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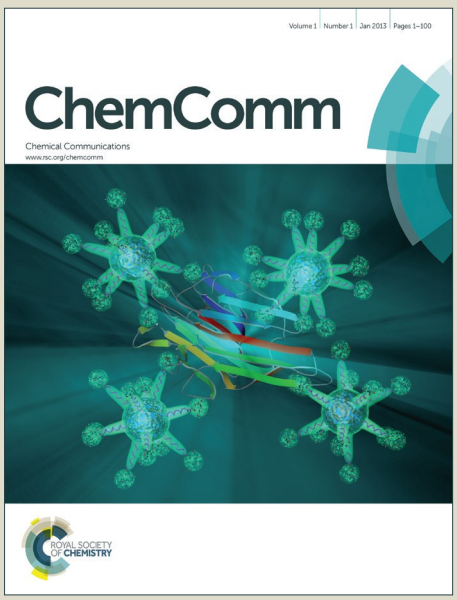

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COMMUNICATION

Chemo- and Regioselective Reductive Transposition of Allylic Alcohol Derivatives via Iridium or Rhodium Catalysis

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We report highly chemo- and regioselective reductive transpositions of methyl carbonates to furnish olefin products with complementary regioselectivity to that of established Pd-catalysis. These Rh- and Ir- catalyzed transformations proceed under mild conditions and enable selective deoxygenation in the presence of functional groups that are susceptible to reduction by metal hydrides.

Deoxygenation reactions are important transformations in synthetic organic chemistry, finding applications in areas ranging from biomass conversion to the preparation of complex bioactive molecules.[1,2] Mild, catalytic, chemoselective reductive deoxygenation of alcohols remains underdeveloped owing in large part to the difficulties associated with delivery of hydride equivalents to C–O sigma bonds in preference to C=C, C=O or C–X bonds.[3] Thus classical methods that use stoichiometric additives such as the Barton-McCombie reaction[4] or Mitsunobu reactions with diazene-precursors[5,6] are still widely employed.

With specific regard to allylic substrates, Pd-based strategies have been developed to address some of the limitations associated with selective deoxygenation catalysis. For example, while deoxygenation of allylic alcohols via Mitsunobu reaction with diazene precursors NBSH or IPNBSH requires stoichiometric reagents such as diethyl azodicarboxylate (DEAD) (Fig. 1A),[4] Movassaghi and co-workers reported an alternative IPNBSH-mediated reductive transposition using Pd-catalysis (Fig. 1B).[7,8] The regiochemical outcome of the amination follows that expected for Pd-catalysed allylic substitution, generally featuring substrate steric control in the amination of a Pd-allyl species.[9] Under these conditions, terminal olefin products are formed from both branched and linear allylic carbonates after sigmatropic elimination of dinitrogen from a linear monoalkyl diazene (Fig. 1 B-1),[10] while both formal S_N2 and S_N2' displacement are observed with internal branched substrates (Fig.1 B-2).[7] Similar to Pd-catalysed allylic reductions employing formate, generation of the alternative olefin regioisomers is not possible; thus complete regiocontrol of catalytic reductive transposition of allylic alcohol derivatives remains a significant unmet challenge. Furthermore, catalytic and chemoselective diazene-mediated deoxygenation in the presence of other reducible functional groups has not been demonstrated broadly. Herein we report a strategy to address these deficits by employing Ir- and Rh-catalysis (Fig. 1C). Under mild conditions, highly chemo- and regioselective reductive transposition

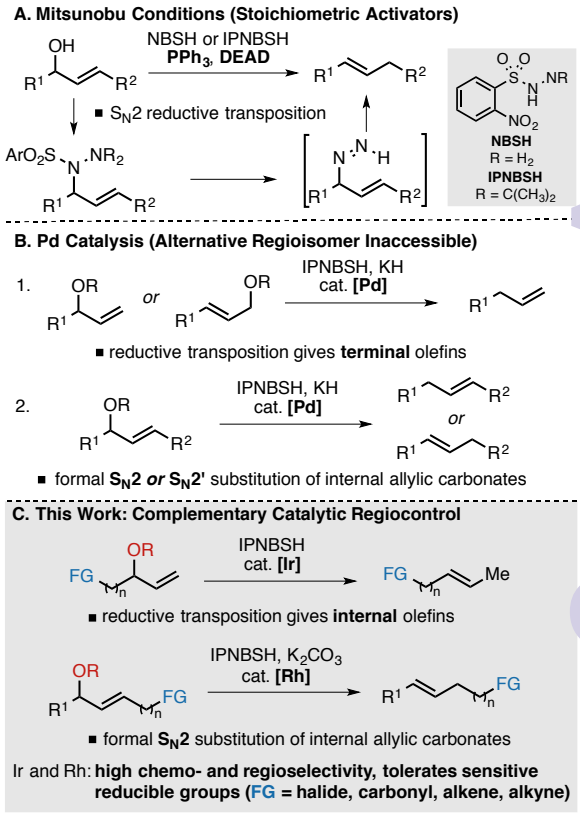

Fig. 1 Overview of diazene-mediated reductive transposition of allylic alcohol derivatives.

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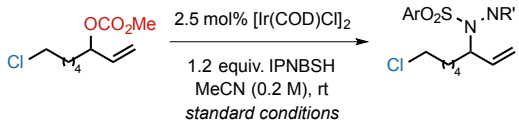
† Electronic Supplementary Information (ESI) available: synthetic procedures and characterization data See DOI: 10.1039/x0xx00000x

is observed for allylic methyl carbonates. This new method can be considered a direct, catalytic alternative to stoichiometric Mitsunobu protocols for deoxygenation of allylic alcohols embedded within functionalised molecules.[13]

Conditions were optimized such that reactive functionalities, such as aliphatic chlorides are tolerated. Table 1 highlights how simple modifications to the conditions have a significant effect on the selectivity of the transformation when employing bulky diazene precursors.[14,15a] Under optimized conditions employing 2.5 mol% $[Ir(COD)Cl]_2$, the desired branched N-alkyl N-sulfonyl hydrazone product formed in 91% yield at room temperature with no detectable amount of the linear allylic isomer. Rh- and Ru-based catalysts proved ineffective under these conditions (Table 1, entries 2 and 3). In solvents other than MeCN product yields were significantly lower and formation of the undesired byproducts was observed. The hydrazine reagent NBSH provided suboptimal yields (10%, Table 1, entry 6). Methyl carbonate is the preferred leaving group, as use of alternative alkyl carbonates or a phosphate ester resulted in lower yields.[15b] Finally, in situ hydrolysis and sigmatropic rearrangement of the allylic sulfonyl hydrazone at room temperature yielded the desired internal olefin in 71% isolated yield (eq 1).[15c] Of note, experiments under similar conditions using ammonium formate as the reducing agent resulted in unselective consumption of the substrate.

Both simple and functionalised alkyl-substituted allylic carbonates can be converted to the corresponding internal olefins in moderate to excellent yields with very high regioselectivities (Table 2).[16] The reaction is tolerant of substitution β to the carbonate (Table 2, entries 2, 3 and 7), as well as oxygen, nitrogen, and halogen functional groups (Table 2, entries 2–5).[15d] For substrates containing pendant unsaturation in the form of an alkyne, alkene or α,β-unsaturated ester, no over-reduction is observed allowing for facile deoxygenation of polyunsaturated carbonates (Table 2, entries 6–8).[17] In a particularly striking example of chemoselective deoxygenation, methyl carbonate reduction proceeds smoothly in the presence of an allylic acetate gr… (Table 2, entry 9).[18]

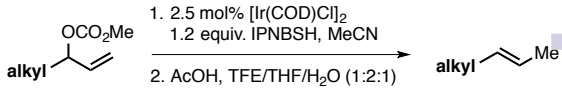
Table 1. Effect of reaction parameters on the catalytic, chemoselective allylic amination employing diazene precursors

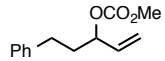
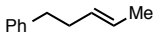
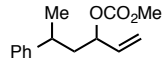
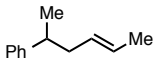
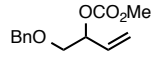
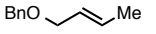
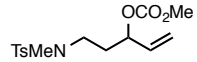
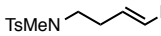
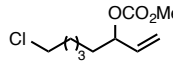
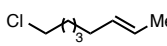
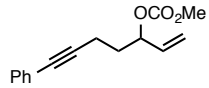
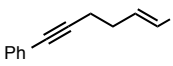
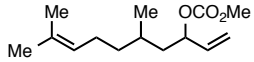
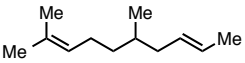
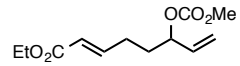
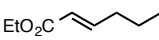
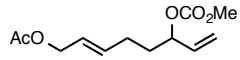
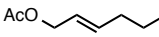


entry	change from the standard conditions	conv	yield (%)
1	**none**	**>98**	**91**
2	$[Rh(COD)Cl]_2$ instead of $[Ir(COD)Cl]_2$	8	<2
3	$RuCp^*(MeCN)_3PF_6$ instead of $[Ir(COD)Cl]_2$	94	10
4	THF instead of MeCN	74	15
5	CH_2Cl_2 instead of MeCN	61	12
6	NBSH instead of IPNBSH	23	10
7	CO_2t-Bu instead of CO_2Me	64	44

[a] 0.05 mmol scale, 24 h, conversions and yields determined by ^1H NMR using Bn_2O as an internal standard.

Table 2. Reductive deoxygenation of alkyl substituted al… carbonates.



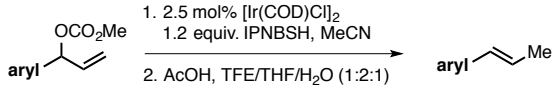
entry	substrate	product	yield
1			**84%**
2			**68%**[a]
3[b]			**71%**
4			**88%**
5			**71%**
6			**74%**
7			**57%**
8			**75%**
9[c]			**65%**[d]

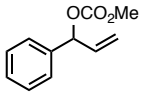
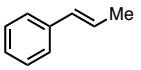
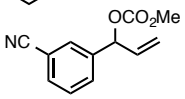
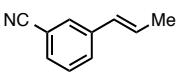
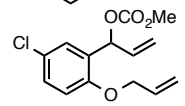
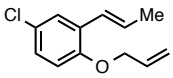
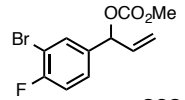
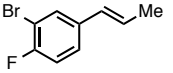
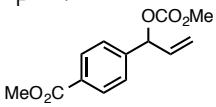
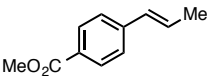
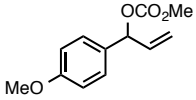
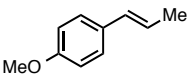
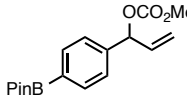
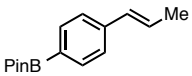
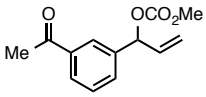
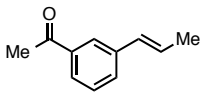
Yields are of isolated material. Regioisomer ratios are ≥95:5, *E/Z* ratios are ≥92:8 in all cases. See Supporting Information for details. [a]91:9 regioisomer ratio. [b]5 mol% $[Ir(COD)Cl]_2$ [c]allylic acetate *E/Z* = 85:15 in starting material [d]allylic acetate *E/Z* = 85:15.

Without change to the standard conditions, aryl-substituted allylic carbonates are suitable substrates, allowi… g for the synthesis of functionalised β-methyl styrenes (Table 3). Electron-rich and electron-poor aryl-substituted carbonat… can be deoxygenated under mild conditions. Potentia… reactive functional groups that are prone to reduction und… radical or metal hydride treatment, such as an aryl bromid… and chloride, an allylic ether, ester, nitrile, ketone, and an ary… boronic ester, are tolerated highlighting the excelle… t chemoselectivity of the reduction.

Allylic carbonates with an internal alkene were resistan… to amination with IPNBSH under the standard Ir-catalyz… conditions described above. Subsequent optimizatio… however, revealed that the use of catalytic mixtures o… $[Rh(COD)Cl]_2$ and $P(OPh)_3$ with K_2CO_3 led to good yields an… excellent regioselectivities (Table 4).[15e, f, 19] Aryl, alkenyl, alkynyl, and ethereal allylic methyl carbonates can b… deoxygenated under these Rh-catalysed conditions, providing

Table 3. Scope of reductive deoxygenation of aryl substituted allylic carbonates.



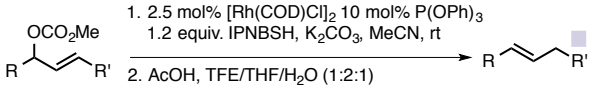
entry	substrate	product	yield (%)
1			**69**
2			**63**
3			**71**
4			**94**
5			**56**[a]
6			**45**
7			**55**
8			**77**

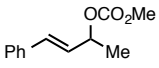
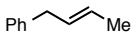
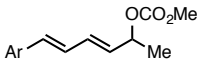
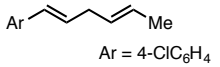
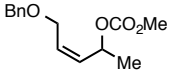
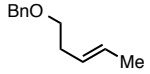
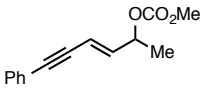
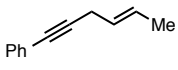
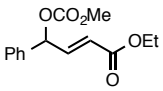
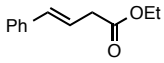
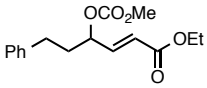
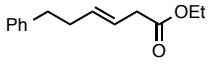
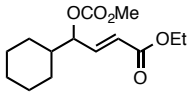
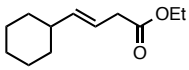
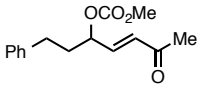
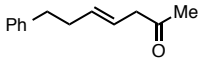
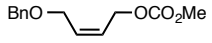
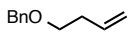
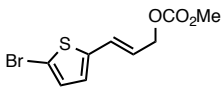
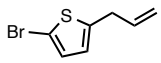
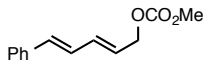
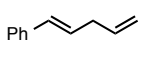
Yields are of isolated material, 1.0–0.6 mmol scale. Regioisomer ratios are ≥93:7 and *E/Z* ratios are ≥95:5 unless noted. See Supporting Infomation for details. [a] 83:17 regioisomer ratio.

a simple and mild strategy for the preparation of sensitive skipped dienes and enynes (Table 4, entries 2 and 4). Allylic carbonates substituted with electron-withdrawing groups, such as an ester or ketone, also undergo amination with high formal S_N2-selectivity, and upon reductive transposition, γ-unsaturated carbonyl compounds can be obtained (Table 4 entries 5–8). The reaction tolerates sterically demanding carbonates, such as an α-branched substrate (Table 4, entry 7). Collectively, these results demonstrate an attractive means to convert easily accessible conjugated systems into more valuable 1,4-polyunsaturated compounds that are otherwise difficult to prepare. In keeping with the observation of remarkably high formal S_N2 amination selectivity, alkyl-, heteroaryl-, and alkenyl-substituted *primary allylic carbonates generate terminal olefin products* under the standard Rh-catalysed reaction conditions (Table 4, entries 9–11).

Both of the methods reported herein proceed well on larger scales, as demonstrated by the gram-scale syntheses of a halogenated β-methyl styrene via Ir-catalysis (eq 2) and a γ-unsaturated ester via Rh-cataysis (eq 3).[15g]

Table 4. Rh-catalysed reductive deoxygenation of substituted allylic carbonates.



entry	substrate	product	yield (%)
1[a]			**62**
2[a]		 Ar = 4-ClC$_6$H$_4$	**57**
3[a,b]			**79**
4[a]			**64**
5			**66**
6			**71**
7[b]			**69**
8			**56**
9[b]			**78**
10[b]			**52**
11[b]			**65**

Yields are of isolated material, 0.7–0.3 mmol scale. Regioisomer ratios are ≥95:5 and *E/Z* ratios are ≥94:6 in all cases. [a] Reaction performed at 40 ºC. [b] Using 5 mol% $[Rh(COD)Cl]_2$ and 20 mol% $P(OPh)_3$.

In summary, we have developed new catalytic strategies for the mild and selective reductive transposition of allylic alcohol derivatives employing Ir- or Rh-based catalysts. The deoxygenation process tolerates a wide range of functional groups that are susceptible to radical or hydride reduction.

provides complementary regioselectivity to that of Pd-catalyzed methodologies. The ability of this method to be used in place of stoichiometric Mitsunobu-type deoxygenation processes should result in widespread appeal.

Acknowledgments

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Notes and references

1 For a review see: J. M. Herrmann, B. König, *Eur. J. Org. Chem.* **2013**, *2013*, 7017-7027.

2 For select recent examples of new deoxygenation methods see: (a) L. L. Adduci, T. A Bender, J. A. Dabrowski, M. R. Gagné, *Nature Chem.* **2015**, *7*, 576-581; (b) H. Dang, N. Cox, G. Lalic, *Angew. Chem. Int. Ed.* **2014**, *53*, 752-756; (c) L. L. Adduci, M. P. McLaughlin, T. A. Bender, J. J. Becker, M. R. Gagne, *Angew. Chem. Int. Ed.* **2014**, *53*, 1646-1649; (d) M. Shiramizu, F. D. Toste, *Angew. Chem. Int. Ed.* **2013**, *52*, 12905-12909; (e) J. Cornella, E. Gómez-Bengoa, R. Martin, *J. Am. Chem. Soc.* **2013**, *135*, 1997-2009.

3 For reviews that discuss such problems in modern organic chemistry see: (a) J. Mahatthananchai, A. M. Dumas, J. W. Bode, *Angew. Chem. Int. Ed.* **2012**, *51*, 10954-10990; (b) N. A. Afagh, A. K. Yudin, *Angew. Chem. Int. Ed.* **2010**, *49*, 262-310.

4 For a review see: (a) S. W. McCombie, W. B. Motherwell, M. J. Tozer, The Barton-McCombie Reaction. In *Org. React. Vol. 77*, John Wiley & Sons, Inc.: **2012**; for recent applications in complex molecule synthesis see: (b) H. Sugimura, S. Sato, K. Tokudome, T. Yamada, *Org. Lett.* **2014**, *16*, 3384-3387; (c) M. Zhang, N. Liu, W. Tang, *J. Am. Chem. Soc.* **2013**, *135*, 12434-12438; (d) B. S. Fowler, K. M. Laemmerhold, S. J. Miller, *J. Am. Chem. Soc.* **2012**, *134*, 9755-9761; (e) M. Bian, Z. Wang, X. Xiong, Y. Sun, C. Matera, K. C. Nicolaou, A. Li, *J. Am. Chem. Soc.* **2012**, *134*, 8078-8081.

5 For diazene mediated alcohol reduction with sulfonyl hydrazine reagents see: (a) M. Movassaghi, O. K. Ahmad, *J. Org. Chem.* **2007**, *72*, 1838-1841; (b) A. G. Myers, M. Movassaghi, B. Zheng, *J. Am. Chem. Soc.* **1997**, *119*, 8572-8573; (c) A. G. Myers, B. Zheng, *J. Am. Chem. Soc.* **1996**, *118*, 4492-4493; (d) A. G. Myers, B. Zheng, *Tetrahedron Lett.* **1996**, *37*, 4841-4844.

6 For selected applications of reductions employing sulfonyl hydrazine reagents in complex molecule synthesis see: (a) D. Yang, G. C. Micalizio, *J. Am. Chem. Soc.* **2012**, *134*, 15237-15240; (b) M. Shan, E. U. Sharif, G. A. O'Doherty, *Angew. Chem. Int. Ed.* **2010**, *49*, 9492-9495; (c) M. Movassaghi, G. Piizzi, D. S. Siegel, G. Piersanti, *Angew. Chem. Int. Ed.* **2006**, *45*, 5859-5863; (d) M. G. Charest, C. D. Lerner, J. D. Brubaker, D. R. Siegel, A. G. Myers, *Science* **2005**, *308*, 395-398.

7 M. Movassaghi, O. K. Ahmad, *Angew. Chem. Int. Ed.* **2008**, *47*, 8909-8912.

8 For acid catalysed substitution reactions of activated propargylic substrates with sulfonyl hydrazines to generate allenes see: (a) Z. Liu, P. Q. Liao, X. Bi, *Chem. Eur. J.* **2014**, *20*, 17277-17281; (b) D. A. Mundal, K. E. Lutz, R. J. Thomson, *J. Am. Chem. Soc.* **2012**, *134*, 5782-5785.

9 For a detailed discussion of the topic see: B. S. Kim, M. T. Hussain, P. O. Norrby, P. J. Walsh, *Chem. Sci.* **2014**, *5*, 1241-1250 and references therein.

10 A. Jabbari, E. J. Sorensen, K. N. Houk, *Org. Lett.* **2006**, *8*, 3105-3107.

11 For a review see: (a) J. Tsuji, T. Mandai, *Synthesis* **1996**, 1-28; strong hydride donors such as DIBAL-H or SmI_2 can afford the opposite regioisomers, but these reagents would exhibit minimal chemoselectivity in the presence of reducible groups. For more recent examples of Pd-catalyzed formate reduction see: (b) A. Chau, J.-F. Paquin, M. Lautens, *J. Org. Chem.* **2005**, *71*, 1924-1933; (c) T. Konno, T. Takehanna, M. Mishima, T. Ishihara, *J. Org. Chem.* **2006**, *71*, 3545-3550; in very rare cases, select substrates can be converted to the internal alkene, see: (d) H. Cheng, C. Sun, D. Hou, *J. Org. Chem.* **2007**, *72*, 2674-2677;

12 For the phosphine-catalysed reduction of allylic bromides with $LiAlH(OtBu)_3$ to terminal olefins see: K. D. Reichl, N. T. Dunn, N. J. Fastuca, A. T. Radosevich, *J. Am. Chem. Soc.* **2015**, *137*, 5292-5295.

13 For an unselective Ir-catalysed deoxygenation process (alkenes are also reduced) employing hydrazine at 160 °C see: J. L. Huang, X. J. Dai, C. J. Li, *Eur. J. Org. Chem.* **2015**, 6496-6500.

14 For early examples of Ir- and Rh-catalysed allylic amination see: (a) P. A. Evans, J. E. Robinson, J. D. Nelson, *J. Am. Chem. Soc.* **1999**, *121*, 6761-6762; (b) R. Takeuchi, N. Ue, K. Tanabe, K. Yamashita, N. Shiga, *J. Am. Chem. Soc.* **2001**, *123*, 9525-9534. For Ir-catalysed allylation of hydrazines and hydrazones see: c) R. Matunas, A. J. Lai, C. Lee, *Tetrahedron* **2005**, *61*, 6298-6308.

15 Notes: (a) the stable, crystalline reagents NBSH and IPNBSH are commercially available, or readily synthesized on decagram scale; (b) for additional optimization data see the supporting information; (c) hydrolysis was performed by removal of MeCN prior to addition of THF/TFE/H_2O (2:1:1), and AcOH, direct addition of TFE/H_2O without THF resulted in ~10% lower yields; (d) electron-rich aryl methyl carbonates are prone to rearrangement to the linear isomer, pyridine and quinoline substrates are aminated effectively but undergo reduction with low yield and regioselectivity, cyclic allylic methyl carbonates are not viable substrates, as is generally observed in Ir- and Rh-catalysed allylic functionization; (e) see supporting information for details on optimization of internal allylic substrates; (f) these conditions are effective for terminal allylic carbonates, however the reactions proceeds with slightly diminished branched/linear selectivity compared to the use of $[Ir(COD)Cl]_2$; (g) no glovebox is required for these reactions, see the supporting information.

16 Aside from being useful chemical building blocks, methyl-substituted olefins are found in numerous bioactive molecules, such as cyclosporines, corallopyronins and penibruguieramide A.

17 Free diazene generated from sulfonyl hydrazines can reduce olefins, for examples see: (a) B. J. Marsh, D. R. Carbery, *J. Org. Chem.* **2009**, *74*, 3186-3188; (b) M. H. Haukaas, G. A. O'Doherty, *Org. Lett.* **2002**, *4*, 1771-1774.

18 Secondary allylic acetates are less reactive substrates. Under the standard Ir-catalysed conditions with the acetate version of the substrate in Table 3, entry 1, 27% (>20:1 b/l) product is observed, compared to >95% for the allylic methyl carbonate substrate, (the isolated yield of olefin is lower due to volitility of the product). Under the standard Rh-catalysed conditions 34% (20:80 b/l) product is observed.

19 For the Rh-catalyzed allylation of sulfonamides see: P. A. Evans, J. E. Robinson, K. K. Moffett, *Org. Lett.* **2001**, *3*, 3269-3271.

