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Enantioselective TADMAP-Catalyzed Carboxyl Migration Reactions for the Synthesis of Stereogenic Quaternary Carbon

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Abstract: The chiral, nucleophilic catalyst TADMAP [**1**, 3-(2,2,2-triphenyl-1-acetoxyethyl)-4-(dimethylamino)-pyridine] has been prepared from 3-lithio-4-(dimethylamino)pyridine (**5**) and triphenylacetaldehyde (**3**), followed by acylation and resolution. TADMAP catalyzes the carboxyl migration of oxazolyl, furanyl, and benzofuranyl enol carbonates with good to excellent levels of enantioselection. The oxazole reactions are especially efficient and are used to prepare chiral lactams (**23**) and lactones (**30**) containing a quaternary asymmetric carbon. TADMAP-catalyzed carboxyl migrations in the indole series are relatively slow and proceed with inconsistent enantioselectivity. Modeling studies (B3LYP/6-31G*) have been used in qualitative correlations of catalyst conformation, reactivity, and enantioselectivity.

Introduction

Chiral nucleophilic catalysis is an important category of organocatalysis and has been demonstrated to mediate a variety of transformations, including phosphorylation, sulfonylation, Baylis−Hillman reactions, and ketene addition reactions.[1,2] However, nucleophilic catalysis is most often used in acyl transfer reactions, and a variety of chiral catalysts have been developed to effect enantioselective variants. Beginning with Wegler's original work using alkaloids,[3a] catalysts have included chiral trialkylamines,[3] 4-(dimethylamino)pyridine (DMAP) derivatives,[4−10] synthetic peptides,[11,12] amidines,[13] nucleophilic heterocyclic carbenes,[14,15] and phosphines.[16]

Chiral DMAP analogues have been particularly attractive targets, since DMAP itself is highly reactive, easy to handle,

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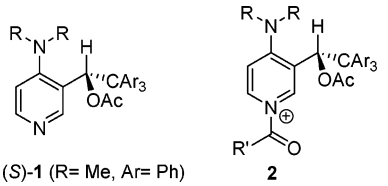


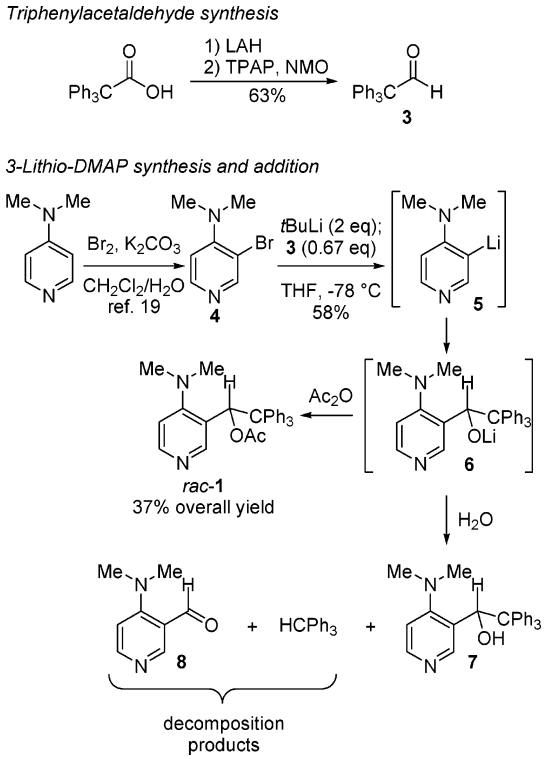
Figure 1. C-3 substituted chiral DMAP derivatives.

and catalytically active for a variety of transformations.[2a−d,g] Strategies for making chiral DMAP analogues have included stereogenic substitution at the C(2) and C(3) positions on the pyridine ring as well as chirality in the dialkylamino group. The most successful strategy so far (Fu et al.) utilizes a planar−chiral DMAP analogue, where the chiral information is communicated to the active pyridine ring nitrogen via a ferrocene group fused to the pyridine core.[5] This catalyst is capable of high enantioselectivity in a variety of transformations.

Work in our laboratory has centered on finding a chiral DMAP-based catalyst that would be easily accessible as well as highly enantioselective.[4] Design considerations are limited by the presence of two mirror planes of symmetry in the DMAP core and by a total of three sites, C(2), C(3), and C(4)−N, where chiral substituents might be attached. Substitution at C(2) is problematic, because of the expected decrease in catalytic reactivity due to steric hindrance,[4a,c,17] and the remaining sites at C(3) and C(4)−N are not ideal because chiral substituents would have to communicate stereochemical information across a substantial distance. Nevertheless, important progress has been made and enantioselective DMAP catalysts have been developed in both structural categories by Fuji et al. [C(4)−N][6] and Spivey et al. [C(3)].[7a,c,d] Several other chiral DMAP catalysts based on variations of the C(3) or the C(4)−N substituent have also been disclosed.[7b,8−10]

With the goal of developing shorter routes to potentially selective catalysts, we chose to study a new class of chiral C(3)-substituted pyridine derivatives **1** (Figure 1). Placing the substitution at C(3) puts it as close to the nucleophilic pyridine nitrogen as possible without hindering the catalytically active site. It was hypothesized that the corresponding *N*-acylpyridinium intermediate **2** would prefer a geometry where the dialkylamino group is nearly coplanar with the pyridine ring, thereby maximizing $n_N \rightarrow \pi$ electron delocalization. The benzylic substituents would rotate to place the bulky, conformationally degenerate trityl group over one face of the pyridine ring, thus ensuring that one face of the pyridinium ring is always "blocked" by a phenyl group. The benzylic hydrogen on the acylated catalyst **2** would be oriented toward the 4-dialkylamino group in order to minimize steric interactions. In this conformer, the acetoxy group creates a chirotopic environment on the "open" face of the pyridine ring. Retrosynthetically, **1** would be available from a 3-metallo-4-(dialkylamino)pyridine and a triarylacetaldehyde. This disconnection provides rapid access to racemic **1** and has potential for asymmetric synthesis as well as variation of catalyst substitution.

Scheme 1. Synthesis of TADMAP (**1**)



Results and Discussion

Synthesis of Enantiomerically Pure TADMAP 1. The synthesis of racemic **1** ["TADMAP", for 3-(2,2,2-*t*riphenyl-1-*a*cetoxyethyl)-4-(*dim*ethyl*a*mino)*p*yridine] began with the conversion of commercially available triphenylacetic acid to triphenylacetaldehyde **3**[18] using a two-step reduction/oxidation sequence ($LiAlH_4$, TPAP/NMO; Scheme 1). Pyridinium chlorochromate (PCC) was originally used for the oxidation,[18] but this required chromatography. In contrast, TPAP/NMO gave crude **3** that could be crystallized to purity on a multigram scale. Aldehyde **3** was then treated with the aryllithium reagent **5** from 3-bromo-4-(dimethylamino)pyridine **4**[19] and *t*BuLi, and the resulting lithium alkoxide **6** was quenched with acetic anhydride to afford racemic **1** (four steps, 37% overall from triphenylacetic acid on a gram scale). No chromatography was required until the final aryllithium coupling reaction.

It was necessary to perform the addition of **5** to **3** under dilute conditions (∼0.10 M) to avoid precipitation of **5**. Reversing the order of addition and adding **3** to the precipitated **5** produced a modest yield of **1** on a 200-mg scale (43%), but only 13% on a 800-mg scale. Even under the former (dilute) conditions, it was necessary to use 1.5 equiv of **5** to achieve complete conversion of **3**, and it was important to add **5** with vigorous stirring and careful temperature control at −78 °C to minimize the formation of byproducts. If the alkoxide **6** was quenched with water instead of acetic anhydride, the products included triphenylmethane and trace amounts of aldehyde **8** in addition to the pyridyl alcohol **7**. Evidently, the alkoxide **6** fragments to give trityllithium and **8** in the latter experiment. Fragmentation

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of the triphenylmethyl group did not occur when the analogous alkoxide intermediate was generated from **3** and phenyllithium, suggesting that synergistic electron donation involving both the alkoxide and the arene ring in **6** is necessary to generate enough "push" to release the basic trityl anion ($pK_{aMeCN} = 44$, $pK_{aDMSO} = 30.6$).[20]

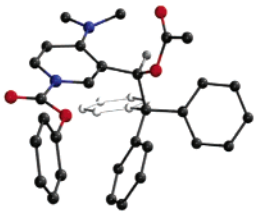
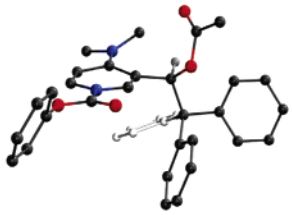
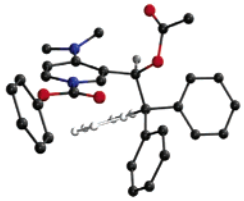
With multigram quantities of racemic catalyst **1** in hand, resolution of the enantiomers was necessary. Initially, small quantities of *rac*-**1** were resolved by HPLC over a chiral support, but this laborious process was not suited to gram-scale synthesis. Fortunately, enantiomerically pure TADMAP was readily obtained via classical resolution. Treatment of *rac*-**1** with 0.5 equiv of (−)-camphorsulfonic acid (CSA) in warm toluene produced the enantiomerically enriched salt **9**. After neutralization with NaOH, the procedure was repeated on the scalemic material to give (*R*)-**1** with >99% ee. The (*S*)-**1**-enriched mother liquor of the initial crystallization was treated analogously with (+)-CSA, producing (*S*)-**1** in >96% ee. Using this procedure, 7.4 g of racemate was resolved to give 0.7 g of (*R*)-**1** (>99% ee) and 1 g of (*S*)-**1** (98.3% ee), with 4.7 g of scalemic **1** available for further resolution (>85% recovery over the crystallization sequence).

To better understand the three-dimensional structure of catalyst **1**, the *N*-carboxylpyridinium salt **2** (Ar = Ph, R = Me, R′ = OPh) was studied using computational methods. Electron donation from the C-4 nitrogen into the pyridine ring was expected to play a major role in conformational bias. Therefore, DFT (B3LYP/6-31G*) methods were used that take mesomeric stabilization into account.[21] The choice of the *N*-(phenoxycarbonyl)pyridinium environment for computation was made to address the best results of carboxyl migration experiments to be discussed later. Three energy minima were located having nearly equal energies (Table 1). As expected, the trityl group was oriented over one face of the pyridine ring in the favored conformers to minimize steric interactions, and the side chain ethyl backbone was in a staggered conformation. The acetate adopts the standard secondary ester geometry with the carbonyl group nearly eclipsing the adjacent benzylic C−H bond and the dialkylamino group in each minimum is nearly coplanar with the pyridinium ring.

The energy minima have similar geometry, but differ in conformational details involving the phenoxycarbonyl group. Thus, both N−CO rotamers were found (Table 1, entry 1 vs entries 2 and 3), and the phenyl ring of the phenoxycarbonyl subunit was twisted out of the carbonyl plane. The same geometry was also found as an energy minimum for the unsubstituted DMAP-derived cation **10** (Figure 2, θ = ca. 60°) and was favored by ~0.5 kcal/mol over the coplanar structure (Figure 2, θ = 0°). The conformational profile for **10** also showed a small energy maximum where the phenyl ring is perpendicular to the carbonyl/pyridine plane (θ = 90°).

Although TADMAP (**1**) was resolved with CSA, the resulting crystals were not suitable for X-ray analysis. Dibenzoyl-L-tartaric acid, on the other hand, was ineffective as a resolving agent, but crystallization of a 1:1 mixture of resolved (+)-**1** and dibenzoyl-L-tartaric acid gave suitable crystals of the salt **11** (Figure 3). This allowed assignment of the absolute stereochemistry as well as the solid state conformation and revealed good qualitative agreement with features of the computed energy minima (Table 1), including the coplanar dialkylamino group, the trityl group extending over one face of the pyridine, and the relative orientation of the benzylic hydrogen.

Table 1. Energy Minima for *N*-(Phenoxycarbonyl)pyridinium Ion **2**[a]

Entry	Geometry[b]	E_{rel} (kcal/mol)
1		0.17
2		0.13
3		0.00

[a] Ar = Ph, R = Me, R′ = OPh. [b] Energy minima located using DFT computations (B3LYP/6-31G*).

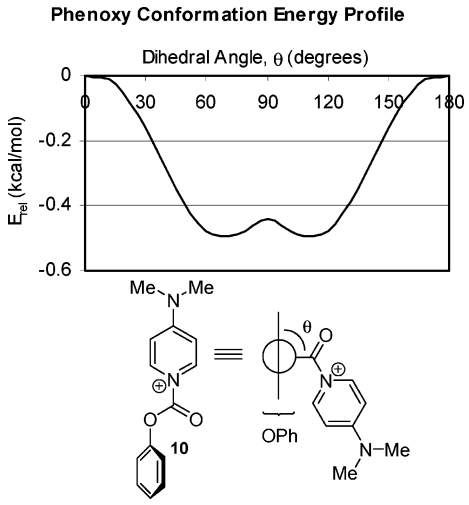


Figure 2. *N*-(Phenoxycarbonyl)-DMAP energy profile (B3LYP/6-31G*).

Enantioselective Steglich Rearrangement of Oxazolyl Carbonates. The Steglich rearrangement (Scheme 2)[22,23] was selected for a systematic investigation of carboxyl migration using catalyst **1**. Oxazolyl carbonates **13** are easily synthesized

(20) pK_{aDMSO}: (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. pK_{aMeCN}: (b) *ChemFiles*, Fluka, vol. 3.
(21) *Wavefunction, PC SPARTAN PRO*, ver 1; Wavefunction, Inc.: Irvine, CA, 1999.

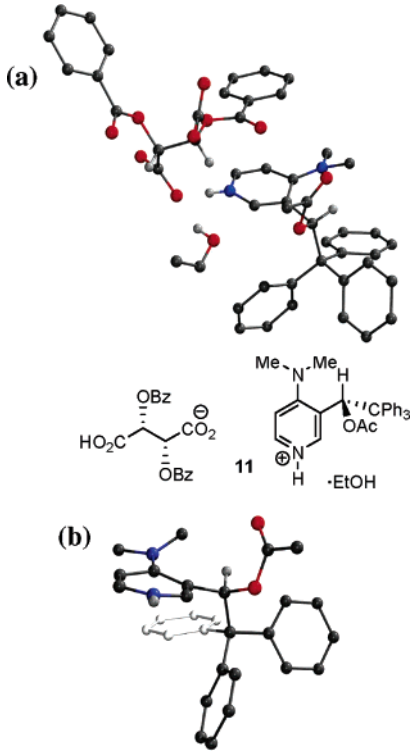
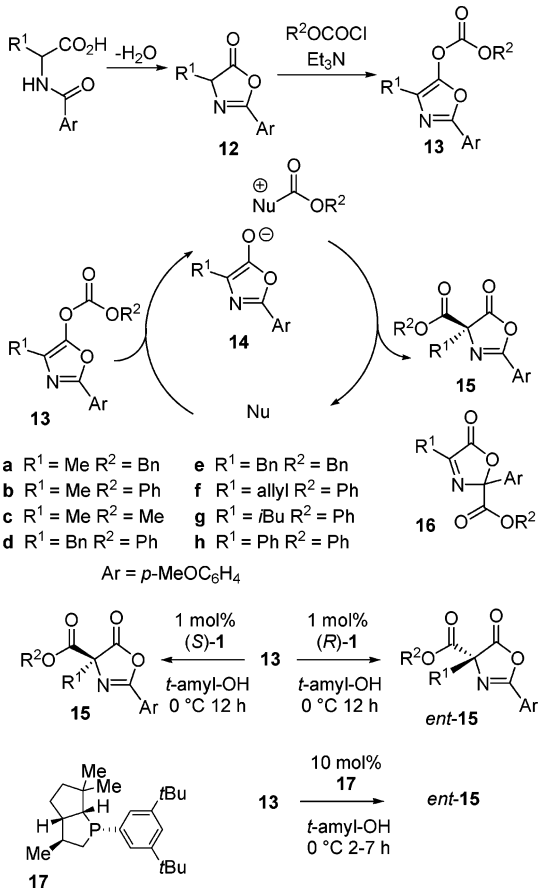


Figure 3. (a) Structure of TADMAP·dibenzoyl-L-tartaric acid·EtOH **11**. (b) **11** from a different perspective with counterion and ethanol atoms omitted.

Scheme 2. Steglich Rearrangement



from *N*-aroylamino acids via azlactones **12**, and treatment with DMAP as a nucleophilic catalyst results in generation of an ion pair **14** followed by carboxyl migration to give the *C*-carboxyl azlactone **15**. The rearrangement is high yielding if Ar = *p*-MeOC$_6$H$_4$, but the corresponding reaction with Ar = Ph affords a significant amount of the undesired C-2 carboxylated isomer **16**.[22] Fu and Ruble have reported a highly enantioselective version of the Steglich rearrangement of **13** (R^2 = Bn) using a planar−chiral pyridine catalyst.[23] Comparisons with their results were expected to provide a basis for evaluating **1** as a chiral nucleophilic catalyst for synthesis of chiral quaternary carbon-containing molecules.[24]

In the initial experiments, the alanine-derived oxazolyl carbonate **13a**[23] was treated with 1 mol % of (*S*)-TADMAP (**1**) in CH_2Cl_2. The rearranged *C*-carboxylated isomer **15a** was obtained in high yield as the only product, but the ee value was only 30%. Similar results were obtained with a methoxycarbonyl analogue **13c** in preliminary screens. However, changing the migrating group to phenoxycarbonyl (**13b**, R = Ph) and lowering the temperature to 0 °C gave a dramatic increase in selectivity and afforded the *C*-carboxyl product **15b** with 73% ee. Further improvement to 84−89% ee was observed in toluene or in ether solvents, and the best result was obtained in *tert*-amyl alcohol (91% ee). Decomposition was noted in more polar solvents such as acetonitrile, so *tert*-amyl alcohol was used in subsequent experiments to define the scope of the carboxyl migration.

A variety of substituted oxazolyl carbonates **13** were treated with 1 mol % of the enantiomeric TADMAP catalyst (*R*)-**1** using the optimized *tert*-amyl alcohol conditions. Excellent yields (90−99%) and enantiomeric excess (91−95% ee) were observed for all of the phenoxycarbonyl substrates **13b**,**d**,**f**,**g** bearing an unbranched methylene side chain. However, the benzyloxycarbonyl derivative **13e** gave lower ee (*ent*-**15e**, 71% ee), similar to the behavior of **13a**. Lower enantioselectivity was also observed with the phenylglycine-derived **13h** to afford the *C*-carboxylated azlactone product *ent*-**15h** (58% ee). Furthermore, the corresponding isopropyl-substituted oxazolyl carbonate derived from valine gave no migration product at all, apparently due to excessive steric hindrance. These findings underscore the importance of substrates **13** having unbranched alkyl substituents R^1 for the enantioselective Steglich rearrangement to **15** or *ent*-**15** as well as the critical role of the phenoxycarbonyl migrating group.

The optimized enantioselectivities are comparable to those reported by Fu and Ruble, although their best results were obtained with the benzyloxycarbonyl migrating group, as in **13a** and **13e**.[23] We were curious to know whether the migrating group would be subject to similar restrictions when the conversion from **13** to **15** is induced by the structurally unique, highly nucleophilic chiral phosphine **17**,[16b,f] so the corresponding carboxyl migration experiments were investigated. Surprisingly, the carboxyl group was unimportant in this system, and nearly identical enantioselectivities in the range of 85−92% ee were

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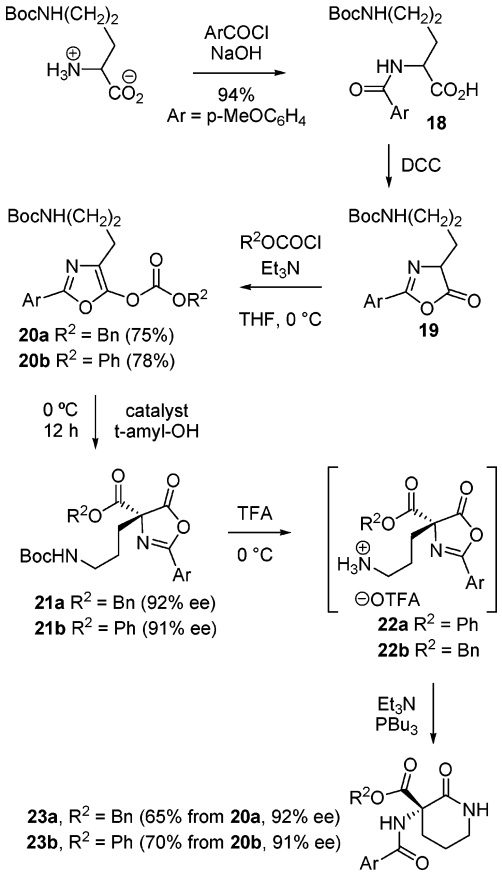
Scheme 3



observed for benzyloxy-, phenoxy-, and methoxycarbonyl substrates **13a**,**b**,**c** (see Table S-3 of the Supporting Information for tabulated results). However, the phosphine catalyst **17** proved to be substantially less reactive than TADMAP (**1**), and efficient substrate conversion required ca. 10 mol % of the catalyst.

The identity of azlactone *ent*-**15a** obtained from **13a** using **17** was established by comparing NMR data and the sign of optical rotation with known material.[23] A chemical correlation was then performed to define the configuration of **15b** [prepared from **13b** and catalyst (*S*)-**1**] by ring opening with benzyl alcohol, or the corresponding ring opening of ent-**15a** with phenol. Both reactions were conducted under nucleophilic catalysis conditions (tributylphosphine/benzoic acid), and both gave the same enantiomer of an amido-malonate diester via alcoholysis of the azlactone (see Supporting Information for details).

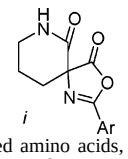
On the basis of the enantioselective carboxyl migrations briefly summarized above, good results were expected with oxazole substrates containing additional functionality designed to allow intramolecular bond formation following the carboxyl rearrangement step. Thus, the protected ornithine **18** was converted into the oxazole carbonates **20a** and **20b** via the azlactone **19** (Scheme 3). In accordance with the precedents, the benzyloxycarbonyl derivative **20a** rearranged to **21a** with good enantioselectivity (92% ee) upon treatment with 10 mol % of the chiral phosphine **17**. Alternatively, the phenoxycarbonyl analogue **20b** gave **21b** in 91% ee when 1 mol % of (*R*)-**1** was used as the catalyst.

Deprotection of either of the oxazolyl carbonates **21a** or **21b** with trifluoroacetic acid followed by treatment of the intermediate salts **22a**,**b** with Et_3N/Bu_3P to neutralize the salt and to catalyze nucleophilic azlactone cleavage afforded the lactams **23a** or **23b** (65−70% overall). In the case of **22b**, replacing the nucleophilic Bu_3P catalyst with the more basic DMAP or using excess Et_3N without an added nucleophile gave a byproduct, apparently resulting from phenoxy displacement by the side chain amine.[25] This side reaction was not observed from **22a** because the benzyloxycarbonyl subunit is less activated compared to phenoxycarbonyl, but the same conditions for lactam formation were used as a precautionary measure. Lactams **23a** and **23b** were isolated with 92% ee and 91% ee, respectively, evidence that intermediates in the carboxyl migration retain the absolute configuration of the precursors **22a**,**b** and do not undergo interconversion of the ester and azlactone carboxyl groups during conversion to **23**.

In a similar sequence (Scheme 4), the protected homoserine **24** was *N*-aroylated, saponified to the carboxylic acid **25**, and cyclized to the azlactone **26** by treatment with DCC. Subsequent conversion into the oxazolyl carbonates **27a** or **27b** was carried out in the usual way, and carboxyl migration was effected using 10 mol % of the phosphine catalyst **17** with **27a** or 1 mol % of (*R*)-**1** with **27b**. The carboxyl migration products **28a** (89% ee) and **28b** (91% ee) were obtained in excellent yield and good enantiomeric purity. Subsequent silyl ether cleavage by treatment with HF•pyridine resulted in the direct conversion to the lactones **30a** and **30b** in >85% yield. The intermediate alcohols **29a**,**b** were not detected in this case, and no additional catalysts were required for azlactone cleavage. However, use of the acidic fluoride source was critical as treatment of either **28a** or **28b** with the more basic TBAF reagent led to the formation of the α-amido lactone **31**. Presumably, this occurs via a retro-Claisen/cyclization sequence, but the mechanistic details were not investigated. In any event, the results of Schemes 3 and 4 suggest a number of potential applications of the enantioselective carboxyl migration methodology for synthesis of unusual amino acid derivatives containing a stereogenic quaternary carbon.[26]

Enantioselective Carboxyl Migration of Furan-Derived Enol Carbonates. Among the early goals of this program was to establish a route to chiral quaternary carbon-containing intermediates of the general structure **33** as part of our effort to obtain diazonamide A by total synthesis. An approach based on the Black rearrangement from a benzofuran **32** was therefore initiated (Scheme 5),[27,28] but using chiral nucleophiles in place of Black's DMAP catalyst. The mechanism of this reaction is believed to be closely analogous to that of the Steglich rearrangement discussed earlier. However, the original structure of the diazonamide A core (**34**) proved to be wrong, and a revised structure **35** has now been defined.[29] In principle, **35** might also be accessed via Black rearrangement from benzofuran substrate **36** or from the analogous rearrangement of indole **37**. Although strategic considerations eventually resulted in a different solution for the diazonamide quaternary carbon

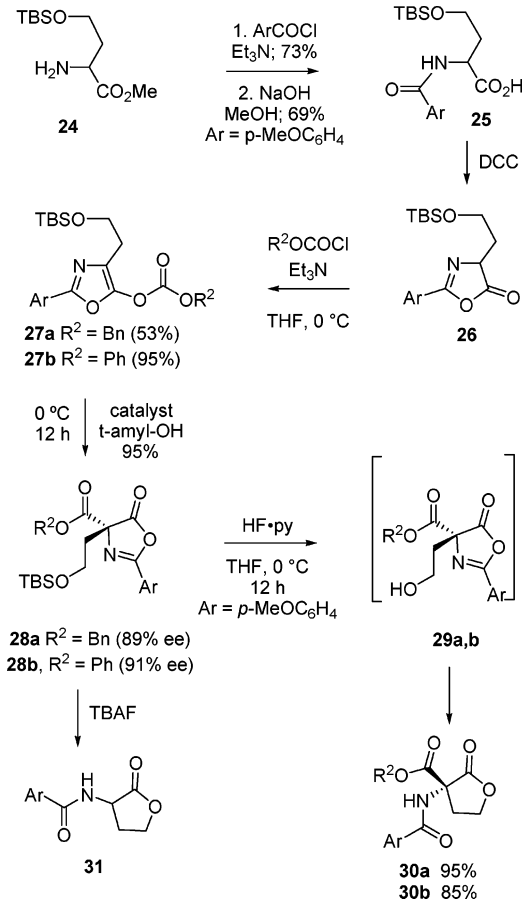
(25) Structure *i* for the byproduct is consistent with NMR and IR data.



i

(26) For reviews α,α-disubstituted amino acids, see: (a) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (b) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645. For an alternative approach to α,α-disubstituted amino acids from azlactones, see: (c) Trost, B. M.; Chulbom, L. *J. Am. Chem. Soc.* **2001**, *123*, 12191.

Scheme 4



problem,[30] the relevant benzofuran and indole rearrangements have been explored in depth in our laboratory, as described below. Similar substrates have been studied by Fu and Hills using their chiral DMAP catalyst with excellent results.[31]

Simple benzofuranyl enol carbonates **39** and **41** were easily obtained from the known benzofuranones **38** (Scheme 6),[32,33] but the enantioselective carboxyl rearrangement of 3-phenyl derivative **39** as a model for the hypothetical conversions from **32** to **33** proved to be a challenging problem. Treatment of the phenoxycarbonyl derivative **39a**[27] with 1 mol % of (*S*)-TADMAP (**1**) produced the *C*-carboxylated product **40a** at room temperature, but the reaction was nonselective (2% ee). A variety of other enol carbonates **39b**−**e** were prepared and the carboxyl migrations were screened using (*S*)-**1**. The ethoxycarbonyl migrating group (**39b**) gave **40b** with modest 26−44% ee in a variety of solvents at room temperature, while the isopropoxycarbonyl derivative **39c** gave totally racemic **40c**. Only a small improvement was observed for the conversion of **39b** to **40b** at −20 °C (52−59% ee in ether, THF, or toluene). Fortunately, a larger temperature effect was found for **39d**, and **40d** was obtained in 86% ee and 92% yield by carrying out the reaction at −40 °C in dichloromethane. However, improved ee came at the cost of a significant rate decrease that required the use of 20 mol % of (*S*)-TADMAP (**1**) over 18 h. If desired, 95% of the TADMAP catalyst could be recovered via chromatography, but the high catalyst loading and long reaction time raised concerns about potential applications to more hindered substrates such as **32** or **36**. Reactivity problems were also encountered in preliminary attempts to use chiral phosphine catalysts for the carboxyl rearrangement from **39** or its analogues.[34]

After the struggle to optimize the rearrangement from **39** to **40**, it was gratifying to find that the enantioselective carboxyl migration from the 3-alkyl benzofuranyl carbonates **41** to benzofuranones **42** is quite easy and follows the substrate preferences observed earlier with the oxazole substrates. This study was conducted using the enantiomeric TADMAP catalyst (*R*)-**1** and began with a comparison of the methoxycarbonyl (**41a**) and phenoxycarbonyl (**41b**) migrating groups in dichloromethane. As with the oxazole substrates, the reaction was more highly selective with the phenoxycarbonyl migrating group (Table 2, entry 1 vs 2), although the best ee's were obtained in ether (entry 4) rather than *tert*-amyl alcohol (entry 6). Several other 3-alkyl benzofuranyl carbonates were investigated (entries 7−9) under the same conditions [ether, room temperature, 1 mol % of (*R*)-**1**] and afforded the desired *C*-phenoxycarbonyl benzofuranones **42c**−**e** in good yield (88−97%) and enantiomeric excess (92−93% ee). The absolute stereochemistry of the *C*-carboxylated isomers **42b**−**e** was assigned on the basis of analogy with the oxazole studies and with furanone derivatives to be discussed in the next section.

Table 2. 3-Alkylbenzofuran Enol Carbonate Rearrangements

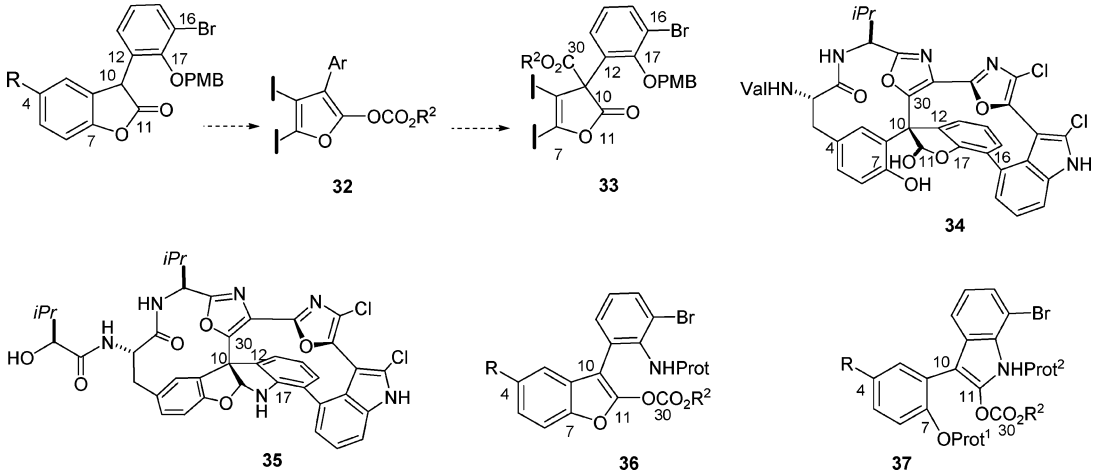
entry	substrate	solvent	yield (%)	ee (%)
1	**41a**	CH_2Cl_2	NA	44
2	**41b**	CH_2Cl_2	97	71
3	**41b**	THF	97	87
4	**41b**	Et_2O	92	92
5	**41b**	toluene	89	89
6	**41b**	*t*-amyl-OH	NA	70
7	**41c**	Et_2O	88	92
8	**41d**	Et_2O	96	93
9	**41e**	Et_2O	97	93

[a] Reaction at room temperature, 4 h.

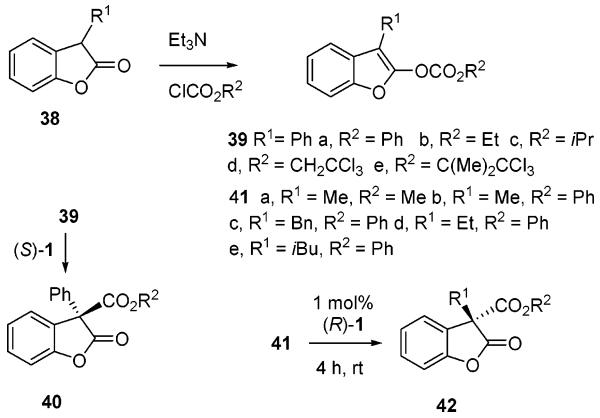
The TADMAP-catalyzed carboxyl migration reaction was extended to monocyclic furanone-derived enol carbonates **44**.

(27) Black, T. H.; Arrivo, S. M.; Schumm, J. S.; Knobeloch, J. M. *J. Org. Chem.* **1987**, *52*, 5425.
(28) (a) Studies Toward the Asymmetric Synthesis of Diazonamide A. Wang, J., Ph.D. Thesis, University of Wisconsin, 1997; *Diss. Abs. Int., B* **1998**, *59*, 1121. (b) Vedejs, E.; Wang, J. *Org. Lett.* **2000**, *2*, 1031.
(29) (a) Li, J.; Burgett, A. W. G.; Esser, L.; Amezcua, C.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4770. (b) Nicolaou, K. C.; Bella, M.; Chen, D. Y. K.; Huang, X. H.; Ling, T. T.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 3495. (c) Nicolaou, K. C.; Rao, P. B.; Hao, J. L.; Reddy, M. V.; Rassias, G.; Huang, X. H.; Chen, D. Y. K.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1753. (d) Burgett, A. W. G.; Li, Q.; Wei, Q.; Harran, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4961.
(30) Peris, G.; Vedejs, E. To be published.
(31) (a) Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921. (b) A related acyl migration approach to saturated furanones is reported: Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 5604.
(32) **38** with R^1 = Me: Piccolo, O.; Filippini, L.; Tinucci, L.; Valoti, E.; Attilio, C. *J. Chem. Res. Synop.* **1985**, 258.
(33) **38** with R^1 = misc. alkyls: Yoneda, E.; Sugioka, T.; Hirao, K.; Zhang, S.-W.; Takahashi, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 477. R = Ph: Padwa, A.; Dehm, D.; Oine, T.; Lee, G. A. *J. Am. Chem. Soc.* **1975**, *97*, 1837.
(34) The rearrangement of **39b** works very well using simple phosphine catalysts and is complete within 2 h at room temperature with 1 equiv of Et_3P or Bu_3P or within 24 h using Et_2PPh (see ref 28, p 149). A modestly enantioselective version of the rearrangement can be effected using the P−Ph analogue of **16** (32% ee, 84−87% yield after 24 h at room temperature with ca. 7% of the catalyst in CH_2Cl_2). However, attempts to achieve similar rearrangement with more highly substituted enol carbonates of general structure **32** resulted in low reactivity and formation of the parent benzofuranone as a side product. This side reaction, superficially corresponding to enolate protonation at the stage of the ion pair, was observed in nearly all attempts, and little *C*-carboxylated product was obtained even with simple phosphines. The side reaction was also dominant in the case where 10% Et_3P was used to catalyze the rearrangement of **39b** with Ph replaced by *o*-tolyl (Barda, D. A.; Vedejs, E. Unpublished results).

Scheme 5



Scheme 6



Scheme 7

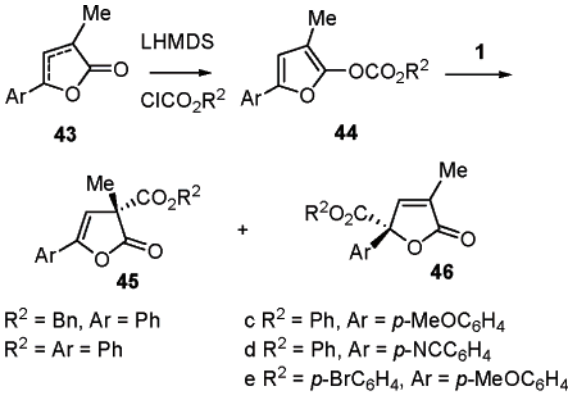
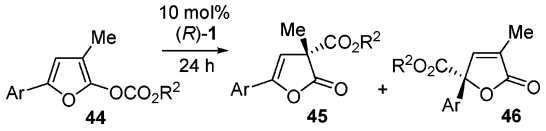


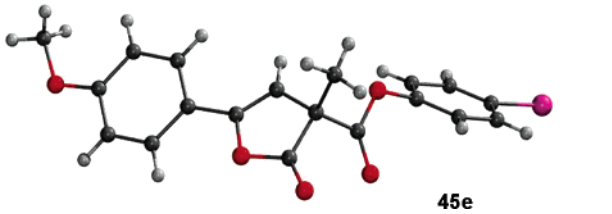
Table 3. 3-Methyl-5-arylfuran Enol Carbonate Rearrangement



entry	substrate	solvent	**45**:**46**[a]	ee$_{major}$ (%)
1[b]	**44a**	CH_2Cl_2	3:2	75
2[b]	**44b**	CH_2Cl_2	3:2	91
3	**44c**	CH_2Cl_2	5:1	82
4	**44c**	THF	10:1	90[c]
5	**44c**	Et_2O	11:1	83
6	**44c**	toluene	10:1	74
7	**44c**	*tert*-amyl-OH	6:1	91
8[d]	**44d**	CH_2Cl_2	1:4	63
9[d]	**44d**	THF	1:4	74
10[d]	**44d**	Et_2O	1:4	90[e]
11[d]	**44d**	toluene	1:4	83
12[d]	**44d**	*tert*-amyl-OH	1:4	50

[a] Ratio based on NMR assay; >95% conversion. [b] 1 mol % of catalyst **1**. [c] **45**, 83% yield; **46**, 7% yield (80% ee). [d] reaction complete in 4 h. [e] **46**, 75% yield; **45**, 25% yield.

Treatment of the benzyloxy or phenoxy derivatives **44a** or **44b** with 1 mol % of TADMAP **1** led to the formation of two regioisomeric *C*-alkoxycarbonyl products **45a** and **46a** or **45b** and **46b**, respectively (Table 3, entries 1 and 2; 3:2 **45**:**46**). However, as observed earlier in the azlactone series, the phenoxycarbonyl group migrated with higher enantioselectivity (entry 2; 91% ee for **45b**), so the phenoxy derivatives were explored in greater depth.

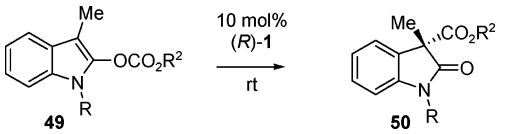


45e

In an attempt to improve regiocontrol, the electronic effect of the C-5 aryl substituent was varied. The relatively electron-rich methoxyphenyl derivative **44c** produced a better ratio (up to 11:1) favoring the α-carboxyl isomer **45c** (Table 3, entries 3−7). However, the electron-deficient **44d** gave a reversed 4:1 ratio favoring the γ-carboxyl product **46d** (entries 8−12). After optimization of solvent for each substrate, good yields and ee values were obtained for the major product in each example. The striking electronic effect of donor or acceptor substituents at C(5) aryl in these reactions is reminiscent of the trends reported by Steglich and Höfle for the related oxazole rearrangements, as already mentioned in connection with Scheme 2.[22]

The absolute stereochemistry of the furanones was probed in the case of the *p*-bromophenyl furanone **45e** (Scheme 7), obtained in the usual way (88% ee, 75% yield from **44**, using (*R*)-**1**), along with a small amount of isomer **46e**. After crystallization, the major product **45e** was analyzed by X-ray crystallography (anomalous dispersion) and was shown to possess the (*R*)-**45e** absolute stereochemistry. The absolute configurations of other furanone carboxyl migration products

Table 4. 3-Alkylindole Enol Carbonate Rearrangement



entry	substrate	solvent	time[a]	ee (%)
1	**49a**	CH_2Cl_2	35 d	23
2	**49a**	THF	35 d	55
3	**49a**	Et_2O	35 d	55
4	**49a**	toluene	35 d	45
5	**49a**	*tert*-amyl-OH	35 d	33
6	**49b**	CH_2Cl_2	8 d	37
7	**49b**	THF	8 d	2
8	**49c**	CH_2Cl_2	8 d	7
9	**49c**	THF	8 d	18
10	**49d**	CH_2Cl_2	28 d	48
11	**49d**	THF	28 d	50
12	**49e**	CH_2Cl_2	24 h	2
13	**49e**	THF	24 h	23
14	**49f**	CH_2Cl_2	24 h	<1
15	**49f**	THF	24 h	<1
16	**49g**	CH_2Cl_2	24 h	10
17	**49g**	THF	24 h	5
18	**49h**	CH_2Cl_2	24 h	39
19	**49h**	*tert*-amyl-OH	24 h	49
20	**53**	CH_2Cl_2	3 h	65
21	**53**	THF	5 h	61
22	**53**	CH_2Cl_2	24 h	75[b]
23	**53**	*tert*-amyl-OH	5 h	44
24	**53**	*tert*-amyl-OH	24 h	78[b]

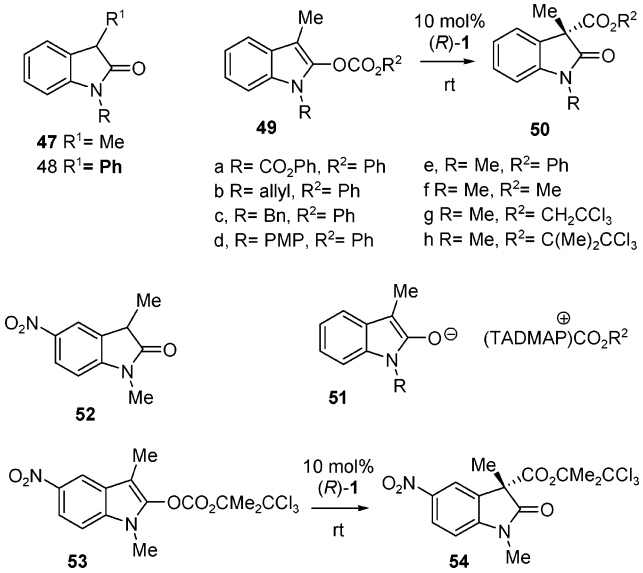
[a] Time required for >95% conversion of **49** or **53**. [b] Reaction at 0 °C; >98% yield.

were assigned by analogy. This stereochemistry is similar to that observed for the corresponding methyl substituted azlactone **15b**, as expected given the structural similarities.

Enantioselective Carboxyl Migration of 3-Substituted 2-Alkoxycarbonyloxyindoles. Extension of the carboxyl migration methodology to 2-indolyl enol carbonates proved difficult and somewhat problematic. Treatment of **49a** with 10 mol % of TADMAP (**1**) afforded the desired **50** as the sole product (Table 4, entries 1−5). However, the reaction was very slow, requiring over a month to reach completion at room temperature. While the enantioselectivity was in the promising range in the best solvents (45−55% ee), ee improvement at lower temperatures was not an option due to poor reactivity. Evidently, the enolate subunit of the necessary ion pair intermediate **51** is not sufficiently stabilized, an effect that can be attributed to the substituent at indole nitrogen, R = *N*-CO_2Ph. Although the inductive effect of amide carbonyl is expected to help stabilize a simple enolate,[35] there is an opposing factor in **51** because the nitrogen electron pair is potentially part of a delocalized indole π-system while amide delocalization with R = *N*-CO_2-Ph works against aromaticity. According to this rationale, substrates **49b**−**e** containing relatively electron rich (R = allyl, benzyl, *p*-methoxyphenyl, methyl) substituents at the indole nitrogen may be more reactive due to increased stability for **51**.

Enol carbonates **49b**−**e** were screened, and improved reactivity was indeed observed (entries 6−13). However, the enantioselectivities were marginal at best and poor for the most highly reactive *N*-methylindole **49e**. In an attempt to address this problem, optimization of the migrating group was investigated

Scheme 8



(entries 14−18). The best result was obtained with **49h** (trichlorobutoxycarbonyl as the migrating group, 49% ee). No attempt was made to correlate absolute configuration in view of the modest ee values, so the configurations as drawn are tentative and are based on the furan and oxazole analogies.

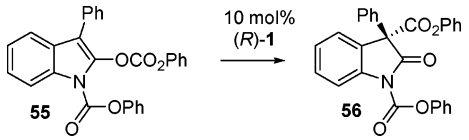
To provide greater flexibility for optimization in the indole series at low temperatures, the substrate was modified by the introduction of an electron-withdrawing nitro group to help stabilize the intermediate ion pair (Scheme 8). The starting nitrooxindole **52** was prepared by oxidation of the corresponding indole[36] and was converted into enol carbonate **53**. Compared to the analogous **49h**, the carboxyl migration rate upon treatment with 10 mol % of the catalyst **1** increased by ca. 8-fold at room temperature. Additionally, the selectivity improved substantially (entries 20 and 21), and could be further enhanced by lowering the temperature to 0 °C (entries 22 and 24), leading to the functionalized *C*-carboxylated oxindole **54** in 75−78% ee, >98% yield.

In a final series of experiments, the carboxyl migration methodology was extended to the *N*-protected 3-phenylindole **55** as a model substrate corresponding to **37**, the indole precursor that would be needed in a carboxyl migration approach to diazonamide A as discussed in connection with Scheme 5. Enol carbonate **55** was obtained in 87% yield by reaction of 3-phenyloxindole with phenyl chloroformate and triethylamine. Subsequent treatment of **55** with 10 mol % TADMAP, (*R*)-**1**, produced the desired carboxyl migration product **56**. The enantioselectivity in various solvents was good to excellent (Table 5), but the reaction was slow compared to the *N*-alkyl-3-methylindole examples of Table 4 (entries 12−18). Reactivity was improved for **55** compared to the *N*-(phenoxycarbonyl)-3-methyl analogue **49a**, probably due to the stabilizing effect of the 3-phenyl substituent at the stage of the ion pair intermediate, but several days or more were required for conversion of **55** at room temperature. Fortunately, the reaction could be conducted at 35−40 °C with only modest erosion of the enantiomeric excess (Table 5, entries 3, 5, 7, 9), resulting in good conversion within 18 h. In the best case (entry 9), using *tert*-amyl alcohol

(35) Garst, M. E.; Bonfiglio, J. N.; Grudoski, D. A.; Marks, J. *J. Org. Chem.* **1980**, *45*, 2307.

(36) Takase, S.; Uchida, I.; Tanaka, H.; Aoki, H. *Tetrahedron* **1986**, *42*, 5879.

Table 5. 3-Phenylindole Enol Carbonate Rearrangement



entry	solvent	temp (°C)	time[a] (h)	ee (%)
1	CH_2Cl_2	23	96	73
2	THF	23	96	82
3	THF	40	18	82
4	Et_2O	23	96	90
5	Et_2O	40[b]	18	83
6	toluene	23	96	87
7	toluene	40	18	74
8	*tert*-amyl-OH	23	96	90
9	*tert*-amyl-OH	40	18	86[c]

[a] Time required for >95% conversion of **55**. [b] Sealed tube. [c] 93% isolated yield.

as the solvent, the desired oxindole **56** was formed in 93% yield and 86% ee.

Compared to the relatively facile, highly enantioselective phenoxycarbonyl migrations with oxazole, furan, and benzofuran substrates, the analogous indole enol carbonates are substantially less reactive, and the enantioselectivity trends in Tables 4 and 5 are somewhat different. Much of the reactivity difference probably reflects the decreased stability of ion pair **51** compared to analogous intermediates in the oxazole, furan, and benzofuran series. Qualitatively, this difference can be appreciated by comparing the pK_a values of the unsubstituted benzofuranone **38** with R^1 = H (pK_a = 11.9) and the corresponding *N*-methyloxindole **47** with R^1 = H (pK_a = 15.7),[37] adjusted for the added delocalization by R^1 = Ph (pK_a 8.4 for **38** with R^1 = Ph).[38]

Assuming that the enantioselectivity-determining transition states for product formation in the more facile oxazole and furan enol carbonate rearrangements resemble tetrahedral intermediates leading to the *C*-carboxylated products, two isomeric transition structures, **57** or **58**, can be considered for substrates, where R^1 has a methylene group connected to the ring (Figure 4). Structure **57** would be formed from the less hindered phenoxycarbonyl pyridinium salt conformer and should be favored since it would also have fewer interactions between the phenoxy and trityl groups. As drawn, these structures somewhat exaggerate the role of one of the trityl phenyl groups in blocking the lower face of the pyridine ring,[39] but preferred bonding from the top face is expected. Analogous structures are plausible in the most highly enantioselective oxazole (**59**), furan (**60**), and benzofuran (**61**) rearrangements, provided that R^a corresponds to the eventual carbonyl group in the product, R^b is the unbranched carbon substituent required for optimum ee, and R^c is the aromatic substituent (C_2 aryl in **59**, C_5 aryl in **60**, and benzo-fused ring in **61**). In these examples, the favored conformer is relatively devoid of unfavorable steric interactions, and the qualitative models correspond to the sense of enantioselectivity. However, the analogous indole structure (**62**) would project the *N*-R substituent toward the acetoxy group of the catalyst. The added steric requirements of the indole *N*-R group may contribute to the decreased reactivity of **49a**−**d** as well as to the low enantioselectivity observed with **49e**. Thus, the faster rearrangements are observed with the smallest *N*-R group (Me > allyl or benzyl; Table 4, entry 12 vs entries 6, 8). However, there is no simple correlation of reactivity with enantioselectivity in Table 4. The qualitative model sheds no light on the preferred geometry for the indole rearrangements and does not address the detailed differences among the alkoxycarbonyl migrating groups.

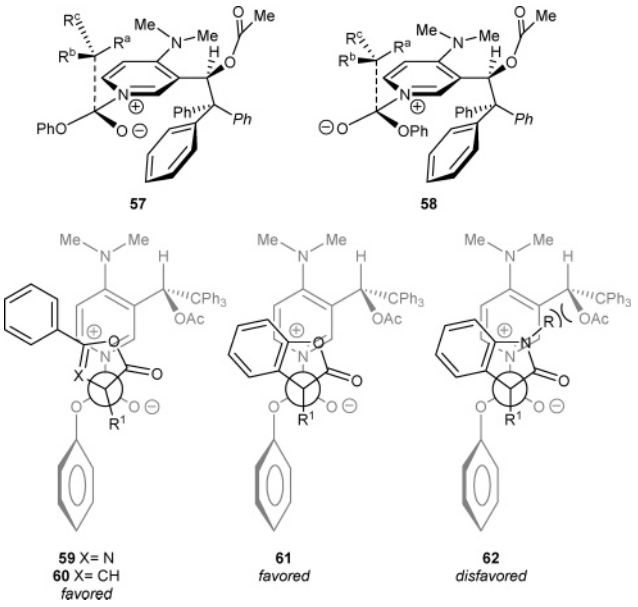


Figure 4. Qualitative models for stereochemical induction.

Summary

TADMAP (**1**) has been shown to catalyze the carboxyl migration of oxazolyl, furanyl, and benzofuranyl enol carbonates with good to excellent levels of enantioselection. In general these findings compare well in terms of yield, reactivity, and catalyst loading to the results reported earlier by Fu et al. using their planar chiral catalyst for similar rearrangements,[23,31] although the enantioselectivities are somewhat lower for the benzofuran and indole substrates. The oxazole reactions are especially efficient, and applications in more highly functionalized substrates allow the synthesis of convenient precursors of chiral lactams and lactones containing a quaternary asymmetric carbon. The analogous TADMAP-catalyzed indole reactions suffer from inconsistent enantioselectivity and low reactivity, requiring the use of 10 mol % of catalyst. Better enantioselection was observed by Fu et al. for the indoles, although a similar reactivity problem was encountered. Further studies will be needed to improve reactivity as well as catalyst accessibility. Even with the relatively short synthesis, TADMAP is probably not suitable for applications where 10% catalyst loading is necessary. However, shorter routes to analogous 3-substituted DMAP derivatives are easily imagined, and relevant studies are under way.

As a final comment, we will briefly note that TADMAP is only modestly selective as a catalyst for kinetic resolution. In a preliminary study, the best enantioselectivity, s = 4.4, was

(37) Kresge, A. J.; Meng, Q. *J. Am. Chem. Soc.* **2002**, *124*, 9189.
(38) Heathcote, D. M.; De Boos, G. A.; Atherton, J. H.; Page, M. I. *J. Chem. Soc., Perkin Trans. 2* **1998**, 535.
(39) A more more sterically demanding analogue of TADMAP was prepared with the trityl group replaced by tris(3,5-dimethylphenyl)methyl. Virtually identical results were obtained using this catalyst in dichloromethane (room temperature) for the carboxyl migrations of **39b** (28% ee) and **41b** (73% ee) compared to TADMAP, while lower enantioselectivities were observed starting with **13a** (12% ee) and **44b** (79% ee).

observed for the isobutyroylation of 1-naphthyl-1-ethanol at room temperature. If kinetic resolution had been used as the exclusive probe for the potential utility of TADMAP as a chiral nucleophilic catalyst, we may have opted to explore new catalysts and to bypass the experiments leading to the highly enantioselective carboxyl migrations reported above.

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

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