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Formal [4 + 2] Cycloadditions of Anhydrides and α,β-Unsaturated *N*-Tosyl Ketimines

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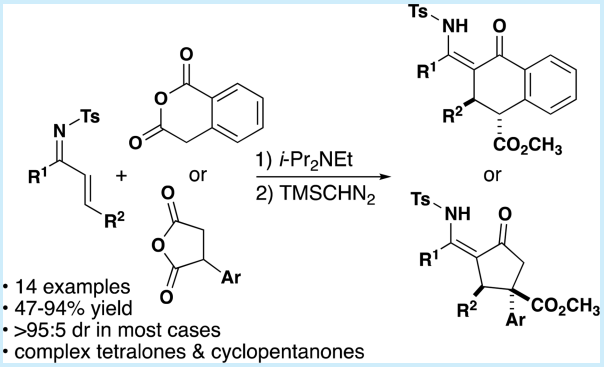
Supporting Information

ABSTRACT: A method for the diastereoselective synthesis of highly substituted β-enamino ketones from anhydrides and ketone-derived imines is reported. Cyclic, enolizable anhydrides undergo a base-promoted conjugate addition reaction with α,β-unsaturated *N*-tosyl ketimines, followed by an intramolecular acylation to give formal [4 + 2] cycloaddition products. The carboxylic acid-containing products are formed with modest selectivity for the *cis*-diastereomer and can be fully epimerized to the *trans*-diastereomer upon esterification.



Cyclic anhydrides are useful dipolar synthons for the synthesis of complex organic molecules through formal cycloaddition reactions.[1] The most widely studied reaction involves the addition to imines to form lactams, recently referred to as the Castagnoli–Cushman reaction (Figure 1).[1b] Although most previous studies of this reaction employed *N*-alkyl imines, the reaction of *N*-sulfonyl imines was recently shown to proceed by base mediation[2] and rendered asymmetric using organocatalysts.[3] Although *N*-aryl imines are less commonly used, they exhibit excellent reactivity in a recently reported catalytic reaction.[3b] In parallel, Tamura has demonstrated that homophthalic anhydride undergoes base-mediated addition to alkynes to form, after decarboxylation, highly substituted naphthalenes.[4] Early studies included limited examples of addition to alkenes to form substituted tetralins,[4,5] and more recently, Connon developed an asymmetric variant of this process.[6] We initiated a study of α,β-unsaturated ketimines, which have the potential to exhibit merged "Tamura-like" and "Cushman-like" reactivity. Herein, we report the first reactions of cyclic anhydrides in reactions with electron-deficient unsaturated imines,[7] which proceed in high diastereoselectivity and, for the first time, exhibit "Tamura-like" reactivity to form 5-membered ring products.

For our initial investigation of this reaction, we used the readily enolizable homophthalic anhydride and methoxy-substituted chalcone imine **1c** (Table 1). Chalcone-derived imines were chosen for their ease of synthesis and diversification. Our favored conditions for the base-catalyzed anhydride–Mannich reaction (AMR), 1 equiv of TMG in acetonitrile, provided the desired product in full conversion but with virtually no diastereoselectivity (entry 1).[8] Similar results were observed with 20 mol % of TMG with either 1.0 or 1.2 equiv of anhydride (entries 2 and 3). Switching the base to 1 equiv of *i*-Pr_2NEt resulted in a reversal of selectivity to the *cis* isomer (entry 12), and performing the reaction in CH_2Cl_2 provided a dr of 94:6 (entry 14). Attempts at using substoichiometric quantities of *i*-Pr_2NEt resulted in lower conversion (entry 15). We attribute the reduced reactivity in this case to the acidity of the *N*-tosyl vinylogous amide proton, which results in a catalyst inhibition by protonation.

Acid **3c** was converted to the corresponding methyl ester for ease of purification. Upon treatment with TMS-diazomethane, the diastereomer ratio of the resulting ester shifted to varying degrees and with the addition of DBU seemed to invert completely. As such, we suspected that the configuration of the initially formed acid was *cis*, and as a result of base-mediated epimerization of the stereogenic center α to the carboxyl group, the configuration of the ester was *trans*. To support our hypothesis, the ester **4c** was hydrolyzed back to the acid using LiOH (Figure 2). We hoped to obtain an X-ray crystal structure by converting the carboxylic acid to a benzyl amide. After examining several conditions for amide coupling, those of Knapp and co-workers resulted in the formation of a less polar product lacking the expected amide protons.[9] X-ray crystallography revealed that the nitrile had been formed, presumably through a von Braun-like mechanism proceeding through cleavage of the PMB amide.[10] Additionally, this structure showed the relative stereochemistry of nitrile **5** to be *trans*. Given the similarity in coupling constants between ester **4c** and nitrile **5**, we conclude that both compounds have a *trans* configuration between the adjacent stereogenic centers.[11]

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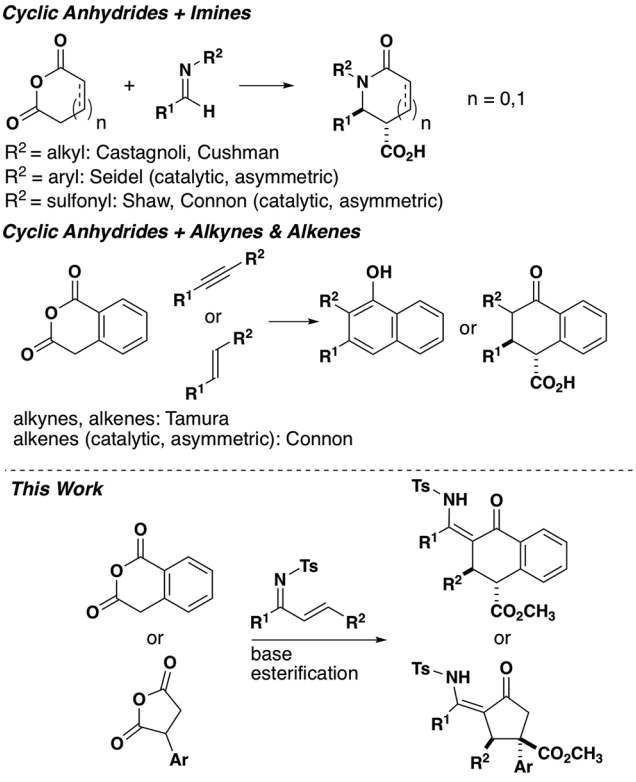
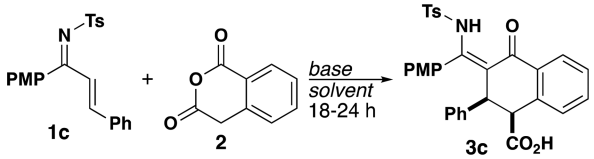


Figure 1. Imine–anhydride formal [4 + 2] cycloadditions.

Table 1. Reaction Optimization for Chalcone-Derived α,β-Unsaturated *N*-Tosyl Imine 1c



entry	base (equiv)	**2** (equiv)	solvent	dr[a]	conv[a] (%)
1	TMG (1.0)	1.0	CH_3CN	57:43	100
2	TMG (0.2)	1.0	CH_3CN	54:46	82
3	TMG (0.2)	1.2	CH_3CN	51:49	85
4	TMG (1.0)	1.0	CH_2Cl_2	29:71	97
5	TMG (1.0)	1.0	THF	21:79	91
6	TMG (1.0)	1.0	EtOAc	23:77	95
7	TMG (1.0)	1.0	toluene	26:74	94
8	TMG (1.0)	1.0	DMF	31:69	82
9	TMG (1.0)	1.0	*n*-hexane	N/A	0
10	TMG (1.0)	1.0	1,4-dioxane	29:71	90
11	TMG (1.0)	1.0	acetone	45:55	79
12	*i*-Pr_2NEt (1.0)	1.0	CH_3CN	79:21	93
13	*i*-Pr_2NEt (1.0)	1.0	THF	64:36	58
14	*i*-Pr_2NEt (1.0)	1.0	CH_2Cl_2	94:6	81
15	*i*-Pr_2NEt (0.2)	1.0	CH_2Cl_2	>95:5	20
16	*i*-Pr_2NEt (1.2)	1.0	CH_2Cl_2	79:21	89
17	***i*-Pr_2NEt (1.0)**	**1.2**	**CH_2Cl_2**	**93:7**	**97**

[a]Determined by the ^1H NMR spectrum of the unpurified reaction mixture.

Chalcone imines with a variety of substituents provided formal cycloaddition products in high yield (Figure 3). The electronics of the aryl ring adjacent to the imine had a noticeable effect on the diastereoselectivity of the reaction,

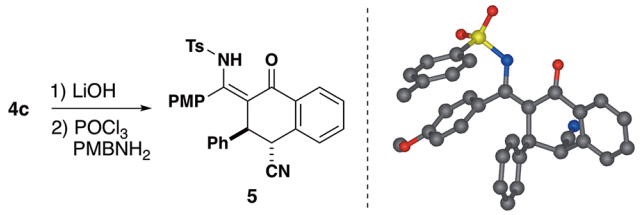


Figure 2. Conversion of **4c** to nitrile **5**; X-ray crystal structure of nitrile **5**.

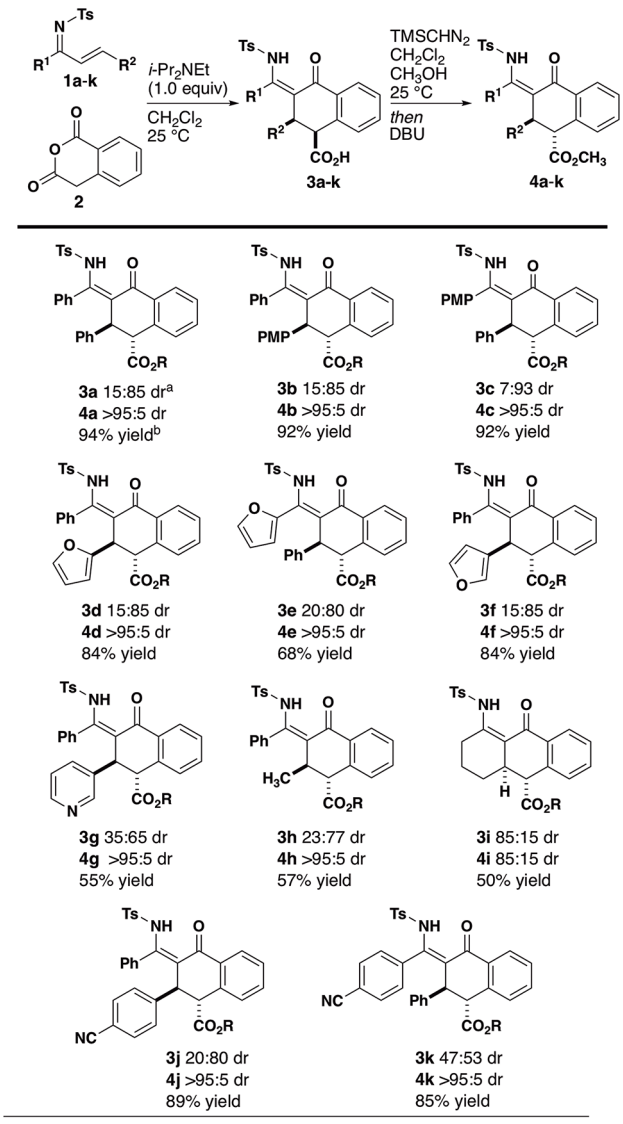


Figure 3. α,β-Unsaturated *N*-tosyl imine scope of the aza-Tamura reaction.

with electron-donating groups giving an improved dr for the *cis*-diastereomer. Alternatively, electron-withdrawing groups resulted in an erosion of dr, which can be explained by a faster rate of epimerization to the *trans*-diastereomer under the reaction conditions. Enolizable imines (**1h**) and (**1i**) were tolerated under the reaction conditions as well (Figure 3). Methyl-substituted homophthalic anhydride and phenyl succinic anhydride also give formal cycloaddition products (Figure 4). The relative stereochemistries of **4i** and **7** were

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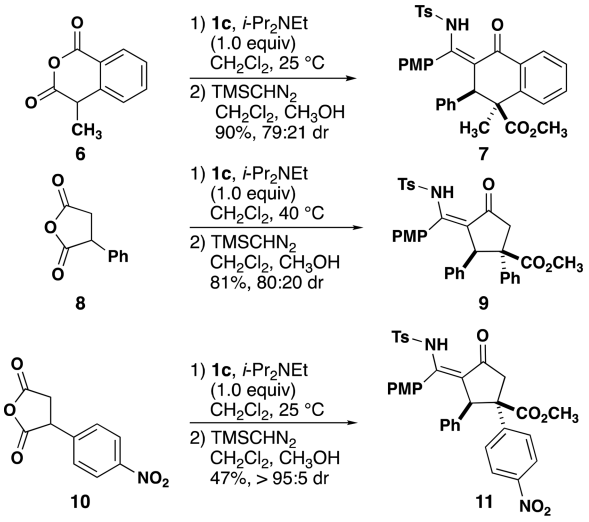
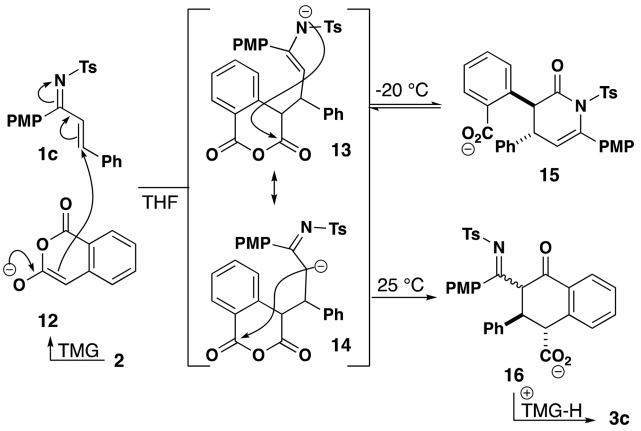


Figure 4. Expanded scope of the aza-Tamura reaction.

assigned by computational NMR.[11,12] Product **9** was converted to the corresponding nitrile, which provided an X-ray crystal structure for the stereochemical assignment of **9** and **11**.[11]

We hypothesize that the mechanism for this reaction involves conjugate addition of the anhydride enolate to the imine, followed by an intramolecular acylation (Scheme 1).

Scheme 1. Mechanistic Hypothesis

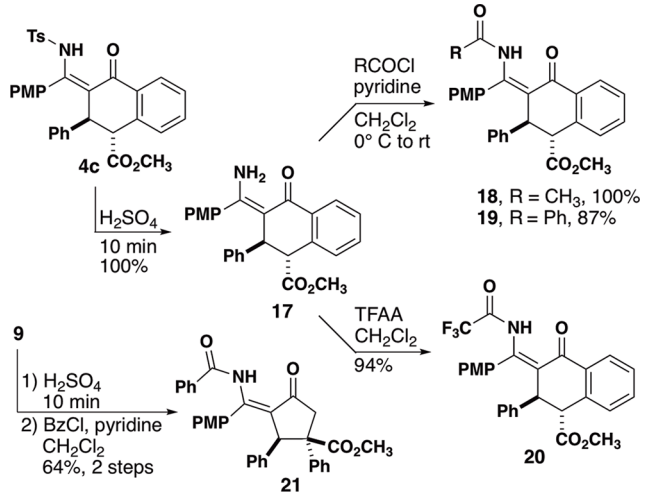


The ambident enamine anion resulting from conjugate addition can undergo *N*-acylation to form a δ-lactam (**15**) or *C*-acylation followed by tautomerization to form a β-enamino cyclohexanone (**3a–k**).

We have observed the *N*-acylation product of type **15** in ^{1}H NMR studies as a transient, kinetically favored intermediate that converts to the β-enamino ketone over the course of the reaction. The structure of this intermediate was assigned on the basis of comparison of ^{1}H NMR signals with similar molecules that have been previously synthesized by Smith and co-workers.[13] Product **15** was formed exclusively when the reaction was run overnight at −20 °C in THF using TMG as the base, albeit in low conversion. Resubjection to reaction conditions at room temperature gave full conversion to **3c.**

The *N*-Ts products can be cleanly detosylated by dissolution in neat sulfuric acid.[14] As exemplified with **4c**, the resulting β-enamino ketone (**17**) can then be acylated with various acid chlorides and reagents of similar reactivity (Scheme 2). β-Enamino ketones have been shown to undergo condensation reactions; however, we found the carbonyl of our β-enamino cyclohexanone substrate to be inert to these conditions.[15]

Scheme 2. Derivatization of Aza-Tamura Products 4c and 9



In summary, we have developed a base-promoted reaction between α,β-unsaturated *N*-tosyl ketimines and cyclic, enolizable anhydrides. Although the reaction can be run catalytically with TMG, the use of stoichiometric Hünig's base provides higher yield and diastereomer ratio. Conversion to the methyl ester allows for full epimerization to the *trans*-diastereomer by subsequent treatment with DBU. The resulting β-enamino ketone products can be detosylated and derivatized with a variety of acylating reagents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b04091.

Experimental procedures, computational NMR data, X-ray crystallographic data, ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1887468 and 1887611 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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