Communication

N-Heterocyclic Carbene Catalyzed Ireland-Coates Claisen rearrangement: Synthesis of functionalized #-lactones

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/ja310449k • Publication Date (Web): 17 Dec 2012

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

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Supporting Information Placeholder

ABSTRACT: The 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) affording 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] Recently, *N*-heterocyclic carbene (NHC) catalyzed Claisen rearrangements have been reported[2] 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 an active area of research, to date only transformations involving Coates type intermediates (i.e. **I**) are known. As part of studies into the chemistry 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 (i.e. **2a**) as precursors to **VI**.[9] It was proposed that acyl azolium formation from acyl fluorides (i.e. **3a**) should trigger desilylation and retro-aldol reaction of the cyclopropane to provide **VI**.[10] When this

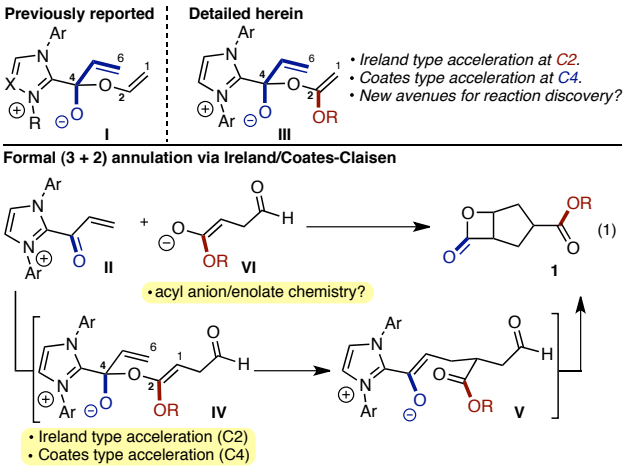
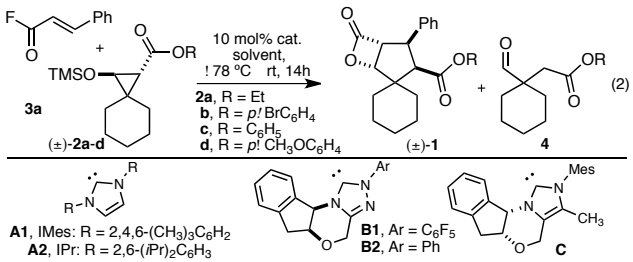


Figure 1. Reaction design.

strategy was trialed with cyclopropane **2a**, and acyl fluoride **3a**, using 10 mol% IMes (**A1**), diastereomerically pure cyclopentane **1a** formed, as determined by ^{1}H-NMR, 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 THF improved the yield of **1a**, however **4a** remained a significant byproduct (Table 2, entry 2). Imidazolium derived NHCs free from salt byproducts have previously improved related transformations,[12] although this was not the case with this reaction (Table 1, entry 3). Further acceleration of the Claisen, and elimination of competing side reaction, was attempted by replacing the ethyl ester (**2a**) with progressively more electron rich aromatics, culminating in *p*-$CH_3OC_6H_4$ **2d**. Gratifyingly this improved the yield of **1** to 89% (Table 1, entries 4-6). In all cases cyclopentane **1** formed as a single diastereomer with relative stereochemistry assigned by nOe.[13] The reaction was sensitive to the catalyst, with IPr (**A2**) increasing formation of aldehyde **4d**, and decreasing stereoselectivity, **1d** now formed as a 1:1 mixture with **1d'** (*vide infra*) (Table 1, entry 7). Finally chiral triazolium (**B1** and **2**) and imidazolium (**C**)[14] derived catalysts

failed to convert the starting materials (Table 1, entry 8-10).[15]

Table 1. Optimization studies



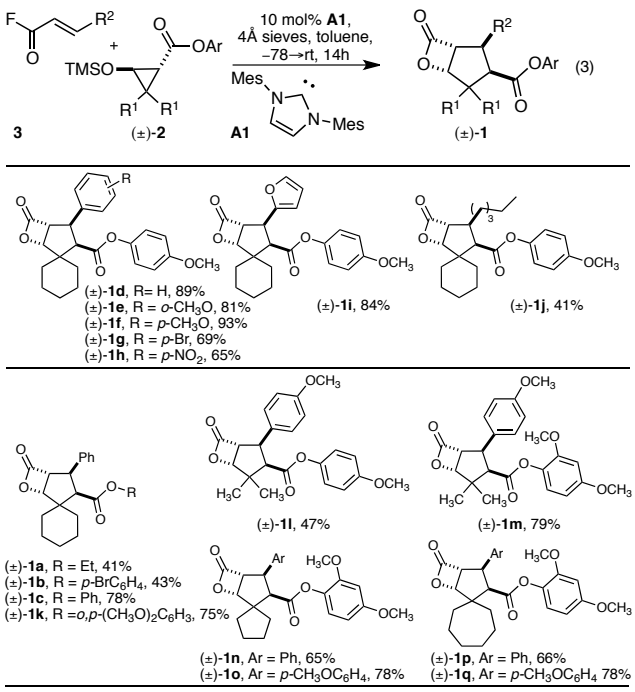
entry	cat[a]	solvent/additive	2	1:4[b]	Yield of 1[c,d]
1	**A1**	Toluene	**2a**	1:2	30[e] (>20:1 dr)
2	**A1**	THF/4Å sieves	"	1:1	41 (>20:1 dr)
3	**A1**[f]	"	"	1:1	33 (>20:1 dr)
4	**A1**	"	**2b**	1:1	43 (>20:1 dr)
5	**A1**	"	**2c**	5:1	78 (>20:1 dr)
6	**A1**	"	**2d**	**25:1**	**89 (>20:1 dr)**
7	**A2**	"	"	2:1	62 (1:1 dr)
8	**B1**	"	"	NR[g]	-
9	**B2**	"	"	NR[g]	-
10	**C**	"	"	NR[g]	-

[a]NHC generated using equimolar KHMDS [b]Determined by ^{1}H-NMR analysis [c]Isolated yield [d]Diastereomeric ratio determined by ^{1}H-NMR analysis [e]Conversion judged by ^{1}H-NMR analysis [f]Performed with NHC filtered from KCl [g]NR=No reaction

Initially the scope of the reaction was examined using a range of α,β-unsaturated acyl fluorides **3** (Table 2). In all cases good yields of electron rich (**1e** and **f**) and electron poor (**1g** and **h**) cyclopentanes were obtained, with the products isolated as a single diastereoisomer (dr >20:1). 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 dimethyl substituents replaced the cyclohexyl the yield of **1l** was a disappointing 47% (cf. 93% with cyclohexyl, **1f**). However, changing the ester to the more electron rich *o,p*-$(CH_3O)_2C_6H_3$ provided dimethyl cyclopentane **1m** in an acceptable 79% yield. Use of this electron rich ester was often beneficial, with cyclopenytl products **1n** and **o**, and cycloheptyl **1p** and **q**, formed in good yields.

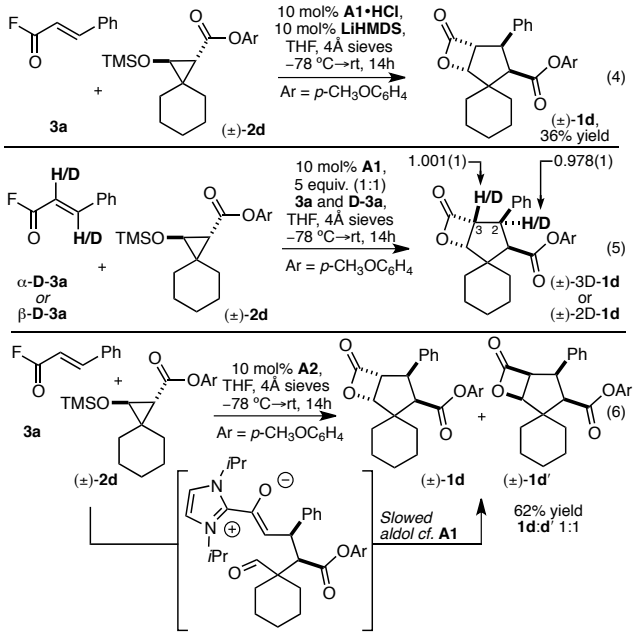
To clarify the mechanism of the reaction (Scheme 1) salt effects were examined. The role of the counter ion in the anionic oxy-Cope rearrangement is well documented,[16] with lithium providing negligible rate acceleration compared to potassium. Thus generation of the NHC using LiHMDS rather than KHMDS was examined,

Table 2. Scope of the formal (3 + 2) annulation.[a,b]



[a]Isolated yield following column chromatography [b]**A1** generated from the imidazolium salt with KHMDS

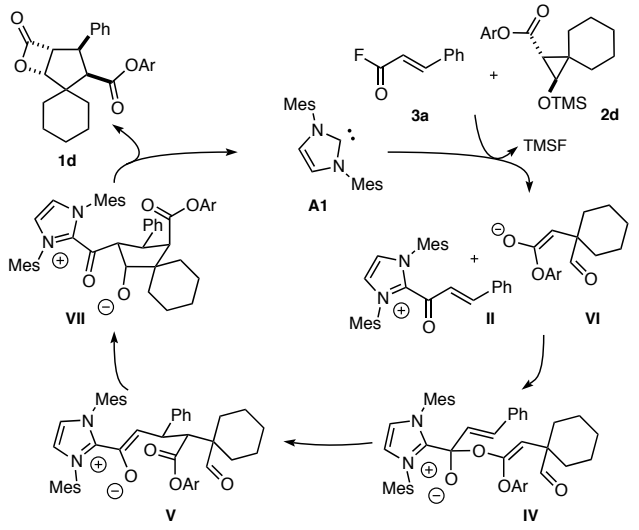
providing LiCl rather than KCl as the salt byproduct. This modification resulted in significant erosion in yield (eq. 4), a result consistent with anion accelerated Claisen rearrangement. Further support for turnover limiting Claisen was observed by determining the secondary kinetic isotope effects (SKIE) α- and β-to the carbonyl (eq. 5). While internal completion studies can give ambiguous results,[17b] cyclopropyl ring opening should be rapid,[9] therefore labeled substrate will be involved in the turn



Scheme 1. Mechanistic studies.

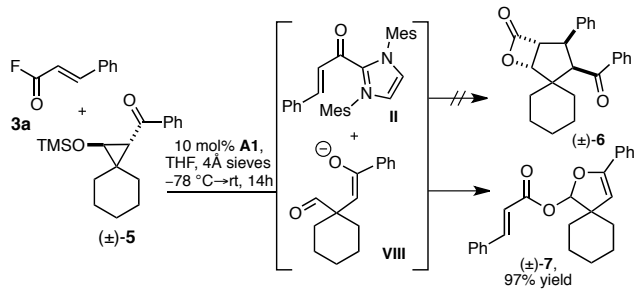
over limiting step, hence this approach should be appropriate.[17] While no SKIE was observed at the α-position a modest inverse SKIE was observed at the β-position, supportive of turn over limiting Claisen rearrangement.[6] Finally the reaction shows a marked sensitivity to the bulk of the catalyst, with **A2** eroding the diastereoselectivity (eq. 6). This relates not to the Claisen step, but rather the aldol/lactonization which is presumably slowed by the bulk of the catalyst, allowing rotation of enolate **III** 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).



Scheme 2. Postulated mechanism

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



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 are available free of charge via the Internet at http://pubs.acs.org

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Funding Sources

No competing financial interests have been declared.

ACKNOWLEDGMENT

We acknowledge the support of James (Zhen) Wang for instrumental analysis, financial support from the ARC through the Discovery and Future Fellowship programs and Monash University through the Research Accelerator Program. We thank Professor Tomislav Rovis (Colorado State University) for donation of the imidazolium precursor to **B2**.

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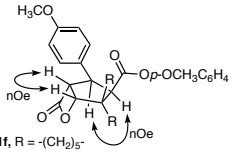

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Graphical Abstract