Construction of Aromatic [5,5] Spiroketals via Hypoiodite-Catalyzed Etherification Combined in Relay Cascades
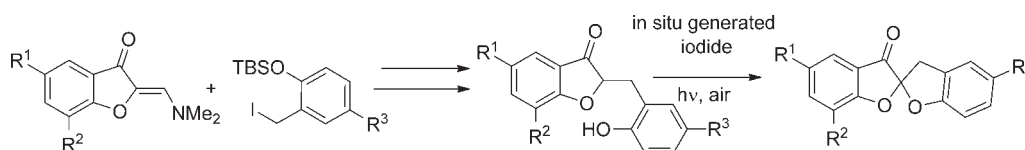
Wei Wei, Yao Wang, Jianpeng Yin, Jijun Xue,* and Ying Li*

State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, P.R. China

xuejj@lzu.edu.cn; liying@lzu.edu.cn

ABSTRACT

An approach is developed for the synthesis of bisbenzannelated spiro[5,5]ketals via a catalytic relay reaction cascade involving a new cyclo-etherification, which is prompted by fluoride and catalyzed by the hypoiodite species generated in situ from irradiative aerobic oxidation of an iodide ion formed in the former step of the reaction cascade.

Intramolecular α-oxyphenylation of carbonyl compounds has proven to be highly useful for the formation of oxa-benzocycles.[1] Generally, oxidative conditions are used in α-oxyphenylation. There are relatively few reports of the α-oxyphenylation of carbonyl compounds, making investigations on new conditions and their adaptability necessary and worthwhile. Organohypervalent iodine reagents have attracted significant recent interest as versatile and environmentally benign oxidants with many applications in organic synthesis.[2,3] Most recent research found organohypervalent iodine reagents useful for the α-cyclo-etherification of carbonyl compounds, which may be applicable for the construction of bisbenzannulated spiroketals.

For synthetic chemists, developing efficient and elegant chemical processes that allow for the rapid creation of skeleton-defined molecular complexity and diversity is still valuable and challenging work.[4] To achieve this goal, cascade reactions have been considered as one of the most effective approaches, in which multiple transformations have occurred in a single vessel and increase resource efficiency for the overall process.[5] Furthermore, the combination of two catalysts has been elegantly employed in one-pot and in cascade reactions.[6,7] In particular, catalysts with orthogonal, but mutually compatible, reactant activation modes have proven to be ideal catalysts for the relay catalysis.[8] This development is very interesting in that the

(1) (a) Uyanik, M.; Okamoto, H.; Yasui, T.; Ishihara, K. *Science* **2010**, *328*, 1376–1379. (b) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5331–5334.

(2) (a) Quideau, S.; Lyvinec, G.; Marguerit, M.; Bathany, K.; Ozanne-Beaudenon, A.; Buffeteau, T.; Cavagnat, D.; Chénedé, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4605–4609. (b) Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3787–3790. (c) Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2175–2177. (d) Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4402–4404. (e) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299–5358. (f) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073–2085. (g) Uyanik, M.; Ishihara, K. *Chem. Commun.* **2009**, 2086–2099.

(3) Zhdankin, V. V. *J. Org. Chem.* **2011**, *76*, 1185–1197.

(4) (a) Reetz, M. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 284–310. (b) Wu, C. Y.; Chang, C. F.; Szu, J.; Chen, Y.; Wong, C. H.; Lin, C. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4661–4664. (c) Balkenhohl, F.; von dem Bussche-Hunnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed.* **1996**, *35*, 2288–2337. (d) Kodadek, T. *Chem. Commun.* **2011**, *47*, 9757–9763. (e) Duart, M. J.; Antón-Fos, G. M.; Alemán, P. A.; Gay-Roig, J. B.; González-Rosende, M. E.; Gálvez, J.; García-Domenech, R. *J. Med. Chem.* **2005**, *48*, 1260–1264.

(5) (a) Gehrmann, T.; Fillol, J. L.; Scholl, S. A.; Wadepohl, H.; Gade, L. H. *Angew. Chem., Int. Ed.* **2011**, *50*, 5757–5761. (b) Wang, L.; Peng, S. Y.; Wang, J. *Chem. Commun.* **2011**, *47*, 5422–5424. (c) Li, W. J.; Li, X.; Wu, W. B.; Liang, X. M.; Ye, J. X. *Chem. Commun.* **2011**, *47*, 8325–8327. (d) Padmanaban, M.; Biju, A. T.; Gloriu, F. *Org. Lett.* **2011**, *13*, 5624–5627. (e) Davies, K. A.; Wulff, J. E. *Org. Lett.* **2011**, *13*, 5552–5555.

(6) (a) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797. (b) Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2008**, *130*, 14452–14453. (c) Han, Z. Y.; Xiao, H.; Chen, X. H.; Gong, L. Z. *J. Am. Chem. Soc.* **2009**, *131*, 14452–14453. (d) Latheop, S. P.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13628–13630. (e) Wang, Y.; Han, R. G.; Zhao, Y. L.; Yang, S.; Xu, P. F.; Dixon, D. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9834–9838.

byproduct from the first cycle takes part in the subsequent reaction as a catalyst.
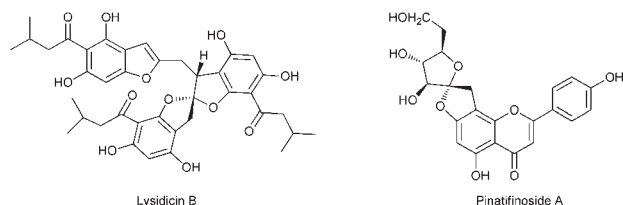

Figure 1. Natural products within spiro[5,5]ketal cores.

The reports on the synthesis of bisbenzannelated spiroketals especially spiro[5,5]ketal skeletons (Figure 1) have not fully elucidated them, despite the importance of these skeletons in the larger spirocycle family. Therefore, as a continuation of our previous work on the synthesis of spiroketal cores[9] and to relay the significance and novelty of the reaction cascade, we proposed to integrate the Hetero-Diels−Alder (HDA) reaction for a new, more combined relay catalysis, new transformation conditions, and a synthesis of the bioactive spiroketals. Through this investigation, three reactions were found to be combined in a reaction cascade, including a silica gel-mediated[10] hydrolyzation of amino acetal, silica gel-mediated decarbonylation of acetal, and in situ generated hypoiodite-catalyzed cyclo-etherification of carbonyl compounds. The cyclo-etherification in this case is a new catalytic application of hypoiodite reagents, in which two novelties are very important: (1) the hypoiodite in this transformation is generated from irradiative aerobic oxidation of iodide ion; (2) this is also a new oxidative nucleophile substitution of hydrogen prompted by fluoride. In this cascade, silica gel and TBAI acted as catalysts in succession, forming a catalytic relay. This is a new type of catalytic relay where TBAI, the byproduct of HDA reaction,[11] acted as a

catalyst in the α-oxyphenylation, which was the last step of the reaction cascade.

Our investigation was initiated by reacting HDA with **1a** and **2a**. In the presence of tetrabutylammonium fluoride

Scheme 1. Silica Gel-Mediated and Irradiative Reaction
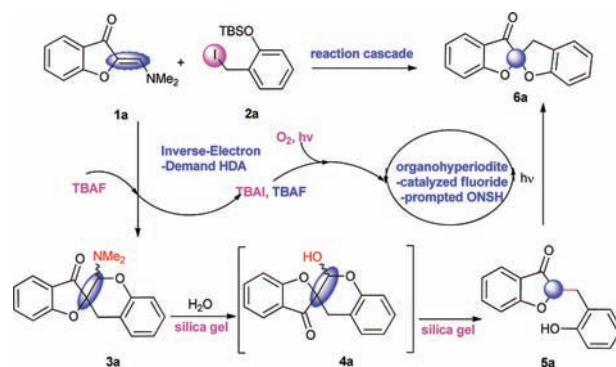
(TBAF), **2a** was deprotected and converted to a reactive species, *o*-quinone methide (*o*-QM), which was captured immediately and formed **3a**. However, when the crude HDA solution was eluted onto silica gel, **5a** along with a small amount of **4a** and **6a** was found, indicating that **3a** can be converted to **4a** or **5a** by silica gel. To investigate further, a successive experiment was performed. After the HDA reaction was completed, silica gel was added to the resultant solution in a clear round bottle flask in the daytime under natural light and stirred for several hours in petroleum ether (PE) in the air. Surprisingly, the yield of **6a** increased and **5a** formed subsequently decreasing with increasing reaction time. We postulated that the cascade reaction developed through the steps shown in Scheme 1. The HDA reaction formed the amino acetal **3a**, which then was hydrolyzed by H_2O under a silica gel reaction to yield the acetal **4a**. The subsequent degradation of **4a** under a silica gel reaction formed **5a**, which was converted to **6a** through the α-oxyphenylation of a carbonyl compound.

To demonstrate our postulation, purified **3a**[12] was treated with silica gel in petroleum ether, resulting in **5a** with a 93% yield and a small amount of **4a** being found in the residue in the initial stage of the process. This result clearly showed that **3a** converted to **5a** using **4a** as an intermediate.

Further optimization and substrate screening were conducted at each stage of the reaction. First, experiments were performed to optimize the HDA reaction.[13] Solvents at varying ratios of **1a**/**2a**/TBAF were screened. Dichloromethane (DCM) was found to be the best solvent, and the best result was obtained when the ratio of **1a**, **2a**, and TBAF of 1:2:2.8 was used. Subsequently, the sequence of adding substrates and reagents was also studied.

(7) (a) Enders, D.; Huettl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861–863. (b) Alabugin, I. V.; Gilmore, K.; Patil, S.; Manoharan, M.; Kovalenko, S. V.; Clark, R. J.; Ghiviriga, I. *J. Am. Chem. Soc.* **2008**, *130*, 11535–11545. (c) Liu, Y. H.; Song, F. J.; Guo, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 11332–11333. (d) Albert, B. J.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 2747–2749. (e) Enders, D.; Huettl, M. R. M.; Runsink, J.; Raabe, G.; Wendt, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 467–469. (f) Cui, H. F.; Dong, K. Y.; Zhang, G. W.; Wang, L.; Ma, J. A. *Chem. Commun.* **2007**, *43*, 2284–2286.

(8) (a) Dong, G. B.; Teo, P. L.; Wickens, Z. K.; Grubbs, R. H. *Science* **2011**, *333*, 1609–1612. (b) Chen, Q. A.; Wang, D. S.; Zhou, Y. G.; Duan, Y.; Fan, H. J.; Yang, Y.; Zhang, Z. *J. Am. Chem. Soc.* **2011**, *133*, 6126–6129.

(9) (a) Zhou, G. L.; Zhu, J. R.; Xie, Z. X.; Li, Y. *Org. Lett.* **2008**, *10*, 721–724. (b) Zhang, Y.; Xue, J. J.; Xin, Z. J.; Xie, Z. X.; Li, Y. *Synlett* **2008**, *6*, 940–944. (c) Xin, Z. J.; Zhang, Y.; Tao, H.; Xue, J. J.; Li, Y. *Synlett* **2011**, *11*, 1579–1584.

(10) (a) Zheng, H. J.; Zheng, J. Y.; Yu, B. X.; Chen, Q.; Wang, X. L.; He, Y. P.; Yang, Z.; She, X. G. *J. Am. Chem. Soc.* **2010**, *132*, 1788–1789. (b) Serra-Muns, A.; Guérinot, A.; Reymond, S.; Cossy, J. *Chem. Commun.* **2010**, *46*, 4178–4180. (c) Basu, B.; Paul, S.; Nanda, A. *Green Chem.* **2010**, *12*, 767–771. (d) Yadav, J. S.; Satheesh, G.; Murthy, C. V. S. R. *Org. Lett.* **2010**, *12*, 2544–2547.

(11) Barrero, A. F.; Quílez del Moral, J. F.; Mar Herrador, M.; Arteaga, P.; Cortés, M.; Benites, J.; Rosellon, A. *Tetrahedron* **2006**, *62*, 6012–6017.

(12) Compound **3** was purified by chromatography in a silica gel support doped with NEt_3.
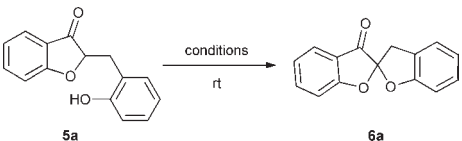
(13) See Supporting Information.

Using the modified conditions, the combination reaction of HDA/hydrolyzation of amino acetal/degradation of acetal was investigated with varied **1** and **2**. The main products of the reaction, **5a**–**5j**, are formed, and the yields were good to excellent. Similar to the HDA reactions, the yield of **5** changed with the change of the electronic effect of R^3.

This mechanism of the cyclo-etherification still does not specify the reagent and conditions that prompted the cyclization of **5a** to **6a**. To gain a better understanding of this process, a series of controlled experiments were conducted with the purified substrate **5a**. Initially, irradiation was screened. It was found that **6a** did not form in the dark (Table 1, entry 1). Furthermore, purified **5a** was treated under irradiative conditions, without any additives (Table 1, entry 2). However, neither natural light nor ultraviolet light produced a diagnosable reaction. Another controlled experiment was designed, and the reaction was carried out in the absolute absence of oxygen. Purified **5a** was treated with TBAI (20 mol %) and TBAF (30 mol %) under irradiation of UV light and an argon atmosphere. Dramatically, no reaction happened at all (Table 1, entry 3). This result showed that oxygen is obligatory for the transformation. So air and oxygen were introduced respectively into the reaction mixture of **5a**, TBAI, and TBAF in THF. Compound **6a** was obtained smoothly in moderate yield. This work describes a new method for the α-oxyphenylation of a carbonyl compound. All of these experiments showed that irradiation, TBAI, and oxygen are obligatory (Table 1, entry 4), TBAF is a good auxiliary reagent for this transformation (Table 1, entry 5), and oxygen gave better results than air (Table 1, entry 5, 6). At the same time, a hypothesis was proposed for the cyclo-etherification. The iodide may be oxidized to iodine by oxygen, and the iodine generated in situ catalyzed the cyclization. In order to prove this process, iodine was used to catalyze the reaction instead of TBAI. However, iodine gives an obviously lower yield than TBAI (Table 1, entry 7). Furthermore, increasing the amount of TBAF to 40 mol % increased the yield to 76% (Table 1, entry 8).

In this transformation, iodide was shown to be the main catalyst, with TBAF possibly acting as a cocatalyst. To the best of our knowledge, there is no precedent for the aerobic irradiative reactions catalyzed by iodide and prompted by fluoride for the α-oxyphenylation of carbonyl compounds, but our protocol described here provides a new synthetic mode.

According to the above results and the literature[14] on hypoiodite and oxidative cyclo-etherification, a mechnism was hypothesized as follows (Scheme 2): iodide was oxidized by oxygen to hypoiodite and fluoride promoted the enolization of ketone **5a** to **7a**. Then an eletrophilic substitution of **7a** and hypoiodite gave the iodo or hypoiodo **8a**. The subsequent intramolecular S_N1 displacement of an iodo or a hypoiodo group in **8a** by a phenolic hydroxyl
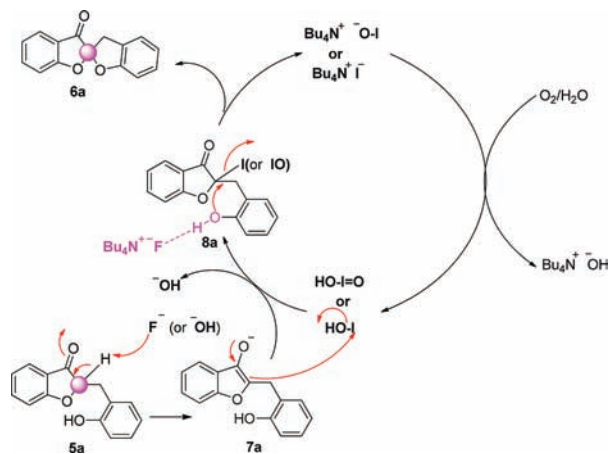
(14) Ochiai, M.; Takeuchi, Y.; Katayama, T.; Sueda, T.; Miyamoto, K. *J. Am. Chem. Soc.* **2005**, *127*, 12244–12245.

Table 1. Synthetic Conditions of Cyclization of Compound **6a**

entry	solvent	additive (mol %)	light source	atm	time (h)	yield[a,b] (%)
1	THF[c]	TBAI (20)	none	O$_2$/air	12	0
2	THF	none	natural light or UV[d]	O$_2$/air	12	0
3	THF	TBAI (20) TBAF (30)	UV	Ar	3	0
4	THF	TBAI (20)	UV	air	3	17
5	THF	TBAI (20) TBAF (30)	UV	air	3	44
6	THF	TBAI (20) TBAF (30)	UV	O$_2$	3	56
7	THF	I$_2$ (20) TBAF (30)	UV	air	3	26
8	THF	TBAI (20) TBAF (40)	UV	O$_2$	3	76

[a] Yields were calculated after column chromatography by silica gel. [b] Unless otherwise noted, all reactions were carried out with **5a** (0.1 mmol) in 3 mL of THF. [c] THF was dried by distillation over LiAlH$_4$. [d] Unless otherwise noted, photolysis was performed in a flask under irradiation at $\lambda = 200-700$ nm.

Scheme 2. Hypothesized Mechanism of Hypoiodite-Catalyzed Cyclo-etherification


group activated by a hydrogen bond with fluoride affords spiroketal **6a**.

Using the modified cyclo-etherification conditions (Table 1, entry 8), varied substrates were investigated in this transformation. Under irradiation of a UV lamp, the mixture of **5**, TBAI, and TBAF in THF formed **6** in moderate to good yields. Obviously, R^1, R^2, and R^3 have different effects on

Table 2. Synthesis of Varied Bisbenzannelated Spiro[5,5]ketals via Irradiative Aerobic Cyclization
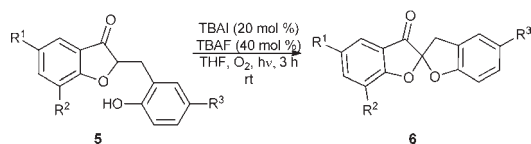
entry	R^1	R^2	R^3	products	yield[a] (%)
1	H	H	H	**6a**	76
2	H	H	Me	**6b**	83
3	H	H	Br	**6c**	69
4	H	H	COOEt	**6d**	60
5	H	MeO	Br	**6e**	59
6	H	MeO	COOEt	**6f**	55
7	MeO	H	Br	**6g**	64
8	MeO	H	COOEt	**6h**	60
9	Br	H	Br	**6i**	62
10	Br	H	COOEt	**6j**	59

[a] Unless otherwise noted, all reactions were carried out with compound **5** (0.1 mmol) in 3 mL of THF.

Table 3. Synthesis of Varied Compound **6** via Cascade Reaction

entry	R^1	R^2	R^3	products	yield[a,b] (%)
1	H	H	H	**6a**	59
2	H	H	Me	**6b**	60
3	H	H	Br	**6c**	47
4	H	H	COOEt	**6d**	42
5	H	MeO	Br	**6e**	40
6	H	MeO	COOEt	**6f**	37
7	MeO	H	Br	**6g**	48
8	MeO	H	COOEt	**6h**	46
9	Br	H	Br	**6i**	39

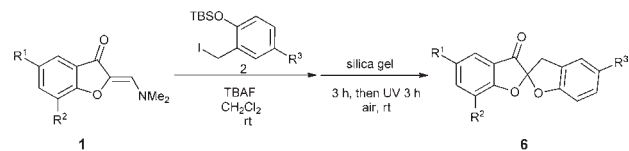[a] Yields were calculated after 4 steps and column chromatography by silica gel. [b] Unless otherwise noted, all reactions were carried out with compound **5** (0.25 mmol).

the conversion. The electron-donating R^1 group slightly decreased the yield (Table 2, entries 3 and 7, entries 4 and 8). The electron-donating R^2 group, however, obviously decreased the efficiencies (Table 2, entries 3 and 5, entries 4 and 6). In contrast to R^1 and R^2, the electron-donating R^3 group obviously increased the conversion (Table 2, entries 1, 2) and the substrate with an electron-withdrawing R^3 group gave a low yield (Table 2, entries 3, 4).

Finally, the entire cascade reaction was investigated, and the investigations showed that **6a**−**6j** were formed in moderate to good yields from **1a**−**1d** and **2a**−**2d**, which is summarized in Table 3. Of the tested substituents, R^3 had the most obvious effect on the conversion. Electron-donating R^3 groups benefited the conversion. Hence, the reaction of **1a** and **2b** was more efficient than that of **1a** and **2a**. **6d** gave the lowest yield when R^3 is an electron-withdrawing group.

In summary, a new approach toward the synthesis of the bisbenzannelated spiro[5,5]ketal cores has been developed. This approach involves a catalytic relay cascade of TBAF-induced HDA, silica gel-mediated hydrolyzation/degradation, and cyclo-etherification catalyzed by in situ generation of a hypoiodite catalyst based on the irradiative aerobic oxidation of an iodide ion. This is a new catalytic application of an organohypo iodite reagent and new fluoride-prompted oxidative nucleophilic substitution of aliphatic hydrogen. This approach also yielded an interesting new relay catalysis reaction, where the byproduct of the first transformation took part in the subsequent reaction cycle as a catalyst. We hope that this work will arouse more attention on multistep cascade reactions and the synthesis of spiroketal compounds.

Supporting Information Available. Experimental procedures, CIF files, and NMR spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.