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Concise Synthesis, Preparative Resolution, Absolute Configuration Determination, and Applications of an Atropisomeric Biaryl Catalyst for Asymmetric Acylation

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A new three-step synthesis and resolution of nucleophilic catalyst **1** suitable for large-scale preparation has been developed, and this catalyst has been shown to be effective for the kinetic resolution and asymmetric desymmetrization of a range of *sec*-alcohol substrates.

Introduction

Small organic molecules that catalyze enantioselective acyl transfer have attracted great interest in the synthetic community in recent years.[1] As a result, a number of chiral nucleophilic catalysts have been designed that deliver useful levels of enantioselectivity in acylative kinetic resolutions (KRs), asymmetric desymmetrizations (ASDs), and related transformations.[2−9] In particular, effective enzyme substitutes have been made by the groups of Vedejs,[2] Fu,[3] Oriyama,[4] Fuji,[5] and Miller,[6] and Campbell[7] (e.g. catalysts **I**−**VI**, respectively, Figure 1). We, too, have previously reported that axially chiral, atropisomeric biaryl 4-aminopyridine **1** is an effective catalyst for KR of various aryl alkyl *sec*-alcohols (Figure 1).[9]

With the notable exceptions of Oriyama's proline-derived diamine **III**, which is limited to the catalysis of benzoylation processes, and Campbell's α-methylproline-derived 4-aminopyridine **VI**, which appears to have limited substrate generality, the preparation of these

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(1) For an overview of organocatalysis see: Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726−3748. For a review of asymmetric catalysis of acyl transfer see: Spivey, A. C.; Maddaford, A.; Redgrave, A. *Org. Prepr. Proc. Int.* **2000**, *32*, 331−365.

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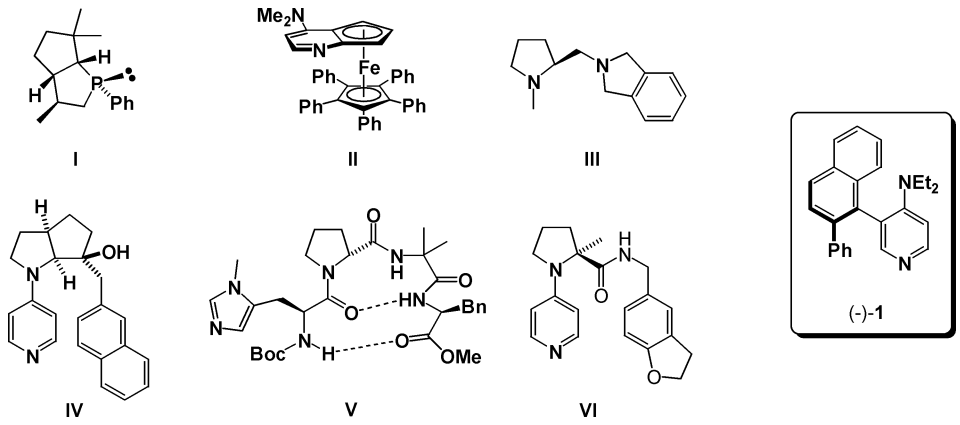


FIGURE 1. Nucleophilic catalysts for asymmetric acylation.

catalysts involve multistep syntheses. For catalysts **II** and **1**, preparative-scale chiral stationary phase (CSP) HPLC is also required. Such inaccessibility constitutes a significant disincentive to the widespread use of these catalysts and compromises their viability as practical enzyme substitutes.

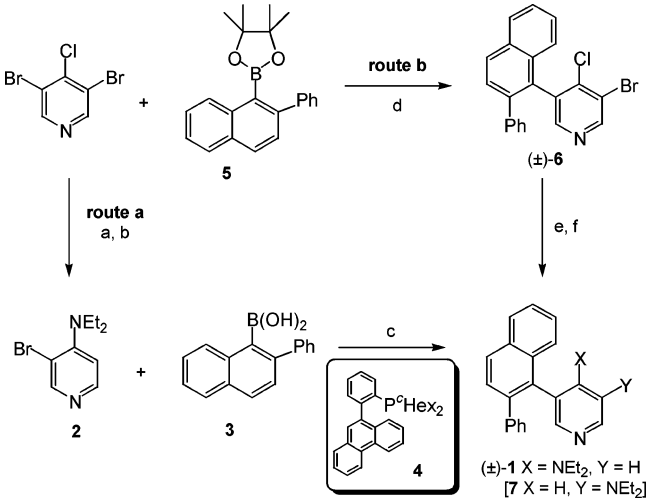
Here, we report a three-step synthesis of biaryl (±)-**1** from commercially available 3,5-dibromo-4-chloropyridine via a 3,4-pyridyne intermediate, a gram-scale method for its resolution by crystallization with a tyrosine derivative identified by parallel salt screening using differential scanning calorimetry (DSC), and demonstrate the utility of this now readily accessible catalyst for the KR and ASD of a range of secondary alcohols. The absolute configuration of the catalyst has also been established, allowing a hypothesis regarding the sense of induction in these processes to be formulated.

Results and Discussion

Two approaches to the rapid synthesis of biaryl (±)-**1** from 3,5-dibromo-4-chloropyridine were envisaged (Scheme 1).

Both routes require the direct formation of a highly hindered tri-ortho-substituted biaryl axis but differ in the order of introduction of the 4-diethylamino substituent.[10] Despite intensive efforts, we were unable to develop a satisfactory protocol via route a, because the Suzuki reaction between bromopyridine **2** and 2-phenyl-1-naphthaleneboronic acid (**3**) proved to be low yielding (20%) and resisted scale-up in our hands.[11] In contrast, a robust protocol via route b was developed starting with the Suzuki reaction between 3,5-dibromo-4-chloropyridine and pinacolato-boronic ester **5** using a method developed

SCHEME 1. Approaches to the Synthesis of Biaryl (±)-1[a]



[a] Conditions: (a) Et_2NH, $HCONEt_2$, 170 °C, 20 h, 94%,[9e] (b) *i*-PrMgCl then H_2O, 62%, (c) K_3PO_4, $Pd_2(dba)_3$ (4 mol %), **4** (9 mol %), toluene, 110 °C, 96 h, 20%, (d) Ag_2CO_3, $Pd(PPh_3)_4$ (5 mol %), PhH, 80 °C, 96 h, 80%, (e) *i*-PrMgCl then H_2O, 99%, (f) Et_2NLi, Et_2NH, THF, 67 °C, 16 h, 30% [+ 3-diethylamino isomer, 62%].

by Chaumeil et al.[12] This gave the coupled product **6** reproducibly in 80% yield on a multigram scale. The use of boronic ester **5** as opposed to the corresponding boronic acid **3** is advantageous, as this compound is easier to prepare and purify. The 4-chloro substituent in dihalopyridine **6** proved resistant to both S_NAr[9e,13] and Buchwald/Hartwig-type Pd(0)-catalyzed C−N cross coupling[14] with diethylamine, presumably due to steric constraints. Reasoning that the steric situation would be more favor-

(9) (a) Malardier-Jugroot, C.; Spivey, A. C.; Whitehead, M. A. *J. Mol. Struct. (THEOCHEM)* **2003**, *623*, 263−276; (b) Spivey, A. C.; Charbonneau, P.; Fekner, T.; Hochmuth, D. H.; Maddaford, A.; Malardier-Jugroot, C.; Redgrave, A. J.; Whitehead, M. A. *J. Org. Chem*. **2001**, *66*, 7394−7401; (c) Spivey, A. C.; Maddaford, A.; Leese, D.; Redgrave, A. J. *J. Chem. Soc., Perkin Trans 1*. **2001**, 1785−1794; (d) Spivey, A. C.; Maddaford, A.; Fekner, T.; Redgrave, A.; Frampton, C. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3460−3468; (e) Spivey, A. C.; Fekner, T.; Spey, S. E. *J. Org. Chem*. **2000**, *65*, 3154−3159; (f) Spivey, A. C.; Fekner, T. S.; Spey, S. E.; Adams, H.; *J. Org. Chem*. **1999**, *64*, 9430−9443; (g) Spivey, A. C.; Fekner, T.; Adams, H.; *Tetrahedron Lett*. **1998**, *39*, 8919−8922.

(10) Our inability to form the hindered biaryl axis of biaryl (±)-**1** by direct coupling previously led us to develop an indirect synthesis that proceeded via two sequential less hindered coupling reactions. See ref 9e.

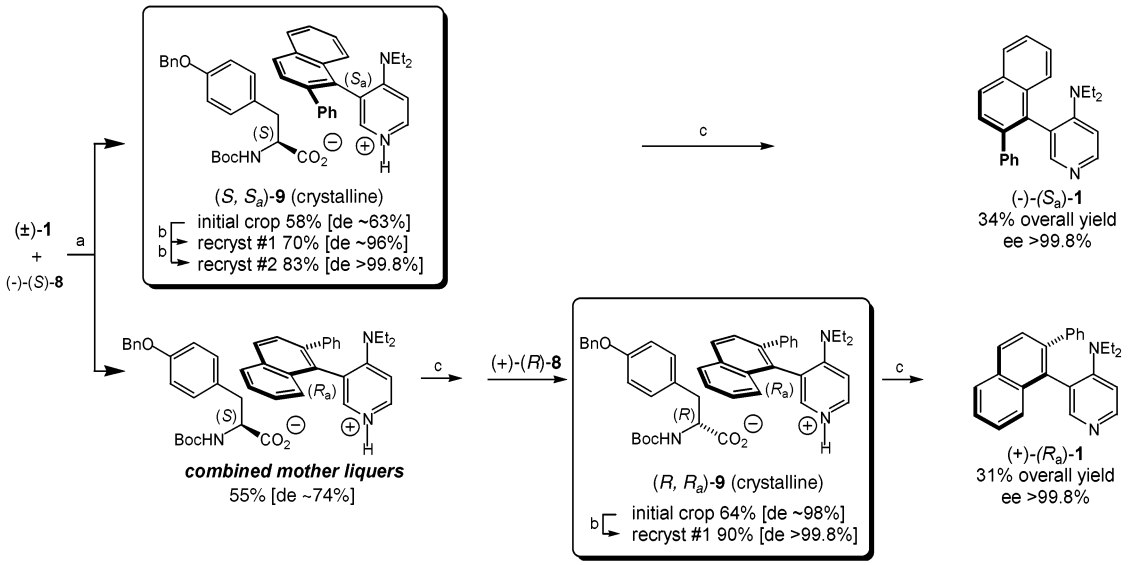
(11) Buchwald's phenanthryl ligand **4** was the only ligand that allowed coupling between bromopyridine **2** and boronic acid **3**. See: (a) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051−12052; (b) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162−1163.

(12) Chaumeil, H.; Signorella, S.; Le Drian, C. *Tetrahedron* **2000**, *56*, 9655−9662.

(13) Attempted "activation" of 4-chloropyridine **6** by conversion the corresponding *N*-oxide, 4-fluoro, and 3-desbromo derivatives and/or the use of the diethylaluminium amide of diethylamine also failed to facilitate S_NAr.

(14) For a review see: Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem*. **2002**, *219*, 131. For 4-halopyridine coupling see: Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem*. **2000**, *69*, 1168−1174 and references therein.

SCHEME 2. Resolution of Biaryl (±)-1 by Crystallization with (−)-*N*-Boc-*O*-benzyl-(*S*)-tyrosine [(−)-8] and (+)-*N*-Boc-*O*-benzyl-(*R*)-tyrosine [(+)-8][a]



[a] Conditions: (a) *i*-PrOH, 75 °C, 0.5 H, (b) recryst from *i*-PrOH, (c) CH_2Cl_2/Et_3N (10:1), SiO_2.

able for an elimination−addition (E−A) pathway we explored 3,4-pyridyne formation.[15] This investigation culminated in the development of a convenient protocol for the preparation of biaryl (±)-**1** by treatment of dihalopyridine **6** with *i*-PrMgCl and then water to effect 3-debromination followed by refluxing with lithium diethylamide and diethylamine in THF for 16 h.[16] This gives very clean formation of a readily separable 1:2 mixture of the desired 4-diethylamino product (±)-**1** (30% isolated yield) and its 3-diethylamino isomer **7** (62% isolated yield). Biaryl (±)-**1** is therefore now available in three steps from commercially available 3,5-dibromo-4-chloropyridine in 24% overall yield (i.e. route b, Scheme 1).

Although biaryl (±)-**1** can be resolved by preparative CSP-HPLC,[9e] we envisaged that resolution by crystallization of a diastereomeric salt of biaryl **1** with an appropriate homochiral acid would constitute a much more convenient and economic method. *N*-Boc-*O*-benzyl-(*S*)-tyrosine [(−)-**8**] was identified as the optimal acid partner for this resolution. This followed automated salt synthesis between biaryl (±)-**1** and an array of 63 commercially available homochiral acids using a robot, followed by DSC screening to identify eutectic crystals, trial crystallizations, and then optimization of the crystallization conditions with the aid of the software package Resolution Companion (see Supporting Information).[17] In the optimized protocol, crystallization of a 1:1 mixture of biaryl (±)-**1** and *N*-Boc-*O*-benzyl-(*S*)-tyrosine [(−)-**8**] from *i*-PrOH and recrystallization twice from *i*-PrOH give the salt **9** with >99.8% de (determined by CSP-HPLC). Enantiomerically pure biaryl (−)-**1** (~34% isolated yield) is obtained simply by passing a solution of this salt in CH_2Cl_2/Et_3N (10:1) through a short plug of silica and evaporation of the volatiles. Moreover, the enantiomerically pure antipodal catalyst biaryl (+)-**1** (~31% isolated yield) is similarly obtained from the combined mother liquers following recrystallization with *N*-Boc-*O*-benzyl-(*R*)-tyrosine [(+)-**8**] (Scheme 2).

A single crystal X-ray structure determination on the diastereomerically pure salt **9**, obtained from the first crystallization using *N*-Boc-*O*-benzyl-(*S*)-tyrosine, revealed the absolute configuration of biaryl (−)-**1** as being S_a (Figure 2 and as drawn in Figure 1; see the Supporting Information).[18,19]

Previously, we have shown that biaryl (−)-(S_a)-**1** catalyzes the acylative KR of a range of aryl alkyl *sec*-alcohols with $(i\text{-PrCO})_2O$, giving enantioselectivities (s)[20] in the range 8−29 for formation of the *R*-configured esters.[9e] That $(i\text{-PrCO})_2O$ is the optimal anhydride for these KRs is supported by our subsequent screening of a various alternative acyl donors for the KR of 1-(1-naphthyl)ethanol, all of which gave lower selectivities [$s = 1-13$, cf. $s = 24$ using $(i\text{-PrCO})_2O$; see the Supporting Information]. Using the optimized conditions, we now report the performance of biaryl (−)-(S_a)-**1**, prepared as

(15) For a recent review of aryne chemistry see: Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701−730.

(16) The transformation of dihalopyridine **6** into aminopyridines **1** and **7** can be performed as a single step by employing *s*-BuLi (1.5 equiv) to effect bromine−lithium exchange at −78 °C (30 min), followed by addition of lithium diethylamide (3 equiv), warming to room temperature, and then refluxing for 16 h. However, in our hands this procedure gave a significantly less clean reaction and provided lower yields of the both products following tedious purification.

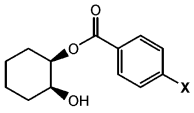
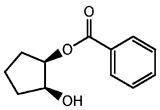
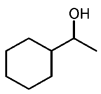
(17) This method of resolving agent selection has been used previously to identify an appropriate chiral amine from a panel of chiral amines for resolution of a racemic carboxylic acid; see: Dyer, U. C.; Henderson, D. A.; Mitchell, M. B. *Org. Proc. Res. Devel.* **1999**, *3*, 161−165. This publication also provides a detailed description of the basis of the method and details of the Resolution Companion software package.

(18) The fused benzenoid ring takes priority over the 2-phenyl substituent when assigning the naphthyl end of the biaryl axis by Cahn−Ingold−Prelog (CIP) priority rules; see: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p 107.

(19) Biaryl (−)-(S_a)-**1** displays a negative Cotton-effect peak in its circular dichroism spectrum at 335 nm. The assignment of the absolute configuration of topologically related atropisomeric catalyst structures is therefore possible by comparison of their Cotton-effect peaks in this region.

(20) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249−330. See also: Straathof, A. J. J.; Jongejan, J. A. *Enzyme Microb. Technol.* **1997**, *21*, 559−571.

TABLE 1. Acylative KR and ASD of *sec*-Alcohols[e]

Entry	Substrate	ee_A, %	ee_E, %	*C*, %[a]	$s^{[20]}$	*Product enantiomer*
1 X=CN		8.2	67.2	11.0	5.5	(-) 1*R*,2*S*[b,5d]
2 X=NO_2		85.3	39.1	69.0	5.7	(-) 1*R*,2*S*[5d]
3 X=NMe_2		17.9	86.4	18.0	16.1	(-) 1*R*,2*S*[5d]
4 X=H		97.7	64.8	64.0	19.7	(+) 1*S*,2*R*[5d]
5		75.4	72.8	51.0	14.2	(+) 1*R*,2*S*[c,5d]
6		61.4	52.8	54.0	5.9	(-) 1*R*,2*R*[4c]
7		14.3	78.0	16.0	9.3	(-) 1*R*,2*S*[21]
8		37.0	71.0	34.0	8.4	(+) *R*[6h]
9		-	44.6	26.0 (yield)	-	(+) 1*S*,2*R*[d,22]
10		-	77.5	20.0 (yield)	-	(-) 1*R*,2*S*[5d]

[a] Conversion $C = 100 \times ee_A/(ee_A - ee_E)$. [b] Tentative assignment assuming that the 4-CN benzoate has the same sense of rotation as the other benzoates in this series (i.e. cf. entries 2−4). [c] Tentative assignment assuming that the benzoate has same sense of rotation as the corresponding 4-NMe_2 benzoate. [d] Tentative assignment assuming that the isobutyrate has the same sense of rotation as the corresponding acetate. [e] Conditions: $(i\text{-PrCO})_2O$ (2.0 mmol), Et_3N (0.75 mmol), (−)-**1** (1 mol %), toluene (2 mL), −78 °C, 9 h.

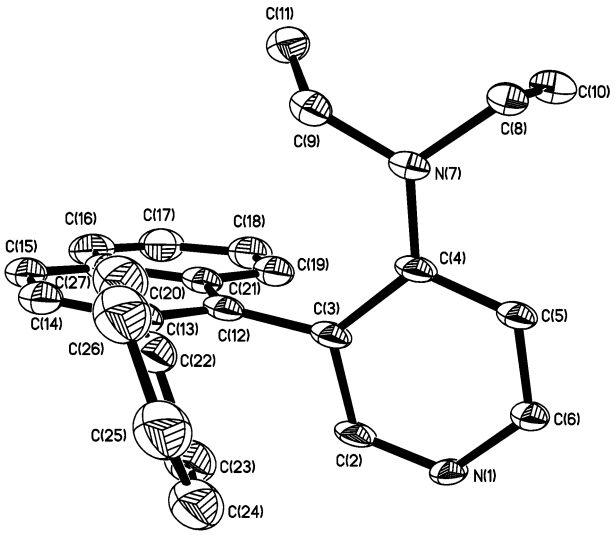


FIGURE 2. ORTEP drawing of the protonated biaryl (−)-(S_a)-**1** component of salt (S,S_a)-**9**.

described above, for the KR and ASD of a range of more structurally diverse *sec*-alcohols (Table 1).

The series of 4-substituted monobenzoates of *cis*-cyclohexane-1,2-diol were studied to probe the possible role of $\pi-\pi$ interactions in determining chirality transfer between the acylpyridinium species derived from catalyst **1** and these substrates (entries 1−4).[5d,7a,23] That these alcohols display selectivities ranging from 5.5 to 19.7 suggests that such interactions may be important, but no clear trend is evident given the switch in sense of induction between the unsubstituted benzoate (entry 4) and the rest of the series. The selectivities observed for this series exceed previous best values using organonucleophiles.[5d,7a,8c] The lower selectivity and reversed sense of induction of the monobenzoyl *cis*-cyclopentane-1,2-diol relative to its cyclohexane analogue (cf. entries 5 and 4) mirrors behavior found by Fuji with catalyst **IV** for which $\pi-\pi$ interactions were postulated.[5d,23] The levels of selectivity displayed by catalyst **1** with *trans*-2-phenylcyclohexanol and *trans*-1-bromo-2-hydroxycyclohexane (entries 6 and 7) are, however, modest compared to the levels exhibited by some other organonucleophiles,[6h] particularly catalyst **III** ($s = 160$ and 130, respectively[4d]). The KR of 1-cyclohexylethanol with $s = 8.4$ (entry 8) is noteworthy as alkyl alkyl *sec*-alcohols are generally poor substrates for enzymes. This value is similar to that achieved by Miller with a pentapeptide catalyst (cf. **V**, $s = 9.0$[6h]) and is slightly lower than the value obtained using catalyst **1** with 1-phenylethanol ($s = 13$[9e]), but with the same sense of induction. Finally, ASD of *meso*-

(21) King, S. B.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 5611−5612.

(22) Nicolosi, G.; Patti, A.; Piattelli, M.; Sanfilippo, C. *Tetrahedron: Asymmetry* **1994**, *5*, 283−8.

(23) Interestingly, although many of the catalysts studied by Campbell (e.g. structure **VI**, Figure 1) are topologically closely related to the catalyst of Fuji (structure **IV**, Figure 1), H-bonding was postulated to be the dominant mediator of chirality transfer for this series of catalysts and no evidence for $\pi-\pi$ stacking was found. See ref 7a.

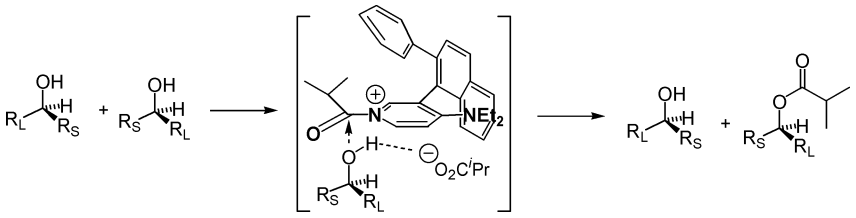


FIGURE 3. Transition state representation for KR using biaryl (−)-(S_a)-**1**/(*i*-PrCO)$_2$O and a *sec*-alcohol.

hydrobenzoin and *cis*-cyclohexane-1,2-diol (entries 9 and 10) proceeded with rather moderate efficiencies compared to analogous ASDs catalyzed by organonucleophiles **I** and **III** (97% ee at 65% yield,[2e] cf. entry 9, and 97% ee at 87% yield,[4e] cf. entry 10, respectively). It is noteworthy that nucleophilic catalysis appears to be advantageous for ASD of this type of substrate as chiral Lewis acid catalysts promote product racemization as the result of intramolecular acyl transfer.[24]

Inspection of Table 1 reveals that, with the exception of the *cis*-1,2-diol monobenzoates (entries 1−5), the alcohol stereoisomers that are preferentially esterified can be predicted on the basis of minimization of steric interactions in a simple transition-state representation (Figure 3).

This model envisages attack by the alcohol, orientated so as to minimize steric repulsion with both the naphthalene and the isopropyl groups, from the opposite face of the acylpyridinium ring to the phenyl substituent. This model also holds for the aryl alkyl *sec*-alcohols reported previously.[9e] The irregular selectivity exhibited by most of the *cis*-1,2-diol monobenzoates (entries 1−3 and 5) possibly results from the intervention of attractive $\pi-\pi$ interactions (vide supra), but real understanding awaits further investigations.

Conclusions

In summary, a new three-step synthesis and resolution of nucleophilic catalyst **1** suitable for large-scale preparations have been developed, and this catalyst has been shown to be effective for the KR and ASD of a range of *sec*-alcohol substrates. Work is ongoing to identify more selective catalysts and to further understand chirality transfer in these reactions.

Experimental Section

(3-Bromopyridin-4-yl)diethylamine 2. To a solution of (3,5-dibromopyridin-4-yl)diethylamine[9e] (153 mg, 0.5 mmol) in THF (1 mL) was added a solution of *i*-PrMgCl in THF (2 M, 300μL, 0.6 mmol) dropwise. The reaction mixture turned yellow and was stirred at room temperature for 3 h before being quenched with water (3.0 mL) and stirred for a further 14 h at room temperature. The resulting reaction mixture was extracted with CH_2Cl_2 (5 × 2 mL), the organic extracts dried ($MgSO_4$) and evaporated in vacuo to give light-yellow oil. Purification by flash chromatography (CH_2Cl_2/EtOAc, 1:1) gave 3-bromopyridine **2** as a yellow oil (71.3 mg, 62%): R_f 0.50 (CH_2Cl_2/EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, J = 7.0 Hz, 6H), 3.34 (q, J = 7.0 Hz, 4H), 6.81 (d, J = 7.0 Hz, 1H), 8.26 (d, J = 7.0 Hz, 1H) and 8.53 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 12.47, 45.08, 114.0, 115.6, 148.3, 153.7 and 155.2; FTIR (neat) ν_{max} 2976, 1578, 1483, 1019 cm^{-1}; MS (EI$^+$) *m*/*z* (rel intensity) 228 (37%, M$^+$) 213 (100) and 185 (59); HRMS (EI$^+$) calcd for $C_9H_{13}{}^{81}BrN_2$ (M$^+$) 230.0242, found 230.0245.

(±)-Diethyl-[3-(2-phenylnaphthalen-1-yl)pyridin-4-yl]-amine 1[9e] (route a). A mixture of (3-bromopyridin-4-yl)-diethylamine[9e] (38.2 mg, 0.17 mmol), arylboronic acid **3**[11a] (62.0 mg, 0.25 mmol, 1.5 equiv), K_3PO_4 (106 mg, 0.5 mmol, 3.0 equiv), $Pd_2(dba)_3$ (6.1 mg, 0.0067 mmol, 4 mol %), and 2-(9-phenanthryl)phenyldicyclohexylphosphine[11b] (7.2 mg, 0.016 mmol, 9.4 mol %) was placed in a Wheaton V-vial, toluene (1.5 mL) was added, and the vial was sealed. The reaction mixture was heated at 110 °C for 96 h and concentrated in vacuo, and the residue was purified by flash chromatography (EtOAc) to give 4-diethylaminopyridine (±)-**1**[9e] as a white solid (11.5 mg, 20%): R_f 0.25 (EtOAc); mp 124−125 °C (cf. lit.[9e] mp 124−125 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.53 (t, J = 6.0 Hz, 6H), 2.73 (m, 4H), 6.51 (d, J = 6.0 Hz, 1H), 7.05−7.23 (5H), 7.42−7.60 (3H), 7.84 (d, J = 8.0 Hz, 1H), 7.93 (m, 2H), 8.19 (s, 1H), 8.23 (d, J = 6.0 Hz, 1H).

4,4,5,5-Tetramethyl-2-(2-phenylnaphthalen-1-yl)[1,3,2]-dioxaborolane 5. To a solution of 1-bromo-2-naphthol (3 g, 13.4 mmol) in pyridine at 0 °C was added trifluoromethanesulfonic anhydride (2.70 mL, 16.1 mmol). The mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature and stirred for a further 3 h. The resulting mixture was partitioned between 2 M HCl (aq) and Et_2O, the organic layer was washed with two further portions of acid and then filtered through a thin pad of silica gel. The solvent was removed in vacuo to give 1-bromo-2-naphthyl triflate (4.60 g, 97%) as a yellow oil which was used without further purification.

To a solution of 1-bromo-2-naphthyl triflate (4.60 g, 13.0 mmol) in Et_2O (16 mL) was added $Pd_2(dba)_3$ (180 mg, 0.195 mmol), 1,3-bis(diphenylphosphino)propane (161 mg, 0.39 mmol), and LiBr (1.13 g, 13.0 mmol). The resulting mixture was stirred at room temperature for 5 min, then a solution of PhMgBr in Et_2O (3.0 M, 5.2 mL, 15.5 mmol) was added using a water bath to cool the mildly exothermic reaction. The mixture was then stirred at room temperature for 7 h, before quenching with methanol (1.5 mL) and filtering through a plug of silica gel with Et_2O and the solvent removed in vacuo to give 1-bromo-2-phenylnaphthalene as a yellow oil (3.68 g, 100%) which was used without further purification.

To a solution of 1-bromo-2-phenylnaphthalene (3.68 g, 13.0 mmol) in Et_2O (35 mL) at −78 °C was added a solution of *n*-BuLi in hexanes (2.5 M, 5.7 mL, 14.3 mmol) dropwise. After 15min at −78 °C, 2-isopropoxy-4,4,5,5-tetramethyl[1,3,2]-dioxaborolane (2.66 g, 14.3 mmol) was added in one portion. After 1 h at −78 °C, the mixture was allowed to warm to room temperature and stirred for a further 2 h. The resulting mixture was quenched with HCl in Et_2O (1.0M, 13.0 mL, 13.0 mmol) and stirred for 45 min at room temperature. The solvent was removed in vacuo to give an off white semisolid. Purification by flash chromatography (petrol/CH_2Cl_2, 2:1) gave the boronic ester **5** as a colorless solid (4.04 g, 94%): mp 52−53 °C; R_f 0.56 (petrol/CH_2Cl_2, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 12H), 7.36−7.70 (8H), 7.92 (m, 2H), 8.17 (d, J = 8.0 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.1 (4q), 84.1 (2s), 125.5 (d), 126.4 (d), 127.1 (d), 127.3 (d), 127.9 (d), 128.1 (d), 128.3 (d), 129.3 (d), 129.4 (d), 132.0 (s), 136.2 (s), 143.9 (s), 145.4 (s); FTIR (neat) ν_{max} 3056, 2978, 1312, 1134 cm^{-1}; MS-

(24) Trost, B. M.; Mino, T. *J. Am. Chem. Soc.* **2003**, *125*, 2410−2411.

(EI$^+$) *m/z* (rel intensity) 330 (67%, M$^+$), 214 (100%); HRMS (EI$^+$) calcd for $C_{22}H_{23}BO_2$ 330.1791, found 330.1786.

(±)-3-Bromo-4-chloro-5-(2-phenylnaphthalen-1-yl)-pyridine 6. To a solution of 3,5-dibromo-4-chloropyridine[9e] (3.90 g, 14.3 mmol) and 4,4,5,5-tetramethyl-2-(2-phenylnaphthalen-1-yl)[1,3,2]dioxaborolane **5** (6.13 g, 18.6 mmol) in benzene (100 mL) were added silver(I) carbonate (5.13 g, 18.6 mmol) and $Pd(PPh_3)_4$ (0.826 g, 0.72 mmol), and the resulting mixture was heated to reflux for 96 h. The reaction mixture was filtered, washed with water, and dried ($MgSO_4$), and then the solvent was removed in vacuo to give the crude product. Purification by flash chromatography (petrol−EtOAc/petrol, 1:20) gave dihalopyridine (±)-**6** as an off white solid (5.64 g, 80%): mp 118−119 °C; R_f 0.25 (EtOAc/petrol, 1:20); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.16−7.25 (5H), 7.32 (1H, d, J = 8.5 Hz), 7.46 (m, 1H), 7.54 (m, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H) 8.24 (s, 1H), 8.68 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 121.4 (s), 125.3 (d), 126.2 (d), 127.1 (d), 127.2 (d), 127.9 (d), 128.0 (2d), 128.3 (d), 129.1 (2d), 129.3 (d), 130.4 (s), 131.6 (s), 132.5 (s), 136.1 (s), 139.8 (s), 140.7 (s), 144.5 (s), 151.2 (d), 151.3 (d); FTIR (neat) ν_{max} 3057, 1494, 1395, 1200 cm^{-1}; MS(EI$^+$) *m/z* (rel intensity) 397 (25%, M$^+$(^{81}Br^{37}Cl)), 395 (100%, M$^+$(^{81}Br^{35}Cl or ^{79}Br^{37}Cl), 393 (77%, M$^+$(^{79}Br^{35}Cl); HRMS (EI$^+$) calcd for $C_{21}H_{13}N^{81}Br^{35}Cl$ 394.9899, found 394.9904.

4-Chloro-3-(2-phenylnaphthalen-1-yl)pyridine. To a solution of (±)-3-bromo-4-chloro-5-(2-phenylnaphthalen-1-yl)-pyridine **6** (1.50 g, 3.8 mmol) in THF (10 mL) was added dropwise at room temperature a solution of *i*-PrMgCl in THF (2.0M, 2.28 mL, 4.56 mmol). After stirring at room temperature for 2 h the resulting brown solution was treated with water (10 mL). The mixture was partitioned between water and CH_2Cl_2, the organic layer dried ($MgSO_4$), and the solvent removed in vacuo to give the crude product as a pale yellow solid. Purification by flash chromatography (EtOAc/petrol, 1:10) gave the 4-chloro-3-(2-phenylnaphthalen-1-yl)pyridine as an off white solid (1.18 g, 99%): mp 161−162 °C; R_f 0.10 (EtOAc/petrol, 1:20); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.13−7.28 (5H), 7.30−7.70 (5H), 7.95 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.5 Hz, 1H), 8.37 (s, 1H), 8.43 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 124.1 (d), 125.5 (d), 126.0 (d), 126.9 (2d), 127.9 (2d), 128.0 (d), 128.2 (d), 129.0 (d), 129.3 (2d), 130.6 (s), 131.9 (s), 132.5 (s), 134.4 (s), 139.9 (s), 140.9 (s), 144.6 (s), 149.2 (d), 153.1 (d); FTIR (neat) ν_{max} 3056, 1547, 1495, 1085 cm^{-1}; MS-(EI$^+$) *m/z* (rel intensity) 317 (33%, M$^+$(^{37}Cl)), 315 (100%, M$^+$(^{35}Cl); HRMS (EI$^+$) calcd for $C_{21}H_{14}N^{35}Cl$ 315.0815, found 315.0813.

(±)-Diethyl-[3-(2-phenylnaphthalen-1-yl)pyridin-4-yl]-amine 19e and diethyl-[5-(2-phenylnaphthalen-1-yl)pyridin-3-yl]amine 7 (route b). To a solution of 4-chloro-3-(2-phenylnaphthalen-1-yl)pyridine (2.75 g, 8.7 mmol) in THF (25 mL) was added diethylamine (9.0 mL, 87 mmol). A freshly prepared solution of lithium diethylamide in THF [prepared via addition of a solution of *n*-BuLi in hexanes (2.5 M, 7.2 mL, 18 mmol) to a solution of diethylamine (1.55 mL, 15 mmol) in THF (100 mL) at −78 °C followed by warming to 0 °C and stirring for 1 h] was then added at room temperature via cannula. The mixture was heated at reflux for 16 h then the solvent removed in vacuo. The residue was partitioned between CH_2Cl_2 and water, the organic layer dried ($MgSO_4$), and the solvent removed in vacuo. Purification of the residue by flash chromatography (EtOAc/petrol, 1:2 −EtOAc) gave the following.

4-Diethlyaminopyridine (±)-**1**[9e] as a white solid (0.92 g, 30%): Spectroscopic data as previously reported (above and ref 9e).

3-Diethylaminopyridine 7 as a white solid (1.91 g, 62%): R_f = 0.80 (EtOAc); mp 101−102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (t, J = 7.0 Hz, 6H), 3.25 (m, 4H), 6.67 (s, 1H), 7.12−7.27 (5H), 7.50 (m, 2H), 7.61 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.88 (s, 1H), 7.91−8.05 (4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.1 (2q), 44.2 (2t), 121.5 (d), 125.8 (d), 126.4 (2d), 126.5 (d), 127.8 (2d), 127.9 (d), 128.0 (d), 128.2 (d), 129.9 (2d), 130.2 (s), 132.6 (s), 132.7 (s), 132.8 (d), 134.6 (s), 138.7 (s), 138.9 (d), 141.6 (s), 142.9 (s); FTIR (neat) ν_{max} 3054, 2970, 1586; MS-(EI$^+$) *m/z* (rel intensity) 352 (10, M$^+$), 337 (22), 281 (100), 154 (50), 94 (30); HRMS (EI$^+$) calcd for $C_{24}H_{25}N_2$ (M$^+$) 352.1939, found 352.1930.

Resolution Protocol for Biaryl 1. A suspension of biaryl (±)-**1** (500 mg, 1.42 mmol) and *N*-Boc-*O*-benzyl-(*S*)-tyrosine (−)-**8** (527.5 mg, 1.42 mmol) in *i*-PrOH (4.95 mL) was heated to 75 °C for 0.5 h to furnish a clear solution. Heating was removed and the solution allowed to cool to room temperature naturally. After 14 h the precipitated solid was collected by suction and washed with the minimum of cold *i*-PrOH (ca. 20−30 mL at 5−10 °C). The resulting solid was dried in a vacuum oven at 40 °C for 4 h to yield the salt (*S*,*S*$_a$)-**9** (594 mg, 58%, 63% de by CSP-HPLC). Recrystallization of 500 mg of this salt from hot *i*-PrOH (2.4 mL) and isolation as above gave the salt (*S*,*S*$_a$)-**9** (350 mg, 70%, 96% de by CSP-HPLC). Recrystallization of 238 mg of this salt from hot *i*-PrOH (1.14 mL) and isolation as above gave the pure salt (*S*,*S*$_a$)-**9** (196 mg, 83%, >99.8% de by CSP-HPLC). This salt was dissolved in CH_2Cl_2/Et_3N (10:1, 3 mL), stirred for 14 h at room temperature, concentrated in vacuo, and passed through a plug of flash silica eluting with EtOAc to give biaryl (−)-(*S*$_a$)-**1** {95 mg, 34% from racemate, >99.8% ee by CSP-HPLC, $[\alpha]^{25}_D$ −124 (*c* 0.58 in $CHCl_3$)}. Spectroscopic data as previously reported (above and ref 9e).

The combined mother liquers from the initial crystallization and the first recrystallization were concentrated in vacuo to give salt (*S*,*R*$_a$)-**9** as a white gum (563 mg, 55%, 0.78 mmol, 74% de by CSP-HPLC). This gum was dissolved in CH_2Cl_2 (10 mL), and Et_3N (110 mL, 0.78 mmol) was added. The resulting solution was stirred for 14 h at room temperature, concentrated in vacuo, and passed through a plug of flash silica eluting with EtOAc to give biaryl (+)-(*R*$_a$)-**1** as a white powder (268 mg, 98%, 0.76 mmol, 74% ee by CSP-HPLC). A suspension of this biaryl **1** and *N*-Boc-*O*-benzyl-(*R*)-tyrosine (+)-**8** (282.5 mg, 0.76 mmol) in *i*-PrOH (2.66 mL) was heated to 75 °C for 1 h to furnish a clear solution. Heating was removed and the solution allowed to cool to room temperature naturally. After 14 h the precipitated solid was collected by suction and washed with the minimum of cold *i*-PrOH (ca. 10−15 mL at 5−10 °C). The resulting solid was dried in a vacuum oven at 40 °C for 4 h to yield the salt (*R*,*R*$_a$)-**9** (350 mg, 64%, 98% de by CSP-HPLC). Recrystallization of 290 mg of this salt from hot *i*-PrOH (1.39 mL) and isolation as above gave the pure salt (*R*,*R*$_a$)-**9** (260 mg, 90%, >99.8% de by CSP-HPLC). This salt was dissolved in CH_2Cl_2/Et_3N (10:1, 8 mL), stirred for 14 h at room temperature, concentrated in vacuo, and passed through a plug of flash silica eluting with EtOAc to give biaryl (+)-(*R*$_a$)-**1** {126 mg, 31% from racemate, >99.8% ee by CSP-HPLC, $[\alpha]^{25}_D$ +126 (*c* 0.57 in $CHCl_3$)}. Spectroscopic data as previously reported (above and ref 9e).

CSP-HPLC Assay Conditions. Salt (*S*,*S*$_a$)-**9** and biaryl (−)-(*S*$_a$)-**1** were analyzed using the same conditions and gave the same retention times, as did salt (*R*,*R*$_a$)-**9** and biaryl (+)-(*R*$_a$)-**1**. In the case of salts **9**, the *N*-Boc-*O*-benzyltyrosine is retained on the column under these conditions: Chiralcel OD 1.0 × 25 cm; hexane/EtOAc/Et_3N (80:19.6:0.4); 4.0 mL/min; temp = 30 °C; UV detection 254 nm (±10), Ref to 525 nm (±50); retention time: 9.6min (−)-(*S*$_a$)-**1**, 15.0min (+)-(*R*$_a$)-**1**.

General Procedure for Analytical-Scale Catalytic Acylative Kinetic Resolution/Asymmetric Desymmetrization (Table 1). A solution of (±)-alcohol (1.00 mmol), Et_3N (104 μL, 0.75 mmol), and biaryl (−)-(*S*$_a$)-**1** (3.5 mg, 10 μmol, >99.8% ee) in toluene (2.0 mL) was cooled to −78 °C. During vigorous stirring, (*i*-PrCO)$_2$O (331 μL, 2.00 mmol) was added dropwise over 3 min. After 9.0 h, the reaction mixture was quenched by dropwise addition of MeOH (5.0 mL) over 2 min. After 15 min at −78 °C and 15 min at room temperature, the solvents were evaporated in vacuo. For entries 1−8 (i.e. KRs) the alcohol and ester were separated by flash chromatography

and the enantiomeric excess for the unreacted alcohols and esters were established by analytical CSP-HPLC. For entries 9 and 10 (i.e. ASDs), the enantiomeric excess for the product ester was established directly by either analytical CSP-HPLC or GC (see Supporting Information).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for compounds **2** and **5**−**7**, details of the resolving agent screen and test crystallizations for optical resolution of biaryl **1**, X-ray data for salt **9**, HPLC analysis for Table 1, and results of acylative KR of 1-(1-naphthyl)ethanol with various acyl donors. This material is available free of charge via the Internet at http://pubs.acs.org.

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