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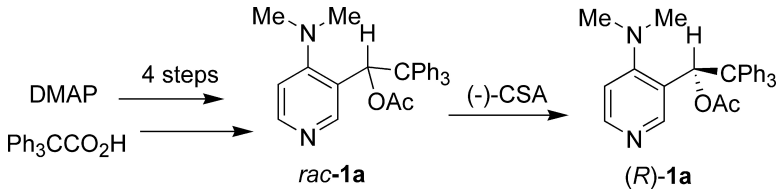

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Development of Chiral Nucleophilic Pyridine Catalysts: Applications in Asymmetric Quaternary Carbon Synthesis

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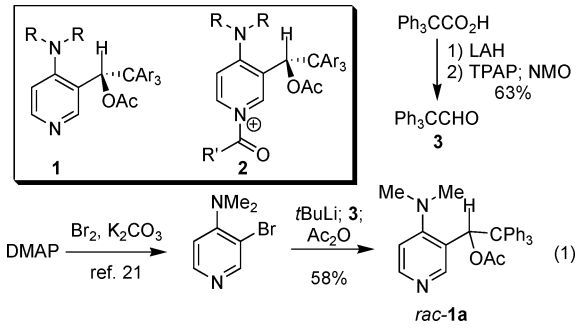
Organocatalysis is an important strategy in asymmetric synthesis.[1−8] One of the most intensively studied areas is acyl transfer using chiral nucleophiles,[6−8] including chiral trialkylamines,[9] synthetic peptides,[10] and phosphines.[11] Chiral (dimethylamino)pyridine (DMAP) analogues have been particularly attractive targets, in view of DMAP's broad utility.[12] Early work with chiral 2-substituted DMAP derivatives[13] demonstrated that the derived *N*-alkoxycarbonyl pyridinium salts are enantioselective carboxylating agents. However, steric hindrance from the 2-substituent inhibits catalytic turnover. Soon thereafter, Fu and co-workers reported the synthesis of a family of ferrocene-fused DMAPs[14] and demonstrated their use in a variety of catalytic asymmetric processes with impressive levels of stereocontrol. Examples of atropisomeric biaryl DMAPs[6,15] and DMAP analogues containing chiral amino groups[16−18] have since been reported. Several of these newer catalysts are capable of moderate to high levels of selectivity in acyl transfer reactions.

With the goal of developing an enantioselective DMAP catalyst that would be easily synthesized in enantiomerically pure form, we chose to study a new class of chiral pyridine derivatives **1**. It was hypothesized that the corresponding *N*-acylpyridinium intermediate **2** would be restricted to a geometry where the dialkylamino group is nearly coplanar with the pyridine ring, thereby maximizing nitrogen lone pair delocalization. The benzylic substituents would rotate to place the bulky trityl group on one open face of the pyridine ring and orient the benzylic hydrogen toward the ortho-dialkylamino group. In this conformer, the acetoxy group creates a chirotopic environment on the other face of the pyridine ring. Support for this geometry is provided by an ab initio evaluation of pyridinium ion **2** (Figure 1), shown as the most stable conformer located thus far.[19] Catalysts **1** should be readily available in modular fashion from 3-halopyridines, triarylacetaldehydes, and anhydrides and should therefore be amenable to easy variation.

The synthesis of racemic **1a** ("TADMAP"; short for 2,2,2-triphenyl-1-acetoxyethyl DMAP) began with the conversion of triphenylacetic acid to triphenylacetaldehyde (eq 1).[20] This aldehyde



was then treated with the aryllithium derived from 3-bromo-4-(dimethylamino)pyridine,[21] and the resulting alkoxide was quenched with acetic anhydride. Racemic **1a** was prepared on gram scale in four steps (37% overall yield). No chromatography was required until the final aryllithium coupling reaction.

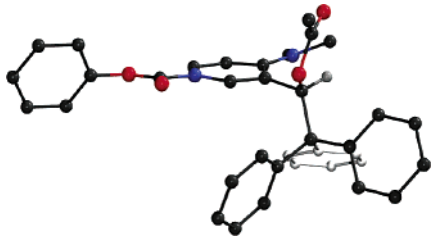


Figure 1. Ab initio geometry of acyl pyridinium **2**.[19]

Enantiomerically pure **1a** was obtained via classical resolution. Treatment of racemic **1a** with 0.5 equiv of (−)-camphorsulfonic acid (CSA) in toluene produced enantiomerically enriched crystals of [(*R*)-**1a**·(−)-CSA] that were neutralized using NaOH. Repeating this procedure on the scalemic material led to (*R*)-**1a** in >99% ee.[22] The (*S*)-**1a** enriched mother liquor of the initial crystallization was treated analogously with (+)-CSA, producing (*S*)-**1a** in >96% ee. When this procedure was used, 7.4 g of racemate was resolved to give 0.7 g of (*R*)-**1a** (>99% ee) and 1 g of (*S*)-**1a** (98.3% ee), with 4.7 g of scalemic **1a** available for further resolution (>85% recovery through the crystallization sequence).

The first test of catalyst **1a** was the enantioselective Steglich rearrangement of enol carbonates **4**[23] to azlactones **5**, containing an asymmetric quaternary carbon.[24] Fu and Ruble have reported good results in this reaction using a chiral pyridine catalyst.[25] Treating alanine derived oxazoles **4a** or **4b** with catalyst **1a** (room temperature, CH_2Cl_2) showed that phenoxycarbonyl migrates with higher selectivity than benzyloxycarbonyl (**5a**, 73% ee vs **5b**, 30% ee). As in the analogy of Fu and Ruble,[25] *t*-amyl alcohol at 0 °C gave the best results overall, affording **5a** in 92% yield and 91% ee (1 mol % of catalyst **1a**), but the solvent effect was small.[26]

With these optimized conditions, a variety of oxazole enol carbonates **4a**−**j** were tested (Table 1), comparing the results with those using the nucleophilic phosphabicyclooctane (PBO) catalyst **6**, developed earlier in our laboratory for enantioselective acyl transfer.[11b] The benzyloxycarbonyl group was better suited for migration reactions catalyzed by **6**, in contrast to the result with **1a** (best with phenoxycarbonyl). The migration reactions proceeded in excellent yield and enantioselectivity using either **1a** or **6** as the catalysts for substrates having an unbranched methylene side chain (**4a**−**h**). For phenyl-substituted oxazoles **4i**−**j**, the selectivity was diminished.

To probe the sense of absolute stereochemistry for the carboxyl migrations, the azlactone products *ent*-**5a** (from **4a** and (*S*)-**1a**) and **5b** (from **4b** and **6**) were converted into the same disubstituted malonate **7** (Figure 2). This was accomplished via nucleophilic ring opening, starting from *ent*-**5a** and benzyl alcohol, or from **5b** and phenol. The stereochemistry of the TADMAP-catalyzed process could then be deduced from the sign of optical rotation reported for **5b**.[25]

The scope of asymmetric carboxyl migration with TADMAP (**1a**) was briefly explored using several heteroaromatic enol

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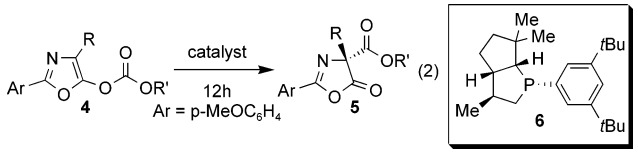

Table 1. Azlactone Acyl Migration

substrate	R	R′	catalyst[a]	% yield	% ee
4a	Me	Ph	**1a**	95	91
4b	Me	Bn	**6**	88	89
4c	Bn	Ph	**1a**	99	95
4d	Bn	Bn	**6**	90	90
4e	allyl	Ph	**1a**	90	91
4f	allyl	Bn	**6**	91	90
4g	*i*Bu	Ph	**1a**	90	91
4h	*i*Bu	Bn	**6**	87	92
4i	Ph	Ph	**1a**	95[b]	58
4j	Ph	Bn	**6**	96	20

[a] 1 mol % (*R*)-**1a** or 10 mol % **6**, *t*-amyl alcohol, 0 °C. [b] Yield determined by NMR.

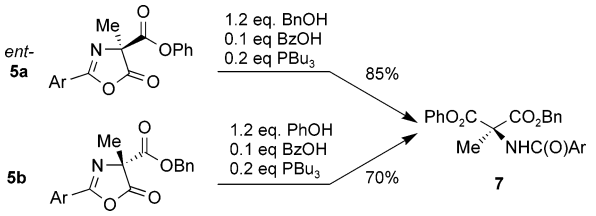

Figure 2. Determination of product stereochemistry.

carbonates. Furan enol carbonate **8** rearranged (eq 3) to give a 10:1 mixture of α- and γ- *C*-carboxylated isomers **9** (83%; 90% ee) and **10** (7%; 80% ee). Furanone **9** is potentially useful, as three of the quaternary carbon substituents should be readily elaborated. Analogous DMAP-catalyzed carboxyl migrations of benzofuran and indole derived enol carbonates related to **11** have also been reported.[14g,27,28] Preliminary results using our catalyst **1a** are promising. Fair to excellent levels of enantioselectivity were observed in the benzofuranone and oxindole products (Table 2), although the reactions from **11c** (24 h) or **11d** (18 h) were relatively slow using 10% of the catalyst.

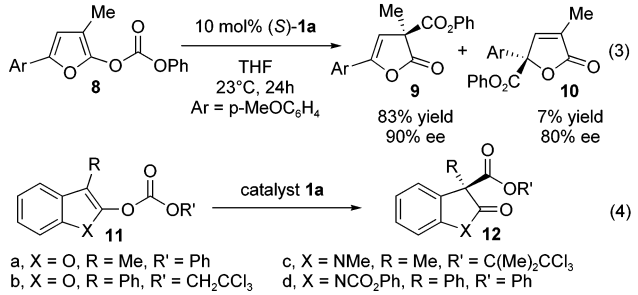

Table 2. Benzofuranone and Oxindole Acyl Migration

substrate	solvent	temp (°C)	% yield	% ee
11a[a]	Et_2O	23	92	92
11b[b]	CH_2Cl_2	−40	92	86
11c[c]	*t*-amyl alc.	23		49
11d[c]	*t*-amyl alc.	40	93	86

[a] 1 mol % **1a**. [b] 20 mol % **1a**, 95% cat. recovered. [c] 10 mol % **1a**.

Work is underway to further develop the new family of chiral catalysts, to expand the scope of acyl migration applications, to better understand the basis for enantioselectivity, and to evaluate several options for the enantioselective synthesis of **1**.

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Supporting Information Available: Experimental procedures and characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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