



Tetrahedron Letters 44 (2003) 911-914

TETRAHEDRON LETTERS

Indium-mediated allylation of carbonyl compounds with an allylic bromide in aqueous media: anomalous *syn*-diastereoselectivity regardless of allylic bromide geometry

Teck-Peng Loh,^{a,*} Zheng Yin,[†] Hong-Yan Song and Kee-Leng Tan

^aDepartment of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore

Received 26 September 2002; revised 27 November 2002; accepted 6 December 2002

Abstract—Anomalous *syn*-diastereoselectivity of indium-mediated coupling of aldehydes with bromides Z-**3b** and E-**3b** is reported. The reaction afforded high *syn* selectivity regardless of the allylic bromide geometry. Preliminary studies on the enantioselective indium-mediated allylation were attempted and found to give the desired products in moderate yield with high *syn* selectivity and enantioselectivity. © 2003 Elsevier Science Ltd. All rights reserved.

Indium-promoted allylation of carbonyl compounds has proved to be one of the most useful methods for the preparation of synthetically useful homoallylic alcohols.¹ Furthermore, the possibility of carrying out this reaction in aqueous media has made this reaction a potentially useful tool for the construction of complex molecules. Our group has been interested in applying this reaction to sophisticated chemical synthesis. However, during this work, we were frequently frustrated by the limitation of existing methods and the lack of stereochemical studies, although recent contributions from Chan, Li, Whitesides,² Paquette, our group and

others have expanded further the scope of this reaction.³ In this paper, we report anomalous *syn*diastereoselectivity of the indium-mediated allylation reaction regardless of the allylic bromide geometry and its application to the total synthesis of antillatoxin $1.^4$

As part of our studies towards the total synthesis of antillatoxin 1, we are interested in the synthesis of a key intermediate, the advanced homoallylic alcohol 2, having the *anti*-configuration at C4 and C5 via an indiummediated allylation strategy (Scheme 1). Since a cyclic or Zimmerman–Traxler⁵ transition state model has been



Scheme 1. Retrosynthetic analysis.

0040-4039/03/\$ - see front matter @ 2003 Elsevier Science Ltd. All rights reserved. PII: S0040-4039(02)02773-9

^{*} Corresponding author. Tel.: 65-68747851; fax: 65-67791691; e-mail: chmlohtp@nus.edu.sg

[†] Current address: S*Bio Pte Ltd, 1 Science Park Road, #05-09 The Capricorn, Singapore Science Park II, Singapore 117528

proposed to explain characteristic diastereoselectivity, we envisaged that the *E*-allylic bromide **3b** would afford the *anti*-product while the *Z*-allylic bromide **3b** should give the *syn*-product.

Synthesis of the prequisite E- and Z- allylic bromides 3b is shown in Scheme 2. Synthesis of Z-3a was accomplished by DIBAL-H reduction of methyl (Z)-2-(bromomethyl)-2-butenate 5, which was prepared according to a literature procedure.⁶ Treatment of Z-3a with TBDPS-Cl in the presence of imidazole afforded the desired allylic bromide Z-3b in 92% yield. The allylic bromide E-3b was also synthesized starting from 5. Exposure of 5 to excess sodium acetate in refluxing methanol followed by the addition of one equivalent of K_2CO_3 to affect acetate cleavage produced the butenoate 6 in 82% yield.⁷ Protection of the hydroxy group of 6 with TBDPS followed by DIBAL-H reduction gave the butenol 7. Bromination of the butenol 7 with NBS in the presence of PPh₃ provided the desired allylic bromide E-3b in 90% yield.

Before embarking on the reaction with the complex aldehyde 4^8 for the antillatoxin synthesis, we carried out model studies using these bromides (*E*-**3b** and *Z*-**3b**) with various carbonyl compounds. The results are shown in Table 1. In all cases, the reactions were carried out in THF-H₂O (1:1) with indium in the presence of an external Lewis acid and afforded the corresponding homoallylic alcohols in moderate yields. Contrary to our expectation, the *syn* products were obtained as the major products regardless of the allylic bromide geometry. Especially noteworthy is the fact that in the absence of lanthanide triflate, no allylation was observed. Of mechanistic interest is that the excess of the bromides could be recovered without isomerization of the double bond.

Based on the fact that this reaction does not work in the absence of $La(OTf)_3$, and the configurations of the recovered allylic bromides remain the same, we propose that an open-chain *anti*-periplanar transition state may be playing a role (Fig. 1). Allylic indium generated



Scheme 2. Reagents and conditions: (i) DIBAL-H, CH_2Cl_2 , 0°C, 1 h; (ii) TBDPS-Cl, imidazole, DMF, rt., 10 h; (iii) NaOAc, MeOH, reflux, 3.5 h; K_2CO_3 ; (iv) NBS, PPh₃, CH_2Cl_2 , -78°C, 0.5 h. DIBAL-H=diisobutylaluminum hydride; TBDPSCl=tert-butyl diphenyl silyl chloride; NBS = *N*-bromosuccinimide.

Table 1. Indium-mediated allylation reactions using the allylic bromides Z-3b and E-3b with various aldehydes^{*a*}



 a A mixture of aldehyde (1 mmol), Indium (2 mmol), allylic bromide (1.5 mmol), La(OTf)_3 (1 mmol) in THF-H_2O (1:1) (30 mL) was stirred vigorously at room temperature for 16 hours. b Isolated yield; c Determined by $^1{\rm H}$ NMR



Figure 1. Proposed mechanism.

using allylic bromide and indium powder in aqueous media has been shown to exist as an indium(I) species. This has been reported by Chan and co-workers.⁹

Using the optimized conditions, we proceeded to investigate the indium-promoted allylation of bromides Z-3band E-3b with the aldehyde 4 (Scheme 3). As before, the desired products were obtained in good yields with the *syn* product as the major product, irrespective of which allylic bromide was employed and the pure *syn* isomer was easily obtained by flash column chromatography.

Preliminary studies on the enantioselective indiummediated allylation using a method established in our group were attempted (Scheme 4).¹⁰ ¹¹ No reaction was









Z-3b (X = OTBDPS) No reaction Z-3a (X = OH) 36% (85% ee, syn : anti = 99:1)



(-)-cinchonidine

Scheme 4.

observed with Z-3b. However, the reaction proceeded with Z-3a to afford the product in moderate yield with high *syn* selectivity (*syn:anti=99:1*) and enantioselectivity (85% ee).

In conclusion, anomalous syn diastereoselectivity in the Lewis-acid promoted indium-mediated coupling of aldehydes with allylic bromides Z-3b and E-3b was observed. The reaction proceeded smoothly with a variety of aldehydes and afforded high syn selectivity regardless of the allylic bromide geometry. The experimental protocol is simple without the need of strictly anhydrous conditions. In addition, preliminary studies on the enantioselective indium-mediated allylation were attempted providing the product in moderate yield with high syn selectivity and enantioselectivity. Furthermore, this has provided a novel and efficient method under very mild conditions to a key intermediate for the total synthesis of antillatoxin.

Acknowledgements

This research was supported by grants from the National University of Singapore.

References

- 1. For the pioneering work on the indium-mediated allylation reaction of carbonyl compounds: (a) Li, C. J. Chem. Rev. 1993, 93, 2023; (b) Chan, T. H.; Li, C. J.; Lee, M. C.; Wei, Z. Y. Can. J. Chem. 1994, 72, 1181; (c) Cintas, P. Synlett. 1995, 1087; (d) Chan, T. H.; Lee, M. C. J. Org. Chem. 1995, 60, 4228; (e) Chan, T. H.; Yang, Y. J. Am. Chem. Soc. 1999, 121, 3228; (f) Araki, S.; Ito, H. J. Org. Chem. 1988, 53, 1831; (g) Paquette, L. A.; Lobben, P. C. J. Am. Chem. Soc. 1996, 118, 1917; (h) Paquette, L. A.; Mitzel, T. M. J. Am. Chem. Soc. 1996, 118, 1931; (i) Fujiwara, N.; Yamamoto, Y. J. Org. Chem. 1997, 62, 2318; (j) Paquette, L. A.; Mitzel, T. M. J. Org. Chem. 1997, 62, 4293; (k) Isaac, M. B.; Paquette, L. A. J. Org. Chem. 1997, 62, 5333; (1) Hirashita, T.; Kamei, T. J. Org. Chem. 1999, 64, 172; (m) Paquette, L. A.; Rothhaar, R. R. J. Org. Chem. 1999, 64, 217.
- (a) Gordon, D. M.; Whitesides, G. M. J. Org. Chem. 1993, 58, 7937; (b) Choi, S. K.; Lee, S.; Whiteside, G. M. J. Org. Chem. 1996, 61, 8739.
- Lanthanide triflate has been shown to increase the rate and selectivity of the indium-mediated allylation reaction of carbonyl compounds: (a) Wang, R. B.; Lim, B. K., Sim K. Y.; Loh, T. P. *Tetrahedron: Asymmetry* **1995**, *6*, 1825; (b) Ho, D. S.-C.; Sim, K. Y.; Loh, T. P. *Synlett.* **1996**, *3*, 263; (c) Loh, T. P.; Wang, R. B.; Tan, K. L.; Sim, K. Y. *Main Group Metal Chemistry*, **1997**, *20*, 237; (d) Loh, T. P.; Cao, G. Q.; Pei, J. *Tetrahedron Lett.* **1998**, *39*, 1453.
- (a) Orjala, J.; Nagle, G. D.; Hsu, L. V.; Gervick, W. H. J. Am. Chem. Soc. 1995, 117, 8281–8282; (b) Yokokawa, F.; Shioiri, T. J. Org. Chem. 1998, 63, 8638; (c) Yokokawa, F.; Fujiwara, H.; Shioiri, T. Tetrahedron Lett. 1999, 40, 1915; (d) White, J. D.; Hanselmann, R.; Wardrop, D. J. Am. Chem. Soc. 1999, 121, 1106; (e) Yokokawa, F.; Fujiwara, H.; Shioiri, T. Tetrahedron 2000, 56, 1759.
- (a) Zimmerman, H. E.; Traxler, M. D. J. Am. Chem. Soc. 1957, 79, 1920; (b) Heathcock, C. H. In Asymmetric Synthesis; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 3.
- 6. Brown, J. M.; Evans, P. L. Organic Syntheses 1990, 68, 64.
- 7. Roush, W. R.; Brown, B. B. J. Org. Chem. 1993, 58, 2151.
- 8. Loh, T. P.; Cao, G. Q.; Pei, J. *Tetrahedron Lett.* **1998**, *39*, 1457–1460.
- 9. Chan, T. H.; Yang, Y. J. Am. Chem. Soc. 1999, 121, 3228–3229.
- 10. Loh, T. P.; Zhou, J. R.; Yin, Z. Org. Lett. 1999, 1, 1855–1857.
- Typical experimental procedure: To a 50 mL round-bottom flask containing an egg-shaped stirring bar were added (–)-cinchonidine (0.5 mmol) and indium powder (0.5 mmol, 57 mg). The solids were azeotropically dried

twice with 3 mL of dry THF and then treated with 3 mL of dry THF and allylic bromide (1.5 mmol). The mixture was stirred vigorously until it turned into a clear solution, to which was added dropwise 1 mL of dry hexane. The resulting clear solution was cooled to -78° C, followed by introduction of the aldehyde (0.25 mmol) dropwise. The reaction mixture was stirred at -78° C for 2 h, then

allowed to warm to room temperature, and finally quenched with 10 mL of dilute HCl solution. The aqueous layer was extracted with hexane (10 mL×3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , concentrated under vacuum, and purified by flash column chromatography to afford the homoallylic alcohol.