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Kinetic Resolution of Alcohols Using a 1,2-Dihydroimidazo[1,2-*a*]quinoline Enantioselective Acylation Catalyst

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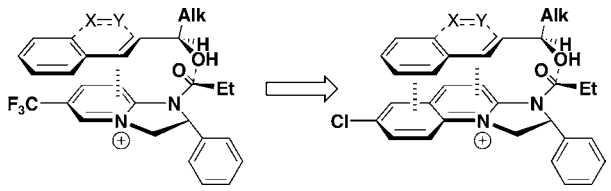
ABSTRACT



A new enantioselective acylation catalyst (Cl-PIQ), designed to provide enhanced π-stacking with benzylic and cinnamyl alcohol substrates, was found to give considerably increased reaction rates and selectivities compared with the first-generation catalyst CF_3-PIP.

We have recently reported a new class of enantioselective acylation catalysts based on the 2,3-dihydroimidazo[1,2-*a*]-pyridine (DHIP) core. One of these easily accessible compounds, 2-phenyl-6-trifluoromethyl-dihydroimidazo[1,2-*a*]pyridine (**1**, abbreviated as CF_3-PIP), proved to be particularly effective in kinetic resolution of secondary benzylic alcohols (Figure 1). Our experimental data suggested that

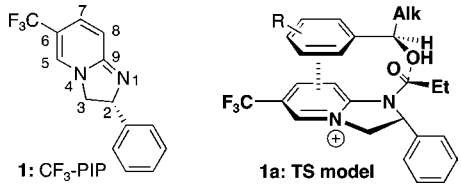


Figure 1. CF_3-PIP, the best first-generation catalyst.

the chiral recognition in this process was dependent on the $\pi-\pi$ and cation$-\pi$ interactions between the reactive acylated intermediate and the aryl moiety in the substrate. This led us to propose transition state model **1a**.[1−3]

Having achieved good selectivities with benzylic alcohols (s = 20−85), we decided to explore kinetic resolution of other classes of secondary alcohols that are capable of π-stacking.[4,5] In particular, we were curious whether cin-

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(2) For leading references to other nonenzymatic asymmetric acylation catalysts, see: (a) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542. (b) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **2003**, *125*, 4166. (c) Kawabata, T.; Stragies, R.; Fukaya, T.; Nagaoka, Y.; Schedel, H.; Fuji, K. *Tetrahedron Lett.* **2003**, *44*, 1545. (d) Terakado, D.; Koutaka, H.; Oriyama, T. *Tetrahedron: Asymmetry* **2005**, *16*, 1157. (e) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601. (f) Spivey, A. C.; Zhu, F.; Mitchell, M. B.; Davey, S. G.; Jarvest, R. L. *J. Org. Chem.* **2003**, *68*, 7379. (g) Naraku, J.; Shimomoto, N.; Hanamoto, T.; Inanaga, J. *Enantiomer* **2000**, *5*, 135. (h) Lin, M.-H.; RajanBabu, T. V. *Org. Lett.* **2002**, *4*, 1607. (i) Priem, G.; Pelotier, B.; Macdonald, S. J. F.; Anson, M. S.; Campbell, I. B. *J. Org. Chem.* **2003**, *68*, 3844. (j) Jeong, K.-S.; Kim, S.-H.; Park, H.-J.; Chang, K.-J.; Kim, K. S. *Chem. Lett.* **2002**, 1114. (k) Matsumura, Y.; Maki, T.; Murakami, S.; Onomura, O. *J. Am. Chem. Soc.* **2003**, *125*, 2052. (l) Mizuta, S.; Sadamori, M.; Fujimoto, T.; Yamamoto, I. *Angew. Chem., Int. Ed.* **2003**, *42*, 3383. (m) Suzuki, Y.; Yamauchi, K.; Muramatsu, K.; Sato, M. *Chem. Commun.* **2004**, 2770. (n) Ishihara, K.; Kosugi, Y.; Akakura, M. *J. Am. Chem. Soc.* **2004**, 126, 12212. (o) Dalaigh, C. O.; Hynes, S. J.; Maher, D. J.; Connon, S. J. *Org. Biomol. Chem.* **2005**, *3*, 981. (p) Kano, T.; Sasaki, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 1347. (q) Yamada, S.; Misono, T.; Iwai, Y. *Tetrahedron Lett.* **2005**, *46*, 2239.

(3) Recent reviews: (a) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, 44, 3974. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (c) Jarvo, E. R.; Miller, S. J. Asymmetric Acylation. In *Comprehensive Asymmetric Catalysis*, Supplement 1; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Heidelberg, 2004; Chapter 43. (d) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985. (e) Spivey, A. C.; Maddaford, A.; Redgrave, A. J. *Org. Prep. Proc. Int.* **2000**, *32*, 331.

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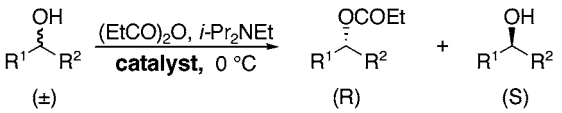
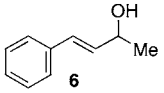
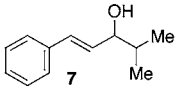
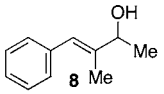
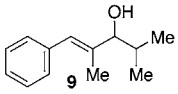
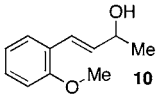
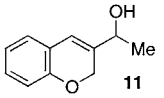
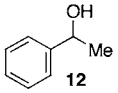
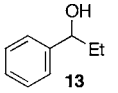
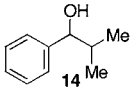
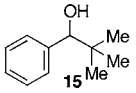
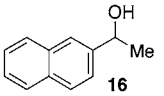
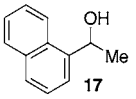
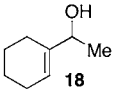
Table 1. Kinetic Resolution of Alcohols Catalyzed by CF_3-PIP **1** and Cl-PIQ **2**



entry	substrate	CF_3-PIP selectivity (conv/time)	Cl-PIQ selectivity (conv/time)
1[a]	 **6**	11 (14%/8h)	27 (44%/8h)
2[a]	 **7**	21 (30%/8h)	24 (53%/8h)
3[a]	 **8**	9 (14%/8h)	17 (38%/8h)
4[a]	 **9**	13 (9%/8h)	22 (32%/8h)
5[a]	 **10**	6 (27%/8h)	31 (56%/8h)
6[a]	 **11**	26 (50%/8h)	57 (55%/4h)
7[a]	 **12**	26 (32%/8h)[c]	33 (55%/8h)
8[a]	 **13**	36 (39%/8h)[c]	41 (53%/8h)
9[a]	 **14**	50 (43%/8h)	59 (50%/4h)
10[a]	 **15**	85 (48%/52h)[c]	117 (42%/8h)
11[a]	 **16**	42 (50%/8h)	74 (51%/2h)
12[a]	 **17**	56 (51%/8h)[c]	55 (56%/8h)
13[b]	 **18**	11 (40%/32h)	17 (47%/11h)

[a] Conditions: 1.0 M substrate, 0.75 M $(EtCO)_2O$, 0.75 M *i*-Pr_2NEt, 0.02 M catalyst, $CHCl_3$, 0 °C. [b] Conditions: 1.0 M substrate, 0.75 M $(EtCO)_2O$, 0.75 M *i*-Pr_2NEt, 0.1 M catalyst, $CDCl_3$, 0 °C. [c] Data from previous work.[1]

namyl alcohols would be resolved with useful levels of enantioselectivity. Under the standard set of conditions, CF_3-PIP-catalyzed enantioselective acylation of the simplest cinnamyl substrate, β-styryl methyl carbinol **6**, proceeded much more slowly and less selectively than that of phenyl methyl carbinol **12** (Table 1, entries 1 and 7). This result is not surprising considering that the phenyl group in **6** is positioned too far to interact with the pyridinium moiety of the catalyst, while π-stacking with the olefin is less efficient than with an aromatic ring. It occurred to us that extending the π-system of the catalyst might provide a simple and effective solution to this problem (Figure 2).

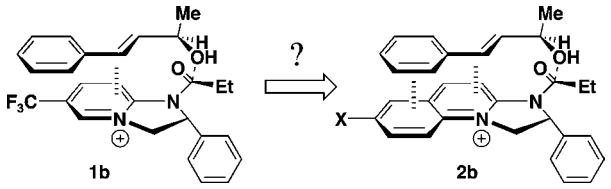
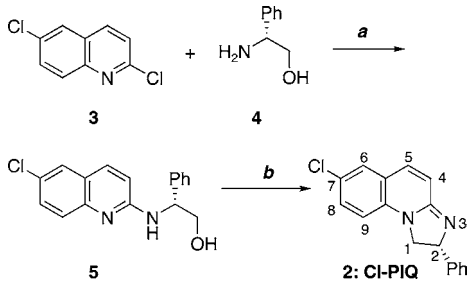


Figure 2. Design of the second-generation catalyst.

On the basis of our experience with catalysts in the DHIP series, where variation of the electron-withdrawing group at C6 was used to fine tune the system to achieve the maximum catalytic activity and the phenyl group at the C2 chiral center proved to be optimal for the enantioselectivity,[6] we decided to prepare and test the 2-phenyl-7-chloro derivative of the 1,2-dihydroimidazo[1,2-*a*]quinoline (DHIQ) tricyclic core.[7] Its synthesis from the commercially available 2,6-dichloroquinoline **3** and (*R*)-phenylglycinol **4** was achieved in excellent yield via the standard two-step procedure previously used to obtain DHIP derivatives[1] (Scheme 1). We were pleased

Scheme 1. Preparation of Cl-PIQ (**2**)[a]



[a] Reagents and conditions: (a) *i*-Pr_2NEt, 130 °C, 2.5 days, 87%, (b) $SOCl_2$, $CHCl_3$, reflux, then $NaHCO_3$, NaOH, 91%.

to observe that both the selectivity and the reaction rate improved dramatically when the kinetic resolution of **6** was

(4) Allylic alcohols, both with and without aryl substituents, have been previously resolved via catalytic enantioselective acyl transfer: (a) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492. (b) Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794. (c) Bellemin-Laponnaz, S.; Tweddell, J.; Ruble, J. C.; Breitling, F. M.; Fu, G. C. *Chem. Commun.* **2000**, 1009. (d) Vedejs, E.; MacKay J. A. *Org. Lett.* **2001**, *3*, 535; (e) ref 2p. (f) ref 2q.

(5) Propargylic alcohols have also been resolved: (a) Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 5091; (b) ref 2q.

performed using the new catalyst (**2**, abbreviated Cl-PIQ) instead of CF_3-PIP (entry 1). At this point, we decided to compare the two catalysts systematically, using both cinnamyl (entries 1−6) and benzylic (entries 7−12) substrates.

As can be seen from the data collected in Table 1, the use of Cl-PIQ results in acceleration of the reaction rates relative to those with CF_3-PIP in all cases studied. The enantioselectivities are also noticeably enhanced in most of the cases (up to 5-fold, in entry 5).

As may be expected, the influence of the substitution pattern of the substrates on the selectivity follows roughly similar trends with both of the catalysts. However, several cases are worthy of special comment.

Comparison of the results obtained with *o*-methoxyphenyl substrate **10** and its conformationally restricted analogue **11** (entries 5 and 6, respectively) suggests that the coplanarity of the aromatic ring and the double bond is important for both the reaction rate and the enantioselectivity. This factor probably contributes to the generally lower conversions and/or selectivities observed with cinnamyl alcohols (entries 1−4) compared with their benzylic counterparts (entries 7 and 9), especially when a methyl group is introduced *cis* to the phenyl (entries 3 and 4).

2-Naphthyl methyl carbinol **16**, which we had expected to provide "the perfect fit" with the quinolinium moiety of Cl-PIQ, was indeed resolved with excellent selectivity ($s = 74$) and reached 51% conversion in only 2 h using the new catalyst. This result constituted a significant improvement over that obtained with CF_3-PIP (entry 11). In contrast, 1-naphthyl methyl carbinol, in which the second benzene ring cannot participate in π-stacking effectively, produced similar conversions and selectivities with both catalysts (entry 12).

Finally, we decided to test whether an unconjugated allylic alcohol could be resolved using our catalysts. Cyclohexenyl methyl carbinol **18** was found to react much more slowly than benzylic or cinnamyl alcohols, as might be expected on the basis of the proposed model and earlier observations by Fu et al.[4c] Therefore, increased catalyst loadings (10 mol %) were employed to obtain comparable reaction rates (entry 13). Once again, Cl-PIQ proved to be more effective than CF_3-PIP. Although the conditions have not yet been optimized, these results demonstrate that the new catalyst is suitable for the kinetic resolution of allylic alcohols lacking an aryl substituent. A detailed investigation of the structure-selectivity trends in this series will be the subject of future studies.

In conclusion, the second generation catalyst Cl-PIQ, rationally designed to address certain limitations of CF_3-PIP, has fulfilled our expectations. Studies aimed at the exploration of its usefulness in enantioselective acylation of other classes of substrates, as well as further optimization of the DHIQ-based catalyst design, are currently underway.[8]

Acknowledgment. We thank NIGMS (NIH Grant R01 GM072682) and Washington University for providing financial support for this study. Mass spectrometry was provided by the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant P41RR0954).

Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Birman, V. B.; Li, X.; Jiang, H.; Uffman, E. W. *Tetrahedron* **2005**, Symposium-in-Print on Organocatalysis, in press.

(7) (a) Preparation of the unsubstituted DHIQ: Grout, R. J.; Hynam, B. M.; Partridge, M. W. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1314. (b) Preparation of racemic 2-phenyl-DHIQ: Cookson, R. F.; Nowotnik, D. P.; Parfitt, R. T.; Airey, J. E.; Kende, A. S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 201.

(8) Part of this work has been presented: Birman, V. B.; Jiang, H. *Abstracts of Papers*, 229th National Meeting of the American Chemical Society, San Diego, CA, March 13−17, 2005; American Chemical Society: Washington, DC, 2005; ORGN 313.