A DyI₃-catalyzed Mannich-type Reaction of 1-Methylcyclopropanecarboxylate-type Donors for the Stereoselective Synthesis of Pyrrolidines with Quaternary Stereocenters

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Stereoselective synthesis of functionalized pyrrolidines with all-carbon quaternary stereocenters is described. DyI₃ 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 carboncarbon bond-forming reactions is a straightforward approach to provide α -carbonyl quaternary stereocenters. In this context, we recently reported Sc³⁺-catalyzed direct aldol-type additions of *N*-benzoylcyclopropanecarboxamides. Either a mixture of Sc(OTf)₃/TMSCl/NaI or ScI₃ 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 MgI2-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 Mannichtype reactions. There remains, however, much room for improvement in the use of α -substituted cyclopropanecarboxvlate-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 ScI₃, 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, DyI₃ gave the best reactivity at room temperature in CH₂Cl₂, giving product **3aa** in 66% yield and >96:4 diastereoselectivity (Entry 4). MgI₂ was not a suitable catalyst for the cyclopropane ring opening of 1a under identical reaction conditions (Entry 6).7 Addition of Na₂SO₃ 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 ₂ SO ₃ (0.3)	84	>96:4

^aIsolated yield after purification by column chromatography. ^bDetermined by ¹H NMR analysis. ^cReaction 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-Mesubstituted imine 2e, the slow addition of donor 1b over 8h 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%) vield). In general, alkyl imines, especially linear alkyl imines, are rather difficult substrates in direct catalytic Mannich-type reactions⁹ 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



Table 2. DyI₃-catalyzed ring-opening/Mannich-type reaction/ intramolecular cyclization sequence



Entry	1	Imine 2: R		3	/h	Yield" /%	Dr ^b
1	1b	C ₆ H ₅	2a	3ba	30	84	>96:4
2	1b	4-Cl-C ₆ H ₄	2b	3bb	30	86	>96:4
3	1b	4-Ac-C ₆ H 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 ₆ H 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 ₆ H ₄	2g	3ag	48	66	95:5
8	1a	1-Naphthyl	2h	3ah	48	72	>96:4
9	1b	(CH ₃) ₂ CHCH ₂	2i	3bi	48	58	89:11
10	1b	PhCH ₂ CH ₂	2ј	3bj	48	71	84:16
11	1b	$CH_3(CH_2)_3$	2k	3bk	48	72	94:6
12 ^d	1b	C ₆ H ₅	2a	3ba	56	80	>96:4

^aIsolated yield after purification by column chromatography. ^bDetermined by ¹H NMR analysis. ^c**1b** was slowly added over 8 h. ^d10 mol % DyI₃ and 60 mol % Na₂SO₃ 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 DyI₃-catalyzed cyclopropane ring-opening/Mannich-type addition/intramolecular cyclization sequence. The ring expansion reaction proceeded at room temperature with catalytic amount of DyI₃, giving functionalized pyrrolidines bearing α -carbonyl quaternary stereocenter in 86–58% yield and >96:4–84:16 diastereoselectivity.¹²

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