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Tetraethylammonium Iodide Catalyzed Synthesis of Diaryl Ketones via the Merger of Cleavage of C-C Double Bond and Recombination of Aromatic Groups

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An efficient method for synthesizing diaryl ketones via merging of oxidative cleavage of C-C double bond and recombination of aromatic groups is developed with Et$_4$NI (2.5 mol%) as the catalyst and NaIO$_4$ as the oxidant. The control experiments provide valuable mechanistic insights into the formation of diaryl ketones, and suggest that NaIO$_4$ serves as epoxidation and nucleophilic deformylation reagents.

The oxidative cleavage of a carbon-carbon double bond is a fundamental transformation in organic synthesis.[1] Depending on the appropriate workup, the olefin could be directly cleaved into a variety of functionalized products, such as aldehydes, ketones and carboxylic acid. Ozonolysis[2] and Lemieux-Johnson protocol[3] are accepted as the principal methods for this direct transformation, however, their utilities generally suffer from the safety concerns. Alternative approaches were achieved through the transition metal catalysis including Ru,[4] Au,[5] Pd,[6] Os,[7] etc, a co-oxidant was required to regenerate the active catalyst for oxidative cleavage of olefins.[8] Also, the metal-free systems that employ equivalent oxidant such as aryl-λ^3-iodanes, phenyliodonium diacetate, were intensively studied.[9] Very recently, an environmentally benign *N*-hydroxyphthalimide or *tert*-butyl nitrite catalyzed aerobic oxidative cleavage of olefins to ketones has been developed.[10] The first example of biocatalytic regioselective oxidative cleavage of dialkenes was also successfully achieved with enzyme preparation from *Trametes hirsute*.[11] Despite great progress has been achieved in this field, almost all of these approaches involve the scission of 1,2-disubstituted alkenes to aldehydes or carboxylic acids, whereas ketone products are usually obtained from respective 1,1-disubstituted alkenes. However, the synthesis of diaryl ketone and heterocyclic ketone starting from easily available 1,2-disubstituted alkenes by R^1-C=C-R^2 bond cleavage reaction is rarely documented.[12]

Aryl ketones or diaryl ketones are an important class of compounds and widely used in the synthesis of various pharmaceuticals, natural products, agrochemicals and other functional materials;[13] therefore, the development of efficient way toward these compounds synthesis is highly desirable.[14] As a continuation of our interest in alkenes oxidation,[15] we aimed to extend iodine complexes catalyzed alkenes functionalization to carbonylation using hypervalent iodine as oxidant. Herein, we report the efficient catalyst system for removing a carbon atom from C-C double bond (R^1-C=C-R^2) via merging of oxidative cleavage and recombination of aromatic groups to synthesize symmetrical/unsymmetrical diaryl ketones, including the substrate scope, selectivity, and mechanistic studies. This method employs tetraethylammonium iodide as catalyst with NaIO$_4$ as terminal oxidant.
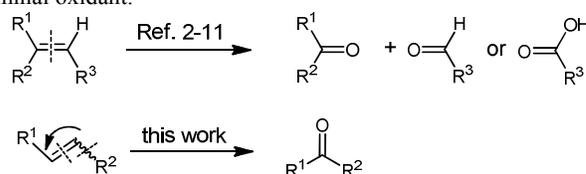

Scheme 1 The oxidative cleavage of alkenes.

An initial screening of the reaction conditions was performed with *trans*-stilbene (**1a**) as the model substrate, and the results were shown in Table 1. We chose tetraethylammonium iodide (Et$_4$NI) as catalyst and NaIO$_4$ as oxidant in MeCN, resulting in the desired benzophenone in trace at 105 ºC for 12 h (Table 1, entry 1). The result may ascribe to the bad solubility of NaIO$_4$ in MeCN. Gratifyingly, benzophenone was got in 53% by using the mixture solvent MeCN/H$_2$O (1:1) under the same conditions (entry 2). The choice of solvent appeared to be crucial, and water is one of the indispensable components. After rough test of the ratio of the mixed solvents and the kinds of the organic solvent, the acetonitrile-water system (4:1) gave the highest yield of benzophenone (entries 3-7). And the result indicated that only 11% yield of the benzophenone was gotten without Et$_4$NI as catalyst (entry 8). Other catalysts, such as CuI, I$_2$, (*n*-Bu)$_4$NI and (*n*-Bu)$_4$NBr were also investigated under the same reaction conditions (entries 9-12). Obviously, Et$_4$NI was the optimal catalyst (entry 4). The yield almost remained the same by elevating the temperature to 120 ºC, and lower reaction temperature resulted in reduced yield (entries 13 and 14). Other oxidants such as oxone and K$_2$S$_2$O$_8$ did not perform well (entries 15-16). Then, the loading of Et$_4$NI was examined (entries 17-19). To our delight, 91% yield of desired ketone was isolated when the catalyst loading was decreased from 10 mol% to 2.5 mol% (entry

18). Besides, the yield would decrease markedly by using only 2 equiv. NaIO$_4$ (entry 20). As a result, the reaction conditions described in entry 18 were selected as the standard conditions for further investigations.

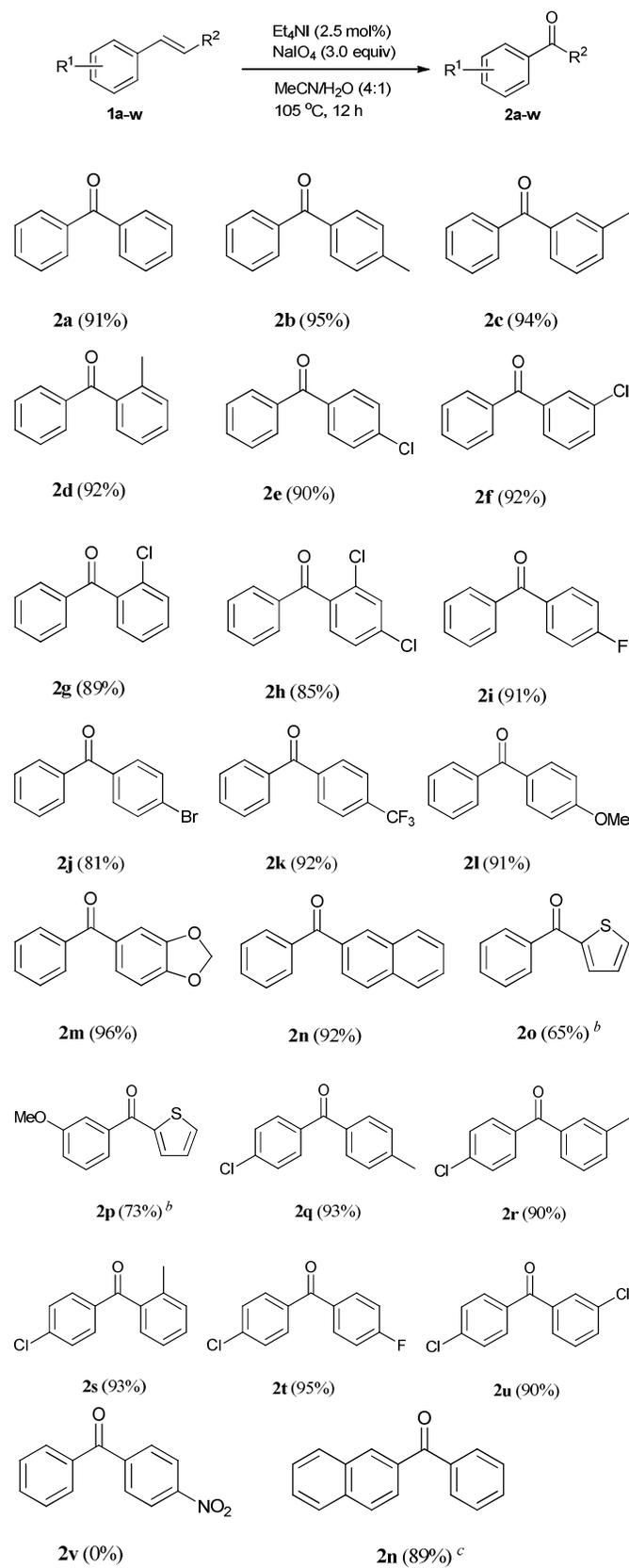**Table 1** Optimization of conditions for cascade oxidative cleavage of *trans*-stilbene[a]
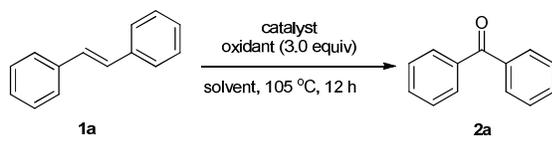
Entry	Solvent	Catalyst(mol%)	Oxidant	Yield[%][b]
1	MeCN	Et$_4$NI (10)	NaIO$_4$	trace
2	MeCN/H$_2$O (1:1)	Et$_4$NI (10)	NaIO$_4$	53
3	MeCN/H$_2$O(1:4)	Et$_4$NI (10)	NaIO$_4$	10
4	MeCN/H$_2$O (4:1)	Et$_4$NI (10)	NaIO$_4$	83
5	THF/H$_2$O (4:1)	Et$_4$NI (10)	NaIO$_4$	43
6	DMF/H$_2$O (4:1)	Et$_4$NI (10)	NaIO$_4$	trace
7	Acetone/ H$_2$O (4:1)	Et$_4$NI (10)	NaIO$_4$	11
8	MeCN/H$_2$O(4:1)	-	NaIO$_4$	11
9	MeCN/H$_2$O(4:1)	CuI (10)	NaIO$_4$	30
10	MeCN/H$_2$O(4:1)	I$_2$ (10)	NaIO$_4$	17
11	MeCN/H$_2$O(4:1)	(*n*-Bu)$_4$NI (10)	NaIO$_4$	78
12	MeCN/H$_2$O(4:1)	(*n*-Bu)$_4$NBr (10)	NaIO$_4$	41
13	MeCN/H$_2$O(4:1)	Et$_4$NI (10)	NaIO$_4$	81[c]
14	MeCN/H$_2$O(4:1)	Et$_4$NI (10)	NaIO$_4$	65[d]
15	MeCN/H$_2$O(4:1)	Et$_4$NI (10)	Oxone	47
16	MeCN/H$_2$O(4:1)	Et$_4$NI (10)	K$_2$S$_2$O$_8$	17
17	MeCN/H$_2$O(4:1)	Et$_4$NI (5)	NaIO$_4$	87
18	MeCN/H$_2$O(4:1)	Et$_4$NI (2.5)	NaIO$_4$	91
19	MeCN/H$_2$O(4:1)	Et$_4$NI (1)	NaIO$_4$	80
20[e]	MeCN/H$_2$O(4:1)	Et$_4$NI (2.5)	NaIO$_4$	41[f]

[a] Reaction conditions: **1a** (0.2 mmol), catalyst, oxidant (3.0 equiv.) and solvent (1.0 mL) at 105 ºC (oil bath temperature) for 12 h in a sealed tube. [b] Isolated yield. [c] The reaction was performed at 120 ºC for 12 h. [d] The reaction was performed at 95 ºC for 12 h. [e] NaIO$_4$ (2.0 equiv). [f] 20% Epoxide and 5% 2,2-diphenylacetaldehyde were obtained determined by GC.

To explore the generality and scope of the methodology, a variety of stilbene derivatives and styrenes were examined under the standard reaction conditions. As shown in Scheme 2, *trans*-stilbenes with different substituted groups at one of the aromatic rings (*ortho-*, *meta-* and *para*-position), such as CH$_3$, OCH$_3$, Cl, Br, F, CF$_3$, could be converted to the corresponding ketones **2a-n** in excellent yields. Furthermore, unsymmetrical heteroaromatic ketones containing thienyl group **2o**, **2p** were obtained in good yields at 130 ºC for 15 h. The reaction of *trans*-stilbenes with both substituted aromatic rings also proceeded well with excellent yields (Scheme 2, **2q-2u**). Unfortunately, *trans*-stilbene with strong electron-withdrawing group was inert in the catalytic system (Scheme 2, **2v**). Besides, the *cis*-stilbenes could be smoothly transformed into the desired ketone products in excellent yields under the standard reaction conditions (Scheme 2, **2n^c**). It should be noted that terminal alkenes such as styrene or 1,1-disubstituted alkenes could also be converted into the corresponding benzaldehyde or ketones in Et$_4$NI/NaIO$_4$ system as previously reported (see Supporting Information, Table S1 benzaldehyde **2x**, benzophenone **2a**, acetophenone **2z**).[5,10a]

A series of control experiments were carried out to gain insights into the reaction mechanism (Scheme 3). Recently, we developed a chemoselective protocol for the synthesis of benzil derivatives via oxidation of stilbenes in an I$_2$–H$_2$O system under air.[15b] Thus, the reaction was firstly carried out with benzil **3**, however, no further

Scheme 2 Cascade oxidative cleavage of various alkenes[a]

2a (91%) 2b (95%) 2c (94%)
2d (92%) 2e (90%) 2f (92%)
2g (89%) 2h (85%) 2i (91%)
2j (81%) 2k (92%) 2l (91%)
2m (96%) 2n (92%) 2o (65%) [b]
2p (73%) [b] 2q (93%) 2r (90%)
2s (93%) 2t (95%) 2u (90%)
2v (0%) 2n (89%) [c]

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reaction took place [Scheme 3, (I)]. Taking into account that NaIO₄ could be used as an oxidant for the epoxidation of olefins,[16] epoxide may be an intermediate of the present catalytic system. We were delighted to find that *trans*-stilbene oxide was converted to desired enzophenone in good yield (Scheme 3, (II)). 2-Iodo-1,2-diphenylethanol was thought to be a further intermediate generated from the ring-opening of *trans*-stilbene oxide, but it could not be synthesized because of its instability. Accordingly, 2-bromo-1,2-diphenylethanol **5** instead of 2-iodo-1,2-diphenylethanol was examined in the presence of NaIO₄ to give the benzophenone in 95% yield in the absence of Et₄NI [Scheme 3, (III)].
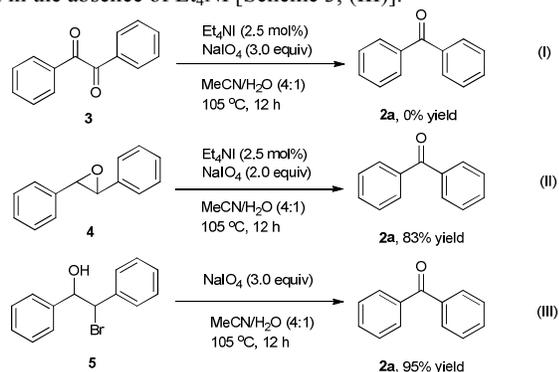
Scheme 3. Control experiments for proving the mechanism.

On the basis of these studies, the following tentative mechanism for this transformation is proposed (Scheme 4). Firstly, epoxide **A** was formed in the presence of Et₄NI/NaIO₄[17] and then it could be transferred to **B** via ring-opening reaction. The loss of iodide from **B** gives a carbocation intermediate **C**, which undergoes rearrangement to provide a more stable aldehyde **D**.[18] For the reaction of *trans*-stilbene, the corresponding *trans*-stilbene oxide and diphenylacetaldehyde could be observed during the reaction by GC-MS and ¹H NMR (see Supporting Information, Figure S1-7). Subsequently, aldehyde deformylation by a nucleophilic reaction with NaIO₄ takes place, providing the desired diarylketone **2**, along with the release of formic acid.[19]
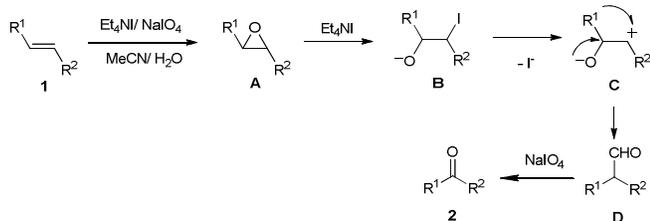
Scheme 4 Tentative mechanism for cascade oxidative cleavage of various alkenes.

Conclusions

In summary, we have developed an Et₄NI-catalyzed method for the synthesis of symmetrical/unsymmetrical diaryl ketones from stilbenes, through merging of oxidative cleavage and recombination of aromatic groups with NaIO₄. Through the mechanistic studies in this transformation, NaIO₄ may play dual roles, serving as epoxidation and nucleophilic deformylation regents. The further application of this methodology to other reactions is now in progress in our laboratory.

Notes and references

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[b] College of Biological, Chemical Sciences and Engineering, Jiaxing University, Jiaxing, 314001, China.
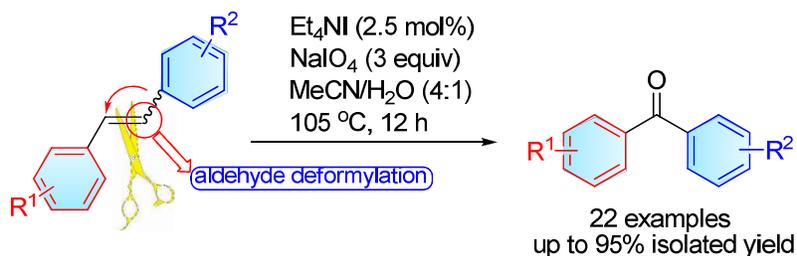
Electronic Supplementary Information (ESI) available: [Experimental procedures, NMR data and spectra of the products, GC-MS of mechanism study]. See DOI: 10.1039/c000000x/

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