Organocatalytic Enantioselective Direct Aldol Reaction in Aqueous Media Catalyzed by a Bifunctional Diamine Catalyst

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Received 26 October 2010

Abstract: Organocatalytic direct asymmetric *anti*-aldol reaction was developed in aqueous medium using a BINOL-derived diamine/protic acid bifunctional catalyst. The catalytic protocol could offer the opportunity to access *anti*-aldol products with high level of enantioselectivities with moderate diastereoselectivities.

Key words: aldol reaction, aqueous medium, organocatalyst, diamine, protic acid, enantioselectivity

Stereoselective construction of C–C bond through organocatalytic direct aldol reaction is currently one of the most promising areas of research which has drawn a great deal of attention from synthetic standpoint.[1] Since the pioneering discovery of L-proline-catalyzed intermolecular aldol reactions involving enamine intermediates in 2000,[2] L-proline and its derivatives have been found to serve as excellent catalytic systems for a direct asymmetric aldol reaction.

Among all the three types of asymmetric ways to carry out aldol reactions viz biocatalysis,[3] metal-catalyzed procedures,[4] and the asymmetric organocatalytic direct methods,[5] the third approach has become the most vital and fancy. Recent literature has witnessed many highly efficient small organic molecules as organocatalysts,[6] which have successfully been applied for asymmetric aldol reaction. The advantages of organocatalysis have been demonstrated by the facile preparation of the catalysts, the mild reaction conditions, and by their environmentally benign aspects as compared to metal catalysis.[7] From a green chemistry perspective, performing these organocatalytic reactions in aqueous media gains further importance as it is safe to use and environmentally friendly.[8]

To perform asymmetric transformations in aqueous media, a special design of catalyst is always required to have sufficient hydrophobic effect to facilitate the reaction. Water imposes strong ionic interactions through its hydrogen bonding abilities which can often alter the enantioselectivity and thus it is not easy to access high level of enantioselection in most of such asymmetric catalytic processes.[9] Inspired by the principle of the action of aldolase antibodies[10] which contain a hydrophobic active site, Barbas, Takabe and co-workers in 2006 developed an elegant highly enantioselective catalytic *anti*-aldol reaction that could be performed in water using diamine **1** as a catalyst having appropriate hydrophobic groups (Figure 1). According to them, the diamine **1** with nonpolar hydrophobic groups along with hydrophobic reactant molecules keep themselves away and assemble in small volume when water is the medium carrying out the reaction via a compact transition state.[11]

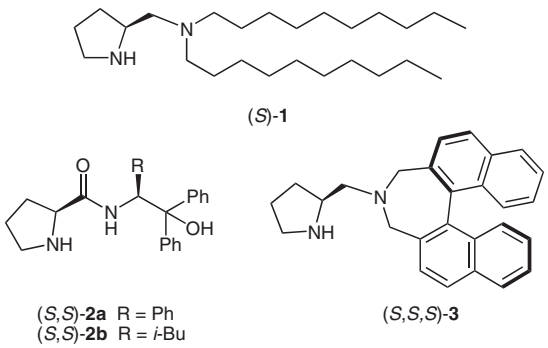


Figure 1 Selected organocatalysts in asymmetric aldol reactions

In the year 2007, we disclosed the organocatalytic direct asymmetric Michael reaction of unmasked ketones with β-nitrostyrenes in the presence of a BINOL-derived diamine/protic acid bifunctional organocatalyst.[12] We were especially interested in BINOL-derived diamine **3** (Figure 1), based on our belief, that the presence of substituted nonpolar dibenzylic-type hydrophobic groups in the tertiary amine part, would facilitate the reaction in aqueous medium and should also work in organic medium due to the aromatic nature of the binaphthyl part.[13] We found that our catalytic protocol was compatible with water as well as with various other conventional organic solvents providing high enantio- and diastereoselectivities in the asymmetric Michael reaction of ketones with both aryl and alkyl nitroolefins.

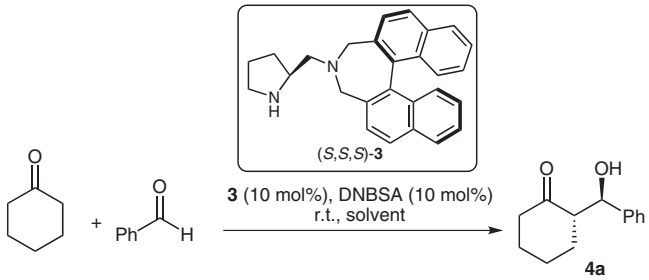
For the last few years, our group has been engaged in the development of L-prolinamide-type organocatalysts (**2**, Figure 1), which have successfully been applied to highly enantioselective direct asymmetric aldol reactions by us[14] and others.[15] Encouraged by Barbas and Takabe's work, herein, we wish to report an efficient enamine-based organocatalytic direct asymmetric aldol reaction using our BINOL-derived diamine **3** in conjunction with 2,4-dini-

SYNLETT 2011, No. 4, pp 0481–0484
Advanced online publication: 02.02.2011
DOI: 10.1055/s-0030-1259524; Art ID: Y02410ST

trobenzenesulfonic acid (DNBSA) as a bifunctional catalyst in the presence of water. These reactions afforded the desired *anti*-aldol products in high enantioselectivities with reasonably good level of diastereoselectivities and high yields.[16] Optimized conditions revealed that the organocatalyst **3** in the presence of DNBSA or TFA is the best catalytic system to carry out asymmetric aldol reactions in analogy with our earlier work.[12]

At the outset, the preliminary experiments were conducted by taking cyclohexanone as a donor and benzaldehyde as an acceptor using 10 mol% of the diamine **3** in the presence of 10 mol% of DNBSA in different solvents (Table 1). It was found that almost all organic solvents afforded high level of enantioselection (74–84% ee, entries 1–6, Table 1) and very high diastereoselectivities (dr up to 98:2, entries 3 and 5, Table 1) in good yields. The enantioselectivities of the aldol reaction were equally good on switching to water as medium. Further, we found that, using brine instead of water led to accelerated reactions with comparatively high enantioselectivity (83% ee) and diastereoselectivity (95:5), in good yield (85%) under optimized conditions (entries 8 and 9, Table 1).

Table 1 Solvent Study for Organocatalytic Direct Aldol Reaction

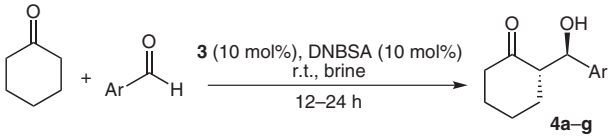


Entry	Solvent	Time (h)	Yield (%)[a]	Ratio *syn*/*anti*[b]	ee (%)[c]
1	DMSO	16	77	94:6	78
2	DMF	18	65	94:6	79
3	MeCN	15	87	98:2	74
4	$CHCl_3$	18	48	97:3	76
5	DME[d]	18	80	98:2	78
6	MeOH	20	77	96:4	84
7	THF	18	48	97:3	75
8	H_2O	15	80	98:2	77
9	brine	12	85	95:5	83

[a] Yields are reported after column chromatography.
[b] Diastereoselectivities were determined by ^{1}H NMR analysis of the products.
[c] The ee values were determined by HPLC using chiral columns.
[d] DME = dimethoxyethane.

With the optimized conditions in hand for asymmetric aldol reaction, we looked forward to examine the possible substrate scope (Table 2). It was found that aromatic aldehydes having an electron-withdrawing group at the *para* position were proved to be good substrates yielding aldol products in high enantioselectivities (entries 2 and 4, Table 2) but with moderate diastereoselectivities. In addition to electron-withdrawing substrates, furfural and β-naphthaldehyde were also found to be good substrates in terms of achieving very high level of enantioselectivities (entries 6 and 7, Table 2). However, aromatic aldehydes having halogen and electron-donating groups gave enantioselectivity in the range of 86–87% (entries 3 and 5, Table 2). Unfortunately, except benzaldehyde, in all the cases diastereoselectivities were found to be moderate.[17]

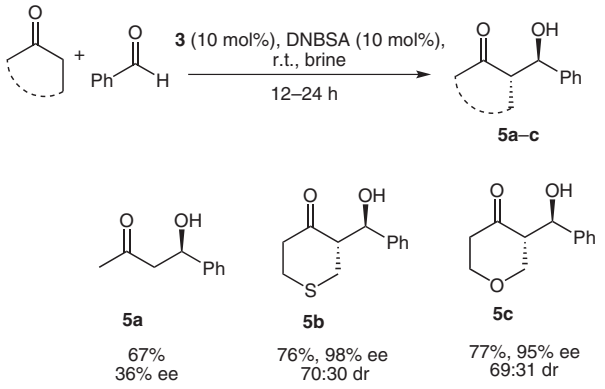
Table 2 Aldehyde Scope in Asymmetric Direct Aldol Reaction



Entry	Ar	Product	Yield (%)[a]	Ratio *anti*/*syn*[b]	% ee[c]
1	Ph	**4a**	85	95:5	83
2	4-$O_2NC_6H_4$	**4b**	89	78:22	94
3	4-$MeOC_6H_4$	**4c**	83	75:25	87
4	4-$F_3CC_6H_4$	**4d**	82	69:31	95
5	4-ClC_6H_4	**4e**	91	71:29	86
6	2-furyl	**4f**	80	88:12	96
7	2-naphthyl	**4g**	88	88:12	96

[a] Yields are reported after column chromatography.
[b] Diastereoselectivities were determined by ^{1}H NMR analysis of the products.
[c] The ee values were determined by HPLC using chiral columns.

The reaction was extended to other donors and the results are summarized in Scheme 1. Only 36% ee was obtained when acetone was used as a donor (**5a**, Scheme 1). The asymmetric aldol reaction was extended to other six-membered ketones as well (**5b** and **5c**, Scheme 1) where excellent enantioselectivities were observed with moderate level of diastereoselection.



Scheme 1 Scope of ketones as donors in asymmetric direct aldol reaction

The faster reaction rates and the excellent level of enantioselectivity in brine could be explained by the hydrophobic environment created by the binaphthyl group and salting out effect[18a] which leads to volume constriction bringing the reactant molecules in close vicinity thus facilitating the reaction via a compact transition state.[18b,6d] The stereochemical outcome could be explained on the basis of similar type of transition state as given by Yamamoto et al.[19] in which attack from *Re*-face of aldehyde gives rise to *anti*-aldol product (Figure 2).

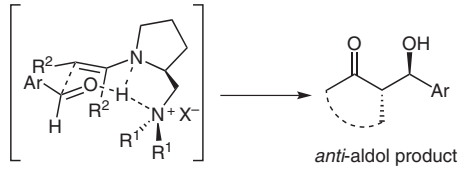


Figure 2 Proposed transition state for asymmetric induction in asymmetric aldol reaction

In conclusion, we have developed an efficient catalytic protocol using the diamine **3** derived from BINOL, in conjunction with DNBSA as a bifunctional catalyst, which has successfully been applied to the asymmetric *anti*-selective aldol reaction of ketones with aromatic aldehydes.[20] The sense of asymmetric induction was explained by invoking a similar kind of transition state proposed earlier in the literature.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgement

V.K.S. thanks the Department of Science and Technology (DST), India for a research grant through J. C. Bose Fellowship. V.B. thanks the Council of Scientific and Industrial Research (CSIR) for a Senior Research Fellowship (SRF).

References and Notes

(1) (a) *Modern Aldol Reactions*, Vol. 1; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, **2004**. (b) For metal-catalyzed reactions, see: *Modern Aldol Reactions*, Vol. 2; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, **2004**. (c) For a review, see: Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929.

(2) List, B.; Lerner, R. A.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

(3) (a) Machajewski, T. D.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2000**, *39*, 1352. (b) Gijsen, H. J. M.; Qiao, L.; Fitz, W.; Wong, C.-H. *Chem. Rev.* **1996**, *96*, 443. (c) Wagner, J.; Lerner, R. A.; Barbas, C. F. III. *Science* **1995**, *270*, 1797. (d) Dean, S. M.; Greenberg, W. A.; Wong, C.-H. *Adv. Synth. Catal.* **2007**, *349*, 1308. (e) Li, C.; Feng, X.-W.; Wang, N.; Zhou, Y.-J.; Yu, X.-Q. *Green Chem.* **2008**, *10*, 616.

(4) (a) Li, H.; Da C, S.; Xiao, Y.-H.; Li, X.; Su, Y.-N. *J. Org. Chem.* **2008**, *73*, 7398. (b) Kantam, M. L.; Ramani, T.; Chakrapani, L.; Kumar, K. V. *Tetrahedron Lett.* **2008**, *49*, 1498. (c) Paradowska, J.; Stodulski, M.; Mlynarski, J. *Adv. Synth. Catal.* **2007**, *349*, 1041. (d) Evans, D. A.; Downey, C. W.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 8706. (e) Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2497. (f) Kumagai, N.; Matsunaga, S.; Yoshikawa, N.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 1539.

(5) For reviews on asymmetric organocatalytic aldol reactions, see: (a) Guillena, G.; Najera, C.; Ramon, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249. (b) Tanaka, F.; Barbas, C. F. III. *In Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, **2007**, 19. (c) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267. (d) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

(6) (a) Duarte, F. J. S.; Cabrita, E. J.; Frenking, G.; Santos, A. G. *J. Org. Chem.* **2010**, *75*, 2546; and references cited therein. (b) Luo, S.; Qiao, Y.; Zhang, L.; Li, J.; Li, X.; Cheng, J.-P. *J. Org. Chem.* **2009**, *74*, 9521. (c) Xiong, Y.; Wang, F.; Dong, S.; Liu, X.; Feng, X. *Synlett* **2008**, 73. (d) Luo, S.; Xu, H.; Zhang, L.; Li, J.; Cheng, J.-P. *Org. Lett.* **2008**, *10*, 653. (e) Hayashi, Y.; Itoh, T.; Aratake, S.; Ishikawa, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 2082. (f) Xu, X.-Y.; Wang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2007**, *9*, 4247. For reviews, see: (g) Raj, M.; Singh, V. K. *Chem. Commun.* **2009**, 6687. (h) List, B. *Acc. Chem. Res.* **2004**, *37*, 548. (i) Notz, W.; Tanaka, F.; Barbas, C. F. III. *Acc. Chem. Res.* **2004**, *37*, 580. (j) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601. (k) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570.

(7) (a) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638. For recent reports on organocatalytic aldol reactions, see: (b) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.-P. *J. Am. Chem. Soc.* **2007**, *129*, 3074. (c) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2007**, *129*, 288. (d) Wang, F.; Xiong, Y.; Liu, X.; Feng, X. *Adv. Synth. Catal.* **2007**, *349*, 2665. (e) Rodriguez, B.; Rantanen, T.; Bolm, C. *Angew. Chem. Int. Ed.* **2006**, *45*, 6924. (f) D'Elia, V.; Zwicknagl, H.; Reiser, O. *Org. Lett.* **2008**, *73*, 3262. (g) Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 3055.

(8) (a) Breslow, R.; Rizzo, C. J. *J. Am. Chem. Soc.* **1991**, *113*, 4340. (b) Herrmann, W. A.; Kohlpaintner, C. W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1049. For reviews, see: (c) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751. (d) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209.

(9) (a) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (b) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 1983. (c) Nyberg, A. I.; Usanp, A.; Pihko, P. M. *Synlett* **2004**, 1891. (d) Cordova, A.; Notz, W.; Barbas, C. F. III. *Chem. Commun.* **2002**, 3024. (e) Darbre, T.; Machuqueiro, M. *Chem. Commun.* **2003**, 1090. (f) Tang, Z.; Yamg, Z.-H.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Org. Lett.* **2004**, *6*, 2285. (g) Chimni, S. S.; Mahajan, D.; Suresh Babu, V. V. *Tetrahedron Lett.* **2005**, *46*, 5617.

(10) (a) Heine, A.; Desantis, G.; Luz, J. G.; Mitchell, M.; Wong, C.-H.; Wilson, I. A. *Science* **2001**, *294*, 369. (b) Zhu, X.; Tanaka, F.; Hu, Y.; Heine, A.; Fuller, R.; Zhing, G.; Olson, A. J.; Lerner, R. A.; Barbas, C. F. III.; Wilson, I. A. *J. Mol. Biol.* **2004**, *343*, 1269.

(11) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2006**, *128*, 734.

(12) Maya, V.; Singh, V. K. *Org. Lett.* **2009**, *9*, 1117.

(13) For asymmetric aldol reaction using BINOL-derived primary amine, see: Liu, Q.-Z.; Wang, X.-L.; Luo, S.-W.; Zheng, B.-L.; Qin, D.-B. *Tetrahedron Lett.* **2008**, *49*, 7434.

(14) (a) Raj, M.; Maya, V.; Ginotra, S. K.; Singh, V. K. *Org. Lett.* **2006**, *8*, 4097. (b) Maya, V.; Raj, M.; Singh, V. K. *Org. Lett.* **2007**, *9*, 2593. (c) Gandhi, S.; Singh, V. K. *J. Org. Chem.* **2008**, *73*, 9411. (d) Raj, M.; Maya, V.; Singh, V. K. *J. Org. Chem.* **2009**, *74*, 4289.

(15) (a) Song, L.; Chen, X.; Zhang, S.; Zhang, H.; Li, P.; Luo, G.; Liu, W.; Duan, W.; Wang, W. *Org. Lett.* **2008**, *10*, 5489. (b) Zhang, H.; Zhang, S.; Liu, L.; Luo, G.; Duan, W.; Wang, W. *J. Org. Chem.* **2010**, *75*, 368.

(16) For a diamine derived from *trans*-1,2-diaminocyclohexane and its application to direct asymmetric aldol reaction from our group, see: (a) Raj, M.; Parashari, G. S.; Singh, V. K. *Adv. Synth. Catal.* **2009**, *351*, 1284. (b) Raj, M.; Veerasamy, N.; Singh, V. K. *Tetrahedron Lett.* **2010**, *51*, 2157.

(17) **General Procedure for the Direct Aldol Reaction with the Catalyst 3 in Brine**: An aldehyde (0.5 mmol) was added to a mixture of ketone (2 mmol) and an organocatalyst **3** (10 mol%) with DNBSA (10 mol%) in brine (0.5 mL) at r.t. The reaction mixture was stirred and the progress of the reaction was monitored by TLC. After reaction was over (as indicated by TLC), the reaction mixture was diluted with EtOAc (2 mL). The organic layer was separated and dried over anhyd Na_2SO_4. It was purified over silica gel by column chromatography. The enantiomeric excess(ee) of the aldol product was determined by chiral HPLC analysis. The relative and absolute configurations of the products were determined by comparison with the known ^{1}H NMR, chiral HPLC analysis, and optical rotation values.

(18) (a) Kumar, A.; Pawar, S. S. *Tetrahedron* **2003**, *59*, 5019. (b) Kleiner, C. M.; Schreiner, P. R. *Chem. Commun.* **2006**, 4315.

(19) (a) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167. (b) Ishii, T.; Fiujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558. (c) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413.

(20) Compound characterization data for selected compounds: **(2S,1′*R*)-2-[Furan-2-yl(hydroxy)methyl]cyclohexan-1-one (4f)**: It was obtained in a maximum of 80% yield and 96% ee. The optical purity was determined by HPLC on chiralpak AD-H column (hexane–2-propanol, 90:10); flow rate 0.5 mL/min, 220 nm; $t_{R(major)}$ = 26.8 min, $t_{R(minor)}$ = 31.2 min; $[\alpha]^{25}_D$ +21 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23–1.35 (m, 1 H), 1.61–1.71 (m, 3 H), 1.83–1.85 (m, 1 H), 2.10–2.37 (m, 1 H), 2.38–2.49 (m, 2 H), 2.89–2.95 (m, 1 H), 3.89 (br s, 1 H), 4.83 (d, *J* = 8.6 Hz, 1 H), 6.27–6.34 (m, 2 H), 7.36–7.38 (m, 1 H). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.09; H, 7.25.
(2S,1′*R*)-2-[Hydroxy(naphthalene-2-yl)methyl]-cyclohexan-1-one (4g): It was obtained in a maximum of 88% yield and 96% ee. The optical purity was determined by HPLC on chiralpak AS-H column (hexane–2-propanol, 90:10); flow rate 0.5 mL/min; $t_{R(major)}$ = 26.6 min, $t_{R(minor)}$ = 30.8 min; $[\alpha]^{25}_D$ +5.8 (*c* = 1.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25–1.35 (m, 2 H), 1.48–1.76 (m, 3 H), 2.04–2.09 (m, 1 H), 2.36–2.51 (m, 2 H), 2.69–2.75 (m, 1 H), 4.08 (br s, 1 H), 4.96 (d, *J* = 8.8 Hz, 1 H), 7.45–7.49 (m, 2 H), 7.71–7.89 (m, 5 H). Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.18; H, 7.11.
(2S,1′*R*) 3-[Hydroxy(phenyl)methyl]tetrahydrothio-pyran-4-one (5b): It was obtained in a maximum of 77% yield and 98% ee. The optical purity was determined by HPLC on chiralpak OD-H column (hexane–2-propanol, 98:2); flow rate 0.5 mL/min, $t_{R(major)}$ = 60.6 min, $t_{R(minor)}$ = 87.1 min; $[\alpha]^{25}_D$ +17.1 (*c* = 1.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.48–2.60 (m, 2 H), 2.75–2.81 (m, 1 H), 2.83–2.88 (m, 1 H), 2.92–3.04 (m, 3 H), 3.42 (br s, 1 H), 4.97 (d, *J* = 8.8 Hz, 1 H), 7.26–7.39 (m, 5 H). Anal. Calcd for $C_{12}H_{14}O_2S$: C, 64.83; H, 6.35. Found: C, 64.89; H, 6.33.