Organocatalytic Mukaiyama Mannich Reactions of 2,5-Bis(trimethylsilyloxy)furan

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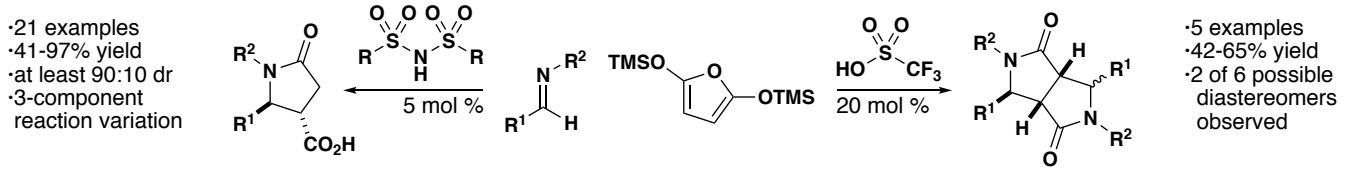
Supporting Information Placeholder



ABSTRACT: The organocatalytic synthesis of densely substituted mono- and bis-γ-lactams involving the Mukaiyama Mannich addition of 2,5-bis(trimethylsilyloxy)furan to imines is described. Use of a ditoluenesulfonylimide catalyst produces γ-lactams from mono-addition, whereas a more acidic catalyst (triflic acid) produces fused bis-lactams from double addition. Optimized organocatalytic conditions allow for the selective synthesis of either desired core as well as the one-pot, multicomponent assembly of the tri-substituted mono-lactams from aldehydes, amines and bis-trimethylsilyloxyfuran. An examination of chiral acids found these organocatalysts to be highly active and diastereoselective in the mono-addition reaction, albeit with no enantioselectivity.

The stereoselective synthesis of γ-lactams has been studied extensively due to the prevalence of this scaffold in natural products and biologically relevant molecules.[1] As a result, a variety of methods for the synthesis of γ-lactams have been developed.[2] Our group and others have been interested in the synthesis of lactams via formal [4 + 2] cycloadditions of imines and cyclic, enolizable anhydrides for years (Figure 1A).[3] This interest has led to many advances since the introduction of the Castagnoli-Cushman reaction. A related four-component reaction,[4] the introduction of new anhydrides as reaction substrates,[5] and improved mechanistic insight have all been reported.[6] Based on current mechanistic understanding, we now call this the anhydride-Mannich reaction (AMR) because the key step involves the addition of an anhydride enolate to an iminium ion. Recent contributions to this field include the development of the first catalytic variants of the AMR (Figure 1B).[7] In these reports, selecting substrates with inherently slow thermal AMR rates allowed base and/or hydrogen-bond-donating organocatalytic activation of the anhydride to form the key enolate intermediate. Despite these successes, all reported catalytic examples of the AMR involve reactions of homophthalic anhydride, the most readily enolizable cyclic anhydride substrate. We have developed a novel method for the Lewis acid-catalyzed synthesis of di-substituted γ lactams, and also report the first ever one-step synthesis of fused bis-lactams.

We envisioned a strategy for catalyzing the AMR in analogy to the Mukaiyama aldol reaction (Figure 1C).[8] Organocatalysis has emerged as a useful tool for performing organic transformations without the cost and toxicity associated with transition metal-catalyzed systems. The design of Brønsted acid organocatalysts has seen significant exploration, largely due to the successful application of BINOL-derived Brønsted acids in asymmetric catalysis.[9] Phosphoric acids[10], phosphoramides[11], disulfonic acids[12], and disulfonimides[13] are among the most commonly used Brønsted acidic catalytic moieties for organocatalytic transformations. Although these Brønsted acids are often used as proton donors in electrophile activation, recent reports show that disulfonimides are also capable of Lewis acid activity in Mukaiyama aldol[13-14] and Mannich[14c, 15] reactions. Based on this precedent, we proposed that protodesilylation of anhydride-derived silyl ketene acetal **1** would allow access to Lewis-acidic

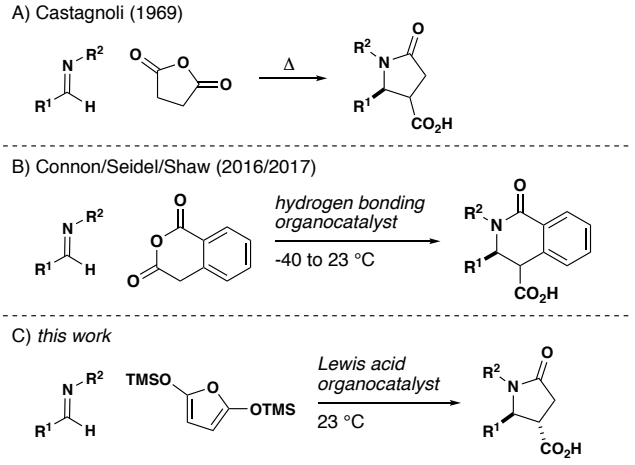
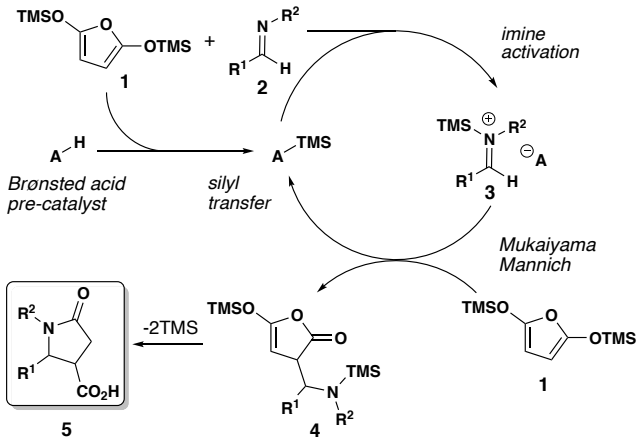


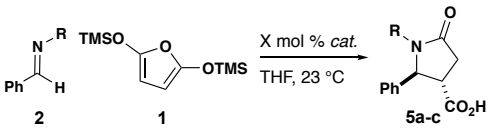
Figure 1 Reactions of imines and cyclic anhydrides or their derivatives for the synthesis of lactams.

Scheme 1 Proposed mechanism of the catalytic Mukaiyama anhydride Mannich reaction.



silylated disulfonimides, enabling the organocatalytic Mukaiyama AMR (Scheme 1). Initial triflic acid- and disulfonimide-catalyzed Mukaiyama AMRs of bis(trimethylsilyloxy)furan **1** with variously *N*-substituted, benzaldehyde-derived imines were carried out at room temperature for 24 or 48 hours (Table 1). Although the triflimide and *ortho*-benzenedisulfonimide (*o*-BDSI)-catalyzed reactions of *N*-Boc and *N*-Cbz imines appeared promising, the products of these reactions proved prohibitively difficult to isolate, precluding further investigation. By comparison, the lactam products of *N*-PMP imines proved easily isolable, albeit with somewhat diminished conversion. While the triflic acid-catalyzed reaction of *N*-PMP imine showed nearly full consumption of starting materials, only a small quantity of desired lactam was identified by ^{1}H NMR of the unpurified reaction mixture. Ultimately, optimized conditions using the easily synthesized ditoluenesulfonimide catalyst with slightly increased catalyst loadings, longer reaction times, and two equivalents of furan were selected.

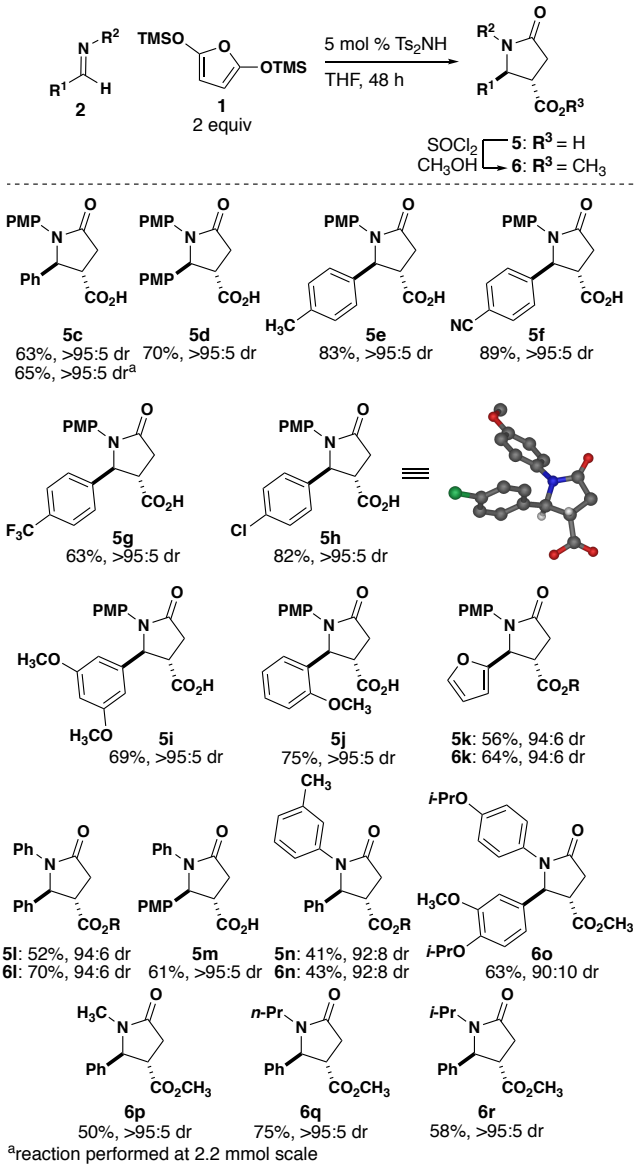
Table 1 The effect of imine *N*-substituent and catalyst on conversion and diastereomeric ratio of the Mukaiyama AMR.



entry	R	catalyst	time (h)	% conv. **5**[a]	d.r. **5**[a]
1	Boc (5a)	2 mol % TfOH	24	<5	n.d.
2	Boc (5a)	2 mol % Tf_2NH	24	<5	n.d.
3[b]	Boc (5a)	2 mol % *o*-BDSI	48	89	74:26
4[b]	Cbz (5b)	2 mol % Tf_2NH	24	>95	>95:5
5[b]	Cbz (5b)	2 mol % *o*-BDSI	48	>95	>95:5
6	PMP (5c)	2 mol % TfOH	24	7	n.d.
7	PMP (5c)	2 mol % Tf_2NH	24	54	>95:5
8	PMP (5c)	2 mol % Ts_2NH	24	62	90:10
9[c]	PMP (5c)	5 mol % Ts_2NH	48	86	93:7

[a]As determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture
[b]imine formed in situ from corresponding amidosulfone
[c]Two equivalents of bis(trimethylsilyloxy)furan **1** used

With our optimized conditions in hand, we screened a number of *N*-aryl imines in reactions with **1**. All examined *p*-substituted benzaldehyde-derived substrates were well tolerated, yielding a single *trans* diastereomer of lactam products in good yield (Figure 2). Similarly, 3,5-dimethoxy-substituted and *ortho*-methoxy-substituted imines also yielded lactams **5i** and **5j**, respectively, good yield with excellent diastereomeric ratio. Notably however, the



[a]reaction performed at 2.2 mmol scale

Figure 2 Scope of Mukaiyama AMR.

organocatalytic reactions of **1** with *N*-PMP imines derived from 2-napthaldehyde and mesitaldehyde showed no conversion by ^{1}H NMR spectroscopy of the unpurified reaction mixture, suggesting a limit to the substrate sterics tolerated by the reaction. *N*-aryl substituents other than *N*-PMP were also proven productive, albeit with slightly lower yields and diastereoselectivities.

In hopes of expanding our scope to aliphatic aldehyde derived imines, we turned our attention to the synthesis of imines derived from isobutyraldehyde and hydrocinnamaldehyde. The isolation of these imines proved to be nontrivial, as the imines decomposed prior to subjecting to reaction conditions. Interested in overcoming this setback, we began to screen the catalytic, multicomponent assembly of γ-lactams by reaction of aldehydes, amines, and furan **1** in the presence of desiccants (Figure 3). Lactam **5c**, previously isolated in 74% from the reaction of **1** with imine **2c**, was formed from the 3-component reaction as a single diastereomer in 92% yield following esterification (**6c**). Furthermore, the previously unobserved aliphatic aldehyde-derived lactams could be isolated in fair to excellent yield.

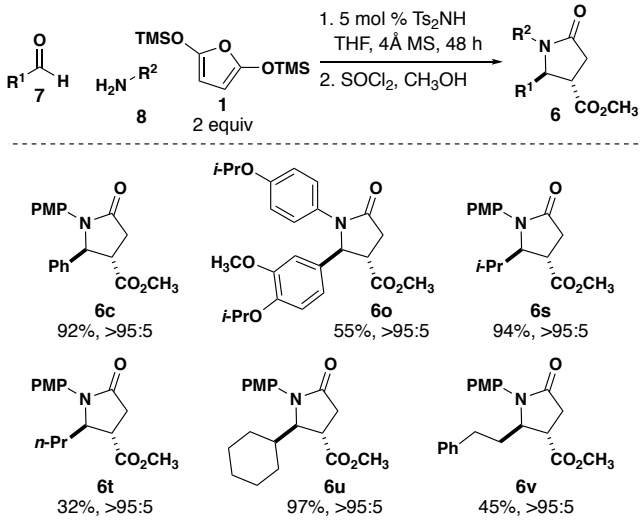
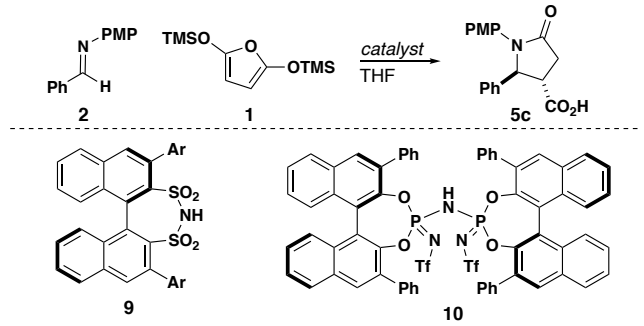


Figure 3 Scope of the one-pot, three-component Mukaiyama AMR.

A preliminary screen of chiral catalysts revealed high conversion and diastereoselectivity, albeit with no discernible enantioselectivity (Table 2). Sulfonimides C1 and C2 showed exclusive formation of **5c**, confirming that these catalysts exhibit similar reactivity to ditoluenesulfonimide. Although imidodiphosphorimidate-type (IDPi) catalyst C3 is more acidic than ditoluenesulfonimide, lactam **5c** is still the only observed product. This result suggests that the bulkier steric environment of this catalyst may preclude the addition of a second equivalent of imine. The complete lack of enantioselectivity observed with two structurally distinct catalysts suggests that this reaction may require a high level of customization in order to realize useful levels of asymmetric induction.

Table 2 Mono-addition reactions using chiral catalysts.



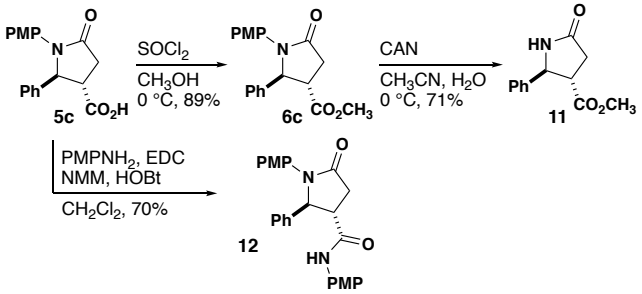
9a; **Ar** = 3,5-(3,5-$[CF_3]_2C_6H_3)_2C_6H_3$
9b; **Ar** = 3,5-$(CF_3)_2C_6H_3$

entry	time (h)	catalyst	% conv. **5c**[a,b]	trans:cis **5c**[a]	er **5c**[c]
1	24	2 mol % **9a**	95	>95:5	50:50
2	24	2 mol % **10**	94	>95:5	50:50
3[d]	24	5 mol % **(*S*)-9b**	100	>95:5	50:50
4[d,e]	24	5 mol % **(*S*)-9b**	100	>95:5	50:50

[a]As determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture
[b]No conversion to bis-γ-lactam product was observed
[c]As determined by chiral HPLC of the corresponding methyl ester
[d]2 equiv. 4Å MS added
[e]5 mol% 2,6-DTBP added

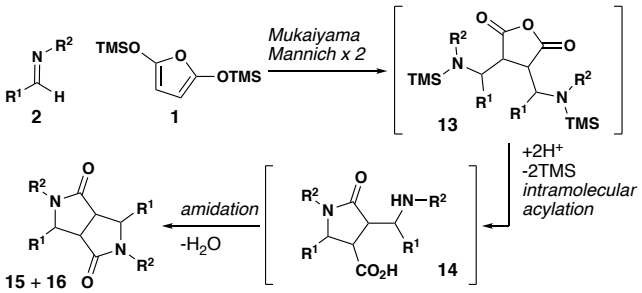
Having explored the scope of the diastereoselective, organocatalytic method, we sought to further functionalize lactam **5c** (Scheme 2). Amidation and esterification of the carboxylic acid moiety were achieved in high yield and CAN-mediated PMP-cleavage of esterified lactam **6c** provided *N*–H lactam **11** in good yield.

Scheme 2 Lactam product derivatization.



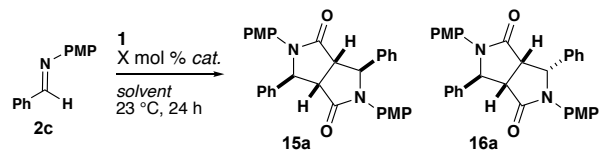
We revisited the results of our initial achiral catalyst screen in order to better understand of the divergent reactivity observed in triflic acid-catalyzed reaction of **1** and **2c**. Purification of the crude reaction mixture by flash column chromatography revealed the formation of two diastereomeric bis-γ-lactams, the C_2-symmetric **15a** and the C_1-symmetric **16a**. We hypothesize that this uncommon core structure may be formed via two successive Mukaiyama Mannich reactions followed by global protodesilylation, intramolecular acylation, and amidation (Scheme 3).[16] Although the two products are formed in similar quantities, *no trace of the other four possible diastereomers could be detected in the reaction mixture.* This core structure has only been previously observed once as a synthetic product and once as the core of a natural product.[17] The analogous fully unsaturated heterocycle, i.e. diketopyrrolopyrrole (DPP) is a common building block for photoactive dyes and polymers.[18]

Scheme 3 Proposed mechanism for the synthesis of bis-γ-lactams.



Further reaction screening showed that triflic acid remains catalytically active with the addition of equimolar 2,6-di-tert-butylpyridine, when added as a pyridine salt, and when replaced by catalytic trifluoromethanesulfonate (Table 3). This suggests that the catalytic activity of triflic acid in this reaction is the result of Lewis, not Brønsted, acid activity, following *in situ* silylation. While this reactivity is apparently similar to that proposed for the disulfonimide catalysts, triflic acid presumably must provide greater catalytic activation in order to selectively effect two Mannich additions.

Table 3 Effect of catalyst on conversion to bis-γ-lactams.



entry	catalyst	solvent	% conv.[a]	d.r. **15:16**[a]
1	2 mol % TfOH	THF	80	55:45
2	2 mol % TfOH	CH_3CN	62	61:39
3	20 mol % TfOH	CH_3CN	81	51:49
4	20 mol % TfOH, 20 mol% 2,6-(*t*-Bu)$_2$Py	CH_3CN	78	51:49
5	20 mol % 2,6-(*t*-Bu)$_2$Py·TfOH	CH_3CN	84	48:52
6	20 mol % Py·TfOH	CH_3CN	85	48:52
7	20 mol % TMSOTf	CH_3CN	77	53:47

[a]As determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture

Despite efforts at optimization, the diastereomeric product ratio appeared independent of reaction conditions. After reoptimizing the reaction method to favor double addition by increasing catalyst loading, employing anhydrous sodium sulfate, and using two equivalents of imine, we screened a small number of reactions to probe the scope of double Mukaiyama AMR (Figure 4). Yields were generally slightly lower than those of the single addition reactions of corresponding imines, and products were always formed as a mixture of two diastereomers. Several attempts to employ sequential addition of two different imines to produce completely unsymmetrical bis-lactam products were unsuccessful. Although imines with *ortho*-substituted *N*-aryl groups were found to be either synthetically inaccessible or unproductive Mukaiyama-AMR substrates, lactam **15e** represents the first synthesis of the C_2-symmetrical bis-lactam core of natural product (±)-bisavenanthramide B-1.[19]

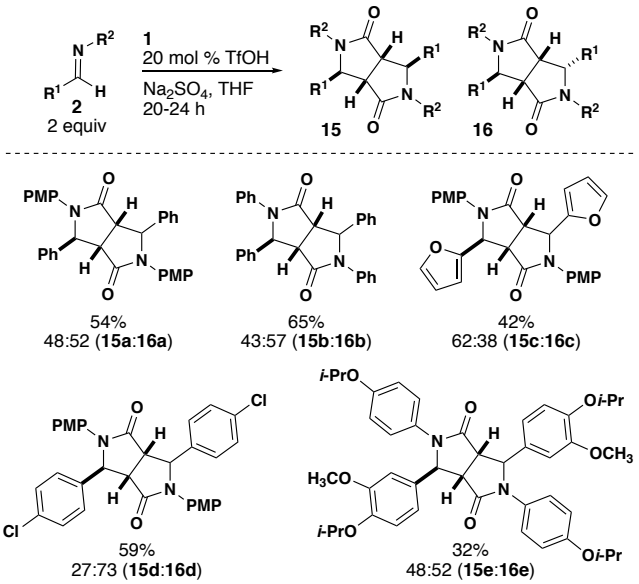


Figure 4 Scope of the double Mukaiyama AMR for the synthesis of bis-γ-lactams.

In conclusion, we report the development of a new acid-catalyzed, organocatalytic Mukaiyama-variant of the anhydride Mannich reaction. This method allows for highly diastereoselective access to challenging tri-substituted lactam targets in high yield. Although imines derived from alkyl aldehydes can be synthetically inaccessible substrates, a three-component reaction variation allows for the expansion of scope by forming these electrophiles in situ. Additionally, excellent catalyst control for single versus double Mukaiyama Mannich addition was observed.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ACKNOWLEDGMENT

This work was supported by the National Science Foundation (CHE-1764309-0, CHE-1414298). S.W.L. acknowledges Professor Benjamin List (Max-Planck-Institut für Kohlenforschung) for hosting laboratory work that was funded by an NSF supplement (to CHE-1414298). R.M. acknowledges the Basque Government Fellowship (Spain) for supporting international graduate research. S.M. acknowledges the Fudan University Overseas Summer Research Foundation for supporting international undergraduate research. We also acknowledge support from the NSF (CHE-0840444) for a dual-source X-ray diffractometer. The authors thank Professor Dean Tantillo, Carla Saunders, and Amy Bellinghiere (University of California, Davis) for input into computational NMR and preparation of the supporting information.

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