CL-151116 Received: December 3, 2015 | Accepted: December 24, 2015 | Web Released: January 8, 2016

Enantio- and Diastereoselective Cross-annulation of Enal and Ketone with New Chiral Bicyclic *N*-Heterocyclic Carbene Catalysts

Momo Hasegawa,[1] Kazuhiro Yoshida,*[1,2] and Akira Yanagisawa*[1,2]
[1]*Department of Chemistry, Graduate School of Science, Chiba University, Yayoi-cho, Inage-ku, Chiba 263-8522*
[2]*Molecular Chirality Research Center, Chiba University, Yayoi-cho, Inage-ku, Chiba 263-8522*

(E-mail: kyoshida@faculty.chiba-u.jp, ayanagi@faculty.chiba-u.jp)

The enantio- and diastereoselective cross-annulation of cinnamaldehyde (**6**) and 2,2,2-trifluoroacetophenone (**7**) was examined to evaluate the performance of newly developed chiral bicyclic imidazolium salts **3** and **4** as catalyst precursors. The reaction proceeded to give desired γ-lactone **8** with high diastereoselectivities (up to 10/1) and moderate enantioselectivities (up to 71% ee) when the sterically demanding catalyst precursors were used.

Keywords: *N*-Heterocyclic carbene (NHC) | Cross-annulation | Chiral bicyclic NHC catalyst

Chiral *N*-heterocyclic carbenes (NHCs) have become an indispensable tool in the fields of coordination chemistry and asymmetric catalysis.[1,2] In 2010, we reported a modular synthesis of chiral bicyclic imidazolium salts **3**–**5** based on the alkylation of newly prepared imidazoles **1** and **2** with the intent of applying them to NHC/metal-catalyzed asymmetric reactions (Figure 1).[3] One of the advantages of the method is the rapid preparation of a diverse array of imidazolium salts simply by changing the combinations of imidazoles and alkylating agents. In fact, very recently, we have synthesized many NHC/Ir complexes by using this method and succeeded in finding an excellent catalyst precursor for the asymmetric transfer hydrogenation of ketones.[4]

Although NHCs generated from structurally similar bicyclic triazolium salts and imidazolium salts to **3** and **4** are well-known chiral organocatalysts,[2,5] most of them have aryl groups on the nitrogen atom.[6] The use of analogs having alkyl groups on the nitrogen atom is rather limited.[7] In 2008, Ishida and Saigo prepared various chiral *N*-alkyl bicyclic imidazolium salts by the alkylation of their own morpholine-fused imidazole, and reported that one of those salts could be used as a catalyst precursor for the asymmetric cross-annulation of cinnamaldehyde (**6**) and 2,2,2-trifluoroacetophenone (**7**).[8] Since the seminal reports by the groups of Glorius[9a] and Bode,[9b] the chemistry of NHC-catalyzed homoenolates has greatly developed, enabling the synthesis of many useful molecules.[2,10] However, the asymmetric version of the reaction between enals and carbonyl compounds to afford γ-lactones still presents a challenge.[11] Here, we report our investigation of this reaction to form γ-lactone **8** catalyzed by *N*-alkyl bicyclic NHCs generated from newly prepared imidazolium salts (*S*)-**3** and (*R*)-**4**.

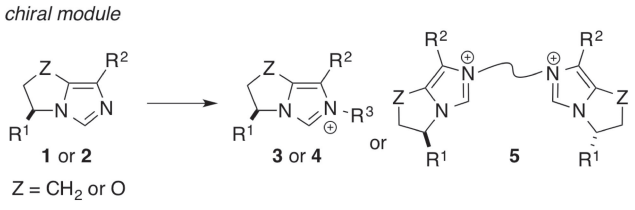


Figure 1. Modular synthesis of chiral bicyclic imidazolium salts **3**–**5**.

At the outset, we synthesized chiral imidazolium salts (*S*)-**3** and (*R*)-**4** having flexibility at substituents R^1 and R^3 from pyrrolidine-fused imidazoles **1**, which were prepared from urocanic acid, and oxazolidine-fused imidazole **2**, which was prepared from amino acids, with various electrophiles (R^3X) (Figure 2).[12]

According to the reaction conditions reported by Ishida and Saigo,[8] we first carried out the cross-annulation of cinnamaldehyde (**6**) and 2,2,2-trifluoroacetophenone (**7**) in the presence of imidazolium salt (*S*)-**3at** (20 mol %) and $KN(SiMe_3)_2$ (20 mol %) in THF at room temperature (Table 1, Entry 1). However, the desired γ-lactone was not generated under those conditions. Then, we screened bases DBU, Cs_2CO_3, and *t*-BuOK and found that *t*-BuOK was the best option, generating **8** in 49% isolated yield with good diastereoselectivity (**8a**/**8b** = 5.7/1) and enantioselectivity (55% ee (**8a**), 50% ee (**8b**)) (Entries 2–4).

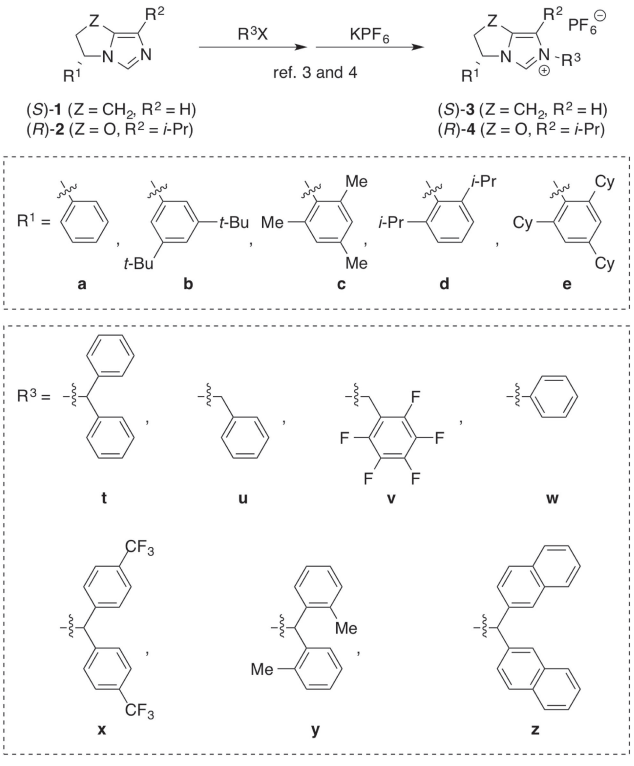
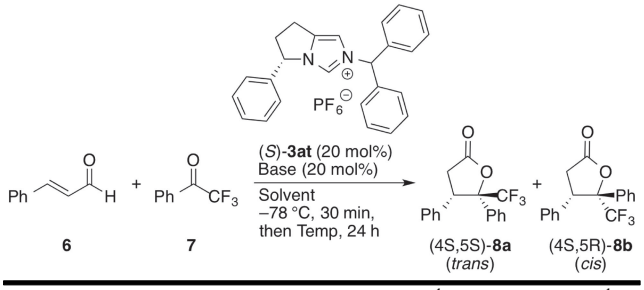


Figure 2. Structures of chiral bicyclic imidazolium salts **3** and **4** for enantio- and diastereoselective cross-annulation.

Table 1. Optimization of reaction conditions for enantio- and diastereoselective cross-annulation of cinnamaldehyde (**6**) and 2,2,2-trifluoroacetophenone (**7**) with (*S*)-**3at**[a]



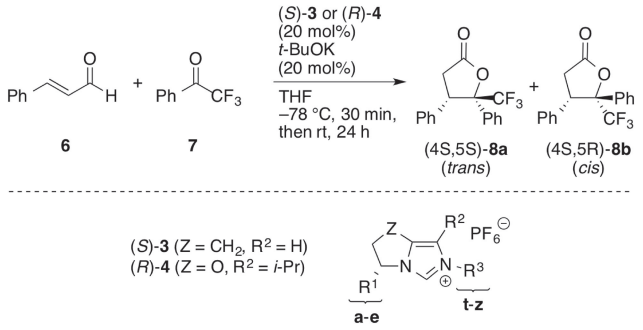
Entry	Base	Solvent	Temp /°C	Yield[b] /%	dr[c] (**8a**/**8b**)	ee[d] (**8a**/**8b**)
1	$KN(SiMe_3)_2$	THF	rt	0	—/—	—/—
2	DBU	THF	rt	17	5.3/1	51/51
3	Cs_2CO_3	THF	rt	34	5.3/1	39/67
4	*t*-BuOK	THF	rt	49	5.7/1	55/50
5	*t*-BuOK	THF	0	33	6.7/1	58/65
6	*t*-BuOK	THF	−40	16	3.6/1	35/38
7	*t*-BuOK	Et_2O	rt	50	7.3/1	57/16
8	*t*-BuOK	toluene	rt	13	4.0/1	52/36
9	*t*-BuOK	CH_2Cl_2	rt	14	6.7/1	46/38
10	*t*-BuOK	MeOH	rt	12	3.8/1	35/26

[a]The cross-annulation was carried out with cinnamaldehyde (**6**) and 2,2,2-trifluoroacetophenone (**7**) (4 equiv) in the presence of imidazolium salt (*S*)-**3at** (20 mol %) and base (20 mol %) in solvent (0.1 mol L^{-1}) for 24 h. [b]Isolated yield. [c]Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by HPLC analysis using a chiral stationary phase column (Chiralcel AS-H).

Lowering the reaction temperature to 0 °C improved both diastereo- and enantioselectivities, but the isolated yields of the products decreased (Entry 4 vs. 5). Further lowering of the temperature to −40 °C worsened the situation: Not only the isolated yield but also the selectivities decreased (Entry 4 vs. 6). Several solvents were then screened to further optimize the reaction conditions. With Et_2O as the solvent, the reaction proceeded with better diastereoselectivity, whereas the enantioselectivity of **8b** decreased (Entry 4 vs. 7). Other solvents, toluene, CH_2Cl_2, and MeOH, were found to significantly decrease the isolated yields of the products (Entries 8–10).

The results of catalyst screening for the enantio- and diastereoselective cross-annulation are shown in Table 2, in which all reactions were performed in the presence of *t*-BuOK as the base at room temperature in THF.[13] First, using the structure of (*S*)-**3at** (Entry 1), the influence of the steric hindrance of substituent R^3 was inspected. It was found that neither decreasing (Entries 2–4) nor increasing (Entries 5–7) the steric hindrance improved the enantioselectivity of **8a**. On the other hand, in regard to diastereoselectivity, (*S*)-**3az**, which has a rather bulky R^3 substituent, the di(2-naphthalenyl)methyl group showed the best result (**8a**/**8b** = 10/1) (Entry 7). Unfortunately, oxazolidine-fused imidazolium salts (*R*)-**4** were found to be inferior to pyrrolidine-fused imidazolium salts (*S*)-**3** in terms of both diastereo- and enantioselectivities (Entry 2 vs. 8; Entry 3 vs. 9). A measurable improvement in enantioselectivity was

Table 2. Enantio- and diastereoselective cross-annulation of cinnamaldehyde (**6**) and 2,2,2-trifluoroacetophenone (**7**) with various imidazolium salts (*S*)-**3** and (*R*)-**4**[a]



Entry	**3** or **4**	Yield[b] /%	dr[c] (**8a**/**8b**)	ee[d] (**8a**/**8b**)
1	(*S*)-**3at**	49 (0)	5.7/1	55/50
2	(*S*)-**3au**	56 (1)	5.7/1	34/31
3	(*S*)-**3av**	44 (2)	3.2/1	35/50
4	(*S*)-**3aw**	64 (0)	4.0/1	18/40
5	(*S*)-**3ax**	47 (0)	6.3/1	50/54
6	(*S*)-**3ay**	23 (0)	4.3/1	33/24
7	(*S*)-**3az**	27 (1)	10/1	49/40
8	(*R*)-**4au**	51 (0)	4.9/1	25/20
9	(*R*)-**4av**	60 (13)	2.0/1	22/26
10	(*S*)-**3bt**	62 (6)	4.8/1	33/18
11	(*S*)-**3ct**	31 (1)	6.7/1	61/30
12	(*S*)-**3cu**	42 (1)	4.8/1	45/24
13	(*S*)-**3cv**	53 (10)	2.9/1	42/27
14	(*S*)-**3dt**	52 (12)	7.7/1	62/37
15	(*S*)-**3dz**	35 (8)	8.3/1	62/72
16	(*S*)-**3et**	39 (24)	10/1	64/28
17	(*S*)-**3ez**	39 (19)	7.1/1	71/36

[a]The cross-annulation was carried out with cinnamaldehyde (**6**) and 2,2,2-trifluoroacetophenone (**7**) (4 equiv) in the presence of imidazolium salt (*S*)-**3** or (*R*)-**4** (20 mol %) and *t*-BuOK (20 mol %) in THF (0.1 mol L^{-1}) at room temperature for 24 h. [b]Isolated yield and numbers in parenthesis indicate the yield of recovered **6**. [c]Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by HPLC analysis using a chiral stationary phase column (Chiralcel AS-H).

observed when substituent R^1 of (*S*)-**3** was changed. Although the introduction of two *tert*-butyl groups on the 3,5-positions of the phenyl ring decreased both diastereo- and enantioselectivities (Entry 1 vs. 10), the introduction of bulkier substituents on the 2,6-positions of the phenyl ring clearly led to higher enantioselectivity in **8a** (Entry 1 vs. 11, 14, and 16; Entry 2 vs. 12; Entry 3 vs. 13; Entry 7 vs. 15 and 17). In these cases, however, the reaction rates tended to slow down and a certain amount of starting cinnamaldehyde (**6**) was recovered.[14] The highest enantioselectivity of **8a** (71% ee) was observed when (*S*)-**3ez**, which has a 2,4,6-tricyclohexylphenyl group as the R^1 substituent and a di(2-naphthalenyl)methyl group as the R^3 substituent, was used (Entry 17).[15]

In conclusion, we have conducted the enantio- and diastereoselective cross-annulation of cinnamaldehyde (**6**) and 2,2,2-trifluoroacetophenone (**7**), which is known as a challeng-

ing asymmetric reaction, to evaluate the performance of newly developed NHC precursors (*S*)-**3** and (*R*)-**4**. Although the cross-annulation was not entirely successful in terms of satisfying all requirements, namely, yield, diastereoselectivity, and enantioselectivity, some NHC catalysts produced desired γ-lactone **8** with good diastereo- and enantioselectivities.

We appreciate the financial support in the form of a Grant-in-Aid for Scientific Research (Grant #15K05494) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We also gratefully acknowledge financial support from the next generation training program in Chiba University.

References and Notes

1 For recent reviews, see: a) S. Díez-González, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612. b) *N-Heterocyclic Carbenes in Transition Metal Catalysis and Organocatalysis*, ed. by C. S. J. Cazin, Springer, Dordrecht, Heidelberg, London, New York, **2011**. doi:10.1007/978-90-481-2866-2. c) F. Wang, L.-j. Liu, W. Wang, S. Li, M. Shi, *Coord. Chem. Rev.* **2012**, *256*, 804.

2 For recent reviews, see: a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606. b) A. J. Arduengo, III, L. I. Iconaru, *Dalton Trans.* **2009**, 6903. c) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307.

3 K. Yoshida, S. Horiuchi, T. Takeichi, H. Shida, T. Imamoto, A. Yanagisawa, *Org. Lett.* **2010**, *12*, 1764.

4 K. Yoshida, T. Kamimura, H. Kuwabara, A. Yanagisawa, *Chem. Commun.* **2015**, *51*, 15442.

5 For early examples, see: a) R. L. Knight, F. J. Leeper, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1891. b) D. Enders, U. Kallfass, *Angew. Chem., Int. Ed.* **2002**, *41*, 1743. c) M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2002**, *124*, 10298. d) F. Glorius, G. Altenhoff, R. Goddard, C. Lehmann, *Chem. Commun.* **2002**, 2704.

6 For reviews, see: a) T. Rovis, *Chem. Lett.* **2008**, *37*, 2. b) J. Mahatthananchai, J. W. Bode, in *Contemporary Carbene Chemistry*, ed. by R. A. Moss, M. P. Doyle, Wiley-VCH, Hoboken, NJ, **2014**, pp. 237–273. doi:10.1002/9781118730379.ch9.

7 For examples, see: a) J. R. Struble, J. W. Bode, *Tetrahedron* **2008**, *64*, 6961. b) D. Enders, J. Han, A. Henseler, *Chem. Commun.* **2008**, 3989. c) P.-L. Shao, X.-Y. Chen, S. Ye, *Angew. Chem., Int. Ed.* **2010**, *49*, 8412. d) L.-H. Sun, Z.-Q. Liang, W.-Q. Jia, S. Ye, *Angew. Chem., Int. Ed.* **2013**, *52*, 5803. e) L. Candish, C. M. Forsyth, D. W. Lupton, *Angew. Chem., Int. Ed.* **2013**, *52*, 9149. f) L. Candish, A. Levens, D. W. Lupton, *J. Am. Chem. Soc.* **2014**, *136*, 14397.

8 The desired γ-lactone was obtained as a mixture of *trans*- and *cis*-isomers (**8a**: 23% yield (66% ee), **8b**: 5% yield (59% ee)), see: Y. Matsuoka, Y. Ishida, K. Saigo, *Tetrahedron Lett.* **2008**, *49*, 2985.

9 a) C. Burstein, F. Glorius, *Angew. Chem., Int. Ed.* **2004**, *43*, 6205. b) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370.

10 R. S. Menon, A. T. Biju, V. Nair, *Chem. Soc. Rev.* **2015**, *44*, 5040.

11 a) J. R. Struble, J. Kaeobamrung, J. W. Bode, *Org. Lett.* **2008**, *10*, 957. b) Y. Matsuoka, Y. Ishida, D. Sasaki, K. Saigo, *Chem.—Eur. J.* **2008**, *14*, 9215. c) R. B. Strand, T. Helgerud, T. Solvang, C. A. Sperger, A. Fiksdahl, *Tetrahedron: Asymmetry* **2011**, *22*, 1994. d) R. B. Strand, T. Helgerud, T. Solvang, A. Dolva, C. A. Sperger, A. Fiksdahl, *Tetrahedron: Asymmetry* **2012**, *23*, 1350. e) Z. Fu, J. Xu, T. Zhu, W. W. Y. Leong, Y. R. Chi, *Nat. Chem.* **2013**, *5*, 835.

12 For experimental details, see refs 3 and 4. (*S*)-**3aw** was prepared from (*S*)-**3a** with benzyne generated by mixing 2-(trimethylsilyl)phenyl imidazolsulfonate and cesium fluoride.

13 General procedures for the enantio- and diastereoselective cross-annulation: To a suspension of *t*-BuOK (0.02 mmol) in THF (1.0 mL) was added a THF solution of imidazolium salt (*S*)-**3** or (*R*)-**4** (0.02 mmol) at −78 °C. The mixture was stirred at the same temperature for 1 h, and then cinnamaldehyde (**6**) (0.100 mmol) and 2,2,2-trifluoroacetophenone (**7**) (0.400 mmol) were added. After being stirred for 30 min, the mixture was allowed to warm to room temperature and stirred for 24 h. The resulting mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (5 mL × 3). The organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/CH_2Cl_2 = 2/1) to give a mixture of **8a** and **8b**. The products were characterized by comparison of spectroscopic data with those reported previously (ref 8). The diastereomeric ratio of **8** was determined by ^{1}H NMR analysis of the crude reaction mixture. The enantiomeric excess of the products was determined by HPLC analysis with a chiral stationary phase column (Daicel Chiralcel; AS-H, hexane/*i*-PrOH = 90/10, 0.9 mL min^{-1}, **8a** ($t_{4R,5R(\mathrm{minor})}$ = 6.8 min, $t_{4S,5S(\mathrm{major})}$ = 9.7 min), **8b** ($t_{4R,5S(\mathrm{minor})}$ = 10.8 min, $t_{4S,5R(\mathrm{major})}$ = 16.8 min). The absolute configurations of the major enantiomers were assigned as (4*S*,5*S*) for **8a** and (4*S*,5*R*) for **8b** by comparison of the HPLC retention time with literature data, see ref 11b.

14 In the present reaction, the self-annulation of **6** affording another γ-lactone is known as the major side reaction. In our case, a diastereomeric mixture of the side products was likewise produced. The yields were 0–32%, see: Y. Ishida, K. Kawatsu, Y. Matsuoka, K. Yamada, R. Ikariya, J. Sawayama, S. Hirao, N. Nishiwaki, K. Saigo, *Asian J. Org. Chem.* **2013**, *2*, 140.

15 Higher enantioselectivities (74% ee (**8a**), 94% ee (**8b**)) have been achieved using a chiral cyclophane-type NHC, see ref 11b.