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# Catalytic enantioselective oxa-hetero-Diels–Alder reactions of enones with aryl trifluoromethyl ketones†

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The development of oxa-hetero-Diels–Alder reactions of enones with aryl trifluoromethyl ketones to afford tetrahydropyranones bearing trifluoromethyl-substituted tetrasubstituted carbon centers is reported. The reactions were catalyzed by an amine-based catalyst system and afforded the products with er values up to 97: 3.

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Tetrahydropyranones and tetrahydropyrans are important structures found in bioactive natural products and pharmaceutical leads.<sup>1,2</sup> Incorporation of the trifluoromethyl group has been shown to favour bioactivity,3 therefore concise routes to tetrahydropyranone and tetrahydropyran derivatives bearing a trifluoromethyl group are of interest. To synthesize functionalized tetrahydropyranones, we have recently developed enantioselective oxa-hetero-Diels-Alder reactions of enones with isatins that are catalyzed by amine-based catalyst systems.<sup>2</sup> In the reactions, enamines of enones are formed in situ, and the enamines act as dienes of the [4 + 2] cycloaddition resulting in the formation of the tetrahydropyranones under mild conditions.<sup>2</sup> Based on these studies, we reasoned that oxa-hetero-Diels-Alder reactions of enones with trifluoromethyl ketones would provide access to trifluoromethyl-substituted tetrahydropyran derivatives. However, direct use of enones as diene precursors to form tetrahydropyranones is still a challenge; reported reactions of enones with ketones or aldehydes often give aldol products as the main product or as a significant byproduct.4 That is, formation of oxa-hetero-Diels-Alder reaction product is not promised in the reactions of enones with ketones or aldehydes as dienophiles either in racemic or highly enantioselective versions.<sup>2,5</sup> Here, we report enantioselective oxahetero-Diels-Alder reactions of enones with aryl trifluoromethyl

ketones that afford trifluoromethyl-substituted tetrahydropyranones (Scheme 1).

First, we screened catalyst systems for the reaction of enone 1a with ketone 2a to form trifluoromethyl-substituted tetrahydropyranone product 3aa (3aa-1 and/or 3aa-2). Selected results are shown in Table 1. Previously reported catalyst systems (such as A-B, A-B-C, and D-B) for the reactions of enones with isatins to afford tetrahydropyranones in high enantioselectivity<sup>2</sup> did not work efficiently for the reaction with ketone 2a; the use of these catalysts significantly generated aldol product 4aa with oxa-hetero-Diels-Alder product 3aa (Table 1, entries 1-3). The best results for the formation of 3aa with high enantioselectivity (er 97:3 for 3aa-2) were obtained when the reaction was performed in the presence of proline-derived catalyst L and DABCO (K) in toluene at rt (25 °C) (Table 1, entries 11 and 12). The reaction using less loading of L (0.1 equiv.) with K (0.2 equiv.) gave essentially the same results as the reaction using L (0.2 equiv.) and K (0.2 equiv.) (Table 1, entry 12 versus entry 11). The major diastereomer (i.e., 3aa-2) obtained under the catalysis by L-K differed from that obtained under the catalysis by A-B (Table 1, entries 11 and 12 versus entry 1).

Next, using the best catalyst system identified [*i.e.*, L (0.1 equiv.)–K (0.2 equiv.)], reactions of various enones and aryl trifluoromethyl ketones were performed (Table 2). In all cases, trifluoromethyl-substituted tetrahydropyranones were obtained with high enantioselectivities for the major diastereomer



Scheme 1 The oxa-hetero-Diels–Alder reactions of enones with aryl trifluoromethyl ketones catalyzed by amine-based catalyst systems to afford trifluoromethyl-substituted tetrahydropyranones.

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 $<sup>\</sup>dagger$  Electronic supplementary information (ESI) available: Experimental procedures, characterization of compounds,  $^1{\rm H}$  and  $^{13}{\rm C}$  NMR spectra, and HPLC charts. See DOI: 10.1039/c6ra13859d

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#### Table 1 Screening of catalyst systems in the hetero-Diels-Alder reaction of 1a and $2a^a$



Entry	Catalyst system	Time (h)	$3aa:4aa^b$	dr <sup>b</sup> 3aa-1 : 3aa-2	er <sup>c</sup> 3aa-1/3aa-2
1	<b>A</b> (0.2 equiv.)- <b>B</b> (0.4 equiv.)	24	62:38	5.0:1	85:15/20:80
2	<b>A</b> (0.2 equiv.) $-$ <b>B</b> (0.4 equiv.) $-$ <b>C</b> (0.4 equiv.)	36	71:29	2.5:1	ND/ND
3	D(0.2  equiv.) - B(0.4  equiv.)	12	67:33	3.1:1	ND/ND
4	E(0.2  equiv.) - F(0.4  equiv.)	24	95:5	2.0:1	18:82/1:1
5	$\mathbf{G}$ (0.2 equiv.)- $\mathbf{F}$ (0.4 equiv.)	24	>95:5	1.7:1	68:32/ND
$6^d$	H (0.2 equiv.)	$48^d$	_	_	_
$7^e$	$\mathbf{H}$ (0.2 equiv.)	24	>95:5	1.6:1	ND/85:15
8	H(0.2  equiv.) - I(0.2  equiv.)	36	>95:5	1.3:1	ND/91:9
9	$\mathbf{H}$ (0.2 equiv.)– $\mathbf{J}$ (0.2 equiv.)	30	>95:5	1:2.3	ND/91:9
10	H(0.2  equiv.) - K(0.2  equiv.)	36	>95:5	1:1.2	ND/95:5
11	$\mathbf{L}$ (0.2 equiv.)- $\mathbf{K}$ (0.2 equiv.)	24	>95:5	1:1.9	1:1/97:3
12	L(0.1  equiv.) - K(0.2  equiv.)	24	>95:5	1:1.9	1:1/97:3

<sup>a</sup> Reaction was performed by using enone 1a (0.5 mmol) and aryl trifluoromethyl ketone 2a (0.1 mmol) in the presence of the indicated catalyst system in toluene (0.2 mL) at 25 °C until 2a was consumed except where indicated. The relative stereochemistry of 3aa-1 and 3aa-2 was determined to be as shown; the absolute stereochemistry of 3aa-1 and 3aa-2 is tentative; see ESI. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis of the crude mixture. <sup>c</sup> Determined by HPLC analysis. ND = not determined. <sup>d</sup> Conversion <20%. <sup>e</sup> Reaction in DMF.

products, and tetrasubstituted carbon centers were concisely constructed (Table 2). The reactions of phenyl trifluoromethyl ketones bearing electron-withdrawing substituents on the phenyl group (such as the formation of 3ad) were faster than the reactions of those bearing electron-donating groups (such as the formation of 3af). In all cases shown in Table 2, the formation of the aldol product was negligible (3:4 were >95:5 or 95 : 5).

The catalyst system was useful for the reactions of  $\beta$ -alkyl substituted enones and also β-aryl substituted enones to afford the hetero-Diels-Alder reaction products with high enantioselectivities for the major product diastereomers. This is significant because previously reported conditions for the hetero-Diels-Alder reactions of β-alkyl substituted enones often do not work for the  $\beta$ -aryl substituted enones.<sup>2,5c</sup>

Further, the reaction using the L-K catalyst system was easily scaled up: a 1.0 mmol-reaction to form 3bb gave the major isomer, 3bb-2, as a single diastereomer (purity >95%) in 61% vield with er 92 : 8.

When a mixture of 3aa and 4aa (racemic, 3aa/4aa = 2.5 : 1, **3aa-1** : **3aa-2** = 3 : 1) was treated under the hetero-Diels-Alder reaction conditions with the L-K catalyst system, no decomposition of the compounds and no changes in the ratios were detected. This indicates that product 3aa is stable under the L-K catalyst system and that aldol 4aa is not converted to 3aa in the presence of this catalyst system. Thus, the formation of 3aa under the L-K catalyst system is likely a kinetically controlled [4 + 2] cycloaddition reaction of in situ-generated enamine of enone 1aa with ketone 2aa.





<sup>*a*</sup> Reaction conditions: enone **1** (1.0 mmol) and aryl trifluoromethyl ketone **2** (0.2 mmol) in the presence of proline derivative **L** (0.02 mmol) and DABCO (**K**, 0.04 mmol) in toluene (0.4 mL) at 25 °C. The isolated yields of **3** (combined for both the diastereomers) are shown except where noted. The dr was determined by <sup>1</sup>H NMR analysis before purification. The er of the major diastereomer was determined by HPLC analysis. The ratio **3** : **4** (**4** = aldol product) was determined by <sup>1</sup>H NMR analysis before purification: >95 : 5 for the formation of **3aa**, **3ab**, **3ac**, **3af**, **3ag**, **3ah**, **3bb**, **3bc**, and **3bd**; 95 : 5 for the formation of **3ba**. <sup>*b*</sup> Ketone **2** was not consumed. <sup>*c*</sup> Data of 1 mmol-scale reaction; isolated yield of the major isomer, the dr of the major diastereomer after purification.

To demonstrate the use of the hetero-Diels–Alder reactions, the product tetrahydropyranones were transformed into tetrahydropyran derivatives (Scheme 2). Oxime formation, reductive amination, and allylation gave the corresponding products **5–8**. The trifluoromethyl-substituted tetrahydropyranones and tetrahydropyran derivatives that can be synthesized by the methods described here may be useful in the search for biofunctional molecules.



Scheme 2 Transformations of the hetero-Diels-Alder products.

In conclusion, we have developed an organocatalytic enantioselective oxa-hetero-Diels–Alder reaction of enones with aryl trifluoromethyl ketones that afford trifluoromethyl-substituted tetrahydropyranones, which uses novel amine-based catalyst systems. Tetrasubstituted carbon centers bearing a trifluoromethyl group were concisely constructed with the formation of the tetrahydropyranone ring. We have also demonstrated that the hetero-Diels–Alder products can be transformed further to various trifluoromethyl-substituted tetrahydropyran derivatives.

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