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Sc^{3+}-Catalyzed Aldol-Type Additions of *N*-Benzoylcyclopropanecarboxamides via Iodide-Mediated Ring-Opening: Stereoselective Synthesis of γ-Lactams

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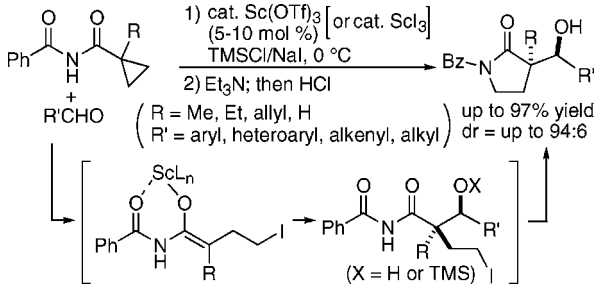
ABSTRACT



A new catalytic aldol-type addition of cyclopropanecarboximides to aldehydes via iodide-mediated ring-opening is presented. The reaction was found to be catalyzed at 0 °C using either a $Sc(OTf)_3$/NaI system or ScI_3. Stereoselective formation of α,α-disubstituted enolates occurred in situ. γ-Lactams bearing α-carbonyl quaternary stereocenters were obtained in 97–57% yield and dr = 90:10–80:20 after ring closure.

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 aldol reactions is a straightforward approach to provide α-carbonyl quaternary stereocenters. Given the many modern variants of the aldol reaction that have been developed,[2] however, it is remarkable that there are few such methods available wherein α-carbonyl quaternary stereocenters are formed selectively.[3,4] This deficiency can be attributed to the difficulty inherent in preparing geometrically well-defined α,α-disubstituted enolates from the corresponding carbonyl compounds under traditional base-mediated conditions. To solve this problem, nonclassical methods for stereoselective metal enolate or silyl enolate generation have been devised.[5] Alternatively, ketenes[6] and silylketene imines[7] have been used as surrogate donors in asymmetric additions to alde-

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(4) For selected recent works in different reactions to construct α-carbonyl quaternary stereocenters using acyclic tetrasubstituted silyl ketene acetals or tributyltin enolates, see: (a) Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 5604. (b) Doyle, A. G.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 3701.

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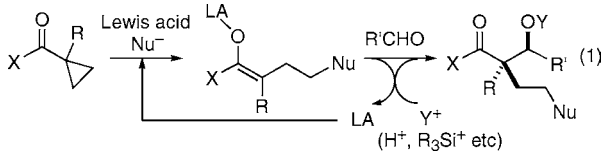
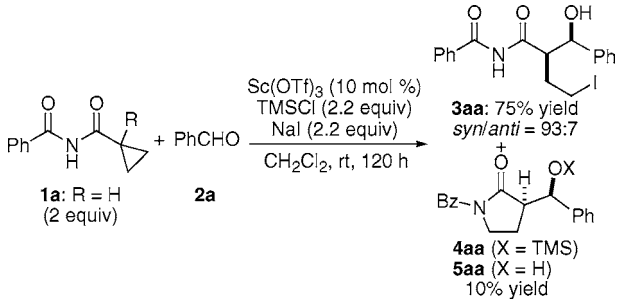
hydes under Lewis base catalysis. On the other hand, aldol reactions using an in situ generated α,α-disubstituted metal enolate to avoid the preformation of an activated donor compound[8] are limited to either donors with specific chelating functional groups[9] or cyclic donors,[10] which skirt the problem of enolate geometry. Notable progress was accomplished by Barbas and co-workers in organocatalytic direct aldol reactions of acyclic α,α-disubstituted aldehydes;[11] however, there still remains much room for improvement in terms of donor scope, especially in metal catalysis. Herein, we report a new Sc^{3+}-catalyzed aldol-type addition of *N*-benzoylcyclopropanecarboxamides **1** to aldehydes via iodide-mediated ring-opening. After ring closure of aldol adducts, γ-lactams bearing α-carbonyl quaternary stereocenters were obtained in up to 97% yield and up to 90:10 dr.

We set out to develop a new aldol-type reaction for the construction of α-carbonyl quaternary stereocenters by exploiting strained cyclopropanecarboxylate-type donors. Since Carreira's seminal reports on MgI_2-catalyzed Mannich-type ring expansion of spiro[cyclopropane-1,3′-oxindoles],[12] various donors, such as cyclopropyl ketones and methylenecyclopropanecarboxamides,[13] have been shown to participate in Mannich-type reactions. In contrast, analogous aldol-type reactions have been observed only with stoichiometric use of strong Lewis acids, such as $TiCl_4$, Et_2AlI, and TMSOTf.[14] Moreover, α-substituted donors have not been utilized in those studies to construct α-carbonyl quaternary stereocenters.[14] Until now, catalytic couplings of cyclopropanes with aldehydes have been limited to donors bearing two activating groups, either cyclopropanedicarboxylates or donor/acceptor cyclopropanes.[15] Therefore, the development of a new catalyst for aldol-type reactions using monoactivated α-substituted cyclopropanecarboxylate donors is desirable. We hypothesized that a suitable combination of Lewis acid catalyst and nucleophile could generate a geometrically well-defined α,α-disubstituted enolate in situ via nucleophilic ring opening and then subsequently promote aldol-type addition with good stereoselectivity (eq 1).



Initially, we screened various cyclopropanecarboxylate-type donors, Lewis acids, nucleophiles, as well as capping reagents (Y^+ in eq 1) and found that 10 mol % of $Sc(OTf)_3$ promoted the addition of *N*-benzoylcyclopropanecarboxamide **1a** (R = H)[16] to benzaldehyde (**2a**) in the presence of TMSCl and NaI (Scheme 1). Aldol adduct **3aa** was obtained

Scheme 1. Result of Initial Screening with α-Unsubstituted Donor **1a**



in 75% yield together with cyclized γ-lactams **4aa** and **5aa** (total 10% yield) as minor coproducts. Although the required reaction time was long at 25 °C (120 h), the high diastereomeric ratio of **3aa** was promising (syn/anti = 93:7). Based on this initial result, we studied the reaction using α-substituted donor **1b** (R = Me) and aldehyde **2a** in detail (Table 1). To simplify reaction analyses, crude reaction mixtures containing aldol adducts and γ-lactams were treated with Et_3N followed by HCl to induce complete cyclization and desilylation, respectively, giving **5ba**. α-Substituted donor **1b** showed higher reactivity than **1a**; 10 mol % of $Sc(OTf)_3$ promoted the reaction of **1b** with aldehyde **2a** at 0 °C, giving **5ba** in high yield and good diastereoselectivity after 48 h (Table 1, entry 1, 97% yield, dr = 89:11). The major diastereomer of product **5ba** was found to be that derived from a *syn*-aldol adduct. Neither other rare earth metal triflates nor $Mg(OTf)_2$ gave satisfactory yields of **5ba** (entries 2−5, trace to 8% yield). The heterogeneous mixture of NaI and TMSCl was superior as an iodide/capping agent com-

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(9) For selected examples, see: (a) Ito, Y.; Sawamura, M.; Shirakawa, E.; Hayashizaki, K.; Hayashi, T. *Tetrahedron* **1988**, *44*, 5253 and references therein. (b) Kuwano, R.; Miyazaki, H.; Ito, Y. *J. Organomet. Chem.* **2000**, *603*, 18. (c) Sunazuka, T.; Hirose, T.; Shirahata, T.; Harigaya, Y.; Hayashi, M.; Komiyama, K.; Omura, S.; Smith, A. B., III. *J. Am. Chem. Soc.* **2000**, *122*, 2122. For related works of α-carbonyl *tert*-alcohol construction: (d) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169.

(10) (a) Mahrwald, R.; Gündogan, B. *J. Am. Chem. Soc.* **1998**, *120*, 413. (b) Ogawa, S.; Shibata, N.; Inagaki, J.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8666.

(11) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420 and references therein.

(12) (a) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186. (b) Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505. (c) Lerchner, A.; Carreira, E. M. *Chem. Eur. J.* **2006**, *12*, 8209 and references therein.

(13) (a) Taillier, C.; Lautens, M. *Org. Lett.* **2007**, *9*, 591 and references therein. (b) Bertozzi, F.; Gustafsson, M.; Olsson, R. *Org. Lett.* **2002**, *4*, 3147. (c) Huang, W.-W.; Chin, J.; Karpinski, L.; Gustafson, G.; Baldino, C. M.; Yu, L.-B. *Tetrahedron Lett.* **2006**, *47*, 4911.

(14) (a) Han, Z.; Uehira, S.; Tsuritani, T.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2001**, *57*, 987. (b) Timmons, C.; Chen, D.-J.; Cannon, J. F.; Headley, A. D.; Li, G. G. *Org. Lett.* **2004**, *6*, 2075. (c) Shi, M.; Yang, Y.-H.; Xu, B. *Tetrahedron* **2005**, *61*, 1893. α-Substituted donors for constructing α-carbonyl quaternary stereocenters have not been utilized in these studies.

(15) (a) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014. (b) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (c) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321 and references therein. For related $Sc(OTf)_3$-catalyzed couplings of cyclopropanedicarboxylates and donor/acceptor cyclopropanes with nitrones, see: (d) Lebold, T. P.; Carson, C. A.; Kerr, M. A. *Synlett* **2006**, 364. See also: (e) Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 4196 and references therein.

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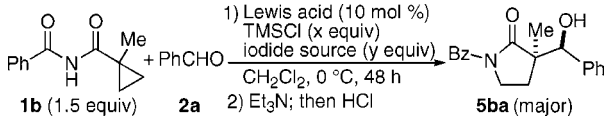
Table 1. Optimization of Reaction Conditions with α-Substituted Donor **1b**



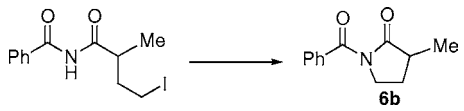
entry	Lewis acid	TMSCl (equiv)	iodide source (equiv)	yield (%)	dr[a]
1	$Sc(OTf)_3$	1.6	NaI (2.0)	97	89:11
2	$La(OTf)_3$	1.6	NaI (2.0)	5	80:20
3	$Gd(OTf)_3$	1.6	NaI (2.0)	5	80:20
4	$Yb(OTf)_3$	1.6	NaI (2.0)	8	83:17
5	$Mg(OTf)_2$	1.6	NaI (2.0)	trace	ND
6	$Sc(OTf)_3$	1.6	LiI (2.0)	trace	ND
7	$Sc(OTf)_3$	1.6	nBu_4NI (2.0)	11	89:11
8[b]	$Sc(OTf)_3$	0	TMSI (1.6)	0	ND
9[c]	$Sc(OTf)_3$	0	NaI (2.0)	42	90:10
10[c]	ScI_3	0	none	59	88:12
11	ScI_3	1.6	none	72	88:12

[a] Determined by ^1H NMR analysis. [b] Complex mixtures of byproducts were obtained. [c] Treatment with HCl was omitted.

bination compared to several sets of heterogeneous (entry 6) and homogeneous conditions (entries 7−8). In entries 2−7, cyclopropane ring-opening did proceed, but aldehyde addition proved problematic, giving γ-lactam **6b**[17] as a major product. In entry 9, the reaction proceeded even in the absence of TMSCl, and **5ba** was obtained in similar diastereoselectivity (90:10) to that of entry 1, albeit in lower yield. Furthermore, ScI_3 alone promoted the reaction with good diastereoselectivity (entry 10, 59% yield, dr = 88:12). The result of entry 10 implies that ScI_3 functions not only as a Lewis acid but also as an iodide source in a manner analogous to that of MgI_2 in related Mannich-type reactions.[12] TMSCl slightly improved the reactivity while maintaining good diastereoselectivity (entry 11, 72% yield, dr = 88:12).

Optimized reaction conditions in terms of yield (Table 1, entry 1) were applied to various aldehydes (Table 2). With nonenolizable aryl, heteroaryl, and alkenyl aldehydes **2a**−**e**, products were obtained in 57−97% yield and 81:19−89:11 dr (entries 1−6).[18] Aldehyde **2c** bearing an electron-donating substituent provided a less satisfactory yield (entry 4). When the loading of $Sc(OTf)_3$ was reduced to 5 mol %, **5ba** was successfully obtained in 94% yield and 87:13 diastereoselectivity (entry 2). Enolizable alkyl aldehydes are often poor substrates for typical direct cross-aldol reactions under basic conditions due to competitive self-aldol condensation.[8,19] It is noteworthy that alkyl aldehydes,

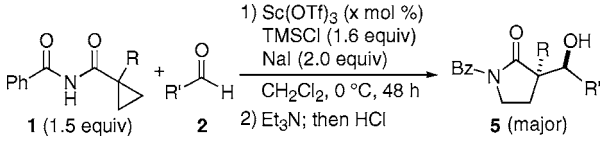
(17) γ-Lactam **6b** formed via ring-expansion without aldehyde incorporation.



6b

(18) The relative stereochemistries of **5bd** and **5aa** were unambiguously determined by single crystal X-ray analysis. The relative stereochemistries of other products are drawn by analogy.

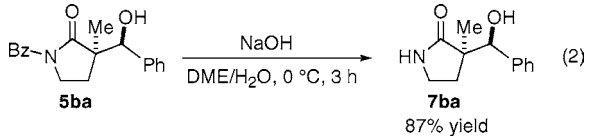
Table 2. Substrate Scope and Limitations of Aldol-Type Reaction/Cyclization Sequence[a]



entry	cat. (mol %)	R	1	R′	2	5	yield[b] (%)	dr[c]
1	10	Me	**1b**	Ph	**2a**	**5ba**	97	89:11
2[d]	5	Me	**1b**	Ph	**2a**	**5ba**	94	87:13
3	10	Me	**1b**	4-ClC_6H_4	**2b**	**5bb**	87	88:12
4	10	Me	**1b**	4-MeC_6H_4	**2c**	**5bc**	57	85:15
5	10	Me	**1b**	2-furyl	**2d**	**5bd**	70	83:17
6	10	Me	**1b**	(*E*)-PhCH=CH	**2e**	**5be**	78	81:19
7	10	Me	**1b**	cyclohexyl	**2f**	**5bf**	87	87:13
8	10	Me	**1b**	1-hexyl	**2g**	**5bg**	87	85:15
9	10	Me	**1b**	(*Z*)-1-hex-3-enyl	**2h**	**5bh**	90	90:10
10	10	Et	**1c**	Ph	**2a**	**5ca**	79	80:20
11	10	Allyl	**1d**	Ph	**2a**	**5da**	82	83:17
12[e]	10	H	**1a**	Ph	**2a**	**5aa**	84	94:6

[a] Reactions were run using 1.5 equiv of **1**, 1.6 equiv of TMSCl, and 2.0 equiv of NaI in CH_2Cl_2 (0.1 M) at 0 °C for 48 h unless otherwise noted. [b] Isolated yield after purification by column chromatography. [c] Determined by ^1H NMR analysis. [d] Reaction time was 72 h. [e] Reaction was run at 25 °C for 96 h.

including readily enolizable linear alkyl aldehydes, are applicable without problems in the present system. Aldehydes **2f**−**h** afforded products in high yield and good diastereoselectivity (entries 7−9, 87−90% yield, dr = 85:15−90:10). No products of self-aldol condensations were observed in entries 7−9. The reaction generality with respect to donor substituents was investigated in entries 10−12. Donors **1c** (R = Et), **1d** (R = allyl), and **1a** (R = H) reacted with aldehyde **2a** to afford products **5ca** (79% yield), **5da** (82% yield), and **5aa** (84% yield), respectively. Removal of the *N*-benzoyl group from **5ba** proceeded smoothly by treatment with NaOH in DME/H_2O at 0 °C; *NH*-lactam **7ba** was obtained in 87% yield (eq 2).



(2)

In the present system, *syn*-aldol adducts **3** were formed as the major products. On the basis of Oshima and co-workers' early work,[14a] we assume that the observed product

(19) For selected exceptional metal-catalyzed direct aldol reactions wherein enolizable linear alkyl aldehydes afforded good results comparable to other aldehydes, see: (a) Magdziak, D.; Lalic, G.; Lee, H. M.; Fortner, K. C.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 7284 and references therein. (b) Evans, D. A.; Downey, C. W.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 8706 and references therein. (c) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367. (d) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466. For other examples, see reviews in ref 2 and references therein.

distribution is governed by kinetic control. Syn selectivity can be rationalized by using stereochemical models based on closed transition states both for iodide attack and addition to aldehyde (Figures 1 and 2). Because ScI_3 afforded product

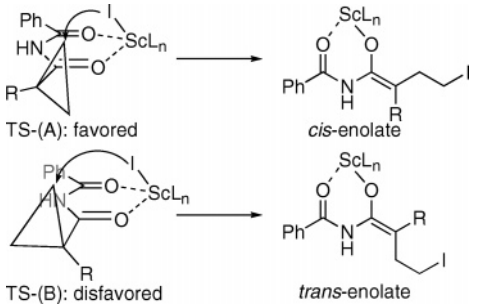


Figure 1. Postulated transition-state models for cyclopropane ring opening.

5ba with similar diastereoselectivity to that obtained with the use of a $Sc(OTf)_3$/NaI system (Table 1, entry 1 vs entry 11; entry 9 vs entry 10), we believe that Sc^{3+}-bound iodide may be the active nucleophile involved in cyclopropane ring-opening. The attack of iodide on the cyclopropane ring can occur perpendicular to the carbonyl group through either TS-(A) or TS-(B). Metal-bound iodide would attack the cyclopropane ring via favorable TS-(A),[20] which is closer to the favorable bisected cis geometry,[21] thereby preferentially generating *cis*-enolate (Figure 1). A proposed catalytic cycle is shown in Figure 2a. *cis*-Enolate addition to aldehyde is believed to proceed via a Zimmerman−Traxler transition state to minimize 1,3-diaxial interactions, affording *syn*-adduct **3**. In the absence of TMSCl, the Sc-aldolate **8** should be protonated by the relatively acidic imide N−H moiety to regenerate the Sc-catalyst. On the other hand, in the presence of TMSCl, the resulting Sc-aldolate **8** can be trapped by silylation, thereby promoting Sc-catalyst regeneration.[22] When using 10 mol % of ScI_3 instead of $Sc(OTf)_3$/NaI, **5aa** was furnished in ≥59% yield (Table 1, entries 10 and 11). These results show that a catalytic amount of iodide source is sufficient to promote the desired reaction. We suspect that the catalyst is regenerated, in this case, through in situ ring closure (Figure 2b). Indeed, γ-lactam **5ba** was observed as a major product by TLC analysis of the reaction mixture in entry 10, Table 1, before treatment with Et_3N.

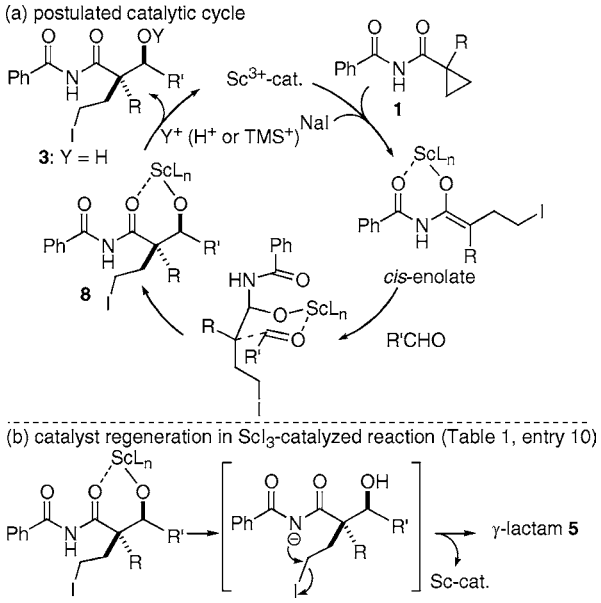


Figure 2. (a) Postulated catalytic cycle of aldol-type addition and (b) catalyst regeneration in ScI_3-catalyzed reaction.

In summary, we have developed a Sc^{3+}-catalyzed aldol-type addition of *N*-benzoylcyclopropanecarboxamides **1** to various aldehydes, including readily enolizable linear alkyl aldehydes, via iodide-mediated ring-opening. The reaction proceeded at 0 °C using either a $Sc(OTf)_3$/NaI system or ScI_3, and γ-lactams bearing α-carbonyl quaternary stereocenters were obtained in 97−57% yield and 90:10−80:20 diastereoselectivity after ring closure. Further studies to improve the reactivity using ScI_3 alone, which is preferable in terms of atom-economy, as well as trials to develop catalytic enantioselective variants, are ongoing.

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Supporting Information Available: Detailed experimental procedures, spectral data for new compounds, and X-ray crystallography data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) We speculate that I^- is better alligned for overlap with the σ* orbital of the cyclopropane C−C bond in TS-(A) than in TS-(B).

(21) In the ground state, donor **1** should stereoelectronically favor the 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 cyclopropylmethyl ketone, bisected cis geometry was reported to be more favorable than trans geometry. Tidwell, T. T. In *The Chemistry of Functional Groups: Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987; Vol. 1, Chapter 10, pp 565−632. For a related discussion, see ref 14a.

(22) Although the involvement of a Mukaiyama-type reaction pathway in the presence of TMSCl cannot be completely ruled out, we believe that this mechanism is less probable on the basis of certain control experiments (Table 1). Similar diastereoselectivities were observed even in the absence of TMSCl, either with $Sc(OTf)_3$/NaI or ScI_3 as a catalyst (Table 1, entry 1 vs entry 9; entry 10 vs entry 11). Attempts to isolate a relevant *N*-acylsilylketeneaminal failed. Thus, we could not perform definitive control experiments to clarify the mechanism.