Indium-Catalyzed Barbier Reactions of Amino Aldehydes

Steffen Steurer, Joachim Podlech*

Institut für Organische Chemie der Universität Stuttgart, Pfaffenwaldring 55, 70569 Stuttgart, Germany
Fax: (+49) 711-685-4269, E-mail: joachim.podlech@po.uni-stuttgart.de

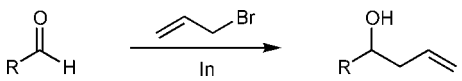
Received November 11, 2000; Accepted January 3, 2001

Abstract: The indium-catalyzed Barbier-type reaction of Cbz-protected amino aldehydes with methyl 2-(bromomethyl)acrylate in the presence of aluminum or manganese/Me_3SiCl was investigated. Best results were obtained using 0.15 equiv. $InCl_3$ with excess aluminum. No significant differences between catalyzed and stoichiometric reaction conditions were observed. Addition of chiral auxiliaries did not improve selectivities in indium-mediated allyl additions.

Keywords: amino alcohols; amino aldehydes; Barbier reaction; C–C coupling; indium; water as solvent

The indium-catalyzed Barbier-type reaction of Cbz-protected amino aldehydes with methyl 2-(bromomethyl)acrylate in the presence of aluminum or manganese/Me_3SiCl was investigated. Best results were obtained using 0.15 equiv. $InCl_3$ with excess aluminum. No significant differences between catalyzed and stoichiometric reaction conditions were observed. Addition of chiral auxiliaries did not improve selectivities in indium-mediated allyl additions.

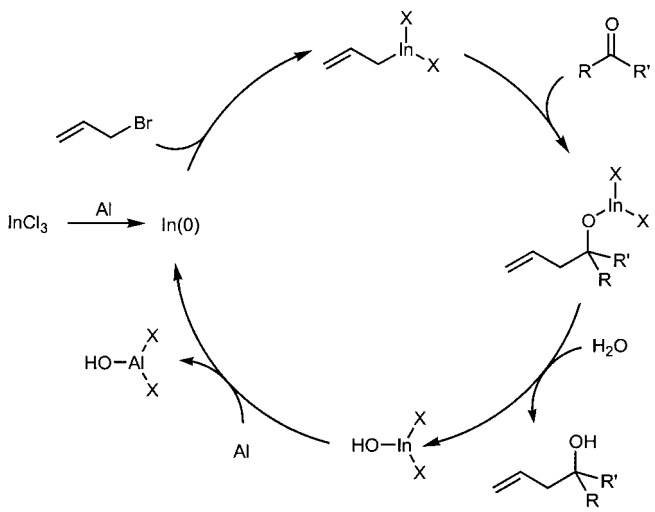
Indium as a reducing agent in Barbier-[1] or Reformatsky-type reactions has attracted attention during the last years, since it usually leads to improved yields and selectivities (Scheme 1).[2]



Scheme 1.

In addition, these reactions are favorably performed in water or water-containing solvents, which is advantageous when unprotected, water-soluble substrates (like carbohydrates) are transformed. We investigated Barbier-type reactions with indium as mediating metal using amino aldehydes as starting materials, which we further used for the preparation of γ-aminoalkyl-substituted α-methylene γ-butyrolactones.[3] Since indium is more expensive than zinc or tin,[4] we have tried to use only catalytic amounts and to regenerate it by use of less expensive metals. Schmid and co-workers mentioned that indium can be recovered after the allyl addition by electrochemical reduction, which might be especially useful when larger amounts of indium are used.[5] Araki, Butsugan et al. published an *in situ* regeneration by aluminum or zinc, but tin or manganese in the presence of Me_3SiCl have been used as well.[6] The proposed catalytic cycle of this reaction is depicted in Scheme 2.[6a]

Nevertheless, up to now, just very simple substrates bearing no stereogenic centres have been used with these catalytic reaction conditions. We were interested to determine whether higher functionalized substrates can be used with these or similar catalytic reaction conditions (Scheme 3).



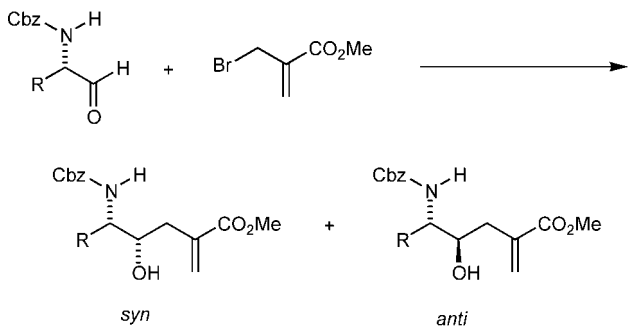
Scheme 2.

  1615-4150/01/34301-251–254 $ 17.50-.50/0

Table 1. Indium-catalyzed Barbier reaction of Cbz-valinal and methyl 2-(bromomethyl)acrylate (see Scheme 3).

Entry	Conditions[a]	catalyst	yield[b] (%)	d. r.[c] (*syn/anti*)	$[\alpha]_{20}^{D}$ (*c*)[d]	
					syn	*anti*
1	1.1 equiv. In, rt, 16 h[e]	–	82	80:20	–22.3 (1.00)	–9.3 (1.01)
2	1.3 equiv. Al, rt, 44 h	0.15 equiv. $InCl_3$	79	77:23	–22.6 (1.02)	–7.9 (0.97)
3	1.3 equiv. Al, 40 °C, 48 h	0.10 equiv. $InCl_3$	68	76:24	–24.6 (1.02)	–9.0 (1.04)
4	1.3 equiv. Al, 40 °C, 72 h	0.05 equiv. $InCl_3$	55	75:25	–21.5 (0.99)	–7.5 (1.02)
5	1.3 equiv. Al, 40 °C, 90 h	0.01 equiv. $InCl_3$	36[f]	68:32	–17.9 (0.98)	–6.2 (0.97)
6	1.3 equiv. Al, 30 °C, 110 h	0.15 equiv. In	49[f]	81:19	–20.7 (0.93)	–8.0 (1.13)
7	1.3 equiv. Al, 40 °C, 60 h	0.15 equiv. In	50[f]	79:21	–[g]	–[g]
8	1.3 equiv. Al, 40 °C, 48 h	–	no reaction		–	–
9	5 equiv. Mn, 5 equiv. Me_3SiCl, rt, 48 h[h]	0.10 equiv. $InCl_3$	14[i]	70:30	–24.3 (0.98)	–9.8 (0.75)
10	5 eq. Mn, 5 eq. Me_3SiCl, rt, 48 h[h]	0.10 eq. In	31[i]	67:33	–23.0 (0.94)	–6.3 (0.98)
11	5 equiv. Mn, 5 equiv. Me_3SiCl, rt, 60 h[h]	–	no reaction	–	–	

[a] Cbz-valinal (2–25 mmol), 1.7 equiv. methyl 2-(bromomethyl)acrylate and the reducing agent were stirred in THF/H_2O (1:1).
[b] Yields of isolated and separated isomers.
[c] Diastereomeric ratio determined by ^1H NMR spectroscopy and HPLC.
[d] Optical rotation was determined in $CHCl_3$.
[e] The solvent system was EtOH/H_2O (4:1). The reaction was usually finished after 4 h (TLC), but was stirred for 16 h.
[f] 30–35% of starting material was recovered.
[g] Not determined.
[h] 2.5 equiv methyl 2-(bromomethyl)acrylate were used. Reaction was performed in THF under an N_2 atmosphere.
[i] No starting material could be recovered.



Scheme 3.

We therefore reacted benzyloxycarbonyl (Cbz)-protected valinal with methyl 2-(bromomethyl)acrylate in the presence of excess aluminum and 0.15 equiv. of $InCl_3$. When the reaction was performed in H_2O/EtOH (4:1), the best solvent system for the non-catalyzed reaction, we observed no significant reaction even after 48 h. Therefore, we switched to H_2O/THF (1:1) and found essentially identical selectivities and yields as in the non-catalyzed reaction (Table 1, entries 1, 2). Although the reaction time was prolonged from 4 to 44 h, no racemization occurred, which was checked by measuring the optical rotation of the separated isomers and by transforming them to the Mosher-esters followed by NMR analysis.[7]

The sensitivity of the reaction towards the used solvent was surprising, but not unknown in indium-mediated reactions.[3d] Further reduction of the amount of catalyst to 0.05 equiv. was possible, although the reaction time further increased and the yields were slightly lower (entries 3 and 4). When 0.01 equiv. $InCl_3$ were used, the reaction was not complete even after 90 h. In addition, the stereochemical integrity was not longer given, the isolated diastereoisomers were partially racemized (entry 5). Similarly, indium itself could be used as a catalyst, though the reaction was somewhat slower and usually not complete even after 5 d (entries 6 and 7).[8] Manganese in the presence of Me_3SiCl, which has been used as reducing agent for catalytic amounts of indium[6c] did not effect a clean Barbier-type reaction with our highly functionalized substrates. Although diastereoselectivities were comparable and the stereochemical integrity was maintained, the yields were substantially lower, not exceeding 30% (entries 9 and 10). No starting material could be recovered in these

Table 2. Indium-catalyzed Barbier reactions with optimized reaction conditions (see Scheme 3)

Entry	R	catalyzed[a]		stoichiometric[b]	
		yield[c] (%)	d. r.[d] (*syn/anti*)	yield[c] (%)	d. r.[d] (*syn/anti*)
1	Me	63	68:32	69	68:32
2	*i*Pr	79	77:23	82	80:20
3	*i*Bu	64	68:32	81	75:25

[a] 1.7 equiv. methyl 2-(bromomethyl)acrylate, 1.3 equiv. Al, 0.15 equiv. $InCl_3$, THF/H_2O (1:1), rt, 44 h.
[b] 1.7 equiv. methyl 2-(bromomethyl)acrylate, 1.1 equiv. In, EtOH/H_2O (4:1), rt, 4 h.[5a]
[c] Yields of isolated and separated isomers.
[d] Diastereomeric ratio determined by ^1H NMR spectroscopy and HPLC.

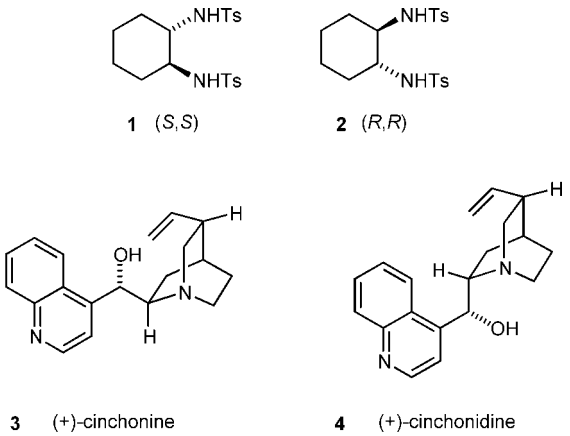


Figure 1. Chiral additives.

Table 3. Effect of chiral additives on the indium-mediated Barbier reaction

Entry	solvent	additive	yield[a] (%)	d. r.[b] (*syn*/*anti*)
1	$EtOH/H_2O$[c]	–	74	68:32
2	$EtOH/H_2O$[c]	**1**	60	60:40
3	$EtOH/H_2O$[c]	**2**	72	65:35
4	CH_2Cl_2[d]	**3**	no allyl addition	
5	CH_2Cl_2[d]	**4**	no allyl addition	

[a] Yields of isolated and separated isomers.
[b] Diastereomeric ratio determined by ^1H NMR spectroscopy and HPLC.
[c] 1 equiv. Cbz-phenylalaninal, 1.7 equiv. methyl 2-(bromomethyl)acrylate, 1.1 equiv. In, 1.1 equiv. additive, rt, 15 h.
[d] 6 equiv. methyl 2-(bromomethyl)acrylate, 2 equiv. In, 2 equiv. additive, CH_2Cl_2, then 1 equiv. Cbz-phenylalaninal in hexane, rt, 15 h.

cases. To confirm that $InCl_3$ was actually necessary as a catalyst, we performed reactions without $InCl_3$ and found that aluminum or manganese/Me_3SiCl were not able to mediate this Barbier-type reaction (entries 8 and 11).

With the optimum conditions (0.15 equiv. $InCl_3$, 1.3 equiv. aluminum) we tested further amino aldehydes (Cbz-alaninal and isoleucinal) and found similar results on comparing catalyzed and non-catalyzed reactions (Table 2).

We tested whether the diastereoselectivity of the indium-mediated Barbier reaction could be further improved by addition of chiral additives. Here we used Cbz-phenylalaninal as the aldehyde moiety. Since selectivities were rather poor with this substrate (Table 3, entry 1),[3a] a possible improvement should be more meaningful.

Loh et al. published enantioselective allyl additions to benzaldehyde or fluorinated acetophenone in the presence of cinchonidine (**4**) (Figure 1).[9] We found that these additives were not compatible with methyl 2-(bromomethyl)acrylate. Tertiary bases like the *Cinchona* alkaloids **3** and **4** are able to attack α,β-unsaturated carboxylic esters as in the first step of the Morita-Baylis-Hillman reaction.[10] The resulting adduct most probably loses bromide and thus would not give allyl adducts.

Utilization of bissulfonamides **1** and **2**[11] did not suppress allyl addition, but on the other hand did not lead to improved selectivities (Table 3).

In summary we found that Barbier-type reactions using catalytic amounts of indium chloride can be used for the allyl addition of methyl 2-(bromomethyl)-acrylate to amino aldehydes without significant alteration of yields and selectivities.

Experimental Section

Typical Procedure for Allyl Additions to Amino Aldehydes Using Aluminum and Catalytic Amounts of $InCl_3$ or In

The Cbz-protected α-amino aldehyde (1.00 mmol,) was dissolved in THF (3 mL) at room temperature in an inert atmosphere (N_2). After addition of water (3 mL), methyl 2-(bromomethyl)acrylate (1.7 mmol, 304 mg), $InCl_3$ or In (0.15 mmol) and aluminum powder (1.3 mmol, 35 mg), the mixture was stirred at least 48 h at room temperature (for differing reaction conditions see Table 1). 1 N aqueous HCl (5 mL) was added and the mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were subsequently washed with saturated $NaHCO_3$ solution (10 mL) and brine (10 mL) and dried ($MgSO_4$). The solvents were removed at the rotatory evaporator yielding the crude product, which was dissolved in ethyl acetate and filtered through a short pad of silica gel (5 g). The diastereomeric ratio was determined by HPLC (hexane/ethyl acetate). Purification and separation of the isomers was achieved by MPLC (petroleum ether/ethyl acetate).

Typical Procedure for an Allyl Addition to Amino Aldehydes Using Manganese/Me_3SiCl and Catalytic Amounts of $InCl_3$ or In

Manganese powder (5.00 mmol, 275 mg) and $InCl_3$ or In (0.10 mmol) were stirred for 5 min under N_2. Dry THF (5 mL), methyl 2-(bromomethyl)acrylate (2.5 mmol, 448 mg), the Cbz-protected valinal (1.00 mmol, 235 mg) and Me_3SiCl (5.00 mmol, 633 μL) were subsequently added. The mixture was stirred 48 h at room temperature and worked up as described above.

General Procedure for a Allyl Addition to Amino Aldehydes in the Presence of Chiral Additives

Indium (363 μmol, 42 mg) was suspended in the solvent ($EtOH/H_2O$ or CH_2Cl_2, 2 mL) in an inert atmosphere (N_2). After addition of the chiral additive (363 μmol) the mixture was stirred 5 min at room temperature, before methyl 2-

(bromomethyl)acrylate (561 μmol, 100 mg) and Cbz-protected phenylalaninal (330 μmol, 94 mg) were added. The reaction mixture was stirred overnight and worked-up as described above.

Acknowledgements

The generous support of Prof. Dr. V. Jäger and Prof. Dr. Dr. h. c. F. Effenberger (University of Stuttgart) is gratefully acknowledged. We are greatly indebted to J. Rebell (NMR). This work was supported by the Fonds der Chemischen Industrie, the *Deutsche Forschungsgemeinschaft, the Stiftungsfonds Mitsubishi Electric Europe, the Landesgraduiertenförderung Baden-Württemberg and the Degussa AG (gift of amino acids).*

References

[1] C. Blomberg, *The Barbier Reaction and Related One-Step Processes*; Springer, Heidelberg, **1994**.

[2] (a) A. Lubineau, J. Augé, Y. Queneau, *Synthesis* **1994**, 741; (b) P. Cintas, *Synlett* **1995**, 1087; (c) C.-J. Li, *Tetrahedron* **1996**, *52*, 5643; d) C.-J. Li, T.-H. Chan, *Organic Reactions in Aqueous Media*; Wiley-Interscience, New York, **1997**; (e) A. Lubineau, J. Augé, Y. Queneau in *Organic Synthesis in Water* (Ed.: P. A. Grieco), Blackie Academic, London, **1998**, p. 102; (f) L. A. Paquette in *Green Chemistry. Frontiers in Benign Chemical Syntheses and Processes* (Eds.: P. T. Anastas, T. C. Williamson), Oxford University Press, Oxford, **1998**, p. 250; (g) A. S. K. Hashmi, *J. Prakt. Chem.* **1998**, *340*, 84; (h) D. Lainé, *Synlett* **1999**, 1331; (i) A. Lubineau, J. Augé, *Top. Curr. Chem.* **1999**, *206*, 1; (j) T.-P. Loh, R.-B. Wang, K.-L. Tan, K.-Y. Sim, *Main Group Met. Chem.* **1997**, *20*, 237; (k) T.-P. Loh, J.-M. Huang, K.-C. Xu, S.-H. Goh, J. J. Vittal, *Tetrahedron Lett.* **2000**, *41*, 6511 and references cited therein.

[3] (a) S. Steurer, J. Podlech, *Eur. J. Org. Chem.* **1999**, 1551; (b) S. Steurer, J. Podlech, *Org. Lett.* **1999**, *1*, 481; (c) for the original publication of this method see: E. Öhler, K. Reininger, U. Schmidt, *Angew. Chem.* **1970**, *82*, 480; *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 457; (d) independent work was published by L. A. Paquette, T. M. Mitzel, M. B. Isaac, C. F. Crasto, W. W. Schomer, *J. Org. Chem.* **1997**, *62*, 4293.

[4] The price for indium is about 5 US $/mmol.

[5] R. H. Prenner, W. H. Binder, W. Schmid, *Liebigs Ann. Chem.* **1994**, 73.

[6] (a) Aluminum or zinc as regenerant: S. Araki, S.-J. Jin, Y. Idou, Y. Butsugan, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1736–1738; (b) Tin: T.-P. Loh, X.-R. Li, *Angew. Chem.* **1997**, *109*, 1029; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 980; (c) Manganese: J. Augé, N. Lubin-Germain, A. Thiaw-Woaye, *Tetrahedron Lett.* **1999**, *40*, 9245.

[7] J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512.

[8] (a) These results are momentarily not well understood by us. Obviously, the catalytic cycle is somewhat more complicated than depicted in Scheme 2; (b) see also: T. H. Chan, Y. Yang, *J. Am. Chem. Soc.* **1999**, *121*, 3228.

[9] (a) T.-P. Loh, J.-R. Zhou, X.-R. Li, *Tetrahedron Lett.* **1999**, *40*, 9333; (b) T.-P. Loh, J.-R. Zhou, Z. Yin, *Org. Lett.* **1999**, *1*, 1855; (c) Enantioselective indium-Reformatsky reactions have been published as well: P. S. Johar, S. Araki, Y. Butsugan, *J. Chem. Soc., Perkin Trans. 1* **1992**, 711.

[10] (a) D. Basavaiah, P. D. Rao, R. S. Hyma, *Tetrahedron* **1996**, *52*, 8001; (b) E. Ciganek, *Org. React.* **1997**, *51*, 201; (c) Morita-Baylis-Hillman reactions with *Cinchona* alkaloids as chiral bases have been published: Y. Iwabuchi, M. Nakatani, N. Yokoyama, S. Hatakeyama, *J. Am. Chem. Soc.* **1999**, *121*, 10219; (d) P. Langer, *Angew. Chem.* **2000**, *112*, 3177; *Angew. Chem. Int. Ed.* **2000**, *39*, 3049.

[11] (a) H. Takahashi, T. Kawakita, M. Ohno, M. Yoshioka, S. Kobayashi, *Tetrahedron* **1992**, *48*, 5691; (b) Y. L. Bennani, S. Hanessian, *Chem. Rev.* **1997**, *97*, 3161; (c) J. E. A. Luithle, J. Pietruszka, *J. Org. Chem.* **1999**, *64*, 8287.