Centre as supplementary publication nos. CCDC-149074 (**3**) and -149075 (**4**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[10] For recent references, see a) T. Marahashi, T. Otani, E. Mochizuki, Y. Kai, H. Kurosawa, *J. Am. Chem. Soc.* **1998**, *120*, 4536; b) P. Lord, M. M. Olmstead, A. L. Balch, *Angew. Chem.* **1999**, *111*, 2930; *Angew. Chem. Int. Ed.* **1999**, *38*, 2761.

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[13] NH_2^- was used to mimic the pyridine moieties of 2,5-bis(2-pyridyl)-phosphole. The DFT calculations[16] performed on **3′** indicate that the symmetrically bridging coordination of the P atoms is energetically preferred over an unsymmetrical semibridging coordination mode.

[14] a) D. G. Gilheany, *Chem. Rev.* **1994**, *94*, 1339; b) D. B. Chesnut, A. Savin, *J. Am. Chem. Soc.* **1999**, *121*, 2335.

[15] Complex **3** exhibits electronic absorptions at 326 ($\lg\varepsilon = 4.43$), 391 ($\lg\varepsilon = 4.08$), and 446 nm ($\lg\varepsilon = 3.96$) in CH_2Cl_2. However, the absorption of lower energy cannot be unambiguously assigned to a Pd–Pd $\sigma \rightarrow \sigma^*$ excitation because of possible metal–ligand charge transfer bands. For comparison, complex **4** exhibits a maximum electronic absorption at 407 nm ($\lg\varepsilon = 3.96$).

[16] The DFT calculations (E. J. Baerends, D. E. Ellis, P. Ros, *Chem. Phys.* **1973**, *2*, 41) were carried out with the Amsterdam Density Functional (ADF) program (release 2.3, Vrije Universiteit, Amsterdam, The Netherlands, **1997**), using nonlocal exchange (A. D. Becke, *Phys. Rev. A* **1988**, *38*, 3098) and correlation (J. P. Perdew, *Phys. Rev. B* **1986**, *33*, 8822; Erratum: J. P. Perdew, *Phys. Rev. B* **1986**, *34*, 7406). Standard ADF STO basis set IV was used. The frozen-core approximation was considered.

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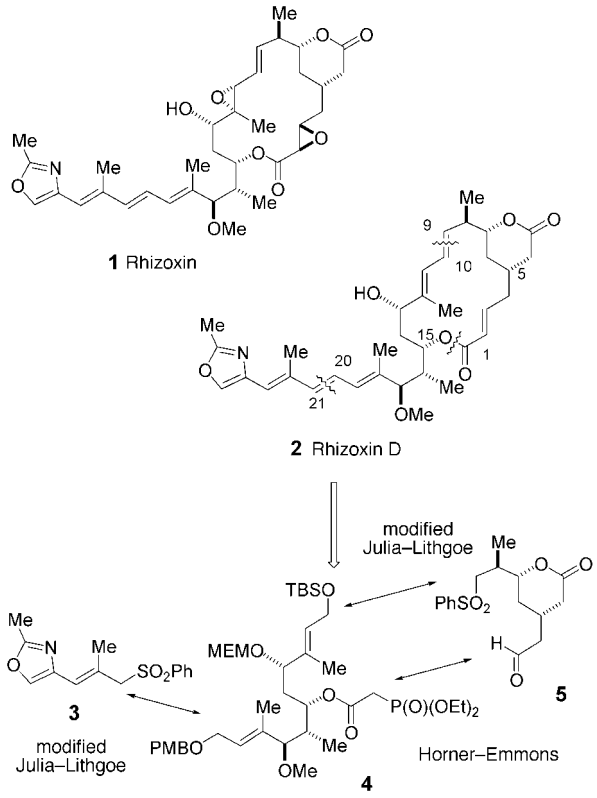
Asymmetric Total Synthesis of Rhizoxin D**

Gary E. Keck,* Carrie A. Wager, Travis T. Wager, Kenneth A. Savin, Jonathan A. Covel, Mark D. McLaws, Dhileep Krishnamurthy, and Victor J. Cee

Rhizoxin (**1**, Scheme 1) and five closely related compounds have been isolated from *Rhizopus chinensis* by Iwasaki and co-workers.[1] In addition to antibiotic and antifungal activity, these materials have been shown to possess potent antitumor activity,[2] including activity against vincristine- and adriamycin-resistant cells.[3] These compounds have attracted considerable interest with respect to synthesis, and one total synthesis of rhizoxin has been reported,[4] as well as three syntheses of rhizoxin D (**2**).[5] We describe herein the synthesis of rhizoxin D by an approach utilizing catalytic asymmetric allylation as a key strategic element.



Scheme 1. Structures of rhizoxin and rhizoxin D and retrosynthesis of the latter (see ref. [6] for abbreviations).

The overall approach to this synthesis is illustrated in Scheme 1 and relied upon disconnections at the C9–C10 and C20–C21 disubstituted alkenes to yield the three major subunits indicated. In the route described herein, both of these alkene linkages are established by a modified Julia–Lithgoe protocol developed previously in our laboratories,[7] and the macrocycle is closed by an intramolecular Horner–Emmons reaction. This strategy provides inherent flexibility in the timing of the necessary operations and also allows for other ring closure options to be investigated using the same basic subunits.

In principle the "lactone" subunit could be utilized as either the sulfone component or the aldehyde subunit in the proposed Julia coupling; the choice shown was made based upon model studies. The synthesis of this subunit used a thermodynamic approach for control of stereochemistry at C5 as we have previously described.[8] Thus, condensation of the aldehyde **6** with the boron enolate of (*S*)-3-(1-oxopropyl)-4-(phenylmethyl)-2-oxazolidinone afforded the aldol product[9] as a single diastereomer, which was reduced with $LiBH_4$ to afford the diol **7** (Scheme 2). Elaboration to the sulfone **8** followed by oxidative olefin cleavage provided, upon silyation with TBSCl, the all-equatorial protected lactol **9**. The stereochemistry at C5 is thus set in this sequence by the preference

[*] Prof. G. E. Keck, C. A. Wager, T. T. Wager, K. A. Savin, J. A. Covel, M. D. McLaws, D. Krishnamurthy, V. J. Cee
Department of Chemistry, University of Utah
315 South 1400 East, Rm 2020
Salt Lake City, UT 84112-0850 (USA)
Fax: (+1) 801-581-7055
E-mail: keck@chemistry.utah.edu

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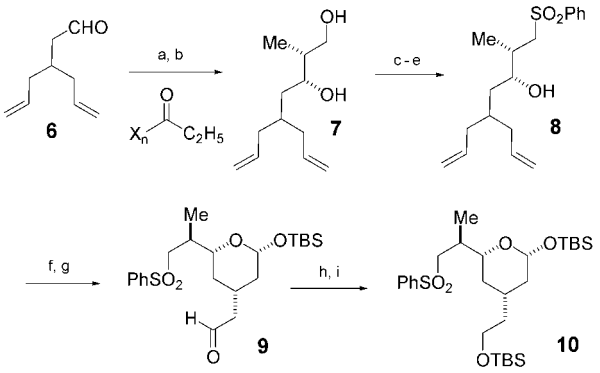
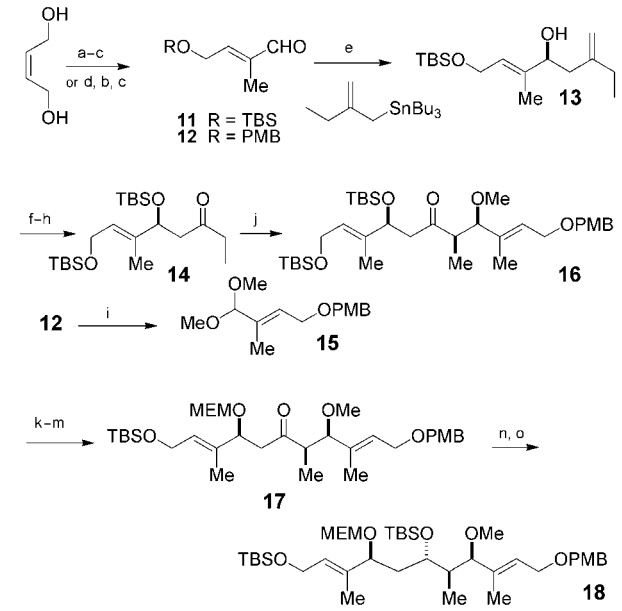


Scheme 2. Synthesis of the C1–C9 subunit. a) Bu_2BOTf, Et_3N, CH_2Cl_2, $-78\,^{\circ}C$; pH 7 phosphate buffer, 30% H_2O_2, MeOH, 86%; b) $LiBH_4$, THF, MeOH, $0\,^{\circ}C$, 90%; c) TsCl, pyr, CH_2Cl_2, $-10\,^{\circ}C$, 87%; d) PhSH, KO*t*Bu, DMF, RT, 87%; e) Oxone, MeOH/H_2O, $0\,^{\circ}C$, 100%; f) OsO_4, $NaIO_4$, THF/H_2O, RT; g) TBSCl, imid, CH_2Cl_2, $0\,^{\circ}C \rightarrow$RT; h) $NaBH_4$, MeOH, $0\,^{\circ}C$; i) TBSCl, imid, CH_2Cl_2, $0\,^{\circ}C \rightarrow$RT, 55% (4 steps).

for an equatorial disposition of the side chain at C5 in the hemiacetal form of the hydroxy dialdehyde, which thus differentiates the two prochiral formyl groups generated by oxidative cleavage.

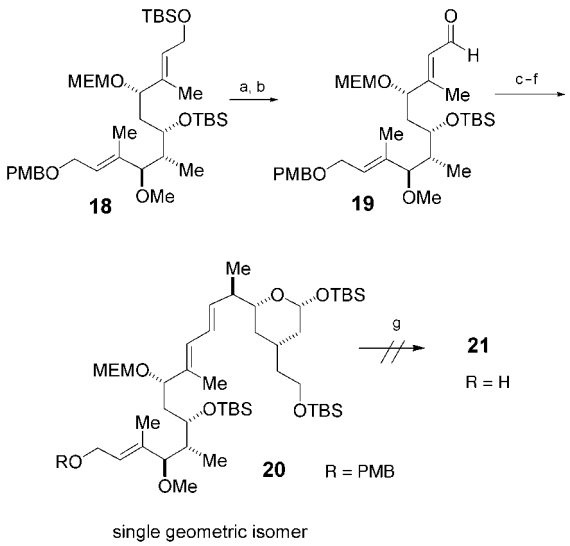
The synthesis of the C10–C20 subunit was accomplished by an approach which formally corresponds to sequential asymmetric aldol condensations of methyl ethyl ketone with an enal; for purposes of further elaboration the termini of these enals were differently protected. The synthesis began by protection of butene 1,4-diol as either the bis-TBS or the bis-PMB derivative (Scheme 3). Oxidative cleavage of the bis-TBS alkene by ozonolysis yielded the TBS-protected glyceraldehyde which was homologated by Wittig reaction with $Ph_3P{=}C(CH_3)CHO$ directly to the *E*-enal **11** in 73% overall yield. This material was then used in a catalytic asymmetric allylation reaction[10] with tributyl-(2-ethylallyl)-stannane and BITIP-catalysis to afford the alcohol **13** in 78% yield and 99% *ee*. It is noteworthy that this reaction proved very amenable to scale since it could be conducted in very concentrated solution; thus, to process 65 mmol of **11** requires only 130 mL of solvent. After protection of the free alcohol as the TBS ether, the terminal methylene group was oxidatively cleaved to give the ketone **14** in 74% yield.



Scheme 3. Preparation of the C10–C20 subunit. a) TBSCl, imid, CH_2Cl_2, $0\,^{\circ}C$, 99%; b) O_3, CH_2Cl_2, $-78\,^{\circ}C$, then Ph_3P, RT; c) 2-(triphenylphosphoranylidene)propionaldehyde, tol, $80\,^{\circ}C$; d) PMB-Br, NaH, DMF, 72%; e) (*S*)-BINOL, Ti(O*i*Pr)$_4$, TFA, 4 Å MS, CH_2Cl_2, $-78 \rightarrow -20\,^{\circ}C$, 65 h, 78%, 99% *ee*; f) TBSOTf, *i*Pr_2NEt, THF, $0\,^{\circ}C$, 97%; g) OsO_4, NMO, *t*BuOH, THF, H_2O, RT; h) $NaIO_4$, THF, H_2O, RT, 74% (2 steps); i) $(MeO)_3CH$, MeOH, NH_4Cl j) $TiCl_4$, *i*Pr_2NEt, CH_2Cl_2, $-90\,^{\circ}C$, 52%; k) 1% HCl, MeOH, RT, 95%; l) TBSCl, imid, CH_2Cl_2, RT; m) MEMCl, *i*Pr_2NEt, CH_2Cl_2, $0\,^{\circ}C \rightarrow$RT, 93% (2 steps); n) SmI_2, MeOH, THF, $0\,^{\circ}C \rightarrow$RT; o) *i*Pr_2NEt, TBSOTf, CH_2Cl_2, RT, 60% (2 steps).

In preparation for the next event, the bis-PMB protected diol was processed by Wittig homologation as described above to yield the enal **12**. This enal was then converted to the dimethyl acetal **15** and used in an aldol reaction employing the Evans $TiCl_4/NEt_3$ conditions.[11] This afforded what proved to be the desired aldol adduct **16** as a single stereoisomer.[12, 13] Reduction of the C15 oxo group proved problematic, as no hydride reducing agent could be found which would give the desired stereochemical outcome. Ultimately, application of a protocol developed for this specific problem proved successful.[14] Removal of the TBS ether and protection of the hydroxy group as the MEM ether gave **17** in 88% yield. Reduction of the ketone by using SmI_2 in THF containing 20 equiv of methanol cleanly gave the desired alcohol with good stereoselectivity (91:9 on small scale, 88:12 on scale up) and chemical yield. Protection of this alcohol as the TBS ether provided the C10–C20 subunit **18**.

The fragment-assembly sequence deemed most promising commenced by application of our modified Julia protocol to the coupling of the sulfone **10** with the enal **19**, which was prepared by removal of the TBS group in **18** followed by MnO_2 oxidation (Scheme 4). Condensation of the lithiated sulfone **10** (metalation with *n*BuLi in THF) with **19** led to a mixture of all four possible diastereomeric β-hydroxy sul-



single geometric isomer

Scheme 4. The initial approach to rhizoxin D. a) HF·pyr, THF, $0\,^{\circ}C$; b) MnO_2, $CHCl_3$/hexanes, RT, 89%, (2 steps); c) *n*BuLi, C1–C9 subunit **10**, THF, $-78\,^{\circ}C$; d) Ac_2O, DMAP, pyr, RT; e) DBU, CH_2Cl_2, RT; f) SmI_2, DMPU, MeOH, THF, RT, 70% (4 steps); g) DDQ, $NaHCO_3$.

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fones, which were processed without purification through a sequence of acetylation, elimination with DBU, and finally reduction with SmI_2/DMPU/MeOH in THF to give the desired *E* alkene as a single geometric isomer in 70% overall yield. However, we were unable to remove the PMB protecting group in this intermediate and thus were forced to reverse the order of coupling, thus the oxazole–triene segment was incorporated first.

The PMB group in **18**, in contrast, was easily removed by reaction with DDQ and bicarbonate buffer in 98% yield. After MnO_2 oxidation, condensation with the oxazole–sulfone **3**[15] (metalation with Li-HMDS), and processing as described above afforded the desired triene **23** as a single geometric isomer and in 73% overall yield (Scheme 5).

Selective removal of the primary TBS group followed by oxidation using MnO_2 afforded the enal **24**, which was utilized in a second such Julia sequence with the sulfone **10** as described above (anion formation with *n*BuLi) to give **25** in 84% overall yield, again as a single *E* isomer. Selective removal of two of the three TBS groups was easily accomplished using HF-pyridine, and oxidation with TPAP-NMO in acetonitrile afforded the desired lactone aldehyde in 51% yield from **25**. Removal of the final TBS group in the presence of the aldehyde proved difficult but could be accomplished in 50% yield using HF-pyridine. Phosphorylation of the obtained alcohol with $ClC(O)CH_2P(O)(OEt)_2$ provided the phosphonate **26** necessary for intramolecular Emmons reaction, which was accomplished in 87% isolated yield using the general procedure of Roush and Masamune et al. (LiCl, Hünig's base, CH_3CN).[16] Finally, removal of the MEM ether using bromodimethyl borane in 1:1 THF/CH_2Cl_2 afforded rhizoxin D, with spectral data in excellent agreement with those previously reported.[2,17]

Received: August 21, 2000 [Z15672]

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[6] Abbreviations: Ac = acetyl, Ac_2O = acetic anhydride, BINOL = (1,1′-binaphthyl-2,2′-diol), BITIP = catalyst prepared from BINOL and $Ti(OiPr)_4$, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, *de* = diastereomeric excess, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, DMPU = *N*,*N*′dimethylpropyleneurea, *ee* = enantiomeric excess, HMDS = hexamethyldisilazide, imid = imidazole, MEM = 2-methoxyethoxymethyl, MS = molecular sieves, NMO = *N*-methylmorpholine *N*-oxide, PMB = *para*-methoxybenzyl, pyr = pyridine, RT = room temperature, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid, THF = tetrahydrofuran, tol = toluene, TPAP = tetrapropylammonium perruthenate, Ts = *para*-toluenesulfonyl, X_n = (*S*)-4-(phenylmethyl)-2-oxazolidinone.

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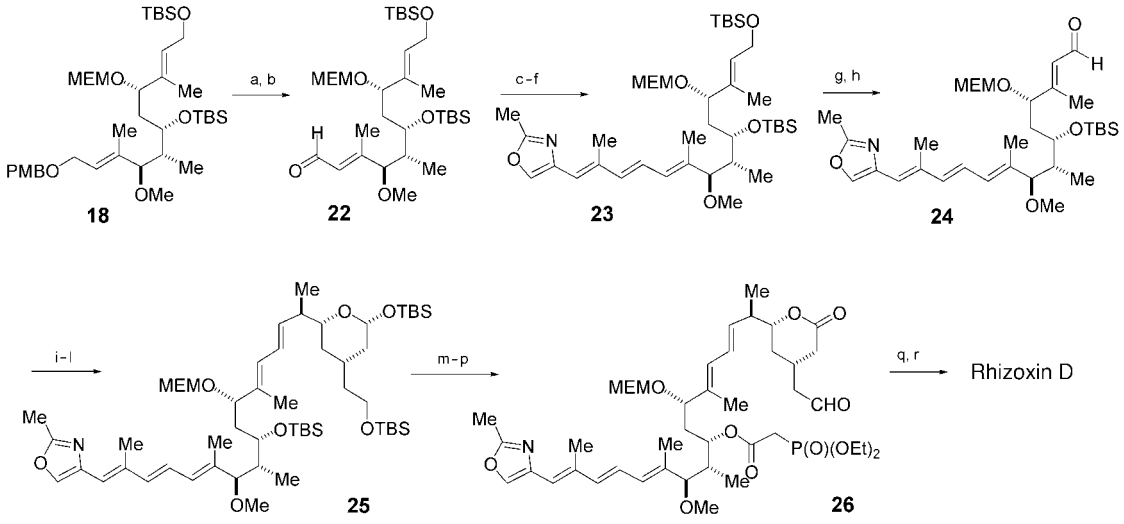

Scheme 5. Fragment coupling and completion of the synthesis of rhizoxin D. a) (DDQ, $NaHCO_3$; in portions), CH_2Cl_2, RT, 98%; b) MnO_2, $CHCl_3$/hexanes, RT, 95%; c) LiHMDS, oxazole subunit **3**, THF, −78 °C; d) Ac_2O, DMAP, pyr, RT; e) DBU, THF, RT; f) SmI_2, DMPU, MeOH, THF, RT, 73% (4 steps); g) HF · pyr, THF, 0 °C; h) MnO_2, $CHCl_3$/hexanes, RT, 80% (2 steps); i) *n*BuLi, C1–C9 subunit **10**, THF, −78 °C; j) Ac_2O, DMAP, pyr, RT; k) DBU, THF, RT; l) SmI_2, DMPU, MeOH, THF, RT, 84% (4 steps); m) HF · pyr, THF, 0 °C, 78%; n) TPAP, NMO, CH_3CN, RT, 65%; o) HF · pyr, THF, 0 °C, 49%; p) diethylphosphonoacetyl chloride, pyr, THF, −20 °C → RT, 82%; q) LiCl, iPr_2NEt, CH_3CN, RT, 87%; r) Me_2BBr, THF/CH_2Cl_2, −78 → 0 °C, 78%.

[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.
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[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.
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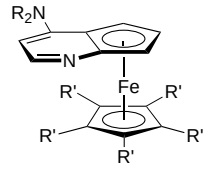


NR_2 = dimethylamino, pyrrolidino
R' = Me, Ph

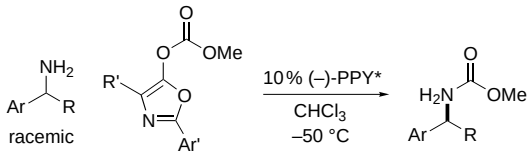
NR_2 = pyrrolidino, R' = Me: (–)-PPY* (**1**)

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

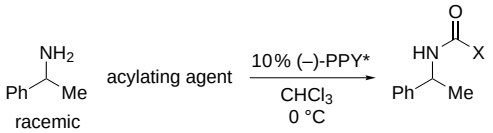
During the past four years, several groups have reported a diverse array of interesting approaches to the development of nonenzymatic acylation catalysts for the kinetic resolution of alcohols, and certain classes of alcohols can now be resolved with useful levels of stereoselection (selectivity factor $s \geq 10$).[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.

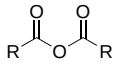
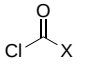
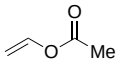
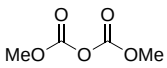


(1)

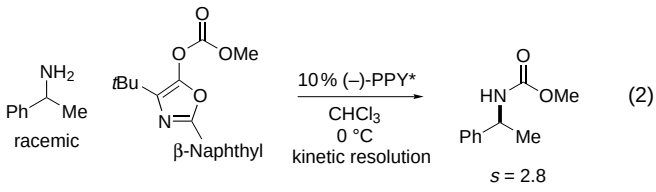
In earlier studies, we established that planar-chiral DMAP derivatives such as PPY* can serve as useful catalysts for several different enantioselective acylation processes, including the kinetic resolution of secondary alcohols (DMAP = 4-dimethylaminopyridine).[8] Our initial efforts to extend this 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

[*] Prof. Dr. G. C. Fu, Dr. S. Arai, Dr. S. Bellemin-Laponnaz
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
Fax: (+1) 617-258-7500
E-mail: gcf@mit.edu

[**] 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.

  1433-7851/01/4001-0234 $ 17.50+.50/0