Organic LETTERS

Letter

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Catalytic Asymmetric Conjugate Addition of Carboxylic Acids via Oxa-Michael Reaction of Peroxy Hemiacetals followed by Kornblum DeLaMare Fragmentation

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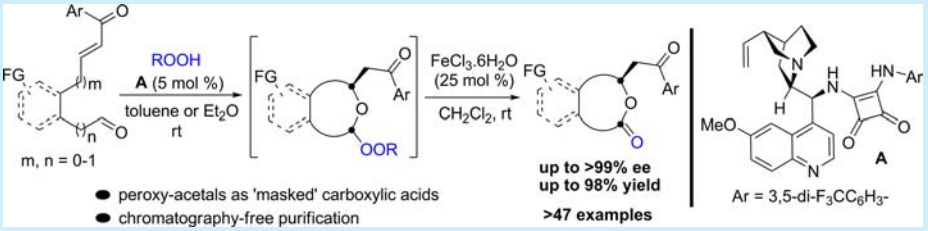
Supporting Information

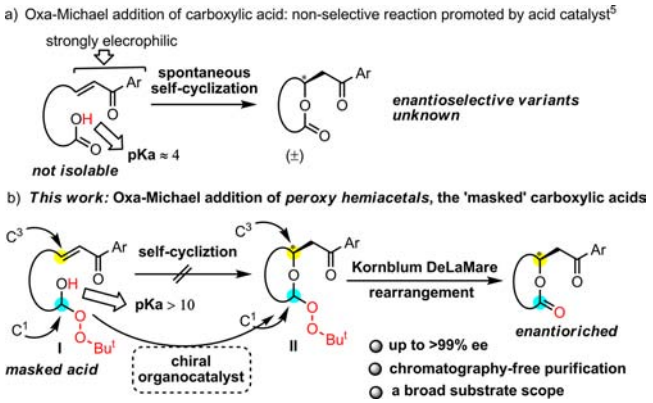


ABSTRACT: Disclosed herein an overall methodology constitutes an equivalent to the long sought after enantioselective intramolecular oxa-Michael (IOM) reaction of carboxylic acids. An organocatalyzed IOM reaction of in situ formed peroxy hemiacetals followed by a Kornblum DeLaMare type rearrangement cascade provides a broad class of chiral lactones in good yields and with excellent enatioselectvities. Remarkably, the pure chiral lactones are obtained without any silica gel column chromatography, and in many cases, the enantioselectivity is further increased by a simple hexane wash of the isolated solid products.

Intramolecular oxa-Michael (IOM) reaction of α,β-unsaturated carbonyls is one of the most fundamental and frequently employed methodologies for the construction of a variety of O-heterocycles.[1] Significant efforts have been directed toward the development of catalytic asymmetric IOM reactions using alcohols as nucleophiles to furnish chiral cyclic ethers.[2−4] Remarkably, despite the considerable synthetic potential of the analogous IOM reaction of carboxylic acids for the construction of variety of lactones,[5] the development of the asymmetric variants has been entirely elusive to date. The complications stem from the rapid self-promoted cyclization of carboxylic acids (pK_a in DMSO ≈ 4) with electrophilic enones and enals, even in the absence of external catalyst (Scheme 1a).[6] This phenomenon prevents the development of their corresponding asymmetric version.[7]

To suppress the rapid cyclization, we hypothesized that a masked carboxylic acid with higher pK_a would be useful. We presumed that peroxy acetal intermediate **II** might provide a chiral lactone if the Kornblum DeLaMare fragmentation[9] of peroxy acetal to an ester could be conducted without epimerization of the C^3 stereocenter (Scheme 1b). Recently, we reported a method for the enantioselective oxa-Michael reaction of peroxy hemiacetals (**I**)[4] in which the pK_a of OH group is not significantly low (pK_a in DMSO ≈ 10 for **I**)[8] to promote rapid self-cyclization. Notably, the stereochemistry at the C^1 center in intermediate **II** would not be important if the absolute stereochemistry at the C^3 center remains same. However, finding an appropriate condition for the Kornblum DeLaMare type rearrangement is challenging as it usually occurs in the presence

Scheme 1. Intramolecular Oxa-Michael Addition of (a) Carboxylic Acid and (b) Peroxy Hemiacetals



of a base, which might enhance the reversibility of oxa-Michael addition process and, thus, the loss of enantioselectivity. Nevertheless, if the oxa-Michael addition and Kornblum DeLaMare type rearrangement are achieved sequentially, the overall methodology would be an equivalent of the long sought after asymmetric oxa-Michael reaction of carboxylic acids where the peroxy hemiacetals would serve as a masked synthon of carboxylic acids. Notably, decomposition of a peroxide unit into

Received: August 17, 2016
Published: October 3, 2016

DOI: 10.1021/acs.orglett.6b02463
Org. Lett. 2016, 18, 5220−5223

other functional groups remained an attractive strategy in organic chemistry.[10]

Developing enantioselective routes to 1-isochromanone should be particularly rewarding, as this is a scaffold often associated with bioactivity (Figure 1).[11] Although they are rich

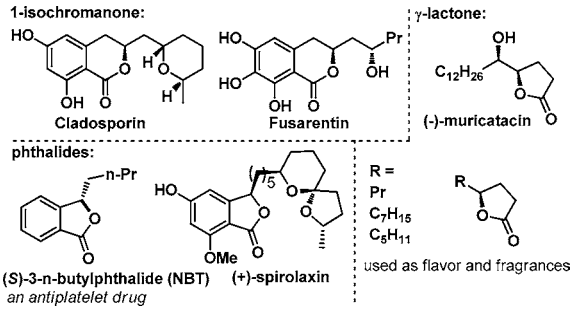
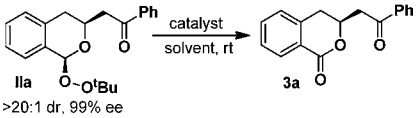


Figure 1. 1-Isochromanone, phthalide, and γ-lactone moieties containing bioactive molecules.

with biological significances, there are limited preceding examples for their catalytic enantioselective synthesis.[12] On the other hand, chiral 3-substituted phthalides represent an important structural motif featured in numerous natural products, registered drugs, and bioactive molecules.[13a] Owing to their diverse biological activities, a number of approaches have been developed to access this moiety with high enantioselectivity.[13] Although many protocols have been proven to be effective for a particular class of lactone, synthesis of a wider range lactones has not been successful. Herein, we report the development of an efficient, unified approach toward the synthesis of a wide variety of lactones such as 1-isochromanones, 3-isochromanones, phthalides, and γ-lactones with excellent enantioselectivities.

To test our hypothesis, we first examined the Kornblum DeLaMare rearrangement of substrate **IIa**, which was prepared using our previous method.[4] In the presence of bases such as Et_3N and DBU (entries 1 and 2, Table 1) the desired lactone **3a** was formed; unfortunately, the enantioselectivity was completely lost. Therefore, we turned our attention to screen the various Lewis acids such as $InCl_3$, $ZnCl_2$, $FeCl_3{\cdot}6H_2O$, $Bi(OTf)_3$, $In(OTf)_3$, etc. as catalyst (entries 3–7). Interestingly, as shown in entry 5, $FeCl_3{\cdot}6H_2O$ (10 mol %) provided the best conversion

Table 1. Optimization of the Reaction Conditions[a]



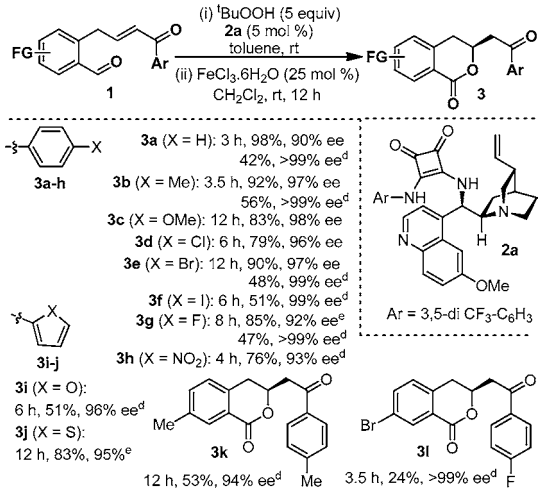
entry	catalyst (mol %)	solvent	conv[b] (%)	ee[c] (%)
1	Et_3N (10)	CH_2Cl_2	31	0
2	DBU (10)	CH_2Cl_2	100	0
3	$InCl_3$ (10)	CH_2Cl_2	8	92
4	$ZnCl_2$ (10)	CH_2Cl_2	10	93
5	$FeCl_3.6H_2O$ (10)	CH_2Cl_2	94	97
6	$Bi(OTf)_3$ (10)	CH_2Cl_2	10	80
7	$In(OTf)_3$ (10)	CH_2Cl_2	6	78
8	**$FeCl_3{\cdot}6H_2O$ (25)**	**CH_2Cl_2**	**100**	**97**

[a]All reactions are carried out on a 0.03 mmol scale. The reaction mixture was filtered through a small plug of silica gel. [b]NMR conversions were calculated by using anisole as an internal standard. [c]The ee was determined by chiral HPLC analysis.

(94% based on ^1H NMR) and enantioselectivity (97% ee). The screening of solvents as well as catalyst loading was performed (see the SI), and encouragingly, 25 mol % of $FeCl_3{\cdot}6H_2O$ in CH_2Cl_2 as solvent was found to be the best condition for this process (entry 8). It is also an important point to mention that a loss of enantioselectivity was realized during the purification of **3a** via column chromatography on silica gel (see the SI). However, filtration through a plug of silica followed by removal of solvent provided a pure product (based on NMR).

Once the optimized reaction conditions for Kornblum DeLaMare type rearrangement of intermediate **IIa** were identified (Table 1, entry 8), we became interested in examining the one-pot reaction development of the enantioselective oxa-Michael reaction of peroxy hemiacetals (**I**) using catalyst **2a** followed by the decomposition of the peroxy acetal center to provide the chiral lactone **3**. As shown in Scheme 2, we examined

Scheme 2. Substrate Scope: 1-Isochromanones[a−c]



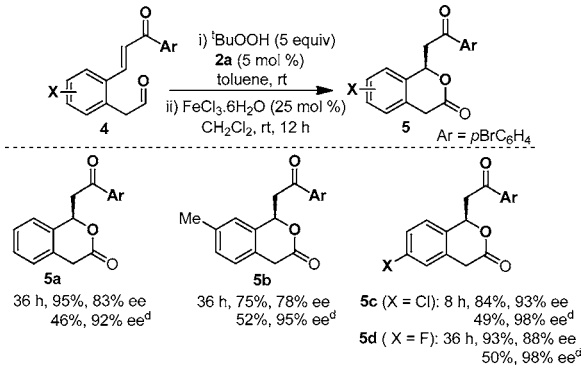
[a]Reaction conditions: **1** (0.1 mmol), ^tBuOOH (0.5 mmol, 5 equiv), **2a** (0.005 mmol, 5 mol %) in toluene. [b]Isolated products. [c]Ee's were determined by HPLC analysis. [d]Yield and ee after *n*-hexane wash. [e]Et_2O was used as solvent for the first step.

the scope of the terminal aryl moieties of *o*-formyl homochalcones. Overall, good to excellent yields and enantioselectivities were obtained with a range of substrates. Besides the electron-neutral aryl group (**3a**), a variety of aryls substituted with electron-rich grops, such as *p*-Me-(**3b**), *p*-MeO- (**3c**), as well as electron-withdrawing groups, such as *p*-Cl- (**3d**), *p*-Br- (**3e**), *p*-I- (**3f**), *p*-F- (**3g**), and *p*-O_2N- (**3h**), were competent with the present reaction conditions, generally giving 1-isochromanones in moderate to good yields and in high enantioselectivities. Heteroaromatic rings such as 2-furyl (**3i**) and 2-thiophene (**3j**) also worked nicely to provide the desired products. Further, the substitutions on the central aryl moiety were tested. Both electron-donating (**3k**) and electron-withdrawing groups (**3l**) on aryl ring afforded the desired products with high enantioselectivity. Notably, all these products were purified without performing a column chromatography. Interestingly, a simple hexane wash increased the enantioselectivity to a considerable extent, for example from 90% ee to >99% ee for **3a**; from 97% ee to >99% ee for **3b**; from 97% ee to >99% ee for **3e**; from 92% ee to >99% ee for **3g**, etc. Then, we focused on the *o*-homoformyl chalcones (**4**) as substrates for analogues reaction (Scheme 3). In

DOI: 10.1021/acs.orglett.6b02463
Org. Lett. 2016, 18, 5220−5223

general, good yields and high enantioselectivities were achieved to provide the corresponding six-membered lactones (**5a–d**).

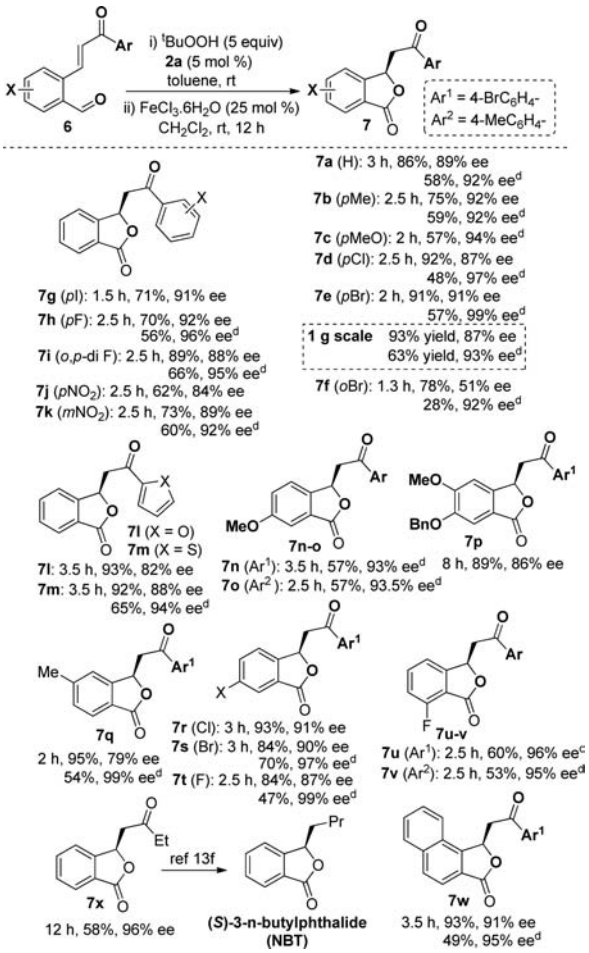
Scheme 3. Substrate Scope: 3-Isochromanone[a]



[a]Reaction conditions: same as Scheme 2.

To further explore the scope of the reaction, peroxy hemiacetalization/oxa-Michael addition/decomposition was performed with the *o*-formyl chalcones (**6**) (summarized in Scheme 4). Overall, a smooth reaction was observed, providing

Scheme 4. Scope of Phthalides[a]

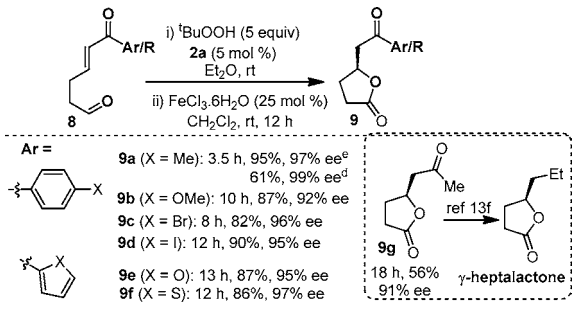


[a]Reaction conditions: **1** (0.2 mmol), tBuOOH (1.0 mmol, 5 equiv), **2a** (0.01 mmol, 5 mol %) in toluene. [b]Yields are isolated products. [c]Ee's were determined by HPLC analysis. [d]After *n*-hexane wash.

the corresponding 5-membered lactones (phthalides). It is noteworthy that the reaction outcome is essentially unaffected by the ring size of the product, as proven by the high yields and optical purity of products **7**. Terminal aryl moieties having a wide range of functional groups such as *p*-Me- (**7b**), *p*-MeO-(**7c**), *p*-Cl- (**7d**), *p*-Br- (**7e**), *o*-Br- (**7f**), *p*-I- (**7g**), *p*-F- (**7h**), *o*,*p*-di-F- (**7i**), *p*-O_2N- (**7j**), and *m*-O_2N- (**7k**) worked efficiently to provide the expected phthalides. Heteroaromatic groups such as 2-furyl (**7l**) and 2-thiophene-yl (**7m**) also worked smoothly, affording the desired products in good yields and high enantioselectivities. We next investigated the substrate scope of this reaction concerning differently substituted internal aryl moiety of phthalides. Both electron-donating and electron-withdrawing groups on aryl ring afforded products **7n–v** with outstanding enantioselectivity (up to >99% ee).

Notably, irrespective of the position of substitution, e.g., *o*- (**7u–v**), *m*- (**7r–t**), or *p*- (**7q**) to the formyl moiety of phthalides, the reaction worked nicely to give the corresponding products in good yields and with high enantioselectivities. Replacing the internal phenyl moiety with naphthyl moiety was also successfully reacted to provide 93% yield and up to 91% ee (**7w**). To showcase the scalability and the practicality of the process, we also performed a gram-scale reaction. For example, *o*-formyl chalcone **6e** (1.0 g, 3.2 mmol) was reacted under the standard reaction conditions using 5 mol % catalyst loading, and the desired phthalide (**7e**) was obtained in 93% yield and 87% enantioselectivity. To illustrate the practical synthetic utility of our methodology, we performed enantioselective synthesis of lactones **7x**, an advanced intermediate for the synthesis of bioactive phthalide (*S*)-3-*n*-butyl phthalide (NBT). Moreover, this shows a compatibility of the methodology with an aliphatic α,β-ketone moiety. Besides the 1-isochromanone, 3-isochromanone, and phthalides, where the formyl group and enone moiety are tethered with an aromatic moiety, this strategy was also tested for the synthesis of chiral lactones in which the above two groups are tethered with an aliphatic moiety. As shown in Scheme 5, β-

Scheme 5. Chiral γ-Lactones[a–c]



[a]Reaction conditions: **8** (0.1 mmol), tBuOOH (0.5 mmol, 5 equiv), **2a** (0.005 mmol, 5 mol %) in Et_2O. [b]Yields shown are based on isolated products. [c]Ee's were determined by HPLC analysis. [d]After *n*-hexane wash. [e]The first step was carried out in toluene.

formyl enones (**8**) efficiently furnished the γ-lactones **9a–f** with high levels of stereocontrol. Notably, the synthesis of lactone **9g** having an alkyl substitution on the α,β-ketone moiety provided an advanced intermediate for bioactive γ-heptalactone. The absolute stereochemistry of the chiral 3-substituted phthalide (**7a**) was established by comparing optical rotation values with literature data (see the SI).[3a] This result unambiguously shows the absolute configuration of product **7a** to be the (*R*)-form. The absolute configurations of all other compounds were assigned by

DOI: 10.1021/acs.orglett.6b02463
Org. Lett. 2016, 18, 5220–5223

analogy. To explain the observed absolute stereochemistry of product, a transition state similar to those previously proposed for the squaramide/thiourea catalysts in the oxa-Michael reaction of enone is presumed.[2−4]

In summary, a catalytic enantioselective strategy to suppress the rapid cyclization for enantioselective intramolecular oxa-Michael reactions of carboxylic acids was developed. The enantioenriched lactones were synthesized via a tandem peroxy acetalization/asymmetric oxa-Michael addition/Lewis acid catalyzed Kornblum DeLaMare type rearrangement of *o*-homoformyl chalcones or *o*-formylhomochalcones. A simple hexane wash was enough to purify these enantiopure products in good yields and excellent enatioseleectvities (up to >99 ee). Notably, the synthetic design was highly flexible and can be readily adapted to various other substrates enabling direct access to a broad range of chiral lactones. Further investigations toward the scope and limitations of this methodology are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02463.

Experimental procedures and characterization data (PDF)
NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work has been supported by CSIR, New Delhi, and IISER Bhopal. B.P. thanks CSIR, New Delhi, and S.M. thanks UGC, New Delhi, India, for fellowships.

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DOI: 10.1021/acs.orglett.6b02463
Org. Lett. 2016, 18, 5220−5223