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Indium- and zinc-mediated Barbier-type allylations of an *N*,*N*-(dimethylsulfamoyl)-protected aldimine and subsequent deprotection

Sara Källström,[a] Tiina Saloranta,[a] Adriaan J. Minnaard[b,*] and Reko Leino[a,*]

[a]*Laboratory of Organic Chemistry, Åbo Akademi University, FI-20500 Åbo, Finland*
[b]*Department of Organic and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands*

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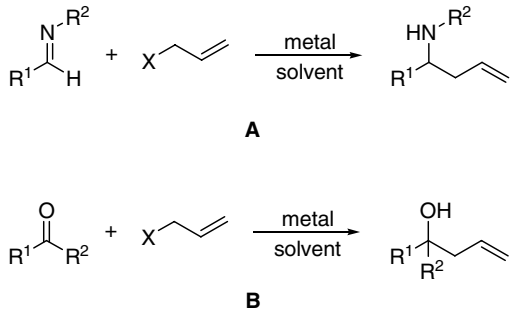
Abstract—Barbier-type Zn and In-mediated allylations of an *N*,*N*-(dimethylsulfamoyl)-protected aldimine with different allyl bromides were investigated for the preparation of *N*-homoallylic sulfamides. The desired *N*,*N*-(dimethylsulfamoyl)-protected products were obtained in moderate to high yields in THF as the optimal solvent. Their further derivatization was demonstrated by a facile preparation of a functionalized dehydropiperidine by an allylation/olefin metathesis reaction sequence. A high yielding deprotection of the *N*,*N*-dimethylsulfamoyl group was likewise demonstrated.

Methods for generating new carbon–carbon bonds constitute the essence of organic synthesis and provide the means for the preparation of more complex molecules from simpler ones.[1] Among these methods, the addition of allyl metal derivatives to imines is particularly useful for the preparation of other nitrogen-containing compounds.[2] The homoallylic amines obtained are important intermediates in the synthesis of a range of pharmaceutically active substrates and other biologically active compounds.[3]

Imines are less electrophilic and thus less reactive towards nucleophiles than the corresponding carbonyl compounds.[2c,4] This problem may, however, be circumvented by the use of more electrophilic imines or by enhancing the strength of the nucleophile by selecting a suitable metal.

Several metals have been employed as mediators for the allylations of both imines (**A**) and aldehydes or ketones (**B**) (Scheme 1).[5,6] Among these, indium[7] and zinc[8] are widely represented. The use of In metal as a mediator in the addition of allyl bromides to carbonyl compounds



Scheme 1.

under Barbier-type conditions was first reported in 1988.[9] Compared to other metals, indium offers a number of advantages, including its low toxicity, tolerance towards air and moisture and, due to its low ionization potential, a high reactivity in the absence of external activators and proton sources.[10] Zinc was first employed in Barbier-type allylations by Wolinsky and co-workers in 1977,[11] and has likewise proved to be a highly useful mediator for the allylation of various substrates. In contrast to In-mediated allylations, which commonly are carried out in water/THF mixtures without additives, the use of Zn generally requires the application of saturated aqueous NH_4Cl as a proton source together with the organic solvent.

* Corresponding authors. Tel.: +31 50 3634258; fax: +31 50 3634296 (A.J.M.); tel.: +358 2 2154132; fax: +358 2 2154866 (R.L.); e-mail addresses: a.j.minnaard@rug.nl; reko.leino@abo.fi

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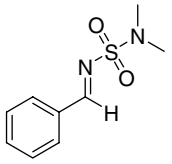
In a recent study, Lu and Chan investigated the In and Zn-mediated allylations of various sulfonimines in aqueous media.[6c] The corresponding homoallylic sulfonamides were generally obtained in high yields. Allylations with crotyl and cinnamyl halides gave high regioselectivities and in some cases moderate diastereoselectivities. Reactions with Zn required the use of saturated aqueous NH_4Cl solution in combination with THF. In a separate study, Lin and co-workers recently reported high diastereoselectivities in the Zn-mediated allylation of chiral *N*-*tert*-butylsulfinyl imines in THF in the presence of additives.[12] Analogously, chiral aldimines derived from phenylglycinol have been subjected to In-mediated allylations in methanol to provide both aliphatic and aromatic homoallylic amines in good yields and diastereoselectivities.[13] Barbier-type In or Zn-mediated allylations of unactivated aldimines in alcoholic solvents[14] and trifluoromethyl aldimines in DMF and THF[15] have likewise been investigated earlier.

With the exception of the sulfinyl and phosphanoyl groups, the activating and protecting groups applied have in common that their removal after the allylation is not trivial. Hydrogenolysis is not possible in the presence of the olefin and removal of sulfonyl groups requires either harsh conditions, for the tosyl group, or environmentally unfriendly reagents like thiophenol in DMF for the nosyl group. Here, we report the results of our initial investigation on the Zn- and In-mediated Barbier-type allylation of the *N*,*N*-(dimethylsulfamoyl)-protected aldimine **1** (Fig. 1) under both anhydrous and aqueous conditions. The *N*,*N*-dimethylsulfamoyl group was recently introduced as an inexpensive, low-molecular weight protecting/activating group for the rhodium-catalyzed asymmetric arylation of aldimines.[16] We anticipated that it would also serve as a suitable activating group for allylations being simultaneously readily subjected to cleavage under mild conditions for the preparation of the corresponding homoallylic amines.

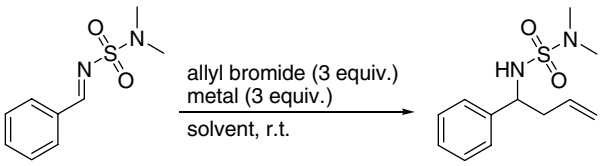
The allylation of **1** was first studied in different solvents (THF, water, NH_4Cl_{aq}, and mixtures thereof) by in situ formation of the allyl metal species from In or Zn powder and allyl bromide at room temperature.[17] The results are presented in Table 1. The In- and Zn-mediated allylations in anhydrous THF gave full conversions and high yields independent of the metal employed (Table 1, entries 1 and 4). The use of aqueous NH_4Cl as a solvent or in combination with THF in the Zn-mediated reaction resulted in undesired hydrolysis of the



1

Figure 1. The *N*,*N*-(dimethylsulfamoyl)-protected aldimine substrate **1**.

Table 1. Metal-mediated allylation of *N*,*N*-(dimethylsulfamoyl)-benzaldimine **1** in different solvents[a]



1 **2**

Entry	Metal	Solvent	Conversion[b] (%)	Yield[d] (%)
1	In	THF	100	90
2	In	THF/H_2O 1:1	89[c]	81
3	In	H_2O	19[c]	13
4	Zn	THF	100	81
5	Zn	THF/NH_4Cl_{aq} 1:1	74[c]	50
6	Zn	NH_4Cl_{aq}	84[c]	54

[a] Allylations were performed at rt on a 0.10–0.30 mmol scale with 3 equiv of metal and allyl bromide, respectively.
[b] Conversions were determined by ^1H NMR.
[c] Lower conversions are due to formation of 1-phenyl-3-buten-1-ol as a result of hydrolysis of **1** in the aqueous solvent and subsequent allylation.
[d] Isolated yield.

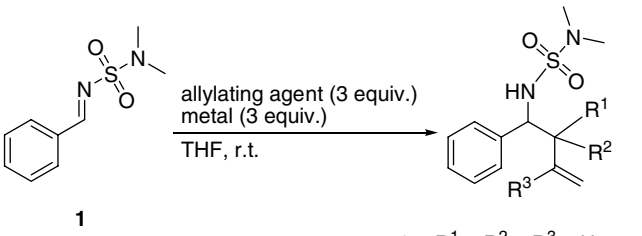
aldimine decreasing the yield of the amine product **2** (Table 1, entries 5 and 6). Similar results were obtained for the In-mediated allylation of **1** in aqueous media (Table 1, entries 2 and 3). Nevertheless, a comparison of the reactions performed with In and Zn in aqueous media alone (Table 1, entries 3 and 6) demonstrates the substrate and metal surface activation in the Zn mediated reaction by NH_4Cl.[18] This, supposedly, leads to the more efficient formation of the allylating reagent as well as the product **2**.

Next, the In or Zn-mediated allylation of **1** was continued by investigating different allylating agents. The results are presented in Table 2. In order to avoid substrate hydrolysis, the reactions were carried out in anhydrous THF. Excellent conversions and isolated yields were observed in all reactions with allyl, methallyl, crotyl and prenyl bromides in the presence of either Zn or In. Conversions lower than 100% were obtained with the bulkier prenyl bromide reagent only (Table 2, entries 4 and 8). Here, moderate yields of **2d** were obtained (In = 63%, Zn = 46%), most likely due to the steric constraints induced by the bulkier allylating agent.

Recently, it has been demonstrated that the *N*,*N*-dimethylsulfamoyl group is readily removed from diarylamines in two hours by microwave-assisted transamination under mild conditions.[16] Deprotection of the *N*-homoallylic sulfamide **2a** was thus investigated in a similar fashion (Scheme 2).[19] In the case of **2a**, the deprotection took place cleanly in refluxing 1,3-diaminopropane by conventional heating with an oil bath. The reaction was complete in 2 h and the homoallylic amine **3** was obtained in 92% yield.

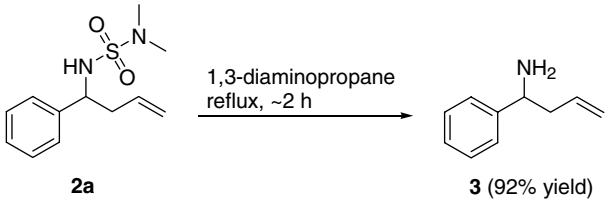
As an example of the use of the allylation products in the synthesis of nitrogen-containing heterocycles, com-

Table 2. Metal-mediated allylation of *N*,*N*-(dimethylsulfamoyl)-benzaldimine **1** with different allylating agents[a]



Entry	Metal/allylating agent	R^1, R^2, R^3	Conversion[b] (%)	Yield[c] (%)
1	In/allyl bromide	H, H, H	100	90
2	In/methallyl bromide	H, H, Me	100	87
3	In/crotyl bromide	Me, H, H	100	89[d]
4	In/prenyl bromide	Me, Me, H	75	63
5	Zn/allyl bromide	H, H, H	100	81
6	Zn/methallyl bromide	H, H, Me	100	72
7	Zn/crotyl bromide	Me, H, H	100	68[d]
8	Zn/prenyl bromide	Me, Me, H	89	46

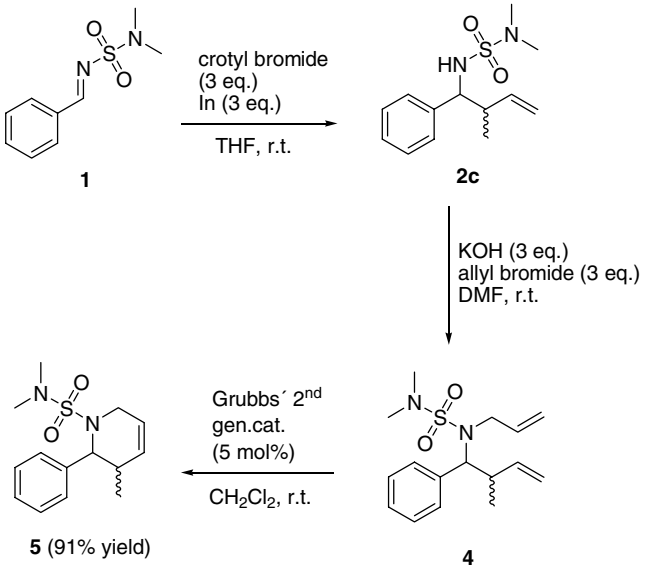
[a] Allylations were performed at rt on a 0.10–0.30 mmol scale with 3 equiv of metal and allylating agent, respectively.
[b] Conversions were determined by ^{1}H NMR.
[c] Isolated yield.
[d] The crotylated products were determined to be racemic mixtures of the *syn*/*anti* diastereoisomers (entries 3 and 7) by ^{1}H NMR of the crude product.



Scheme 2.

pound **2c** was converted into the corresponding diallylic sulfamide **4** in excellent yield (Scheme 3).[20] Exposure of a degassed CH_2Cl_2 solution of **4** to Grubbs' 2nd generation Ru-catalyst (NHC)(PCy_3)Cl_2Ru=CHR at room temperature provided, after purification, the functionalized dehydropiperidine **5** in 91% yield.[21] This reaction generates a double bond in the six-membered ring for further derivatization and shows the compatibility of the sulfamoyl group with ruthenium-catalyzed metathesis reactions.[21,22] Similar preparation of dehydropiperidines has been previously described by Couty and co-workers.[23] Further research on the synthesis of analogous piperidine building blocks and removal of the sulfamoyl group in these systems is currently in progress.

In summary, we have shown that the Zn- and In-mediated Barbier-type allylations of an *N*,*N*-(dimethylsulfamoyl)-protected aldimine with different allylating agents takes place in a highly efficient manner in anhydrous THF, providing the corresponding *N*-homoallylic sulfamoylamides in very good yields. The reaction proceeds fairly well in aqueous media but is accompanied by the concomitant hydrolysis of the imine substrate. The *N*,*N*-dimethylsulfamoyl protecting group can be efficiently cleaved from the product amides by transamination. Finally, the *N*-homoallylic sulfamides can be further utilized for the preparation of heterocyclic building blocks. Allylation followed by ring-closing olefin metathesis provides access to functionalized dehydropiperidines in excellent yield, demonstrating the potential of the protocol.



Scheme 3.

Acknowledgements

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Supplementary data

Complete experimental and analytical details, spectral data and copies of ^{1}H NMR and ^{13}C NMR spectra of selected compounds are available as Supporting data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.167.

References and notes

1. Corey, E. J.; Cheng, X. M. *The Logic of Chemical Synthesis*; John Wiley & Sons: New York, 1989.

2. For reviews, see: (a) Pilli, R. A.; Russowski, D. *Trends Org. Chem.* **1997**, *6*, 101–123; (b) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895–1946; (c) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407–1438; (d) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094; (e) Alvaro, G.; Savoia, D. *Synlett* **2002**, 651–674; (f) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095–3166.
3. (a) Ohfune, Y.; Hori, K.; Sakitani, M. *Tetrahedron Lett.* **1986**, *27*, 6079–6082; (b) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1527–1528; (c) Laschat, S.; Kunz, H. *J. Org. Chem.* **1991**, *56*, 5883–5889; (d) Franciotti, M.; Mann, A.; Mordini, A.; Taddei, M. *Tetrahedron Lett.* **1993**, *34*, 1355–1358; (e) Jones, A. D.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1996**, 915–916; (f) Graziani, L.; Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **1996**, *7*, 1341–1346; (g) Jo, E.; Na, Y.; Chang, S. *Tetrahedron Lett.* **1999**, *40*, 5581–5582; (h) Deloisy, S.; Tietgen, H.; Kunz, H. *Collect. Czech. Chem. Commun.* **2000**, *65*, 816–828; (i) Jones, A. D.; Knight, D. W.; Hibbs, D. E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1182–1203; (j) Pannecoucke, X.; Outurquin, F.; Paulmier, C. *Eur. J. Org. Chem.* **2002**, 995–1006; (k) Ochoa-Puentes, C.; Kouznetsov, V. *J. Heterocycl. Chem.* **2002**, *39*, 595–614.
4. Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3823–3825.
5. For reviews, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293; (b) Russo, D. A. *Chem. Ind. N.Y.* **1996**, *64*, 405–439; (c) Li, C.-J. *Tetrahedron* **1996**, *52*, 5643–5668; (d) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763–2794.
6. See, for example: (a) Uneyama, K.; Kamaki, N.; Moriya, A.; Torii, S. *J. Org. Chem.* **1985**, *50*, 5396–5399; (b) Wang, D.-E.; Dai, L.-X.; Hou, X.-L.; Zhang, Y. *Tetrahedron Lett.* **1996**, *37*, 4187–4188; (c) Lu, W.; Chan, T. H. *J. Org. Chem.* **2000**, *65*, 8589–8594; (d) Xu, X.; Zha, Z.; Miao, Q.; Wang, Z. *Synlett* **2004**, 1171–1174; (e) Shen, K.-H.; Yao, C.-F. *J. Org. Chem.* **2006**, *71*, 3980–3983.
7. See, for example: (a) Beuchet, P.; Le Marrec, N.; Mosset, P. *Tetrahedron Lett.* **1992**, *33*, 5959–5960; (b) Paquette, L. A.; Rothhaar, R. R.; Isaac, M.; Rogers, L. M.; Rogers, R. D. *J. Org. Chem.* **1998**, *63*, 5463–5472; (c) Chan, T. H.; Lu, W. *Tetrahedron Lett.* **1998**, *39*, 8605–8608; (d) Källström, S.; Erkkilä, A.; Pihko, P. M.; Sjöholm, R.; Sillanpää, R.; Leino, R. *Synlett* **2005**, 751–756; (e) Vilaivan, T.; Winotapan, C.; Banphavichit, V.; Shinada, T.; Ohfune, Y. *J. Org. Chem.* **2005**, *70*, 3464–3471; (f) Källström, S.; Jagt, R. B. C.; Sillanpää, R.; Feringa, B. L.; Minnaard, A. J.; Leino, R. *Eur. J. Org. Chem.* **2006**, 3826–3833.
8. See, for example: (a) Waldmann, H. *Synlett* **1990**, 627–628; (b) Hanessian, S.; Yang, R.-Y. *Tetrahedron Lett.* **1996**, *37*, 5273–5276; (c) Chung, W. J.; Higashiya, S.; Oba, Y.; Welch, J. T. *Tetrahedron* **2003**, *59*, 10031–10036; (d) Keltjens, R.; Vadivel, S. K.; de Gelder, R.; Klunder, A. J. H.; Zwanenburg, B. *Eur. J. Org. Chem.* **2003**, 1749–1758.
9. Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831–1833.
10. (a) Pae, A. N.; Cho, Y. S. *Curr. Org. Chem.* **2002**, *6*, 715–737; (b) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633–655; (c) Paquette, L. A. *Synthesis* **2003**, 765–774.
11. Killinger, T. A.; Boughton, N. A.; Runge, T. A.; Wolinsky, J. *J. Organomet. Chem.* **1977**, *124*, 131–134.
12. Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2006**, *8*, 4979–4982.
13. Vilaivan, T.; Winotapan, C.; Banphavichit, V.; Shinada, T.; Ohfune, Y. *J. Org. Chem.* **2005**, *70*, 3464–3471.
14. Vilaivan, T.; Winotapan, C.; Shinada, T.; Ohfune, Y. *Tetrahedron Lett.* **2001**, *42*, 9073–9076.
15. Legros, J.; Meyer, F.; Coliboeuf, M.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J.-P. *J. Org. Chem.* **2003**, *68*, 6444–6446.
16. Jagt, R. B. C.; Toullec, P. Y.; Geerdink, D.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2789–2791.
17. *Standard procedure for* Tables 1 and 2: In a Schlenk tube flushed with argon, **1** (21–65 mg, 0.10–0.30 mmol) was dissolved in the aqueous or organic solvent (1.0–3.0 mL). Metal (3 equiv) and the allylating agent (3 equiv) were added and the mixture was stirred overnight at room temperature. Quenching with 1 N HCl and extraction with ether was followed by washing with satd $NaHCO_3$ and brine and drying over Na_2SO_4. After evaporation, the crude product was purified by flash chromatography (eluent: 20% EtOAc in hexane). For analytical data, see Supplementary data.
18. (a) Pétrier, C.; Luche, J.-L. *J. Org. Chem.* **1985**, *50*, 910–912; (b) Zhang, J.; Blazecka, P. G.; Berven, H.; Belmont, D. *Tetrahedron Lett.* **2003**, *44*, 5579–5582.
19. *Deprotection procedure*: 0.20 mmol of **2a** in 2 mL of 1,3-diaminopropane was heated to 140 °C and refluxed for 2 h. After cooling to rt, the mixture was diluted with CH_2Cl_2 and washed with water. Subsequent extraction of the aqueous layer with CH_2Cl_2, drying with Na_2SO_4 and evaporation gave **3** (92%) as a light yellow oil. For analytical data, see Supplementary data.
20. Wang, F.; Wang, J.; Zhang, S. *Molecules* **2004**, *9*, 574–582.
21. Compound **2c** (67 mg, 0.25 mmol) was dissolved in DMF (1.0 mL). KOH (42 mg, 0.75 mmol) and allyl bromide (65 μL, 0.75 mmol) were added and the resulting mixture was stirred for 1 h at rt. Quenching with H_2O and extraction with ether was followed by drying over anhydrous Na_2SO_4. Concentration gave **4** as a colorless oil, which was used in the subsequent step without further purification. Next, a Schlenk tube flushed with argon was charged with a solution of **4** (30.0 mg, 0.10 mmol) in anhydrous CH_2Cl_2 (0.7 mL) and degassed using three evacuation/argon-fill cycles. In a separate tube, a degassed solution of Grubbs' 2nd generation catalyst in anhydrous CH_2Cl_2 (0.3 mL) was prepared. The solution of **4** was cooled on an ice bath and treated dropwise with the catalyst solution over a period of 5 min. The reaction mixture was removed from the ice bath, allowed to warm to room temperature and stirred overnight. After 12 h, the product was purified by flash chromatography by passing the reaction mixture through a silica gel column affording **5** (25.5 mg, 91%) as a light yellow oil. For analytical data, see Supplementary data.
22. Maier, M. E.; Bugl, M. *Synlett* **1998**, 1390–1392.
23. Agami, C.; Couty, F.; Evano, G. *Tetrahedron: Asymmetry* **2000**, *11*, 4639–4643.