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Catalytic $Sc(OTf)_3$ mediated direct asymmetric aldol reaction of (−)-menthyl isothiocyanatoacetate with aldehydes by using (−)-menthol as chiral auxiliary

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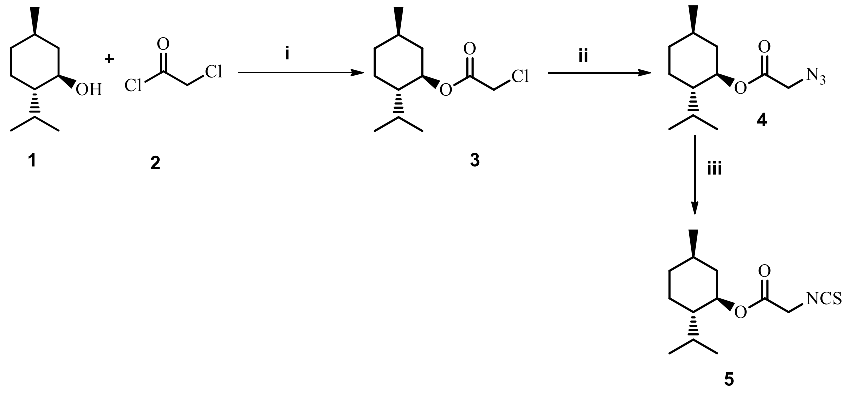
Abstract

This method involves the direct asymmetric aldol reaction of (−)-menthyl isothiocyanatoacetate **5** with a variety of substituted aromatic aldehydes, which offers a convenient method for the synthesis of intermediate containing biologically relevant α-amino β-hydroxyl groups in oxazolidine ring. In this methodology, the products show remarkable diastereoselectivity using $Sc(OTf)_3$ as a catalyst and easily accessible (−)-menthol as a chiral auxiliary. This approach includes some important aspects such as mild reaction conditions, high yields, and excellent diastereoselectivity with a number of substituted aromatic aldehydes. The optimization and effect of different catalysts were studied at different reaction conditions and it is found that $Sc(OTf)_3$ shows excellent diastereoselectivity at −45°C.

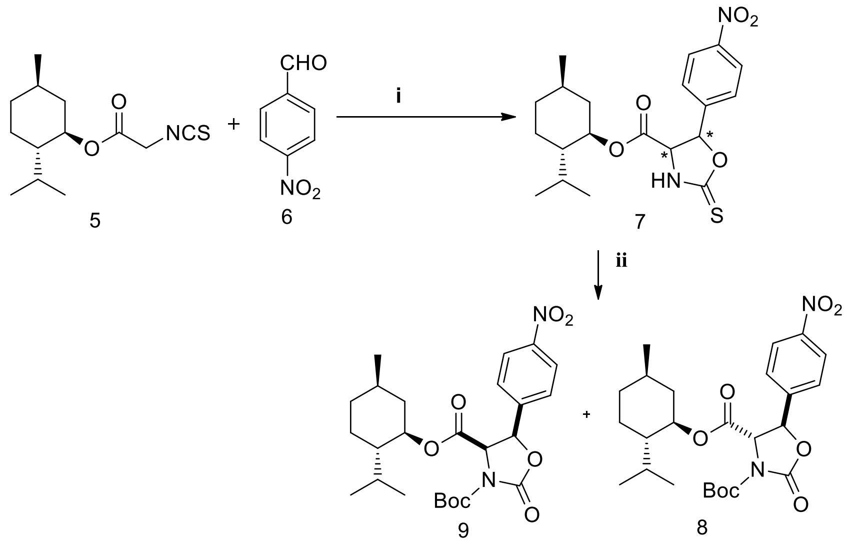
α-Amino acids (α-AAs) constitute one of the most important families of natural products and are essential molecules in a biological system and other scientific endeavor.[1] Many natural and unnatural amino acids were synthesized by diastereoselective addition of chiral auxiliary substituted enolate over aldehyde. The previous method involves the reaction of aldehyde with α-isothiocyanato imide or ester.[2] In recent year the reaction which involves the formation of C—C bond by aldol reaction has gained much interest via enolate or direct aldol adducts formation.[3] In other reports of related aldol reaction includes the organocatalytic approach,[4] metal enolate,[5] and stoichiometric catalytic Lewis acid and catalytic Lewis bases.[6] Herein, we report the diastereoselective aldol reaction for the synthesis of α-amino β-hydroxyl using a catalytic amount of $Sc(OTf)_3$.

Stability of $Sc(OTf)_3$ toward water and moisture is a unique feature inconsistent to that of the other Lewis acids reported in the literature.[7] In other method naturally occurring (−)-menthol is used as a chiral auxiliary in the form of (−)-menthyl isothiocyanatoacetate for direct aldol reaction.[8] In current methodology (Scheme 1), chiral auxilary based reagent (−)-menthyl isothiocyanatoacetate **5** was prepared by three step sequential reaction of the (−)-menthol **1** with chloroacetyl chloride **2** in presence pyridine at 0°C to afford compound **3** which on treatment with sodium azide in DMF displaced chlorine by azido functionality at 40°C to get azido functionality **4** which was then finally transferred to desired key intermediate isothiocyanatoacetate **5** through aza-wittig reaction in CS_2 as solvent at room temperature.[9]

In a typical experiment (Scheme 2), we tried asymmetric aldol reaction of a chiral (−)-menthyl isothiocyanatoacetate **5** with 4-nitrobenzaldehyde **6** in the presence of scandium triflate as Lewis acid and the diisopropylethylamine (Hünig Base) as a base to afford product **7**.



SCHEME 1 i) Pyridine, CH_2Cl_2, 0°C, 98%; ii) NaN_3, DMF, 40°C, 90%; iii) PPh_3, CS_2, THF, RT, 81%



SCHEME 2 i) (10 mol%) $Sc(OTf)_3$, DIPEA, THF, −45°C, 85%; ii) Boc_2O, DMAP, H_2O_2, HCO_2H, K_2CO_3:H_2O, DCM, 95%

The reaction was optimized for different catalyst (Table 1) was performed in anhydrous tetrahydrofuran at −45°C, and the formation of the product was found with good diastereoselective as govern by syn to anti ratio of the reaction. As it is very difficult to separate both the diastereomer as retardation factor (rf value) value found to be the same. The stereochemical outcome of the condensation reaction was assigned on the basis of the literature report mentioned for the aldol condensation and as spectroscopic evidences confirm the formation of aldol product.[10,11a]

The syn/trans product distribution mostly depends on the nature of metal used, reaction condition, and bulkiness of the substituents on the reactants. As the reaction proceeds via six membered transition state formation, syn/trans product is mostly affected by E/Z ratio of enolates. As, *E*-enolate formation is favored over the Z-enolate. *E*-enolates predominantly give anti products while Z-enolates give syn products (Scheme 3). Also, Z-enolates proceeds through an unstable six-member transition state in which NCS group is axial as compared to the stable transition state of *E*-enolate in which NCS group is equatorial. Hence, the formation of trans-isomer is predominating over syn isomer. [10a]

The diastereomeric ratio of the product was found to be 80:20 and it was confirmed by the ^{1}H-NMR spectrum.[11a] As spectroscopic evidences for the thio-oxazolidine ring with syn addition product of **7** contain in ^{1}H NMR spectrum 4.40 to 4.43 (d, J = 6.5 Hz, 1H) for 4CH, 6.00 to 6.02 (t, J = 6.6 Hz, 1H) for benzylic 5CH proton respectively and to identify the second isomer the compound **7** were acylated with ditert-butyl pyrocarbonate. In this reaction, a solution of aq. hydrogen peroxide and formic acid was added to exchange the sulfur with oxygen to afforded N-boc-oxazolidinone **8**. This carbamate **8** was useful for the stereochemical outcome. The anti-configuration was confirmed by the coupling constant and NOE experiment which shown very weak coupling between 4H and 5H.[11,12] For anti-addition respective proton shows 4.7 to 4.7 (d, J = 4.3 Hz, 1H), 5.6 to 5.63 (d, J = 6.2 Hz, 1H).

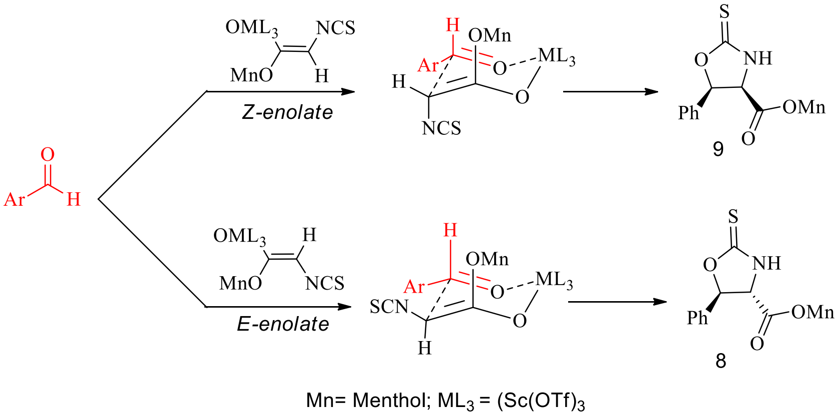
TABLE 1 Study of several transition metal catalyst at 10 mol%[a, b, c]

Sr.No.	Catalyst	Reaction time (h)	Yield %	Ratio of distereomers
1	$Sc(OTf)_3$	4	85	80:20
2	$Cu(OTf)_3$	7	65	60:40
3	$Yb(OTf)_3$	16	60	50:50
4	$Mg(OTf)_3$	12	65	60:40
5	$TiCl_4$	20	40	65:35
6	$MgCl_2$	20	30	52:48
7	CuI	>24	—	—
8	$InCl_2$	>24	—	—
9	SmI_2	>24	—	—
10	$RuCl_3$	>24	—	—
11	$Fe(acac)_2$	>24	—	Mixture

[a] All the reaction performed in tetrahedron solvent keeping cataylst at 10 mol%.

[b] All the catalyst were screened in different solvents such as CH_2Cl_2, $CHCl_3$, THF, CCl_4, Toluene.

[c] All the reaction was carried out by using metal (0.10 mmol) and Menthyl 2-isothiocyanatoacetate **2** (300 mg, 1.17 mmol), Aldehhydes (1.29 mmol) and diisopropylethylamine (0.22 mL, 1.29 mmol) in 5 mL of THF at −45°C with stirring.



SCHEME 3 Proposed mechanism for aldol reaction

However, the reaction becomes more diastereoselectivity at low temperature and it could be identified through analysis of the diastereomeric ratio. The formation of the product with maximum diastereomeric ratio observed was 90:10 at −45°C. While THF is the best suitable solvent for the reaction, since it gives good yield and diastereoselectivity of the products. In addition, remaining solvents such as CH_2Cl_2 and $CHCl_3$ showed lower diastereoselectivity whereas toluene shown comparable diastereoselectivity with THF.

The numbers of transition metal catalyst and typical rare earth metal‘s triflate were evaluated in the reaction as shown in the Table 1.

Comparing yield and diastereoselectivity of selected catalysts only scandium triflate shows good yield and diastereoselectivity, while other catalysts were not so active and selective toward the product formation. The $Sc(OTf)_3$ has lead over not only the stability, recovery, reusability as well as possess high catalytic activity.

Catalyst optimization allowed for reducing catalyst from 1 equivalent to 10 mol%. Lowering of the catalyst below10 mol% does not shown prominent effect on diastereoselectivity of the reaction (Table 2). Having optimized result in hand various aryl substituted product was synthesized as listed in given Table 3.

However, excellent diastereoselectivity was achieved for electron withdrawing group on phenyl ring. Nitro and cyano substituted phenyl group shown excellent yield and diastereoselectivity with more than 80% was observed. Low yield and diastereoselectivity of the reaction were observed when phenyl ring have electron donating substituent.

In conclusion, we have developed an efficient method for the synthesis of α-amino ester using menthol

TABLE 2 Optimization of scandium triflate catalyst

Entry	Catalyst in mol%	Reaction time (h)	Yield	Ratio of distereomers
1	0	24	Mix.	—
2	5	12	70	60:40
3	10	4	85	80:20

TABLE 3 Various aldehydes for the asymmetric aldol condensation[a, b]

Entry	Substrate	Reaction time (h)	Yield in %	Diastereose-lectivity in ratio
10	C_6H_5	6	78	78:22
11	2-ClC_6H_4	10	72	75:25
12	4-ClC_6H_4	12	75	69:31
13	4-FC_6H_4	8	70	75:25
14	4-BrC_6H_4	12	70	70:30
15	4-$MeOC_6H_4$	12	65	70:30
7	4-$NO_2C_6H_4$	4	85	80:20
16	2-$NO_2C_6H_4$	5	78	91:09
17	3-$NO_2C_6H_4$	6	78	75:25
18	4-CNC_6H_4	5	84	80:20

[a] All the reaction was carried out by using Scandium triflate (57 mg, 0.10 mmol) and Menthyl 2-isothiocyanatoacetate **2** (300 mg, 1.17 mmol), Aldehhydes (1.29 mmol) and diisopropylethylamine (0.22 mL, 1.29 mmol) in 5 mL of THF at −45°C with stirring.

[b] Diastereomer ratio determined by either 300 MHz NMR instrument or HPLC.

mediated asymmetric aldol condensations. Our synthetic strategy involved catalytic amount of $Sc(OTf)_3$. For which overall yield obtained was 65% to 85%.[13] The disteroselectivity ratio of isomers was found to be in the range by chiral HPLC.

General experimental procedures for Scheme 2: In a solution of Scandium triflate (0.10 mmol) and Menthyl 2-isothiocyanatoacetate **2** (1.17 mmol) was added to the solution of diisopropylethylamine (1.29 mmol) in 5 mL of THF at −45° C with stirring. 4-substituted benzaldehyde (1.29 mmol) was added slowly with stirring in the reaction mixture. The reaction was monitored by TLC and quenched after the complete disappearance of the starting material. The solvent was evaporated under reduced pressure on rotary evaporator. The residue obtained was extracted with dichloromethane (20 mL × 2). The combined organic layer was washed with 2 N HCl (2 mL) followed by water and was dried over Na_2SO_4.

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DATA AVAILABILITY STATEMENT

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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REFERENCES

[1] C. M. Harris, H. Kopecka, T. M. Harris, *J. Am Chem. Soc.* **1983**, *105*, 6915.

[2] D. A. Evans, D. L. Rieger, M. T. Bilodeau, F. Urpi, *J. Am. Chem. Soc.* **1991**, *113*, 1047.

[3] a) B. Tao, G. Schlingloff, K. B. Sharpless, *Tetrahedron Lett.* **1998**, *39*, 2507. b) S. E. Denmark, G. L. Beutner, *Angew Chem. Int. Ed.* **2008**, *47*, 1560.

[4] a) L. Li, E. G. Klauber, D. Seidel, *J. Am. Chem. Soc.* **2008**, *130*, 12248. b) C. Xiaohong, Z. Yin, Q. Zhen, X. Mingsheng, L. Lili, L. Xiaohua, F. Xiaomingm, *Chem. Eur. J.* **2010**, *16*, 10124. c) M. C. Willis, G. A. Cutting, V. J.-D. Piccio, M. J. Durbin, M. P. John, *Angew. Chem. Int. Ed.* **2005**, *44*, 1543.

[5] D. A. Evans, A. E. Weber, *J. Am. Chem. Soc.* **1986**, *108*, 6757.

[6] a) S. Kobayashi, M. Sugiura, H. Kitagawa, W. L. Lam, *Chem. Rev.* **2002**, *102*, 2227. b) K. Makino, T. Goto, Y. Hiroki, Y. Hamada, *Am. Ethnol.* **2004**, *116*, 900.

[7] M. T. Crimmins, K. Chaudhary, *Org. Lett.* **2000**, *2*, 775.

[8] S. Mettath, G. S. C. Srikanth, B. S. Dangerfield, S. L. Castle, *J. Org. Chem.* **2004**, *69*, 6489.

[9] M. Periasamy, G. S. Selva, S. Surisetti, *Tetrahedron: Asymm.* **2010**, *21*, 385.

[10] a) S. E. Denmark, B. R. Henke, *J. Am. Chem. Soc.* **1991**, *113*, 2177. b) B. M. Trost, C. S. Brindle, *Chem. Soc. Rev.* **2010**, *39*, 1600.

[11] a) T. D. W. Claridge, S. G. Davies, M. E. C. Polywka, P. M. Roberts, A. J. Russell, E. D. Savory, A. D. Smith, *Org. Lett.* **2008**, *10*, 5433.

[12] X. Cheng, P. N. Horton, M. B. Hursthouse, K. Kuok Hii, *Tetrahedron: Asymm.* **2004**, *15*, 2241.

[13] Created and maintained by INFLIBNET Centre, http://hdl.handle.net/10603/92911 (accessed: July 2012).

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