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Orthogonally Protected 1,2-Diols from Electron-Rich Alkenes Using Metal-Free Olefin *syn*-Dihydroxylation

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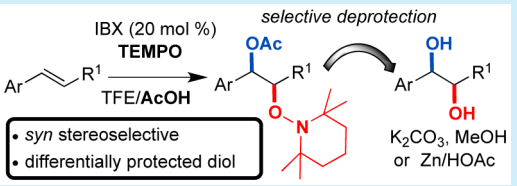
Supporting Information

ABSTRACT: A new method for the stereoselective metal-free *syn*-dihydroxylation of electron-rich olefins is reported, involving reaction with TEMPO/IBX in trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP) and the addition of a suitable nucleophile. Orthogonally protected *syn* 1,2-diols were obtained with high levels of diastereocontrol, and these products were selectively deprotected and selectively functionalized into synthetically useful compounds.



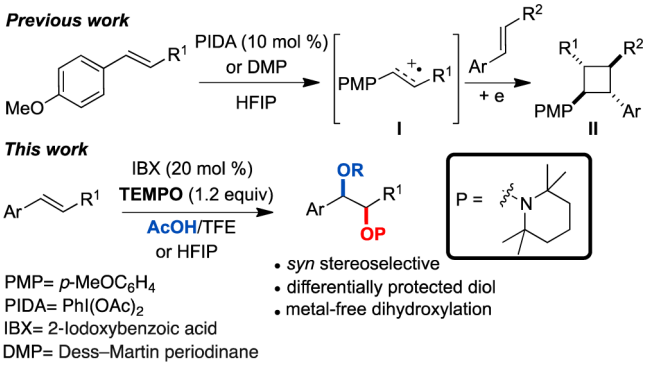
Olefin dihydroxylation is one of the most powerful tools in organic chemistry. The functionalization of vicinal carbons via double C−O bond formation can be achieved in a single step, and established dihydroxylation methods give high levels of stereospecificity.[1] In particular, OsO_4 has been used extensively in organic synthesis for the *syn* dihydroxylation of olefins, although its toxic nature is well recognized.

The development of new methods to overcome the use of toxic reagents is of great interest, and many groups have been devoted to finding new metal-free dihydroxylation procedures.[2] Peroxides,[3] hydroxamic acids[4] and hypervalent iodine reagents[5] used in stoichiometric amounts give good yields of *syn*-dioxygenation products, with modest to good diastereocontrol. Chiral hypervalent iodine reagents have also been used in diacetoxylation[6] and lactonization reactions.[7] In addition, the use of substochiometric amounts of hypervalent iodine reagents has been developed recently.[8] Alternatively the use of stable persistent radicals such as nitroxyl radicals, in particular (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), has allowed a breakthrough in this area.[9] Although great advances have been made in the functionalization of olefins using TEMPO, with an emphasis on stereoselective intermolecular aminooxygenation,[10] azidooxygenation,[11] oxyarylation,[12] and trifluorooxygenation,[13] the dioxygenation reaction itself remains underexplored.[14]

Following our recent research on the stereoselective synthesis of cyclobutanes **II** via oxidation of styrenes to a radical cation **I**, we became intrigued with the idea of trapping this radical cation intermediate (Scheme 1).[15] The use of TEMPO has led to the discovery of a new metal-free dihydroxylation process with the incorporation of both TEMPO and an external nucleophile (or the solvent in its absence).

We began using *trans*-anethole **1a** as a model alkene under previously optimized conditions for the synthesis of cyclobutanes (10 mol % of PIDA in hexafluoroisopropanol (HFIP) at rt), with the addition of 1.2 equiv of TEMPO as a radical trapping agent (Table 1, entry 1). The protected diol **2a** was obtained in 37% yield as a single *syn* diastereoisomer. Using hypervalent iodine(V) gave better results, with IBX as the most promising, affording **2a** in 66−76% yield (Table 1, entries 2 and 3).

Scheme 1. Metal-Free Dihydroxylation Using Hypervalent Iodine and TEMPO in Fluorinated Solvents



Changing to trifluoroethanol (TFE) gave no product with any of the hypervalent iodine reagents used (Table 1, entries 4−6).[16] Increasing the oxidant loading, using 20 mol % of IBX in HFIP, improved the yield up to 85% with high *syn* stereocontrol (Table 1, entry 7). Interestingly, the use of an acidic nonfluorinated solvent, such as AcOH, gave the analogous product **3a**, but with much lower diastereocontrol (Table 1, entry 8). In sharp contrast when using a polar protic but nonacidic solvent, such as EtOH, no product was observed. Finally, some control experiments were carried out without using any hypervalent iodine additive. While the use of TFE gave no reaction (Table 1, entry 10, in agreement with entries 4−6), surprisingly the reaction in HFIP or AcOH allowed isolation of the corresponding product **2a**/**3a** (Table 1, entries 11 and 12), in low yield (compare entries 11 vs 7 and 12 vs 8). It is also noteworthy that much better diastereocontrol is again observed with HFIP than with AcOH. Finally taking advantage of the lack of reactivity in TFE (compared to HFIP) using a 1:1 mixture of TFE/AcOH gave **3a**

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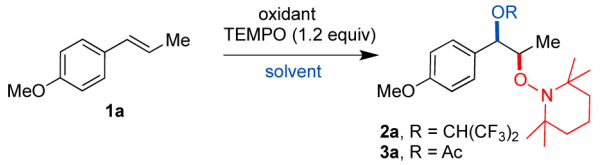
Table 1. Optimization of the Dioxygenation of 1a



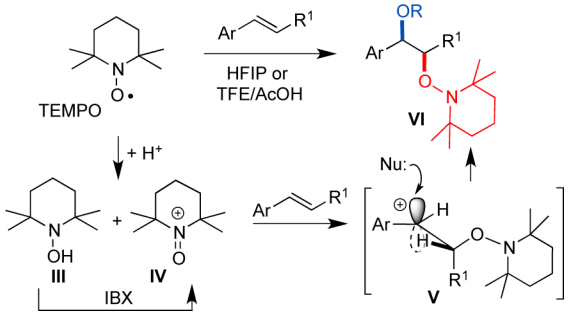
entry	solvent	oxidant	yield of **2** or **3** (%)	dr
1	HFIP	10 mol % PIDA	**2a** (37)	≥95:5
2	HFIP	10 mol % DMP	**2a** (66)	≥95:5
3	HFIP	10 mol % IBX	**2a** (76)	≥95:5
4[a]	TFE	10 mol % PIDA	0	–
5[a]	TFE	10 mol % DMP	0	–
6[a]	TFE	10 mol % IBX	0	–
7	HFIP	20 mol % IBX	**2a** (85)	≥95:5
8	AcOH	20 mol % IBX	**3a** (70)	60:40
9	EtOH	20 mol % IBX	0	–
10	TFE	–	0	–
11[b]	HFIP	–	**2a** (45)	≥95:5
12[b]	AcOH	–	**3a** (42)	60:40
13	TFE/AcOH	20 mol % IBX	**3a** (93)	≥95:5

[a]Traces of the corresponding cyclobutane were observed; however, almost all starting material was recovered. [b]50% of starting material was recovered.

in 93% yield and with high diastereocontrol (Table 1, entry 13 vs 8).

Based on the above experiments our mechanistic proposal is shown in Scheme 2. Observing a strong background reaction in

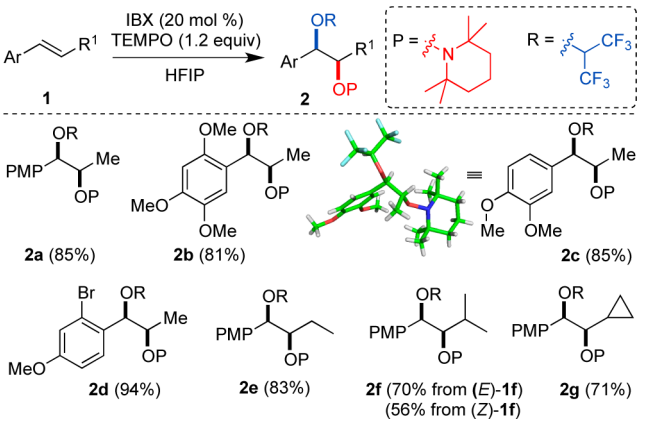
Scheme 2. Proposed Reaction Pathway



the absence of a hypervalent iodine reagent (Table 1, entries 11–12), and being aware of the ability of TEMPO to disproportionate in acidic solvents,[17] we propose the generation of hydroxylamine **III** and oxoamonium cation **IV**.[18] Electron-rich olefin **1a** may react with oxoamonium cation **IV** to form benzylic cation intermediate **V**,[19] which will then be trapped by a nucleophile (either an external carboxylic acid or HFIP).[20] The beneficial role of IBX in this reaction may then be to generate oxoamonium cation **IV** *in situ*, therefore improving the yield.[21] The stereochemical outcome of the cation trapping can be rationalized using intermediate **V**, with the external nucleophile approaching antiperiplanar to the R^1 group, in a conformation that minimizes allylic strain, thus rendering a net *syn* dihydroxylation. At this point we do not rule out the possibility of the OTEMP nitrogen atom in the intermediate cation playing a role in directing the nucleophile. The high levels of diastereocontrol displayed when using fluorinated solvents may be related to their larger dielectric constant (ε = 26 for TFE and ε = 18 for HFIP) compared to AcOH (ε = 6.2), which may influence the conformation and reactivity of a cationic intermediate.[22] At this point we cannot comment on the role that ion pairing plays in controlling the cation reactivity, and this factor may well differ between the two solvent regimes. Control experiments which involved resubjecting mixtures or single diastereoisomers of **3a** to the reaction conditions in HFIP or AcOH solvent led to no change in product composition, thus ruling out equilibration at the benzylic center.

Next, we decided to explore the reaction scope for both the addition of HFIP leading to products **2** (Scheme 3) and the

Scheme 3. Scope of the Metal-Free Dioxygenation with Hexafluoroisopropanol Incorporation



incorporation of AcOH to give orthogonally protected 1,2-diols **3** (Scheme 4). The scope for the dioxygenation of alkenes via HFIP addition was explored using styrenes with different electron-rich aromatic rings; therefore, starting from *E*-asarone (Ar = 2,4,5-trimethoxyphenyl) or from the 3,4-dimethoxy derivative, products **2b** and **2c** were obtained. The incorporation of an *ortho*-Br substituent in the aromatic ring is tolerated, without diminishing the reactivity (**2d**) (Scheme 3). Moreover, substituents on the allylic position, such as ethyl, *i*-Pr, or cyclopropyl, were all compatible (**2e–g**) (Scheme 3). When (*Z*)-**1f** styrene was used under these conditions, the same *syn* diastereoisomer **2f** was observed; this stereoconvergence is supporting evidence for the proposed mechanistic pathway proceding via a free cation (see Scheme 2). Note that the regiochemistry and *syn* relative stereochemistry was proven based on an X-ray crystal structure of **2c**,[23] and the remaining products in Scheme 3 were assigned by analogy.

We then focused our efforts on studying the scope of carboxylic acid incorporation because of the easy and selective deprotection protocols that exist. We also decided to concentrate on 1,2-disubstituted alkenes in order to study the diastereocontrol of the process. Keeping the *p*-methoxyphenyl ring (PMP) constant we first investigated the compatibility of the allylic substitution. Aliphatic linear (**3b**), branched (**3c**) (Scheme 4), or alicyclic (**3d**) substitution resulted in good yields of the corresponding TEMPO/acetate products (Scheme 4). Furthermore, different functional groups such as protected alcohol (**3e**) (Scheme 4), halide (**3f**) (Scheme 4), or ester (**3g**) (Scheme 4) were examined, all with very good results. For all of the examples above only the *syn* diastereoisomer was observed by NMR spectroscopy. However, when an alkene substrate containing a carboxylic acid was tested, *δ*-lactone **3h** derived from intramolecular attack was obtained in excellent yield. In this case the *anti*-isomer was formed selectively; this change in stereo-

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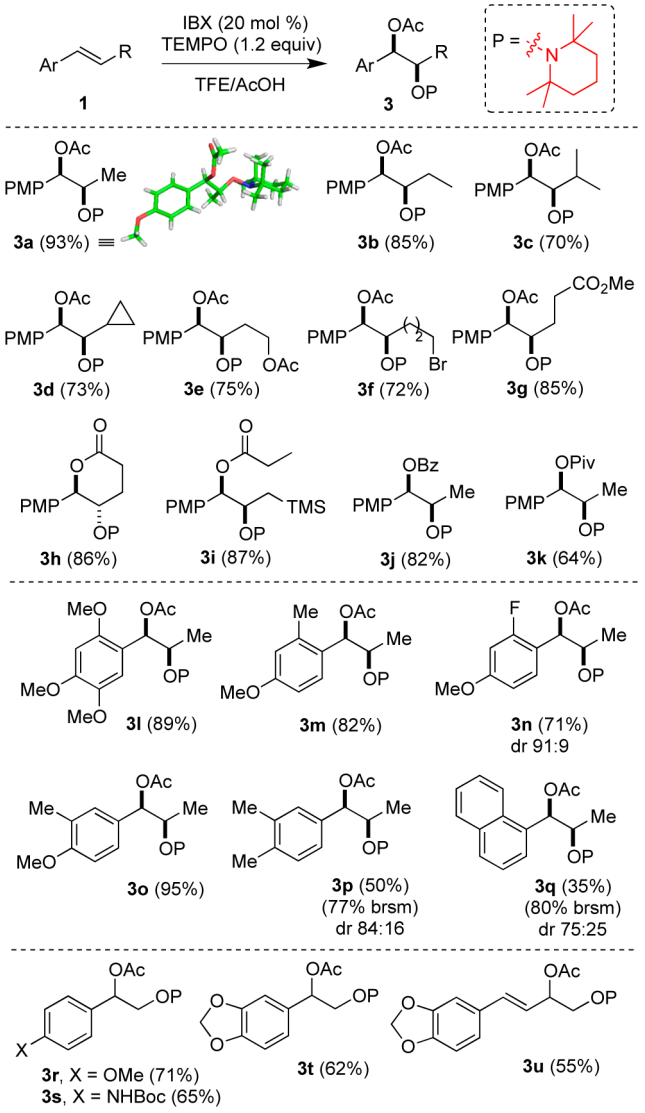
Scheme 4. Scope of the Metal-Free Dioxygenation with Carboxylic Acid Incorporation

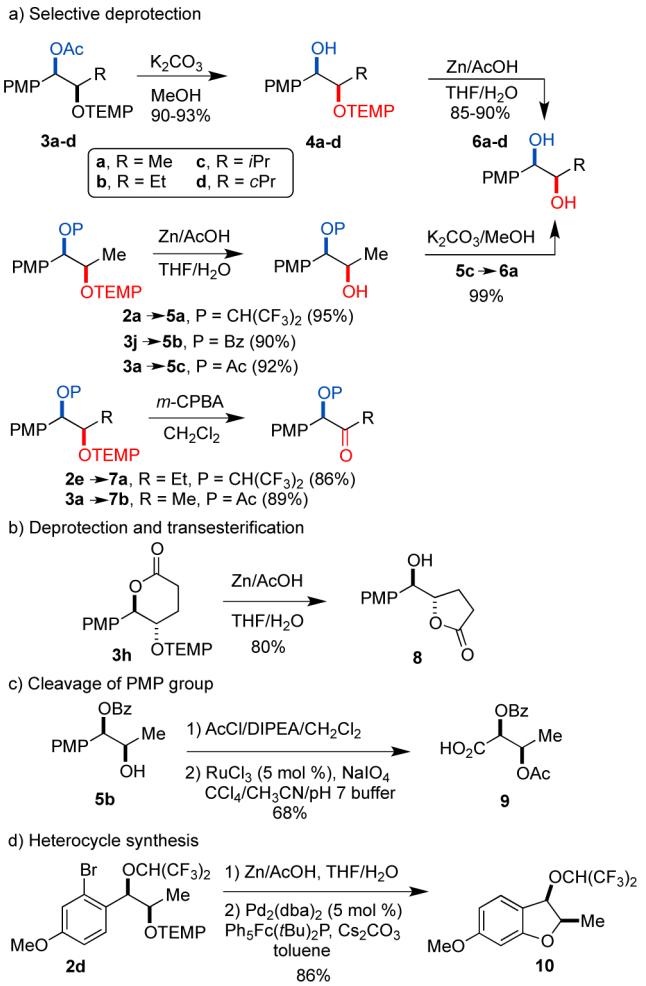


chemistry is due to the intramolecular nature of the nucleophile and supports our mechanistic proposal (see attack of a nucleophile from within the R^1 group in **V**, Scheme 2).[24] Different carboxylic acid nucleophiles can be used; thus allyl TMS substrate in combination with propionic acid gives **3i** with good results. Alternatively adding an aromatic acid or pivalic acid offers the possibility of accessing *syn* 1,2-diols **3j** and **3k** with diverse protecting groups.

Moving to the aromatic ring we examined electron-rich examples such as *E*-asarone (**3l**) (Scheme 4), 2-methyl (**3m**) (Scheme 4), or 3-methyl (**3o**) derivatives (Scheme 4) as well as those bearing other substituents, for example 2-fluoro (**3n**) (Scheme 4). The aryl olefin is not limited to *p*-methoxy styrenes, and the method also works with less electron-donating substituents, for example 3,4-dimethyl (**3p**) or naphthalene substituents (**3q**) (Scheme 4); however, in these cases the yield and diastereocontrol are compromised. Moreover, a representative group of terminal styrenes **3r**−**t** (Scheme 4) and a diene **3u** (Scheme 4) were tested with the latter example showing regioselectivity in favor of oxidation of the terminal olefin. Although the reaction scope is quite broad, the olefin must remain electron-rich for the reaction to proceed. In Scheme 4, the *syn* relative stereochemistry was proven using the X-ray crystal structure of **3a**,[23] and the remaining compounds were assigned by analogy or by correlation of derivatives to compounds that are known in the literature, *vide infra*.

Finally in order to demonstrate the utility of this new method we addressed the selective deprotection of both hydroxy groups. First, treating acetates **3a**−**d** with K_2CO_3 in MeOH gave monoprotected alcohols **4a**−**d** in excellent yields (Scheme 5a).

Scheme 5. Functionalization of the OTEMP Adducts



In order to deprotect the OTEMP functionality, hexafluoroisopropyl ether **2a** and esters **3a** and **3j** were subjected to reductive cleavage under standard conditions using Zn/AcOH to form alcohols **5a**−**c** in very good yields (Scheme 5a). Note that when acetate **3a** was used alcohol **5c** was obtained together with the acetate migration product (not shown, see Supporting Information (SI)). Fully deprotected *syn* 1,2-diols **6a**−**d** were prepared by reaction of a monodeprotected product under the complementary set of conditions (see **4a**−**d** → **6a**−**d** via N−O bond cleavage and **5c** → **6a** by acetate cleavage).

The spectroscopic data for *syn* 1,2-diols **6a**/**6c** were in agreement with those previously reported in the literature, and the $^1H/^{13}C$ NMR spectroscopic data of diols **6b** and **6d** matched those of authentic *syn* diols made by OsO_4 catalyzed dihydroxylation of the corresponding *E*-alkene (see Supporting Information). In addition, ketones **7a**−**b** were obtained by oxidative cleavage of the N−O bond with *m*-CPBA from **2e** or **3a**

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(Scheme 5a).[25] The deprotection of lactone **3h** under reductive conditions resulted in the formation of transesterified product **8** in good yield, and the NMR data for this *anti*-compound matched those in the literature (Scheme 5b). Alternatively the electron-rich aromatic PMP ring can be oxidized to a carboxylic acid using catalytic $RuCl_3$,[26] forming orthogonally protected α,β-dihydroxy acids **9**. Deprotection of **2d** via reductive N−O bond cleavage and subsequent Pd catalyzed intramolecular *O*-arylation furnished dihydrobenzofuran **10** (Scheme 5d). Furthermore, NOE experiments on **10** supported its *cis*-stereochemistry and therefore the *syn* stereochemistry of **2d**.

A new method for the *syn*-selective metal-free dioxygenation of electron-rich olefins in fluorinated solvents has been presented; the procedure involves a proposed reaction with an *in situ* generated oxoammonium cation, followed by the addition of a suitable nucleophile.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02959.

Full experimental details, copies of spectral data (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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