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Efficient N-Heterocyclic Carbene-Catalyzed *O*- to C-Acyl Transfer

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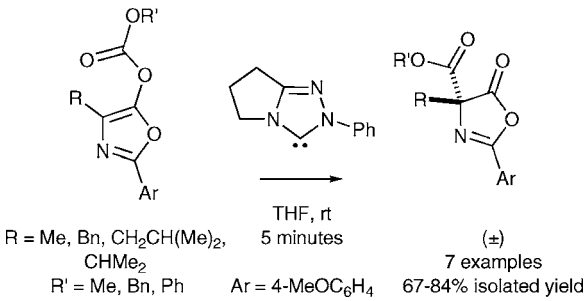
ABSTRACT



An N-heterocyclic carbene promotes the rearrangement of α-amino acid derived *O*-acyl carbonates to their corresponding C-acylated isomers, generating a C–C bond and a quaternary stereocenter with high efficiency, under mild reaction conditions and with low catalyst loadings.

N-Heterocyclic carbenes (NHCs) have recently been shown to promote a range of organocatalytic reactions.[1] Within this rapidly expanding field of research, two mechanistically distinct reaction pathways are widely recognized, involving the use of NHCs as either acyl anion equivalents or acyl transfer reagents. The ability of NHCs to generate acyl anion equivalents for C−C bond-forming applications has been demonstrated for benzoin- and Stetter-type transformations[2] and has been extended to nucleophilic substitution[3] and homoenolate reactions,[4] although these reaction protocols typically require >5 mol % of catalyst. NHCs have been utilized as catalytic acyl transfer agents to promote transesterification reactions,[5−7] and these methods have been extended to the kinetic resolution of racemic alcohols using chiral NHCs.[8] Although these resolutions proceed with high levels of stereoselectivity, relatively high catalyst loadings (typically 5−30 mol %) and long reaction times (up to 48 h) are needed to achieve significant reaction conversion. To date, applications of NHCs as catalytic acyl transfer reagents have been limited to acyl transfer to alcohols;[9] to the best of our knowledge, their application in truly catalytically

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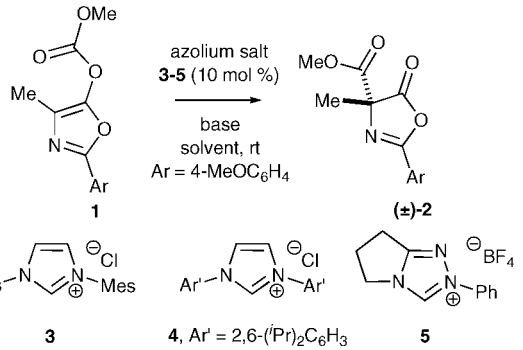
efficient C−C bond-forming reactions has not been demonstrated.

In 1970, Steglich and Höfle showed that DMAP and 4-(pyrrolidino)pyridine could act as nucleophilic catalysts and promote the rearrangement of 5-acyloxyoxazole derivatives to their corresponding 4- or 2-acyl-azlactones.[10] This process allows access to synthetically useful α,α-disubstituted α-amino acid derivatives,[11−13] although the regioselectivity of this transformation is dependent upon both the steric and electronic nature of the 2- and 4-substituents of the acyloxyoxazole. Fu[11] and Vedejs,[12] among others,[13] have elegantly shown that chiral DMAP derivatives can induce enantiocontrol in this reaction. Herein, we report that NHCs can also promote the efficient rearrangement of *O*-acyl carbonates to their corresponding C-acylated isomers with low catalyst loadings (<1 mol %) and short reaction times at ambient temperature.

Initial investigations focused upon screening the ability of a number of NHCs, generated under standard reaction conditions from the corresponding azolium salt (10 mol %), to promote this rearrangement pathway. The rearrangement of alanine-derived *O*-acyl methyl carbonate **1** to the corresponding azlactone (±)-**2** was chosen as a model system to allow reaction optimization. Treatment of imidazolium salts **3** or **4** with ^{t}BuOK and addition of carbonate **1** gave a complex mixture of products that contained <20% of the desired azlactone (±)-**2** (runs 1 and 2), whereas treatment of triazolium salt **5** with either NEt_3 or $^i Pr_2NEt$, followed by addition of carbonate **1**, returned only starting material (runs 3 and 4). However, treatment of triazolium salt **5** with KHMDS and addition of methyl carbonate **1** promoted the rearrangement to azlactone (±)-**2** in quantitative conversion within 5 min (run 5). Using toluene as the reaction solvent with the same catalyst loading (run 6) gave a crude product mixture containing ∼40% of (±)-**2**, whereas quantitative conversion of **1** to **2** was observed using Et_2O (run 7) (Table 1). These results demonstrate the importance of using a metalated base to deprotonate triazolium salt **5** in this reaction protocol.[14]

Subsequent studies focused upon probing the catalytic efficiency of this transformation using THF as the solvent by successively decreasing the precatalyst loading (Table 2). Addition of KHMDS (4 mol %, 1.5 mol %, and 0.9 mol %) to an excess of triazolium salt **5** (5 mol %, 2 mol %, and 1 mol %, respectively) and subsequent addition of *O*-acyl carbonate **1** gave, in each case, quantitative conversion to (±)-**2** within 5 min at room temperature. Chromatographic purification of the crude reaction product from runs 3 and 4 allowed the isolation of (±)-**2** in 82% and 84% yield, respectively.

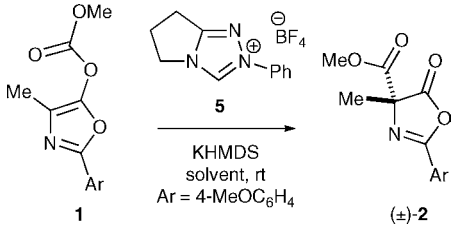
Table 1. Screening of Conditions for the Rearrangement of **1** to **2**



run	salt	base (mol %)	solvent	product conversion[a]
1	**3**	^{t}BuOK (9)	THF	<20%
2	**4**	^{t}BuOK (9)	THF	<20%
3	**5**	NEt_3 (9.5)	THF	0
4	**5**	$^i Pr_2NEt$ (9.5)	THF	0
5	**5**	KHMDS (9)	THF	quantitative
6	**5**	KHMDS (9)	toluene	∼40%
7	**5**	KHMDS (9)	Et_2O	quantitative

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

Table 2. Optimization of the Rearrangement of **1** to (±)-**2**



run	**5** (mol %)	KHMDS (mol %)	reaction time (min)	yield (%)[a]
1	10	9	5	
2	5	4	5	
3	2	1.5	5	82
4	1	0.9	5	84

[a] Isolated yields of homogeneous samples after chromatographic purification.

Control experiments indicated that addition of *O*-acyl carbonate **1** to triazolium salt **5** (10 mol %), KHMDS (9 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 (±)-**2** even after prolonged reaction times (>4 h), consistent with carbene **6** being the catalytically active species in this reaction. A simplistic mechanism of this transformation may be considered to involve initial depro-

(9) Thiazolium salts have been used for the oxidative formation of thioesters from benzaldehyde and a thiol: Kageyama, Y.; Murata, S. *J. Org. Chem.* **2005**, *70*, 3140. For hydroacylation using NHCs derived from triazolium salts, see: Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4558.

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(14) Deprotonation of **5** with KHMDS generates a conjugate acid (HMDS, pK_a 26 in THF) incapable of acting as a proton donor under the reaction conditions.

tonation of triazolium salt **5** with KHMDS to generate carbene **6**, followed by nucleophilic attack by carbene **6** at the carbonate carbonyl giving the reactive acyl transfer intermediate **7** and enolate **8**. Subsequent regioselective C-acylation of enolate **8** results in C−C bond formation, giving the desired product (±)-**2** and regenerating the carbene **6** necessary for reaction turnover (Figure 1).

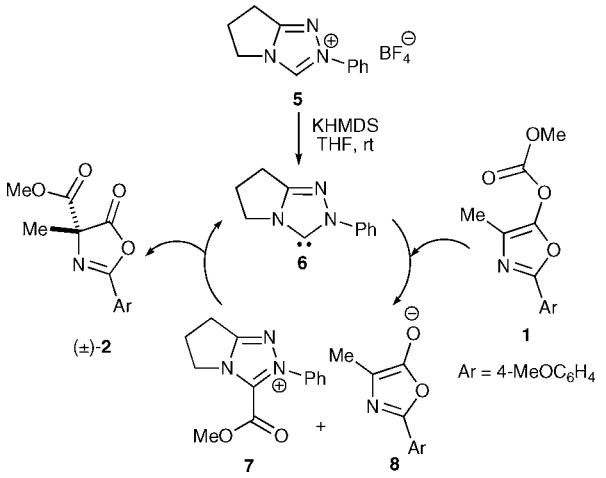
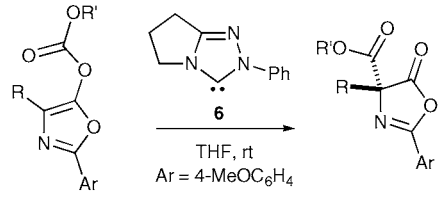
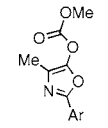
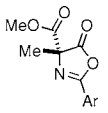
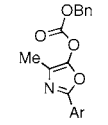
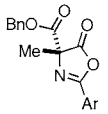
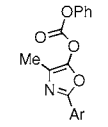
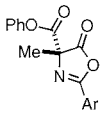
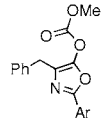
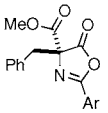
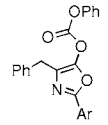
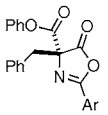
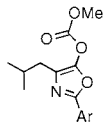
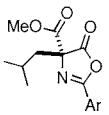
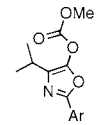
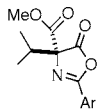


Figure 1. Proposed reaction pathway for the carbene-promoted rearrangement of **1** to (±)-**2**.

Having demonstrated the efficiency of this carbene-catalyzed rearrangement protocol in our model system, the generality of this process was then investigated. Treatment of oxazoles **9**−**14** incorporating structural diversity at C(4) and within the carbonate functionality gave complete conversion to the corresponding (±)-C-acylated isomers **15**−**20** within 5 min at ambient temperature using 4 mol % of carbene **6**. Optimization showed that only 0.9 mol % of carbene **6** was required to promote the rearrangement of alanine-derived *O*-benzyl and *O*-phenyl carbonates **9** and **10**, giving (±)-**15** and (±)-**16**, respectively, in quantitative conversion and in good isolated yields after chromatographic purification. Similarly, rearrangement of the phenylalanine-derived *O*-methyl and *O*-phenyl carbonates **11** and **12** with 0.9 mol % of carbene **6** proceeded efficiently, giving (±)-**17** and (±)-**18** in 82% and 80% isolated yields, respectively. At catalyst loadings of <1 mol % of **6**, rearrangement of the C(4)-*β*- or α-branched carbonates **13** and **14** proved sluggish, requiring relatively long reaction times to achieve satisfactory conversion. In the leucine-derived series, complete conversion of **13** to (±)-**19** within 5 min could be achieved consistently using 1.5 mol % of carbene **6**, giving (±)-**19** in 79% yield after chromatography. The valine-derived α-branched carbonate **14** required the use of 4 mol % of carbene **6** to promote its rearrangement within 5 min, giving (±)-**20** in 67% isolated yield (Table 3). It is particularly notable that this carbene-catalyzed *O*- to C-acyl transfer reaction tolerates α-branching in the generation of a quaternary center, a transformation that has proven difficult with chiral DMAP derivatives.[15]

Table 3. Generality of the *O*- to *C*-Acyl Rearrangement Process



	O-acyl oxazole	**6** (mol %)[a]	(±)-C-acyl product	yield (%)[b]
1		0.9	**2** 	84
9		0.9	**15** 	77
10		0.9	**16** 	82
11		0.9	**17** 	82
12		0.9	**18** 	80
13		1.5	**19** 	79
14		4	**20** 	67

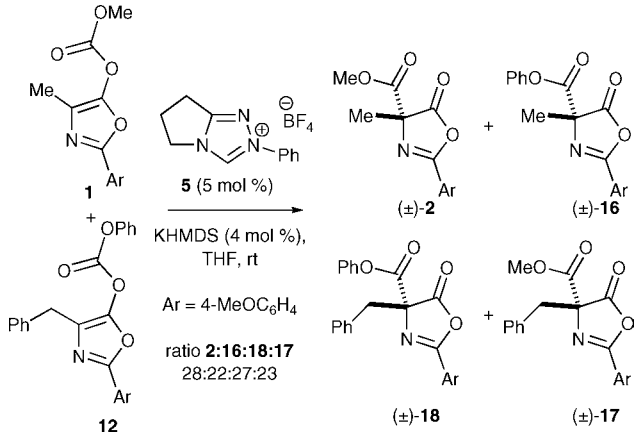
[a] Carbene loading based on mol % of KHMDS added to an excess of triazolium salt **5** assuming quantitative deprotonation. [b] Isolated yields of homogeneous samples after chromatographic purification.

Preliminary mechanistic investigations were directed toward analysis of the product distributions arising from crossover experiments. Treatment of triazolium precatalyst **5** (5 mol %) with KHMDS (4 mol %) and subsequent

(15) Vedejs et al. have reported that treatment of a valine-derived enol carbonate with a chiral TADMAP catalyst gave no acyl rearrangement product, which is proposed to be due to excessive steric hindrance; see ref 12.

addition of a 50:50 mixture of *O*-acyl carbonates **1** and **12** gave, after 5 min and at complete reaction conversion, a 28:22:27:23 mixture of the four possible rearrangement products (±)-**2**, (±)-**16**, (±)-**18**, and (±)-**17**, respectively (Scheme 1).[16]

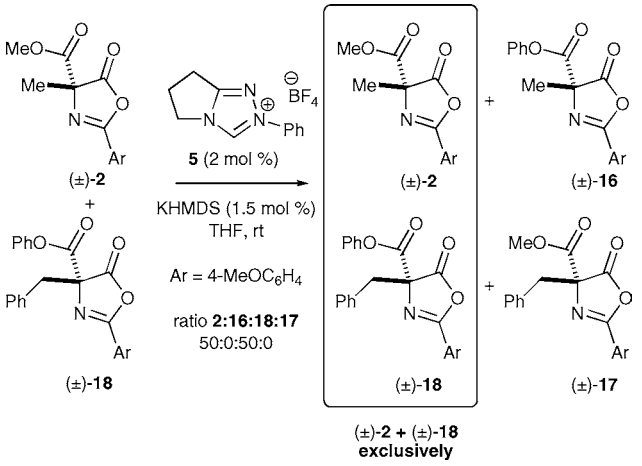
Scheme 1. Product Distribution from the Crossover Experiment



Furthermore, treatment of precatalyst **5** (2 mol %) with KHMDS (1.5 mol %) and subsequent addition of a 50:50 mixture of (±)-**2** and (±)-**18** returned, after 5 min, exclusively (±)-**2** and (±)-**18** with no crossover products (±)-**16** and (±)-**17** observed (Scheme 2).

Following the simple mechanistic scheme assumed in Figure 1, the product distribution in Scheme 1 is consistent with the C−C bond-forming step between the enolate and the acyl transfer intermediate proceeding via an intermolecular pathway and not through a discrete ion pair.[17] The appearance of no crossover products upon treatment of a 50:50 mixture of (±)**2** and (±)**18** with carbene **6** (Scheme 2) is consistent with the C−C bond-forming step being irreversible under the reaction conditions.

Scheme 2. Product Stability Crossover Experiment



In conclusion, we have demonstrated that the NHC **6** generated in situ from triazolium salt **5** with KHMDS can catalyze efficiently the rearrangement of *O*-acyl carbonates to their corresponding C-acyl-azlactones. This reaction proceeds readily at ambient temperatures and with low catalyst loadings (<1 mol %), generating a new C−C bond and a quaternary stereocenter, allowing access to precursors of α,α-disubstituted α-amino acid derivatives. Further investigations concerned with probing the mechanism of this transformation and the introduction of diastereo- and enantioselective versions of this reaction are currently underway within this laboratory.

Acknowledgment. The authors would like to thank the Royal Society for a University Research Fellowship (A.D.S.) and the EPSRC and EaStChem for funding (J.E.T.).

Supporting Information Available: Experimental procedures and spectroscopic data for all new products are available. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061380H

(16) Within experimental error, this product distribution (as determined by ^{1}H NMR spectroscopic analysis of the crude reaction product) is consistent with a near statistical mixture of products.

(17) An intermolecular step at some stage of the mechanism is necessary to account for this product distribution. An alternative and equally plausible mechanistic rationale would involve a rapid preequilibrium first step resulting in scrambling of the 50:50 mixture of **1** and **12** to give an equimolar mixture of **1**:**10**:**11**:**12**, followed by irreversible C−C bond formation. At the present time, we are unable to distinguish between these mechanistic pathways, although further work is underway to delineate unambiguously the course of this transformation.