# (*S*)-Proline-Derived Catalysts for the Acylative Kinetic Resolution of Alcohols: A Remote Structural Change Allows a Complete Selectivity Switch

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**Abstract:** A systematic preliminary study has identified a suite of catalysts, all readily prepared and derived from (*S*)-proline, which differ by a remote substituent only. If this substituent is capable of hydrogen-bond donation the catalyst will promote the resolution of secondary alcohols with the opposite sense of enantiodiscrimination to that observed when the substituent is capable of accepting hydrogen bonds.

**Key words:** amines, acylation, alcohols, nucleophiles, kinetic resolution

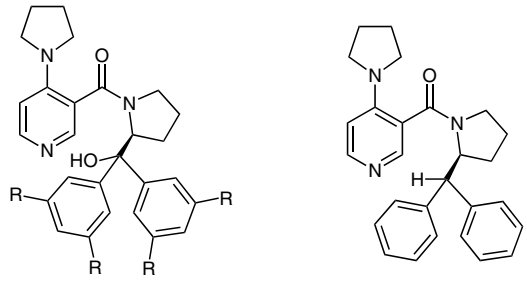
Enantioenriched secondary alcohols are arguably one of the most important broad classes of building block available to those interested in asymmetric synthesis. Among the most straightforward methodologies for accessing these compounds is the acylative kinetic resolution (KR) of the corresponding racemic materials. While enzymatic catalysis-based protocols have been available for some time,[1] the development of artificial small-molecule catalysts for these reactions has emerged as a powerful alternative tool over the past two decades.[2] A variety of catalytic systems for the acylative KR of secondary alcohols have been developed which were recently categorised by Schreiner and Müller[2e] as belonging to one of five distinct groups: phosphines[3] and phosphinites,[4] 4-*N*,*N*-dialkylaminopyridines,[5] *N*-alkylimidazoles,[6] amidines,[7] vicinal diamines[8] and N-heterocyclic carbenes.[9]

Our group has been engaged in the development of organocatalysts for the acylative KR of secondary alcohols[10] and thiols.[11] The 3-substituted 4-*N*,*N*-dialkylaminopyridine analogues **1** and **2** (Figure 1)[10] were designed to circumvent the traditional activity-selectivity conundrum associated with DMAP-based catalyst systems (i.e. installation of the chiral information at C-2 of the pyridine ring leads to an inactive catalyst) by undergoing a conformational change upon acylation in the acylative KR of secondary alcohol substrates (an 'induced-fit'-type mechanism pioneered by Fuji some years earlier[5b]) which allows the chiral information to influence the stereochemical outcome without retarding the rate of catalyst acylation to an impractical extent.

This strategy was a qualified success: the optimum catalysts **1a**[10a,b] and **1d**[10c] are readily prepared from (*S*)-proline and were capable of synthetically useful enantioselective acylation (s >10, maximum of 30)[12] of a variety of secondary alcohols (including challenging $sp^2$–$sp^2$ carbinol substrates[10c]). Leigh et al. have subsequently utilised **1a** as a tool in the operation of a molecular ratchet.[13] However, with the exception of their ability to resolve $sp^2$–$sp^2$ carbinols, these catalysts are easily outperformed by the benchmark literature systems in the KR of all other classes of secondary alcohols. In addition, the factors which are responsible for enantiodiscrimination are numerous and subtle. For instance, a combination of catalyst screening, $^1$H NMR spectroscopic, X-ray crystallographic and computational studies[10a,b] provided evidence that four characteristics of the acylated catalyst (for a representation see **3**, Figure 1) are crucial:

**A**: More enantioselective acylation occurs using substrates bearing electron-rich aromatic rings, indicating possible π-stacking with the pyridinium unit.

**B**: The presence of the hydroxyl group is important. When this is replaced with a hydrogen atom (e.g. catalyst **2**),



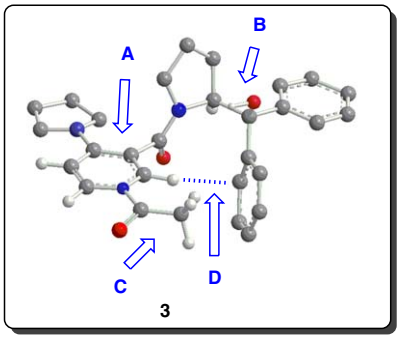




**Figure 1** Previously developed C-3-substituted chiral DMAP analogues and factors which influence enantiodiscrimination in reactions catalysed by **1a**. **A**: π-stacking, **B**: hydrogen-bonding, **C**: rotameric preference, **D**: π–H interaction (counteranion omitted).

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both activity and selectivity diminish. In addition the opposite substrate enantiomer is preferred (albeit with very low selectivity).

**C**: The larger alkyl group of the acyl unit resides in the more hindered catalyst hemisphere.

**D**: A rigidifying C–H–π interaction between the pyridine H-2 and one of the pendant aromatic rings which strengthens considerably upon acylation of the catalyst.

While the impact of **A**, **C** and **D** was investigated by altering the substrate, acylating agent and catalyst aromatic substituents, the clearly dominant influence of **B** (i.e. the hydroxyl group) was only investigated in a superficial fashion. Since this moiety influences both catalyst activity and the magnitude/sense of enantiodiscrimination, we were interested in ascertaining if this key functionality could be used as a enantiodiscrimination switch, i.e. could a pair of catalysts, both derived from the considerably less expensive (*S*)-proline enantiomer, be designed to participate in acylative KR processes while selecting for opposite enantiomers with approximately equal facility?

We therefore synthesised a small library of novel catalysts in which the hydroxyl group has been exchanged with either another H-bond donating moiety (i.e. **4** and **5**), a small group which would not be expected to readily participate in H-bonding interactions (i.e. **6**), a weak H-bond acceptor (i.e., **7**) or a relatively strong H-bond acceptor (i.e., **8**). These were then evaluated as catalysts for the KR of a range of secondary alcohols **9**–**12**. The results of these experiments (using the inexpensive and more readily available acetic anhydride rather than the more commonly used isobutyric anhydride) are outlined in Table 1. Beginning with the mono-protected *cis*-diol **9**, it was found that the H-bond donating catalysts **4** and **5** preferentially catalysed the acylation of the same enantiomer of *rac*-**9** as **1a**, however with considerably lower activity. While the amide-substituted material **4** promoted the reaction with higher selectivity than **1a**, the use of **5** led to almost racemic products (Table 1, entries 1–3). Most interestingly, catalysts devoid of H-bond donating functionality selected for the opposite enantiomer in the acylation process, with the use of the catalyst **8** resulting in considerably more selective KR than is possible using either **1a** or any of the novel catalysts utilised in this study (Table 1, entries 4–6). This trend was repeated when the corresponding *trans*-diastereomer **10** was employed as the starting material: reactions involving catalyst equipped with hydrogen-bond donors (i.e. **4** and **5**) led to the preferential acylation of the same enantiomer as that observed in resolutions promoted by **1a**, while use of the basic catalyst **8** furnished antipodean products. As had been observed in previous studies,[10] the *trans*-diol is a less suitable substrate than the *cis*-diastereomer. Similarly, the use of either the benzyl alcohol **11** (Table 1, entries 11–13) or *trans*-2-phenylcyclohexanol (**12**; Table 1, entries 14–18) led to the same overall result: catalyst **8**, which possesses the same configuration at the molecule's only chiral centre as **1a**, promotes the KR with the opposite sense of enantiodiscrimination. It should be noted that **6** proved to be somewhat of an exception here (preferring to catalyse the acylation of the same enantiomer of **12** as that favoured by **1a**); however, in this instance the catalyst is inactive (8% conversion) and promotes the acylation with low selectivity ($s$ <2; Table 1, entry 16).

We were also interested in ascertaining the influence of reaction temperature on the process. Accordingly, the acylative KR of **9** catalysed by **8** was carried out at 20-degree intervals from 0 °C to –80 °C. Intriguingly, the enantioselectivity of the process increased with decreasing temperature until –60 °C (Table 1, entries 19–22), after which lowering the temperature further had little effect initially (Table 1, entry 23) and then brought about a considerable loss of selectivity (Table 1, entry 24). Considerable experimentation confirmed that this dependence was entirely reproducible.[14]

Catalyst **8** could be used to promote the acylation of other alcohols (Table 2). Cyclopentanol **17** could be resolved with reasonable enantioselectivity ($s$ = 10), allowing the isolation of the alcohol in 99% ee at 73% conversion (Table 2, entry 1). Similarly, **9** could be enantioselectively acylated ($s$ = 8.3) and the alcohol was recovered in 91% ee at 65% conversion (Table 2, entry 2). Consistent with the results of studies by Fuji et al.[5b] and our group,[10d] larger ring systems proved more challenging: the seven- and eight-membered cyclic alcohols **18** and **19** underwent less selective acylation, however the enantioselectivity of the process was sufficient to allow the isolation of the alcohols in high and excellent ee at ca. 70% conversion (Table 2, entries 3 and 4). The heterocyclic alcohol **20** proved a poor substrate in these processes (Table 2, entry 5).

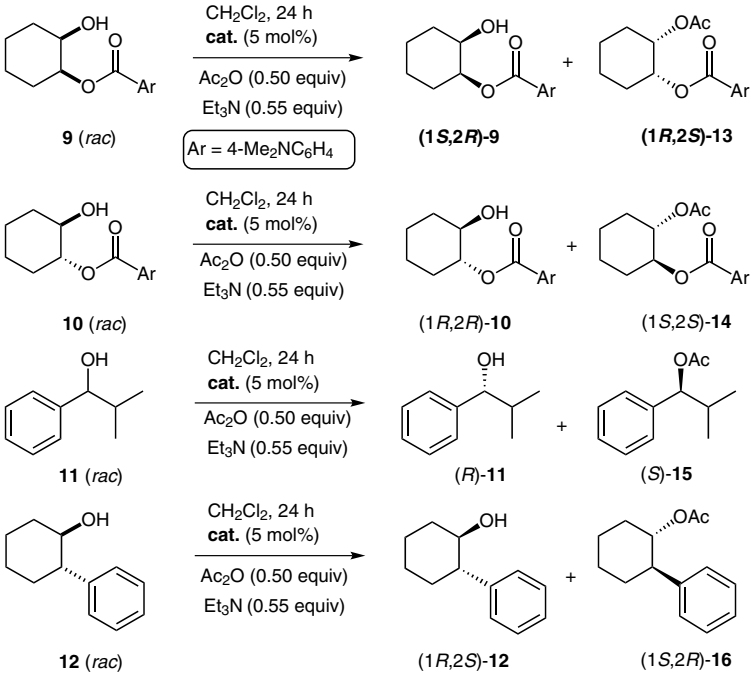
In an attempt to shed light on the origin of the ability of **1a** and **8** to preferentially acylate opposing enantiomers of secondary alcohols, we undertook a comparative $^1$H NMR spectroscopic analysis of both systems, a technique which had proven useful in elucidating the mode of action of **1a** previously (Table 3).[10,15] An analysis of this data is intriguing: the π–H interaction (see **D**, Figure 1), which is clearly a feature of both **1a** and its methylated and acylated counterparts **1aMe** and **1Ac**, respectively (as can be seen from the sign and magnitude of ΔδH-2) is not detected in the case of the free-base catalyst **8** (Table 3, entries 1–4). Upon methylation of **8** to give **8a** (Table 3, entry 5), an upfield shift at H-2 occurs which is characteristic of a conformational change driven by the π–H interaction. It is significant that this interaction appears to be weaker in this system (i.e. ΔδH-2 = –0.53; as opposed to –0.81 in the case of **1a** → **1aMe**; Table 3, entries 1, 2, 4 and 5). The same interaction can be observed upon acetylation of **8** to yield **8Ac** (Table 3, entry 6). These conformational changes can perhaps be best appreciated by comparing the data associated with **1a** and **8** (and their methylated/acylated derivatives) with the data associated with the corresponding achiral materials **21**, **21Me** and **21Ac** (Table 3, entries 7–9). Here one can see that in the case of catalyst **8**, δH-2, δH-5 and δH-6 are almost identical to the corresponding resonances associated with **21** (implying that no π–H in-

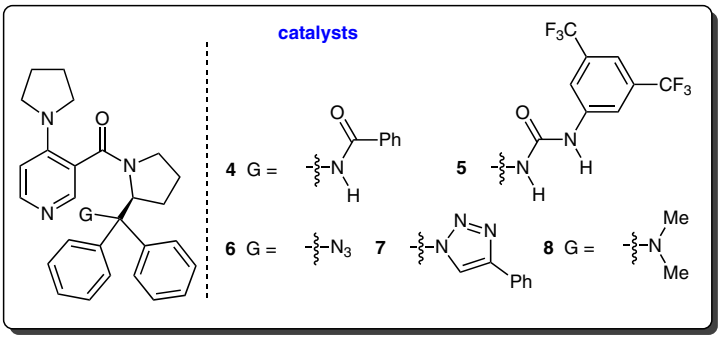


teractions are taking place), however upon both alkylation and acylation of **8**, the change in chemical shift at H-2 is clearly consistent with the development of such an interaction.

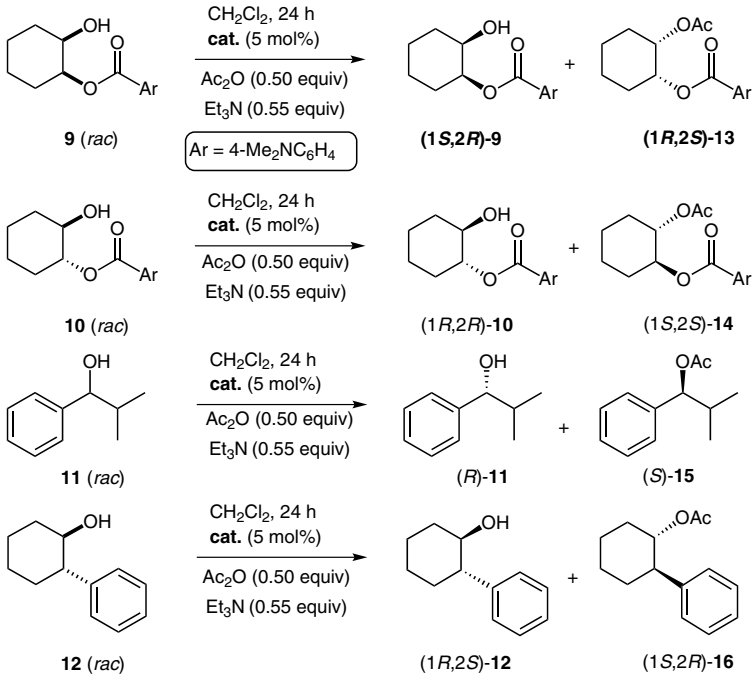
**Table 1** Catalyst Evaluation

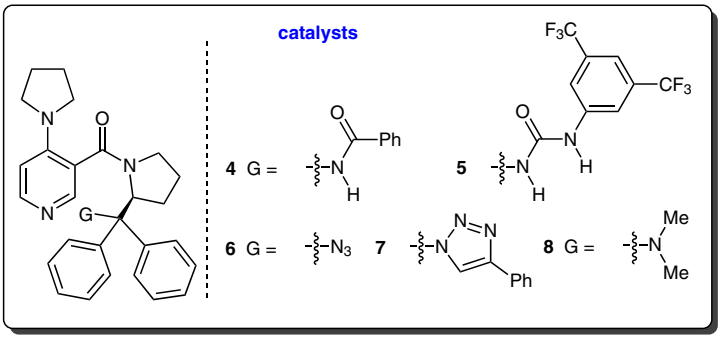



| Entry | ROH | Cat. | Temp. (°C) | Conv. (%)[a] | $ee_{alcohol}$ (%)[b] | $ee_{ester}$ (%)[b] | *s*[c] |
|---|---|---|---|---|---|---|---|
| 1 | **9** | **1a** | –30 | 48 | 31 | 33 | 2.6 |
| 2 | **9** | **4** | –30 | 5 | 3 | 58 | 3.9 |
| 3[d] | **9** | **5** | –30 | 18 | 1 | 4 | 1.1 |
| 4 | **9** | **6** | –30 | 37 | –29 | –49 | –3.9 |
| 5 | **9** | **7** | –30 | 13 | –7 | –47 | –2.9 |
| 6 | **9** | **8** | –30 | 37 | –38 | –65 | –6.9 |
| 7 | **10** | **1a** | –30 | 50 | 25 | 25 | 2.1 |
| 8 | **10** | **4** | –30 | 7.2 | 1 | 18 | 1.5 |
| 9[d] | **10** | **5** | –30 | 36 | 11 | 19 | 1.6 |
| 10 | **10** | **8** | –30 | 22 | 7 | 24 | –1.7 |
| 11 | **11** | **1a** | –30 | 50 | 26 | 26 | 2.1 |
| 12[d] | **11** | **5** | –30 | 38 | 12 | 20 | 1.7 |
| 13 | **11** | **8** | –30 | 55 | –26 | –21 | –2.0 |

**Table 1** Catalyst Evaluation (continued)

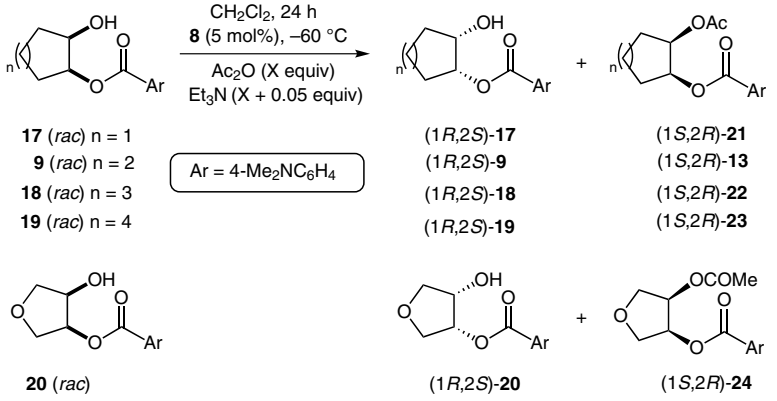


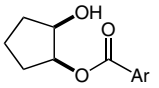
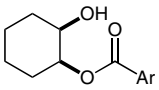
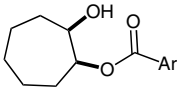
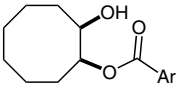
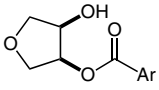




| Entry | ROH | Cat. | Temp. (°C) | Conv. (%)[a] | $ee_{alcohol}$ (%)[b] | $ee_{ester}$ (%)[b] | *s*[c] |
|---|---|---|---|---|---|---|---|
| 14 | **12** | **4** | –30 | 16 | 2 | 8 | 1.2 |
| 15[d] | **12** | **5** | –30 | 27 | 9 | 23 | 1.7 |
| 16 | **12** | **6** | –30 | 8 | 2 | 28 | 1.8 |
| 17 | **12** | **7** | –30 | 35 | 1 | 1 | 1.0 |
| 18 | **12** | **8** | –30 | 38 | –8 | –13 | –1.4 |
| 19[e] | **9** | **8** | 0 | 66 | –80 | –41 | –5.4 |
| 20[e] | **9** | **8** | –20 | 60 | –77 | –50 | –6.4 |
| 21[e] | **9** | **8** | –40 | 57 | –74 | –55 | –7.3 |
| 22[e] | **9** | **8** | –60 | 49 | –61 | –63 | –8.0 |
| 23[e] | **9** | **8** | –70 | 42 | –48 | –67 | –7.9 |
| 24[e] | **9** | **8** | –80 | 31 | –30 | –65 | –6.4 |

[a] Conversion: which could be determined (with excellent agreement) either by $^1$H NMR spectroscopy or CSP–HPLC, where conversion = 100 × $ee_{alcohol}/(ee_{alcohol} + ee_{ester})$.
[b] Determined by CSP–HPLC.
[c] *s* = enantioselectivity (see ref. 12). Note that where negative values are given, this is to indicate that the sense of enantiodiscrimination is opposite to that shown in the graphic above.
[d] Benzoic anhydride was employed as the acylating agent.
[e] The amount of acetic anhydride used was 0.7 equiv.

**Table 2** Substrate Scope




| Entry | ROH (*rac*) | X | Conv. (%)[a] | $ee_{alcohol}$ (%)[b] | *s*[c] |
|---|---|---|---|---|---|
| 1 |  **17** | 1.0 | 73 | 99 | 10.0 |
| 2 |  **9** | 2.5 | 65 | 91 | 8.3 |
| 3 |  **18** | 2.5 | 70 | 81 | 4.7 |
| 4 |  **19** | 2.5 | 74 | 90 | 5.1 |
| 5 |  **20** | 0.7 | 52 | 37 | 2.8 |

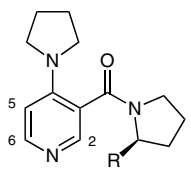
[a] Conversion: which could be determined (with excellent agreement) either by $^1$H NMR spectroscopy or CSP–HPLC, where conversion = $100 \times ee_{alcohol}/(ee_{alcohol} + ee_{ester})$.
[b] Determined by CSP–HPLC.
[c] *s* = enantioselectivity (see ref. 12).

More difficult to explain is the Δδ at H-6 when **8** is acetylated (i.e. **8Ac**; Table 3, entry 9): an unexpectedly low chemical shift of 8.06 was observed (compare entries 3 and 6 in Table 3). In addition, we could not detect an NOE with either H-2 or H-6 when the methyl group of the acetyl moiety was irradiated. What is clear is that the conformation/rotameric preferences of **8Ac** are similar but not exactly analogous to those of **1aAc**. Therefore, the opposing preferences exhibited by **1a** and **8** may be due to both conformational factors and hydrogen-bond donation/acceptance by the pendant functionality.

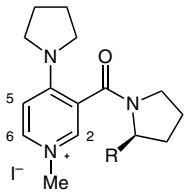
In conclusion, we have developed a unique suite of readily prepared, (*S*)-proline-derived catalysts which differ only by the characteristics of a remote substituent. When this substituent is capable of donating H-bonds, the catalyst promotes the preferential acylation of the opposite enantiomer of a racemic alcohol to that acylated when the substituent is capable of accepting H-bonds, despite both catalysts possessing the same configuration at their only stereogenic centre. Catalyst **8** exhibited a similar activity/selectivity profile to that associated with the literature catalyst **1a**; thus it is now possible to access both enantiomers of a given racemic alcohol from catalysts derived from one antipode of proline.[16] $^1$H NMR spectroscopic analysis indicates that **8** undergoes a similar, yet not exactly analogous conformational change to **1a** upon methylation/acylation which brings the remote stereochemical information to bear on the acylation event via an 'induced-fit'-type mechanism. Further studies to exploit

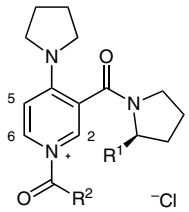
**Table 3** Selected $^1$H NMR Data for **1a**, **8**, **21** and Methylated/Acylated Analogues



**1a** R = $COHPh_2$
**8** R = $CNMe_2Ph_2$
**21** R = H



**1aMe** R = $COHPh_2$
**8Me** R = $CNMe_2Ph_2$
**21Me** R = H



**1aAc** $R^1$ = $COHPh_2$, $R^2$ = $CHMe_2$
**8Ac** $R^1$ = $CNMe_2Ph_2$, $R^2$ = Me
**21Ac** $R^1$ = H, $R^2$ = $CHMe_2$

| Entry | Cat. | δH-2[a,b,c] | δH-5[a,b,c] | δH-6[a,b,c] | $\delta CH_3/HCR_2$ |
|---|---|---|---|---|---|
| 1 | **1a** | 7.33 | 6.45 | 8.09 | – |
| 2 | **1aMe** | 6.52 (–0.81) | 6.80 (0.45) | 8.04 (–0.05) | **3.88** |
| 3 | **1aAc** | 8.06 (0.73) | 7.15 (0.70) | 9.10 (1.01) | 4.14 |
| 4 | **8** | 8.26 | 6.48 | 8.15 | – |
| 5 | **8Me** | 7.71 (–0.53) | 6.97 (0.49) | 8.43 (0.28) | 4.17 |
| 6 | **8Ac** | 8.24 (–0.02) | 6.68 (0.20) | 8.06 (–0.09) | 2.25 |
| 7 | **21** | 8.19 | 6.47 | 8.16 | – |
| 8 | **21Me** | 8.17 (–0.02) | 6.90 (0.43) | 8.21 (0.05) | 4.21 |
| 9[d] | **21Ac** | 8.72 (0.53) | 7.32 (0.85) | 9.32 (1.16) | 4.11 |

[a] The δ value is quoted in ppm in $CDCl_3$ as solvent.
[b] Value in parenthesis represents Δδ: the change in chemical shift of the proton indicated on methylation or acylation (in ppm), a negative value for Δδ indicates an upfield shift.
[c] All pyridine ring proton resonances were unambiguously assigned by NMR spectroscopy ($^1$H–$^1$H COSY, $^1$H–$^{13}$C COSY, NOE and 1-D TOCSY experiments).

this phenomenon further and to determine the precise mode of action of **8** are underway.

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

## References and Notes

(1) For selected reviews, see: (a) Chen, C.-S.; Sih, C. *Angew. Chem. Int. Ed.* **1989**, *28*, 695. (b) Theil, F. *Chem. Rev.* **1995**, *95*, 2203.
(2) For recent reviews, see: (a) Connon, S. J. *Lett. Org. Chem.* **2006**, *3*, 333. (b) Wurz, R. P. *Chem. Rev.* **2007**, *107*, 5570. (c) Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560. (d) Spivey, A. C.; Arseniyadis, S. *Top. Curr. Chem.* **2010**, *291*, 233. (e) Müller, C. E.; Schreiner, P. R. *Angew. Chem. Int. Ed.* **2011**, *50*, 6012. (f) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 1613.
(3) For examples, see: (a) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430. (b) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813. (c) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **2003**, *125*, 4166. (d) MacKay, J. A.; Vedejs, E. *J. Org. Chem.* **2004**, *69*, 6934.
(4) Mizuta, S.; Sadamori, M.; Fujimoto, T.; Yamamoto, I. *Angew. Chem. Int. Ed.* **2003**, *42*, 3383.
(5) For representative examples, see: (a) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809. (b) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169. (c) Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794. (d) Spivey, A. C.; Fekner, T.; Adams, H. *Tetrahedron Lett.* **1998**, *39*, 8919. (e) Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 5091. (f) Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 10452. (g) Spivey, A. C.; Fekner, T.; Spey, S. E.; Adams, H. *J. Org. Chem.* **1999**, *64*, 9430. (h) Spivey, A. C.; Maddaford, A.; Fekner, T.; Redgrave, A. J.; Frampton, C. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3460. (i) Naraku, G.; Shimomoto, N.; Hanamoto, T.; Inanaga, J. *Enantiomer* **2000**, *5*, 135. (j) Kawabata, T.; Yamamoto, K.; Momose, Y.; Yoshida, H.; Nagaoka, Y.; Fuji, K. *Chem. Commun.* **2001**, 2700. (k) Jeong, K.-S.; Kim, S.-H.; Park, H.-J.; Chang, K.-J.; Kim, K. S. *Chem. Lett.* **2002**, 1114. (l) Priem, G.; Anson, M. S.; Macdonald, S. J. F.; Pelotier, B.; Campbell, I. B. *Tetrahedron Lett.* **2002**, *43*, 6001. (m) Seitzberger, J. G.; Dissing, C.; Søtofte, I.; Norrby, P.-O.; Johannsen, M. *J. Org. Chem.* **2005**, *70*, 8332. (n) Yamada, S.; Misono, T.; Iwai, Y. *Tetrahedron Lett.* **2005**, *46*, 2239. (o) Poisson, T.; Penhoat, M.; Papamical, C.; Dupas, G.; Dalla, V.; Marsais, F.; Levacher, V. *Synlett* **2005**, 2285. (p) Nguyen, H. V.; Butler, D. C. D.; Richards, C. J. *Org. Lett.* **2006**, *8*, 769. (q) Nguyen, H. V.; Motevalli, M.; Richards, C. J. *Synlett* **2007**, 725.
(6) For examples, see: (a) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629. (b) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638. (c) Jarvo, E. R.; Vasbinder, M. M.; Miller, S. J. *Tetrahedron* **2000**, *56*, 9773. (d) Vasbinder, M. M.; Jarvo, E. R.; Miller, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 2824. (e) Ishihara, K.; Kosugi, Y.; Akakura, M. *J. Am. Chem. Soc.* **2004**, *126*, 12212. (f) Hrdina, R.; Müller, C. E.; Schreiner, P. R. *Chem. Commun.* **2010**, *46*, 2689.
(7) For representative examples, see: (a) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226. (b) Birman, V. B.; Jiang, H. *Org. Lett.* **2005**, *7*, 3445. (c) Li, X.; Liu, P.; Houk, K. N.; Birman, V. B. *J. Am. Chem. Soc.* **2008**, *130*, 13836. (d) Birman, V. B.; Li, X. *Org. Lett.* **2008**, *10*, 1115. (e) Zhang, Y.; Birman, V. B. *Adv. Synth. Catal.* **2009**, *351*, 2525. (f) Hu, B.; Meng, M.; Wang, Z.; Du, W.; Fossey, J. S.; Hu, X.; Deng, W.-P. *J. Am. Chem. Soc.* **2010**, *132*, 17041.
(8) For representative examples, see: (a) Oriyama, T.; Hori, Y.; Imai, K.; Sasaki, R. *Tetrahedron Lett.* **1996**, *37*, 8543. (b) Oriyama, T.; Imai, K.; Hosoya, T.; Sano, T. *Tetrahedron Lett.* **1998**, *39*, 397. (c) Oriyama, T.; Imai, K.; Sano, T.; Hosoya, T. *Tetrahedron Lett.* **1998**, *39*, 3529.
(9) For representative examples, see: (a) Suzuki, Y.; Yamauchi, K.; Muramatsu, K.; Sato, M. *Chem. Commun.* **2004**, 2770. (b) Suzuki, Y.; Muramatsu, K.; Yamauchi, K.; Morie, Y.; Sato, M. *Tetrahedron* **2006**, *62*, 302. (c) Kano, T.; Sasaki, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 1347.
(10) (a) O'Dálaigh, C.; Hynes, S. J.; Maher, D. J.; Connon, S. J. *Org. Biomol. Chem.* **2005**, *3*, 981. (b) O'Dálaigh, C.; Hynes, S. J.; O'Brien, J. E.; McCabe, T.; Maher, D. J.; Watson, G.

W.; Connon, S. J. *Org. Biomol. Chem.* **2006**, *4*, 2785. (c) O'Dálaigh, C.; Connon, S. J. *J. Org. Chem.* **2007**, *72*, 7066. (d) Gleeson, O.; Tekoriute, R.; Gun'ko, Y. K.; Connon, S. J. *Chem. Eur. J.* **2009**, *15*, 5669. (e) Gleeson, O.; Davies, G.-L.; Peschiulli, A.; Tekoriute, R.; Gun'ko, Y. K.; Connon, S. J. *Org. Biomol. Chem.* **2011**, *9*, 7929.

(11) Peschiulli, A.; Procuranti, B.; O'Connor, C. J.; Connon, S. J. *Nat. Chem.* **2010**, *2*, 380.

(12) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

(13) Alvarez-Pérez, M.; Goldup, S. M.; Leigh, D. A.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2008**, *130*, 1836.

(14) It is tempting to speculate that reduced access to a catalytically relevant conformation which is not the lowest energy conformation available is responsible; however a definitive explanation must await further studies.

(15) The data associated with **1a**, **21** and their acylated/alkylated analogues are taken from ref. 10b and are included here to facilitate analysis only.

(16) (a) General Procedure for the Acylative Kinetic Resolution of Secondary Alcohols **9**, **17**, **18**, **19**, and **20** Promoted by Catalyst 8 (Table 2): A 1 mL reaction vessel charged with catalyst 8 (5.0 mol%) and a small magnetic stirring bar was placed under an atmosphere of argon. The appropriate secondary alcohol was added followed by $CH_2Cl_2$ (0.20 M). After allowing the reaction mixture to equilibrate (ca. 10 min), $Et_3N$ (1.05–2.55 equiv) was added. The resulting solution was left stirring (ca. 30 min) at –60 °C, followed by the addition of acetic anhydride (1.00–2.50 equiv) via syringe. After the reaction was complete, the reaction was quenched by the addition of MeOH (10.0 equiv). Solvents were removed in vacuo. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude in $CH_2Cl_2$ through a pad of silica gel. Analytical data for catalyst **8**: mp 79–81 °C; $[\alpha]^{20}_D$ –191.5 (*c* = 0.85, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.02–1.10 (m, 1 H, H-17), 1.27–1.37 (m, 1 H, H-18), 1.44–1.53 (m, 1 H, H-9), 1.84–2.23 (br m, 12 H, $NMe_3$, H-10, H-11, H-12, H-15, H-16, H-19), 2.97–3.05 (m, 2 H, H-7, H-8), 3.20–3.26 (m, 1 H, H-20), 3.44–3.52 (m, 2 H, H-13, H-14), 5.94 (dd, *J* = 7.0, 7.0 Hz, 1 H, H-21), 6.48 (d, *J* = 8.5 Hz, 1 H, H-5), 7.30–7.48 (m, 10 H, ArH), 8.14 (d, 1 H, H-6), 8.25 (s, 1 H, H-2). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 23.4, 25.6, 27.4, 40.3, 49.1, 49.7, 51.6, 57.9, 75.9 (q), 108.5, 117.7, 126.7, 126.8, 127.1, 130.5, 131.4, 148.9 (q), 149.6 (q), 150.0 (q), 170.3 (q). IR (neat): 2950, 2870, 2831, 2786, 1631, 1584, 1396, 1136, 976, 723, 706, 682 cm$^{-1}$. HRMS (ES): *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{35}N_4O$: 455.2811; found: 455.2818.



 