Kinetic Resolution

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Kinetic Resolution of Quaternary and Tertiary β-Hydroxy Esters**

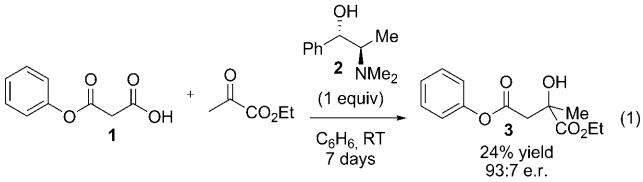
*Derek J. Schipper, Sophie Rousseaux, and Keith Fagnou**

Despite remarkable advances in enantioselective synthesis, the preparation of single enantiomer quaternary stereocenters remains a challenging and important goal in organic chemistry.[1] The difficulties associated with the use of ketone electrophiles is illustrative, where attenuated reactivity, challenging carbonyl enantiofacial differentiation, and diminished stability to retroaldol decomposition can explain, in part, the wealth of techniques for enantioselective aldol additions to aldehydes[2] compared to ketones.[3] In such instances, kinetic resolution of a racemic product may be an attractive alternative to enantioselective synthesis and remains an important method of accessing enantiopure material.[4,5]

Whereas the kinetic resolution of secondary alcohols has been studied extensively,[4,5] there are few examples of tertiary alcohol resolutions. In addition to enzymatic processes[6] which have limited substrate scope, Angione and Miller have described a peptide based catalyst for the acylation of α-amino alcohols.[7] Hoveyda, Snapper, and co-workers also used a peptide based catalyst for selective silylation of 1,2-diols, including three examples of tertiary alcohols,[8a] as well as the desymmetrization of triols.[8b] Oestreich and co-workers have shown that stereogenic silanes can be used to resolve chiral donor-functionalized tertiary alcohols.[9] Matsunaga, Shibasaki, and co-workers also developed a resolution of tertiary nitroaldols through a retro-nitroaldol reaction catalyzed by mixed La/Li heterobimetallic complexes.[10] Recently, Shintani, Takatsu, and Hayashi reported a rhodium-catalyzed resolution of tertiary homoallylic alcohols.[11]

Herein, we demonstrate unique reactivity and selectivity associated with (1*S*,2*R*)-*N*-methylephedrine in the resolution of tertiary alcohols arising from ketone aldol reactions. Even though the tertiary stereogenic center is three atoms removed from the reactive site, high selectivities are observed—with *s* factors in excess of 20 in many instances. The method is technically simple to perform, and employs a cheap and readily available[12] resolving agent (1*S*,2*R*)-*N*-methylephedrine (a chiral compound that is commonly used as a stoichiometric chiral auxiliary in diastereoselective carbon–carbon bond-forming processes).[13] Given the ease with which these racemic aldol processes may be performed, and the ease with which the products may be resolved, this chemistry should find application in the preparation of a wide array of natural and synthetic organic molecules.

The unique reactivity of *N*-methylephedrine was inadvertently discovered while evaluating the feasibility of amine catalyzed asymmetric decarboxylative ketone aldol reactions [Eq. (1)].[14] While performing the addition of **1** to ethyl



(1)

pyruvate in the presence of (1*S*,2*R*)-*N*-methylephedrine (**2**) as a chiral base, significant levels of enantiomeric excess were obtained when the reaction was allowed to proceed to completion over several days. Further evaluation of this process indicated that the enantiomeric excess had arisen from a kinetic resolution of the racemic product.

Following the initial discovery, a broad range of readily available chiral nucleophiles was evaluated for the kinetic resolution of **3**. With chiral alcohols such as **5**–**9**, no reaction was observed at room temperature in the absence of other additives. In these cases, improved outcomes could be obtained by the addition of one equivalent of triethylamine and heating the reaction mixture to 60 °C (Table 1, entries 2–6). From these screens, (*R*)-(−)-pantolactone (**7**) (Table 1, entry 4) and (1*S*,2*R*)-*N*-methylephedrine (**2**) (Table 1, entry 14) provided promising *s* factors of 3.7 and 3.5, respectively. Whereas further optimization with **7** failed to produce superior results, the continued evaluation of *N*-methylephedrine (**2**) revealed that by increasing the reaction temperature to 60 °C, the selectivity factor could be dramatically improved from 3.5 to 21 (Table 1, entry 16). This can be further enhanced to 38 by using two equivalents of **2** (Table 1, entry 17). The reaction progress occurs over several hours and may be monitored by HPLC methods using a chiral stationary phase. Conveniently, the reaction may be performed in toluene without necessitating the exclusion of air or moisture.

These optimized conditions were applied to a variety of compounds as illustrated in Table 2. In addition to **3**, which can be isolated in 49% yield and 94:6 enantiomeric ratio (e.r.), other tertiary alcohol compounds can be effectively resolved. A number of functionalities at the quaternary center may be present, including alkyl (Table 2, entries 1 and 5), aryl (Table 2, entries 2 and 4), ester (Table 2, entries 1–3), trifluoromethyl (Table 2, entries 3 and 4), and ketone (Table 2, entry 5) substituents. Although the method is optimized for tertiary alcohol compounds, this method may also be applied

[*] D. J. Schipper, S. Rousseaux, Prof. Dr. K. Fagnou
Center for Catalysis Research and Innovation
Department of Chemistry, University of Ottawa
10 Marie Curie, Ottawa, ON K1N 6N5 (Canada)
Fax: (+1) 613-562-5170
E-mail: keith.fagnou@uottawa.ca

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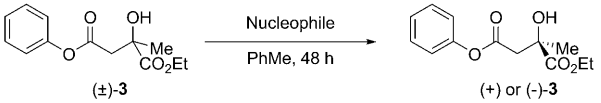
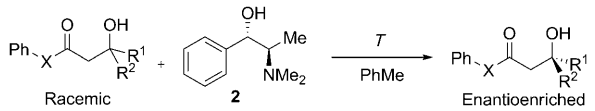
Table 1: Kinetic resolution with chiral nucleophiles.[a]

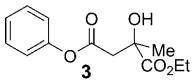
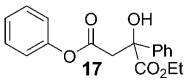
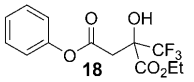
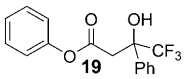
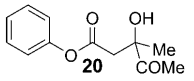
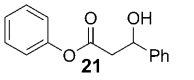
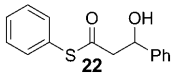
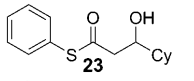
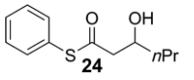
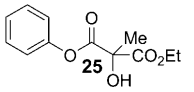


Entry	Nucleophile	*T* [°C]	Conv. [%][b]	e.r. of **3**[b]	*s*[c]
1	(+)-cinchonine (**4**)	RT	22	51.5:48.5	1.3
2	(*S*)-methyl lactate (**5**)	60	0	50:50	–[d]
3	(*R*)-phenylethanol (**6**)	60	0	50:50	–[d]
4	(*R*)-(−)-pantolactone (**7**)	RT	34	62.5:37.5	3.7[d]
5	(2*R*,3*R*)-tartaric acid diethyl ester (**8**)	60	0	50:50	–[d]
6	(2*S*,3*S*)-tartaric acid (**9**)	60	0	50:50	–[d]
7	(*R*)-1-cyclohexylethanamine (**10**)	RT	30	52:48	1.3
8	(*R*)-1-phenylethanamine (**11**)	RT	10	51:49	1.5
9	(1*S*,2*S*)-diphenylethylenediamine (**12**)	60	12	50:50	1.0
10	(1*R*,2*R*)-1,2-cyclohexanediamine (**13**)	RT	31	55:45	1.7
11	(*R*)2-phenylglycine (**14**)	RT	9	51.5:48.5	1.9
12	(1*S*,2*S*)-*N*-tosyldiphenylethylene-diamine (**15**)	RT	23	51:49	1.2
13	(1*S*,2*R*)-norephedrine (**16**)	RT	33	58.5:41.5	2.4
14	(1*S*,2*R*)-*N*-methylephedrine (**2**)	RT	42	66:34	3.5
15	(*R*)-(−)-pantolactone (**7**)	60	12	53:47	2.7[d,e]
16	(1*S*,2*R*)-*N*-methylephedrine (**2**)	60	49	88.5:11.5	21[e]
17	(1*S*,2*R*)-*N*-methylephedrine (**2**)	60	51	94.5:5.5	38[f,g]

[a] Reaction conditions: Substrate and nucleophile were dissolved in toluene and heated in an oil bath; for structures of **4**–**16** see the Supporting Information. [b] Conversion and e.r. were determined by HPLC analysis using a Chiracel AS-H column and 1,3,5-trimethoxybenzene as an internal standard. [c] The *s* factors were determined using the procedure of Kagan and Fiaud.[4c] [d] With one equivalent of triethylamine. [e] 24 hour reaction time. [f] Using two equivalents of **2**. [g] 18 hour reaction time.

Table 2: Kinetic resolution scope.[a]



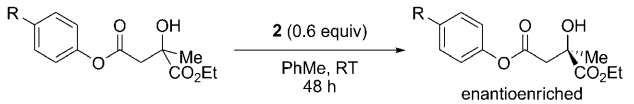
Entry	Substrate	Equiv of **2**	*T* [°C]	Conv. [%][b]	e.r.[b]	*s*[c]	Yield [%][d]	e.r.[b]
1	 **3**	2	60	51	94.5:5.5	38	49	94:6
2	 **17**	2	80	58	98:2	21	41	98:2
3	 **18**	0.8	60	46	87.5:12.5	35	41	>99:1
4	 **19**	1	RT	28	67:33	21	31	97:3
5	 **20**	1	60	51[e]	85:15	10	41	85:15
6	 **21**	0.6	RT	22[f]	60.5:39.5	8.4	27	95:5
7	 **22**	0.7	60	38	75:25	16	42	92:8
8	 **23**	2	60	48[e]	90:10	34	52	90:10
9	 **24**	2	60	56[e]	88:12	9	44	88:12
10	 **25**	0.7	60	46	54:46	1.3	–	–

[a] Reaction conditions: Substrate and **2** were dissolved in toluene and heated in an oil bath. [b] Conversion and e.r. were determined by HPLC analysis using Chiracel columns and 1,3,5-trimethoxybenzene as an internal standard. [c] The *s* factors were determined using the procedure of Kagan and Fiaud.[4c] [d] Isolated product. [e] Conversion determined by isolating remaining substrate. [f] Conversion determined by ^{1}H NMR analysis.

to aldehyde aldol products. Under our optimized reaction conditions the selectivity is lower with these substrates. We were pleased to find, however, that the selectivity with secondary alcohols can be improved by modifying the aryloxy substituent of the ester. For example, by changing the leaving group from an oxyester (Table 2, entry 6) to a thioester (Table 2, entry 7), the *s*-factor is doubled from 8 to 16. Synthetically useful selectivities are also attained with aliphatic aldehyde products (Table 2, entries 8 and 9). In contrast, low selectivities are obtained when the stereogenic center is directly adjacent to the reaction site (Table 2, entry 10).

Encouraged by the ability to modulate selectivity through modification of the leaving group (Table 2, entries 6 and 7), we also investigated this influence in reactions performed at room temperature employing only 0.6 equivalents of the resolving agent **2** (Table 3). Under these reaction conditions, reaction of the unsubstituted phenol ester **3** results in only 10% conversion and an *s* factor of 3.6 (Table 3, entry 1). Gratifyingly, this can be significantly improved through the use of a 4-cyano-substituted aryl ester. In this case, 42% conversion is observed over the same time period and with an *s* factor of 29.3 (Table 3, entry 3).

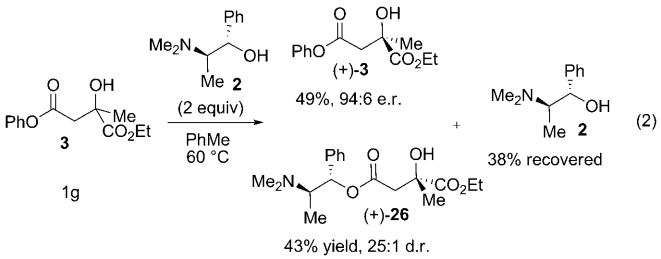
Table 3: Effect of leaving group modification in the establishment of a room-temperature protocol employing 0.6 equivalents of **2**.[a]



Entry	R	Conv. [%][b]	e.r.[c]	*s*[d]
1	H	9.9	53:47	3.6
2	OMe	8.3	53:47	5.2
3	CN	42.2	82:18	29.3

[a] Reaction conditions: Substrate and **2** were dissolved in toluene and stirred at room temperature for 48 h. [b] Conversion determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] The e.r. was determined by HPLC analysis using Chiracel columns. [d] The *s* factors were determined using the procedure of Kagan and Fiaud.[4c]

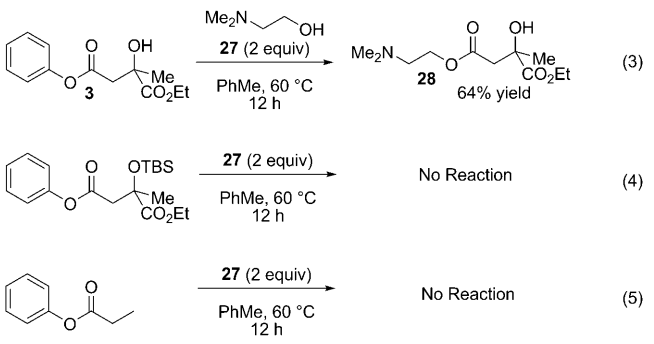
This chemistry may also be performed on larger scale [Eq. (2)]. For example, treatment of one gram of **3** under the



(2)

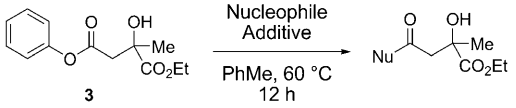
standard reaction conditions results in the isolation of (+)-**3** in 49% yield and 94:6 e.r. The other enantiomer of **3** can be isolated as the transesterified product (+)-**26** as one major diastereomer (25:1 d.r.) in 43% yield along with 38% of unreacted **2**. The overall yield of the reaction is 92% when considering the recovery of both enantiomers. Moreover, the use of excess **2** is mitigated by its subsequent recovery from the reaction.

To gain mechanistic insights into the reactivity and high selectivity associated with the use of **2**, a variety of experiments were carried out [Eqs. (3)–(5)]. In these studies, a simplified system was employed by conducting the reaction with achiral 2-(dimethylamino)ethanol (**27**) instead of **2**. To establish baseline reactivity, **3** was treated with two equivalents of **27** in toluene at 60 °C. After 12 hours, a 64% conversion into ester **28** was observed [Eq. (3)]. In contrast, if the alcohol of **3** is protected as a *tert*-butyldimethylsilyl (TBS) ether, or if it is absent as in the case of phenylpropionate, no reaction is observed after the same reaction time [Eqs. (4) and (5)]. These results, in conjunction with the inferior outcomes associated with the use of α-hydroxyesters (Table 2, entry 10), point to a key role of the β-hydroxy moiety in establishing high reactivity and selectivity with these nucleophiles.



In a similar fashion, the role of the dimethylamine functionality of **2** and **27** on reactivity was evaluated. For example, no reaction is observed with benzyl alcohol under the standard reaction conditions established for the resolution of **3** with **2** (Table 4, entry 1). Upon addition of one equivalent of triethylamine, up to 21% conversion is observed after 12 hours, indicating that the base can accelerate the transesterification process (Table 4, entry 2). When the amine base is attached to the alcohol nucleophile, as with **27**, an additional increase in the conversion is observed (Table 4, entry 3). When the more sterically encumbered **2** is employed, a drop in conversion is noted over the same reaction time (Table 4, entry 4) and this conversion is not influenced by the addition of an extra equivalent of triethylamine to the reaction mixture (Table 4, entry 5). These results indicate that the presence of a base is a key element in enhancing the reactivity of the alcohol nucleophile through hydrogen-bonding interactions, and that this property is enhanced when the alcohol and the amine are tethered as in **2** and **27**.

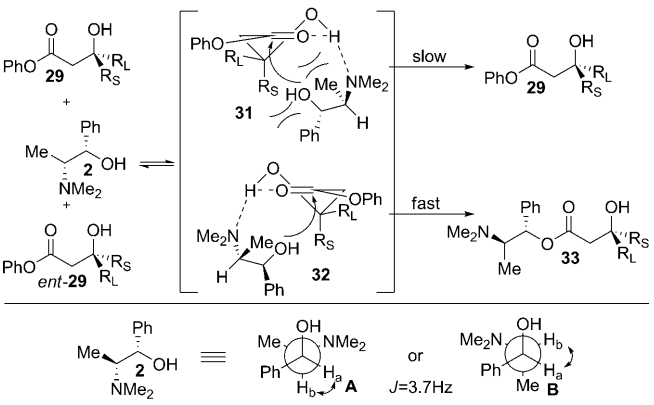
Table 4: Effect of nucleophile on rate.[a]



Entry	Nucleophile	Additive	Conv. [%][b]
1	BnOH	none	0
2	BnOH	NEt_3	21
3	**27**	none	64
4	**2**	none	35
5	**2**	NEt_3	36

[a] Reaction conditions: Nucleophile, **2**, and 1,3,5-trimethoxybenzene were dissolved in C_6D_6 and stirred at 60 °C for 12 h. [b] Conversion was determined by measuring consumption of **3** by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

A proposal for the origin of selectivity in these reactions is shown in Scheme 1. Since no reactivity is observed when the alcohol of the substrate is protected or removed [Eqs. (4) and



Scheme 1. Proposed origin of selectivity.

(5)], hydrogen bonding of the alcohol to the carbonyl group of the phenyl ester may be a key element of electrophilic activation (Scheme 1). Conformational and NMR analysis of **2** support **A** as the predominant conformer in solution. A coupling constant of $J_{H1-H2} = 3.7$ Hz, which changes only slightly upon heating or changing solvents, indicates a gauche relationship and is consistent with previous reports.[15] Both conformations, **A** and **B**, should give rise to the same selectivity based upon the current analysis. Given the rate

acceleration associated with **27** and **2**, compared to the combined use of an alcohol nucleophile and an amine base, we propose that hydrogen bonding of the substrate alcohol to the amine of **2** may be important for reactivity and selectivity. If nucleophilic attack of **2** on either **29** or *ent*-**29** occurs from the bottom face on stereoelectronic grounds, more severe steric interactions between the substituents of **29** and **2** should occur (see **31**) as compared to the interactions between *ent*-**29** and **2** (see **32**). Under these circumstances, **29** remains unreacted but *ent*-**29** undergoes transesterification to give **33**.

In conclusion, we have developed a method for the kinetic resolution of tertiary alcohols arising from ketone aldol reactions and extended this reactivity to other aldol products. These reactions employ commercially available (1*S*,2*R*)-*N*-methylephedrine as the resolving agent and are technically simple to perform. Given the challenge associated with the generation of quaternary stereocenters, this methodology should contribute meaningfully to the repertoire of techniques available to chemists for the preparation of single enantiomer tertiary alcohols of this type.

Experimental Section

Representative experimental procedure (**3**): A 50 mL round-bottom flask was charged with **3** (1 g, 3.96 mmol), (1*S*,2*R*)-*N*-methylephedrine (**2**, 1.42 g, 7.92 mmol), and toluene (20 mL). The reaction vessel was then sealed and the resulting solution was heated to 60 °C and then stirred for 29 h. Solvent was then removed in vacuo and the resulting residue was purified by using column chromatography (SiO_2, hexanes/ethyl acetate 9:1) to yield 49 % of (+)-**3** in 94:6 e.r.

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[1] a) I. Marek, *Chem. Eur. J.* **2008**, *14*, 7460 – 7468; b) I. Marek, G. Sklute, *Chem. Commun.* **2007**, 1683 – 1691; c) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369 – 396; d) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473 – 1482; e) J. Christoffers, *Chem. Eur. J.* **2003**, *9*, 4862 – 4867; f) J. Christoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725 – 4732; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591 – 4597.

[2] a) C. Palomo, M. Oiarbide, J. M. Garcia, *Chem. Soc. Rev.* **2004**, *33*, 65 – 75; b) C. Palomo, M. Oiarbide, J. M. Garcia, *Chem. Eur. J.* **2002**, *8*, 36 – 44; c) P. Arya, H. Quin, *Tetrahedron* **2000**, *56*, 917 – 947; d) C. J. Cowden, I. Paterson, *Org. React.* **1997**, *51*; e) T. Bach, *Angew. Chem.* **1994**, *106*, 433 – 435; *Angew. Chem. Int. Ed.* **1994**, *33*, 417 – 419; f) D. A. Evans, J. V. Nelson, T. R. Taber, *Top. Stereochem.* **1982**, *13*, 1 – 115; g) M. Braun in *Stereoselective Synthesis Houben-Weyl*, *Vol. E21/3* (Eds.: G. Helmchen, R. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, **1996**, p. 1603; h) C. H. Heathcock in *Asymmetric Synthesis*, *Vol. 3* (Ed.: J. D. Morrison, Pergamon, New York, **1984**, p. 111; i) R. Mahrwald, *Chem. Rev.* **1999**, *99*, 1095 – 1120; j) T. Mukaiyama, *Org. React.* **1994**, *46*; k) T. D. Machajewski, C.-H. Wong, *Angew. Chem.* **2000**, *112*, 1406 – 1430; *Angew. Chem. Int. Ed.* **2000**, *39*, 1352 – 1375; l) E. M. Carreira in *Comprehensive Asymmetric Catalysis*, *Vol. 3* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, p. 997; m) H. Gröger, E. M. Vogl, M. Shibasaki, *Chem. Eur. J.* **1998**, *4*, 1137 – 1141; n) S. G. Nelson, *Tetrahedron: Asymmetry* **1998**, *9*, 357 – 389; o) K. Narasaka, *Synthesis* **1991**, 1 – 11; p) B. Alcaide, P. Almendros, *Angew. Chem.* **2003**, *115*, 884 – 886; *Angew. Chem. Int. Ed.* **2003**, *42*, 858 – 860; q) B. Alcaide, P. Almendros, *Eur. J. Org. Chem.* **2002**, 1595 – 1601; r) J. L. Vicario, D. Badía, L. Carrillo, E. Reyes, J. Etxebarria, *Curr. Org. Chem.* **2005**, *9*, 219 – 235; s) D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127.

[3] a) J.-R. Chen, X.-P. Liu, X.-Y. Zhu, L. Li, Y.-F. Qiao, J.-M. Zhang, W.-J. Xiao, *Tetrahedron* **2007**, *63*, 10437 – 10444; b) S. Adachi, T. Harada, *Org. Lett.* **2008**, *10*, 4999 – 5001; c) J. Sedelmeier, T. Hammerer, C. Bolm, *Org. Lett.* **2008**, *10*, 917 – 920; d) D. A. Evans, C. S. Burgey, M. C. Kozlowski, S. W. Tregay, *J. Am. Chem. Soc.* **1999**, *121*, 686 – 699; e) M. Langner, P. Remy, C. Bolm, *Chem. Eur. J.* **2005**, *11*, 6254 – 6265; f) L. C. Akullian, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2006**, *128*, 6532 – 6533; g) A. Bøgevig, N. Kumaragurubaran, K. A. Jørgensen, *Chem. Commun.* **2002**, 620 – 621; h) J. Liu, Z. Yang, Z. Wang, F. Wang, X. Chen, X. Liu, X. Feng, Z. Su, C. Hu, *J. Am. Chem. Soc.* **2008**, *130*, 5654 – 5655; i) S. E. Denmark, Y. Fan, *J. Am. Chem. Soc.* **2002**, *124*, 4233 – 4235; j) S. E. Denmark, Y. Fan, M. D. Eastgate, *J. Org. Chem.* **2005**, *70*, 5235 – 5248; k) K. Oisaki, D. Zhao, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 7164 – 7165; l) X. Moreau, B. Bazan-Tejeda, J. M. Campagne, *J. Am. Chem. Soc.* **2005**, *127*, 7288 – 7289.

[4] For reviews on kinetic resolution, see: a) E. Vedejs, M. Jure, *Angew. Chem.* **2005**, *117*, 4040 – 4069; *Angew. Chem. Int. Ed.* **2005**, *44*, 3974 – 4001; b) P. Somfai, *Angew. Chem.* **1997**, *109*, 2849 – 2851; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2731 – 2733; c) H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249 – 330; For some recent examples see: d) D. Minato, Y. Nagasue, Y. Demizu, O. Onomura, *Angew. Chem.* **2008**, *120*, 9600 – 9603; *Angew. Chem. Int. Ed.* **2008**, *47*, 9458 – 9461; e) C. E. Müller, L. Wanka, K. Jewell, P. R. Schreiner, *Angew. Chem.* **2008**, *120*, 6275 – 6278; *Angew. Chem. Int. Ed.* **2008**, *47*, 6180 – 6183; f) R. M. Trend, B. M. Stoltz, *J. Am. Chem. Soc.* **2008**, *130*, 15957 – 15966; g) S. Arita, T. Koike, Y. Kayaki, T. Ikariya, *Angew. Chem.* **2008**, *120*, 2481 – 2483; *Angew. Chem. Int. Ed.* **2008**, *47*, 2447 – 2449; h) A. T. Radosevich, V. S. Chan, H.-W. Shih, F. D. Toste, *Angew. Chem.* **2008**, *120*, 3815 – 3818; *Angew. Chem. Int. Ed.* **2008**, *47*, 3755 – 3758; i) I. Coldham, J. J. Patel, S. Raimbault, D. T. E. Whittaker, *Chem. Commun.* **2007**, 4534 – 4536; j) H. F. T. Klare, M. Oestreich, *Angew. Chem.* **2007**, *119*, 9496 – 9499; *Angew. Chem. Int. Ed.* **2007**, *46*, 9335 – 9338; k) T. G. Driver, J. R. Harris, K. A. Woerpel, *J. Am. Chem. Soc.* **2007**, *129*, 3836 – 3837; l) Y.-B. Kang, X.-L. Sun, Y. Tang, *Angew. Chem.* **2007**, *119*, 3992 – 3995; *Angew. Chem. Int. Ed.* **2007**, *46*, 3918 – 3921; m) M. Nechab, D. N. Kumar, C. Philouze, C. Einhorn, J. Einhorn, *Angew. Chem.* **2007**, *119*, 3140 – 3143; *Angew. Chem. Int. Ed.* **2007**, *46*, 3080 – 3083; n) I. Coldham, S. Dufour, T. F. N. Haxell, J. J. Patel, G. Sanchez-Jimenez, *J. Am. Chem. Soc.* **2006**, *128*, 10943 – 10951.

[5] a) A. C. Spivey, A. Maddaford, A. Redgrave, *Org. Prep. Proced. Int.* **2000**, *32*, 331 – 365; b) "Asymmetric Acylation": E. R. Jarvo, S. J. Miller in *Comprehensive Asymmetric Catalysis, Supplement 1* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **2004**, chap. 43; c) S. E. Denmark, G. L. Beutner, *Angew. Chem.* **2008**, *120*, 1584 – 1663; *Angew. Chem. Int. Ed.* **2008**, *47*, 1560 – 1638; d) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248 – 5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138 – 5175; e) D. E. J. E. Robinson, S. D. Bull, *Tetrahedron: Asymmetry* **2003**, *14*, 1407 – 1446; f) G. C. Fu, *Acc. Chem. Res.* **2000**, *33*, 412 – 420; g) S. Rendler, G. Auer, M. Oestreich, *Angew. Chem.* **2005**, *117*, 7793 – 7797; *Angew. Chem. Int. Ed.* **2005**, *44*, 7620 – 7624; h) V. B. Birman, X. Li, H. Jiang, E. W. Uffman, *Tetrahedron* **2006**, *62*, 285 – 294; i) J. A. MacKay, E. Vedejs, *J. Org. Chem.* **2006**, *71*, 498 – 503; j) C. Mazet, S. Roseblade, V. Kohler, A.

Pfaltz, *Org. Lett.* **2006**, *8*, 1879 – 1882; k) Y.-Y. Li, X.-Q. Zhang, Z.-R. Dong, W.-Y. Shen, G. Chen, J.-X. Gao, *Org. Lett.* **2006**, *8*, 5565 – 5567.

[6] a) D. O'Hagan, N. A. Zaidi, *J. Chem. Soc. Perkin Trans. 1* **1992**, 947 – 949; b) D. O'Hagan, N. A. Zaidi, *Tetrahedron: Asymmetry* **1994**, *5*, 1111 – 1118; c) I. Brackenridge, R. McCague, S. M. Roberts, N. J. Turner, *J. Chem. Soc. Perkin Trans. 1* **1993**, 1093 – 1094; d) S. Hari Krishna, M. Persson, U. T. Bornscheuer, *Tetrahedron: Asymmetry* **2002**, *13*, 2693 – 2696; e) B. Heinze, R. Kourist, L. Fransson, K. Hult, U. T. Bornscheuer, *Protein Eng. Des. Sel.* **2007**, *20*, 125 – 131; f) R. Kourist, S. Bartsch, U. T. Bornscheuer, *Adv. Synth. Catal.* **2007**, *349*, 1393 – 1398; g) B. List, D. Shabat, G. Zhong, J. M. Turner, A. Li, T. Bui, J. Anderson, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **1999**, *121*, 7283 – 7291; h) R. Kourist, G.-S. Nguyen, D. Struebing, D. Boettcher, K. Liebeton, C. Naumer, J. Eck, U. T. Bornscheuer, *Tetrahedron: Asymmetry* **2008**, *19*, 1839 – 1843.

[7] M. C. Angione, S. J. Miller, *Tetrahedron* **2006**, *62*, 5254 – 5261.

[8] a) Y. Zhao, A. W. Mitra, A. H. Hoveyda, M. L. Snapper, *Angew. Chem.* **2007**, *119*, 8623 – 8626; *Angew. Chem. Int. Ed.* **2007**, *46*, 8471 – 8474; b) Z. You, A. H. Hoveyda, M. L. Snapper, *Angew. Chem.* **2009**, *121*, 555 – 558; *Angew. Chem. Int. Ed.* **2009**, *48*, 547 – 550.

[9] B. Karatas, S. Rendler, R. Frohlich, M. Oestreich, *Org. Biomol. Chem.* **2008**, *6*, 1435 – 1440.

[10] a) S. Tosaki, K. Hara, V. Gnanadesikan, H. Morimoto, S. Harada, M. Sugita, N. Yamagiwa, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 11776 – 11777; b) K. Hara, S. Tosaki, V. Gnanadesikan, H. Morimoto, S. Harada, M. Sugita, N. Yamagiwa, S. Matsunaga, M. Shibasaki, *Tetrahedron* **2009**, *65*, 5030 – 5036.

[11] R. Shintani, K. Takatsu, T. Hayashi, *Org. Lett.* **2008**, *10*, 1191 – 1193.

[12] (1*S*,2*R*)-*N*-methylephedrine is available from Sh-Icon Inc. for approximately $3/g.

[13] a) C. Gennari, F. Molinari, P. Cozzi, A. Oliva, *Tetrahedron Lett.* **1989**, *30*, 5163 – 5166; b) F. Laurent, R. Sebastien, C. Patrice, C. Janine, *Org. Lett.* **2006**, *8*, 3441 – 3443.

[14] N. Blacquiere, D. G. Shore, S. Rousseaux, K. Fagnou, *J. Org. Chem.* **2009**, DOI: 10.1021/jo901022.

[15] H. Tsai, J. D. Roberts, *Magn. Reson. Chem.* **1992**, *30*, 828 – 830, and references therein.

