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Metal-Free, Organocatalytic *Syn* Diacetoxylation of Alkenes

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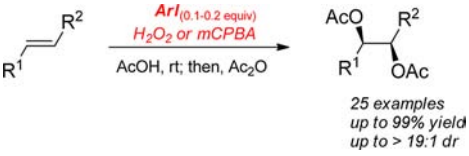
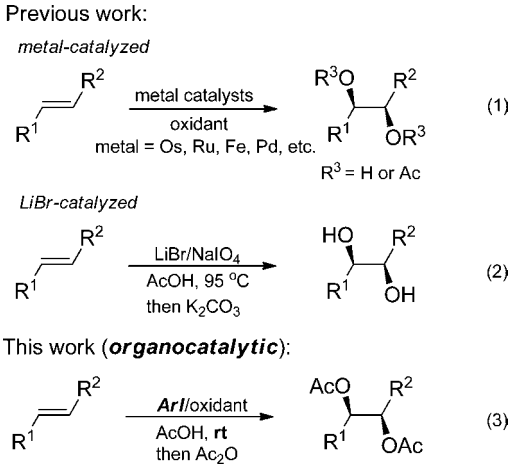
ABSTRACT



A novel method for the organocatalytic *syn* diacetoxylation of alkenes has been developed using aryl iodides as efficient catalysts. A broad range of substrates, including electron-rich as well as electron-deficient alkenes, are smoothly transformed by the new procedure, furnishing the desired products in good to excellent yields with high diastereoselectivity (up to >19:1 dr).

Metal-catalyzed dioxygenation of alkenes has emerged as one of the most powerful methods for the preparation of valuable *syn*-1,2-diols.[1] Among them, OsO_4-catalyzed *syn* dihydroxylation of alkenes along with its asymmetric version developed by Sharpless et al., has been elegantly demonstrated and widely used in organic synthesis.[2] Because of the high cost and toxicity of Os complexes, other alternative metal catalysts such as ruthenium,[3] manganese,[4] iron,[5] and palladium[6] have been applied to *syn* dioxygenation of alkenes (Scheme 1). However, most of the metal catalysts are costly and toxic to some degree, which limits their applications on an industrial scale. Therefore, the development of metal-free alkene *syn* dioxygenation procedures represents an attractive area of research. Herein, to the best of our knowledge,[7] we report the first organocatalytic *syn* diacetoxylation of alkenes by using aryl iodide as catalyst,[8] which was in situ oxidized to generate hypervalent iodine(III) species in the presence of peroxide.

Scheme 1. Catalytic *Syn* Dioxygenation of Alkenes



Although the metal-free dioxygenation of alkenes remains a fascinating objective, only a few methods have been described. In 2005, Sudalai and co-workers developed

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(3) Selected examples for ruthenium catalysis: (a) Ho, C.-M.; Yu, W.-Y.; Che, C.-M. *Angew. Chem., Int. Ed.* **2004**, *43*, 3303. (b) Plietker, B.; Niggemann, A.; Pollrich, A. *Org. Biomol. Chem.* **2004**, *2*, 1116. (c) Yip, W.-P.; Yu, W.-Y.; Zhu, N.; Che, C.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14239. (d) Yip, W.-P.; Ho, C.-M.; Zhu, N.; Lau, T.-C.; Che, C.-M. *Chem.—Asian J.* **2008**, *3*, 70. (e) Plietker, B.; Neisius, N. M. *J. Org. Chem.* **2008**, *73*, 3218.

(4) (a) Brinksma, J.; Schmieder, L.; van Vliet, G.; Boaron, R.; Hage, R.; De Vos, D. E.; Alsters, P. L.; Feringa, B. L. *Tetrahedron Lett.* **2002**, *43*, 2619. (b) de Boer, J. W.; Brinksma, J.; Browne, W. R.; Meetsma, A.; Alsters, P. L.; Hage, R.; Feringa, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 7990. (c) Chow, T. W.-S.; Liu, Y.; Che, C.-M. *Chem. Commun.* **2011**, 11204.

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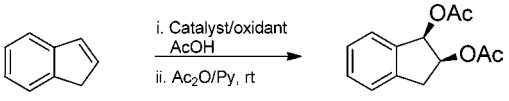
a catalytic version of the Woodward–Prevost reaction employing LiBr as the catalyst, and the *syn* dioxygenation products were obtained with high diastereoselectivities in the presence of $NaIO_4$ at a high temperature.[9] Quite recently, Tomkinson et al. reported an effective alkene *syn* dihydroxylation with malonoyl peroxides, and most of the products were obtained with excellent stereoselectivity.[8,10a] In recent years, there has been an increasing interest in the area of oxidative transformations mediated by hypervalent iodine reagents, owing to their good oxidizing properties and availability.[11] As one important application, hypervalent iodine reagent mediated alkene dioxygenation has been well developed recently.[12] However, stoichiometric use of hypervalent iodine leads to equimolecular amounts of aryl iodides as a waste and is mostly castigated by synthetic chemists. To address this issue, development of aryl iodide-based organocatalytic transformations has attracted much attention.[11b,13] In these reactions, aryl iodides are oxidized to hypervalent compounds, which then undergo oxidative reactions and release the aryl iodides to achieve a catalytic pathway. We envisioned that by employing an aryl iodide as a catalyst in the presence of an oxidant we might be able to realize a novel organocatalytic *syn* dioxygenation procedure for alkenes.

With this in mind, we began our studies with indene as a model substrate. When indene was reacted with iodobenzene (0.1 equiv) in the presence of H_2O_2 with $BF_3\cdot OEt_2$ as additive at room temperature, a good yield of the dioxygenated product was obtained, though in low diastereoselectivity (Table 1, entry 1). We inferred that the *anti* products, arose from oxidation of the substrate by peroxy compounds in two steps: epoxidation followed by a ring-opening process.[14] Further increasing of the loading of iodobenzene did not provide significant improvement in product yield and stereoselectivity. To our delight, oxidation was achieved in good yield as well as diastereoselectivity when the substrate was delivered slowly via syringe pump over 12 h (Table 1, entry 3). Moreover, detailed studies showed that employing TfOH[12c] as the additive was more efficient than $BF_3\cdot OEt_2$[12d,e] under these circumstances (see the Supporting Information). Subsequently, a series of aryl iodides bearing electron-withdrawing (Table 1, entries 5 and 6) or electron-donating (Table 1, entries 7–9) substituents were investigated, and the results indicated that iodomesitylene served as the most efficient catalyst for this transformation. The main reason for the enhanced reactivity of iodomesitylene is attributed to this aryl iodide with electron-donating groups being more easily oxidized to form the reactive hypervalent iodine(III) species, suppressing the unfavorable side reactions accordingly. Furthermore, lower catalyst loading also furnished the desired products in good yield, albeit with decreased diastereoselectivities (Table 1, entries 11 and 12).

Table 1. Optimization of Aryl Iodide Catalyzed Indene Diacetoxylation[a]



1a 2a

entry	catalyst (mol %)	additive (mol %)	yield[b] (%)	dr[c]
1	PhI (10)	$BF_3\cdot OEt_2$ (10)	71	3.7:1
2	PhI (20)	$BF_3\cdot OEt_2$ (10)	73	3.8:1
3[d]	PhI (20)	$BF_3\cdot OEt_2$ (10)	78	10:1
4	PhI (20)	TfOH (2)	82	12.5:1
5	4-IC_6H_4I (20)	TfOH (2)	78	10:1
6	4-ClC_6H_4I (20)	TfOH (2)	81	5.3:1
7	4-MeC_6H_4I (20)	TfOH (2)	84	12.5:1
8	4-$MeOC_6H_4I$ (20)	TfOH (2)	85	6.7:1
9	2,4,6-$Me_3C_6H_2I$ (20)	TfOH (2)	84	14:1
10	2,4,6-$Me_3C_6H_2I$ (20)	TfOH (5)	90	14:1
11	2,4,6-$Me_3C_6H_2I$ (15)	TfOH (5)	84	9:1
12	2,4,6-$Me_3C_6H_2I$ (10)	TfOH (5)	79	6:1
13	[e]	TfOH (5)	62	2:1
14	2,4,6-$Me_3C_6H_2I$ (20)	[e]	48	3.3:1

[a] 1.0 mmol scale of **1a**, 3.0 equiv of H_2O_2 (30%), 1.3 mL of Ac_2O, 2.0 mL of AcOH, rt; then 3.0 mL of pyridine and 0.7 mL of Ac_2O, rt. [b] Isolated yield. [c] Determined by ^{1}HNMR integration (*syn*/*anti*). [d] Entries 3–14: **1a** was added via syringe pump over 12 h. [e] Not added.

With the optimized conditions identified, we next explored the generality of this new procedure. As shown in Scheme 2, a variety of terminal alkenes, including

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(6) (a) Li, Y.; Song, D.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 2962. (b) Wang, A.; Jiang, H.; Chen, H. *J. Am. Chem. Soc.* **2009**, *131*, 3846. (c) Wang, W.; Wang, F.; Shi, M. *Organometallics* **2010**, *29*, 928. (d) Park, C. P.; Lee, J. H.; Yoo, K. S.; Jung, K. W. *Org. Lett.* **2010**, *12*, 2450. (e) Zhu, M.-K.; Zhao, J.-F.; Loh, T.-P. *J. Am. Chem. Soc.* **2010**, *132*, 6284. (f) Wang, A.; Jiang, H. *J. Org. Chem.* **2010**, *75*, 2321.

(7) Santi et al. developed a novel olefin dihydroxylation catalyzed by diphenyl diselenide, but the diastereoselectivity was dependent on the substrate: Santoro, S.; Santi, C.; Sabatini, M.; Testaferri, L.; Tiecco, M. *Adv. Synth. Catal.* **2008**, *350*, 2881.

(8) Schwarz, M.; Reiser, O. *Angew. Chem., Int. Ed.* **2011**, *50*, 10495.

(9) Emmanuvel, L.; Ali Shaikh, T. M.; Sudalai, A. *Org. Lett.* **2005**, *7*, 5071.

(10) Peroxide mediated dihydroxylation of alkenes: (a) Griffith, J. C.; Jones, K. M.; Picon, S.; Rawling, M. J.; Kariuki, B. M.; Campbell, M.; Tomkinson, N. C. O. *J. Am. Chem. Soc.* **2010**, *132*, 14409. (b) Yuan, C.; Axelrod, A.; Varela, M.; Danysh, L.; Siegel, D. *Tetrahedron Lett.* **2011**, *52*, 2540. (c) Jones, K. M.; Tomkinson, N. C. O. *J. Org. Chem.* **2012**, *77*, 921.

(11) Recent reviews, see: (a) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656. (b) Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4402. (c) Ochiai, M. *Chem. Rec.* **2007**, *7*, 12. (d) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (e) Ochiai, M.; Miyamoto, K. *Eur. J. Org. Chem.* **2008**, 4229. (f) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073. (g) Uyanik, M.; Ishihara, K. *Chem. Commun.* **2009**, 2086. (h) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (i) Zhdankin, V. V. *J. Org. Chem.* **2011**, *76*, 1185.

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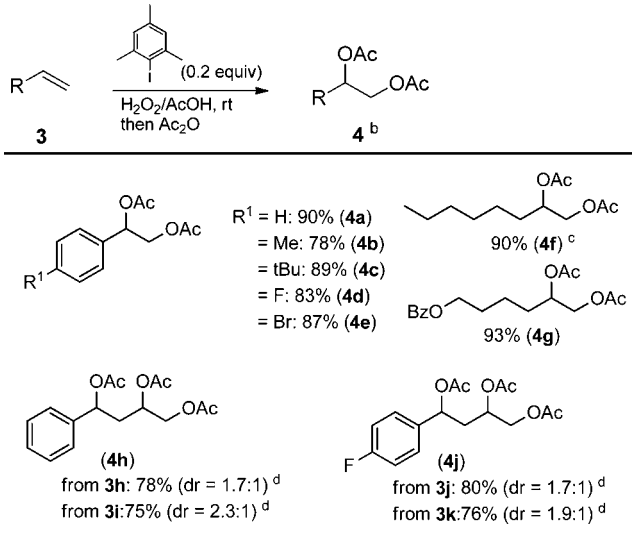
alkyl-substituted and aryl-substituted derivatives were efficiently elaborated to the corresponding products in good to excellent yield, merely catalyzed by iodomesitylene and H_2O_2 at ambient temperature. During the preparation of our manuscript, Gade et al.[15a] developed a triflic acid catalyzed diacetoxylation of alkenes in the presence of peroxyacids.[15] *m*-Chloroperbenzoic acid (*m*-CPBA) was necessary to improve the reaction efficiency in some cases, and the diacetoxylation of internal alkenes was usually obtained with low diastereoselectivity. In our procedure, all of the substrates were smoothly functionalized by using environmentally benign H_2O_2 as oxidant. In order to further investigate the stereoselectivity of this procedure, a series of internal alkenes were subjected to the standard conditions.

Significantly, most of the internal alkenes were compatible with this methodology and afforded the diacetoxylation products in moderate to excellent yield as well as

Scheme 2. Organocatalytic Diacetoxylation of Terminal Alkenes[a]



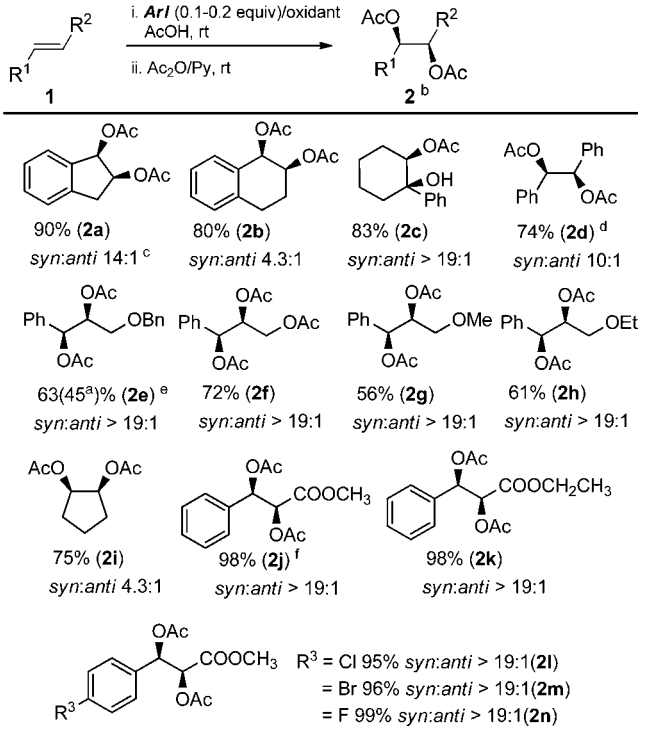
[a] Standard conditions, see Table 1, entry 10; then 0.7 mL Ac_2O, rt, overnight.

[b] Yield of isolated product.

[c] **4f**–**j**: Substrate was added over 24 h, and 0.1 equiv of TfOH was used.

[d] *Syn*/*anti*.

Scheme 3. Oganocatalytic *Syn* Diacetoxylation of Internal Olefins[a]



[a] Standard conditions, see Table 1, entry 10.

[b] Isolated yield.

[c] Determined by ^1H NMR integration.

[d] 0.2 equiv of PhI was used.

[e] **2e**–**i**: 0.2 equiv of 4-MeC_6H_4I; substrate was added over 24 h.

[f] **2j**–**n**: 4-MeC_6H_4I (0.1 equiv), $BF_3 \cdot OEt_2$ (3.0 equiv), *m*-CPBA (1.2–1.4 equiv) was added in two batches, rt.

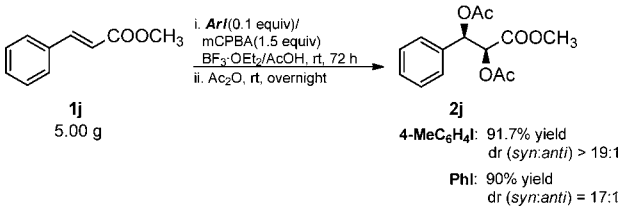
diastereoselectivity (summarized in Scheme 3), which represents an unprecedented oganocatalytic alkene *syn* dioxygenation. When cinnamyl benzyl ether was exposed to the standard procedure, a 45% yield of product was obtained (Scheme 3, **2e**). Gratifyingly, the use of 4-MeC_6H_4I as catalyst gave rise to a 63% yield. We reasoned that the low efficiency of iodomesitylene in this case might be due to steric preference for linear internal alkenes. Reactions of other cinnamyl alcohol derivatives catalyzed by 4-MeC_6H_4I furnished the desired products in moderate to good yield and excellent diastereoselectivity (Scheme 3, **2f**–**h**). However, attempts to perform the reaction with *trans*-methyl cinnamate resulted in trace amounts of product, and the majority of starting material recovered. Continuous efforts focused on searching for alternative oxidants, such as oxone, peracetic acid and *tert*-butyl hydroperoxide, but were unsuccessful. Finally, we found that 0.1 equiv of 4-MeC_6H_4I smoothly catalyzed

(13) Selected examples: (a) Ochiai, M.; Takeuchi, Y.; Katayama, T.; Sueda, T.; Miyamoto, K. *J. Am. Chem. Soc.* **2005**, *127*, 12244. (b) Dohi, T.; Maruyama, A.; Yoshimura, M.; Morimoto, K.; Tohma, H.; Kita, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 6193. (c) Sheng, J.; Li, X.; Tang, M.; Gao, B.; Huang, G. *Synthesis* **2007**, 1165. (d) Altermann, S. M.; Richardson, R. D.; Page, T. K.; Schmidt, R. K.; Holland, E.; Mohammed, U.; Paradine, S. M.; French, A. N.; Richter, C.; Bahar, A. M.; Witulski, B.; Wirth, T. *Eur. J. Org. Chem.* **2008**, 5315. (e) Miyamoto, K.; Sei, Y.; Yamaguchi, K.; Ochiai, M. *J. Am. Chem. Soc.* **2009**, *131*, 1382. (f) Uyanik, M.; Akakura, M.; Ishihara, K. *J. Am. Chem. Soc.* **2009**, *131*, 251. (g) Quideau, S.; Lyvinec, G.; Marguerit, M.; Bathany, K.; Ozanne-Beaudenon, A.; Buffeteau, T.; Cavagnat, D.; Chénedé, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4605. (h) Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2175. (i) Ngatimin, M.; Frey, R.; Andrews, C.; Lupton, D. W.; Hutt, O. E. *Chem. Commun.* **2011**, 11778. (j) Antonchick, A. P.; Samanta, R.; Kulikov, K.; Lategahn, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 8605. (k) Rodríguez, A.; Moran, W. J. *Org. Lett.* **2011**, *13*, 2220. (l) Miyamoto, K.; Sakai, Y.; Goda, S.; Ochiai, M. *Chem. Commun.* **2012**, 982.

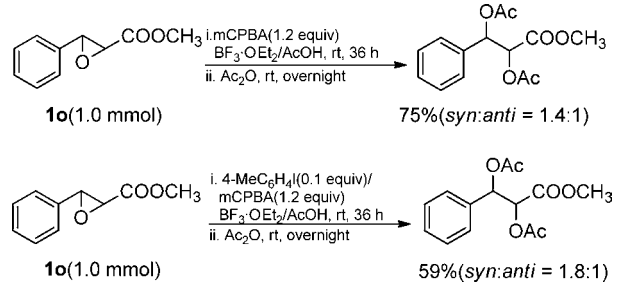
(14) Plesnicar, B. *Oxidations in Organic Chemistry*; Trahanovsky, W. S., Ed.; Academic Press: New York, 1978; Part C, p 211.

(15) Brønsted acid catalyzed dioxygenation of olefins: (a) Kang, Y.-B.; Gade, L. H. *J. Org. Chem.* **2012**, *77*, 1610. (b) Usui, Y.; Sato, K.; Tanaka, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5623. (c) Rosatellaa, A. A.; Afonsoa, C. A. M. *Adv. Synth. Catal.* **2011**, *353*, 2920.

Scheme 4. Multigram Scale *Syn* Diacetoxylation of Methyl Cinnamate



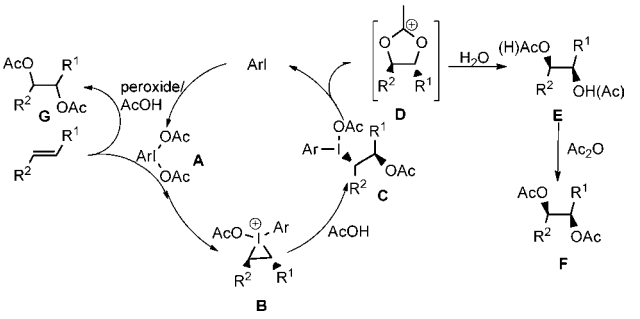
Scheme 5. Control Experiment



the dioxygenation of *trans*-methyl cinnamate applying *m*-CPBA as oxidant without slow addition of substrate, giving up to 98% yield and up to >19:1 (*syn*/*anti*) selectivity (Scheme 3, **2j**). Subsequent exploration of other methyl cinnamate derivatives also provided excellent yields as well as diastereoselectivities (Scheme 3, **2k**–**n**). Notably, a 5.00 g scale of reaction could be conducted, further demonstrating the synthetic practicality of this new procedure (Scheme 4).

When *trans*-methyl 2,3-epoxy-3-phenylpropanoate (**1o**) was subjected to the conditions, in the presence or absence of aryl iodide (Scheme 5), the diacetate products were obtained with low diastereoselectivities, indicating that an oxirane intermediate may not be involved in the selective *syn* dioxygenation process. A plausible mechanism is proposed in Scheme 6 which accords with the results mentioned above. As electron-rich alkenes tend to engage in epoxidation[14] in the presence of peroxide, leading to the poor stereoselective products (**G**), slow addition allows the substrate to be oxidized by the in situ generated hypervalent iodine(III) species (**A**) that is activated by TfOH[12c]

Scheme 6. Proposed Mechanism for Aryl Iodide Catalyzed Alkene *Syn* Dioxygenation



or $BF_3 \cdot OEt_2$[12d,e] and undergoes electrophilic addition to alkenes to yield intermediate **B**, providing the *syn* diacetates through a Woodward pathway (**B** to **F**). We found that electron-deficient alkenes (α,β-unsaturated esters) were tolerated with the oxidants, and most of the starting material was recovered in the absence of aryl iodide catalyst, in accord with the result that excellent diastereoselectivities were obtained without the slow addition procedure (Table 3, **2j**–**n**).

In summary, the first metal-free organocatalytic alkene *syn* diacetoxylation procedure has been developed through use of readily available aryl iodides as catalysts. A broad range of alkenes, electron-rich as well as electron-poor, were found to be well-tolerated, and the reactions could be carried out at room temperature. The procedure can also be applied on multigram scale to deliver the desired products in excellent yield as well as diastereoselectivity. Considering the mild conditions and environmental benignity, we anticipate that this new methodology may represent a valuable alternative to the existing metal-catalyzed methods.

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Supporting Information Available. All experimental procedures and data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.