Axially Chiral Analogues of 4-(Dimethylamino)pyridine: Novel Catalysts for Nonenzymatic Enantioselective Acylations

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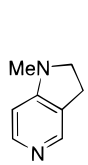
A concise seven-step synthesis of atropisomeric 3-aryl analogues of DMAP from 4-pyridone **8** has been developed. A representative compound of this class, biaryl (±)-**15**, has been resolved using CSP HPLC and shown to be an efficient nucleophilic catalyst for kinetic resolution of a series of secondary alcohols on both an analytical and preparative scale (stereoselectivity factors, $s = 8.9-29$).

Introduction

Recent years have witnessed an explosion of interest in the development of nonenzymatic nucleophilic catalysts for enantioselective acyl transfer.[1] As a result of these endeavors, a number of families of chiral nucleophilic catalysts have been discovered that offer practically useful levels of stereoselectivity in acylative kinetic resolution (KR)[2,3] and asymmetric desymmetrization[4] of alcohols,[5] as well as other transformations.[6] In particular, the results achieved with planar-chiral derivatives of 4-(dimethylamino)pyridine (DMAP) by Fu and co-workers,[5c,d,h,j,k] with proline-derived diamines by Oriyama and co-workers,[5f,p] and with chiral bicyclic phoshines by Vedejs and Daugulis[5m,o] represent significant milestones in the search for low-molecular-weight compounds that can serve as alternatives to enzymes in transformations amenable to nucleophilic catalysis.

Previously, we reported on a short synthetic approach toward a novel class of catalysts such as **3** and **4** incorporating 1-methyl-2-pyrrolino[3,2-*c*]pyridine **1** as a nucleophilic core.[7] Chirality of such compounds stems from restricted rotation about an aryl−aryl bond, and their configurational stability and high nucleophilicity have been unequivocally demonstrated. We now describe the results of our initial studies on catalytic kinetic resolution (CKR) of aryl alkyl carbinols in the presence of these and related axially chiral analogues of DMAP.[8]



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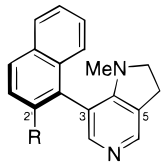

2: R = OTf
3: R = Me
4: R = Ph

Results and Discussion

Substituents *ortho* to the pyridyl nitrogen in DMAP derivatives strongly attenuate their catalytic activity in acyl transfer processes.[9] Cognizant of this, we designed catalysts **3** and **4** with stereogenic axes *meta* to their pyridyl nitrogen and lacking *ortho* substituents such that they retained the high nucleophilicity of parent amine **1**.[7b] Although this places the stereogenic element distant from the reactive center, we anticipated that it would allow rapid acyl transfer even when carrying out CKR at low temperature and that this, in turn, would be beneficial for enantiodiscrimination. Disappointingly, catalyst (+)-**3** showed low levels of enantioselectivity (stereoselectivity factor[10] $s = 1.3-1.5$ depending on

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‡ Single-crystal X-ray analysis.

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(10) s = (rate constant of fast-reacting enantiomer)/(rate constant of slow-reacting enantiomer).

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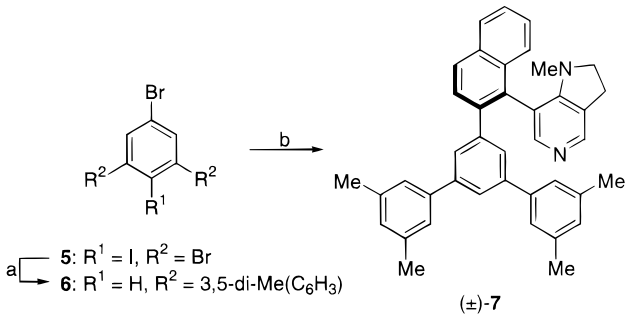
Scheme 1[a]

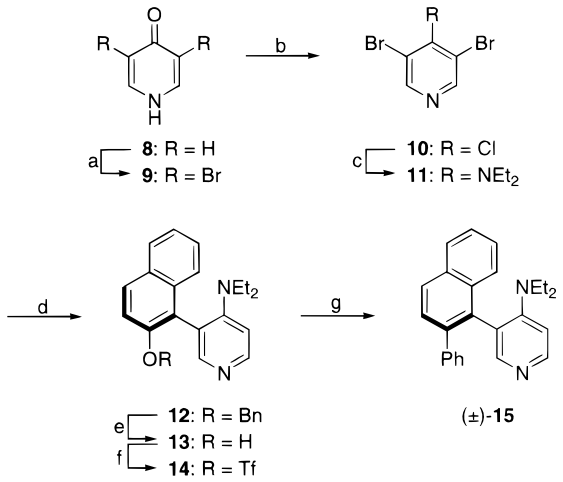


[a] Reagents and conditions: (a) 3,5-di-Me(C_6H_3)MgBr, THF, rt → reflux, 17 h; 37%; (b) i. Mg, I_2, Et_2O, THF, rt → reflux, 30 min; ii. **3**, $PdCl_2$(dppp), Et_2O, THF, reflux, 15 h; 19% (69% if based on recovered **3**).

solvent; see Supporting Information) in CKR of 1-phenylethanol. The results indicated, however, that the acyl transfer is reasonably fast (conversion, $C = 7.6-61.2\%$ after 2 h, depending on solvent) even at −78 °C. Similarly, catalyst (−)-**4** gave unsatisfactory levels of enantioselection ($s = 2.1$ at $C = 26.0\%$ in toluene after 2 h) in CKR of 1-phenylethanol. In an attempt to develop more selective catalysts it was initially assumed that the low levels of enantioselection observed for catalysts **3** and **4** could be attributed to insufficient differentiation between access to the two faces of the pyridine ring. If such differentiation is not secured, two enantiomeric nucleophiles (alcohols) may approach opposite faces of the acylpyridinium intermediates derived from DMAP-type catalysts **3** or **4** at comparable rates, thereby rendering KR ineffective. Molecular modeling studies[11] indicated that analogues of biaryls **3** and **4** incorporating sterically more demanding substituents at the 2′-position would provide more effective top-from-bottom differentiation for the incoming nucleophiles. These considerations led us to select biaryl **7**, possessing no additional stereogenic axes that would have complicated optical resolution, as the next catalyst candidate. Thus (Scheme 1), treatment of 2,4,6-tribromoiodobenzene **5**[12] with the Grignard reagent derived from 5-bromo-*m*-xylene according to the methodology of Hart et al.[13] gave aryl bromide **6**, which underwent Kharash-type cross-coupling via the corresponding arylmagnesium bromide with aryl triflate **2**[7b] to give racemic biaryl **7** in low yield. Optical resolution of biaryl (±)-**7** was performed using semipreparative CSP HPLC. Although biaryl **7** proved a more enantioselective catalyst than either biaryl **3** or **4**, giving $s = 4.7$ for CKR of 1-(1-naphthyl)ethanol, it still was not sufficient for practical applications (KRs giving $s > 7$ are regarded as practically useful because they guarantee at least a 20% recovery of the less reactive enantiomer with 99% ee).[2] Hence, further attempts to optimize the structure of the catalysts were undertaken.

Having addressed the issue of top-from-bottom differentiation in the design of biaryl **7**, we turned our attention to left-from-right differentiation on the more accessible face of such molecular systems. If the latter differentiation is not well-pronounced, two enantiomeric

Scheme 2[a]



[a] Reagents and conditions: (a) Br_2, KOH, H_2O, 0 °C, 1 h; (b) PCl_5, 160 °C, 3 h; 72% over two steps; (c) Et_2NH, $HCONEt_2$, 170 °C, 20 h; 94% (d) 2-(phenylmethoxy)-1-naphthaleneboronic acid, NaOH, $Pd(PPh_3)_4$, PhMe, H_2O, EtOH, reflux, 22 h; 59%; (e) H_2 (1 atm), Pd/C, EtOH, rt, 5 h; (f) Tf_2O, pyridine, 0 °C, 2 h; 76% over two steps; (g) PhMgBr, $PdCl_2$(dppp), Et_2O, reflux, 22 h; 93%.

nucleophiles (alcohols) may approach the more accessible face of a derived acylpyridinium intermediate with similar ease and with inevitable detriment to the outcome of CKR. As a consequence of this reasoning, we postulated that the substitution pattern in biaryls **3**, **4**, and **7**, in which both the 3- and 5-positions on the pyridine ring bear non-hydrogen substituents, did not secure a sufficiently high level of dissymmetry on the more accessible face of the pyridine ring. The above considerations led us to select biaryl **15** as the next catalyst candidate,[14] which was subsequently prepared in enantiomerically pure form. Thus (Scheme 2), 4-pyridone **8** was brominated according to a modified method of Tee and Paventi[15] to give dibromide **9**, which upon heating with PCl_5 was converted to trihalopyrdine **10**.[16] Heating in a sealed high-pressure tube with Et_2NH in the presence of *N*,*N*-diethylformamide furnished dibromoamine **11** in excellent yield. Suzuki cross-coupling[17] with 2-(phenylmethoxy)-1-naphthaleneboronic acid[7b] in the presence of NaOH gave biaryl **12** in moderate yield.[18] Catalytic hydrogenolysis furnished phenol **13**, which was treated with Tf_2O/pyridine to give aryl triflate **14**. A final Kumada−Corriu cross-coupling[19] with PhMgBr in the presence of $PdCl_2$(dppp) furnished racemic biaryl **15** in excellent yield. The synthetic approach described above is highly flexible, and by varying the secondary amine used in the

(11) Computer program: *CS Chem3D Pro*, version 4.0; Cambridge Soft Corp.: U.S., 1997.

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(14) Comparative atropisomerization kinetic studies for 3-aryl analogues of amine **1** and DMAP (ref 7b) indicated that biaryl **15** would be configurationally sufficiently stable at room temperature, enabling its optical resolution and convenient use in enantiopure form without any risk of racemization.

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(18) An analogous coupling in the presence of Na_2CO_3 instead of NaOH as base gives the 5-bromo derivative of biaryl **12** in a 30% yield. Further functionalization of the 5-position can open access to a variety of novel catalyst candidates. Suzuki cross-coupling of aryl dibromide **11** with sterically less demanding arylboronic acids (i.e., 1-naphthalene- or 3-methoxybenzeneboronic acid) affords the products of bis-coupling in high yield (74% and 97%, respectively).

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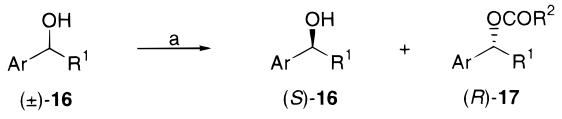
Table 1. Kinetic Resolution of Acohols 16 Catalyzed by Biaryl (−)-15[a]



(±)-**16** (*S*)-**16** (*R*)-**17**

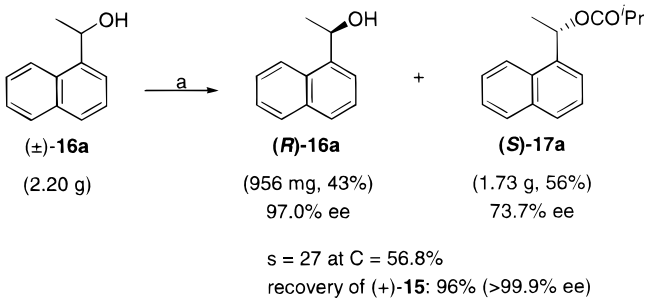
		(±)-**16**[b]					(*S*)-**16**	(*R*)-**17**		
entry	alcohol, ester	Ar	R^1	R^2 (mmol)[c]	solvent	time, h	ee_A, %[d]	ee_E, %[d]	*C*, %[e]	*s*[f]
1	**16a**, **17a$_1$**	1-naphthyl	Me	Me (0.75)	CH_2Cl_2	2.0	18.6	69.5	21.2	6.6
						6.3	43.1	63.7	40.3	6.8
2	**16a**, **17a$_1$**	1-naphthyl	Me	Me (0.75)	Et_2O	2.0	5.1	79.5	6.0	9.2
						7.6	14.6	77.1	15.9	8.9
3	**16a**, **17a$_1$**	1-naphthyl	Me	Me (0.75)	THF	2.0	2.9	74.9	3.7	7.2
						10.3	10.2	73.0	12.2	7.1
4	**16a**, **17a$_1$**	1-naphthyl	Me	Me (0.75)	PhMe	2.0	4.9	80.5	5.7	9.7
						7.3	17.5	77.4	18.5	9.3
5	**16a**, **17a$_1$**	1-naphthyl	Me	Me (2.0)	PhMe	2.0	14.2	77.1	15.5	8.9
						8.4	46.6	69.9	40.0	8.9
6	**16a**, **17a**	1-naphthyl	Me	^{i}Pr (2.0)	PhMe	2.0	18.6	89.3	17.2	21
						8.4	62.4	83.6	42.7	21
7	**16a**, **17a**	1-naphthyl	Me	^{i}Pr (2.0)	PhMe	9.0	69.2	84.1	45.1	24
8	**16a**, **17a**	1-naphthyl	Me	^{i}Pr (2.0)	EtOAc	9.3	76.1	70.9	51.8	13
9	**16b**, **17b**	Ph	Me	^{i}Pr (2.0)	PhMe	7.6	49.9	78.1	39.0	13
10	**16c**, **17c**	Ph	Et	^{i}Pr (2.0)	PhMe	9.7	43.1	79.2	35.2	13
11	**16d**, **17d**	Ph	^{i}Pr	^{i}Pr (2.0)	PhMe	10.1	29.8	72.7	29.1	8.4[g]
12	**16e**, **17e**	Ph	^{t}Bu	^{i}Pr (2.0)	PhMe	10.5	18.8	88.8	17.5	20
13	**16f**, **17f**	2-Me(C_6H_4)	Me	^{i}Pr (2.0)	PhMe	9.5	60.7	86.0	41.4	25
14	**16g**, **17g**	2-OMe(C_6H_4)	Me	^{i}Pr (2.0)	PhMe	12.1	40.2	81.5	33.0	15
15	**16h**, **17h**	2,6-di-Me(C_6H_3)	Me	^{i}Pr (1.0)	PhMe	8.0	21.3	90.7	19.0	25

[a] Key: (a) $(R^2CO)_2O$, Et_3N (0.75 mmol), solvent (2 mL), (−)-**15** (10 μmol, >99.9% ee), −78 °C. [b] Reactions were performed using 1.0 mmol of (±)-**16**. [c] The amount of acylating agent $(R^2CO)_2O$ used. [d] Established by CSP HPLC. [e] Conversion $C = 100 \times ee_A/(ee_A + ee_E)$. [f] See ref 2. [g] $s = 7.6$ in a duplicate run.

reaction with trihalopyridine **10** and the two organometallic partners used for construction of the 3-substituent (with or without further functionalization at the 5-position), a wide range of modified biaryl catalyst candidates can be conveniently prepared. The structure of biaryl **15** was confirmed by single-crystal X-ray analysis, and its optical resolution was performed using semipreparative CSP HPLC. A series of CKRs in the presence of catalyst **15** were carried out (Table 1). The solvent-effect studies (entries 1−4) in the CKR of alcohol **16a** using Ac_2O as acyl donor demonstrated that carrying out the reaction in toluene gives the best results ($s = 9.3-9.7$ vs 6.6−9.2 for other solvents tested). A 2.5-fold increase in the amount of Ac_2O used (entries 4 and 5) resulted in a ca. 2.5-fold initial acylation rate enhancement with a slight decrease in the *s* value observed (from 9.3−9.7 to 8.9). A remarkable increase in selectivity was observed (entries 5−7) when using $(^i PrCO)_2O$ in place of Ac_2O as acyl donor ($s = 8.9$ and 24, respectively). Using the optimized conditions, a series of secondary alcohols (entries 9−15) were subjected to CKR with good levels of selectivity ($s = 8.4-25$). Interestingly, in the series of 1-alkylphenylethanols **16b**−**e** (entries 9−12) the stereoselectivity factor initially *decreases* (entries 9−11) as the steric demand of the alkyl group *increases*, but the order changes (entries 11 and 12) for the most bulky alkyl group. The results obtained for a series of 1-arylethanols **16a**, **16b**, **16f**−**h** (entries 7, 9, and 13−15) indicate that the increase in *ortho*-substitution of the aryl group results in a marked increase in the stereoselectivity factor. Using a more polar solvent for carrying out CKR (entries 7 and 8), which widens the range of alcohols soluble at −78 °C, causes dramatic decrease (from 24 to 13) in the stereoselectivity factor.[20]

The catalytic system developed can be conveniently used for preparative-scale CKR. Thus (Scheme 3), KR of

Scheme 3[a]



[a] Reagents and conditions: (a) $(^i PrCO)_2O$ (3.2 mL, 19 mmol), Et_3N (1.3 mL, 9.6 mmol), PhMe (25 mL), (+)-**15** (45 mg, 0.13 mmol, >99.9% ee), −78 °C, 30 h.

alcohol **16a** using the **(+)-15**/$(^i PrCO)_2O$ catalytic system proceeded uneventfully to give optically highly pure alcohol **(*R*)-16a** along with enantiomerically significantly enriched ester **(*S*)-17a**. The process gives a quantitative overall yield of products and allows almost complete recovery of the enantiopure catalyst **(+)-15**. The ease of preparation of both enantiomers of catalyst **15** makes further CKR of enantiomerically enriched ester **(*S*)-17a**, after its saponification, an attractive option (i.e., so-called "double CKR").[21]

Table 2 details the results of comparative studies on CKR of 1-(1-naphthyl)ethanol via isobutyrylation in the presence of all four biaryl DMAP analogues. Catalyst **3** is essentially unselective, whereas catalyst **4** confers selectivity higher than that of catalyst **7**.[22] The marked difference in selectivity ($s = 7.6$ vs 29) observed for

(20) Low solubility in toluene at −78 °C prevented the use of benzoic anhydride as an acylating agent. Similarly, some alcohols, such as **16** [Ar = 2,6-di-OMe(C_6H_3), R^1 = Me], were not sufficiently soluble at −78 °C for CKR to be carried out.

Table 2. Kinetic Resolution of Alcohol 16a by Isobutyrylation in the Presence of Biaryl DMAP Derivatives[a]

entry	catalyst	(*R*)-16a ee_A, %[b]	(*S*)-17a ee_E, %[b]	*C*, %[c]	s[d]
1	(+)-**3**	1.9	1.7	53.4[e]	1.1
2	(+)-**4**	87.7	48.0	64.6	7.6
3	(+)-**7**	37.8	44.3	46.0	3.7
4	(+)-**15**	26.3	91.4	22.3	29

[a] Reaction conditions: $(^iPrCO)_2O$ (1.0 mmol), Et_3N (0.75 mmol), (±)-**16a** (1.0 mmol), PhMe (2 mL), catalyst (10 μmol, >99.9% ee), −78 °C, 8 h. [b] Established by CSP HPLC. [c] Conversion $C = 100 \times ee_A/(ee_A + ee_E)$. [d] See ref 2. [e] Established by ^1H NMR.

catalysts **4** and **15**, respectively, probably reflects the degree of dissymmetry on the more accessible face of the pyridine ring, with the difference in substitution at the 5-position (ring CH_2 vs H) being most crucial.

Conclusions

In summary, a short and general synthesis of atropisomeric 3-aryl analogues of DMAP from commercially available and inexpensive 4-pyridone **8** has been developed. A representative compound of this novel class of nucleophilic catalysts, biaryl **15**, has been shown to be an efficient catalyst in CKR of a series of secondary alcohols via acylation with achiral anhydrides. The ease of preparation and both chiral and chemical stability of biaryl **15** and its congeners render such compounds attractive catalysts for various nucleophile-catalyzed transformations. Structure-selectivity optimization studies aimed at developing yet more effective catalysts and elucidating the origin of the enantiodiscrimination are ongoing, and results of these studies will be reported shortly.

Experimental Section

General Methods. The methods described previously were applied.[7b] CSP HPLC analyses were performed on Diacel columns: Chiralcel OD (4.6 mm × 25 cm) for alcohols **16a**−**e**, Chiralcel OB (4.6 mm × 25 cm) for alcohols **16f,g** and Chiralpak AD (4.6 mm × 25 cm) for alcohol **16h** using conditions described elswhere.[5o,23]

1,5-Bis(3,5-dimethylphenyl)-3-bromobenzene (6). To a mixture of Mg (4.6 g, 0.19 mol) and a crystal of I_2 in THF (250 mL) was added 5-bromo-*m*-xylene (29.0 g, 0.157 mol) over 40 min. To remove the excess magnesium, the resulting arylmagnesium bromide solution was transferred via cannula to another flask and treated with a solution of 2,4,6-tribromoiodobenzene **5**[12] (13.8 g, 31.4 mmol) in THF (100 mL) over 30 min. After 15 h at room temperature, the mixture was refluxed for 2 h, cooled in an ice bath, and quenched with 1 M HCl (200 mL). The reaction mixture was then extracted with CH_2Cl_2, and the combined extracts were dried ($MgSO_4$) and evaporated in vacuo to give a white solid. Purification by flash chromatography (petroleum ether), followed by crystallization from EtOAc/EtOH, gave the title compound **6** (4.22 g, 37%) as a white solid: $R_f = 0.30$ (petroleum ether); mp 145.0−146.5 °C (EtOAc/EtOH); ^1H NMR (250 MHz, $CDCl_3$) δ 2.28 (s, 12H), 6.91 (s, 2H), 7.11 (s, 4H), and 7.56 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.50, 123.1, 124.9, 125.2, 128.8, 129.7, 138.5, 139.9, and 143.9; IR ($CHCl_3$) ν_{max} 1593 and 1560 cm^{-1}; MS (EI^+) *m*/*z* (rel intensity) 366/364 (100%, M^+); HRMS calcd for $C_{22}H_{21}Br$ (M^+) 364.0827, found 364.0817.

7-{2-[3,5-Bis(3,5-dimethylphenyl)phenyl]naphthyl}-1-methyl-2-pyrrolino-[3,2-*c*]pyridine (7). To a suspension of aryl bromide **6** (566 mg, 1.55 mmol) and Mg (57 mg, 2.3 mmol) in Et_2O (5 mL) and THF (2 mL) was added a crystal of I_2, and the mixture was gently heated to initiate the reaction. The resulting arylmagnesium bromide was transferred via syringe to a solution of aryl triflate **2**[7b] (316 mg, 0.78 mmol) and $PdCl_2$-(dppp) (23 mg, 39 μmol) in Et_2O (2 mL). The resulting brown solution was stirred at room temperature for 1 h and refluxed for 15 h. After cooling to room temperature, the reaction mixture was quenched with water (10 mL) and extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2) to give the recovered starting material **2** (183 mg, 58%) along with the title compound **7** (80 mg, 19%) as a yellow oil. Biaryl **7**: $R_f =$ 0.55 (EtOAc/Et_3N, 95/5); ^1H NMR (250 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.38 (s, 12H), 2.92−3.18 (m, 2H), 3.44−3.52 (m, 2H), 6.99 (s, 2H), 7.11 (s, 4H), 7.41−7.67 (m, 6H), 7.70 (d, $J = 8.5$ Hz, 1H), 7.81 (s, 1H), 7.95 (m, 1H), 7.99 (d, $J = 8.5$ Hz, 1H), and 8.02 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.45, 25.69, 34.97, 55.48, 114.4, 124.6, 125.2, 126.0, 126.7, 127.0, 127.5, 128.0, 128.1, 128.5, 129.0, 132.1, 132.5, 133.9, 138.2 (2C?), 139.7, 141.3, 141.5, 142.0, 142.7, 151.7, and 156.6; IR ($CHCl_3$) ν_{max} 2922 and 1593 cm^{-1}; MS (EI^+) *m*/*z* (rel intensity) 544 (60%, M^+) and 277 (100); HRMS calcd for $C_{40}H_{36}N_2$ (M^+) 544.2853, found 544.2878.

Optical Resolution of Biaryl (±)-7. The enantiomers of biaryl **7** were separated using semipreparative CSP HPLC (Chiralcel OD column, 1 cm × 25 cm; hexanes/EtOAc/Et_2NH, 75/24/1; 3 mL min^{-1}; 25 °C). UV detection was performed at 250 nm. Injections of ∼2 mg of the racemate in 30 μL of CH_2Cl_2 were made every 11 min. The enantiomer (−)-**7** was collected from 8.3 to 9.5 min, and the enantiomer (+)-**7** was collected from 12.9 to 14.2 min. The enantiomer (+)-**7** was repurified using the same HPLC conditions with the product collected from 12.6 to 15.1 min. The enantiomers were further purified by flash chromatography (EtOAc) to give final products as clear oils. Analytical CSP HPLC revealed >99.9% ee for both the levorotatory $\{[\alpha]^{25}_D -142$ (*c* 0.90 in $CHCl_3)\}$ and the dextrorotatory $\{[\alpha]^{25}_D +141$ (*c* 0.90 in $CHCl_3)\}$ enantiomer.

3,5-Dibromo-4-chloropyridine (10). The dibromination of 4-pyridone **8** was carried out according to a modified method of Tee and Paventi.[15] Thus, to an ice-cooled and mechanically stirred solution of 4-pyridone **8** (34.9 g, 0.367 mol) and KOH (41.2 g, 0.736 mol) in water (700 mL) was added Br_2 (37.9 mL, 0.735 mol) dropwise over 30 min. After an additional 30 min, the white precipitate was filtered off, washed with a copious amount of water, and dried in vacuo to give the crude dibromide **9** (79.0 g, 85%), which was used in the next step without further purification. Thus, a mixture of dibromide **9** (79.0 g, 0.312 mol) and PCl_5 (79 g, 0.38 mol) was heated at 160 °C for 3 h.[16] The reaction mixture was cooled to 0 °C and quenched by slow addition of water (200 mL). The resulting precipitate was crushed, filtered off, washed with water, and transferred onto the top of a flash silica column, which was then eluted with CH_2Cl_2. The crude product thus obtained was crystallized from EtOH to give the title compound **10** (73.9 g, 72%) as white needles: $R_f = 0.60$ (CH_2Cl_2); mp 95.0−96.5 °C (EtOH) (lit.[16] 98.0−98.5 °C); ^1H NMR (250 MHz, $CDCl_3$) δ 8.65 (s); ^{13}C NMR (63 MHz, $CDCl_3$) δ 121.8, 144.0, and 150.9; IR ($CHCl_3$) ν_{max} 1549, 1524, 1410, and 1394 cm^{-1}; MS (EI^+) *m*/*z* (rel intensity) 271 (100%, M^+) and 192 (30); HRMS calcd for $C_5H_2Br_2ClN$ (M^+) 268.8242, found 268.8231.

(3,5-Dibromo(4-pyridyl))diethylamine (11). A mixture of trihalopyridine **10** (18.8 g, 70.0 mmol), Et_2NH (21.7 mL, 0.210 mol), and *N*,*N*-diethylformamide (35 mL) was heated in a sealed high-pressure tube at 170 °C for 20 h. The reaction mixture was cooled to room temperature, dissolved in EtOAc (300 mL), and washed with 1 M K_2CO_3 (200 mL) and water (8 × 200 mL). The organic layer was dried ($MgSO_4$) and evapo-

(21) For KR of partially enriched compounds and "double" KR, see: (a) Horeau, A. *Tetrahedron* **1975**, *31*, 1307−1309. (b) Brandt, J.; Jochum, C.; Ugi, I.; Jochum, P. *Tetrahedron* **1977**, *33*, 1353−1363. (c) Brown, S. M.; Davies, S. G.; deSousa, J. A. A. *Tetrahedron: Asymmetry* **1991**, *2*, 511−514.

(22) This order for catalysts **4** and **7** was reversed in KRs involving Ac_2O as acyl donor.

(23) Toda, F.; Tohi, Y. *J. Chem. Soc., Chem. Commun.* **1993**, 1238−1240.

rated in vacuo to give a brown oil. Purification by flash chromatography (CH_2Cl_2) gave the title compound **11** (20.3 g, 94%) as a yellow oil: $R_f = 0.45$ (CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.01 (t, $J = 7.0$ Hz, 6H), 3.26 (q, $J = 7.0$ Hz, 4H), and 8.49 (s, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.10, 46.05, 122.9, 151.9, and 154.1; IR ($CHCl_3$) ν_{max} 2976, 1553, 1457, 1167 cm^{-1}; MS (EI$^+$) *m*/*z* (rel intensity) 308 (15%, M$^+$), 193 (100), and 264 (30); HRMS calcd for $C_9H_{12}Br_2N_2$ (M$^+$) 305.9367, found 305.9366.

Diethyl{3-[2-(phenylmethoxy)naphthyl](4-pyridyl)}-amine (12). To a solution of aryl dibromide **11** (5.13 g, 16.7 mmol) in toluene (100 mL) and ethanol (5 mL) was added 2 M NaOH (30 mL) followed by $Pd(PPh_3)_4$ (965 mg, 0.835 mmol) and 2-(phenylmethoxy)-1-naphthaleneboronic acid[7b] (5.56 g, 20.0 mmol). The mixture was refluxed with vigorous stirring for 22 h, cooled to room temperature, and diluted with water (100 mL). The phases were separated, and the extraction was completed with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo to give a brown oil. The residue was purified by flash chromatography ($CH_2Cl_2 \rightarrow$ EtOAc) to give the title compound **12** (3.77 g, 59%) as a yellow oil: $R_f = 0.25$ (EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.70 (t, $J = 7.0$ Hz, 6H), 2.85−3.06 (m, 4H), 5.15 (s, 2H), 6.79 (d, $J = 6.0$ Hz, 1H), 7.20−7.44 (m, 9H), 7.75−8.07 (m, 2H), 8.07 (s, 1H), and 8.31 (d, $J = 6.0$ Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 12.36, 44.83, 70.86, 111.0, 115.0, 120.3, 123.3, 123.9, 125.5, 126.5, 126.8, 127.7, 127.9, 128.4, 129.2, 129.4, 133.2, 137.3, 148.6, 153.1, 153.6, and 155.3; IR ($CHCl_3$) ν_{max} 2979, 1587, 1505, and 1271 cm^{-1}; MS (EI$^+$) *m*/*z* (rel intensity) 382 (15%, M$^+$) and 277 (100); HRMS calcd for $C_{26}H_{26}N_2O$ (M$^+$) 382.2045, found 382.2041.

1-[4-(Diethylamino)-3-pyridyl]-2-naphthyl (trifluoromethyl)sulfonate (14). A solution of benzyl ether **12** (3.48 g, 9.10 mmol) in EtOH (120 mL) was hydrogenated under normal pressure in the presence of 10% Pd/C (1.0 g) for 9 h (TLC). The reaction mixture was filtered through a thin pad of Celite and evaporated in vacuo to give a crude phenol **13** (2.60 g), which was dissolved in pyridine (30 mL) and treated at 0 °C with Tf_2O (1.70 mL, 10.0 mmol). After 2 h, the solvent was evaporated in vacuo, and the residue was partitioned between CH_2Cl_2 and water. The phases were separated and the extraction was completed with additional portions of CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and evaporated in vacuo to give a brown oil. Purification by flash chromatography ($CH_2Cl_2 \rightarrow$ EtOAc) gave the title compound **14** (2.94 g, 76%) as a yellow oil: $R_f = 0.50$ (EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.77 (t, $J = 7.0$ Hz, 6H), 2.77−3.02 (m, 4H), 6.85 (d, $J = 6.0$ Hz, 1H), 7.45−7.59 (m, 3H), 7.77 (d, $J = 5.5$ Hz, 1H), 7.92−7.95 (m, 2H), 8.14 (s, 1H), and 8.38 (d, $J = 6.0$ Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 12.19, 44.87, 112.1, 117.8, 118.3 (q, $J = 320$ Hz), 119.6, 126.5, 127.2, 127.9, 128.4, 129.4, 130.3, 132.7, 132.8, 144.8, 150.1, 153.6, and 155.6; IR ($CHCl_3$) ν_{max} 2978, 1585, 1500, 1421, and 1142 cm^{-1}; MS (EI$^+$) *m*/*z* (rel intensity) 424 (20%, M$^+$), 291 (100), 259 (90), and 219 (45); HRMS calcd for $C_{20}H_{19}F_3N_2O_3S$ (M$^+$) 424.1071, found 424.1068.

(±)-Diethyl[3-(2-phenylnaphthyl)(4-pyridyl)]amine (15). To a solution of triflate **14** (193 mg, 0.45 mmol) in Et_2O (3 mL) was added $PdCl_2$(dppp) (13 mg, 22 μmol), followed by PhMgBr (300 μL, 3.0 M, 0.90 mmol) in Et_2O. The mixture was refluxed for 16 h, cooled to room temperature, quenched with water (10 mL), and extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and evaporated in vacuo to give a brown oil. Purification by flash chromatography (CH_2Cl_2/EtOAc, 3/1 → EtOAc) gave the title compound **15** (147 mg, 93%) as a white solid: $R_f = 0.25$ (EtOAc); mp 124−125 °C ($CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.52 (t, $J = 7.0$ Hz, 6H), 2.55−2.88 (m, 4H), 6.50 (d, $J = 6.0$ Hz, 1H), 7.09−7.18 (m, 5H), 7.41−7.56 (m, 3H), 7.82−7.94 (m, 3H), 8.18 (s, 1H), and 8.22 (d, $J = 6.0$ Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 12.07, 44.56, 111.7, 122.9, 126.0, 126.4, 126.6 (2C), 127.6, 128.1 (2C), 128.6, 129.6, 132.4, 133.1, 134.0, 138.8, 141.7, 148.7, 154.3, and 155.0; IR ($CHCl_3$) ν_{max} 2976, 1586, and 1496 cm^{-1}; MS (EI$^+$) *m*/*z* (rel intensity) 352 (70%, M$^+$), 337 (100), 231 (65), and 77 (60); HRMS calcd for $C_{25}H_{24}N_2$ (M$^+$) 352.1930, found 352.1939.

Optical Resolution of Biaryl (±)-15. The enantiomers of biaryl **15** were separated using semipreparative CSP HPLC (Chiralcel OD column, 1 cm × 25 cm; hexanes/EtOAc/Et_2NH, 80/19.2/0.8; 4 mL min^{-1}; 30 °C). UV detection was performed at 250 nm. Injections of ∼7 mg of the racemate in 70 μL of CH_2Cl_2 were made every 12 min. The enantiomer (−)-**15** was collected from 8.7 to 10.1 min, and the enantiomer (+)-**15** was collected from 13.3 to 15.9 min. The enantiomer (+)-**15** was repurified using the same column (hexanes/EtOAc/Et_2NH, 75/24/1; 4 mL min^{-1}; 30 °C) with the product collected from 11.2 to 13.8 min. The enantiomers were further purified by flash chromatography (EtOAc) to give final products as white solids [mp 105−106 °C ($CHCl_3$)]. Analytical CSP HPLC revealed >99.9% ee for both the levorotatory {$[\alpha]^{25}_D$ −124 (*c* 0.58 in $CHCl_3$)} and the dextrorotatory {$[\alpha]^{25}_D$ +126 (*c* 0.57 in $CHCl_3$)} enantiomer.

1-(2,6-Dimethylphenyl)ethan-1-ol (16h). To a mixture of Mg (875 mg, 36.0 mmol) and a crystal of I_2 in THF (40 mL) was added a solution of 2-bromo-*m*-xylene (5.13 g, 27.7 mmol) in THF (10 mL) over 30 min. To initiate the reaction, the mixture was gently heated during initial stages of the addition. The resulting arylmagnesium bromide solution was cooled in an ice bath and treated with acetaldehyde (2.3 mL, 42 mmol). After 4 h at room temperature and 1 h at reflux, the reaction mixture was cooled in an ice bath, quenched with 1 M HCl (50 mL), and extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and evaporated in vacuo to give a brown oil. Purification by flash chromatography (petroleum ether/CH_2Cl_2, 1/1 → CH_2Cl_2), followed by distillation under reduced pressure, gave the title compound **16h** (2.50 g, 60%) as a pale yellow solid: $R_f = 0.30$ (CH_2Cl_2); mp 68−69 °C (hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.52 (d, $J = 6.5$ Hz, 3H), 2.14 (s, 1H), 2.45 (s, 6H), 5.36 (q, $J = 6.5$ Hz, 1H), and 6.98−7.09 (m, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.68, 21.41, 67.59, 126.9, 129.4, 135.7, and 140.6; IR ($CHCl_3$) ν_{max} 3609, 1470, 1258, and 1066 cm^{-1}; MS (EI$^+$) *m*/*z* (rel intensity) 150 (35%, M$^+$), 135 (100), 107 (75), and 91 (65); HRMS calcd for $C_{10}H_{14}O$ (M$^+$) 150.1038, found 150.1045.

General Procedure for Analytical-Scale Catalytic Kinetic Resolution. CKR of Alcohol (±)-16a (Table 1, entry 6). A solution of (±)-1-(1-naphthyl)ethanol **16a** (172 mg, 1.00 mmol), Et_3N (104 μL, 0.75 mmol), and catalyst (−)-**15** (3.5 mg, 10 μmol, >99.9% 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 2.0 h at −78 °C, ∼1 mL of the reaction mixture was removed rapidly via syringe, added to MeOH (2 mL), and stirred at room temperature for 15 min. The solvents were then evaporated in vacuo and alcohol **16a** and ester **17a** were separated by flash chromatography (petroleum ether/CH_2Cl_2, 1/1 → CH_2Cl_2). After 8.4 h, the remainder of the reaction was quenched by a dropwise addition of MeOH (3 mL) over 2 min. After 15 min at −78 °C and 15 min at room temperature, the solvents were evaporated in vacuo, and alcohol **16a** and ester **17a** were separated as described above. The esters **17a** obtained from the two aliquots were hydrolyzed by heating to reflux in 5% NaOH/MeOH (2 mL) for 5 min.[5o] After evaporation of the solvent, the residue was passed through a short flash silica column eluted with EtOAc. The enantiomeric excess for the unreacted alcohols **16a** and the alcohols obtained by the ester saponification (**17a** → **16a**) was established by analytical CSP HPLC (Chiralcel OD column, 1 cm × 25 cm; hexanes/2-propanol, 90/10; 1 mL min^{-1}; 30 °C). The results are given in Table 1.

Preparative-Scale Catalytic Kinetic Resolution of 1-(1-Naphthyl)ethanol (±)-16a. To a solution of alcohol (±)-**16a** (2.20 g, 12.8 mmol), triethylamine (1.3 mL, 9.6 mmol), and catalyst (+)-**15** (45 mg, 0.13 mmol) in toluene (25 mL) was added dropwise isobutyric anhydride (3.2 mL, 19 mmol) at −78 °C. The reaction mixture was stirred at this temperature for 30 h and quenched by a slow addition of methanol (10 mL). After an additional 15 min at −78 °C, the reaction mixture was allowed to warm to room temperature, and the solvents were evaporated in vacuo. The residue was dissolved in CH_2Cl_2 and washed with 1 M K_2CO_3 and brine. The organic layer was concentrated in vacuo, and the residue was purified by

flash chromatography (CH_2Cl_2/petroleum ether, 1/1 → CH_2Cl_2 → EtOAc) to give ester **(*S*)-17a** (1.73 g, 56%) as a pale yellow oil, alcohol **(*R*)-16a** (956 mg, 43%) as a colorless oil, and catalyst **(+)-15** (43 mg, 96%) as a colorless oil. Ester **(*S*)-17a**: R_f = 0.45 (petroleum ether/CH_2Cl_2, 1/1); $[\alpha]^{25}_D$ −29.3 (*c* 1.1 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.22 (d, *J* = 7.0 Hz, 3H), 1.26 (d, *J* = 7.0 Hz, 3H), 1.74 (d, *J* = 6.5 Hz, 3H), 2.67 (dq, *J* = 7.0, 7.0 Hz, 1H), 6.70 (q, *J* = 6.5 Hz, 1H), 7.47−7.60 (m, 3H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 6.0 Hz, 1H), 7.90 (~d, *J* = 7.5 Hz, 1H), and 8.14 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.05, 21.76, 34.30, 69.21, 123.2, 123.3, 125.4, 125.7, 126.3, 128.4, 129.0, 130.4, 133.9, 137.7, and 176.4; IR ($CHCl_3$) ν_{max} 1725 cm^{-1}; MS (EI$^+$) *m*/*z* (rel intensity) 242 (45%, M^+) and 155 (100); HRMS calcd for $C_{16}H_{18}O_2$ (M^+) 242.1317, found 242.1307. Alcohol **(*R*)-16a**: R_f = 0.25 (CH_2Cl_2); $[\alpha]^{25}_D$ +64.5 (*c* 1.1 in $CHCl_3$), $[\alpha]^{25}_D$ +77.2 (*c* 1.1 in MeOH) {lit.[24] $[\alpha]^{20}_D$ +78 ± 2 (*c* 1.0 in MeOH)}. A small sample of ester **(*S*)-17a** was hydrolyzed with 5%NaOH in MeOH,[5o] and the resulting alcohol was analyzed by CSP HPLC (Chiralcel OD; hexanes/2-propanol 90/10, 1 mL min^{-1}, 35 °C), which showed an enantiomeric excess of 73.7%. Alcohol **(*R*)-16a** was analyzed by the same method, and its enantiomeric excess was shown to be 97.0%. This corresponds to stereoselectivity factor *s* = 26.8 at 56.8% conversion. The recovered catalyst **(+)-15** was shown to retain its optical purity (>99.9% ee) by CSP HPLC analysis (Chiralcel OD; hexanes/ethyl acetate/diethylamine 80/19.2/0.8, 1 mL min^{-1}, 20 °C).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for all compounds, single-crystal X-ray data and ORTEP for compound **15**, and selected CKR experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Fluka *Laboratory Chemicals and Analytical Reagents* catalogue, 1999−2000, p 980, product number 70692.