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

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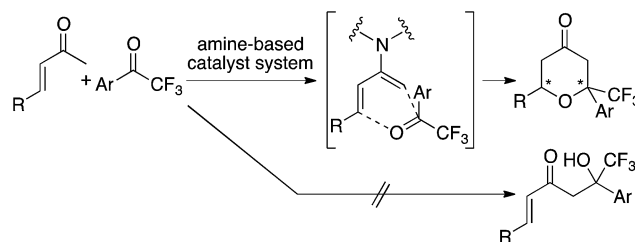
The development of oxa-hetero-Diels–Alder reactions of enones with aryl trifluoromethyl ketones to afford tetrahydropyranones bearing trifluoromethyl-substituted tetrasubstituted carbon centers is reported. The reactions were catalyzed by an amine-based catalyst system and afforded the products with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

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,<sup>3</sup> 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 by-product.<sup>4</sup> 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 oxa-hetero-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).

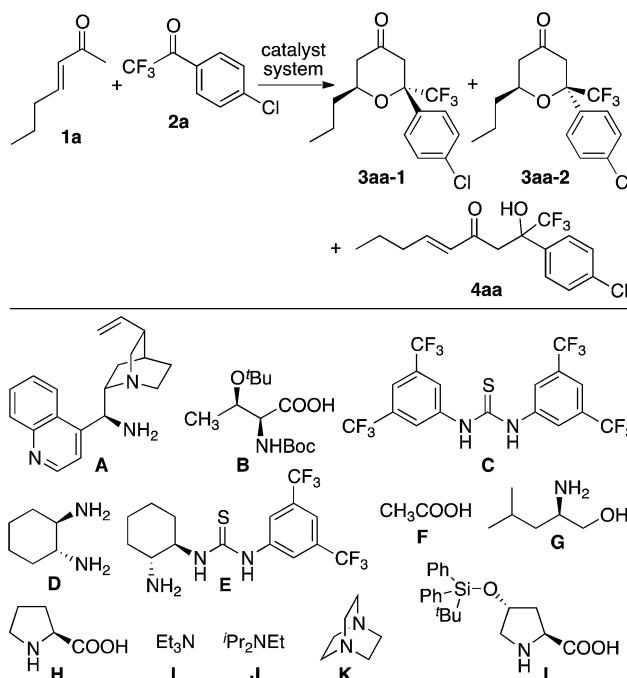
Next, using the best catalyst system identified [*i.e.*, **L** (0.1 equiv.)–**K** (0.2 equiv.)], reactions of various enones and aryl trifluoromethyl ketones were performed (Table 2). In all cases, trifluoromethyl-substituted tetrahydropyranones were obtained with high enantioselectivities for the major 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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Table 1 Screening of catalyst systems in the hetero-Diels–Alder reaction of **1a** and **2a**<sup>a</sup>

Entry	Catalyst system	Time (h)	3aa : 4aa <sup>b</sup>	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	<b>D</b> (0.2 equiv.)– <b>B</b> (0.4 equiv.)	12	67 : 33	3.1 : 1	ND/ND
4	<b>E</b> (0.2 equiv.)– <b>F</b> (0.4 equiv.)	24	95 : 5	2.0 : 1	18 : 82/1 : 1
5	<b>G</b> (0.2 equiv.)– <b>F</b> (0.4 equiv.)	24	>95 : 5	1.7 : 1	68 : 32/ND
6 <sup>d</sup>	<b>H</b> (0.2 equiv.)	48 <sup>d</sup>	—	—	—
7 <sup>e</sup>	<b>H</b> (0.2 equiv.)	24	>95 : 5	1.6 : 1	ND/85 : 15
8	<b>H</b> (0.2 equiv.)– <b>I</b> (0.2 equiv.)	36	>95 : 5	1.3 : 1	ND/91 : 9
9	<b>H</b> (0.2 equiv.)– <b>J</b> (0.2 equiv.)	30	>95 : 5	1 : 2.3	ND/91 : 9
10	<b>H</b> (0.2 equiv.)– <b>K</b> (0.2 equiv.)	36	>95 : 5	1 : 1.2	ND/95 : 5
11	<b>L</b> (0.2 equiv.)– <b>K</b> (0.2 equiv.)	24	>95 : 5	1 : 1.9	1 : 1/97 : 3
12	<b>L</b> (0.1 equiv.)– <b>K</b> (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 β-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 β-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% yield 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**.



Table 2 Scope of the hetero-Diels–Alder reaction<sup>a</sup>

Reaction scheme showing the synthesis of tetrahydropyranone derivatives **3** from enone **1** and aryl trifluoromethyl ketone **2** using catalyst **L** (0.1 equiv) and catalyst **K** (0.2 equiv) in toluene at room temperature (rt).

Structure of **1**:  $\text{R}-\text{CH}=\text{CH}-\text{C}(=\text{O})\text{CH}_3$

Structure of **2**:  $\text{Ar}-\text{C}(=\text{O})\text{CF}_3$

Structure of **3**:  $\text{R}-\text{CH}(\text{O})-\text{CH}(\text{Ar})-\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_3$

Structure of **3aa**:  $\text{R} = \text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{Ar} = 4\text{-Cl-C}_6\text{H}_4$

**3aa**  
24 h, 59%  
dr 1:1.9, er 97:3

Structure of **3ab**:  $\text{R} = \text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{Ar} = 4\text{-Cl-C}_6\text{H}_4$

**3ab**  
48 h, 55%  
dr 1:1.3, er 96:4

Structure of **3ac**:  $\text{R} = \text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{Ar} = 4\text{-S-C}_6\text{H}_4$

**3ac**  
28 h, 52%  
dr 1:1.4, er 91:9

Structure of **3ad**:  $\text{R} = \text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{Ar} = 4\text{-CF}_3\text{-C}_6\text{H}_4$

**3ad**  
18 h, 43%  
dr 1:1.7, er 97:3

Structure of **3ae**:  $\text{R} = \text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{Ar} = 4\text{-Br-C}_6\text{H}_4$

**3ae**  
24 h, 59%  
dr 1:2.4, er 97:3

Structure of **3af**:  $\text{R} = \text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{Ar} = 4\text{-Cl-C}_6\text{H}_4$

**3af**  
72 h, 29%<sup>b</sup>  
dr 1:1.3, er 94:6

Structure of **3ag**:  $\text{R} = \text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{Ar} = 4\text{-F-C}_6\text{H}_4$

**3ag**  
26 h, 55%  
dr 1:2.2, er 96:4

Structure of **3ah**:  $\text{R} = \text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{Ar} = 4\text{-F-C}_6\text{H}_4$

**3ah**  
24 h, 54%  
dr 1:2.2, er 95:5

Structure of **3ba**:  $\text{R} = \text{C}_6\text{H}_5$ ,  $\text{Ar} = 4\text{-Cl-C}_6\text{H}_4$

**3ba**  
24 h, 82%  
dr 1:4.2, er 91:9

Structure of **3bb**:  $\text{R} = 4\text{-Br-C}_6\text{H}_4$ ,  $\text{Ar} = 4\text{-Cl-C}_6\text{H}_4$

**3bb**  
24 h, 63%, dr 1:4.1, er 94:6  
24 h, 61%<sup>c</sup>, dr 1:25<sup>c</sup>, er 92:8<sup>c</sup>

Structure of **3bc**:  $\text{R} = \text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$ ,  $\text{Ar} = 4\text{-Cl-C}_6\text{H}_4$

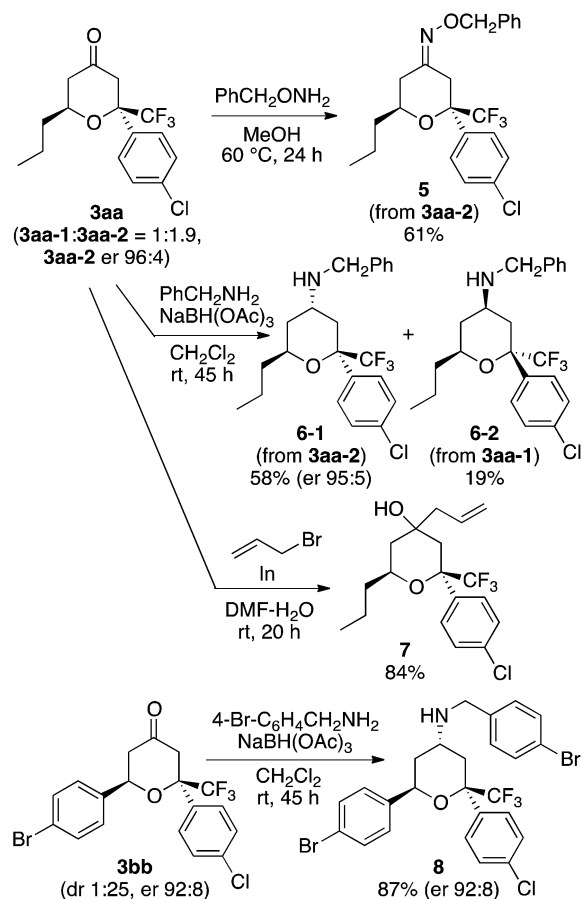
**3bc**  
29 h, 47%  
dr 1:1.7, er 96:4

Structure of **3bd**:  $\text{R} = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{Ar} = 4\text{-Cl-C}_6\text{H}_4$

**3bd**  
26 h, 51%  
dr 1:2.3, er 95:5

<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**, **3ad**, **3ae**, **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 bio-functional 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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