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

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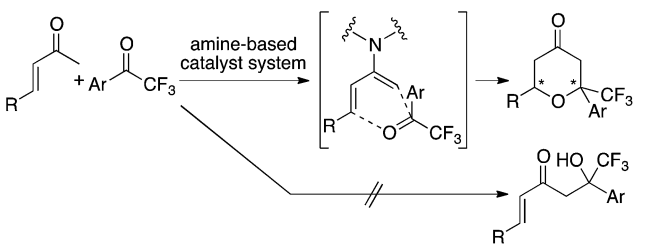
The development of oxa-hetero-Diels–Alder reactions of enones with aryl trifluoromethyl ketones to afford tetrahydropyranones bearing trifluoromethyl-substituted tetrasubstituted carbon centers is reported. The reactions were catalyzed by an amine-based catalyst system and afforded the products with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

Tetrahydropyranones and tetrahydropyrans are important structures found in bioactive natural products and pharmaceutical leads.[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 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.[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).

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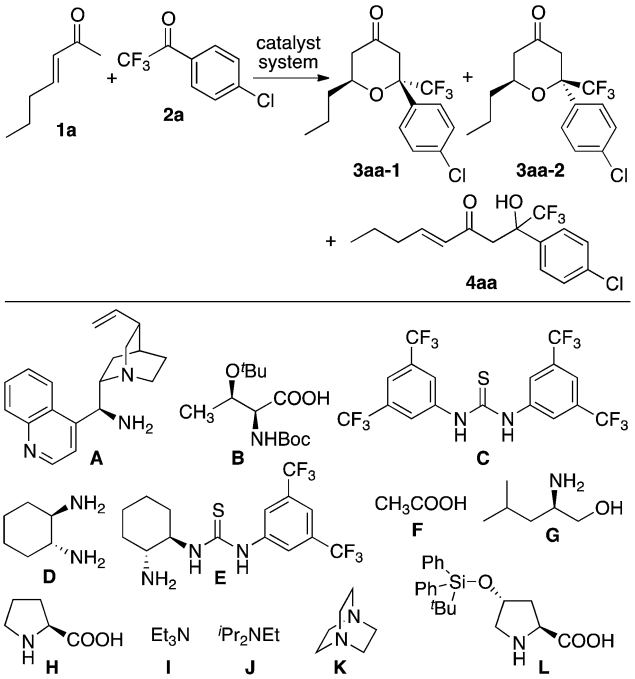
† Electronic supplementary information (ESI) available: Experimental procedures, characterization of compounds, $^{1}H$ and $^{13}C$ NMR spectra, and HPLC charts. See DOI: 10.1039/c6ra13859d

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 ESI. [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.

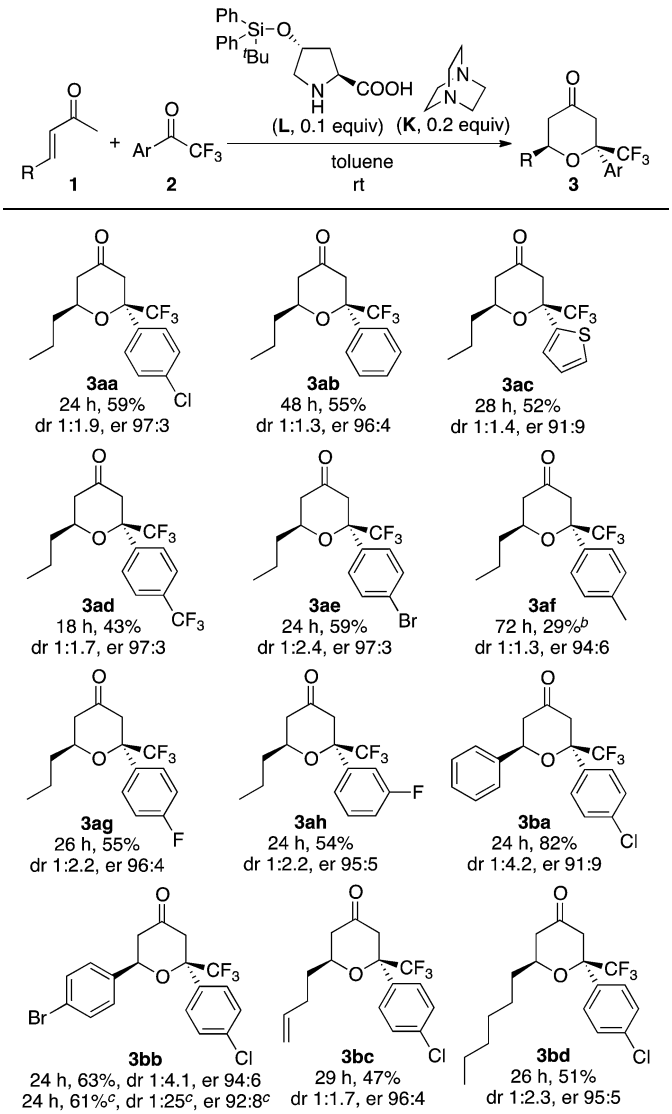
products, and tetrasubstituted carbon centers were concisely constructed (Table 2). The reactions of phenyl trifluoromethyl ketones bearing electron-withdrawing substituents on the phenyl group (such as the formation of **3ad**) were faster than the reactions of those bearing electron-donating groups (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.

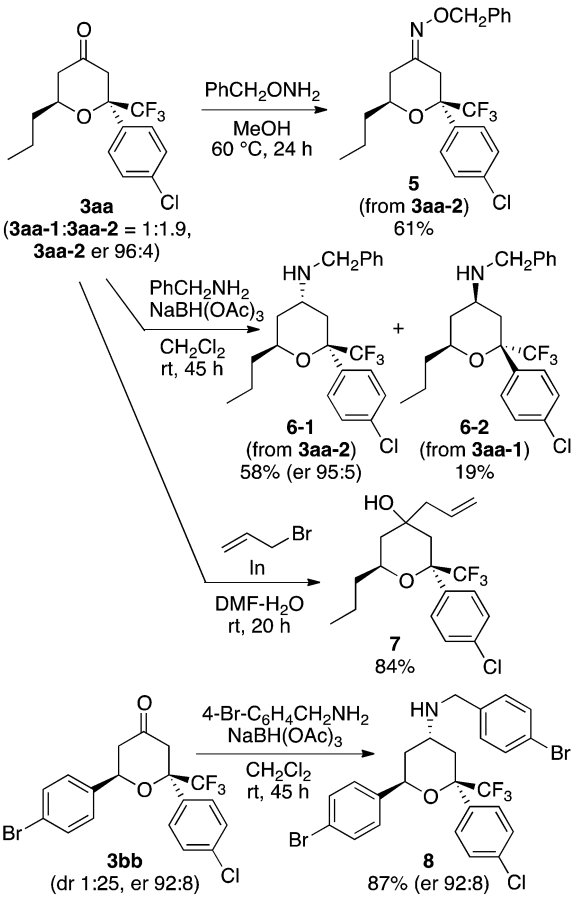
When a mixture of **3aa** and **4aa** (racemic, **3aa**/**4aa** = 2.5 : 1, **3aa-1** : **3aa-2** = 3 : 1) was treated under the hetero-Diels–Alder reaction conditions with the **L–K** catalyst system, no decomposition of the compounds and no changes in the ratios were detected. This indicates that product **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**.

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.

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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