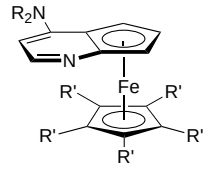
[13] The stereochemistry of this intermediate was rigorously established by a combination of chemical and spectral means. Details will be provided in a full paper.
[14] G. E. Keck, C. A. Wager, *Org. Lett.* **2000**, *2*, 2307 – 2309.
[15] This material was prepared in three steps from the known unsaturated ester: D. L. Boger, T. T. Curran, *J. Org. Chem.* **1992**, *57*, 2235 – 2244.
[16] M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183 – 2186.
[17] J. A. Lafontaine, PhD thesis, University of California at Berkeley (USA), **1999**.



NR_2 = dimethylamino, pyrrolidino
R' = Me, Ph

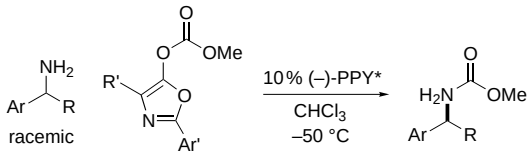
NR_2 = pyrrolidino, R' = Me: (–)-PPY* (**1**)

Kinetic Resolution of Amines by a Nonenzymatic Acylation Catalyst**

Shigeru Arai, Stéphane Bellemin-Laponnaz, and Gregory C. Fu*

Dedicated to Professor David A. Evans on the occasion of his 60th birthday

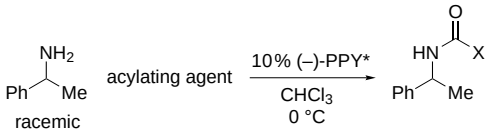
During the past four years, several groups have reported a diverse array of interesting approaches to the development of nonenzymatic acylation catalysts for the kinetic resolution of alcohols, and certain classes of alcohols can now be resolved with useful levels of stereoselection (selectivity factor $s \geq 10$).[1–3] Amines comprise a second important family of substrates,[4] but, unfortunately, there has been no significant progress in the development of nonenzymatic acylation catalysts for their kinetic resolution, although some advances have recently been made in the discovery of enantioselective stoichiometric acylating reagents.[5] Here we describe the first effective nonenzymatic acylation catalyst for the kinetic resolution of amines [Eq. (1)],[6, 7] and we present preliminary mechanistic data.

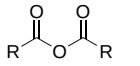
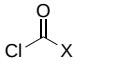
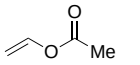
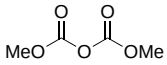


(1)

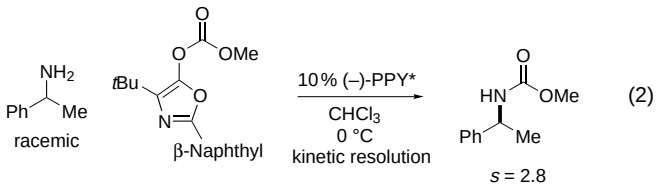
In earlier studies, we established that planar-chiral DMAP derivatives such as PPY* can serve as useful catalysts for several different enantioselective acylation processes, including the kinetic resolution of secondary alcohols (DMAP = 4-dimethylaminopyridine).[8] Our initial efforts to extend this work to the acylation of amines were stymied by the nucleophilicity of the amine—it appears that, rather than awaiting the intervention of the enantiopure catalyst, the amine instead reacts directly with the acylating agent. As illustrated in Table 1, a variety of common reagents acylate (±)-1-phenylethylamine with essentially no stereoselection in the presence of (–)-PPY*.[9]

Table 1. Reaction of (±)-1-phenylethylamine with common acylating agents in the presence of (–)-PPY*.



Acylating agent		*s*
	R = Me, Ph, *t*Bu	1.0
	X = Me, OMe	1.0
		(no reaction)
		1.2

As a fortunate consequence of our studies of enantioselective rearrangement processes,[8c] we discovered an acylating agent, an O-acylated azlactone, that reacts much more rapidly with PPY* than with a primary amine. With this acylating agent, we observed a significant level of stereoselection in the kinetic resolution of (±)-1-phenylethylamine catalyzed by enantiopure PPY* [Eq. (2)].[10]



(2)

Optimization studies produced an enhancement in stereoselection, primarily as a result of the temperature dependence of the selectivity. Thus, by conducting the reaction at $-50\,^{\circ}C$ and adding the acylating agent in two batches, we can resolve

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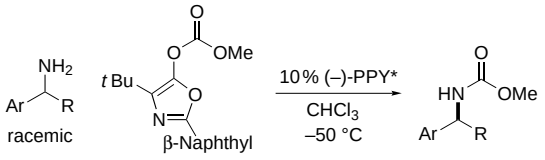
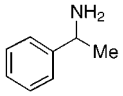
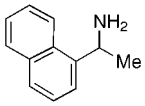
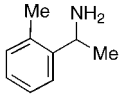
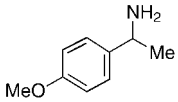
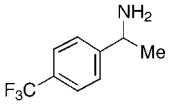
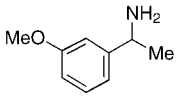
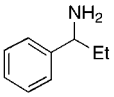
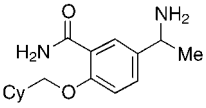
[**] We thank Michael M.-C. Lo, Dr. J. Craig Ruble, and Beata Tao for helpful discussions and preliminary studies, and we also thank Dr. George P. Luke (ARIAD Pharmaceuticals, Inc.) for providing the primary amine illustrated in entry 8 of Table 1. Support has been provided by Bristol-Myers Squibb, Merck, the National Institutes of Health (National Institute of General Medical Sciences, R01-GM57034), Novartis, Pfizer, and Pharmacia.

  0044-8249/01/11301-0240 $ 17.50+.50/0

(±)-1-phenylethylamine with a selectivity factor of 12 (Table 2, entry 1).[11] Other primary amines can also be kinetically resolved with good stereocontrol by PPY*. Higher selectivity factors are obtained for amines in which the aromatic group bears an *ortho* substituent (entries 2 and 3 vs. entry 1).

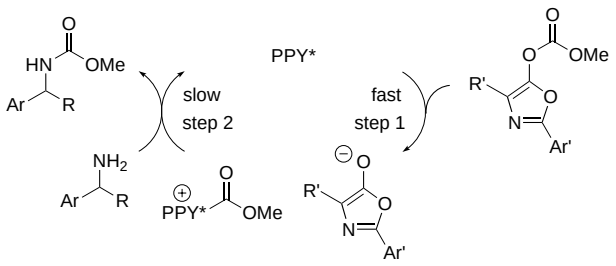
Table 2. Kinetic resolutions catalyzed by (−)-PPY*.



Entry	Amine	*s*
1		12
2		27
3		16
4		11
5		13
6		22
7		16
8		11

Electronic effects due to *para* substitution do not appear to impact significantly on stereoselection (entries 4 and 5 vs. entry 1), although enhanced selectivity is observed for a *meta*-methoxy-substituted amine (entry 6). An increase in the size of the alkyl group also leads to a modest increase in stereoselection (entry 7 vs. entry 1). Entry 8 provides an example of a kinetic resolution of a more highly functionalized amine that has been employed in studies of peptide-based Src SH2 inhibitors.[12]

We believe that these kinetic resolutions proceed through the pathway outlined in Scheme 1. Catalyst PPY* reacts rapidly with the acylating agent, producing an ion pair (step 1), which is the resting state of the catalytic cycle. In the subsequent, stereochemistry-determining step, the methoxycarbonyl group is transferred to the amine, thus furnishing the carbamate and regenerating PPY* (step 2). Consistent



Scheme 1. Proposed mechanism for acylations catalyzed by PPY*.

with this kinetic scheme is our observation that the rate of the reaction is zero order in acylating agent and first order in PPY* and in amine.[13]

Received: September 28, 2000 [Z15872]

[1] a) E. Vedejs, O. Daugulis, S. T. Diver, *J. Org. Chem.* **1996**, *61*, 430–431; E. Vedejs, O. Daugulis, *J. Am. Chem. Soc.* **1999**, *121*, 5813–5814; b) T. Oriyama, Y. Hori, K. Imai, R. Sasaki, *Tetrahedron Lett.* **1996**, *37*, 8543–8546; T. Sano, K. Imai, K. Ohashi, T. Oriyama, *Chem. Lett.* **1999**, 265–266; c) T. Kawabata, M. Nagato, K. Takasu, K. Fuji, *J. Am. Chem. Soc.* **1997**, *119*, 3169–3170; d) S. J. Miller, G. T. Copeland, N. Papaioannou, T. E. Horstmann, E. M. Ruel, *J. Am. Chem. Soc.* **1998**, *110*, 1629–1630; E. R. Jarvo, G. T. Copeland, N. Papaioannou, P. J. Bonitatebus, Jr., S. J. Miller, *J. Am. Chem. Soc.* **1999**, *121*, 11638–11643; e) F. Iwasaki, T. Maki, W. Nakashima, O. Onomura, Y. Matsumura, *Org. Lett.* **1999**, *1*, 969–972; F. Iwasaki, T. Maki, O. Onomura, W. Nakashima, Y. Matsumura, *J. Org. Chem.* **2000**, *65*, 996–1002; f) A. C. Spivey, T. Fekner, S. E. Spey, *J. Org. Chem.* **2000**, *65*, 3154–3159.

[2] a) J. C. Ruble, H. A. Latham, G. C. Fu, *J. Am. Chem. Soc.* **1997**, *119*, 1492–1493; b) J. C. Ruble, J. Tweddell, G. C. Fu, *J. Org. Chem.* **1998**, *63*, 2794–2795; c) C. E. Garrett, M. M.-C. Lo, G. C. Fu, *J. Am. Chem. Soc.* **1998**, *120*, 7479–7483; d) B. Tao, J. C. Ruble, D. A. Hoic, G. C. Fu, *J. Am. Chem. Soc.* **1999**, *121*, 5091–5092; e) S. Bellemin-Laponnaz, J. Tweddell, J. C. Ruble, F. M. Breitling, G. C. Fu, *Chem. Commun.* **2000**, 1009–1010.

[3] Selectivity factor s = (rate of fast-reacting enantiomer)/(rate of slow-reacting enantiomer). For a review of kinetic resolution, see: H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249–330.

[4] For a review of methods for the asymmetric synthesis of amines, see: A. Johansson, *Contemp. Org. Synth.* **1995**, *2*, 393–407.

[5] a) Y. Ie, G. C. Fu, *Chem. Commun.* **2000**, 119–120; b) A. G. Al-Sehemi, R. S. Atkinson, J. Fawcett, D. R. Russell, *Tetrahedron Lett.* **2000**, *41*, 2239–2242.

[6] A wide array of enantiopure α-arylamines display biological activity, including Exelon, a Novartis compound approved in the US in 2000 for the treatment of Alzheimer's disease. For reviews about Exelon, see: a) M. W. Jann, *Pharmacotherapy* **2000**, *20*, 1–12; b) M. D. Gottwald, R. I. Roaznski, *Expert Opin. Invest. Drugs* **1999**, *8*, 1673–1682.

[7] Enantiopure α-arylamines are widely used as reagents in asymmetric synthesis. For example, see: E. Juaristi, J. L. Leon-Romo, A. Reyes, J. Escalante, *Tetrahedron: Asymmetry* **1999**, *10*, 2441–2495.

[8] a) For kinetic resolutions of secondary alcohols, see ref. [2]; b) J. Liang, J. C. Ruble, G. C. Fu, *J. Org. Chem.* **1998**, *63*, 3154–3155; c) J. C. Ruble, G. C. Fu, *J. Am. Chem. Soc.* **1998**, *120*, 11532–11533; d) B. L. Hodous, J. C. Ruble, G. C. Fu, *J. Am. Chem. Soc.* **1999**, *121*, 2637–2638.

[9] We obtain similar results with our other planar-chiral DMAP-derived catalysts.

[10] We have examined the use of a number of O-acylated azlactones. These results will be reported in a future full paper.

[11] Sample experimental: Catalyst (−)-PPY* (5.2 mg, 0.014 mmol), 1-phenylethylamine (17.0 mg, 0.140 mmol), and $CHCl_3$ (2.5 mL) were added to a Schlenk flask under argon. The resulting purple solution was cooled in a −50 °C bath, and a solution of O-acylated azlactone

(13.5 mg, 0.0420 mmol) in $CHCl_3$ (0.15 mL) was added by syringe. After 4 hours, additional O-acylated azlactone (13.5 mg, 0.0420 mmol) in $CHCl_3$ (0.15 mL) was added. After 24 hours (total), the carbamate was isolated by flash chromatography (25% EtOAc/hexanes) (7.3 mg; HPLC analysis: 79% *ee*). For *ee* analysis, the unreacted amine was acylated (NEt_3, Ac_2O, CH_2Cl_2, RT) and then purified by flash chromatography (EtOAc) to furnish the amide (11.4 mg; GC analysis: 42% *ee*). These *ee* values correspond to a selectivity factor *s* of 13 at 35% conversion.

[12] G. P. Luke, D. A. Holt, *Tetrahedron: Asymmetry* **1999**, *10*, 4393 – 4403.

[13] A study of stereoselectivity as a function of catalyst *ee* is consistent with the presence of one catalyst molecule in the stereochemistry-determining step of the process.

High-Nuclearity Chromium – Nickel – Cyanide Clusters: An Open $Cr_8Ni_5(CN)_{24}$ Cage and a C_3-Symmetric $Cr_{10}Ni_9(CN)_{42}$ Cluster Incorporating Three Forms of Cyanonickelate**

Jennifer J. Sokol, Matthew P. Shores, and Jeffrey R. Long*

High-nuclearity metal – cyanide clusters may ultimately provide a vehicle for the design of new single-molecule magnet molecules possessing an energy barrier for magnetic moment reversal.[1] This contention is partly supported by recent work in which an understanding of the factors influencing superexchange interactions across a bridging cyanide ligand has led to the synthesis of Prussian blue type solids[2] with magnetic ordering temperatures as high as 373 K.[3] Typically, such solids are obtained from aqueous assembly reactions between octahedral $[M(H_2O)_6]^{x+}$ and $[M'(CN)_6]^{y-}$ complexes. The synthesis of molecular clusters with similarly adjustable magnetic properties is expected to require inhibition of some reactive sites on the precursor complexes through substitution of inert blocking ligands. For example, the use of 1,4,7-triazacyclononane (tacn) as a face-capping tridentate ligand on each metal complex can direct the formation of $[(tacn)_8M_4M'_4(CN)_{12}]^{z+}$ clusters with core structures consisting of a single cubic unit excised from the Prussian blue type framework.[4, 5]

However, to produce the exceptionally large spin states desired—along with magnetic anisotropy—for increasing the spin reversal barrier in single-molecule magnets, it is necessary to develop methods for constructing larger cluster geometries in which more metal centers can be magnetically coupled.[6] A simple strategy for achieving higher nuclearities involves the use of a blocking ligand on just one of the reaction components, thereby permitting cluster growth to propagate further before a closed structure forms. Accordingly, the reaction between $[Ni(H_2O)_6]^{2+}$ and $[(Me_3tacn)Cr(CN)_3]$ ($Me_3tacn = N,N',N''$-trimethyl-1,4,7-triazacyclononane) in aqueous solution generates $[(Me_3tacn)_8Cr_8Ni_6(CN)_{24}]^{12+}$, a 14-metal cluster featuring a cube of eight Cr^{3+} ions with each square face spanned by a $[Ni(CN)_4]^{2-}$ unit.[7] In further pursuing reactions of this type, we have discovered two new cluster geometries, including a 19-metal species that represents the largest metal – cyanide cluster reported to date.

Reaction of NiI_2 with $[(Me_3tacn)Cr(CN)_3]$ in aqueous solution does not lead to the face-centered cubic $[(Me_3tacn)_8Cr_8Ni_6(CN)_{24}]^{12+}$ cluster obtained with chloride, bromide, nitrate, or perchlorate as counteranions.[7] Instead, crystallographic analysis[8] of a red-brown crystal isolated from the reaction mixture revealed a product of composition **1**,

$$[(Me_3tacn)_8Cr_8Ni_5(CN)_{24}]I_{10}\cdot 27\,H_2O \qquad \mathbf{1}$$

featuring the open-cage cluster depicted in Figure 1. The core structure of this $[(Me_3tacn)_8Cr_8Ni_5(CN)_{24}]^{10+}$ cluster most notably differs from the complete face-centered cubic geometry by having a Ni^{2+} ion missing from one of the cube faces.

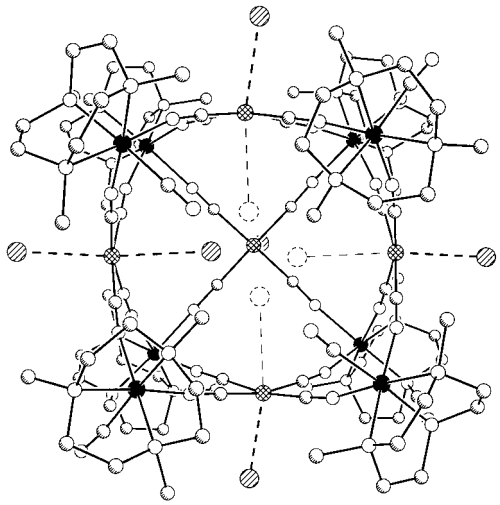


Figure 1. Structure of the $[(Me_3tacn)_8Cr_8Ni_5(CN)_{24}]^{10+}$ cluster and associated I^- anions, as observed in **1**. Black, cross-hatched, shaded, white, and hatched spheres represent Cr, Ni, C, N and I atoms, respectively; H atoms are omitted for clarity. The cluster has maximal point group symmetry C_{2v}. Selected mean interatomic distances [Å] and angles [°]: Cr-N_{CN} 2.05(6), Cr-C 2.04(5), Ni-C 1.86(2), C-N_{CN} 1.14(3), Ni $\cdots$ I_{outer} 2.91(3), Ni $\cdots$ I_{inner} 3.09(3); N_{CN}-Cr-N_{CN} 87(2), N_{CN}-Cr-C 93(3), Cr-N-C_{CN} 170(4), Cr-C-N 172(4), C-Ni-C 89(1), Ni-C-N 177(1).

As with $[(Me_3tacn)_8Cr_8Ni_6(CN)_{24}]^{12+}$,[7] the thermal energy delivered in the course of forming the cluster is apparently sufficient to reorient the cyanide ligands from the Cr^{III}-C-N connectivity of the reactant complex to the more stable Cr^{III}-N-C-Ni^{II} bridging arrangement. This, rather than the reverse bridging cyanide orientation, was clearly favored in the crystal

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