Single-Step Preparation of a 4-(Dimethylamino)pyridine Analogue Bearing a Sulfoxide as New Chiral Inducer. Preliminary Evaluation as Nucleophilic Catalyst

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Abstract: A one-step synthesis of a new chiral DMAP-**1a** equivalent is reported by bromine–magnesium exchange reaction of the 3-bromo-4-(dimethylamino)pyridine (**2**). The chiral sulfoxide appendage is introduced by trapping the resulting Grignard intermediate with (1*R*,2*S*,5*R*)-(–)-(*S*)-menthyl *p*-toluenesulfinate affording (*S*)-**1a** in 60% yield and high optical purity. A preliminary evaluation of **1a** as nucleophilic catalyst has demonstrated promising selectivity ($s = 4.5$) during acylative kinetic resolution of various alcohols.

Key words: chiral DMAP, sulfoxide, kinetic resolution, alcohol

Chiral 4-(dimethylamino)pyridine (DMAP) analogues have received considerable attention in recent years. A number of these chiral DMAP have already demonstrated to be highly effective chiral nucleophilic catalysts in a wide range of synthetically useful catalytic processes.[1] These include, as the main illustrative examples, acylative kinetic resolution of secondary alcohols and amines, C-arylations of silyl ketene acetals and additions of 2-cyanopyrrole to ketenes. In spite of the high potential exhibited by these chiral DMAP reagents, they have not yet gained full popularity due to the multi-step sequences and resolution techniques such as semi-preparative HPLC or crystallization required during their preparation (Figure 1).

The lack of straightforward and general existing methods for the preparation of these attractive synthetic tools stimulated us to develop an approach for the easy access of an array of new chiral DMAP derivatives, in which the chiral appendages would be installed in a single-step operation. Our strategy capitalizes on the expected versatility of the readily available 3-bromo-4-(dimethylamino)pyridine (**2**)[2] which, by means of various conventional chemical transformations should provide access to the desired structural and chiral diversities. In this communication, we assess the potential of the above working hypothesis by reporting the straightforward preparation, based on a bromine–metal exchange, of a new chiral DMAP equivalent **1a** bearing a sulfoxide group (Figure 2, a). We also

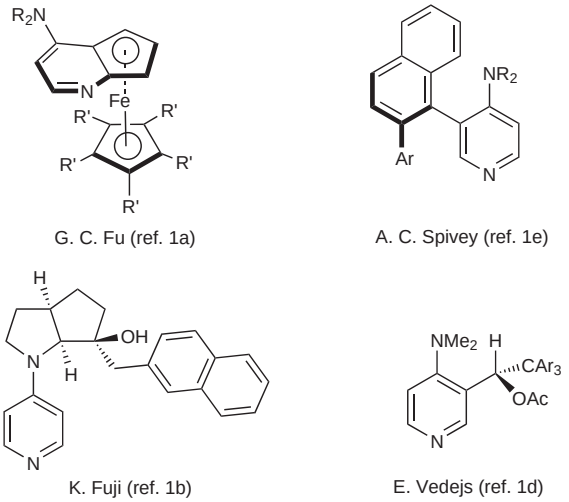

Figure 1 Chiral DMAP analogues previously reported.

comment on the preliminary investigation of its potential during acylative kinetic resolution of various alcohols. By analogy with previous observations reported by Vedejs,[1d] it was anticipated that the proximity of the dimethylamino group would prevent the free rotation of the chiral sulfoxide inducer. A molecular modeling[3] study of DMAP analogue **1a** revealed that the most stable conformation would place the lone pair of the sulfoxide and the pyridine ring in a coplanar arrangement (Figure 2, b). This conformational constraint is expected to be the main driving force in the stereodifferentiation of both faces of the pyridine ring.

Initial attempts to install the chiral sulfoxide by bromine–lithium exchange reaction turned out to be rather disappointing. Treatment of 3-bromo-4-(dimethylamino)pyridine (**2**)[2] with *n*-BuLi (1.2 equiv, –70 °C, THF) followed by deuteriolysis, furnished DMAP **1b** with modest deuterium incorporation (40%). In addition, a substantial amount of unidentified by-products was observed making rather difficult the purification of the crude product (Table 1, entry 1). The situation was even worse when *t*-BuLi was used, affording only traces of the desired deuterated DMAP **1b** along with a myriad of by-products (Table 1, entry 2). Speculating that the formation of these by-products took place because of the low stability of the

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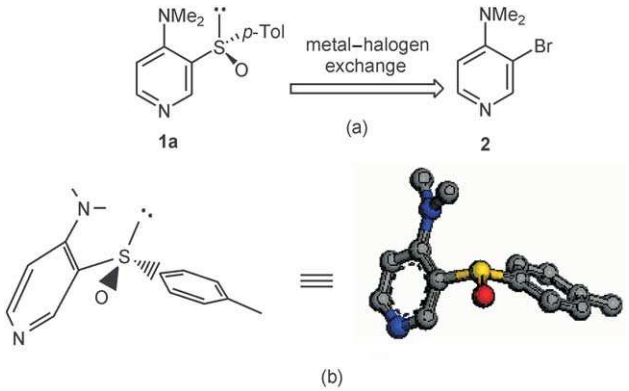
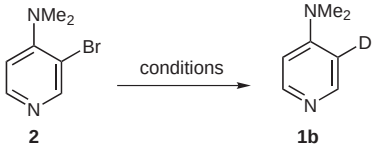


Figure 2 (a) Design of a new chiral DMAP equivalent **1a** bearing a sulfoxide group as chiral inducer; (b) molecular modeling[3] (hydrogen atoms have been omitted for clarity).

3-lithiated DMAP, we next turned our attention to a bromine–magnesium exchange reaction in order to benefit from a milder reactivity of the resultant Grignard species.[4] The reaction was carried out at room temperature by treatment of 3-bromo-4-(dimethylamino)pyridine (**2**) with *i*-PrMgCl for three hours. As anticipated, quenching the reaction mixture with EtOD led to the desired DMAP **1b** with high deuterium incorporation (>95%) in a much cleaner manner (Table 1, entry 3).[5]

Table 1 Optimization of the Halogen–Metal Exchange Reaction

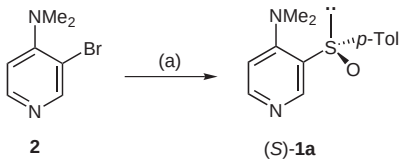


Entry	Bromine–Metal Exchange Conditions	**1b**
1	*n*-BuLi (1.2 equiv), –78 °C, THF, 30 min	%D = 40%[a]
2	*t*-BuLi (1.2 equiv), –78 °C, THF, 5 min	%D = 20%[a]
3	*i*-PrMgCl (1.2 equiv), 20 °C, THF, 3 h	%D > 95%[a]

[a] Determined from ^{1}H NMR Spectrum.

Having optimized the bromine–magnesium exchange conditions, we then undertook the introduction of the chiral sulfoxide appendage by means of (1*R*,2*S*,5*R*)-(–)-(*S*)-menthyl *p*-toluenesulfinate as electrophile. The desired chiral DMAP (*S*)-**1a** was obtained in 60% yield. As revealed by chiral HPLC, the product consisted of a single enantiomer.[6] This single-step approach provides a simple stereoselective access to **1a** and makes, in a certain extent, this novel chiral DMAP more than ever attractive (Scheme 1).

The potential of catalyst **1a** was then investigated during the kinetic resolution of various secondary alcohols. Its catalytic activity was firstly assessed by acylation of 1-phenylethanol under standard conditions at 25 °C in CH_2Cl_2 and compared with that of DMAP (Figure 3). Whereas acylation of 1-phenylethanol with DMAP occurs



Scheme 1 A single-step synthesis of DMAP **1a**. *Reagents and conditions*: (a) *i*-PrMgCl (1.2 equiv), 20 °C, THF, 3 h then (1*R*,2*S*,5*R*)-(–)-(*S*)-menthyl *p*-toluenesulfinate (1.2 equiv), –78 °C to 20 °C, 18 h.

in two hours, catalyst **1a** drives the reaction to completion within 24 hours. These observed rate differences may be attributed to the presence of the chiral sulfoxide, which exhibits an electron-withdrawing full charge dipole. As a result, the formation of the reactive acylpyridinium salt intermediate may possibly be hampered (Figure 3).

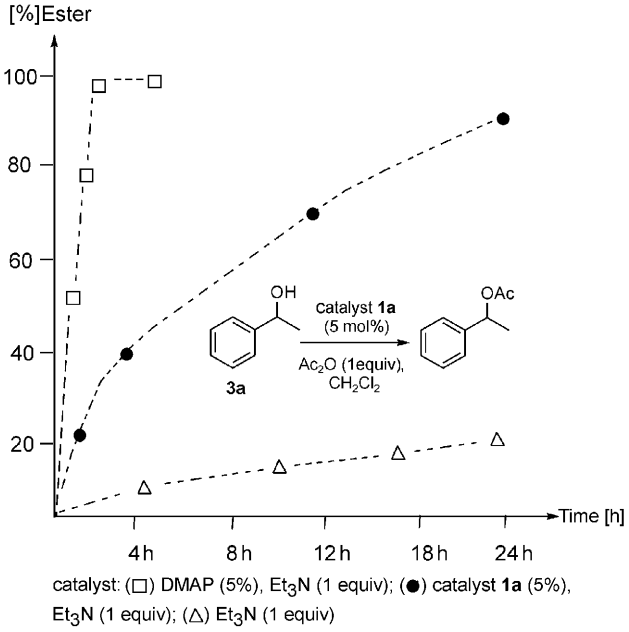
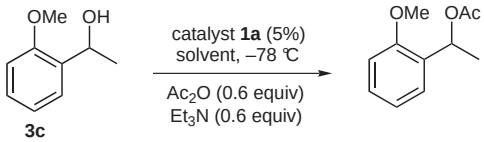


Figure 3 Evaluation of the catalytic activity of **1a** by acylation of 1-phenylethanol. *Reagents and conditions*: Ac_2O, CH_2Cl_2, r.t., catalyst (see legend).

We next examined the influence of the solvent on the selectivity of the catalyst **1a** during the kinetic resolution of 1-(2-methoxyphenyl)ethanol (**3c**) at –78 °C for 18 hours.[7] A literature survey revealed that CH_2Cl_2 and toluene remain the most commonly used solvents in this kinetic resolution process. Whereas both of these solvents have found to provide moderate selectivity values (s = 3.1 and 3.0, respectively), a slight but significant improvement could be observed by conducting the kinetic resolution process in acetone (Table 2, entry 5). It should be noticed that the catalytic activity at this temperature remains particularly modest, giving rise to poor conversion rates ($3.5 < C < 6.7$). The use of Et_2O or THF proved to be totally unproductive at this temperature (Table 2, entries 3, 4).

To probe the scope of the catalyst, the chiral DMAP equivalent **1a** was then subjected to a preliminary screen-

Table 2 Influence of the Solvent on the Kinetic Resolution of 1-(2-Methoxy)phenyl Ethanol (**3c**)



3c

Entry	Solvent	*C* (%)[a]	ee_A (%)[b]	ee_E (%)[b]	*s*[d]
1	CH_2Cl_2	5.7	3.0	50.3	3.1
2	Toluene	3.5	1.8	49.0	3.0
3	Et_2O	<1	–	–	–
4	THF	<1	–	–	–
5	Acetone	6.7	4.2	61.8	4.4

[a] Conversion [$C = 100 \times ee_A/(ee_A + ee_E)$].
[b] The ee of alcohol and ester established by chiral GC (Chiraldex CB 25 m × 0.25).
[c] Selectivity factor, see ref.[8]

ing of reaction conditions with various secondary alcohols **3a**–**d** (Table 3). Each experiment was duplicated at least once and showed to be reproducible in terms of selectivity and conversion. While the selectivity remains modest in all cases, ranging from 1.6 to 4.5, some interesting trends are emerging from Table 3 and deserve several comments. As frequently reported in the literature, when the resolution is conducted at low temperature (–78 °C) in CH_2Cl_2, some improvement of the selectivity is observed, however, to the detriment of the conversion rate (Table 3, entries 1 and 2, 6 and 7, 11 and 12, 16 and 17). By contrast to what has generally been observed in the literature, no enhancement of the selectivity was detected when switching the acylation reagent from Ac_2O to $(i\text{-PrCO})_2O$ (Table 3, entries 3, 8, 13, 18). Finally, the best selectivity could be attained in acetone at –78 °C. However, the presence of two equivalents of Ac_2O is required to guarantee an acceptable conversion level (Table 3, entries 9 and 10, 14 and 15).

In summary, a chiral DMAP equivalent **1a** bearing a sulfoxide as chiral appendage has been prepared. With the main goal to provide straightforward access to new chiral DMAP equivalents, a one-step procedure has been successfully developed from the readily available 3-bromo-4-(dimethylamino)pyridine (**2**). While DMAP **1a** suffers from a moderate catalytic activity, selectivity up to 4.5 could be achieved during the kinetic resolution of secondary alcohols. Although these values are still inferior to the threshold of $s = 7$ usually required for synthetic applications, these preliminary experiments have already demonstrated encouraging results.

Acknowledgment

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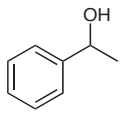
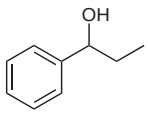
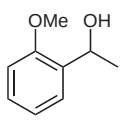
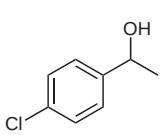
Table 3 Acylative Kinetic Resolution of **3a**–**d** by Means of Catalyst **1a**

Alcohol	Entry	Conditions	*C* (%)	ee_A (%)	ee_E (%)	*s*
	1	Ac_2O (0.6 equiv), Et_3N (0.6 equiv), r.t., CH_2Cl_2	58	12.6	9.2	1.3
	2	Ac_2O (0.6 equiv), Et_3N (0.6 equiv), –78 °C, CH_2Cl_2	17.4	8.6	40.7	2.6
	3	$(i\text{-PrCO})_2O$ (0.6 equiv), Et_3N (0.6 equiv), r.t., CH_2Cl_2	38.5	5.0	8.0	1.4
	4	Ac_2O (2 equiv), Et_3N (0.6 equiv), –78 °C, acetone	15.56	9.4	51.0	3.4
3a						
	6	Ac_2O (0.6 equiv), Et_3N (0.6 equiv), r.t., CH_2Cl_2	54.0	17.3	14.7	1.6
	7	Ac_2O (0.6 equiv), Et_3N (0.6 equiv), –78 °C, CH_2Cl_2	20.0	10.2	41.6	2.6
	8	$(i\text{-PrCO})_2O$ (0.6 equiv), Et_3N (0.6 equiv), r.t., CH_2Cl_2	36.0	10.5	18.6	1.6
	9	Ac_2O (0.6 equiv), Et_3N (0.6 equiv), –78 °C, acetone	6.7	3.6	49.9	3.1
	10	Ac_2O (2 equiv), Et_3N (0.6 equiv), –78 °C, acetone	18.3	10.4	46.3	3.0
3b						
	11	Ac_2O (0.6 equiv), Et_3N (0.6 equiv), r.t., CH_2Cl_2	49.5	20.4	20.8	1.8
	12	Ac_2O (0.6 equiv), Et_3N (0.6 equiv), –78 °C, CH_2Cl_2	5.7	3.0	50.3	3.1
	13	$(i\text{-PrCO})_2O$ (0.6 equiv), Et_3N (0.6 equiv), r.t., CH_2Cl_2	27.6	8.0	21.0	1.7
	14	Ac_2O (0.6 equiv), Et_3N (0.6 equiv), –78 °C, acetone	6.36	4.2	61.8	4.4
	15	Ac_2O (2 equiv), Et_3N (0.6 equiv), –78 °C, acetone	16.7	12.0	59.9	4.5
3c						
	16	Ac_2O (0.6 equiv), Et_3N (0.6 equiv), r.t., CH_2Cl_2	59.3	20.9	14.3	1.6
	17	Ac_2O (0.6 equiv), Et_3N (0.6 equiv), –78 °C, CH_2Cl_2	16.7	9.6	16.7	3.1
	18	$(i\text{-PrCO})_2O$ (0.6 equiv), Et_3N (0.6 equiv), r.t., CH_2Cl_2	51.2	10.4	9.9	1.3
	19	Ac_2O (2 equiv), Et_3N (0.6 equiv), –78 °C, acetone	22.4	12.8	44.3	2.9
3d						

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(3) Geometry optimization was performed with the MS modeling (Accelrys) implementation of the CNFF force field.

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(5) **Preparation of DMAP 1b by Bromine–Magnesium Exchange.**
To a solution of 3-bromo-4-(dimethylamino)pyridine (**2**, 898 mg, 4.47 mmol) in THF (30 mL) is added a solution of *i*-PrMgCl in THF (2.68 mL, 2 M, 5.36 mmol) at r.t. The resultant solution was stirred at this temperature for 3 h under a nitrogen atmosphere. The reaction mixture was quenched with EtOD and the solution stirred for a further 1 h. After adding H_2O (40 mL), the resulting aqueous layer was extracted twice with CH_2Cl_2 (2 × 10 mL), dried ($MgSO_4$) and evaporated under vacuum to give **1b** in high deuterium incorporation (>95%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22 (app t, 2 H, *J* = 6 Hz), 6.48 (d, 1 H, *J* = 6 Hz), 3.00 (3 H, s). HRMS (FAB+): *m/z* calcd for $C_7H_9DN_2$: 123.0907; found: 123.0910.

(6) **Preparation of DMAP (*S*)-1a by Bromine–Magnesium Exchange.**
DMAP **1a** is prepared according to the procedure reported in ref. 5 by means of (1*R*,2*S*,5*R*)-(–)-(*S*)-menthyl *p*-toluenesulfinate (1.45 g, 4.91 mmol) as electrophile in the quenching step of the procedure. The residue was chromatographed on silica gel using EtOAc as eluent to afford **1a** in 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.74 (s, 1 H), 8.27 (d, 1 H, *J* = 6 Hz), 7.37 (d, 2 H, *J* = 8 Hz), 7.17 (d, 2 H, *J* = 8 Hz), 6.56 (d, 1 H, *J* = 6 Hz), 2.95 (s, 6 H), 2.30 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3, 42.2, 109.7, 124.4, 127.3, 128.9, 140.2, 140.5, 148.4, 150.8, 154.2. IR (KBr): 1580, 1407, 1096, 1073, 1044, 957, 813 cm^{-1}. HRMS (FAB+): *m/z* calcd for $C_{14}H_{16}N_2OS$: 260.0903; found: 260.0907. $[\alpha]_D^{20}$ –323 (*c* 0.011, CH_2Cl_2). Following the same procedure, the chiral DMAP (*R*)-**1a** was prepared using (1*R*,2*S*,5*R*)-(–)-(*R*)-menthyl *p*-toluenesulfinate. The optical purity of the DMAP **1a** was established by chiral HPLC analysis using a Chiralcelpak AD (250 × 4.6 mm; 10 μm). Chromatographic conditions: injection: 20 μL (0.5 mg of a racemic mixture of **1a** in 10 mL of heptane). Eluent: heptane–2-PrOH, 80:20. Flow rate: 1 mL/min. Pressure: 300 psi. Temperature: 22 °C. UV detection: λ = 254 nm. Retention time: 16.9 min (*R*-enantiomer) and 20.9 min (*S*-enantiomer).

(7) **Typical Procedure for Catalytic Kinetic Resolution of Secondary Alcohols.**
To a solution of catalyst **1a** (13 mg, 0.05 mmol), 1-(2-methoxyphenyl)ethanol (**3c**, 152 mg, 1 mmol), Et_3N (86 μL, 0.6 mmol) in CH_2Cl_2 (5 mL) was added Ac_2O (57 μL, 0.6 mmol) at –78 °C. The reaction mixture was stirred at this temperature for 18 h after which time 100 μL was removed from the reaction mixture via a syringe and poured immediately in MeOH (2 mL). The conversion and the ee of both the alcohol and the acetate were determined by analytical chiral GC (Chiraldex CB 25 m × 0.25) of the resulting methanolic solution.

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