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N-Heterocyclic Carbene-Catalyzed Ireland–Coates Claisen Rearrangement: Synthesis of Functionalized β-Lactones

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Supporting Information

ABSTRACT: The N-heterocyclic carbene (NHC)-catalyzed Claisen rearrangement of hybrid Ireland–Coates structures has been achieved, allowing the stereoselective synthesis of highly functionalized β-lactones. The reaction proceeds with high diastereoselectivity (>20:1) and affords a diverse range of β-lactone fused cyclopentanes. Mechanistic studies are detailed.

Catalysis of the Claisen rearrangement presents opportunities in reaction discovery that are only beginning to be realized.[1] Recent reports[2] have described N-heterocyclic carbene (NHC)-catalyzed Claisen rearrangements via hemiacetal intermediates analogous to those reported by Coates.[3] While consensus on the mechanism is yet to be established,[4] the transformation is general[5] and often enantioselective. Surprisingly, while this is an active area of research, to date only transformations involving Coates-type intermediates (i.e., **I** in Figure 1) are known. As part of studies into the chemistry

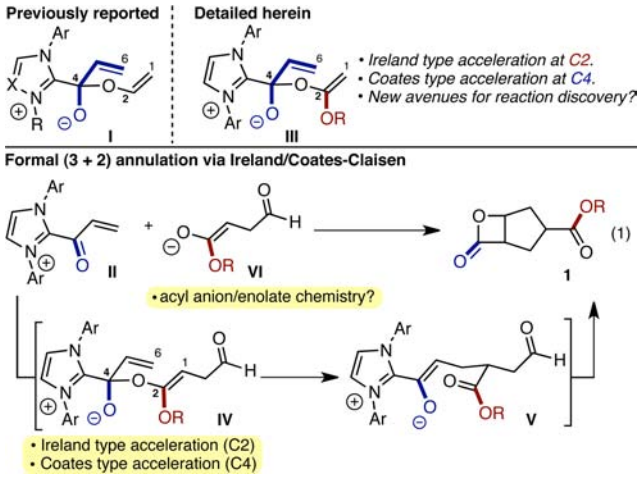
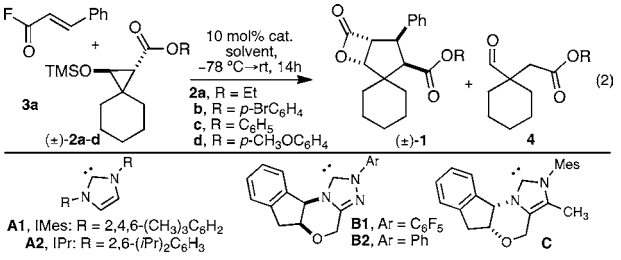


Figure 1. Reaction design.

of α,β-unsaturated acyl azoliums (**II**), we were interested in Claisen rearrangements that in addition to C4 (Coates) acceleration are activated at C2 (Ireland),[6] as in intermediate **III**. It was postulated that such a reaction (i.e., **IV** → **V**) should be orders of magnitude faster than earlier NHC-catalyzed Claisen rearrangements,[2,4,5] thereby providing access to previously unattainable reaction designs (Figure 1). For example, might a rapid Claisen rearrangement allow cascade reactions[7] using bifunctional enolate **VI** without competing aldol or acyl anion equivalent formation? Herein we report the realization of this strategy with the NHC-catalyzed synthesis of highly functionalized β-lactones **1** by a Claisen rearrangement/aldol/β-lactonization[8] reaction cascade (eq 1).

Studies commenced using donor–acceptor cyclopropanes (e.g., **2a**) as precursors to **VI**.[9] It was proposed that acyl azolium formation from acyl fluorides (e.g., **3a**) should trigger desilylation and retro-aldol reaction of the cyclopropane to provide **VI**.[10] When this strategy was attempted with cyclopropane **2a** and acyl fluoride **3a** using 10 mol % IMes (**A1**), diastereomerically pure cyclopentane **1a** was formed, as determined by ^{1}H NMR analysis; however, ester **4a** was the major product, presumably as a result of competing proton transfer (Table 1, entry 1). Solvation of the KCl derived from NHC generation[11] using tetrahydrofuran (THF) improved the yield of **1a**, but **4a** remained a significant byproduct (entry 2).

Table 1. Optimization Studies



entry	cat[a]	solvent/additive	2	1:4[b]	% yield[c] (dr[d]) of 1
1	**A1**	toluene/none	**2a**	1:2	30[e] (>20:1)
2	**A1**	THF/4 Å sieves	**2a**	1:1	41 (>20:1)
3	**A1**[f]	THF/4 Å sieves	**2a**	1:1	33 (>20:1)
4	**A1**	THF/4 Å sieves	**2b**	1:1	43 (>20:1)
5	**A1**	THF/4 Å sieves	**2c**	5:1	78 (>20:1)
6	**A1**	THF/4 Å sieves	**2d**	**25:1**	**89 (>20:1)**
7	**A2**	THF/4 Å sieves	**2d**	2:1	62 (1:1)
8	**B1**	THF/4 Å sieves	**2d**	NR[g]	–
9	**B2**	THF/4 Å sieves	**2d**	NR[g]	–
10	**C**	THF/4 Å sieves	**2d**	NR[g]	–

[a]The NHC was generated using equimolar potassium hexamethyldisilazide (KHMDS). [b]Determined by ^{1}H NMR analysis. [c]Isolated yields. [d]Diastereomeric ratios determined by ^{1}H NMR analysis. [e]Conversion was judged by ^{1}H NMR analysis. [f]Performed with the NHC filtered from KCl. [g]NR = no reaction.

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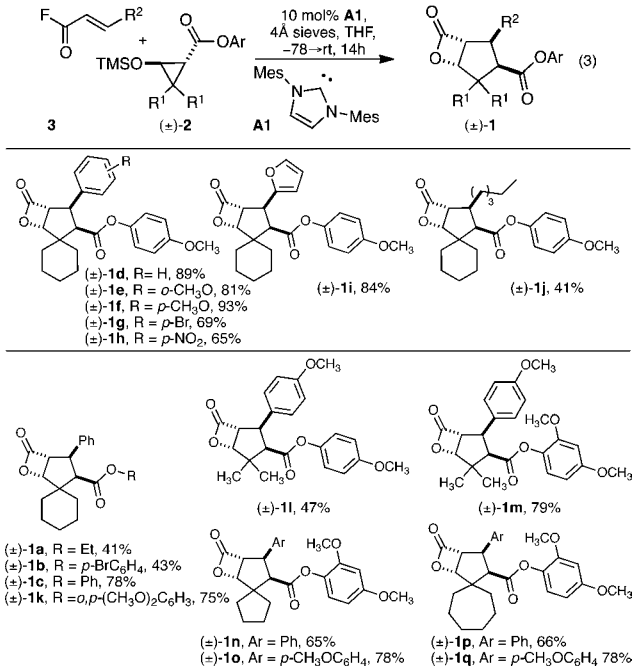
Although imidazolium-derived NHCs free from salt byproducts have previously improved related transformations,[12] this was not the case with the present reaction (entry 3). Further acceleration of the Claisen rearrangement and elimination of the competing side reaction was attempted by replacing the ethyl ester in **2a** with progressively more electron-rich aromatics, culminating in *p*-$CH_3OC_6H_4$ in **2d**. Gratifyingly, this improved the yield of **1** to 89% (entries 4−6). In all cases, cyclopentane **1** was formed as a single diastereomer whose relative stereochemistry was assigned by nuclear Overhauser effect (NOE) analysis.[13] The reaction was sensitive to the catalyst: IPr (**A2**) increased the formation of aldehyde **4d** and decreased the stereoselectivity, with **1d** formed as a 1:1 mixture with **1d′** (vide infra) (entry 7), while chiral triazolium (**B1** and **2**) and imidazolium (**C**)[14] derived catalysts failed to convert the starting materials (entries 8−10).[15]

Initially the scope of the reaction was examined using a range of α,β-unsaturated acyl fluorides **3** (Table 2). In all cases, good

Table 2. Scope of the Formal (3 + 2) Annulation[a,b]

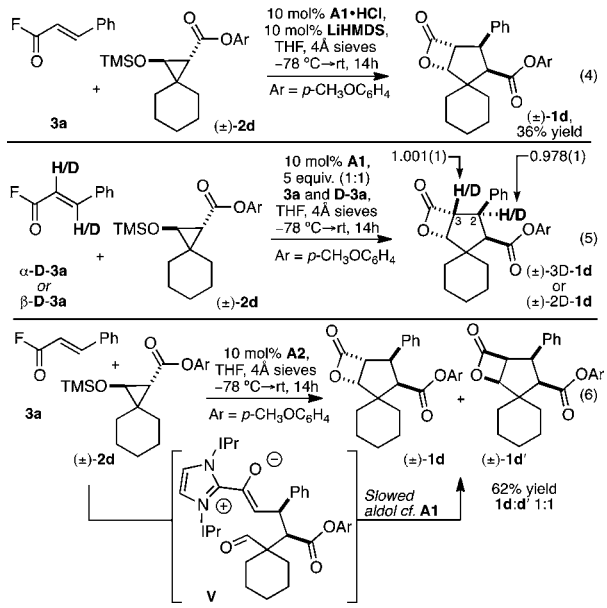


[a]Isolated yields following column chromatography are shown. [b]**A1** was generated from the imidazolium salt using KHMDS.

yields of electron-rich (**1e** and **f**) and electron-poor (**1g** and **h**) cyclopentanes were obtained, with each product isolated as a single diastereoisomer (>20:1 dr). Heteroaromatics were tolerated (furanyl **1i**), while aliphatic acyl fluoride **3j** gave the expected cyclopentane **1j**, although in modest yield. Variation in the cyclopropyl partner was examined next. As discussed, the electronics of the ester play a significant role in the reaction outcome, with more electron-rich aromatics generally providing higher yields. Additionally, when the cyclohexyl ring was replaced by two methyl substituents, the yield of **1l** was a disappointing 47% (cf. 93% for **1f** with the cyclohexyl ring). However, changing the ester to the more electron rich *o,p*-$(CH_3O)_2C_6H_3$ provided dimethylcyclopentane **1m** in an acceptable 79% yield. The use of this electron-rich ester was often beneficial, forming cyclopentyl products **1n** and **1o** and cycloheptyl products **1p** and **1q** in good yields.

To clarify the mechanism of the reaction (Scheme 1), salt effects were examined. The role of the counterion in the

Scheme 1. Mechanistic Studies



anionic oxy-Cope rearrangement is well-documented,[16] with lithium providing negligible rate acceleration compared to potassium. Thus, generation of the NHC using LiHMDS rather than KHMDS, which provides LiCl rather than KCl as the salt byproduct, was examined. This modification resulted in significant erosion in the yield (eq 4), a result consistent with anion-accelerated Claisen rearrangement. Further support for turnover-limiting Claisen rearrangement was observed by determining the secondary kinetic isotope effects (SKIE) α and β to the carbonyl (eq 5). While internal competition studies can give ambiguous results,[17b] cyclopropyl ring opening should be rapid,[9] and labeled substrate will therefore be involved in the turnover-limiting step; hence, this approach should be appropriate.[17] While no SKIE was observed at the α-position, a modest inverse SKIE was observed at the β-position, supportive of turnover-limiting Claisen rearrangement.[6] Finally, the reaction showed a marked sensitivity to the bulk of the catalyst, with **A2** eroding the diastereoselectivity (eq 6). This relates not to the Claisen step but rather to the aldol/lactonization sequence, which is presumably slowed by the bulk of the catalyst, allowing rotation of enolate **V** and hence formation of **1d** and **1d′**.

Taken together, we postulate that addition of IMes (**A1**) to acyl fluoride **3a** results in formation of acyl azolium **II** and, following desilylation and retro-aldol reaction of **2d**, enolate **VI**. Hemiacetal formation and subsequent turnover-limiting Ireland−Coates Claisen rearrangement then provides **V**, which undergoes aldol cyclization and lactonization to afford cyclopentane **1** and regenerate the catalyst (Scheme 2).

To probe the significance of oxygenation at C2, the annulation of **3a** with **5** was examined (Scheme 3). Unfortunately, rather than providing cyclopentane **6**, the reaction formed lactol ester **7** in 97% yield. Presumably this failure is due to the slower Claisen rearrangement, which allows competing O-acylation of the lactolate derived from **VIII**. This result highlights the challenges involved in developing cascades with less facile NHC-catalyzed rearrangements.

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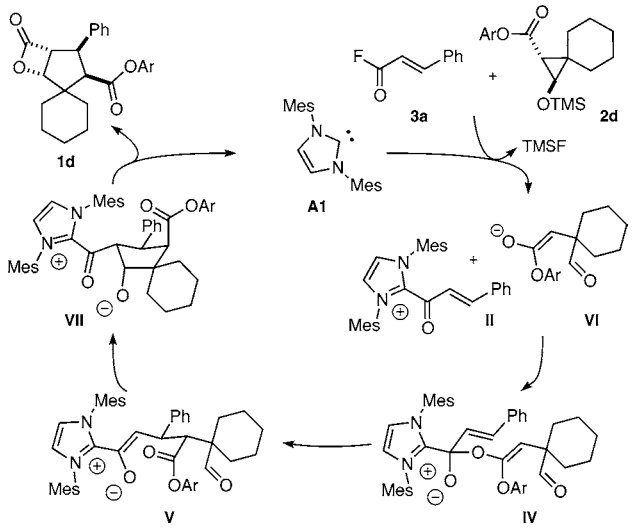
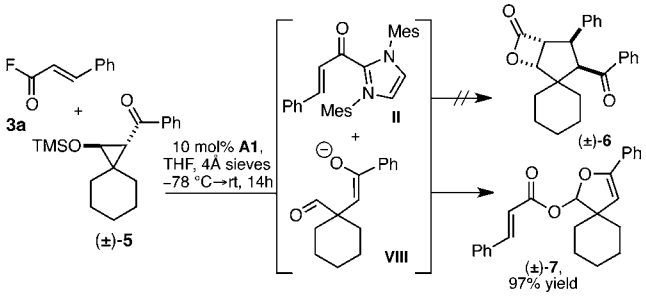
Scheme 2. Postulated Mechanism



Scheme 3. Attempted (3 + 2) Annulation of 3a and 5



A highly rapid Claisen rearrangement under conditions of NHC catalysis has been achieved with substrates bearing C2 and C4 oxygenation. This has allowed the NHC-catalyzed (3 + 2) annulation to be achieved without competing side reactions involving either acyl anion or enolate chemistry. The realization of this transformation represents a new catalytic Claisen rearrangement of synthetic utility. In addition, this reaction should serve to inform and enable future studies in NHC acyl azolium catalysis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Characterization data, ^{1}H and ^{13}C NMR spectra, and detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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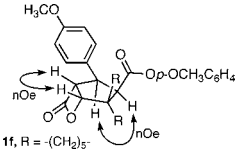
(13) NOE analysis was used to determine the relative stereochemistry. See, for example, **1f**:



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