

HETEROCYCLES, Vol.103, No. 1, 2021, pp. 198 - 204. © 2021 The Japan Institute of Heterocyclic Chemistry  
Received, 11th June, 2020, Accepted, 8th, July, 2020, Published online, 30th July, 2020  
DOI: 10.3987/COM-20-S(K)22

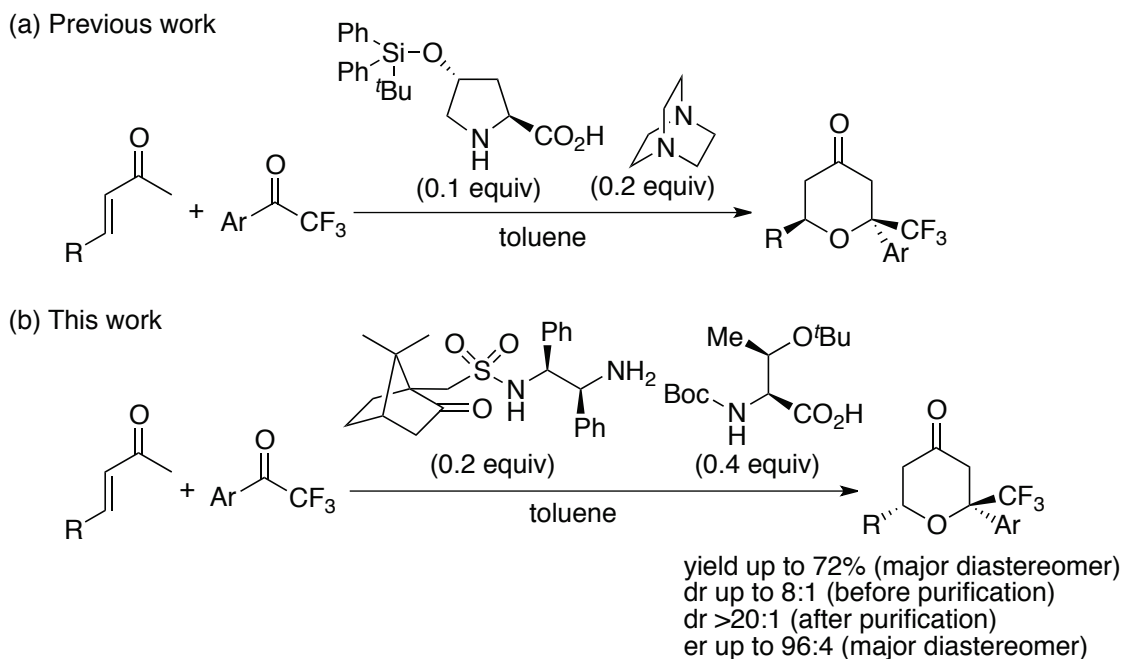
## CATALYTIC ENANTIOSELECTIVE OXA-HETERO-DIELS-ALDER REACTIONS OF ENONES WITH ARYL TRIFLUOROMETHYL KETONES: SYNTHESIS OF TETRAHYDROPYRANONES

Maira Pasha and Fujie Tanaka\*

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

**Abstract** – Diastereo- and enantioselective oxa-hetero-Diels-Alder reactions of enones with aryl trifluoromethyl ketones that afford tetrahydropyranone derivatives catalyzed by an amine-based catalyst system are reported. The major diastereomers of the tetrahydropyranone products obtained in these reactions had the relative stereochemistry different from that of the previously synthesized tetrahydropyranone derivatives.

Tetrahydropyran derivatives are found in bioactive natural products and pharmaceutical leads.<sup>1</sup> Concise access to enantiomerically enriched tetrahydropyran derivatives is of interest in the development of bioactive molecules.<sup>1-3</sup> A trifluoromethyl group is often used to improve the bioactivities.<sup>3-5</sup> Accordingly, methods for the concise synthesis of tetrahydropyran derivatives bearing a trifluoromethyl group are of interest.<sup>3</sup> We previously reported enantioselective oxa-hetero-Diels-Alder reactions of enones with aryl trifluoromethyl ketones that directly afford tetrahydropyranone derivatives using amine-based catalyst systems.<sup>3</sup> In these reactions, the enamines generated from the enones act as dienes and the ketone carbonyl groups of aryl trifluoromethyl ketones act as dienophiles in the [4+2] cycloaddition leading to the tetrahydropyranone derivatives.<sup>3</sup> In these reactions, two diastereomers can be formed. The use of a catalyst system composed of a proline-derivative and DABCO for the reactions led the formation of one type of the diastereomers as the major diastereomers with high enantioselectivities (Scheme 1a).<sup>3</sup> Here we report enantioselective oxa-hetero-Diels-Alder reactions of enones with aryl trifluoromethyl ketones that afford the other type of the diastereomers as the main products (Scheme 1b).



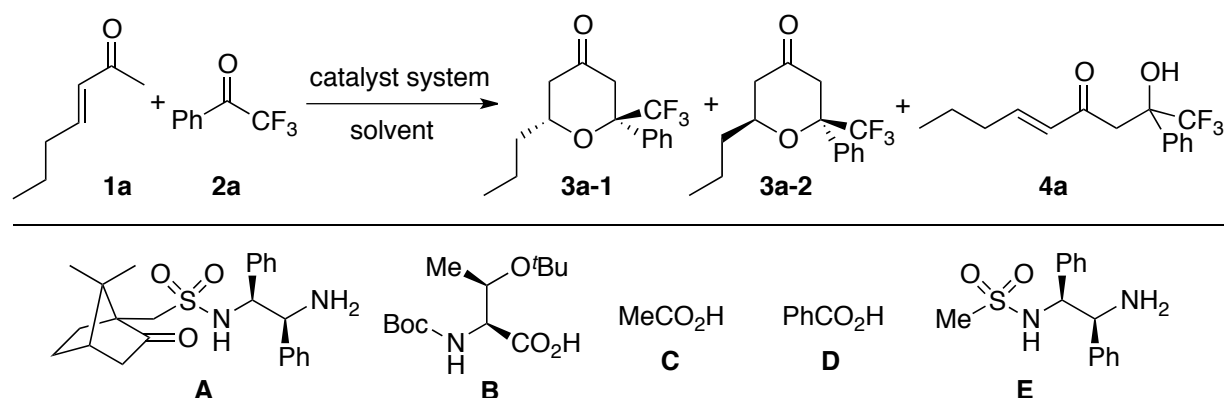
**Scheme 1.** (a) Previously reported enantioselective oxa-hetero-Diels-Alder reactions of enones with aryl trifluoromethyl ketones. (b) Enantioselective oxa-hetero-Diels-Alder reactions of enones with aryl trifluoromethyl ketones. The relative stereochemistry of the major diastereomers in the reaction shown in (b) is different from that of the previously obtained major diastereomers in the reactions shown in (a).

In our previous study, amine derivatives and amine-containing catalyst systems were tested for their abilities to catalyze the reaction of an enone with an aryl trifluoromethyl ketone to lead to the tetrahydropyranone product.<sup>3</sup> In some cases, especially with primary amine derivatives with acids, the major diastereomer was the minor diastereomer obtained from the reaction catalyzed by the proline derivative and DABCO.<sup>3</sup> However, in the previously tested cases, the aldol product was formed in significant amounts with the tetrahydropyranone product and/or the enantioselectivities of the obtained tetrahydropyranones were relatively moderate or low.<sup>3</sup> Further, reactions of enones with ketones or aldehydes often afford aldol products as the main products.<sup>5-7</sup> We hypothesized that additional evaluations of primary amine derivatives with or without acids under various conditions<sup>2a-c</sup> would identify catalyst systems suitable for the oxa-hetero-Diels-Alder reactions affording the other type of tetrahydropyranone diastereomers as the main products with high diastereo- and enantioselectivities.

Amine derivatives were evaluated in the catalysis of the reaction of enone **1a** with 2,2,2-trifluoroacetophenone (**2a**) to afford tetrahydropyranone derivative **3a-1** as the main product in a high yield with high diastereo- and enantioselectivities; selected results are shown in Table 1 (full results will be published in the future). The ratio between **1a**, **3a-1**, its diastereomer **3a-2**, and aldol product **4** were determined by <sup>1</sup>H NMR analysis, and the enantiomer ratios of **3a-1** were determined by HPLC analysis after purification. Of these catalyst systems tested, amine derivative **A**<sup>8</sup> with various acids

provided good results. Then, using amine derivative **A**, reaction conditions were further evaluated. From these evaluations, the use of the catalyst system composed of amine derivative **A** and *N*-Boc-*O*-*t*Bu-L-threonine (**B**) as an acid in toluene at 5 °C was identified as the best among those tested (Table 1, entry 9).

**Table 1.** Evaluations of catalysts and conditions<sup>a</sup>



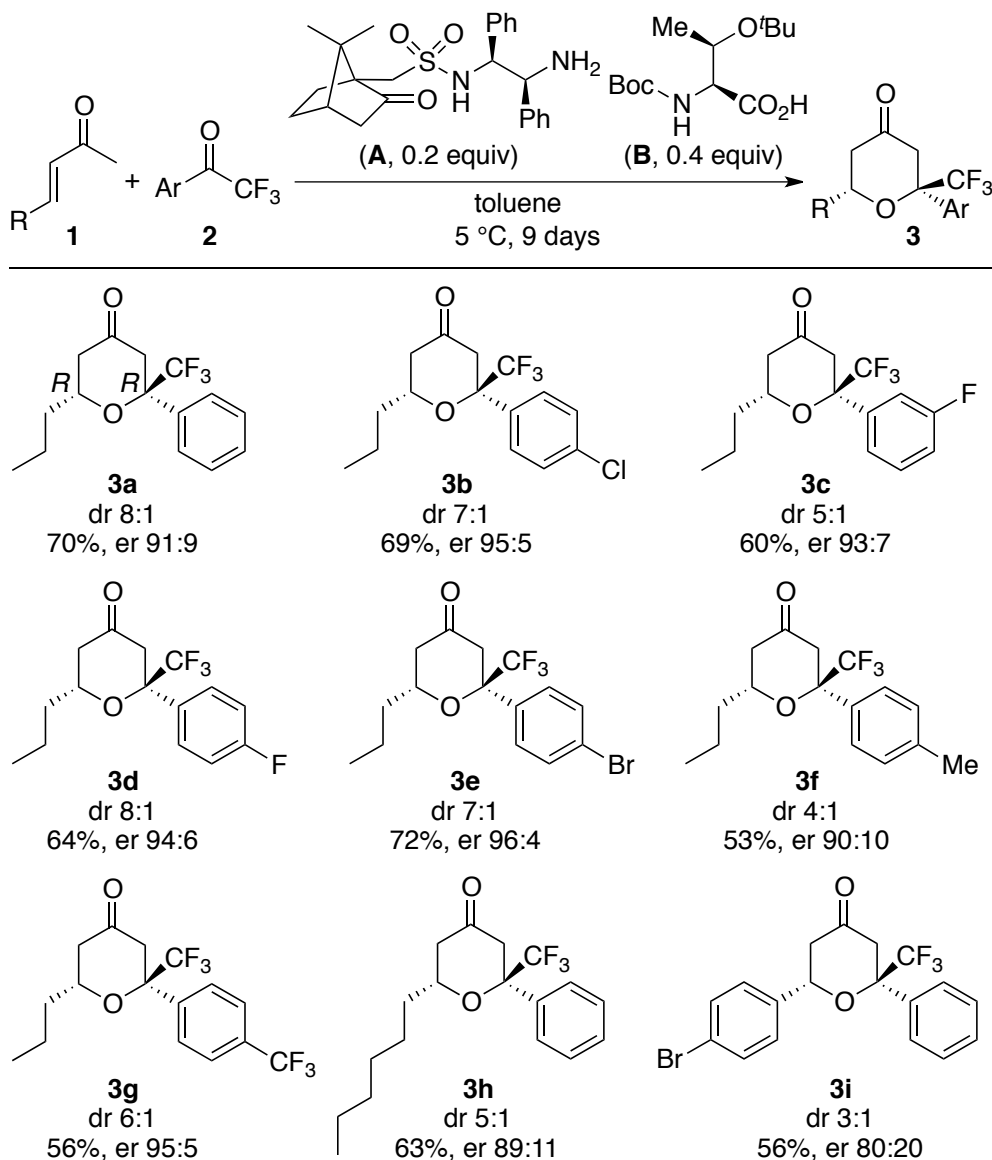
entry	catalyst system		solvent	temp (°C)	time (h)	ratio 1: <b>3a</b> : <b>4a</b>	dr <b>3a-1</b> : <b>3a-2</b>	er of <b>3a-1</b>
	amine	acid						
1	<b>A</b>	<b>B</b>	toluene	25	40	5:82:13	5:1	84:16
2	<b>A</b>	<b>C</b>	toluene	25	72	<1:91:9	4:1	82:18
3	<b>A</b>	<b>D</b>	toluene	25	40	6:75:19	5:1	81:19
4	<b>E</b>	<b>D</b>	toluene	25	40	0:62:38	3:1	59:41
5	<b>A</b>	<b>B</b>	CHCl <sub>3</sub>	25	48	11:81:8	9:1	85:15
6	<b>A</b>	<b>B</b>	DMSO	25	48	100:0:0	—	—
7	<b>A</b>	<b>B</b>	EtOAc	25	96	10:86:4	5:1	86:14
8	<b>A</b>	<b>B</b>	2-PrOH	25	96	2:92:6	3:1	70:30
<b>9</b>	<b>A</b>	<b>B</b>	<b>toluene</b>	<b>5</b>	<b>216</b>	<b>(18~13):82:&lt;5</b>	<b>8:1</b>	<b>92:8</b>

<sup>a</sup> Conditions: enone **1a** (1.0 mmol), aryl trifluoromethyl ketone **2a** (3.0 mmol), amine (0.2 mmol), and acid (0.4 mmol) in toluene (2.0 mL). The progress of the reaction was monitored and <sup>1</sup>H NMR analysis. The ratio **1**:**3a**:**4a** (in which **3a** = **3a-1** + **3a-2**) and the dr (**3a-1**:**3a-2**) were determined before purification at the indicated time by <sup>1</sup>H NMR analysis. The er of purified **3a-1** was determined by HPLC analysis.

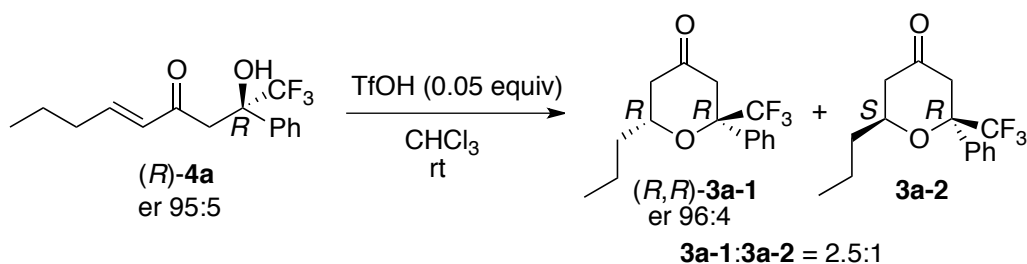
With the best conditions identified, reactions using various enones and aryl trifluoromethyl ketones were performed (Table 2). For the reactions of alkyl enones, product tetrahydropyranone derivatives **3** were obtained with diastereomer ratio (dr) 8:1 ~ 4:1 (**3a-h**). The major diastereomer of **3** was isolated as a single diastereomer in each of all the cases shown in Table 2. The enantiomer ratio (er) values of the major diastereomers obtained from the reactions of alkyl enones were in a range of 96:4 ~ 89:11 (**3a-h**). The absolute configuration of the major diastereomer of **3a** (i.e., **3a-1**) was determined to be (*R,R*) as

shown in Table 2 by correlating with (*R,R*)-**3a-1** obtained from (*R*)-**4a**<sup>6</sup> by an acid-catalyzed oxa-Michael cyclization<sup>9</sup> (Scheme 2).

**Table 2.** Scope of the oxa-hetero-Diels-Alder reaction<sup>a</sup>

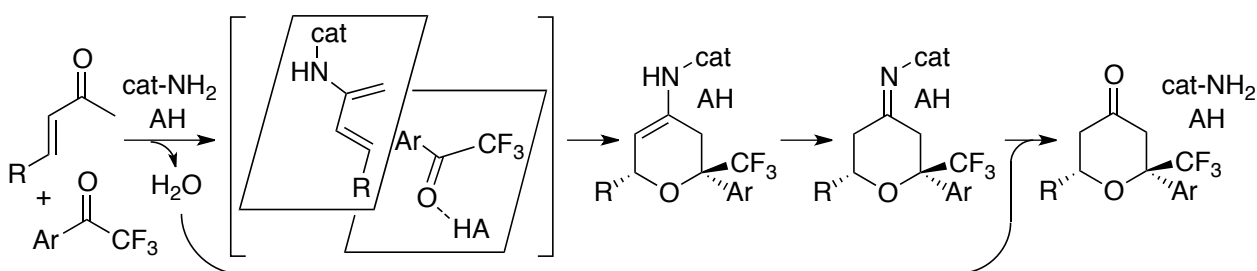


<sup>a</sup> Conditions: enone **1** (1.0 mmol), aryl trifluoromethyl ketone **2** (3.0 mmol), amine catalyst **A** (0.2 mmol), and acid **B** (0.4 mmol) in toluene (2.0 mL) at 5 °C for 9 days. The dr determined by <sup>1</sup>H NMR analysis before purification, the isolated yield of the major diastereomer of **3** as single diastereomer, and the er of the purified major diastereomer of **3** by HPLC analysis are shown.



**Scheme 2.** Transformation used for the determination of the absolute stereochemistry of **3a**

To understand the mechanism of the reactions catalyzed by the catalyst system composed of amine derivative **A** and acid derivative **B**, the formation of **3b** and the corresponding aldol product and the dr and er values of **3b** were analyzed at various time points. From the reaction stage at the 46% conversion (determined by  $^1\text{H}$  NMR analysis as the yield of both diastereomers of **3b**; at 4 days) to the stage at the 80% conversion (at 9 days), the dr of **3b** was essentially the same value (dr 85:15 ~ 87:13) and the er of the major diastereomer of **3b** was 95:5. No significant changes in the dr and the er values were detected during the reaction progress. Aldol product was present in 7% (4 days) to 5% (9 days); no accumulation of the aldol product was observed before the formation of **3b**. These results suggest that tetrahydropyranone derivative **3b** is kinetically formed in the main route of the reaction catalyzed by the amine **A**-acid **B** catalyst system. The main pathway may be the [4+2] cycloaddition reaction of the enamine formed from the enone with the amine *in situ* and the ketone carbonyl group<sup>2a,b,3</sup> (Scheme 3), although further study is required to elucidate the detailed mechanism.



**Scheme 3.** A proposed pathway of the reaction through the [4+2] cycloaddition of the enamine formed from the enone with the amine *in situ* with the aryl trifluoromethyl ketone

In summary, we have developed enantioselective oxa-hetero-Diels-Alder reactions of enones with aryl trifluoromethyl ketones that afford tetrahydropyranone derivatives. With the use of the catalyst system described here, the diastereomers of the tetrahydropyranone derivatives that are different from those obtained in previously reported oxa-hetero-Diels-Alder reactions of enones with aryl trifluoromethyl ketones were synthesized with high diastereo- and enantioselectivities and isolated as single diastereomers in good yields.

## ACKNOWLEDGEMENTS

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.

## SUPPORTING INFORMATION

Supplementary data associated with this article can be found, in the online version, at URL: <https://www.heterocycles.jp/newlibrary/downloads/PDFsi/26668/103/1>

## 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) N. Momiyama, H. Tabuse, and M. Terada, *J. Am. Chem. Soc.*, 2009, **131**, 12882; (f) J. Guin, C. Rabalakos, and B. List, *Angew. Chem. Int. Ed.*, 2012, **51**, 8859; (g) 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; (h) N. M. Nasir, K. Ermanis, and P. A. Clarke, *Org. Biomol. Chem.*, 2014, **12**, 3323; (i) G. C. Tay, C. H. Huang, and S. D. Rychnovsky, *J. Org. Chem.*, 2014, **79**, 8733; (j) Y.-J. Lin, L.-N. Du, T. R. Kang, Q.-Z. Liu, Z.-Q. Chen, and L. He, *Chem. Eur. J.*, 2015, **21**, 11773; (k) B. R. McDonald and K. A. Scheidt, *Acc. Chem. Res.*, 2015, **48**, 1172; (l) F. Vetica, P. Chauhan, S. Dochain, and D. Enders, *Chem. Soc. Rev.*, 2017, **46**, 1661.
- (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; (d) M. Sohail and F. Tanaka, *Commun. Chem.*, 2019, **2**, article number 73, doi: 10.1038/s42004-019-0177-5.
- D. Zhang and F. Tanaka, *RSC Adv.*, 2016, **6**, 61454.
- (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; (f) K. Lee, D. L. Silverio, S. Torker, D. W. Robbins, F. Haeffner, F. W. van der Mei, and A. H. Hoveyda, *Nat. Chem.*, 2016, **8**, 768.
- C. J. Thomson, D. M. Barber, and D. J. Dixon, *Angew. Chem. Int. Ed.*, 2020, **59**, 5359.
- J. Lin, T. Kang, Q. Liu, and L. He, *Tetrahedron: Asymmetry*, 2014, **25**, 949.
- (a) B. M. Trost, S. Shin, and J. A. Sclafani, *J. Am. Chem. Soc.*, 2005, **127**, 8602; (b) 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; (c) C. Baker-Glenn, N. Hodnett, M. Reiter, S. Ropp, R. Anclif, and V. Gouverneur, *J. Am. Chem. Soc.*, 2005, **127**, 1481; (d) Q. Guo, M. Bhanushali, and C.-G. Zhao, *Angew. Chem. Int. Ed.*,

- 2010, **49**, 9460; (e) E. R. Venegas and C. L. Willis, *Org. Lett.*, 2020, **22**, 2548.
8. C. Lu, Z. Luo, L. Huang, and X. Li, *Tetrahedron: Asymmetry*, 2011, **22**, 722.
  9. M. Pasha, M. Sohail, and F. Tanaka, *Heterocycles*, 2020, **101**, 339.