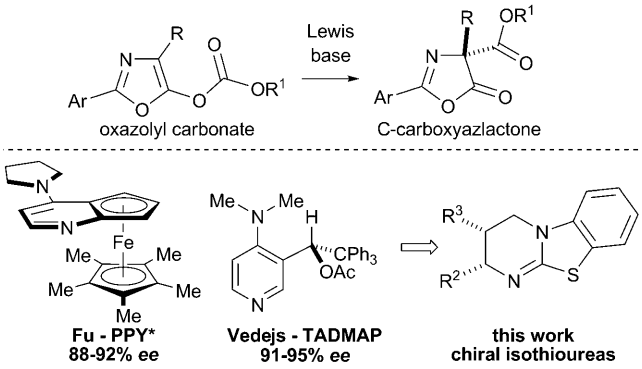
Synthetic Methods

DOI: 10.1002/ange.200904333

Isothiourea-Catalyzed Enantioselective Carboxy Group Transfer**

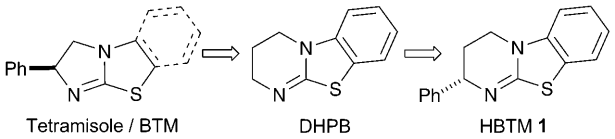
*Caroline Joannesse, Craig P. Johnston, Carmen Concellón, Carmen Simal, Douglas Philp, and Andrew D. Smith**

The rational design and mechanistic understanding of catalytic systems capable of generating quaternary stereocenters in an asymmetric fashion is a recognized challenge in synthesis.[1] A number of asymmetric Lewis base mediated processes have been developed within this area,[2] in which enantiomerically pure derivatives of 4-(pyrrolidino)pyridine (PPY) and 4-dimethylaminopyridine (DMAP) are elegantly employed by the Fu,[3] Vedejs,[4] and Richards groups,[5] as asymmetric catalysts for the rearrangement of 5-oxazolyl carbonates into 4-carboxyazlactones (Scheme 1).[6] This process delivers C-carboxyazlactones bearing a quaternary stereocenter with excellent enantiocontrol.[7]



Scheme 1. The asymmetric Steglich rearrangement.

Among the recent developments in Lewis base catalysis, the ability of isothioureas to efficiently promote alcohol acylation has been demonstrated. Birman and Li first showed that tetramisole and its benzannulated analogue BTM could catalyze effective kinetic resolution[8] and desymmetrization protocols (Scheme 2).[9] Independent studies by Kobayashi and Okamoto, and Birman et al. subsequently introduced



Scheme 2. Evolution of isothiourea catalysts.

DHPB,[10] before Birman and Li developed HBTM (**1**) for the kinetic resolution of aryl cycloalkanols.[11] Building upon these studies,[12,13] Dietz and Gröger have utilized tetramisole (32 mol%) to promote a modestly enantioselective rearrangement of an oxazolyl acetate (63% *ee* at 80% conversion),[14] and we have shown that DHPB represents the optimal catalyst substructure for the carboxyl group transfer reaction of oxazolyl carbonates in the racemic series.[15]

As part of a research program concerned with utilizing Lewis bases as catalysts,[16] we hoped to build upon these precedents by using chiral isothioureas, such as **1**, to promote the Steglich rearrangement with high enantioselectivity. The incorporation of a stereodirecting group at C4, adjacent to the nucleophilic nitrogen atom, is imperative in these catalyst architectures; this contrasts the recognized derogatory effect of the 2-substitution of DMAP or PPY derivatives upon catalytic turnover in acylation reactions.[4a,17] Upon formation of an N-carboxy derivative within the Steglich reaction, this stereodirecting group was predicted to adopt a pseudoaxial conformation.[18] It was anticipated that asymmetric induction would arise from discrimination between the prochiral faces of an azlactone enolate upon addition to this intermediate, preferably *anti* to the C4 stereodirecting unit, with the axial C3–H aiding differentiation between the planar aromatic and aliphatic quadrants (Figure 1).

Initial studies evaluated isothiourea **1** to promote the asymmetric O- to C-carboxyl group transfer of a range of alkyl and aryl oxazolyl carbonates **2**–**4**, with the transfer of the

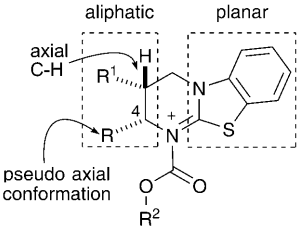


Figure 1. Proposed stereodefined N-carboxy intermediate. The stereodirecting unit at C4 is imperative; the stereodefined N-carboxy intermediate has a pseudoaxial directing substituent; and discrimination between the aliphatic and planar quadrants leads to high *ee*.

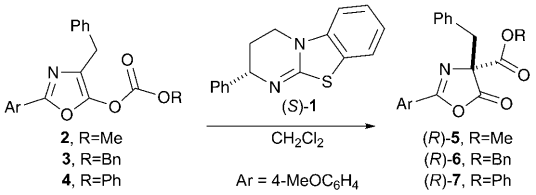
[*] C. Joannesse, C. P. Johnston, Dr. C. Concellón, C. Simal, Prof. D. Philp, Dr. A. D. Smith
EaStCHEM, School of Chemistry
University of St. Andrews
North Haugh, St. Andrews, Fife, KY16 9ST (UK)
E-mail: ads10@st-andrews.ac.uk
Homepage: http://ch-www.st-andrews.ac.uk/staff/ads/group/

[**] We thank the Royal Society (ADS), the EPSRC (C.J.), and the Ministerio de Educación y Ciencia (C.S. and C.C.) for funding and the EPSRC Mass Spectrometry Centre. Prof. Edwin Vedejs is gratefully acknowledged for supplying an authentic sample of (*R*)-TADMAP to allow unambiguous stereochemical assignments.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200904333.

phenoxycarbonyl group proceeding with the highest *ee* (Table 1).[19] The observed *ee* value of the product **7** proved insensitive to a variety of solvents, with the exception of THF

Table 1: Optimization studies.[a]



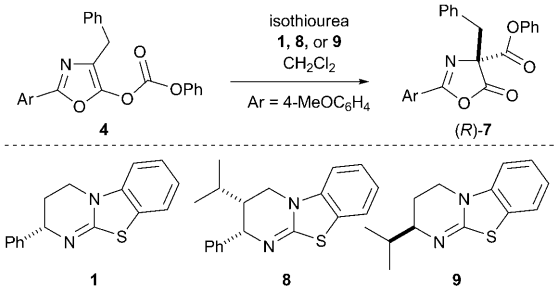
Entry	R	**1** (mol%)	*T* [°C]	Product	*ee* [%][b]
1	Me	10	RT	**5**	70
2	Bn	10	RT	**6**	72
3	Ph	10	RT	**7**	79
4	Ph	2	RT	**7**	79
5	Ph	10	−20	**7**	87
6	Ph	10	−50	**7**	91

[a] Reaction conditions: **2**–**4** (1 mmol), CH_2Cl_2 (1 mL), 1 h (RT) or 16 h (−20 °C or −50 °C). [b] Determined by HPLC analysis.

which gave **7** with a reduced *ee* value.[20] The loading of **1** could be reduced to 2 mol% at room temperature without affecting the product *ee* value. For optimal enantioselectivity, lowering the reaction temperature to −50 °C was necessary, giving **7** in 91% *ee* and 96% yield.[21]

Additional studies probed the ability of isothioureas **8** and **9** to promote the carboxyl group transfer of **4** (Table 2).[22] Isothiourea **8** showed similar reactivity and enantioselectivity to **1** (Table 2, entries 4–6). Isopropyl-substituted isothiourea **9** delivered **7** with high a *ee* value at room temperature but

Table 2: Evaluating chiral isothioureas for the carboxyl group transfer.[a]



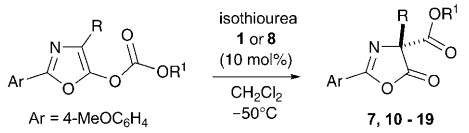
Entry	Cat. (mol%)	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**1** (2)	RT	95	79
2	**1** (10)	−20	96	87
3	**1** (10)	−50	96	91
4	**8** (10)	RT	93	83
5	**8** (10)	−25	92	87
6	**8** (10)	−60	96	93
7	**9** (10)	RT	94	87 (*ent*)
8	**9** (10)	−10	94	91 (*ent*)

[a] Reaction conditions: **4** (1 mmol), CH_2Cl_2 (1 mL), 1 h (RT) or 16 h (−10 °C to −60 °C). [b] Yield of isolated product. [c] Determined by HPLC analysis.

proved less reactive than either **1** or **8**, showing only reasonable catalytic activity between room temperature and −10 °C (Table 2, entries 7 and 8).

The generality of this process was additionally examined using isothioureas **1** and **8**. Rearrangement of the C4-alkyloxazolyl phenyl carbonates (R = Me, Et, *n*Bu, allyl, CH_2CH_2SMe) with either **1** or **8** proceeded with uniformly excellent enantioselectivities to deliver products **10**–**13** (Table 3, entries 3–8). Tyrosine-derived carbonates also

Table 3: Scope of the enantioselective carboxyl group transfer of oxazolyl carbonates with isothioureas **1** and **8**.[a]

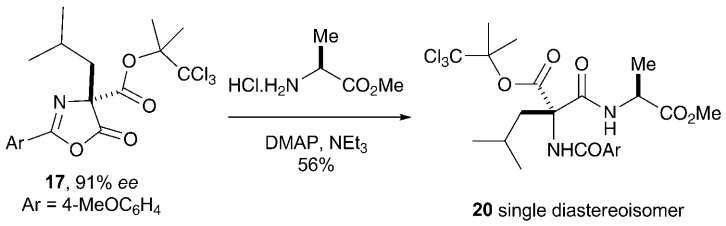


Entry	Cat.	R	R^1	Prod.	Yield [%][b]	*ee* [%][c]
1	**1**	Bn	Ph	**7**	96	91
2	**8**	Bn	Ph	**7**	96	93[d]
3	**1**	Me	Ph	**10**	68	94
4	**8**	Me	Ph	**10**	94	94[e]
5	**1**	Et	Ph	**11**	91	91
6	**8**	Et	Ph	**11**	96	93
7	**1**	*n*Bu	Ph	**12**	65	92
8	**1**	allyl	Ph	**13**	69	89
9	**1**	CH_2CH_2SMe	Ph	**14**	65	90
10	**1**	4-$BnOC_6H_4CH_2$	Ph	**15**	90	91
11	**8**	4-$BnOC_6H_4CH_2$	Ph	**15**	86	86[e]
12	**1**	4-$PhO_2COC_6H_4CH_2$	Ph	**16**	90	90
13	**8**	4-$PhO_2COC_6H_4CH_2$	Ph	**16**	97	87[e]
14	**1**	*i*Bu	$C(Me)_2CCl_3$	**17**	88	89[f]
15	**8**	*i*Bu	$C(Me)_2CCl_3$	**17**	82	91[g]
16	**1**	*i*Pr	Ph	**18**	–	73[f]
17	**1**	*i*Pr	4-$MeOC_6H_4$	**19**	38	78[h]
18	**8**	*i*Pr	4-$MeOC_6H_4$	**19**	30	78[f]

[a] Reaction conditions: oxazolyl carbonate (1 mmol), CH_2Cl_2 (1 mL), 16 h. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] Reaction temperature −60 °C. [e] Reaction temperature −30 °C. [f] Reaction temperature RT. [g] Reaction temperature 40 °C. [h] Reaction temperature 0 °C.

undergo carboxyl group transfer with good enantioselectivity to give products with up to 91% *ee* (Table 3, entries 10–13). Carboxyl group transfer in the leucine series proceeded at room temperature with **1** to give **17** in 88% yield and 89% *ee*, whereas using **8** at 40 °C gave **17** in 82% yield and 91% *ee* (Table 3, entries 14 and 15). Rearrangement of the C4-isopropyl-substituted oxazolyl phenyl carbonate with **1** proceeded readily to give **18** at room temperature, although significant amounts (30–40%) of the parent azlactone, formally corresponding to hydrolysis of the carbonate group, precluded the isolation of homogeneous product (Table 3, entry 16). However, reaction of the corresponding 4-methoxyphenyl carbonate using **8** allowed the isolation of **19**, albeit in modest yield (Table 3, entries 17 and 18), thereby representing, to the best of our knowledge, the first asymmetric rearrangement of C4-α-alkyl-branched oxazolyl carbonates.[4c]

To exemplify the utility of the reaction products, **17** (91% *ee*) was derivatized with L-alanine methyl ester, giving dipeptide **20** as a single diastereoisomer after purification (Scheme 3).[3]



17, 91% *ee*
Ar = 4-MeOC$_6$H$_4$

20 single diastereoisomer

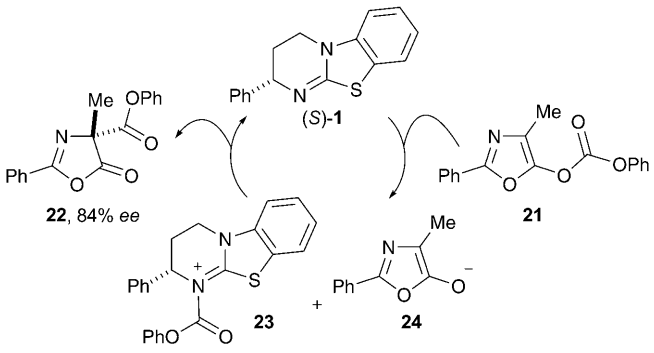
Scheme 3. Derivatization of C-carboxyazlactone product **17**.

Preliminary mechanistic studies show that nonlinear effects are not observed between the *ee* of the product (*R*)-**7** and catalyst **1**, of known *ee*, upon rearrangement of carbonate **4**;[23] this result is consistent with only one molecule of **1** being involved in the stereochemical-determining step of this reaction. Furthermore, control experiments indicate that the C-carboxyazlactone products are configurationally stable under the reaction conditions,[24] consistent with the C–C bond-forming event being irreversible. To understand the factors that govern the observed stereocontrol in this reaction, we performed calculations on the rearrangement of oxazolyl carbonate **21** using isothiourea **1**, which experimentally generates (*R*)-**22** in 84% *ee* at room temperature,[25] at the B3LYP/6-31G(d,p) level of theory.[26] For these calculations, it was assumed that the formation of C-carboxyazlactone (*R*)-**22** is initiated through nucleophilic attack of **1** at the carbonate carbonyl group of **21** which generates, after collapse of the corresponding tetrahedral intermediate, N-carboxy intermediate **23** and azlactone enolate **24**. Subsequent preferential C-carboxylation upon the *Re* face of enolate **24** gives (*R*)-**22** (Scheme 4).

A key question in understanding stereocontrol in this rearrangement reaction is identification of the lowest energy conformation of the N-carboxy intermediate **23**. Calculation of the relative conformational energies of (*S*)-**1** revealed that the Ph group preferentially adopts a pseudoequatorial position. As predicted, N-carboxylation of **1** to give **23** results in a reversal of the conformational bias—a pseudoaxial Ph group in **23** is 4.62 kcal mol^{-1} more favorable than the corresponding pseudoequatorial conformation, presumably reflecting minimization of 1,2-strain in this intermediate. Within **23**, the N-phenoxycarbonyl group preferentially lies approximately co-planar with the isothiourea heterocycle, giving two rotameric forms of intermediate **23**, with the C=O group either *syn* (preferred) or *anti* with respect to the C=N bond. Enolate **24** is therefore predicted to preferentially approach **23** *anti* to the face blocked by the axial Ph group.

This facial selectivity alone is not enough to generate high enantioselectivity in this transformation, as the lateral orientation of prochiral enolate **24** with respect to **23** must also be controlled. The two possible orientations of enolate **24**, combined with the two rotamers of **23**, gives rise to four possible combinations (Figure 2). We calculated the structures and the relative energies of the favored transition state for each permutation. Revealingly, all possible transition-states A–D placed the C2-phenyl group of enolate **24** over the planar aromatic portion of the isothiourea, thereby minimizing interactions with the axial C3–H of the tetrahydropyrimidinium ring. Both transition states leading to the major (*R*)-product enantiomer (TS A and TS B, Figure 2a) are lower in energy than the two transition states leading to the minor (*S*)-product enantiomer (TS C and TS D, Figure 2a). The lowest energy transition state is that accessed from the rotamer of **23** in which the C=O group is *syn* with respect to the C=N bond, permitting additional stabilizing C–H···O interactions between the enolate and both the tetrahydropyrimidinium ring and the *ortho*-hydrogen atoms of the aromatic ring of the phenoxycarbonyl group (Figure 2b).[27] The molecular electrostatic potentials of **23** and **24** were computed next to further understand the origins of this orientational selectivity.[26] These calculations indicated a significant area of positive charge associated with the surface of **23** centered on the tetrahydropyrimidinium ring. In enolate **24** there is considerable charge asymmetry associated with the oxazole ring, with the enolate oxygen atom carrying significant negative charge. Matching of these two areas of opposite charge gives rise to the correct orientation of enolate **24** with respect to **23** at the transition state.

In conclusion, isothioureas **1**, **8**, and **9** promote the rearrangement of a range of oxazolyl carbonates with excellent levels of enantiocontrol (up to 94% *ee*). The factors leading to high stereocontrol in this process have been studied computationally, with a number of discrete features identified as important. Firstly, the preference of the C4-stereodirecting group of N-carboxy intermediate **23** to adopt a pseudoaxial conformation directs the incipient enolate *anti* to the stereodirecting unit. Secondly, electrostatic complementarity between N-carboxy **23** and enolate **24**, assisted by C–H···O interactions and minimization of steric interactions with the axial C3–H, ensures that facial control of the enolate with respect to the C=O group is achieved. Current studies are focused upon probing fully the mechanism of this trans-



22, 84% *ee*

21

23

24

Scheme 4. Proposed catalytic cycle for the asymmetric carboxyl group transfer from the O to C of **21** to generate (*R*)-**22** using (*S*)-**1**.

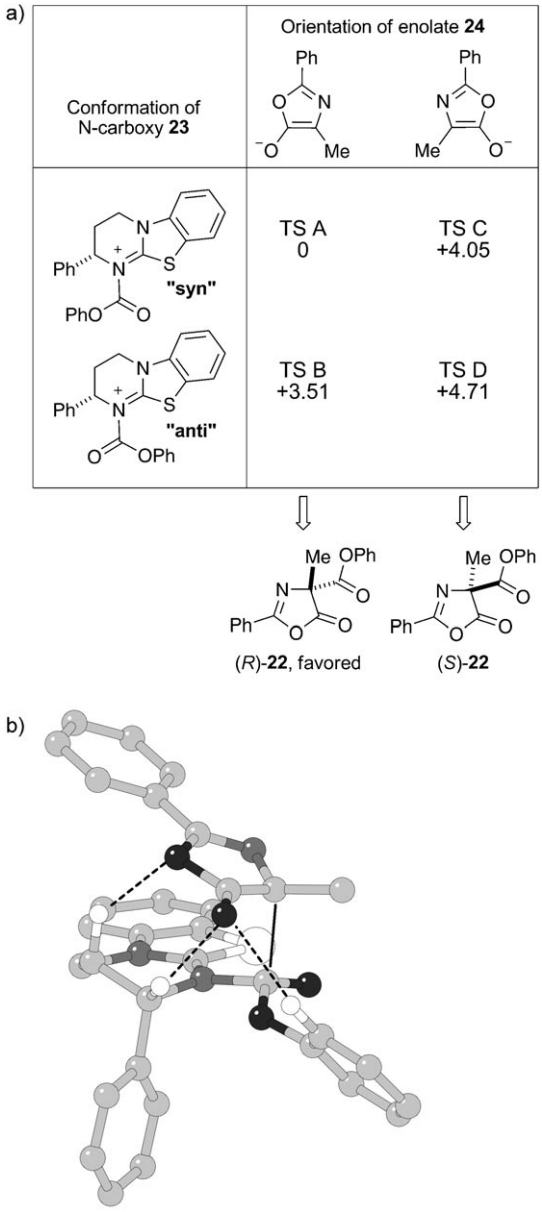


Figure 2. a) Relative transition-state energies (B3LYP/6-31G(d,p)) for the four possible transition states of the reaction of N-carboxy intermediate **23** and enolate **24**. Energies given in kcal mol^{-1}. b) Ball-and-stick representation of the lowest energy transition state (B3LYP/6-31G(d,p)) accessed by N-carboxy intermediate **23** and enolate **24** which leads to (*R*)-**22**. Dashed lines indicate C–H···O interactions and the solid black line indicates the C–C bond forming. Carbon atoms are light gray, nitrogen and oxygen atoms are dark gray, and hydrogen atoms are white.

formation and developing alternative applications of enantiomerically pure isothioureas in asymmetric catalysis.

Received: August 3, 2009
Published online: October 15, 2009

Keywords: asymmetric catalysis · carboxy group transfer · heterocycles · isothioureas · organocatalysis

[1] For a review, see C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363.
[2] For an excellent recent review, see S. E. Denmark, G. L. Beutner, *Angew. Chem.* **2008**, *120*, 1584; *Angew. Chem. Int. Ed.* **2008**, *47*, 1560.
[3] a) J. C. Ruble, G. C. Fu, *J. Am. Chem. Soc.* **1998**, *120*, 11532; for the application of this methodology to the rearrangement of indolyl and benzofuranyl carbonates, see b) I. D. Hills, G. C. Fu, *Angew. Chem.* **2003**, *115*, 4051; *Angew. Chem. Int. Ed.* **2003**, *42*, 3921.
[4] Vedejs et al. have also shown that PBO, a chiral phosphine, can promote this reaction with good enantioselectivity; see a) S. A. Shaw, P. Aleman, E. Vedejs, *J. Am. Chem. Soc.* **2003**, *125*, 13368; b) S. A. Shaw, P. Aleman, J. Christy, J. W. Kampf, P. Va, E. Vedejs, *J. Am. Chem. Soc.* **2006**, *128*, 925. Vedejs et al. have recently developed an alternative catalyst system for the rearrangement of indolyl carbonates and acetates which can tolerate α-branched substituents; c) T. A. Duffey, S. A. Shaw, E. Vedejs, *J. Am. Chem. Soc.* **2009**, *131*, 14.
[5] H. Y. Nguyen, D. C. D. Butler, C. J. Richards, *Org. Lett.* **2006**, *8*, 769.
[6] W. Steglich, G. Höfle, *Tetrahedron Lett.* **1970**, *11*, 4727.
[7] For other enantioselective approaches, see a) J. G. Seitzberg, C. Dissing, I. Søtofte, P.-O. Norrby, M. Johannsen, *J. Org. Chem.* **2005**, *70*, 8332; b) E. Busto, V. Gotor-Fernández, V. Gotor, *Adv. Synth. Catal.* **2006**, *348*, 2626.
[8] V. B. Birman, X. Li, *Org. Lett.* **2006**, *8*, 1351.
[9] V. B. Birman, H. Jiang, X. Li, *Org. Lett.* **2007**, *9*, 3237.
[10] a) M. Kobayashi, S. Okamoto, *Tetrahedron Lett.* **2006**, *47*, 4347; b) V. B. Birman, X. Li, Z. Han, *Org. Lett.* **2007**, *9*, 37.
[11] For the previous preparation of chiral isothiourea **1** and its use in kinetic resolution, see V. B. Birman, X. Li, *Org. Lett.* **2008**, *10*, 1115.
[12] For asymmetric C–C bond-forming reactions employing catalytic quantities of an amidine, see a) A. E. Taggi, A. M. Hafez, T. Dudding, T. Lectka, *Tetrahedron* **2002**, *58*, 8351; for an alternative use of tetramisole, see b) V. C. Purohit, A. S. Matla, D. Romo, *J. Am. Chem. Soc.* **2008**, *130*, 10478.
[13] For select examples of amidines as catalysts, see a) S. Kim H. Chang, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3669; b) V. K. Aggarwal, A. Mereu, *Chem. Commun.* **1999**, 2311; c) W.-C. Shieh, S. Dell, O. Repic, *J. Org. Chem.* **2002**, *67*, 2188; d) B. G. G. Lohmeijer, R. C. Pratt, F. Leibfarth, J. W. Logan, D. A. Long, A. P. Dove, F. Nederberg, J. Choi, C. Wade, R. M. Waymouth, J. L. Hedrick, *Macromolecules* **2006**, *39*, 8574; e) W. Zhang, M. Shi, *Org. Biomol. Chem.* **2006**, *4*, 1671.
[14] F. R. Dietz, H. Gröger, *Synlett* **2008**, 663. In our hands, tetramisole did not promote the carboxyl group transfer of **4**.
[15] C. Joannesse, C. Simal, C. Concellón, J. E. Thomson, C. D. Campbell, A. M. Z. Slawin, A. D. Smith, *Org. Biomol. Chem.* **2008**, *6*, 2900.
[16] a) J. E. Thomson, K. Rix, A. D. Smith, *Org. Lett.* **2006**, *8*, 3785; b) J. E. Thomson, C. D. Campbell, C. Concellón, N. Duguet, K. Rix, A. M. Z. Slawin, A. D. Smith, *J. Org. Chem.* **2008**, *73*, 2784; c) J. E. Thomson, A. F. Kyle, C. Concellón, K. A. Gallagher, P. Lenden, L. C. Morrill, A. J. Miller, C. Joannesse, A. M. Z. Slawin, A. D. Smith, *Synthesis* **2008**, 2805; d) C. D. Campbell, N. Duguet, K. A. Gallagher, J. E. Thomson, A. G. Lindsay, A. C. O'Donoghue, A. D. Smith, *Chem. Commun.* **2008**, 3528.
[17] For reviews of the chemistry of DMAP and PPY derivatives, see a) G. Höfle, W. Steglich, H. Vorbrüggen, *Angew. Chem.* **1978**, *90*, 602; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569; b) A. C. Spivey, S. Arseniyadis, *Angew. Chem.* **2004**, *116*, 5552; *Angew. Chem. Int. Ed.* **2004**, *43*, 5436. For asymmetric synthesis employing a 2-substituted DMAP derivative, see c) E. Vedejs, X. Chen, *J. Am. Chem. Soc.* **1996**, *118*, 1809.

[18] For representative examples that demonstrate the preference of substituents adjacent to an N-acyl group in heterocyclic compounds to adopt a pseudoaxial position, see a) P. J. Sinclair, D. Zhai, J. Reibenspies, R. M. J. Williams, *J. Am. Chem. Soc.* **1986**, *108*, 1103; b) J. F. Dellaria, B. D. Santarsiero, *J. Org. Chem.* **1989**, *54*, 3916; c) M. G. B. Drew, L. M. Harwood, G. Park, D. W. Price, S. N. G. Tyler, C. R. Park, S. G. Cho, *Tetrahedron* **2001**, *57*, 5641.

[19] The absolute configuration of (*R*)-**6** was assigned by comparison of the sign of its specific rotation with that reported in the literature.[3] The absolute configuration of (*R*)-**7** was unambiguously assigned by comparison of the HPLC data derived from rearrangement of **4** into (*R*)-**7** employing an authentic sample of (*R*)-TADMAP that was generously donated by Prof. Edwin Vedejs. The configuration of all other rearrangement products was assigned by analogy.

[20] See the Supporting Information for full details.

[21] As well as giving the highest enantioselectivity, phenoxycarbonyl substrates rearrange at a faster rate than the corresponding methoxy- and benzyloxycarbonyl derivatives, and also allow the reaction temperature to be lowered significantly from room temperature to optimize product *ee* values.

[22] The stereochemical integrity of **1**, **8**, and **9** were all unambiguously assessed as greater than 99% *ee* by HPLC analysis and comparison with racemic standards. **1**, **8**, and **9** were easily synthesized from the corresponding enantiomerically pure γ-amino alcohol derivatives in three simple steps (see the Supporting Information for full experimental details). (*S*)-**1** was prepared directly from commercially available (*S*)-3-amino-3-phenylpropan-1-ol hydrochloride (>99% *ee*, Fluorochem); (3*R*,4*S*)-**8** was readily derived from (1*S*,2*S*)-2-methyl-3-oxo-1-phenylpropylcarbamate (>98% *de*, >99% *ee*) which was prepared using an asymmetric L-proline-catalyzed Mannich reaction; see J. W. Yang, M. Stadler, B. List, *Nat. Protoc.* **2007**, *2*, 1937. (*R*)-**9** was derived from (*R*)-3-amino-4-methyl-pentanoic acid (>99% *ee*, Fluorochem).

[23] For reviews of nonlinear effects in asymmetric catalysis, see a) H. B. Kagan, T. O. Luukas in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, New York, **1999**, chap. 4.1; b) H. B. Kagan, *Adv. Synth. Catal.* **2001**, *343*, 227.

[24] Treatment of (*R*)-**7** (79% *ee*) with either (*S*)-**1** or (±)-**1** (10 mol%) in CH_2Cl_2 at ambient temperature returned (*R*)-**7** (79% *ee*); treatment of (±)-**7** with (*S*)-**1** similarly returned (±)-**7**.

[25] Oxazolyl carbonate **21** was treated with (*S*)-**1** (10 mol%) in CH_2Cl_2 at room temperature, giving (*R*)-**22** in 84% *ee*. See the Supporting Information for details. Fu and co-workers have previously shown that a 4-methoxyphenyl oxazolyl substituent offers the highest rate of rearrangement in this process (see reference [3])and so this substituent was used throughout. Comparable product *ee* values were obtained from the rearrangement of **21** (4-Ph) and the corresponding 4-methoxyphenyl oxazolyl carbonate in our hands.

[26] The Supporting Information contains full computational details, coordinates corresponding to the four lowest energy transition-states A–D and the electrostatic potential surfaces of N-carboxy **23** and enolate **24**.

[27] The observation of the *ortho*-hydrogen atoms of the phenoxycarbonyl intermediate participating in stabilizing C–H···O interactions in the preferred transition state may explain the trend observed in Table 1 in which the highest levels of enantioselectivity are observed with the phenoxycarbonyl, rather than methoxy- or benzyloxycarbonyl substrates.

