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

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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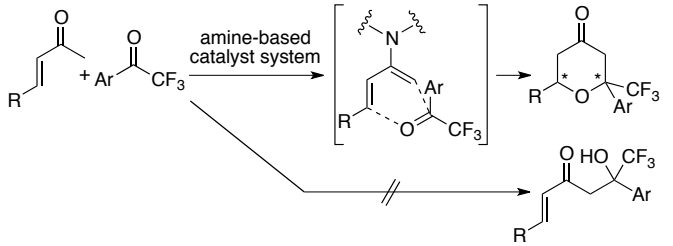
The development of oxa-hetero-Diels-Alder reactions of enones with aryl trifluoromethyl ketones to afford tetrahydropyranones bearing trifluoromethyl-substituted tetrasubstituted carbon centers is reported. The reactions were catalyzed by an amine-based catalyst system and afforded the products with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

Tetrahydropyranones and tetrahydropyrans are important structures found in bioactive natural products and pharmaceutical leads.[1,2] 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.[2] 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.[2] Based on these studies, we reasoned that oxa-hetero-Diels-Alder reactions of enones with trifluomethyl 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.[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.[2,5] Here, we report enantioselective oxa-hetero-Diels-Alder reactions of enones with aryl trifluoromethyl ketones that afford trifluoromethyl-substituted tetrahydropyranones (Scheme 1).



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.

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[2] 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 diatereomer (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).

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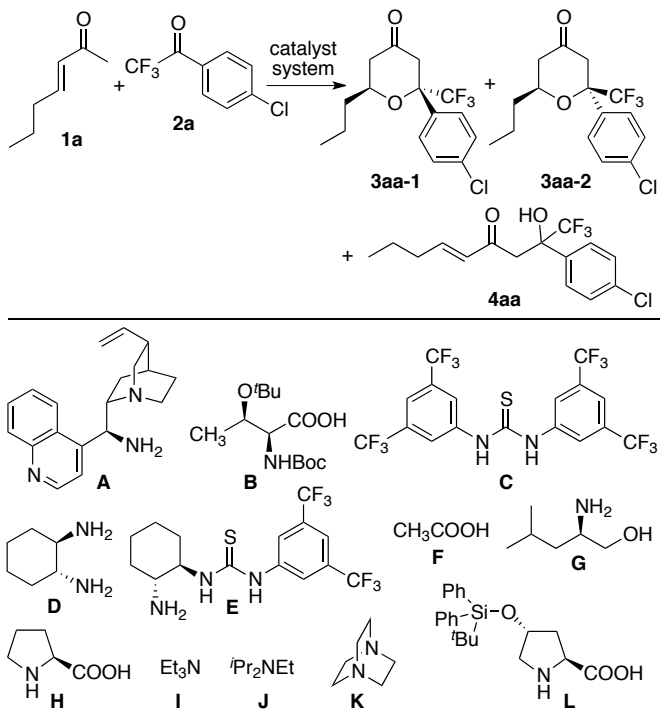
Electronic Supplementary Information (ESI) available: Experimental procedures, characterization of compounds, ^{1}H and ^{13}C NMR spectra, and HPLC charts. See DOI: 10.1039/x0xx00000x

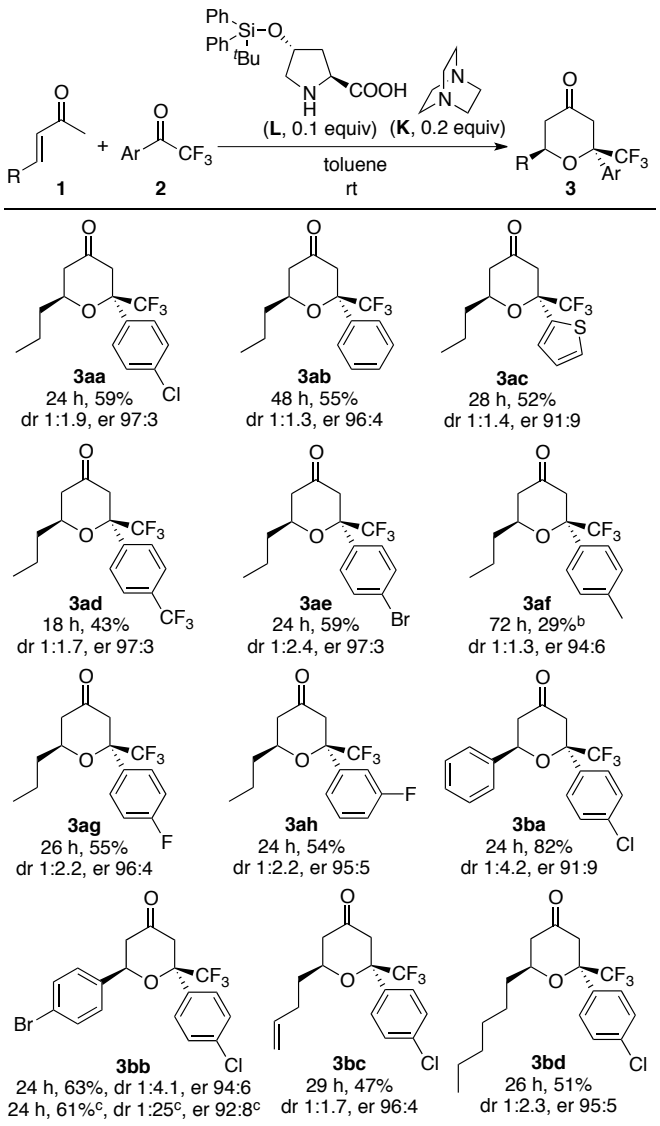
Table 1. Screening of catalyst systems in the hetero-Diels-Alder reaction of **1a** and **2a**.[a]



entry	catalyst system	time (h)	**3aa**:**4aa**[b]	dr[b] **3aa-1**:**3aa-2**	er[c] **3aa-1**/**3aa-2**
1	**A** (0.2 equiv)-**B** (0.4 equiv)	24	62:38	5.0:1	85:15/20:80
2	**A** (0.2 equiv)-**B** (0.4 equiv)-**C** (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	**G** (0.2 equiv)-**F** (0.4 equiv)	24	>95:5	1.7:1	68:32/ND
6[d]	**H** (0.2 equiv)	48[d]	-	-	-
7[e]	**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	**H** (0.2 equiv)-**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	**L** (0.2 equiv)-**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

[a] 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 supporting information. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by HPLC analysis. ND = Not determined. [d] Conversion <20%. [e] Reaction in DMF.

Table 2. Scope of the hetero-Diels-Alder reaction.[a]



[a] 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 ^{1}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 ^{1}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**. [b] Ketone **2** was not consumed. [c] Data of 1 mmol-scale reaction; isolated yield of the major isomer, the dr of the major diastereomer after purification.

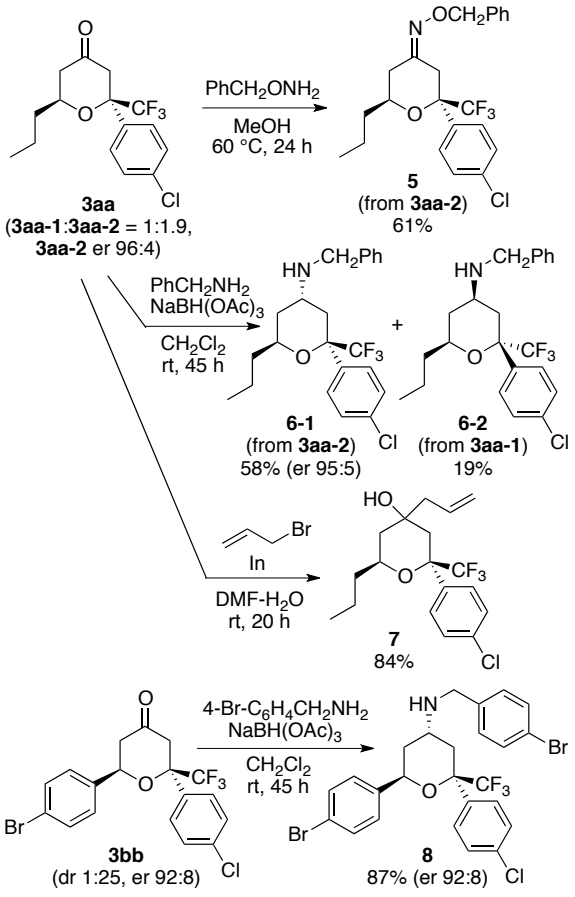
Next, using the best catalyst system identified [i.e., **L** (0.1 equiv)-**K** (0.2 equiv)], reactions of various enones and aryl trifluoromethyl ketones were performed (Table 2). In all cases, trifluoromethyl-substituted tetrahydropyranones were obtained with high enantioselectivities for the major diastereomer 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.[2,5c]

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**.



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

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.

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.

We thank Dr. Michael Chandro Roy, Research Support Division, Okinawa Institute of Science and Technology Graduate University for mass analyses. This study was supported by the Okinawa Institute of Science and Technology Graduate University and by the MEXT (Japan) Grant-in-Aid for Scientific Research on Innovative Areas “Advanced Molecular Transformations by Organocatalysts” (No. 26105757).

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

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TOC

Asymmetric oxa-hetero-Diels-Alder reactions of enones with aryl trifluoromethyl ketones were developed to afford tetrahydropyranones bearing trifluoromethyl-substituted tetrasubstituted carbon centers.