A DyI_3-catalyzed Mannich-type Reaction of 1-Methylcyclopropanecarboxylate-type Donors for the Stereoselective Synthesis of Pyrrolidines with Quaternary Stereocenters

Hidetoshi Noda, Sean H. Wiedemann, Shigeki Matsunaga,* and Masakatsu Shibasaki*
Graduate School of Pharmaceutical Sciences, The University of Tokyo,
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033

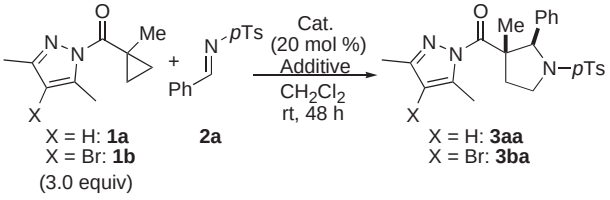
(Received August 27, 2008; CL-080818; E-mail: mshibasa@mol.f.u-tokyo.ac.jp, smatsuna@mol.f.u-tokyo.ac.jp)

Stereoselective synthesis of functionalized pyrrolidines with all-carbon quaternary stereocenters is described. DyI_3 catalyzed the ring opening of cyclopropanecarboxylate equivalents and promoted Mannich-type addition of the resulting α,α-disubstituted enolate intermediates to aryl and isomerizable alkyl imines, giving products in 86–58% yield and >96:4–84:16 diastereoselectivity.

The stereoselective formation of all-carbon quaternary stereocenters remains a formidable challenge in the field of organic synthesis.[1] The use of α,α-disubstituted enolates in carbon–carbon bond-forming reactions is a straightforward approach to provide α-carbonyl quaternary stereocenters. In this context, we recently reported Sc^{3+}-catalyzed direct aldol-type additions of *N*-benzoylcyclopropanecarboxamides. Either a mixture of $Sc(OTf)_3$/TMSCl/NaI or ScI_3 alone effectively promoted the reactions in good diastereoselectivity.[2] Cis selective in situ generation of α,α-disubstituted enolates was the key event in these reactions. In this paper, we describe an extension of the system to Mannich-type reactions for the stereoselective synthesis of functionalized pyrrolidines bearing all-carbon quaternary stereocenters.

Since Carreira's seminal reports on MgI_2-catalyzed Mannich-type ring expansion of spiro[cyclopropane-1,3′-oxindoles],[3] various cyclopropane donors, such as cyclopropyl ketones and methylenecyclopropanecarboxamides,[4,5] have been shown to participate in nucleophile-initiated direct Mannich-type reactions. There remains, however, much room for improvement in the use of α-substituted cyclopropanecarboxylate-type donors. On the basis of our previous aldol-type reactions, we screened various 1-methylcyclopropanecarbonyl donors and imines using rare earth metal iodides as catalysts. The combination of *N*-acylpyrrazole **1** and *N*-Ts imines **2** gave promising results.[6] Optimization studies of the reaction conditions using donor **1a** and imine **2a** are summarized in Table 1. Although ScI_3, which was useful in our previous aldol-type reaction, gave only trace product **3aa** (Entry 1), other rare earth metal iodides promoted the desired ring-opening/Mannich-type reaction with concomitant pyrrolidine ring closure (Entries 2–5). Among metal iodide screened, DyI_3 gave the best reactivity at room temperature in CH_2Cl_2, giving product **3aa** in 66% yield and >96:4 diastereoselectivity (Entry 4). MgI_2 was not a suitable catalyst for the cyclopropane ring opening of **1a** under identical reaction conditions (Entry 6).[7] Addition of Na_2SO_3 effectively improved the yield to 79% without affecting diastereoselectivity (Entry 7).[8] The use of 4-bromo-3,5-dimethylpyrazole as a template instead of 3,5-dimethylpyrazole further improved the reactivity, and product **3ba** was obtained in 84% yield and >96:4 diastereoselectivity after 30 h (Entry 8).

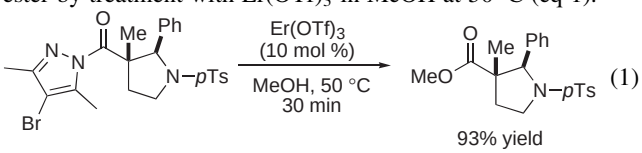
Table 1. Optimization of the reaction conditions



Entry	**1**	Cat.	Additive /equiv	Yield[a] /%	Dr[b]
1	**1a**	ScI_3	none	trace	—
2	**1a**	LaI_3	none	9	>96:4
3	**1a**	SmI_3	none	42	>96:4
4	**1a**	DyI_3	none	66	>96:4
5	**1a**	YbI_2	none	58	>96:4
6	**1a**	MgI_2	none	NR	—
7	**1a**	DyI_3	Na_2SO_3 (0.3)	79	>96:4
8[c]	**1b**	DyI_3	Na_2SO_3 (0.3)	84	>96:4

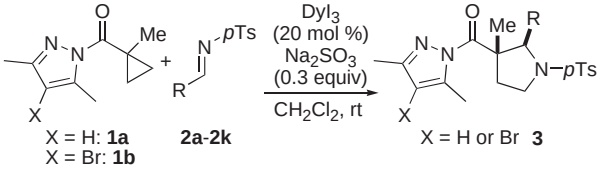
[a]Isolated yield after purification by column chromatography. [b]Determined by ^{1}H NMR analysis. [c]Reaction time was 30 h.

The optimized reaction conditions were applied to various aryl and alkyl imines (Table 2). The reactions of aryl imines **2a**–**2h** proceeded in high diastereoselectivity (Entries 1–8, >96:4–92:8). Aryl imines **2b**–**2d** with electron-withdrawing para-substituents showed good reactivity, and products **3bb**–**3bd** were obtained in 86–77% yield (Entries 2–4). With *p*-Me-substituted imine **2e**, the slow addition of donor **1b** over 8 h was necessary to obtain product **3be** in 60% yield after 72 h (Entry 5). In the case of ortho-substituted imines **2f**–**2h**, donor **1a** gave better results than donor **1b** (Entries 6–8, 72–66% yield). In general, alkyl imines, especially linear alkyl imines, are rather difficult substrates in direct catalytic Mannich-type reactions[9] under Brønsted basic reaction conditions due to competitive isomerization into enamides. Thus, it is noteworthy that the present system was applicable to readily isomerizable alkyl imines **2i** and **2j**. Products were obtained in 72–58% yield and 94:6–84:16 diastereoselectivity (Entries 9–11). Catalyst loading was successfully reduced to 10 mol % without loss of yield and diastereoselectivity, but the reaction rate decreased (Entry 12). The use of donors with bulkier α-substituents than methyl was not successful. In such cases, cyclopropane ring-opening proceeded, but subsequent Mannich-type addition to imine **1a** did not proceed, possibly due to steric hindrance. The *N*-acylpyrazole moiety of product **3ba** was successfully converted to methyl ester by treatment with $Er(OTf)_3$ in MeOH at 50 °C (eq 1).[10]



(1)

Table 2. DyI_3-catalyzed ring-opening/Mannich-type reaction/intramolecular cyclization sequence



Entry	1	Imine 2: R		3	Time /h	Yield[a] /%	Dr[b]
1	**1b**	C_6H_5	**2a**	**3ba**	30	84	>96:4
2	**1b**	4-Cl-C_6H_4	**2b**	**3bb**	30	86	>96:4
3	**1b**	4-Ac-C_6H_4	**2c**	**3bc**	30	85	92:8
4	**1b**	4-CN-C_6H_4	**2d**	**3bd**	40	77	>96:4
5[c]	**1b**	4-Me-C_6H_4	**2e**	**3be**	72	60	>96:4
6	**1a**	2-NO_2-C_6H_4	**2f**	**3af**	48	72	96:4
7	**1a**	2-Me-C_6H_4	**2g**	**3ag**	48	66	95:5
8	**1a**	1-Naphthyl	**2h**	**3ah**	48	72	>96:4
9	**1b**	$(CH_3)_2CHCH_2$	**2i**	**3bi**	48	58	89:11
10	**1b**	$PhCH_2CH_2$	**2j**	**3bj**	48	71	84:16
11	**1b**	$CH_3(CH_2)_3$	**2k**	**3bk**	48	72	94:6
12[d]	**1b**	C_6H_5	**2a**	**3ba**	56	80	>96:4

[a]Isolated yield after purification by column chromatography. [b]Determined by ^1H NMR analysis. [c]**1b** was slowly added over 8 h. [d]10 mol % DyI_3 and 60 mol % Na_2SO_3 were used.

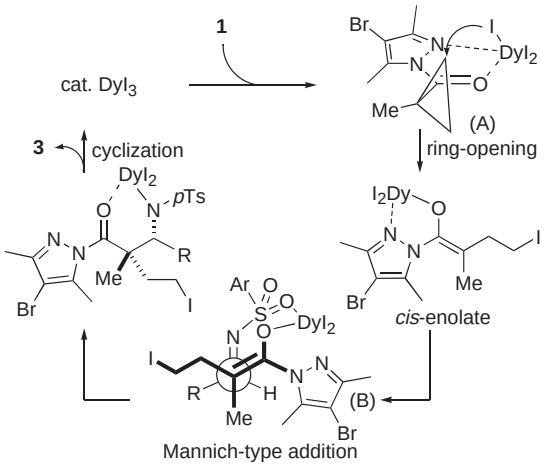


Figure 1. Postulated catalytic cycle of the ring-opening/Mannich-type reaction/intramolecular cyclization sequence promoted by DyI_3.

A postulated catalytic cycle is shown in Figure 1. DyI_3 would act as a Lewis acid to activate the *N*-acylpyrazole. The attack of metal-bound iodide on the cyclopropane ring can occur perpendicular to the carbonyl group through transition state (A),[11] which is close to the favorable bisected cis geometry in the ground state, thereby preferentially generating a *cis*-enolate. The observed relative stereochemistry can be explained by the cyclic transition state (B) for the Mannich-type addition. Finally, intramolecular cyclization affords product **3** and regenerates DyI_3.

In summary, we have developed a DyI_3-catalyzed cyclopropane ring-opening/Mannich-type addition/intramolecular cyclization sequence. The ring expansion reaction proceeded at room temperature with catalytic amount of DyI_3, giving functionalized pyrrolidines bearing α-carbonyl quaternary stereocenter in 86–58% yield and >96:4–84:16 diastereoselectivity.[12]

Support has been provided in part by a Grant-in-Aid for Specially Promoted Research and Grant-in-Aid for Scientific Research on Priority Areas (No. 20037010, Chemistry of Concerto Catalysis for SM).

This paper is dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

References and Notes

1 a) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, ed. by J. Christoffers, A. Baro, Wiley-VCH, Weinheim, Germany, **2005**. b) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369.
2 S. H. Wiedemann, H. Noda, S. Harada, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2008**, *10*, 1661.
3 a) P. B. Alper, C. Meyers, A. Lerchner, D. R. Siegel, E. M. Carreira, *Angew. Chem., Int. Ed.* **1999**, *38*, 3186. b) C. Marti, E. M. Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 11505. c) A. Lerchner, E. M. Carreira, *Chem.—Eur. J.* **2006**, *12*, 8208, and references therein.
4 a) C. Taillier, M. Lautens, *Org. Lett.* **2007**, *9*, 591, and references therein. b) F. Bertozzi, M. Gustafsson, R. Olsson, *Org. Lett.* **2002**, *4*, 3147. c) C. Timmons, D. Chen, J. F. Cannon, A. D. Headley, G. Li, *Org. Lett.* **2004**, *6*, 2075. d) W. Huang, J. Chin, L. Karpinski, G. Gustafson, C.-M. Baldino, L. Yu, *Tetrahedron Lett.* **2006**, *47*, 4911. For related works in aldol reactions, see also: e) Z. Han, S. Uehira, T. Tsuritani, H. Shinokubo, K. Oshima, *Tetrahedron* **2001**, *57*, 987. f) M. Shi, Y.-H. Yang, B. Xu, *Tetrahedron* **2005**, *61*, 1893.
5 For selected examples of related works using doubly activated donor/acceptor cyclopropanes and/or cyclopropanedicarboxylates, see: a) S. K. Jackson, A. Karadeolian, A. B. Driega, M. A. Kerr, *J. Am. Chem. Soc.* **2008**, *130*, 4196, and references therein. See also: b) H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151. c) M. Yu, B. L. Pagenkopf, *Tetrahedron* **2005**, *61*, 321, and references therein.
6 For studies of the *N*-acylpyrazole as an achiral template, see: a) K. Itoh, S. Kanemasa, *J. Am. Chem. Soc.* **2002**, *124*, 13394, and references therein. b) M. P. Sibi, J. J. Shay, M. Liu, C. P. Jasperse, *J. Am. Chem. Soc.* **1998**, *120*, 6615.
7 MgI_2 (20 mol %) afforded product **3aa** in 32% yield and 69:31 diastereoselectivity under the reaction conditions reported in ref 3 (in refluxing THF).
8 We speculate that Na_2SO_3 creates a reducing reaction medium in which the deleterious formation of I_2 is suppressed.
9 For recent reviews on direct catalytic Mannich(-type) reactions, see: a) A. Ting, S. E. Schaus, *Eur. J. Org. Chem.* **2007**, 5797. b) M. Shibasaki, S. Matsunaga, *J. Organomet. Chem.* **2006**, *691*, 2089.
10 D. A. Evans, B. W. Trotter, P. J. Coleman, B. Côté, L. C. Dias, H. A. Rajapakse, A. N. Tyler, *Tetrahedron* **1999**, *55*, 8671.
11 We speculate that the iodide moiety in TS-(A) is well aligned for overlap with the σ^* orbital of the cyclopropane C–C bond to be broken. In the ground state, donor **1** preferentially adopt a bisected conformation wherein two C–C σ-bonds of its cyclopropane ring and the π^* orbital of its carbonyl group experience maximal overlap. For bisected conformations of cyclopropyl methyl ketone, cis geometry was reported to be more favorable than trans geometry. T. T. Tidwell, in *The Chemistry of Functional Groups: Cyclopropyl Group, Vol. 1*, ed. by Rappoport, Z., Wiley, New York, **1987**, pp. 565–632.
12 Supporting Information is also available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

Published on the web (Advance View) November 5, 2008; doi:10.1246/cl.2008.1180