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An enantioselective allylation reaction of aldehydes in an aqueous medium

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Abstract

An enantioselective allylation reaction of aldehydes with enantioselectivities up to 92% has been achieved in an aqueous medium, by using (*S*,*S*)-2,6-bis(4-isopropyl-2-oxazolin-2-yl)pyridine as the chiral source.

Keywords: enantioselectivity; indium; allylation; aldehyde; aqueous.

Indium-mediated allylation of aldehydes has attracted much interest among organic chemists due to the unusual reactivity of indium, particularly in aqueous media.[1] To date, it has been successfully applied to the preparation of complex molecules.[2] However, more than 10 years after the initial report,[3] as far as we know its enantioselective version has not been reported.[4] In this paper, we report our recent progress in the development of a new enantioselective indium-mediated allylation reaction in an aqueous medium (Scheme 1).

Using a standard protocol we screened several chiral ligands. The protocol is as follows. In a 5 mL sample vial was sequentially added indium (10 equivalents), a chiral ligand (2.6 equivalents), 0.5 mL of 1:1 water:ethanol mixed solvent, allyl bromide (10 equivalents) and benzaldehyde (1 equivalent, 0.05 mmol).[5] The reaction mixture was stirred vigorously at room temperature for 0.5 h. With this procedure, the chiral ligands **1**–**6** have been examined, among which (*S*,*S*)-2,6-bis(4-isopropyl-2-oxazolin-2-yl)pyridine **1**[6] gave the best result (95% yield, 70% ee (*R*)). This encouraging observation, combined with previous findings that incorporation of water-stable Lewis acids could improve both yields and diastereoselectivities of this type of reaction,[7] prompted us to systematically investigate the effects of the Lewis acids.[8] The results are summarised in Table 1.

In all cases where 2 equivalents[5] of the Lewis acids were added, the conversion of benzaldehyde was complete within 0.5 h and the desired product was obtained almost quantitatively. Furthermore, most of the Lewis acids were able to enhance the enantioselectivities, the best of which, cerium trifluoromethanesulfonate hydrate (entry 4), afforded the product in 90% yield and 92% ee (*R*). The

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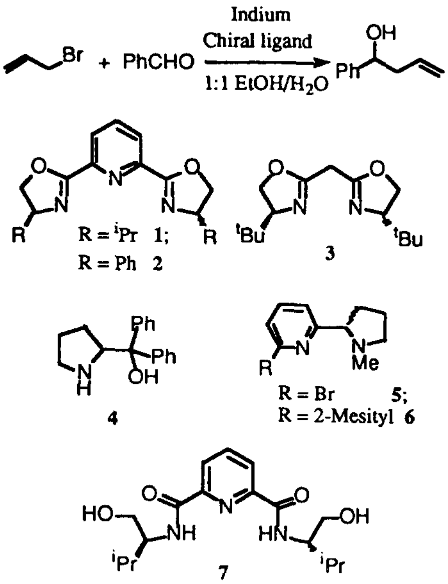

Scheme 1.

Table 1
Screening of Lewis acids

Entry	Lewis acids	Ee[a] (%)[9]	Entry	Lewis acids	Ee (%)
1	$Zn(OTf)_2$	56 (*R*)	9	$Gd(OTf)_3$	84 (*R*)
2	$Sc(OTf)_3.xH_2O$	82 (*R*)	10	$Dy(OTf)_3$	84 (*R*)
3	$Y(OTf)_3$	56 (*R*)	11	$Ho(OTf)_3$	80 (*R*)
4	**$Ce(OTf)_4.xH_2O$**	**92 (*R*)**	12	$Er(OTf)_3$	76 (*R*)
5	$Pr(OTf)_3$	82 (*R*)	13	$Tm(OTf)_3$	78 (*R*)
6	$Nd(OTf)_3$	76 (*R*)	14	$Yb(OTf)_3.xH_2O$	82 (*R*)
7	$Sm(OTf)_3$	82 (*R*)	15	$Lu(OTf)_3$	76 (*R*)
8	$Eu(OTf)_3$	70 (*R*)	16	HOTf	76 (*R*)

[a]Enantioselectivity determined by HPLC analysis employing a Daicel Chiracel OD column. Absolute configuration assigned by comparison with literature values of optical rotation.

use of less than 2 equivalents of $Ce(OTf)_4$ hydrate led to a reduction in the selectivity (76% ee (*R*) for 1 equivalent of $Ce(OTf)_4$ hydrate).

The solvent and temperature effects were surveyed in the presence of 2 equivalents of $Ce(OTf)_4$ hydrate. Changing to other mixed solvents led to lower selectivities (72% ee in 1:1 H_2O:MeCN, 76% ee in 1:1 H_2O:THF and 66% ee in 1:9 H_2O:EtOH). Lowering the reaction temperature from 25°C to 0°C made no observable difference in either yield or selectivity.

Other metals were also tried with allyl bromide under otherwise identical conditions. For example, the use of zinc or tin resulted in complicated mixtures with little of the desired product. Similarly, the reaction of allyl iodide together with indium led to a drop of selectivity from 92% ee to 76% ee, although the homoallylic alcohol was obtained in excellent yield.

Using the optimised reaction conditions described above, other aldehydes were also examined (Table 2). In all cases, good chemical yields were obtained. The aromatic aldehydes and (*E*)-

Table 2
Allylation of aldehydes

Entry	Aldehydes	Yield(%)	Ee (%)
1	Benzaldehyde	90	92 (*R*)
2	3-Methoxybenzaldehyde	83	52[a] (*R*)[10]
3	1-Naphthaldehyde	91	56[b] (*R*)[11]
4	2-Naphthaldehyde	98	66[a] (*R*)[c]
5	(*E*)-Cinnamaldehyde	72	51[a] (*R*)[9]
6	*n*-Hexanal	94	34[d] (*S*)[c]

[a]Enantioselectivities determined by HPLC analysis employing a Daicel Chiracel OD column. Absolute configuration assigned by comparison with literature values of optical rotations. [b]Enantioselectivities determined by HPLC analysis employing a Daicel Chiracel OJ column. [c]Absolute configuration assigned by analogy. [d]Enantioselectivity determined by HPLC analysis employing a Daicel Chiracel OD column of the corresponding 3,5-dinitrobenzoate derivatives.

cinnamaldehyde furnished the products in moderate selectivities (51–66% ee (*R*)) while the aliphatic aldehyde *n*-hexanal gave a lower value.

It was also noticed that the selectivity was decreased to 56% when **1** was pre-stirred with $Ce(OTf)_4$ hydrate for 5 min before the addition of the other reagents and benzaldehyde. With other parameters kept constant, a reduction in the amount of **1** to 1 equivalent or 0.1 equivalent was accompanied by decrease in selectivities (70% ee (*R*) or 12% ee (*R*), respectively). During our attempt to recover the ligand after the reactions, however, **1** was found to have undergone successive hydrolyses under the acidic reaction conditions[12] (about pH 3), giving rise to a complicated mixture. One of the hydrolytic products, the diamide **7** was prepared according to the reported procedure[6] and applied to the allylation of benzaldehyde. Compound **7** afforded the product with almost no selectivity (2% ee (*R*)). All these results suggest that the active allylation species responsible for the allylation reaction is probably an allyl metal complex of **1**.

In conclusion, an aqueous-medium enantioselective indium-mediated allylation of aldehydes was accomplished, although the chiral ligand **1** was not preserved during the course of the reaction and the real species responsible for the reaction still remains obscure. Further work on redesigning acid-resistant, high-affinity chiral ligands applicable to the aqueous reaction is underway in our laboratory.

Acknowledgements

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References

1. For review, see: (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) For mechanistic studies, see: Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228.
2. (a) Chan, T. H.; Li, C.-J. *J. Chem. Soc., Chem. Commun.* **1992**, 747. (b) Gordon, D. M.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 7937. (c) Paquette, L. A.; Stepanian, M.; Mallavadhani, U. V.; Cutarelli, T. D.; Lowinger, T. B.; Klemeyer, H. J. *J. Org. Chem.* **1996**, *61*, 7492. (d) Isaac, M. B.; Paquette, L. A. *J. Org. Chem.* **1997**, *62*, 5333. (e) Loh, T. P.; Cao, G. Q.; Pei, J. *Tetrahedron Lett.* **1998**, *39*, 1453. (f) Yi, X. H.; Meng, Y.; Li, C. J. *Chem. Commun.* **1998**, *11*, 1237. (g) *ibid.* **1998**, *4*, 449.

3. Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831.
4. An enantioselective Reformatsky reaction has been reported: Johar, P. S.; Araki, S.; Butsugan, Y. *J. Chem. Soc., Perkin Trans. 1* **1992**, 711.
5. Later it was realised that as **1** is unstable in the reaction medium, then stoichiometric amounts of indium, allyl bromide, a Lewis acid and **1** have to be used to ensure a fast allyl transfer process and therefore good stereoselection.
6. (a) Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500. (b) Nishiyama, H.; Yamaguchi, S.; Kondo, M.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 4306. (c) For reviews, see: Ghosh, A. K.; Manhivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1.
7. Ho, S.-C. D.; Sim, K.-Y.; Loh, T.-P. *Synlett* **1996**, 263.
8. Kobayashi, S.; Nagayama, S.; Busujima, T. *J. Am. Chem. Soc.* **1998**, *120*, 8287, and references cited therein.
9. Minowa, N.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3697.
10. Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161.
11. Sugimoto, K.; Aoyaji, S.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 2322.
12. For hydrolyses of oxazolines under acidic and Lewis-acidic conditions, see: Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297, and the literature cited therein; Kanemasa, S.; Oderaotoshi, Y.; Yamamoto, H.; Tanaka, J.; Wada, E. *J. Org. Chem.* **1997**, *62*, 6454.