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 ee values up to 97 : 3.

Tetrahydropyranones and tetrahydropyrans are important structures found in bioactive natural products and pharmaceutical leads. Incorporation of the trifluoromethyl group has been shown to favor bioactivity, 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. 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. 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. 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. Here, we report enantioselective oxa-hetero-Diels–Alder reactions of enones with aryl trifluoromethyl ketones that afford trifluoromethyl-substituted tetrahydropyrans (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 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 tetrahydropyrans.
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 3aa-1) 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 (3aa-1 : 3aa-2 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.25c

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 1 Screening of catalyst systems in the hetero-Diels–Alder reaction of 1a and 2a

| Entry | Catalyst system               | Time (h) | 3aa : 4aa | dr | 3aa-1 : 3aa-2 | er | 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    |
| 6d   | H (0.2 equiv.)               | 48       | —         | —   | —             |
| 7e   | 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.) | 36       | >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 (0.1 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 1H NMR analysis of the crude mixture. c Determined by HPLC analysis. ND = not determined. d Conversion <20%. e Reaction in DMF.
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.

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