **1965**, *77*, 368; *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 271; b) E. M. Kosower, *Acc. Chem. Res.* **1971**, *4*, 193; c) E. J. Corey, D. E. Cane, L. Libit, *J. Am. Chem. Soc.* **1971**, *93*, 7016.
[7] See the Supporting Information for details.
[8] Treatment of **1a** with KH affords the stable and storable **1b**.
[9] As well as being versatile synthetic intermediates, hydrazones are also utilized as dyes and as pharmacologically active compounds.

[10] For a review, see: J. Tsuji, T. Mandai, *Synthesis* **1996**, 1.
[11] S. Maity, S. Ghosh, *Tetrahedron Lett.* **2007**, *48*, 3355.
[12] A. G. Myers, P. J. Kukkola, *J. Am. Chem. Soc.* **1990**, *112*, 8208.
[13] B. M. Trost, R. C. Bunt, R. C. Lemoine, T. L. Calkins, *J. Am. Chem. Soc.* **2000**, *122*, 5968.
[14] M. Oshima, H. Yamazaki, I. Shimizu, M. Nisar, J. Tsuji, *J. Am. Chem. Soc.* **1989**, *111*, 6280.
[15] B. M. Trost, R. C. Bunt, *J. Am. Chem. Soc.* **1994**, *116*, 4089.
[16] The absolute configurations given in [Eq. (4)–(6)] are based on analogy to other nucleophiles used in these systems. See: a) B. M. Trost, G. G. Cook, *Tetrahedron Lett.* **1996**, *37*, 7485; b) B. M. Trost, L. S. Chupak, T. Lübbers, *J. Am. Chem. Soc.* **1998**, *120*, 1732.
[17] Substrates (±)-**2c** and **11a** provide examples of both symmetrical and asymmetrical electrophilic π-allyl ligands, respectively, successfully incorporated in the intermediate Pd complex in these processes.