

CrossMark
click for updatesCite this: *RSC Adv.*, 2016, 6, 61454Received 28th May 2016
Accepted 18th June 2016

DOI: 10.1039/c6ra13859d

www.rsc.org/advances

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

Dongxin Zhang and Fujie Tanaka*

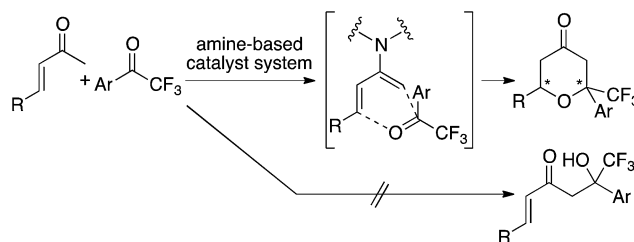
The development of oxa-hetero-Diels–Alder reactions of enones with aryl trifluoromethyl ketones to afford tetrahydropyranones bearing trifluoromethyl-substituted tetrasubstituted carbon centers is reported. The reactions were catalyzed by an amine-based catalyst system and afforded the products with *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 enantioselectivity² 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).

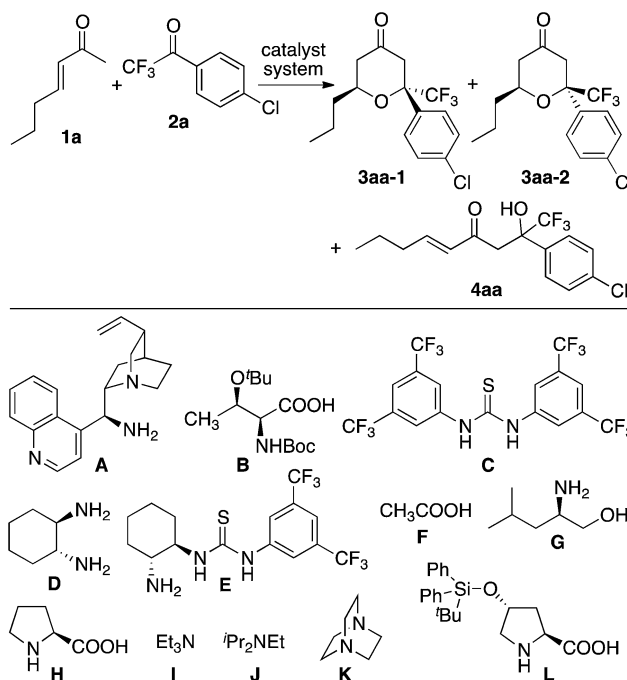
Next, using the best catalyst system identified [*i.e.*, **L** (0.1 equiv.)–**K** (0.2 equiv.)], reactions of various enones and aryl trifluoromethyl ketones were performed (Table 2). In all cases, trifluoromethyl-substituted tetrahydropyranones were obtained with high enantioselectivities for the major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

Chemistry and Chemical Bioengineering Unit, Okinawa Institute of Science and Technology Graduate University, 1919-1 Tancha, Onna, Okinawa 904-0495, Japan. E-mail: ftanaka@oist.jp

† Electronic supplementary information (ESI) available: Experimental procedures, characterization of compounds, ¹H and ¹³C 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 ¹H 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

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

The catalyst structure is a chiral silane derivative: $\text{Ph}_2\text{Si}(\text{O}-\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}-\text{CH}_2\text{CH}_2\text{COOH})\text{Bu}$.

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

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

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

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

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

3af
72 h, 29%^b
dr 1:1.3, er 94:6

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

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

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

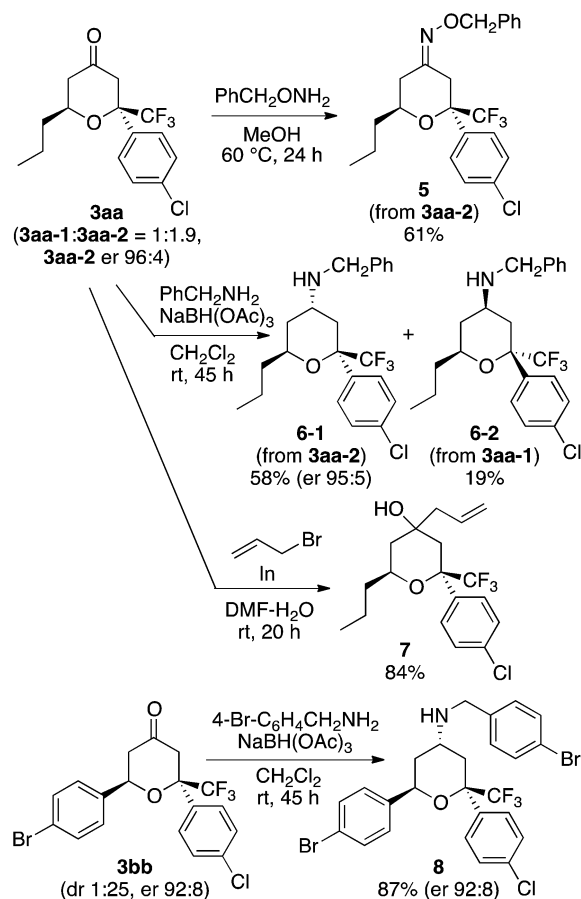
3bb
24 h, 63%, dr 1:4.1, er 94:6
24 h, 61%^c, dr 1:25^c, er 92:8^c

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

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

^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 ¹H 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 ¹H 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 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.

Acknowledgements

We thank Dr Michael Chandroy, 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).

Notes and references

- (a) G. Dossetter, T. F. Jamison and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 1999, **38**, 2398; (b) Y. Yamashita, S. Saito,



- H. Ishitani and S. Kobayashi, *J. Am. Chem. Soc.*, 2003, **125**, 3793; (c) M. Anada, T. Washio, N. Shimada, S. Kitagaki, M. Nakajima, M. Shiro and S. Hashimoto, *Angew. Chem., Int. Ed.*, 2004, **43**, 2665; (d) A. K. Unni, N. Takenaka, H. Yamamoto and V. H. Rawal, *J. Am. Chem. Soc.*, 2005, **127**, 1336; (e) S. Rajaram and M. S. Sigman, *Org. Lett.*, 2005, **7**, 5473; (f) N. Momiyama, H. Tabuse and M. Terada, *J. Am. Chem. Soc.*, 2009, **131**, 12882; (g) J. Guin, C. Rabalakos and B. List, *Angew. Chem., Int. Ed.*, 2012, **51**, 8859; (h) T. Voigt, C. Gerding-Reimer, T. T. N. Tran, S. Bergmann, H. Lachance, B. Scholermann, A. Brockmeyer, P. Janning, S. Ziegler and H. Waldmann, *Angew. Chem., Int. Ed.*, 2013, **52**, 410; (i) N. M. Nasir, K. Ermanis and P. A. Clarke, *Org. Biomol. Chem.*, 2014, **12**, 3323; (j) G. C. Tay, C. H. Huang and S. D. Rychnovsky, *J. Org. Chem.*, 2014, **79**, 8733.
- 2 (a) H.-L. Cui and F. Tanaka, *Chem.-Eur. J.*, 2013, **19**, 6213; (b) H.-L. Cui, P. V. Chouthaiwale, F. Yin and F. Tanaka, *Asian J. Org. Chem.*, 2016, **5**, 153; (c) H.-L. Cui, P. V. Chouthaiwale, F. Yin and F. Tanaka, *Org. Biomol. Chem.*, 2016, **14**, 1777, and references cited therein.
- 3 (a) K. Mueller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (b) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (c) P. Wang, L.-W. Feng, L. Wang, J.-F. Li, S. Liao and Y. Tang, *J. Am. Chem. Soc.*, 2015, **137**, 4626; (d) S. Kawamura, H. Egami and M. Sodeoka, *J. Am. Chem. Soc.*, 2015, **137**, 4865; (e) D. Zhang and F. Tanaka, *Adv. Synth. Catal.*, 2015, **357**, 3458.
- 4 (a) B. M. Trost, S. Shin and J. A. Sclafani, *J. Am. Chem. Soc.*, 2005, **127**, 8602; (b) Q. Guo, M. Bhanushali and C.-G. Zhao, *Angew. Chem., Int. Ed.*, 2010, **49**, 9460; (c) G. Pousse, F. Le Cavelier, L. Humphreys, J. Rouden and J. Blanchet, *Org. Lett.*, 2010, **12**, 3582; (d) G.-G. Liu, H. Zhao, Y.-B. Lan, B. Wu, X.-F. Huang, J. Chen, J.-C. Tao and X.-W. Wang, *Tetrahedron*, 2012, **68**, 3843; (e) T. Yan, X. Wang, H. Sun, J. Liu and Y. Xie, *Molecules*, 2013, **18**, 14505; (f) C. Baker-Glenn, N. Hodnett, M. Reiter, S. Ropp, R. Anclif and V. Gouverneur, *J. Am. Chem. Soc.*, 2005, **127**, 1481; (g) S. Abbaraju and J. C.-G. Zhao, *Adv. Synth. Catal.*, 2014, **356**, 237.
- 5 (a) L.-Q. Lu, X.-N. Xing, X.-F. Wang, Z.-H. Ming, H.-M. Wang and W.-J. Xiao, *Tetrahedron Lett.*, 2008, **49**, 1631; (b) M. Mojzesova, M. Meciarova, M. Marti and R. Sebesta, *New J. Chem.*, 2015, **39**, 2573; (c) Y.-J. Lin, L.-N. Du, T.-R. Kang, Q.-Z. Liu, Z.-Q. Chen and L. He, *Chem.-Eur. J.*, 2015, **21**, 11773.

