JOC Note

pubs.acs.org/joc

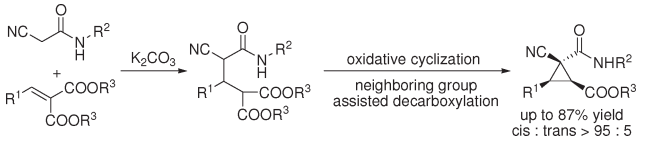
Stereoselective Synthesis of 2-Carbamoyl-2-cyanocyclopropanecarboxylates by Tandem Oxidative Cyclization and Neighboring Group-Assisted Decarboxylation

Hua Wang[†] and Renhua Fan*[,†,‡]

[†]*Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China, and* [‡]*Shanghai Key Laboratory of Molecular Catalysts and Innovative Materials, Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China*

rhfan@fudan.edu.cn

Received July 28, 2010



In this paper, we report a facile synthesis of 2-carbamoyl-2-cyanocyclopropanecarboxylates through a tandem iodosobenzene/tetrabutylammonium iodide-induced oxidative cyclization and a subsequent neighboring group-assisted decarboxylation of the Michael adducts of 2-cyanoacetamides with α,β-unsaturated malonates. This method affords the desired highly functionalized cyclopropanes in moderate to good yields and with excellent diastereoselectivities. In addition, the reaction proceeds smoothly under mild conditions and with good functional group tolerance.

As the smallest cycloalkanes, cyclopropanes[1] not only appear as basic skeltons in a wide range of biologically active natural and unnatural compounds[2] but also as versatile intermediates for the synthesis of various cyclic and acyclic compounds.[3] Despite the considerable amount of effort in the area of cyclopropane synthesis,[4] new and straightforward methods to access these highly constrained cycloalkanes are always highly desirable. In this paper, we introduce an efficient synthesis of 2-carbamoyl-2-cyanocyclopropanecarboxylates with excellent diastereoselectivities via tandem iodine(III)-induced oxidative cyclization and subsequent neighboring group assisted decarboxylation.

2-Carbamoyl-2-cyanocyclopropanecarboxylates have been used as templates for the preparation of many useful functionalized cyclopropanes due to their reactive functionalities.[5] For example, they have been used as key intermediates in the synthesis of cryptophycin analogues, which exhibit high activity against a broad spectrum of solid tumors.[6] The Charette group has reported the reaction of alkenes with α-cyanodiazoacetamide in the synthesis 1-cyanocyclopropane-1-carboxy derivatives.[7] Similarly, Zhang and co-workers developed a cobaltcatalyzed cyclopropanation of various electron-deficient alkenes with diazoacetate to afford 2-cyanocyclopropane carboxylates.[8] However, when a double bond with two electron-withdrawing groups at the same carbon was employed, no reaction occurred (path b, Scheme 1). This kind of reaction with an α,β-unsaturated carbonyl compound has never been addressed in previous literature (path a, Scheme 1). In our previous studies, we found that 2-benzoylcyclopropane- 1,1-dicarboxylate could be prepared through oxidative cyclization of the Michael adducts of malonates with chalcones in the presence of iodosobenzene and tetrabutylammonium iodide.[9] The success of such a procedure encouraged us to investigate this as a novel method for the synthesis of 2-carbamoyl-2-cyanocyclopropanecarboxylates from 2-cyanoacetamides and α,β-unsaturated esters (path c, Scheme 1).

The 2-cyanoacetamide **2a** was prepared as described in the literature in 92% yield.[10] In our initial experiments, we found the Michael addition of 2-cyanoacetamide **2a** to ethyl cinnamate

(1) For selected reviews on cyclopropanes, see: (a) Patai, S.; Rappoport, Z. *The Chemistry of the Cyclopropyl Group*; Wiley & Sons: New York, 1987. (b) *Houblen-Weyl Methods of Organic Chemistry*; Thieme: Stuttgart, 1997; Vol. E17c. (c) *Small Ring Compounds in Organic Synthesis VI*; de Meijere, A., Ed.; Springer: Berlin, 2000; Vol. 207.

(2) (a) de Meijere, A. *Angew. Chem., Int. Ed.* **1979**, *18*, 809. (b) Suckling, C. J. *Angew. Chem., Int. Ed.* **1988**, *27*, 537. (c) Djerassi, C.; Doss, G. A. *New J. Chem.* **1990**, *14*, 713. (d) Wiberg, K. B. *Acc. Chem. Res.* **1996**, *29*, 229. (e) Salaün, J. *Top. Curr. Chem.* **2000**, *207*, 1. (f) Faust, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2251.

(3) (a) Goldschmidt, Z.; Crammer, B. *Chem. Soc. Rev.* **1988**, *17*, 229. (b) Reissig, H.-U. *Top. Curr. Chem.* **1988**, *144*, 73. (c) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (d) Piers, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 971. (e) Hudlicky, T.; Fan, R.; Reed, J.; Gadamasetti, K. G. *Org. React.* **1992**, *41*, 1. (f) Davies, H. M. L. *Tetrahedron* **1993**, *49*, 5203. (g) Nonhebel, D. C. *Chem. Soc. Rev.* **1993**, 347.

(4) (a) Salaün, J. *Chem. Rev.* **1989**, *89*, 1247. (b) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385. (c) Doyle, M. P. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993; p 63. (d) Reissig, H.-U. *Angew. Chem., Int. Ed.* **1996**, *35*, 971. (e) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (f) Li, A. H.; Dai, L. X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341. (g) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (h) Davies, H. M. L.; Antoulinakis, E. *Org. React.* **2001**, *57*, 1. (i) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589. (j) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (k) Pietruszka, J. *Chem. Rev.* **2003**, *103*, 1051. (l) Gnad, G.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603. (m) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625.

(5) (a) Yankee, E. W.; Badea, F. D.; Howe, N. E.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 4210. (b) Yankee, E. W.; Spencer, B.; Howe, N. E.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 4220. (c) Chmurny, A. B.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 4237. (d) Boger, D.; Brotherton, C. *J. Am. Chem. Soc.* **1986**, *108*, 6695. (e) Wurz, R. P.; Lin, W.; Charette, A. B. *Tetrahedron Lett.* **2003**, *44*, 8845. (f) Bagal, S.; Greef, M.; Zard, S. *Org. Lett.* **2006**, *8*, 147. (g) Couty, F.; David, O.; Larmanjat, B.; Marrot, J. *J. Org. Chem.* **2007**, *72*, 1058.

(6) (a) Schwartz, R. E.; Hirsch, C. F.; Sesin, D. F.; Flor, J. E.; Chartrain, M.; Fromtling, R. E.; Harris, G. H.; Salvatore, M. J.; Liesch, J. M.; Yudin, K. *J. Ind. Microbiol.* **1990**, *5*, 113. (b) Varie, D. L.; Shih, C.; Hay, D. A.; Andis, S. L.; Corbett, T. H.; Gossett, L. S.; Janisse, S. K.; Martinelli, M. J.; Moher, E. D.; Schultz, R. M.; Toth, J. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 369.

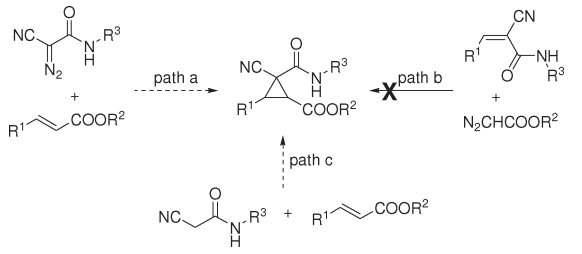
(7) Marcoux, D.; Azzi, S.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 6970.

(8) Chen, Y.; Ruppel, J. V.; Zhang, X. P. *J. Am. Chem. Soc.* **2007**, *129*, 12074.

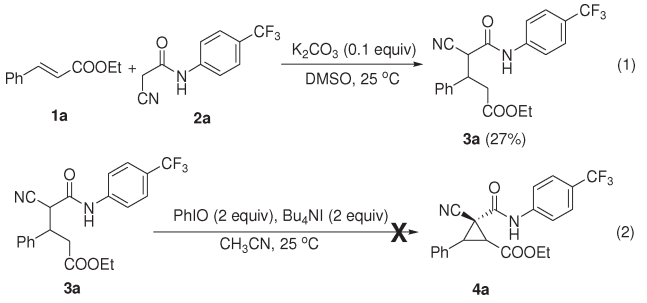
(9) Ye, Y.; Zheng, C.; Fan, R. *Org. Lett.* **2009**, *11*, 3156.

Published on Web 09/21/2010 DOI: 10.1021/jo1014245

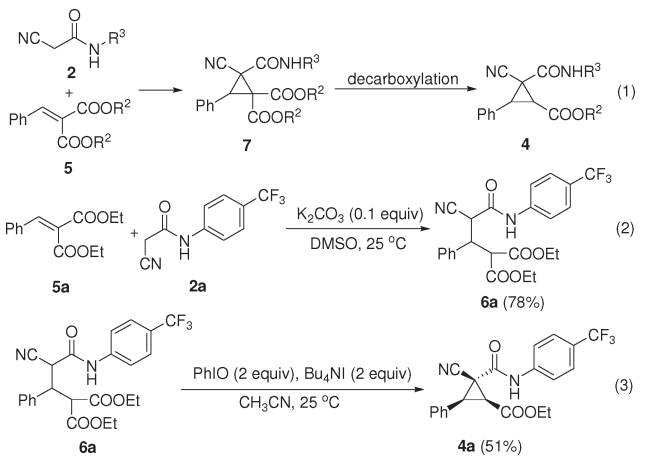
SCHEME 1



SCHEME 2



SCHEME 3



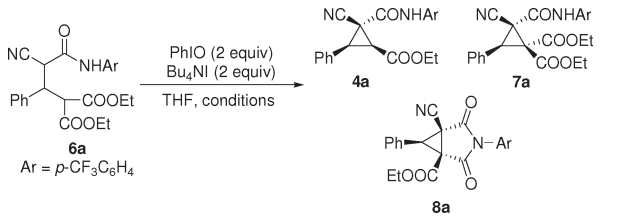
proceeded sluggishly.[11] After the optimization of reaction conditions, Michael adduct **3a** was finally obtained in low yield (Scheme 2, eq 1). However, the subsequent oxidative cyclization of **3a** with the combination of iodosobenzene and tetrabutylammonium iodide failed (Scheme 2, eq 2).

To increase the reactivity for both the α,β-unsaturated ester in Michael addition and the corresponding adduct in oxidative cyclization, another ester group was introduced into the structure of the substrate. The desired 2-carbamoyl-2-cyanocyclopropanecarboxylate was expected to be formed through the decarboxylation of a resultant 2-carbamoyl-2-cyanocyclopropane-1,1-dicarboxylate **7** (Scheme 3, eq 1).

(10) (a) Ried, W.; Schleimer, B. *Angew. Chem.* **1958**, *70*, 164. (b) Gorobets, N. Y.; Yousefi, B. H.; Belaj, F.; Kappe, C. O. *Tetrahedron* **2004**, *60*, 8633.

(11) For selected examples on the reactions of 2-cyanoacetmides, see: (a) Girgis, A. S.; Hosni, H. M.; Barsoum, F. F. *Bioorg. Med. Chem.* **2006**, *14*, 4466. (b) Bheemanapalli, L. N.; Akkinepally, R. R.; Pamulaparthy, S. R. *Chem. Pharm. Bull.* **2008**, *56*, 1342. (c) Rosati, O.; Curini, M.; Marcotullio, M. C.; Oball-Mond, G.; Pelucchini, C.; Procopio, A. *Synthesis* **2010**, 239.

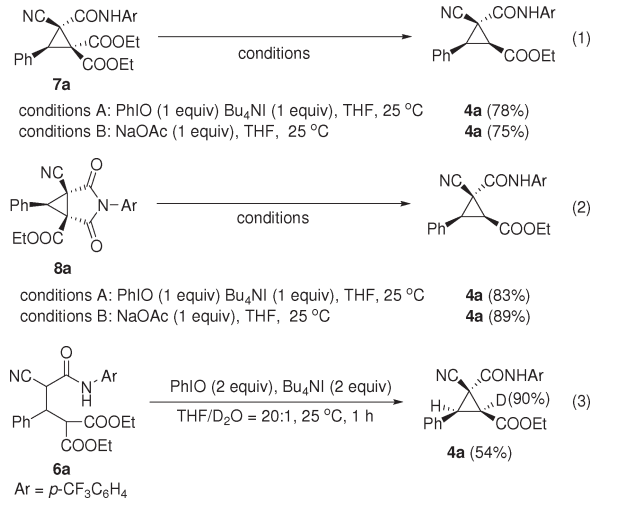
TABLE 1



entry	conditions	**4a** (%)[a]	**7a** (%)[a]	**8a** (%)[a]
1	25 °C, 1 h	75	0	0
2	0 °C, 1 h	31	5	52
3	−15 °C, 1 h	0	61	23
4[b]	−15 °C, 0.5 h	0	81	trace

[a]Isolated yield. [b]1 equiv of PhIO and Bu_4NI were used.

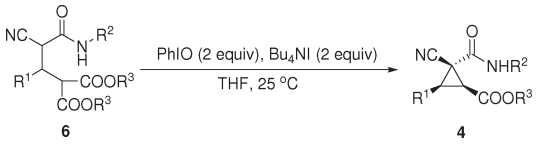
SCHEME 4



Under the optimized Michael addition conditions, the reaction of 2-cyanoacetamide **2a** with 2-benzylidenemalonate **5a** afforded adduct **6a** in 78% yield (Scheme 3, eq 2). Interestingly, when the combination of PhIO and Bu_4NI was used as the oxidative reagent, 2-carbamoyl-2-cyanocyclopropane-1,1-dicarboxylate **7a** was not detected, but the desired 2-carbamoyl-2-cyanocyclopropanecarboxylate **4a** was isolated in 51% yield (Scheme 3, eq 3). In our previous studies, cyclopropane derivatives were normally formed as *trans* diastereoisomers, in which the coupling constants between the two methine protons of the cyclopropanes were 6−7 Hz.[9] However, the observed corresponding coupling constant for product **4a** was 10.4 Hz, which is larger than those for the *trans*-cyclopropane derivatives, and indicates a *cis* configuration for compound **4a**. The *cis* configuration of **4a** was also confirmed by its single-crystal diffraction analysis.

Further studies were conducted to set up the optimal cyclization conditions [PhIO (2 equiv), Bu_4NI (2 equiv), THF, 25 °C, 1 h] to afford product **4a** in 75% yield (Table 1, entry 1). When the reaction was carried out at 0 °C, besides product **4a**, two byproducts formed. They were isolated and assigned as 2-carbamoyl-2-cyanocyclopropane-1,1-dicarboxylate **7a** and ethyl 5-cyano-2,4-dioxo-6-phenyl-3-azabicyclo[3.1.0]hexane-1-carboxylate **8a**, respectively (Table 1, entry 2). When the reaction was further decreased to −15 °C, compound **7a** formed as the major product (Table 1, entry 3). When the

TABLE 2



entry	R^1	R^2	R^3	4	yield[a] (%)
1	C_6H_5	4-$CF_3C_6H_4$	Et	**4a**	75
2	C_6H_5	C_6H_5	Et	**4b**	65
3	C_6H_5	4-$MeOC_6H_4$	Et	**4c**	87
4	4-$NO_2C_6H_4$	Bn	Et	**4d**	40
5	C_6H_5	4-$MeOC_6H_4$	Me	**4e**	61
6	C_6H_5	4-$MeOC_6H_4$	Bn	**4f**	76
7	4-FC_6H_4	4-$MeOC_6H_4$	Et	**4g**	80
8	4-ClC_6H_4	4-$MeOC_6H_4$	Et	**4h**	65
9	2-ClC_6H_4	4-$MeOC_6H_4$	Et	**4i**	70
10	2,4-di−Cl-C_6H_3	4-$MeOC_6H_4$	Et	**4j**	52
11	4-BrC_6H_4	4-$MeOC_6H_4$	Et	**4k**	70
12	4-CNC_6H_4	4-$MeOC_6H_4$	Et	**4l**	80
13	4-$CF_3C_6H_4$	4-$MeOC_6H_4$	Et	**4m**	66
14	4-$NO_2C_6H_4$	4-$MeOC_6H_4$	Et	**4n**	62
15	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Et	**4o**	60
16	4-MeC_6H_4	4-$MeOC_6H_4$	Et	**4p**	65
17	1-naphthyl	4-$MeOC_6H_4$	Et	**4q**	73
18	2-furan	4-$MeOC_6H_4$	Et	**4r**	47
19	2-thiophene	4-$MeOC_6H_4$	Et	**4s**	53
20	*n*-Bu	4-$MeOC_6H_4$	Et	**4t**	trace

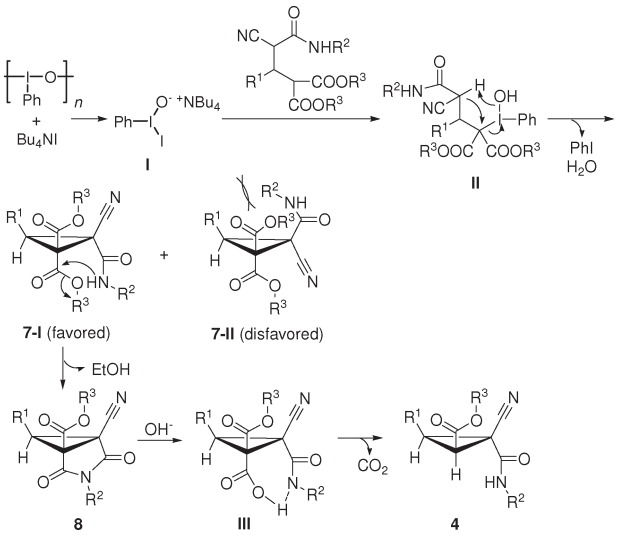
[a]Isolated yield.

amounts of PhIO and Bu_4NI were decreased to 1 equiv, the reaction only afforded compound **7a** after 30 min (Table 1, entry 4). When compounds **7a** and **8a** were treated with the combination of PhIO and Bu_4NI again, both of them were converted into product **4a** with good yields. Moreover, the conversions also proceeded well by treatment with 1 equiv of NaOAc (Scheme 4, eqs 1 and 2). When D_2O was introduced into the reaction mixture, the reaction was monitored by observing the disappearance of the α proton signal of the ester group of compound **6a** in ^1H NMR (Scheme 4, eq 3).

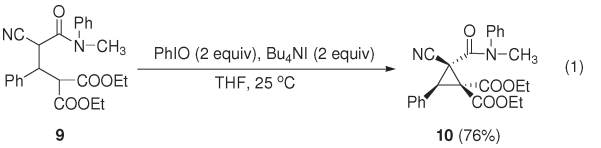
The reaction scope was then investigated under the optimized conditions, and the results are summarized in Table 2. Michael adducts **6** were prepared from corresponding additions of 2-cyanoacetamides with α,β-unsaturated malonates in yields ranging from 62 to 91%. In most cases, 2-carbamoyl-2-cyanocyclopropanecarboxylates **4** were formed in good yields. With respect to the R^2 groups on the nitrogen, both electron-poor and electron-rich aromatic rings afford good yields, while reaction of the substrate with a benzyl group as the R^2 group also afforded the corresponding product **4d** (Table 2, entries 1−4). Michael adducts derived from dimethyl and dibenzyl malonates were also suitable substrates (Table 2, entries 5 and 6). Additionally, the reaction was found to tolerate a range of different groups with different electronic demands on the R^1 aromatic rings (Table2, entries 7−17). 2-Furan- or 2-thiophene-substituted Michael adducts were also utilized as substrates to afford the desired product **4r** or **4s** in 47 or 53% yield, respectively (Table 2, entries 18 and 19). Only trace amounts of product were detected for the reaction of the substrate with butyl as the R^1 group (Table 2, entry 20). All products were formed with excellent diastereoselectivities (cis/trans >95:5, determined by ^1H NMR).

When the amide group of Michael adduct **6b** was protected by a methyl group, the corresponding reaction under

SCHEME 5. Plausible Reaction Pathway



the same conditions only afforded 2-carbamoyl-2-cyanocyclopropane-1,1-dicarboxylate **10** as the product (eq 1).



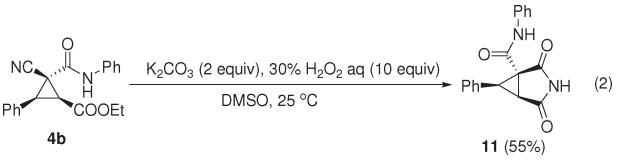
A plausible reaction mechanism is outlined in Scheme 5. Due to the polymeric structure of iodosobenzene, a hydroxylic solvent or a catalyst is normally required to depolymerize $(PhIO)_n$ to generate the reactive species.[12] Besides the useful oxidative nature, a notable feature of the resultant iodine(III) compounds is their ability to undergo ligand exchange reaction and reductive elimination reaction like transition metals.[13] In the presence of the reactive iodine(III) species **I**, which is generated from the depolymerization of iodosobenzene by tetrabutylammonium iodide, an α hyperiodination of Michael adduct **6** yields an intermediate **II**. After an intramolecular attack by the activated methine carbon and a subsequent reductive elimination of PhI, intermediate **II** is converted into 2-carbamoyl-2-cyanocyclopropane-1,1-dicarboxylate **7**.[14] The diastereomer **7I** is the favored product due to steric effects, in which one ester group and one amide group are located on the same side of the plane of the cyclopropane moiety. Subsequently, compound **7I** undergoes an intramolecular cyclization which eventually generates 5-cyano-2,4-dioxo-6-phenyl-3-azabicyclo[3.1.0]hexane-1-carboxylate **8**.[15]

(12) (a) Moriarty, R. M.; Duncan, M. P.; Prakash, O. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1781. (b) Moriarty, R. M.; Rani, N.; Condeiu, C.; Duncan, M. P.; Prakash, O. *Synth. Commun.* **1997**, *27*, 3273. (c) Tohma, H.; Takizawa, S.; Maegawa, T.; Kita, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 1306. (d) Francisco, C. G.; Freire, R.; Gonzalez, C. C.; Leon, E. I.; Riesco-Fagundo, C.; Suarez, E. *J. Org. Chem.* **2001**, *66*, 1861. (e) Tohma, H.; Maegawa, T.; Takizawa, S.; Kita, Y. *Adv. Synth. Catal.* **2002**, *344*, 328. (f) Francisco, C. G.; Herrera, A. J.; Suarez, E. *J. Org. Chem.* **2002**, *67*, 7439. (g) Francisco, C. G.; Herrera, A. J.; Suarez, E. *J. Org. Chem.* **2003**, *68*, 1012.

(13) For selected reviews, see: (a) Moriarty, R. M.; Vaid, R. K. *Synthesis* **1990**, 431. (b) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (c) Zhdankin, V. V.; Stang, P. J. In *Chemistry of Hypervalent Compounds*; Akiba, K., Ed.; VCH Publishers: New York, 1999; Vol. 11, p 327. (d) Grushin, V. V. *Chem. Soc. Rev.* **2000**, *29*, 315. (e) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (f) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997. (g) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (h) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299.

Although we are not certain of the true pathway involving the generation of the *cis*-2-carbamoyl-2-cyanocyclopropanecarboxylate **4** from compound **8**, a possible rationalization could be the selective hydrolysis of compound **8** and the decarboxylation of the resultant intermediate **III**.

Finally, the treatment of 2-carbamoyl-2-cyanocyclopropanecarboxylate **4b** with K_2CO_3 and H_2O_2 in DMSO[16] led to the generation of 2,4-dioxo-*N*,6-diphenyl-3-azabicyclo-[3.1.0]hexane-1-carboxamide **11** in 55% yield (eq 2).



(2)

In conclusion, we have developed a novel method for stereoselective synthesis of 2-carbamoyl-2-cyanocyclopropanecarboxylates by tandem iodine(III)-induced oxidative cyclization, followed by a neighboring group-assisted decarboxylation. This reaction proceeds smoothly to afford the desired highly functionalized cyclopropane in good yield under mild conditions with good functional group tolerance. The future direction for the research will be extending the scope and potential synthetic applications, as well as investigation of asymmetric transformations.

Experimental Section

General Experimental Procedure. The mixture of Michael adduct **6** (0.2 mmol) with PhIO (88 mg, 0.4 mmol) in THF (2 mL) was treated with Bu_4NI (148 mg, 0.4 mmol). The reaction was allowed to stir at 25 °C for 1 h. Upon completion by TLC, the reaction mixture was quenched with saturated $Na_2S_2O_3$ (25 mL) and extracted by ethyl acetate (25 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (15% ethyl acetate in hexanes) to provide 2-carbamoyl-2-cyanocyclopropane carboxylate **4**.

Product 4a: colorless solid; mp 148−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1 H), 7.70 (d, J = 8.7 Hz, 2 H), 7.64 (d, J = 8.7 Hz, 2 H), 7.36−7.40 (m, 5 H), 4.18−4.21 (m, 2 H), 3.61 (d, J = 10.4 Hz, 1 H), 3.17 (d, J = 10.4 Hz, 1 H), 1.20 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 161.9, 139.6, 130.4, 129.1,128.8, 128.6, 128.4, 126.5, 126.4, 120.2, 115.7, 62.1, 37.1, 34.6, 27.5, 13.9; IR (KBr) 2955, 2924, 2843, 2249, 1736, 1697, 1605, 1535, 1409 cm^{-1}; HRMS m/z calcd for $C_{21}H_{17}F_3N_2NaO_3$ ([M + Na]$^+$) 425.1089, found 425.1051.

Acknowledgment. Financial support from the National Natural Science Foundation of China (20702006) and Shanghai Key Laboratory of Molecular Catalysts and Innovative Materials, Department of Chemistry, Fudan University (2009KF02), is gratefully acknowledged.

Supporting Information Available: Experimental procedures, characterization data, copies of ^{1}H NMR and ^{13}C NMR of new compounds, and crystallographic data of compound **4a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

(14) For selected examples on MIRC reactions, see: (a) Zwanenburg, B.; De Kimpe, N. In *Houben−Weyl*, 4th ed.; de Meijere, A., Ed.; Thieme: Stuttgart, 1997; Vol. E17a, p 69. (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (c) Kozhushkov, S. I.; Leonov, A.; De Meijere, A. *Synthesis* **2003**, 956. (d) Giubellina, N.; De Kimpe, N. *Synlett* **2005**, 976. (e) Peppe, C.; das Chagas, R. P.; Burrow, R. A. *J. Organomet. Chem.* **2008**, *693*, 3441. (f) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041. (g) Bagnoli, L.; Scarponi, C.; Testaferri, L.; Tiecco, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1506. (h) Marini, F.; Sternativo, S.; Del Verme, F.; Testaferri, L.; Tiecco, M. *Adv. Synth. Catal.* **2009**, *351*, 1801.

(15) Shchepin, V. V.; Silaychev, P. S. *Chem. Heterocycl. Compd.* **2005**, *41*, 1545.

(16) Nagata, K.; Sano, D.; Shimizu, Y.; Miyazaki, M.; Kanemitsu, T.; Itoh, T. *Tetrahedron: Asymmetry* **2009**, *20*, 2530.