A New Nucleophilic Catalyst for Kinetic Resolution of Racemic *sec*-Alcohols

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A new tertiary amine-based nucleophilic catalyst, derived from a simple combination of commercially available compounds, affords good to excellent kinetic resolution of racemic *sec*-alcohols.

In recent years, remarkable advances have been made in the development of chiral nucleophilic catalysts for the kinetic resolution of racemic alcohols via acylations. Fu,[1] Fuji,[2] Oriyama,[3] Spivey,[4] and others[5] designed and synthesized tertiary amine-based nucleophilic catalysts, with which the kinetic resolution of racemic alcohols has been successfully achieved. On the other hand, Vedejs[6] reported that chiral phosphines could also serve as efficient nucleophilic catalysts for the enantioselective acylation of racemic alcohols. However, there are still some limitations for practical applications of these catalysts, and continued efforts are required for the development of a synthetically more accessible catalyst that can efficiently resolve racemic compounds. Herein we report a new, easily prepared tertiary amine-based nucleophilic catalyst **1** that gives good to excellent resolution of racemic alkylarylcarbinols.

The catalyst **1** consists of three basic components: 4-(*N*,*N*-dimethylamino)pyridine (DMAP) as a catalytic component, binaphthyl as a chiral segment, and Kemp's triacid[7] as a linker. The chiral binaphthyl unit could be tethered to either the 2-(*ortho*) or 3-position (*meta*) of the DMAP. We here chose the *meta* position because the *ortho* substitution may deteriorate the catalytic activity due to the resulting steric congestion around the nitrogen where acyl-transfer actually occurs. The divergent relationship between the *meta* position and the ring nitrogen of the DMAP requires a specific linker molecule that can effectively bring the chiral environment into close proximity with the reaction site. Molecular modeling suggests that Kemp's triacid would be an ideal molecule for this purpose. The energy-minimized structure of the catalyst **1**, obtained by a Monte Carlo search, is shown in Figure 1. It should be noted that by rotating the C (*meta* in DMAP)-N (imide) bond in **1**, the dimethylamino group of the DMAP is placed away from the neighboring binaphthyl unit to avoid otherwise severe steric repulsion between two groups. Consequently, the ring nitrogen atom is completely surrounded by the dissymmetric binaphthyl moiety.

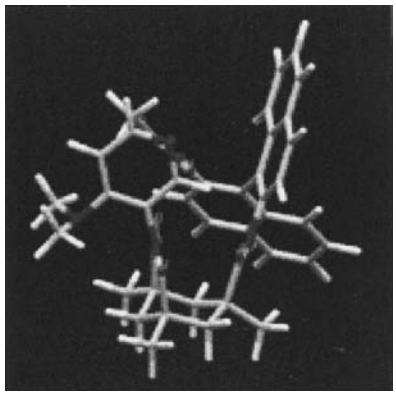
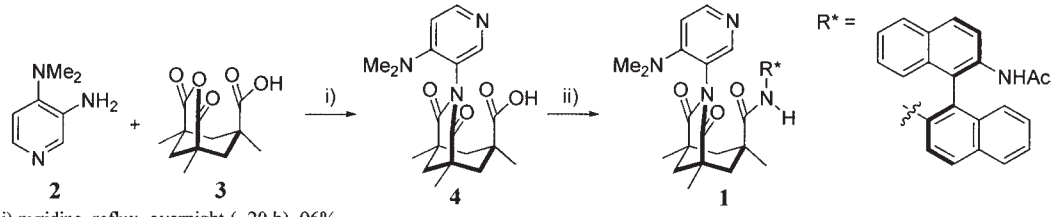


Figure 1. Energy-minimized structure of **1** obtained by a Monte Carlo search using MacroModel 5.5 (MM3 force field).

Synthesis of the catalyst **1** is straightforward and outlined in Scheme 1. 3-Amino-DMAP **2** and anhydride acid **3** were heated at reflux in pyridine to give DMAP-imide acid **4** (96%). After activation of **4** with oxalyl chloride, coupling with (*S*)-(−)-1,1′-binaphthyl-2,2′-diamine (47%), followed by acetylation (67%) with acetic anhydride, gave the nucleophilic catalyst **1**.[8]

We first examined the kinetic resolution of 1-phenylethanol (0.3 M) in various conditions with the catalyst **1** (1 mol%) and acetic anhydride (0.1–0.2 equiv).[9] The enantioselectivity strongly depends on solvent; in dichloromethane, benzene, toluene, tetrahydrofuran, and dimethoxyethane, selectivity factors[10] (s = rate constant of fast-reacting enantiomer/rate constant of slow-reacting enantiomer) are 1.4–2.1, while in *tert*-amyl alcohol $s = 6.2$ (0 °C, 7% conversion).[11] In addition, owing to a small extent of the background reaction that occurs without the catalyst **1**, the s values slightly depend on other factors such as the amounts of acetic anhydride and catalyst, temperature, and added bases. General trends are as follows. First, s values increased with increasing mol% of catalyst **1**, but decreased with increasing amounts of acetic anhydride. Second, higher s values were observed at 0 °C than at room temperature. Third, the reaction proceeded slightly slower in the absence of bases (triethylamine, diisopropylethylamine), but resulted in a small increase of the selectivity factor (s).[12]

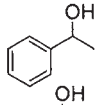
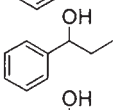
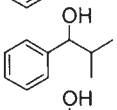
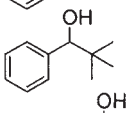
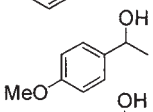
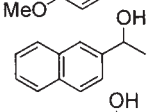
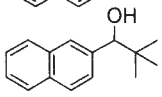
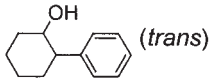
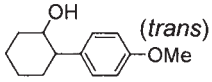


i) pyridine, reflux, overnight (~20 h), 96%
ii) (a) $(COCl)_2$, benzene, room temp., 1 h, then (*S*)-(−)-1,1'-binaphthyl-2,2'-diamine, Et_3N, DMAP, 0°C to room temp., 3 h, 47%
(b) Ac_2O, CH_2Cl_2, room temp., overnight (~15 h), 67%

Scheme 1. Synthesis of the catalyst **1**.

On the basis of these observations, we conducted the kinetic resolution of various racemic *sec*-alcohols (0.3 M) in *tert*-amyl alcohol with acetic anhydride (1 equiv) and the catalyst **1** (1 mol%) for 2–18 h at 0 °C, and the results are summarized in Table 1. As seen in entries 1–4, the stereoselectivity factor (*s*) increases as the steric bulk of the alkyl groups (Me < Et < *i*-Pr < *t*-Bu) increases. Especially, the stereoselectivity factor is remarkably increasing up to 21 in the case of *trans*-2-phenylcyclohexanol (entry 8).

Table 1. Kinetic resolution of racemic *sec*-alcohols with catalyst **1** (1 mol%)

Entry	Substrate	%conversion (time)	ee% (configuration)		*s*
			Alcohol	Ester	
1		70 (11 h)	79 (*S*)	34 (*R*)	4.4
2		67 (16 h)	85 (*S*)	43 (*R*)	6.3
3		77 (17 h)	99 (*S*)	31 (*R*)	8.1
4		59 (12 h)	90 (*S*)	64 (*R*)	13.3
5		72 (15 h)	84 (*S*)	32 (*R*)	4.7
6		72 (15 h)	98 (*S*)	38 (*R*)	8.3
7		63 (3 h)	95 (*S*)	57 (*R*)	12.4
8		62 (2 h)	99 (*1S*, *2R*)	62 (*1R*, *2S*)	21.0
9		68 (4 h)	75	36	4.5

In summary, considering that the catalyst **1** is prepared by a simple combination of commercially available compounds, and also effects kinetic resolution with a high enantioselection, this can be regarded as a significant first step toward the development of a practical nucleophilic catalyst. Currently, work is underway on the modification of **1**, aiming at increasing further selectivity factors and revealing the origin of the enantioselectivity.

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8 Incorporation of any chiral amine or alcohol to **4** may potentially provide a DMAP-based chiral nucleophilic catalyst, but thus far the catalyst **1** was found to be the most efficient for the kinetic resolution of racemic alcohols. Physical and spectroscopic properties of **1**: mp: 252–254 °C; $[\alpha]^{24}_{D} = -92.9^{\circ}$ ($c = 0.1$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.56–8.53 (m, 2H), 8.15–8.14 (m, 1H), 8.14 (s, 1H), 8.09 (d, 1H), 8.04 (d, 1H), 7.94–7.91 (m, 2H), 7.44–7.40 (m, 2H), 7.26 (m, 2H), 7.15 (s, 1H, NH), 7.15–7.13 (m, 1H), 6.97 (d, 1H), 6.83 (s, 1H, NH), 6.62 (d, 1H), 2.72–2.69 (m, 1H), 2.69 (s, 6H), 2.00 (d, 1H), 1.49 (s, 3H), 1.40 (d, 1H), 1.33 (d, 1H), 1.26 (s, 3H), 1.09 (s, 3H), 0.99 (d, 2H), 0.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 175.9, 175.6, 173.0, 169.5, 154.2, 151.5, 149.6, 136.5, 134.5, 132.4, 132.2, 131.6, 131.3, 130.8, 129.7, 128.7, 128.5, 127.5, 127.4, 125.6, 125.5, 125.2, 124.8, 122.8, 121.4, 120.7, 120.6, 120.4, 111.7, 45.2, 44.1, 44.0, 43.2, 42.0, 40.9, 40.8, 31.5, 26.4, 26.3, 24.3; IR ν_{max} (KBr)/cm^{-1} 3411, 3372, 1734, 1691; Anal. Calcd for $C_{41}H_{41}N_5O_4$: C, 73.74; H, 6.19; N, 10.49. Found: C, 73.72; H, 6.23; N, 10.53%.
9 The conversion rate of the reaction between 1-phenylethanol and acetic anhydride with the catalyst **1** was nearly equal to or slightly slower than that with the DMAP itself under similar reaction conditions. This is possibly because the reaction center (ring nitrogen) of **1** is sterically more congested than the DMAP.
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12 For the same observation, see: B. Tao, J. C. Ruble, D. A. Hoic, and G. C. Fu, *J. Am. Chem. Soc.*, **121**, 5901 (1999).