Formal [4+2] Cycloaddition of Imines with Alkoxyisocoumarins

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Formal [4+2] Cycloaddition of Imines with Alkoxyisocoumarins

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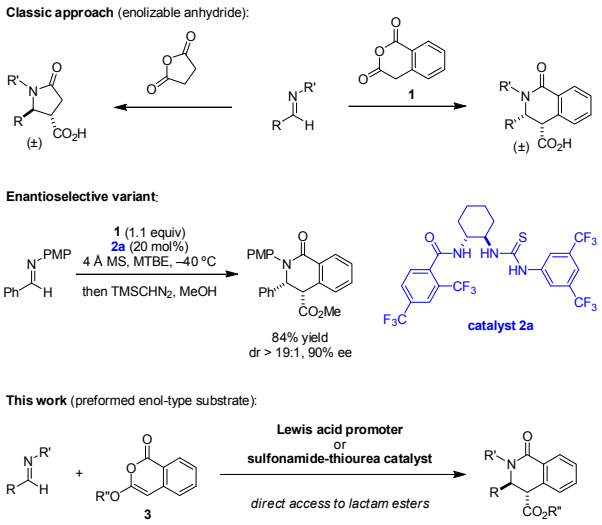
Abstract: A new preparation of δ-lactams is reported. In the presence of a Lewis acid promoter, alkoxyisocoumarins engage a range of *N*-aryl and *N*-alkyl imines to form δ-lactams with a pendent carboalkoxy substituent. A sulfonamide-thiourea catalyst enables the synthesis of these products in moderate to good enantioselectivities.

Formal [4+2] cycloadditions of imines with enolizable anhydrides provide a convenient entry to lactams that bear a pendent carboxylic acid functionality (Scheme 1).[1] Reactions of imines with succinic anhydride furnish γ-lactams, as first shown by Castagnoli.[2] Cushman and Haimova established that δ-lactams can be constructed from homophthalic anhydride (**1**) and related materials.[3] Numerous variants have been reported, and both acyclic and cyclic imines participate in this chemistry.[1,4] The formal [4+2] cycloaddition has been utilized as a key step in alkaloid synthesis,[5] and has enabled the preparation of a range of products with diverse bioactivities and medicinal applications.[6] While asymmetric variants based on enantioenriched starting materials and chiral auxiliaries have been known for some time,[7] a catalytic enantioselective approach was reported by us only recently.[8,9] In the majority of studies, the initially formed carboxylic acid containing products are, for the purpose of easier isolation, purification, and further processing, subsequently converted into the corresponding lactam esters.[1] Here we report an approach that provides lactam esters directly by replacing homophthalic anhydride (**1**) with an alkoxyisocoumarin **3** as the starting material.

A plausible mechanism of the formal [4+2] cycloaddition of enolizable anhydrides such as homophthalic anhydride (**1**) and imines involves an initial Mannich step.[4f,10] This step is likely initiated by protonation of the imine by the relatively acidic



Scheme 1 Approaches to the synthesis of lactams from imines.

anhydride (pK_a of **1** = 8.15)[11] or other acid, followed by collapse of the iminium enol (enolate) pair. A closely related mechanistic alternative is a Mannich reaction involving a hydrogen-bonded complex of the imine with the enol form of the anhydride. The Mannich addition step is followed by Perkin-like intramolecular acyl transfer, leading to the lactam product bearing a carboxylic acid functionality. We reasoned that the initial step could be modified into a Mukaiyama-type Mannich addition by substituting homophthalic anhydride (**1**) with an alkoxyisocoumarin **3**, inasmuch as the latter contains a pre-formed enol-type moiety. Indeed, isolated previous reports hint at this possibility. For instance, 3-alkylamino isochromenones have been reported to form δ-lactam amides upon reaction with imines.[12] Bis(trimethylsilyloxy)furans have been utilized in the synthesis of γ-lactam acids corresponding to the products reported by Castagnoli.[13] To our knowledge, such an approach has not been utilized in the preparation of synthetically valuable δ-lactam esters from imines and

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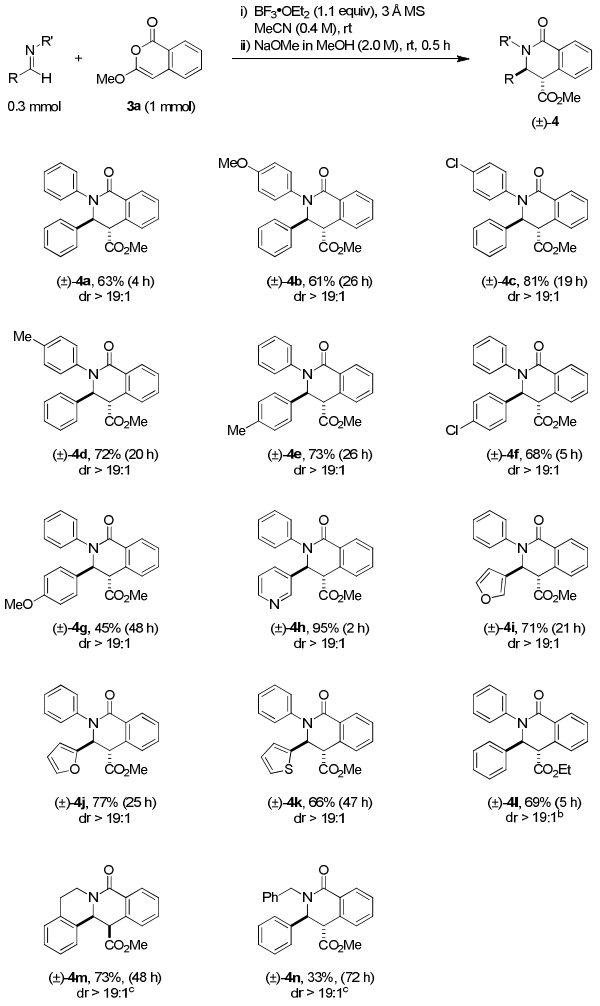
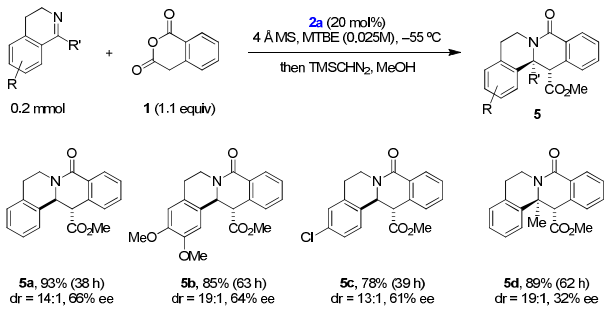
alkoxyisocoumarins. Inspired by known asymmetric Mukaiyama Mannich reactions involving alkyl enol ethers and silyl ketene acetals,[14] we reasoned that the use of alkoxyisocoumarins could provide a platform for the development of a catalytic enantioselective variant.



Scheme 2 Scope of the Lewis acid promoted reaction. Yields reflect chromatographically purified compounds. [b] With ethoxyisocoumarin. [c] Reaction was performed at 45 °C.

Aniline-derived imines were found not to undergo reactions with methoxyisocoumarin (**3a**)[15] at room temperature. Attempted reactions at elevated temperatures in the absence of additives also did not lead to favorable outcomes. Upon evaluation of a range of Lewis acid additives at room temperature, boron trifluoride diethyl etherate (BF_3•OEt_2) was identified as an efficient promoter of the title reaction.[16,17] Crude reaction mixtures were treated with sodium methoxide solution to epimerize the initial *cis*/*trans* mixtures of products to the thermodynamically more stable *trans* isomers. The scope of this transformation is illustrated in Scheme 2. For instance, a reaction of *N*-benzylideneaniline with **3a** provided **4a** in 63% yield. Related imines underwent lactam formation with similar efficiencies. A range of aryl and hetero-aryl groups were well tolerated in this reaction. The combination of *N*-benzyl imine and 3,4-dihydroisoquinoline required heating for several days to give the desired products **4m** and **4n** – partial decomposition of starting materials was observed after extended reaction times.

After establishing the racemic reaction, we sought to develop a catalytic enantioselective variant. As a comparative starting point, and by using conditions already reported,[8] we examined the enantioselective reaction between homophthalic anhydride **1** and several dihydroisoquinolines in the presence of amide-thiourea catalyst **2a** (Scheme 3). The uncatalyzed background reaction for these substrates is exceedingly fast – complete consumption of starting materials was observed within minutes at room temperature. At –55 °C, the relative rate of the catalyzed reaction over the uncatalyzed process was more favorable. Even under these conditions, the enantioselectivities observed for **5a**–**5d** were moderate (up to 66% ee) and the kinetic *trans* isomer was isolated preferentially. Extended reaction times led to poorer diastereoselectivities and slightly reduced enantioselectivities, as partial epimerization to the *cis* isomers occurred.

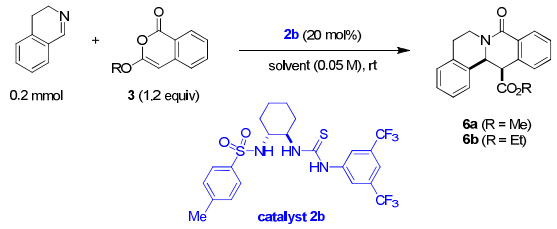


Scheme 3 Catalytic enantioselective reactions of homophthalic anhydride and imines. Yields reflect chromatographically purified compounds. The ee values were determined by HPLC analysis; see the Supporting Information for details. The absolute configurations of the products are tentatively assigned based on comparison with literature values for optical rotation.

Conditions for the catalytic enantioselective addition of alkoxyisocoumarins **3** to dihydroisoquinoline were developed next (Table 1). In the absence of catalyst, only trace amounts of product formed at room temperature over the course of 72 hours (entry 1). Following an extensive screening of hydrogen bond donor organocatalysts[18] with the potential ability to activate the imine electrophile,[19] sulfonamide-thiourea compound **2b**[20g] was identified as a promising catalyst.[20] After a reaction time of 24 h, product **6a** was obtained with excellent diastereoselectivity in 50% yield and 52% ee (entry 2). Notably, the thermodynamically favored *cis* isomer was isolated, rendering this approach complementary to the reaction of dihydroisoquinoline with homophthalic anhydride (**1**). A switch of solvent from toluene to trifluorotoluene

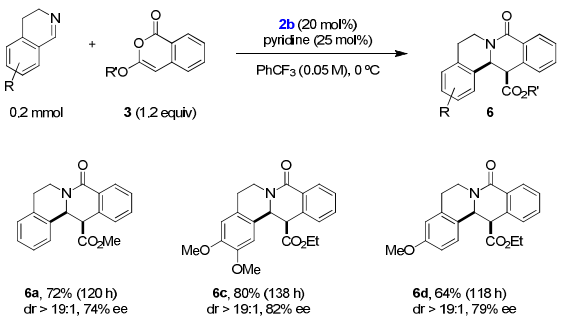
provided a slight increase in enantioselectivity (entry 3). Different alkoxy groups on nucleophile **3** conferred different rates and enantioselectivities,[19] with ethoxyisocoumarin providing the highest enantioselectivities (entries 4 and 5). A marked improvement in product ee was observed upon performing the reaction at 0 °C, accompanied by the expected drop in reaction rate (entry 6). Improved results were obtained by conducting the reaction in the presence of catalytic amounts of pyridine.[21] Product **6b** was isolated with excellent diastereoselectivity in 61% yield and 81% ee (entry 7). A number of substituted dihydroisoquinolines were evaluated under the optimized conditions and were found to provide comparable results (Scheme 4). Unfortunately, aniline-derived imines were insufficiently reactive under these conditions – only trace amounts of product were observed in a number of reactions conducted at room temperature for several days.

Table 1. Evaluation of catalytic enantioselective variant with alkoxyisocoumarins.[a]



entry	R	solvent	time [h]	yield (%)	dr	ee (%)
1[b]	Me	PhMe	72	trace	-	-
2	Me	PhMe	24	50	>19:1	52
3	Me	$PhCF_3$	24	47	>19:1	56
4	Et	PhMe	24	47	>19:1	65
5	Et	$PhCF_3$	24	55	>19:1	68
6[c]	Et	$PhCF_3$	64	35	>19:1	81
7[c,d]	Et	$PhCF_3$	121	61	>19:1	81

[a] Yields reflect chromatographically purified compounds. The ee values were determined by HPLC analysis; see the Supporting Information for details. The absolute configurations of the products are tentatively assigned based on comparison with literature values for optical rotation. [b] The reaction was performed without any catalyst. [c] The reaction was performed at 0 °C. [d] With 25 mol% of pyridine.



Scheme 4 Enantioselective reactions of alkoxyisocoumarins and dihydroisoquinolines. Yields reflect chromatographically purified compounds. The ee values were determined by HPLC analysis; see the Supporting Information for details. The absolute configurations of the products were not established.

Conclusions

We have developed a new preparation of δ-lactams that features an alkoxyisocoumarin nucleophile. The products contain the core structure of the tetrahydroprotoberberine class of alkaloids. A catalytic enantioselective version of this transformation exhibits good levels of enantioselectivity, and the diastereoselectivity is complementary to the classic approach that utilizes homophthalic anhydride as the pro-nucleophile.

Acknowledgements

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Conflicts of interest

There are no conflicts to declare.

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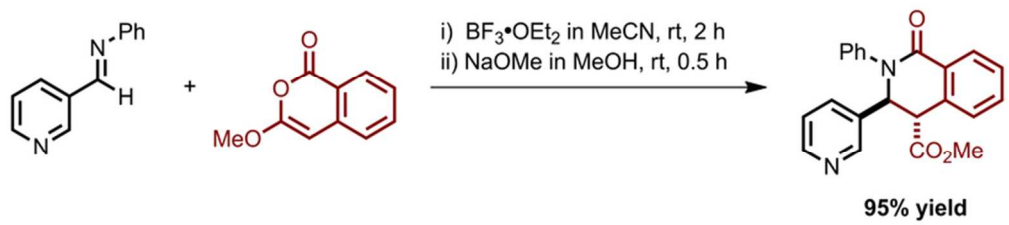
21 While the exact role of the pyridine additive remains unclear at present, it may facilitate catalyst turnover. Additional results in support of this notion are provided on page S-6 of the Supporting Information.



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