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A New H_2O_2/Acid Anhydride System for the Iodoarene-Catalyzed C−C Bond-Forming Reactions of Phenols

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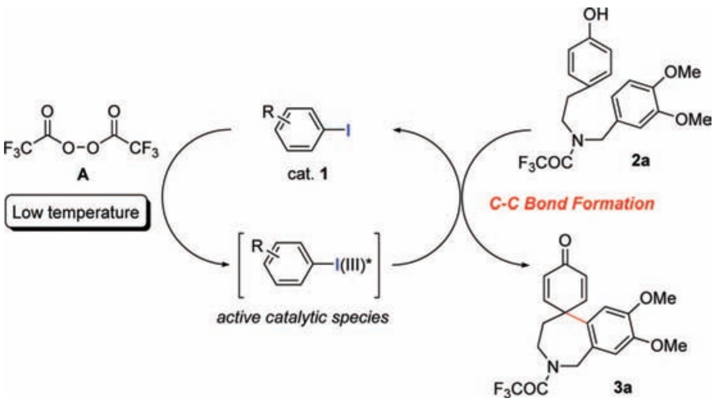
ABSTRACT



We have succeeded in the first versatile iodoarene-catalyzed C−C bond-forming reactions by development of a new reoxidation system at low temperatures using stoichiometric bis(trifluoroacetyl) peroxide A in 2,2,2-trifluoroethanol (TFE). The catalytic system supplies a wide range of substrates and functional availabilities sufficient to be used in the key synthetic process of producing biologically important Amaryllidaceae alkaloids.

The catalytic utilization of hypervalent iodine reagents is increasing in importance, with recent growing interest in the development of environmentally benign synthetic transformations.[1] After the reports of the catalytic reactions using *m*-chloroperbenzoic acid (*m*-CPBA) as the terminal oxidant,[2–4] applications of a variety of useful organoiodine compounds as catalysts that are recyclable[2,4a,b] and chiral[4c] have significantly increased. In this way, the catalytic concept surely contributes to the progress of hypervalent iodine chemistry in organic synthesis.[5]

On the other hand, the most important type of reactions, *the carbon−carbon bond forming reactions*, has never been catalytically accomplished under these conditions. The C−C bond-forming methods mediated by hypervalent iodine reagents significantly comprise some key steps in constructing the structures of various biologically active compounds and natural products.[6] To expand the scope of the catalytic strategy, it is highly important to survey alternative effective terminal oxidants enabling the generation of active iodine(III) species under mild conditions. In this paper, the C−C bond-forming transformations are made catalytic by establishing

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(1) (a) Dohi, T.; Kita, Y. *Kagaku* **2006**, *61*, 68. (b) Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4402.

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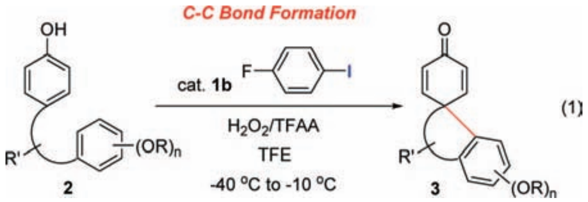
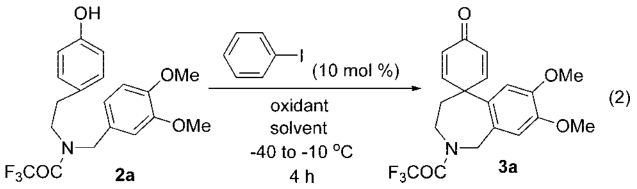
a new reoxidation system using the H_2O_2/acid anhydride, in which the active hypervalent iodine(III) species is rapidly generated in situ at low temperatures. The catalytic reactions of phenols **2a**−**g** furnished the key spiro C−C bonds of the galanthamine-type Amaryllidaceae alkaloids,[6a,b] and hence, it is, we believe, the first successful example utilizing this catalytic concept for the key steps of natural product syntheses (eq 1).



(1)

Table 1. Effect of the Oxidant, Solvent, and TFAA



(2)

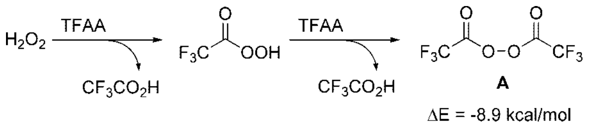
entry	oxidant[a]	solvent	TFAA (equiv)	yield[b] (%)
1[c,d]	*m*-CPBA	CH_2Cl_2	none	36
2[d]	*m*-CPBA	CH_2Cl_2	none	17
3[d]	*m*-CPBA	TFE	none	45
4	urea·H_2O_2[e]	TFE	4	8
5	urea·H_2O_2	TFE	6	60
6	urea·H_2O_2	TFE	8	70
7	H_2O_2 (35%)	TFE	8	16
8	Na_2O_2	TFE	8	28

[a] 2 equiv relative to **2a**. [b] Isolated yield. [c] Reaction was performed at room temperature. [d] CF_3CO_2H (1 equiv) was added. [e] 4 equiv of urea·H_2O_2 was used.

Amaryllidaceae alkaloids are known to have diverse pharmacologic actions and potentially new biological activities.[7,8] Our challenge was the realization of the catalytic oxidative spirocyclization of **2a** to **3a**, as a landmark and versatile catalytic C−C bond-forming process (Table 1, eq 2). Relying on our previous reoxidation conditions of iodoarenes using *m*-CPBA as the terminal oxidant,[2] we first developed the reaction at room temperature in CH_2Cl_2 which only resulted in the low yield of **3a** along with the decomposition of a large amount of **2a** (Table 1, entry 1). Since the conversion of iodobenzene to the corresponding iodine(III) forms was possible, we assumed that the decomposition of **2a** was due to the involvement of some unstable intermediates for **3a**, which are too reactive at ambient temperature.[9] By lowering the reaction temperature the yield may be improved, but *m*-CPBA is not the best oxidant for the generation of iodine(III) species from iodoarenes at low temperatures due to issues of reactivity and solubility regarding the solvents (Table 1, entries 2 and 3).

Trifluoroperacetic acid, CF_3CO_3H, is a powerful oxidant that can oxidize iodoarenes to the corresponding iodine(III) at lower temperatures.[10] On the basis of the recent reports on the in situ preparation method of CF_3CO_3H,[10c] we investigated the catalytic reactions at low temperature under several modified conditions. In this screening, CF_3CO_3H itself was also not suitable for the catalytic process in 2,2,2-trifluoroethanol (TFE) (Table 1, entry 4). Meanwhile, we noted that the increasing ratio of TFAA relative to H_2O_2 led to an improvement in the yield of **3a**, even though the amount of the oxidant decreased (Table 1, entries 5 and 6). This interesting outcome is rationalized by considering the formation of the alternative oxidant, bis(trifluoroacetyl) peroxide **A** (Scheme 1).[11] Thus, the treatment of H_2O_2 with excess TFAA led to the exclusive formation of anhydride **A**, which was also supported by the calculations.[11b] Other screenings

Scheme 1. Formation of Bis(trifluoroacetyl) Peroxide **A**



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(4) Other examples: (a) Yamamoto, Y.; Kawano, Y.; Toy, P. H.; Togo, H. *Tetrahedron* **2007**, *63*, 4680. (b) Akiike, J.; Yamamoto, Y.; Togo, H. *Synlett* **2007**, 2168. (c) Richardson, R. D.; Page, T. K.; Altermann, S.; Paradine, S. M.; French, A. N.; Wirth, T. *Synlett* **2007**, 538.

(5) For recent reviews of hypervalent iodine chemistry, see: (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (b) Kita, Y.; Takada, T.; Tohma, H. *Pure Appl. Chem.* **1996**, *68*, 627. (c) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, 1997. (d) Ochiai, M. In *Chemistry of Hypervalent Compounds*; Akiba, K., Ed.; Wiley-VCH: New York, 1999; Chapter 12. (e) Koser, G. F. *Aldrichim. Acta* **2001**, *34*, 89. (f) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (g) *Hypervalent Iodine Chemistry*; Wirth, T., Ed.,; Springer-Verlag: Berlin, Heidelberg, 2003. (h) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656. (i) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893.

(6) (a) Studies in our laboratory: Kita, Y.; Takada, T.; Gyoten, M.; Tohma, H.; Zenk, M. H.; Eichhorn, J. *J. Org. Chem.* **1996**, *61*, 5857. (b) Kita, Y.; Arisawa, M.; Gyoten, M; Nakajima, M.; Hamada, R.; Tohma, H.; Takada, T. *J. Org. Chem.* **1998**, *63*, 6625. (c) Kita, Y.; Tohma, H.; Inagaki, M.; Hatanaka, K.; Yakura, T. *J. Am. Chem. Soc.* **1992**, *114*, 2175. (d) Tohma, H.; Harayama, Y.; Hashizume, M.; Iwata, M.; Egi, M.; Kita, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 348.

(7) Recent reports: (a) Marco-Contelles, J.; Carreiras, M. C.; Rodriguez, C.; Villarroya, M.; Garcia, A. G. *Chem. Rev.* **2006**, *106*, 116. (b) McNulty, J.; Nair, J. J.; Codina, C.; Bastida, J.; Pandey, S.; Gerasimoff, J.; Griffin, C. *Phytochemistry* **2007**, *68*, 1068. (c) Unver, N. *Phytochem. Rev.* **2007**, *6*, 125.

(8) For synthetic studies using hypervalent iodine reagents, see ref 6a,b and others: (a) Kodama, S.; Takita, H.; Kajimoto, T.; Nishide, K.; Node, M *Tetrahedron* **2004**, *60*, 4901. (b) Kodama, S.; Hamashima, Y.; Nishide, K; Node, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2659. (c) Baxendale, I. R.; Deeley, J.; Griffiths-Jones, C. M.; Ley, S. V.; Saaby, S.; Tranmer, G. K. *Chem. Commun.* **2006**, *24*, 2566.

(9) Formation of reactive phenoxenium ions was proposed in iodine(III)-induced oxidations of phenols: (a) Moriarty, R. M.; Prakash, O. *Org. React.* **2001**, *57*, 327. (b) Kürti, L.; Herczegh, P.; Visy, J.; Simonyi, M.; Antus, S.; Pelter, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 379. (c) Pelter, A.; Ward, R. S. *Tetrahedron* **2001**, *57*, 273.

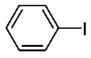
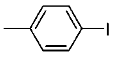
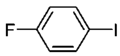
(10) Preparation of $PhI(OCOCF_3)_2$ using trifluoroperacetic acid: (a) Yagupolskii, L. M.; Maketina, I. I.; Kondratenko, N. V.; Orda, V. V. *Synthesis* **1978**, 835. (b) Zhdankin, V. V.; Scheuller, M. C.; Stang, P. J. *Tetrahedron Lett.* **1993**, *34*, 6853. (c) Page, T. K.; Wirth, T. *Synthesis* **2006**, 3153.

(11) (a) Sawada, H. *Chem. Rev.* **1996**, *96*, 1779. (b) Krasutsky, P. A.; Kolomitsyn, I. V.; Carlson, R. M. *Org. Lett.* **2001**, *3*, 2997.

of oxidants (Table 1, entries 7 and 8), solvents, and temperatures did not lead to a further improvement in the yield.

Once the basic conditions were established, we next tried to determine the appropriate iodoarene catalyst for the transformations (Table 2). For the loading of iodobenzene ranging from 10 mol % to 1 mol %, the catalyst turnover numbers (TONs) were 7−16 times (Table 2, entry 1). 4-Iodotoluene **1a**, the most efficient catalyst for the C−O and C−N bond-forming spirocyclizations of the phenols,[2] was an inferior catalyst in this case because of the low solubility of **1a** in TFE at the lower temperature (Table 2, entry 2). Therefore, the use of an affinity catalyst **1b** to TFE is critical for enhancing the TON (Table 2, entry 3). The para-substituted **1b** well maintained the catalytic activities during the reactions over iodobenzene, and the TON of the catalyst reached 44 s.

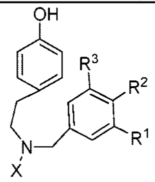
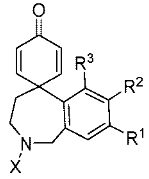
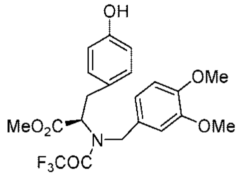
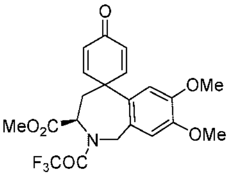
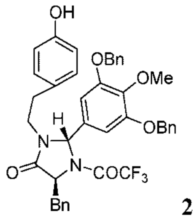
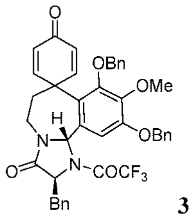
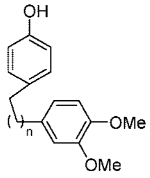
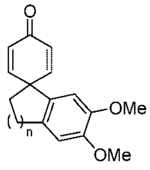
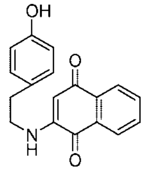
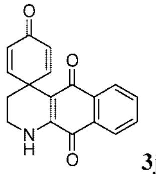
Table 2. Comparison of the Catalytic Activities[a]

entry	iodoarene	loading (mol %)			
		10	5	2.5	1
1		70% (4 h)	61% (7 h)	40% (16 h)	-
2	 **1a**	63% (3 h)	41% (7 h)	36% (16 h)	-
3	 **1b**	76% (2 h)	70% (3 h)	55% (4 h)	44% (4 h)

[a] Reactions were performed under the conditions of entry 6 in Table 1. The percentages indicate the isolated yield of **3a**.

The optimized catalytic conditions with **1b** allowed the versatile C−C bond-forming method for constructing a wide range of spirodienone structures (Table 3).[12] The catalytic reactions successfully offered a family of valuable nitrogen-containing seven-membered ring products **3a**−**g** in moderate to good yields (Table 3, entries 1−7). In these cases, compatibility of the highly functionalized substrates should be noted. Even substrate **2g**[8b] having an oxidizable poly oxygenated ring and active benzyl position afforded the tetracyclic **3g** in a moderate yield, despite the need for the higher loading of **1b** (Table 3, entry 7). Similar to the Amaryllidaceae alkaloid precursors, the alkyl-tethered products **3h** and **3i** were obtained using the catalytic method (Table 3, entries 8 and 9). Thus, it is a general method for the production of five- to seven-membered spirodienones by forming spiro C−C bonds. Moreover, the enamino ketone structures also work as the nucleophilic partner. The phenol **2j**, having an enamino ketone tether, under these conditions afforded **3j**, a model substrate of the discorhabdin marine alkaloids,[6c,d] in 46% yield with the 53% recovery of **2j** (Table 3, entry 10). In all cases, the successful transformations depended on both the selection of the terminal oxidant, TFE solvent, and the temperatures.

Table 3. C−C Bond-Forming Spirocyclization of Phenols **2**[a]

entry	substrate (**2**)		product (**3**)		yield, time
	 **2a-e**		 **3a-e**		
	X	R^1	R^2	R^3	
1	$COCF_3$	OMe	OMe	H	76%, 2 h
2	Boc	OMe	OMe	H	59%, 2 h
3	$COCF_3$	$-OCH_2O-$		H	80%, 4 h
4	$COCF_3$	OBn	OMe	OBn	56%, 3 h
5	$COCF_3$	OBn	Br	OBn	55%, 4 h
6	 **2f**		 **3f**		73%, 2 h
7[b]	 **2g**		 **3g**		51%, 3 h
	 **2h, i**		 **3h, i**		
8		n = 1			74%, 1 h
9		n = 2			64%, 3 h
10	 **2j**		 **3j**		46%, 24 h (98%)[c]

[a] Performed using **1b** (10 mol %), urea•H_2O_2 (2 equiv), and TFAA (8 equiv) in TFE at −40 to −10 °C otherwise noted. [b] 20 mol % of **1b** was used. [c] Isolated yield based on the reacted **2j**.

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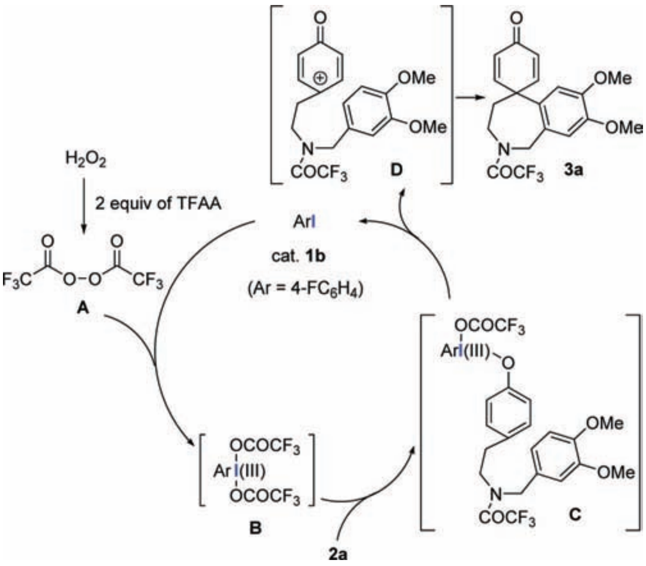
(12) **General Experimental Procedure.** To a stirred solution of urea•H_2O_2 (94 mg, 1 mmol) in TFE (5 mL) was added TFAA (0.60 mL, 4 mmol) at −40 °C. After 30 min, 4-fluoroiodobenzene **1b** (11.1 mg, 0.05 mmol) and phenol **2a** (191.7 mg, 0.5 mmol) were quickly added, and the temperature was allowed to warm slowly toward −10 °C. After addition of AcOEt, the reaction mixture was quenched with aqueous satd sodium thiosulfate and washed with satd $NaHCO_3$ aqueous. The aqueous layer was extracted using AcOEt, and the combined organic phase was washed with brine and then dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (eluent: hexane/AcOEt = 1/1, ca. 300 mL) to give **3a** in 76% yield (144.6 mg, 0.38 mmol) as colorless crystals. The spectroscopic data (^1H and ^{13}C NMR, IR) and mp were consistent with the values from a previous report.[6a]

When the reaction was performed in the absence of the phenols **2**, detection of the active catalytic species in the reactions was anticipated. After the reaction of **1b** at −10 °C for 2 h in TFE, the solvent was removed and the resulting residue was subjected to a ^{1}H NMR analysis in $CDCl_3$. The ^{1}H NMR observation indicated the presence of $4\text{-}FC_6H_4I(OCOCF_3)_2$ **B**[13] as the major species.[14] At this stage, we assumed that the active catalytic species in TFE is **B** itself or its derivatives including the solvent as a ligand (Scheme 2).[15]

Scheme 2. A Plausible Catalytic Cycle



The catalytic cycle should be initiated by the generation of the catalytic iodine(III) species **B** from **1b** by the action of a stoichiometric oxidant under suitable conditions not causing any undesired substrate oxidation. The selection of bis(trifluoroacetyl) peroxide **A** seems to be best suited for the selective oxidation of iodine(I) to the iodine(III) states at low temperatures. The formed iodine(III) species **B** then reacts with the phenolic oxygen of **2a** to produce the type **C** phenoxy iodine(III) intermediates. The liberation of **1b** results in the formation of the phenoxenium ion **D**,[9] which is stabilized by the polar cation-stabilizing solvent, TFE. At low temperatures, the reactive cationic intermediate would be selectively trapped by the internal π-nucleophile at the *ipso*-carbon, to give the final spirocyclized product **3a**. Therefore, the appropriate choices of the terminal oxidant, solvent, and reaction temperature are of considerable significance.

In conclusion, we have established new catalytic conditions at low temperatures involving the bis(trifluoroacetyl) peroxide **A** as a real stoichiometric oxidant for the first effective iodoarene-catalyzed C−C bond forming reactions of phenols **2** that form a series of spirocyclic dienones **3** including the key intermediates for the biologically active Amaryllidaceae alkaloids.

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Supporting Information Available: The experimental procedures and detailed spectroscopic data containing ^{1}H NMR charts of the new compounds and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] Kazmierczak, P.; Skulski, L. *Molecules* **2002**, *7*, 810.

[14] In the control experiment, $4\text{-}FC_6H_4I(OCOCF_3)_2$ **B** was isolated in a nearly quantitative yield after evaporation of TFE, although a trace amount of the μ-oxo-bridged iodine(III) dimer $[4\text{-}FC_6H_4I(OCOCF_3)]_2O$ **B′** was also detected. See the Supporting Information, Chart 1.

[15] On the iodine(III) species including alcohol solvents as ligands: (a) Schardt, B. C.; Hill, C. L. *Inorg. Chem.* **1983**, *22*, 1563. (b) Silva, L. F., Jr.; Lopes, N. P. *Tetrahedron Lett.* **2005**, *46*, 6023. See also ref 5i.