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Probing the Efficiency of N-Heterocyclic Carbene Promoted *O*- to C-Carboxyl Transfer of Oxazolyl Carbonates

Jennifer E. Thomson, Craig D. Campbell, Carmen Concellón, Nicolas Duguet, Kathryn Rix, Alexandra M. Z. Slawin, and Andrew D. Smith*

EaStCHEM, School of Chemistry, University of St. Andrews, North Haugh, St. Andrews KY16 9ST, U.K.

ads10@st-andrews.ac.uk

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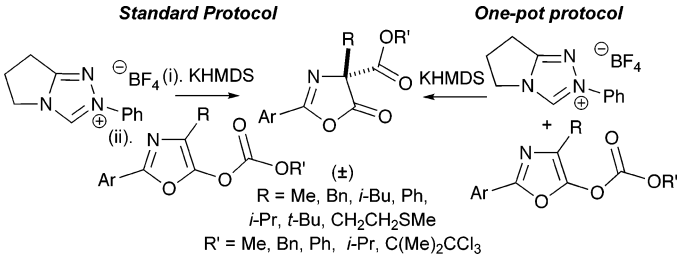

Screening of a range of azolium salts, bases and solvents for reactivity indicates that triazolinylidenes, generated in situ with KHMDS in THF, promote the Steglich rearrangement of oxazolyl carbonates with high catalytic efficiency (typical reaction time 5 min at <1.5 mol % NHC). This protocol shows wide substrate applicability, even allowing the efficient generation of vicinal quaternary centers. An improved experimental procedure is also described that allows a simplified one-pot reaction protocol to be employed with similarly high catalytic efficiency.

Introduction

The area of nucleophilic catalysis encompasses an enormous array of reactions, with the most popular employing amine[1] or phosphine catalysts.[2] DMAP derivatives are widely recognized as potent and general acylation catalysts[3] and are frequently used in diverse synthetic applications such as kinetic resolution,[4] desymmetrization[5] and β-lactam formation.[6] In 1970, Steglich and Höfle showed that both 4-(pyrrolidino)pyridine (PPY) and DMAP could act as nucleophilic catalysts, promoting the rearrangement of 5-oxazolyl carbonate derivatives to their corresponding 4- or 2-carboxyazlactones.[7] Importantly, the regioselectivity of this transformation is dependent upon both the steric and electronic nature of the 2- and 4-substituents within the 5-oxazolyl carbonate. For example, treatment of methyl carbonates **1** and **2** with DMAP gives the corresponding 4-carboxyazlactones **5** and **6** in 70% and 60% yield, respectively,

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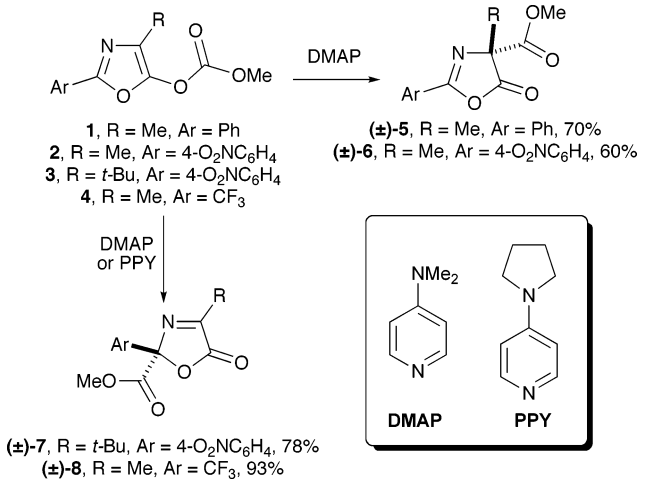

FIGURE 1. DMAP- or PPY-catalyzed *O*-to C-carboxyl transfer.

while treatment of the C(4)-*tert*-butyl substituted oxazolyl carbonate **3** with DMAP, or C(2)-trifluoromethyloxazolyl methyl carbonate **4** with PPY, gave the corresponding 2-carboxyazlactones **7** and **8** in 78% and 93% yield, respectively. The observed regioselectivity in these transformations is consistent with a sterically hindered C(4)-substitutent or a strongly electron-withdrawing substituent at C(2) within the oxazolyl carbonate favoring carboxyl transfer to C(2) rather than C(4) (Figure 1). Fu,[8] Vedejs,[9,10] and Richards,[11] among others,[12] have elegantly shown that chiral DMAP or PPY derivatives can induce high enantioselectivity in the C(4)-carboxylation reaction manifold, while Vedejs has also shown that chiral phosphines are catalytically active.[9] Although effective, these catalysts have not been shown to tolerate α-branched C(4)-substituents, presumably due to steric hindrance.[10]

The remarkable donor properties of N-heterocyclic carbenes (NHCs) have been widely exploited through their use as versatile ligands in organometallic processes,[13] and in recent years their ability to act as organocatalysts in a diverse series of reactions has been identified.[14] NHCs are typically used in polarity reversal or Umpolung techniques, allowing the formation of C−C bonds via acyl anion equivalents of carbonyl compounds or acylsilanes.[15] Although Stetter and Benzoin-type reactions have been investigated extensively,[16] recent advances in the preparation of homoenolates[17] via this technique have been efficiently realized. Aside from their use in multicomponent reactions[18] and as catalysts in cyanosilylation,[19] trifluoromethylation,[20] hydroacylation,[21] amidation,[22] redox reactions[23] and aziridine opening[24] or similar reactions,[25] NHCs have been used as acyl transfer agents. The Nolan and Hedrick groups first showed that NHCs could promote transesterification reactions via nucleophilic catalysis,[26] although Movassaghi and Schmidt have proposed that NHCs function as carbon-centered Brønsted bases in a related reaction protocol.[27] Enantiomerically pure C_2 symmetric NHCs have been applied to the kinetic resolution of racemic alcohols, although relatively high catalyst loadings (typically 5−30 mol %) and long reaction times (up to 48 h) are needed for these resolutions to proceed with high levels of stereoselectivity.[28] As part of our ongoing studies concerned with extending the synthetic utility of NHCs, their use as nucleophilic organocatalysts to promote the Steglich rearrangement of oxazolyl carbonates was investigated. It was proposed that the ability to generate NHCs in situ under a variety of reaction conditions from the corresponding azolium salt, combined with the high reactivity profile of NHCs, would facilitate a truly efficient catalytic process that would be applicable to a wide range of oxazolyl carbonates including C(4)-α-branched derivatives. We delineate herein our full

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investigations within this area, part of which has been communicated previously.[29]

Results and Discussion

Precatalyst Screening for the Rearrangement of Oxazolyl Carbonates. As it is widely recognized that the reactivity of NHCs can be significantly affected by their electronic and steric properties, our initial investigations set out to probe the structural characteristics of the NHC necessary for efficient catalysis in the Steglich rearrangement of oxazolyl carbonates. A range of simple imidazolium, imidazolinium, thiazolium and triazolium salts **12**−**18** were therefore screened as precatalysts, with the rearrangement of alanine-derived methyl carbonate **10**, readily prepared from the parent azlactone **9** and methyl chloroformate with NEt_3, to the corresponding ester (±)-**11** used as a model system for reaction optimization. In each case, addition of base (9.5 or 9 mol %) to a solution of the heteroazolium salt (10 mol %) in THF was used to generate the corresponding NHC (concentration of NHC = 10 mM) in situ before addition of the carbonate **10**. Treatment of imidazolium chlorides **12** or **14** with *t*-BuOK or KHMDS, or tetrafluoroborate **13** with KHMDS, gave complex product distributions containing <30% conversion to the desired ester (±)-**11** (entries 1−5). Deprotonation of imidazolinium chlorides **15** and **16** with KHMDS or *n*-BuLi gave no conversion to product, returning predominantly carbonate **10** contaminated with <20% of azlactone **9**, while addition of KHMDS or NEt_3 to the commercially available thiazolium salt **17** and addition of **10** returned only starting material. Encouragingly, treatment of triazolium salt **18** with KHMDS and addition of methyl carbonate **10** promoted rearrangement to (±)-**11** in quantitative conversion (entry 12), although no conversion to (±)-**11** was seen using the organic bases NEt_3 or *i*-Pr_2NEt (entries 13 and 14, Table 1). Further investigations showed that quantitative conversion of **10** to (±)-**11** using the NHC derived from triazolium salt **18** and KHMDS at this catalyst loading (10 mol %) could be readily achieved at NHC concentrations of 1−50 mM, with poor conversion to (±)-**11** being observed at NHC concentrations of <1 mM. All further rearrangement studies used NHC concentrations within this range.

To evaluate the generality of these findings, the effect of variation in the carbonate group (Me, Ph) and the C(4)-substituent (Me, Bn) within the oxazolyl framework was evaluated using azolium salts **12**, **15** and **18** as precatalysts (Table 2). The C(4)-benzyl substituted methyl carbonate **19** showed marginally improved reactivity relative to carbonate **10**, with the NHC derived from imidazolium salt **12** giving 40% conversion to (±)-**22** (entry 4), although the NHC derived from triazolium salt **18** again gave quantitative rearrangement to **22** (entry 6). A further improvement in reactivity was observed with phenyl carbonates **20** and **21**, with generation of NHCs from imidazolium salt **12** and imidazolinium salt **15** with KHMDS giving >90% conversion of **21** to (±)-**24**, although triazolium salt **18** again proved most efficient as a precatalyst (entries 9 and 12). These reactions indicate that triazolium salt **18** is an efficient precatalyst for the NHC-catalyzed rearrangement of oxazolyl carbonates. Furthermore, the nature of both the C(4)-substituent and carbonate group affects the ease of rearrangement, with the phenyl carbonate optimal.

The distinct differences in reactivity observed between triazolium salt **18** and imidazolium or imidazolinium salts **12**−

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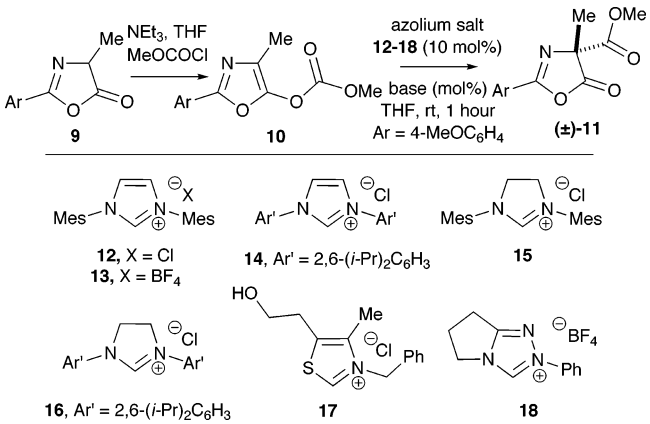
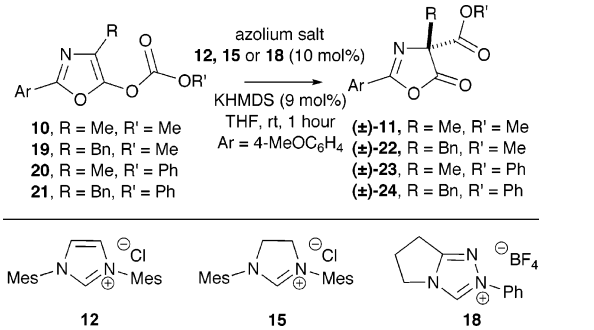
TABLE 1. Initial Evaluation of Azolium Precatalysts and Bases for the Rearrangement of 10 to (±)-11



entry	salt	base (mol %)	product conversion (%)[a]
1	**12**	*t*-BuOK (9)	<20
2	**12**	KHMDS (9)	<30
3	**13**	KHMDS (9)	<20
4	**14**	*t*-BuOK (9)	<20
5	**14**	KHMDS (9)	20
6	**15**	KHMDS (9)	0
7	**15**	*n*-BuLi (9)	0
8	**16**	KHMDS (9)	0
9	**16**	*n*-BuLi (9)	0
10	**17**	KHMDS (9)	0
11	**17**	NEt_3 (9)	0
12	**18**	KHMDS (9)	>98
13	**18**	NEt_3 (9.5)	0
14	**18**	*i*-Pr_2NEt (9.5)	0

[a] All reaction conversions and product distributions were judged by ^1H NMR spectroscopic analysis of the crude reaction product.

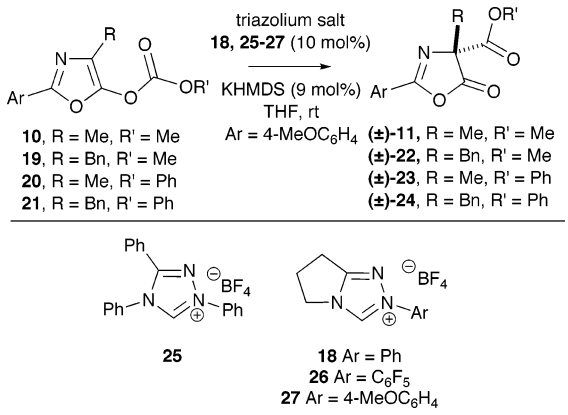
TABLE 2. Product Conversion with Variation of Precatalyst for the Rearrangement of Carbonates 10 and 19−21



entry	carbonate	salt	product conversion (%)[a]
1	**10**	**12**	<30
2	**10**	**15**	0
3	**10**	**18**	>98
4	**19**	**12**	40
5	**19**	**15**	10
6	**19**	**18**	>98
7	**20**	**12**	70
8	**20**	**15**	<5
9	**20**	**18**	>98
10	**21**	**12**	>90
11	**21**	**15**	>90
12	**21**	**18**	>98

[a] All reaction conversions and product distributions were judged by ^1H NMR spectroscopic analysis of the crude reaction product.

TABLE 3. Variation of Reaction Efficiency with Triazolium Precatalysts for the Rearrangement of Carbonates 10 and 19−21



entry	carbonate	salt	product conversion (%)[a]
1	**10**	**25**	<10
2	**19**	**25**	<10
3	**21**	**25**	<10
4	**23**	**25**	>90
5	**19**	**18**	>98
6	**21**	**18**	>98
7	**19**	**26**	>98
8	**21**	**26**	>98
9	**19**	**27**	>98
10	**21**	**27**	>98

[a] All reaction conversions and product distributions were judged by ^{1}H NMR spectroscopic analysis of the crude reaction product.

16 as a precatalyst in this reaction manifold is striking. It was postulated that this reactivity difference could be due to a subtle electronic difference between these NHC families or to the triazolium skeleton minimizing steric constraints by virtue of containing a cyclic N-substituent. To probe this theory, the reactivity of a series of NHCs derived from triazolium salts **18** and **25**−**27** bearing sterically and electronically diverse N-substituents were compared (Table 3).[30,31] In general, the NHC derived from triazolium salt **25** proved substantially less active as a catalyst for the rearrangement of oxazolyl carbonates than any of the NHCs derived from triazolium salts **18**, **26** or **27**, giving <10% product conversion for carbonates **10**, **19** and **20**, although >90% conversion of **21** to (±)-**24** was observed. While not conclusive, these reactions seem to indicate that steric factors may contribute significantly to the reactivity differences observed with change in NHC structure. It is hoped that future rate studies will be able to delineate fully and quantify the effect of varying the steric and electronic nature of the N-substituents within a given NHC class.

Control experiments verified that NHC **28** derived from **18** is the catalytic species in these rearrangements, as addition of methyl and phenyl carbonates **10** and **21** to either salt **18** (10 mol %), HMDS (9 mol %), KBF_4 (9 mol %), or a mixture of HMDS (9 mol %) and KBF_4 (9 mol %) in THF gave no conversion to the corresponding esters (±)-**11** and (±)-**24** even after prolonged reaction times (>4 h). Addition of KHMDS (9 mol %) to **10** also returned exclusively starting material, while

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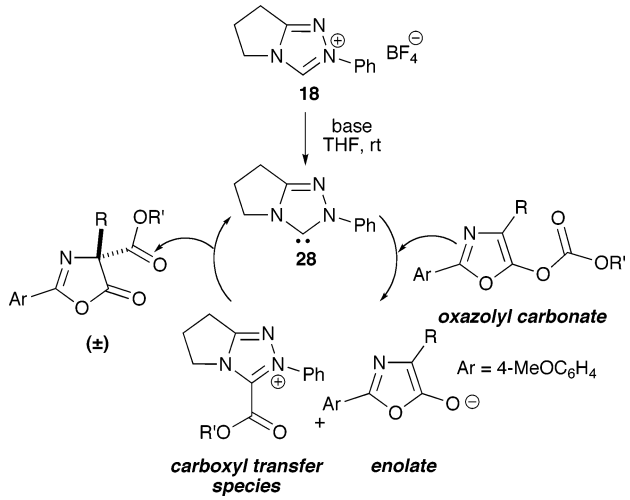


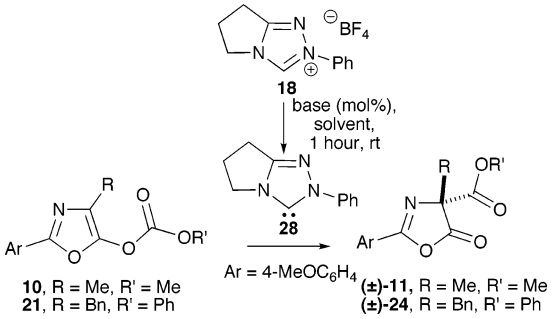
FIGURE 2. Simplified mechanism of NHC-promoted *O*- to C-carboxyl transfer.

addition of KHMDS to **21** gave a complex mixture of products containing <5% of (±)-**24**. Using this information, a simplistic mechanistic scheme may be proposed, involving initial deprotonation of triazolium salt **18** with base to generate NHC **28** that acts as a nucleophilic catalyst. Nucleophilic attack of NHC **28** at the carbonate carbonyl generates the reactive carboxyl transfer intermediate and the corresponding enolate, with C-carboxylation giving the desired product and regenerating NHC **28** (Figure 2). Although preliminary crossover studies are consistent with an intermolecular step in this process,[29] detailed mechanistic studies of this process are underway and will be reported in due course.

Reaction Optimization: Probing Variation in Base, Solvent and Catalyst Loading. Subsequent studies focused upon reaction optimization through variation of the solvent, base and catalyst loading. A range of solvents were tested for the generation of NHC **28** from triazolium salt **18**; at 9 mol % of KHMDS and 10 mol % **18**, the rearrangement of **10** to (±)-**11** proceeded with equal efficacy in THF, Et_2O or CH_2Cl_2, but with lower conversion in toluene (entries 1−4). A base screen in THF indicated that, at 9 mol % of base and 10 mol % **18**, KHMDS, LHMDS, and *n*-BuLi all proved efficient, giving quantitative conversion of **10** to (±)-**11**, although MeMgBr returned only starting material. Upon lowering sequentially the loadings of precatalyst **18** and base, KHMDS proved the most efficient, allowing efficient conversion of **10** to (±)-**11** with <1 mol % base (entries 4−9). For the rearrangement of phenyl carbonate **21**, KHMDS, LHMDS and *n*-BuLi (9 mol %) all proved efficient, allowing good conversion to (±)-**24** irrespective of solvent choice (entries 13−16) or with 0.9 mol % of base in THF (Table 4).

Variation of Carbonate Functionality: Scope and Limitations. Having identified an operative catalytic process, the efficiency of NHC catalysis with variation in carbonate functionality was investigated. In the alanine-derived series using triazolium salt **18** and KHMDS in THF, methyl, benzyl and phenyl carbonates **10**, **29** and **20** undergo rapid and quantitative rearrangement to the corresponding esters within 5 min at room temperature with 0.9 mol % NHC **28**, giving (±)-**11**, (±)-**33** and (±)-**23** in 77−84% isolated yield. The incorporation of an unactivated α-branched carbonate markedly slowed the rearrangement, with 9 mol % of NHC **28** necessary to promote

TABLE 4. Effect of Variation of Base and Solvent for the Rearrangement of Carbonates 10 and 21 with NHC 28



entry	carbonate	base (mol %)	**18** (mol %)	solvent	product conversion (%)[a]
1	**10**	KHMDS (9)	10	THF	>98
2	**10**	KHMDS (9)	10	Et_2O	>98
3	**10**	KHMDS (9)	10	toluene	~40
4	**10**	KHMDS (9)	10	CH_2Cl_2	>90
5	**10**	KHMDS (4)	5	THF	>98
6	**10**	KHMDS (1.5)	2	THF	>98
7	**10**	KHMDS (0.9)	1	THF	>98
8	**10**	LHMDS (9)	10	THF	>98
9	**10**	LHMDS (1.5)	2	THF	50
10	**10**	*n*-BuLi (9)	10	THF	>98
11	**10**	*n*-BuLi (1.5)	2	THF	45
12	**10**	MeMgBr (9)	10	THF	0
13	**21**	KHMDS (9)	10	THF	>98
14	**21**	KHMDS (9)	10	Et_2O	>98
15	**21**	KHMDS (9)	10	toluene	>90
16	**21**	KHMDS (9)	10	CH_2Cl_2	>90
17	**21**	KHMDS (0.9)	1	THF	>98
18	**21**	LHMDS (9)	10	THF	>98
19	**21**	LHMDS (0.9)	1	THF	>98
20	**21**	*n*-BuLi (9)	10	THF	>98
21	**21**	*n*-BuLi (0.9)	1	THF	>98
22	**21**	NaH (9)	10	THF	>98

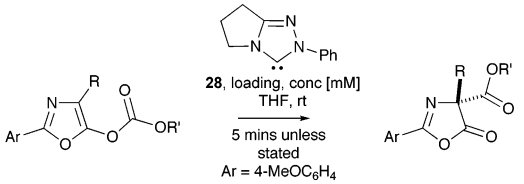
[a] All reaction conversions and product distributions were judged by ^{1}H NMR spectroscopic analysis of the crude reaction product.

complete conversion of **30** to (±)-**34** within 5 min. Complete conversion of **30** to (±)-**34** could be achieved at lower catalyst loadings but required longer reaction times; for example, 4 mol % of NHC **28** gave complete conversion to (±)-**34** within 2 h. Notably, the rearrangement of the sterically hindered, but electronically activated, carbonate **31**[8] proved relatively efficient, with 1.5 mol % of NHC **28** promoting rearrangement to (±)-**35**[32] within 2 h. In the phenylalanine-derived series, methyl, benzyl and phenyl carbonates **19**, **32** and **21** underwent quantitative rearrangement within 5 min using 0.9 mol % NHC **28**, giving the corresponding esters in 80−82% isolated yields (Table 5).

To probe further the nature of the carbonate group upon the reaction efficiency, the development of a diastereoselective rearrangement procedure through the use of a chiral carbonate derivative was investigated. While efficient enantioselective versions of the Steglich rearrangement of oxazolyl carbonates have been developed,[8−10] diastereoselective variants in this heterocyclic series have, to the best of our knowledge, not been investigated, although Vedejs and Peris have reported a diastereoselective variant upon benzofuran derivatives.[33] A range of chiral carbonate derivatives **38**−**47** were therefore prepared

(32) Although **35** has been reported previously in enantiomerically enriched form as an oil,[11] in our hands (±)-**35** was a crystalline solid, whose structure was confirmed unambiguously through X-ray crystallographic analysis. See Supporting Information for full details.

TABLE 5. Scope and Limitations: Variation of Carbonate Functionality



10, R = Me, R' = Me; **29**, R = Me, R' = Bn
20, R = Me, R' = Ph; **30**, R = Me, R' = *i*-Pr
31, R = Me, R' = $C(Me)_2CCl_3$
19, R = Bn, R' = Me; **32**, R = Bn, R' = Bn
21, R = Bn, R' = Ph

(±)-11, R = Me, R' = Me; **(±)-33**, R = Me, R' = Bn
(±)-23, R = Me, R' = Ph; **(±)-34**, R = Me, R' = *i*-Pr
(±)-35, R = Me, R' = $C(Me)_2CCl_3$
(±)-22, R = Bn, R' = Me; **(±)-36**, R = Bn, R' = Bn
(±)-24, R = Bn, R' = Ph

carbonate	R	R′	**28** (mol %)	**28** (mM)[a]	ester	yield (%)[b]
10	Me	Me	0.9	4	**11**	84
29	Me	Bn	0.9	4	**33**	77
20	Me	Ph	0.9	4	**23**	82
30	Me	*i*-Pr	9	13	**34**	72
30	Me	*i*-Pr	4	6.5	**34**	>98[c]
31	Me	$C(Me)_2CCl_3$	4	12	**35**	78
31	Me	$C(Me)_2CCl_3$	1.5	5	**35**	72
19	Bn	Me	0.9	4	**22**	82
32	Bn	Bn	0.9	4	**36**	80
21	Bn	Ph	0.9	4	**24**	80

[a] Calculated concentration of NHC **28** assuming quantitative deprotonation of **18** by KHMDS. [b] Isolated yield of homogeneous product after purification by chromatography. [c] As judged by ^{1}H NMR spectroscopic analysis of the crude reaction product.

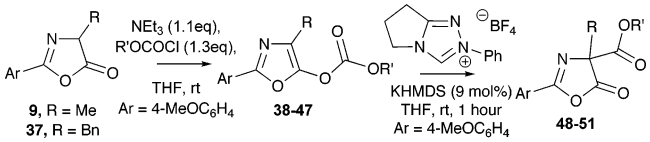
using standard procedures from azlactones **9** and **37**,[34] and subsequently tested for stereoselectivity in the rearrangement protocol using 9 mol % of NHC **28**. Disappointingly, treatment of menthyl carbonates **38** and **39** with NHC **28** gave no reaction, returning starting material even at high (30 mol %) catalysts loadings (entries 1 and 2), while rearrangement of the 1-phenylethyl carbonates **40** and **41** gave a complex mixture of products at low reaction conversions. Rearrangement of the 1-phenylpropan-2-yl carbonates **42** and **43** and 3-methylbutan-2-yl carbonates **44** and **45** showed distinct reactivity differences within the alanine and phenylalanine-derived systems. Treatment of the C(4)-benzyl substrates **43** and **45** with NHC **28** proceeded to give the desired products at high conversion but with low dr, while rearrangement of the C(4)-methyl substrates **42** and **44** proceeded to low conversion with poor diastereocontrol (entries 5−8). In all cases the relative configuration within the products was not determined and exhaustive chromatographic purification was necessary to isolate the desired products. The incorporation of further sterically hindered *β*-branched substituents proved detrimental to reaction efficiency (entries 9 and 10, Table 6).

Probing Generality: Alternative Substituents at C(4). Variation at C(4) upon the efficiency of this transformation was next investigated. The C(4)-*iso*-butyl substituted carbonates **52**−**54** proved relatively sluggish with <1 mol % of NHC **25**, indicating that *β*-branching in this position is slightly detrimental to catalytic efficiency, although complete conversion of **52**−**54** to esters (±)-**59**−(±)-**61** could be achieved within 5 min with 1.5 mol % of NHC **28**. A C(4)-phenyl substituent is readily

(33) Vedejs, E.; Wang, J. *Org. Lett.* **2000**, *2*, 1031. Peris, G.; Vedejs, E. *J. Org. Chem.* **2008**, *73*, 1158.

(34) (1′*S*)-Menthyl chloroformate is commercially available (Aldrich); all other chloroformates were prepared from the corresponding alcohol following a modified procedure from Takeda, K.; Ayabe, A.; Kawashima, H.; Harigaya, Y. *Tetrahedron Lett.* **1992**, *33*, 951.

TABLE 6. Diastereoselective NHC-Promoted Carbonate Rearrangements



entry	carbonate	R	R′	ester	product conversion[a]	dr
1	**38**	Me	(1′*S*)-menthyl		0	
2	**39**	Bn	(1′*S*)-menthyl		0	
3	**40**	Me	CH(Me)Ph		na[b]	
4	**41**	Bn	CH(Me)Ph		na[b]	
5	**42**	Me	$CH(Me)CH_2Ph$	**48**	27	58:42
6	**43**	Bn	$CH(Me)CH_2Ph$	**49**	>90	53:47
7	**44**	Me	$CH(Me)CH(Me)_2$	**50**	41	54:46
8	**45**	Bn	$CH(Me)CH(Me)_2$	**51**	>90	55:45
9	**46**	Me	$CH(Me)CMe_3$		0	
10	**47**	Bn	$CH(Me)CMe_3$		0	

[a] All reaction conversions and product distributions were judged by ^{1}H NMR spectroscopic analysis of the crude reaction product. [b] ^{1}H NMR spectroscopic analysis of the crude reaction product gave a complex mixture of unidentified products.

tolerated, with rearrangement of **55** to (±)-**62** proceeding quantitatively at 1.5 mol % of NHC **28**, although the isolated yield of **62** proved variable (42−81% isolated yield) due to partial decomposition on chromatographic purification to furnish *N*-*p*-anisoylphenylglycine phenyl ester.[35] Rearrangement of carbonates **56**−**58** bearing C(4)-*iso*-propyl and C(4)-*tert*-butyl substituents were next evaluated in order to test fully the substrate tolerance of NHC **28** in this reaction protocol. The valine-derived methyl carbonate **56** required the use of 4 mol % NHC **28** to promote complete rearrangement within 5 min, giving (±)-**63** in 67% isolated yield, while phenyl carbonate **57** rearranged within 5 min using only 1.5 mol % of NHC **25**, affording (±)-**64** in 79% yield. Rearrangement of *tert*-leucine-derived carbonate **58** with 4 mol % of NHC **28** gave (±)-**65,** containing vicinal quaternary carbon centers, in 2 h and in 73% yield (Table 7).[36] It is particularly notable that NHC **28** can tolerate C(4)-α- and α,α-branched substituents in this rearrangement as this transformation has proven difficult with chiral DMAP derivatives.[10] Furthermore, this methodology provides access to a wide range of precursors to synthetically useful α,α-disubstituted α-amino acid derivatives.[37]

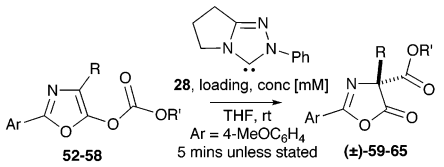
Development of a One-Pot Reaction Protocol. Having demonstrated the versatility of this NHC promoted rearrangement, studies turned to the development of an alternative and experimentally simple one-pot protocol that would negate the need to preform the NHC before addition of the desired carbonate. Addition of KHMDS (9 mol %) to a THF solution of salt **18** (10 mol %) and methyl or phenyl carbonates **19** or **21** gave complete conversion to (±)-**22** and (±)-**24**, respectively, within 5 min, allowing their isolation in 82% yield in both cases. Further optimization indicated that generation of NHC **28** with 0.9 mol % KHMDS can be used in this protocol for the rearrangements of **10**, **19**, **20**, and **21** with equal efficiency.

(35) See Supporting Information for full details and characterization data for *N*-*p*-anisoylphenylglycine phenyl ester that presumably arises from lactone hydrolysis of (±)-**62** and decarboxylation.

(36) Unambiguous structure determination of (±)-**65** was carried out by X-ray analysis; see Supporting Information for full details.

(37) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584. Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517.

TABLE 7. Scope and Limitations: Variation of C(4)-substituent and Carbonate Functionality



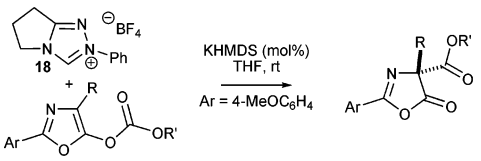
52, R = *i*-Bu, R' = Me; **53**, R = *i*-Bu, R' = Bn; **54**, R = *i*-Bu, R' = Ph; **55**, R = Ph, R' = Ph; **56**, R = *i*-Pr, R' = Me; **57**, R = *i*-Pr, R' = Ph; **58**, R = *t*-Bu, R' = Ph

(±)-**59**, R = *i*-Bu, R' = Me; (±)-**60**, R = *i*-Bu, R' = Bn; (±)-**61**, R = *i*-Bu, R' = Ph; (±)-**62**, R = Ph, R' = Ph; (±)-**63**, R = *i*-Pr, R' = Me; (±)-**64**, R = *i*-Pr, R' = Ph; (±)-**65**, R = *t*-Bu, R' = Ph

carbonate	R	R′	**28** (mol %)	**28** (mM)[a]	ester	yield (%)[b]
52	*i*-Bu	Me	1.5	13	**59**	79
53	*i*-Bu	Bn	1.5	13	**60**	67
54	*i*-Bu	Ph	1.5	13	**61**	76
55	Ph	Ph	4	20	**62**	42−81
55	Ph	Ph	1.5	20	**62**	81
56	*i*-Pr	Me	4	25	**63**	67
57	*i*-Pr	Ph	1.5	10	**64**	79
58	*t*-Bu	Ph	9	10	**65**	71[c]
58	*t*-Bu	Ph	4	5	**65**	73[d]

[a] Calculated concentration of NHC **28** assuming quantitative deprotonation of **18** by KHMDS. [b] Isolated yield of homogeneous product after purification by chromatography. [c] Reaction time 1 h. [d] Reaction time 2 h.

TABLE 8. Development of a One-pot Reaction Protocol



10, R = Me, R' = Me; **20**, R = Me, R' = Ph; **19**, R = Bn, R' = Me; **21**, R = Bn, R' = Ph; **32**, R = Bn, R' = Bn; **54**, R = *i*-Bu, R' = Ph; **57**, R = *i*-Pr, R' = Ph; **66**, R = CH_2CH_2SMe, R' = Ph

(±)-**11**, R = Me, R' = Me; (±)-**23**, R = Me, R' = Ph; (±)-**22**, R = Bn, R' = Me; (±)-**24**, R = Bn, R' = Ph; (±)-**36**, R = Bn, R' = Bn; (±)-**61**, R = *i*-Bu, R' = Ph; (±)-**64**, R = *i*-Pr, R' = Ph; (±)-**67**, R = CH_2CH_2SMe, R' = Ph

carbonate	R	R′	**28** (mol %)	**28** (mM)[a]	ester	yield (%)[b]
10	Me	Me	9	25	**11**	58
10	Me	Me	0.9	25	**11**	>98[c]
20	Me	Ph	9	25	**23**	82
20	Me	Ph	0.9	2.5	**23**	>98[c]
19	Bn	Me	9	25	**22**	82
19	Bn	Me	0.9	2.5	**22**	>98[c]
21	Bn	Ph	0.9	2.5	**24**	82
32	Bn	Bn	1.5	3.6	**36**	83
54	*i*-Bu	Ph	1.5	5.4	**61**	81
57	*i*-Pr	Ph	1.5	4.5	**64**	80
66	CH_2CH_2SMe	Ph	0.9	2.5	**67**	83

[a] Calculated concentration of NHC **28** assuming quantitative deprotonation of **18** by KHMDS. [b] Isolated yield of homogeneous product after purification by chromatography. [c] As judged by ^{1}H NMR spectroscopic analysis of the crude reaction product.

While the standard work up procedure for these reactions involves concentration in vacuo followed by chromatographic purification, the addition of 1 M $HCl_{(aq)}$ to the reaction mixture arising from the rearrangement of **21** to (±)-**24** with NHC **28** (0.9 mol %), followed by an aqueous extraction, allows isolation of homogeneous rearrangement product without the need for chromatographic purification. This one-pot procedure proved generally applicable to a range of oxazolyl carbonates, giving quantitative conversion to the corresponding esters that were isolated in good yield by chromatography in each case (Table 8). Furthermore, the methionine-derived oxazolyl carbonate **66**

undergoes efficient conversion to (±)-**67** using this procedure, indicating that functionalized heteroatom containing substituents are also tolerated in this reaction protocol.

Conclusion

In conclusion, we have shown that the NHC **28** derived from triazolium salt **18** is a highly efficient and versatile catalyst for the rearrangement of oxazolyl carbonates, with variation within the carbonate functionality and C(4)-substitution readily tolerated. A simplified experimental procedure allowing a one-pot protocol to be employed has been investigated. Current studies are focused upon developing an efficient enantioselective version of this NHC-catalyzed reaction process and understanding fully the mechanism of this transformation. Further applications of NHCs in asymmetric catalysis are ongoing.

Experimental Section

For general experimental details see Supporting Information.

General Procedure A. Rearrangement of Oxazolyl Carbonates. KHMDS (0.5 M in toluene) was added to a solution of azolium salt in THF and stirred at room temperature for 30 min. The desired oxazolyl carbonate was added, either as a solution in THF or as a solid, and stirred for the specified time before concentration in vacuo. Chromatographic purification (silica) gave the desired product.

General Procedure B. One-Pot NHC-Catalyzed Rearrangements. KHMDS (0.5 M in toluene) was added to a mixture of azolium salt and oxazolyl carbonate in THF and stirred at room temperature for 5 min before concentration in vacuo. Chromatographic purification (silica) gave the desired product.

Methyl 2-(4-Methoxyphenyl)-4-methyl-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-11. Following general procedure A, KHMDS (0.040 mL, 0.020 mmol, 0.9 mol %), triazolium salt **18** (0.006 g, 0.022 mmol, 1 mol %), THF (5 mL) and carbonate **10** (0.585 g, 2.222 mmol) gave after 5 min and chromatography (petrol/Et_2O 70:30) (±)-**11** (0.497 g, 1.888 mmol, 84%) as a colorless solid. ν_{max} (KBr disc)/cm^{-1} 2954 (C−H), 1751 (C═O), 1645 (C═O), 1497 (C═N) and 1262 (C−O); mp 58−60 °C; δ_H (300 MHz; $CDCl_3$) 8.00−7.95 (2H, m), 7.01−6.96 (2H, m), 3.89 (3H, s), 3.79 (3H, s) and 1.77 (3H, s); δ_C (75 MHz; $CDCl_3$) 175.2, 166.8, 163.7, 162.9, 130.3, 117.4, 114.3, 72.7, 55.6, 53.7 and 20.7; *m*/*z* (ESI+) 264.1 (100, M + H$^+$) and 286.1 (35, M + Na$^+$); HRMS (ESI+) $C_{13}H_{14}NO_5$ requires 264.0872, found 264.0874 (+0.9 ppm).

Methyl 4-Benzyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-22. Following general procedure A, KHMDS (0.030 mL, 0.015 mmol, 0.9 mol %), triazolium salt **18** (0.005 g, 0.016 mmol, 1 mol %), THF (4 mL) and carbonate **19** (0.565 g, 1.665 mmol) gave after 5 min and chromatography (petrol/Et_2O 80:20) ester (±)-**22** (0.465 g, 82%) as a colorless oil. ν_{max} (thin film)/cm^{-1} 2956 (C−H), 1753 (C═O), 1648 (C═O), 1513 (C═N) and 1261 (C−O); δ_H (300 MHz; $CDCl_3$) 7.85−7.80 (2H, m), 7.20−7.14 (5H, m, Ph*H*), 6.94−6.89 (2H, m), 3.85 (3H, s), 3.83 (3H, s), 3.62 (1H, ABq, J = 13.7) and 3.49 (1H, ABq, J = 13.7); δ_C (75 MHz; $CDCl_3$) 173.8, 166.4, 163.6, 162.7, 132.9, 130.4, 130.1, 128.2, 127.6, 117.2, 114.2, 55.5, 53.7, 40.3; *m*/*z* (ESI+) 362.1 (100, M + Na$^+$) and 394.1 (95, M + MeOH + Na$^+$); HRMS (CI) $C_{19}H_{18}NO_5$ requires 340.1185, found 340.1185 (+0.0 ppm).

***iso*-Propyl 2-(4-Methoxyphenyl)-4-methyl-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-34.** Following general procedure A, KHMDS (0.155 mL, 0.077 mmol, 9 mol %), triazolium salt **18** (0.023 g, 0.086 mmol, 10 mol %), THF (3 mL) and carbonate **30** (0.250 g, 0.859 mmol) gave after 5 min and chromatography (petrol/Et_2O 65:35) ester (±)-**34** (0.180 g, 0.618 mmol, 72%) as a colorless solid. ν_{max} (KBr disc)/cm^{-1} 2983 (C−H), 1737 (C═O), 1608 (Ar C═C), 1496 (C═N), 1295 (C−O) and 1260 (C−O); mp 48−50 °C; δ_H (400 MHz; $CDCl_3$) 7.98−7.94 (2H, m), 6.99−6.96 (2H, m), 5.05 (1H, sept, J = 6.3), 3.87 (3H, s), 1.73 (3H, s), 1.25 (3H, d, J = 6.3) and 1.22 (3H, d, J = 6.3); δ_C (100 MHz; $CDCl_3$) 175.5, 165.73, 163.6, 162.8, 130.2, 117.6, 114.3, 72.9, 71.0, 55.5, 21.4 and 20.4; *m*/*z* (CI) 292.1 (45, M + H$^+$); HRMS (CI) $C_{15}H_{18}NO_5$ requires 292.1185, found 292.1183 (−0.7 ppm).

Methyl 4-*iso*-Butyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-59. Following general procedure A, KHMDS (0.040 mL, 0.020 mmol, 1.5 mol %), triazolium salt **18** (0.007 g, 0.027 mmol, 2 mol %), THF (2 mL) and a solution of carbonate **52** (0.407 g, 1.333 mmol) in THF (2 mL) gave after 5 min and chromatography (petrol/Et_2O 80:20) ester (±)-**59** (0.323 g, 79%) as a colorless oil. ν_{max} (KBr disc)/cm^{-1} 2959 (C−H), 1755 (C═O), 1649 (C═O), 1513 (C═N) and 1262 (C−O); δ_H (300 MHz; $CDCl_3$) 8.01−7.96 (2H, m), 7.01−6.96 (2H, m), 3.88 (3H, s), 3.78 (3H, s), 2.37 (1H, ABX, $J_{A,B}$ 14.2, $J_{A,X}$ 5.8), 2.05 (1H, ABX, $J_{B,A}$ 14.2, $J_{B,X}$ 7.2), 1.70 (1H, sept, J = 6.7) and 0.94−0.88 (6H, m); δ_C (75 MHz; $CDCl_3$) 175.1, 166.8, 164.7, 162.4, 130.2, 117.5, 114.3, 76.2, 55.6, 53.6, 42.9, 24.6, 23.7 and 23.0; *m*/*z* (CI) 306.1 (100, M + H$^+$); HRMS (CI) $C_{16}H_{20}NO_5$ requires 306.1341, found 306.1341 (−0.2 ppm).

Methyl 2-(4-Methoxyphenyl)-4-*iso*-propyl-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-63. Following general procedure A, KHMDS (0.080 mL, 0.040 mmol, 4 mol %), triazolium salt **18** (0.014 g, 0.051 mmol, 5 mol %), THF (2 mL) and a solution of carbonate **56** in THF (2 mL) gave after 5 min and chromatography (petrol/Et_2O 85:15) ester (±)-**63** (0.200 g, 67%) as a colorless oil that solidified on standing. ν_{max} (KBr disc)/cm^{-1} 2958 (C−H), 1736 (C═O), 1647 (C═O), 1513 (C═N) and 1261 (C−O); mp 68−70 °C; δ_H (300 MHz; $CDCl_3$) 8.02−7.97 (2H, m), 7.00−6.95 (2H, m), 3.88 (3H, s), 3.81 (3H, s), 2.78 (1H, sept, J = 6.8), 1.06 (3H, d, J = 6.8) and 0.97 (3H, d, J = 6.8); δ_C (75 MHz; $CDCl_3$) 173.7, 166.4, 163.6, 162.5, 130.3, 117.4, 114.3, 80.3, 55.5, 53.5, 34.8, 17.2 and 16.3; *m*/*z* (CI) 292.1 (100, M + H$^+$); HRMS (CI) $C_{19}H_{17}N_5Na$ requires 292.1185, found 292.1188 (+1.1 ppm).

Phenyl 2-(4-Methoxyphenyl)-5-oxo-4-*iso*-propyl-4,5-dihydrooxazole-4-carboxylate (±)-64. Following general procedure A, KHMDS (0.030 mL, 0.015 mmol, 1.5 mol %), triazolium salt **18** (0.006 g, 0.020 mmol, 2 mol %), THF (2 mL) and a solution of carbonate **57** (0.353 g, 1.000 mmol) in THF (2 mL) gave after 5 min and chromatography (petrol/Et_2O 85:15) ester (±)-**64** (0.279 g, 0.790 mmol, 79%) as a colorless oil. ν_{max} (thin film)/cm^{-1} 2971 (C−H), 1818 (C═O), 1764 (C═O), 1651 (C═C), 1513 (C═N) and 1262 (C−O); δ_H (300 MHz; $CDCl_3$) 8.02−7.97 (2H, m), 7.37−7.05 (5H, m), 6.97−6.92 (2H, m), 3.83 (3H, s), 2.87 (1H, sept, J = 6.8), 1.13 (3H, d, J = 6.8) and 0.97 (3H, d, J = 6.8); δ_C (75 MHz; $CDCl_3$) 173.5, 164.6, 163.7, 162.9, 150.3, 130.4, 129.5, 126.4, 121.2, 117.4, 114.3, 80.4, 55.6, 34.8, 17.2 and 16.4; *m*/*z* (CI) 354.1 (65, M + H$^+$); HRMS (CI) $C_{20}H_{20}NO_5$ requires 354.1341, found 354.1344 (+0.7 ppm).

Phenyl 4-*tert*-Butyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-65. Following general procedure A, KHMDS (0.142 mL, 0.071 mmol, 9 mol %), triazolium salt **18** (0.022 g, 0.079 mmol, 10 mol %), THF (4 mL) and a solution of carbonate **58** (0.290 g, 0.790 mmol) in THF (4 mL) gave after 1 h and chromatography (petrol/Et_2O 85:15) ester (±)-**65** (0.207 g, 0.563 mmol, 71%) as an oil which solidified on standing to give an off-white solid. ν_{max} (KBr disc)/cm^{-1} 2963 (C−H), 1817 (C═O), 1647 (C═O), 1608 (C═N), 1514 (C═C), 1261 (C−O) and 1185 (C−O); mp 106−108 °C; δ_H (300 MHz; $CDCl_3$) 8.08−8.03 (2H, m), 7.40−7.33 (2H, m), 7.26−7.21 (1H, m), 7.13−7.08 (2H, m), 7.03−6.98 (2H, m), 3.89 (3H, s) and 1.29 (9H, s); δ_C (75 MHz; $CDCl_3$) 173.3, 163.8, 163.7, 162.4, 150.2, 130.3, 129.5, 126.4, 121.3, 117.5, 114.3, 81.6, 55.6, 39.5 and 25.1; *m*/*z* (ESI+) 390.2 (100, M + Na$^+$); HRMS (ESI+) $C_{21}H_{21}NO_5Na$ requires 390.1318, found 390.1318 (+0.1 ppm).

Phenyl 2-(4-Methoxyphenyl)-4-(2-(methylthio)ethyl)-5-oxo-4,5-dihydrooxazole-4-phenyl carboxylate (±)-67. Following general procedure B, KHMDS (0.010 mL, 0.005 mmol, 0.9 mol %), triazolium salt **18** (0.0014 g, 0.005 mmol, 1 mol %), carbonate **58** (0.200 g, 0.519 mmol) and THF (2 mL) gave after chromatography

(petrol/Et_2O 80:20), ester (±)-**67** (0.166 g, 0.430 mmol, 83%) as a pearlescent oil. ν_{max} (KBr disc)/cm^{-1} 2921 (C−H), 2849 (C−H), 1820 (C═O), 1767 (C═O), 1641 (C═C), 1607 (Ar C═C), 1509 (Ar C═C), 1457 (C−H), 1262 (C−N), 1187 (C−O) and 1173 (C−O); δ_H (300 MHz; CD_2Cl_2) 8.05−8.00 (2H, m), 7.43−7.36 (2H, m), 7.30−7.26 (1H, m), 7.11−7.07 (2H, m), 7.05−7.00 (2H, m), 3.88 (3H, s), 2.75−2.50 (4H, m) and 2.08 (3H, s); δ_C (75 MHz; CD_2Cl_2) 175.0, 165.4, 164.7, 164.5, 151.1, 131.1, 130.4, 127.4, 121.8, 118.1, 115.1, 76.3, 56.4, 34.3, 29.1 and 15.7; *m*/*z* (ESI+) 386.0 (100, M + H^+); HRMS (ESI+) $C_{20}H_{20}NO_5S$ requires 386.1062, found 386.1055 (−1.8 ppm).

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Supporting Information Available: Experimental procedures for the preparation of **9**, **10**, **12**−**16**, **18**−**21**, **23**−**27**, **29**−**33**, **35**−**58**, **60**−**62**, **66**, and **68**; spectroscopic data for **11**−**16**, **18**, **19**, **22**−**27**, **33**−**36**, **38**−**52**, and **56**−**68**; and cif files for (±)-**35**, (±)-**65** and (±)-**68**. This material is available free of charge via the Internet at http://pubs.acs.org.

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