# Catalytic Enantioselective *syn*-Hydroxy-Oxyacylation of Electron Deficient Alkenes

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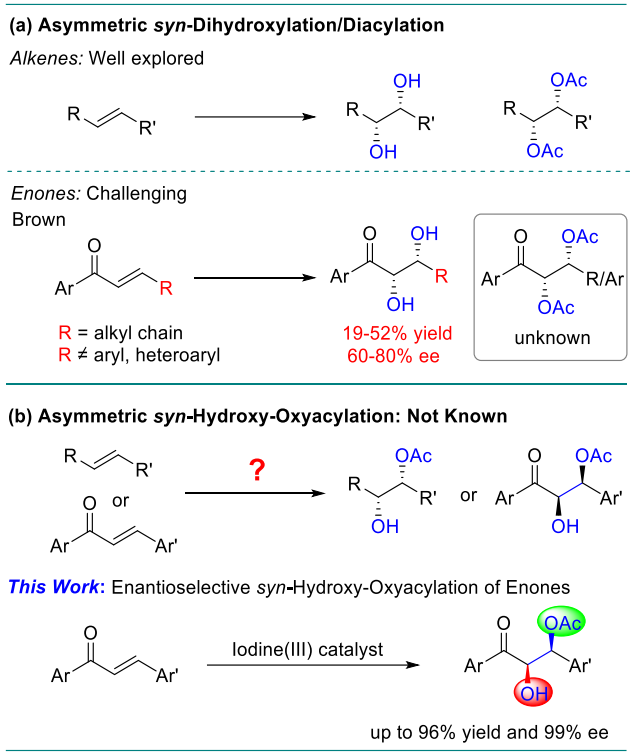
*This paper is dedicated to late Professor Kilian Muniz*

**ABSTRACT:** Asymmetric *syn*-dihydroxylation and dioxyacylation of alkenes have been well established. A direct method for the enantioselective preparation of orthogonally protected *syn*-1,2-diols from alkenes is unprecedented. Here in, we report the first enantioselective hypervalent iodine catalyzed *syn*-hydroxy-oxyacylation of enones. The orthogonally protected diols were obtained with excellent diastereo- and regioselectivity under metal-free condition. For these electron-deficient alkenes, even the *syn*-dihydroxylation and dioxyacylation have remained yet an unfinished challenge.

Orthogonally protected diols and triols are privileged structural motifs in numerous biologically active natural products, pharmaceutics, functionalized materials, and are important intermediates in many syntheses.[1] Therefore, numerous synthetic approaches have been developed to stereoselectively install double *syn* C-O bonds on alkenes (Scheme 1). The oxidative dihydroxylation of alkenes catalyzed by $OsO_4$, especially Sharpless dihydroxylation, has emerged as an extremely reliable variant.[2] However, the high toxicity, expensiveness and volatility of this catalyst led to the renewed interest in developing catalysts based on other transition metals, such as ruthenium,[3] palladium,[4] manganese[5] and iron.[6] The metal-free methods due to their intrinsic properties have also generated a great interest using peroxides,[7] hydroxamic acids,[8] hypervalent iodine reagents,[9] organocatalysts[10] and biocatalysts.[11] The group of Fujita reported the first asymmetric variant of Prevost and Woodward method for the dihydroxylation using chiral hypervalent iodine reagent in 2011.[12] Besides dihydroxylation, asymmetric diacetoxylation[13] and dialkoxylation[14] have also garnered significant importance for the asymmetric functionalization. However, for any effective direct chemoselective transformation, the difunctionalities are ideally desired to be in the differentiated/orthogonally protected form to avoid unproductive protection and deprotection steps in a multistep synthesis.

Enones are an important class of olefins which act as the surrogates for accessing triols after deoxygenation, followed by a selective reduction. It has surprisingly remained beyond the scope of almost all the known methods for enantioselective *syn*-dihydroxylation or diacylation. In 2002, the group of Brown pioneered the 1,2-dihydroxylation of enones using a phase transfer catalyst in a moderate yield of 19-52% and 60-80% ee (Scheme 1a).[10b] This method is compatible with enones

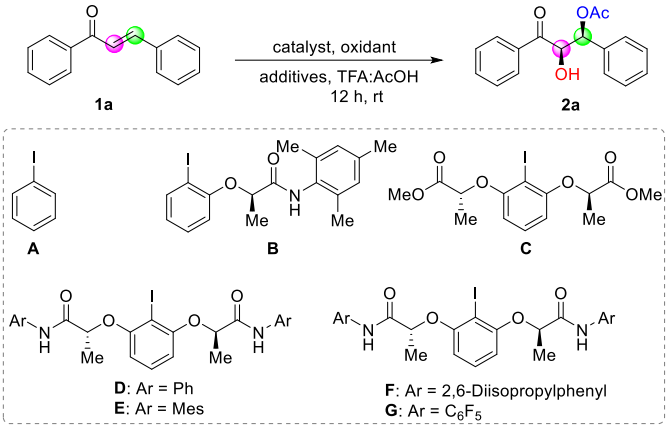
**Scheme 1. Asymmetric Hydroxy-Oxyacetylation of Enones**




substituted with less bulky alkyl chains at the *β*-position, and the sterically demanding (hetero)aryls and polycyclic aryls are beyond its scope. To the best of our knowledge, (i) there is no report on asymmetric *syn*-hydroxy-oxyacylation of electron-deficient alkenes, and (ii) for enones, even the *syn*-dihydroxylation with a high enantioselectivity has remained unfinished task, whereas the dioxyacylation is yet to be reported (Scheme 1b). Herein, we describe the first highly enantio and regioselective *syn*-1,2-hydroxy-oxyacylation of enones using hypervalent iodine catalyst (Scheme 1b). Acetic acid/$H_2O$ (residual water from the reagents) act as the source of acyloxy and hydroxy groups.

Our initial investigation focused on identifying a suitable hypervalent iodine catalyst, generated *in situ*, for the asymmetric

**Table 1. Reaction Condition Optimization**[a]



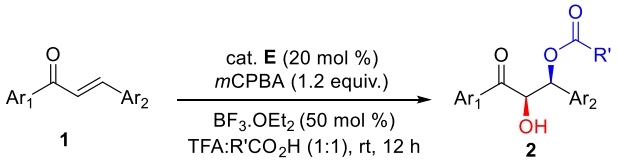

| entry | cat | oxidant | additive | yield (%)[b] | *ee* (%)[c] |
|---|---|---|---|---|---|
| 1 | - | oxone | $Sm(OTf)_3$ | 0 | - |
| 2 | **A** | oxone | $Sm(OTf)_3$ | 42 | - |
| 3 | **B/C** | oxone | $Sm(OTf)_3$ | 0 | - |
| 4 | **D** | oxone | $Sm(OTf)_3$ | 33 | 98 |
| 5 | **E** | oxone | $Sm(OTf)_3$ | 51 | 96 |
| 6 | **F** | oxone | $Sm(OTf)_3$ | 36 | 96 |
| 7 | **G** | oxone | $Sm(OTf)_3$ | 31 | 65 |
| 8 | **E** | selectfluor | $Sm(OTf)_3$ | 0 | - |
| 9 | **E** | *m*CPBA | $Sm(OTf)_3$ | 62 | 96 |
| 10 | **E** | *m*CPBA | $Yb(OTf)_3$ | 78 | 82 |
| 11 | **E** | *m*CPBA | HFIP | 0 | - |
| 12 | **E** | *m*CPBA | TfOH | 56 | 97 |
| 13 | **E** | *m*CPBA | $BF_3.OEt_2$ | 56 | 97 |
| 14[d] | **E** | *m*CPBA | $BF_3.OEt_2$ | 96 | 95 |
| 15[e] | **E** | *m*CPBA | $BF_3.OEt_2$ | 84 | 93 |
| 16[f] | **E** | *m*CPBA | $BF_3.OEt_2$ | 56 | 96 |

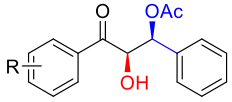
[a]Reaction condition unless otherwise specified: **1a** (0.1 mmol), additive (20 mol %), I(III) catalyst **A-G** (20 mol %), oxidant (1.2 equiv.), solvent (2.0 mL, 1:1 ratio) at rt. [b]Isolated yield. [c]Determined by HPLC analysis on chiral stationary phase. [d]50 mol % of $BF_3.OEt_2$ was used. [e]Reaction performed at 0 °C. [f]30 mol % of catalyst loading was used.

*syn*-1,2-hydroxy-oxyacylation of chalcone **1a** (Table 1). Various class of chiral aryl iodides (**B-G**) were tested as the potential catalysts in the presence of oxone in AcOH:TFA (1:1) as the solvent and $Sm(OTf)_3$ as the additive. Initial breakthrough was observed in the presence of 20 mol% of achiral catalyst **A**, giving the desired hydroxy-oxyacetylated product **2a** as a single diastereomer in 42% yield (entries 1 and 2). Among the different catalysts screened, catalyst **E** provided **2a** with a decent yield of 51% and 96% ee (entry 5). We next evaluated various oxidants. The use of selectfluor was found to be unsuitable while *m*CPBA produced **2a** in 62% yield and 96% ee (entries 8-9). The variation of Lewis/Bronsted acids showed a dramatic effect on the yield and $BF_3.OEt_2$ was the optimal choice giving the desired product in 96% yield with 95% ee (entry 14). The structure and the absolute configuration was unambiguously confirmed through X-ray crystallographic analysis of **2d** (Scheme 2).[15]

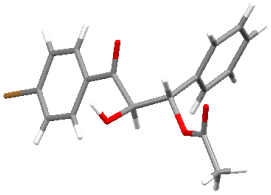
With the optimized reaction condition in hand, chalcones bearing different electron-donating groups (EDG) as well as electron-withdrawing groups (EWG) at *ortho*, *meta* and *para*-position of the aryl rings were examined (Scheme 2). The EDGs

**Scheme 2. Substrate scope**

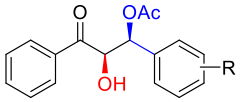


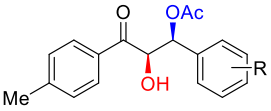
**2a**, R = H, 96%, 95% ee
**2b**, R = 4-Me, 73%, 98% ee
**2c**, R = 4-OMe, 93%, 89% ee
**2d**, R = 4-Br, 76%, 96% ee
**2e**, R = 4-Cl, 64%, 96% ee
**2f,** R = 4-$NO_2$, 21%, 92% ee



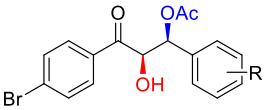
X-ray structure of **2d**



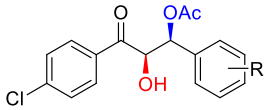
**2g**, R = 4-Me, 68%, 83% ee
**2h**, R = 4-Cl, 60%, 94% ee
**2i**, R = 2-Br, 62%, 96% ee
**2j**, R = 4-Br, 65%, 93% ee
**2k**, R = 4-F, 72%, 92% ee



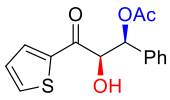
**2l**, R = 4-Me, 60%, 88% ee
**2m**, R = 4-Et, 69%, 91% ee
**2n**, R = 4-Br, 64%, 94% ee
**2o**, R = 4-Cl, 84%, 95% ee



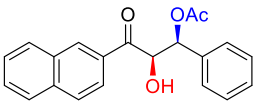
**2p**, R = 3-Me, 68%, 98% ee
**2q**, R = 4-Me, 64%, 91% ee
**2r**, R = 4-Et, 81%, 94% ee
**2s**, R = 4-$^i$Pr, 73%, 96% ee



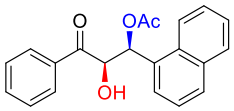
**2t**, R = 3-Me, 81%, 99% ee
**2u**, R = 4-Me, 76%, 94% ee
**2v**, R = 4-Et, 64%, 94% ee
**2w**, R = 4-$^i$Pr, 75%, 93% ee



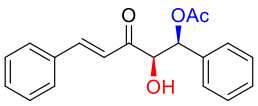
**2x**, 81%, 95% ee



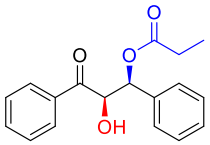
**2y**, 78%, 94% ee



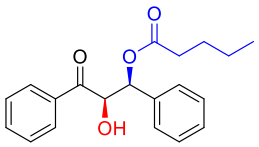
**2z**, 73%[a]



**2aa**, 62%, 98% ee



**2ab**, 66%, 93% ee

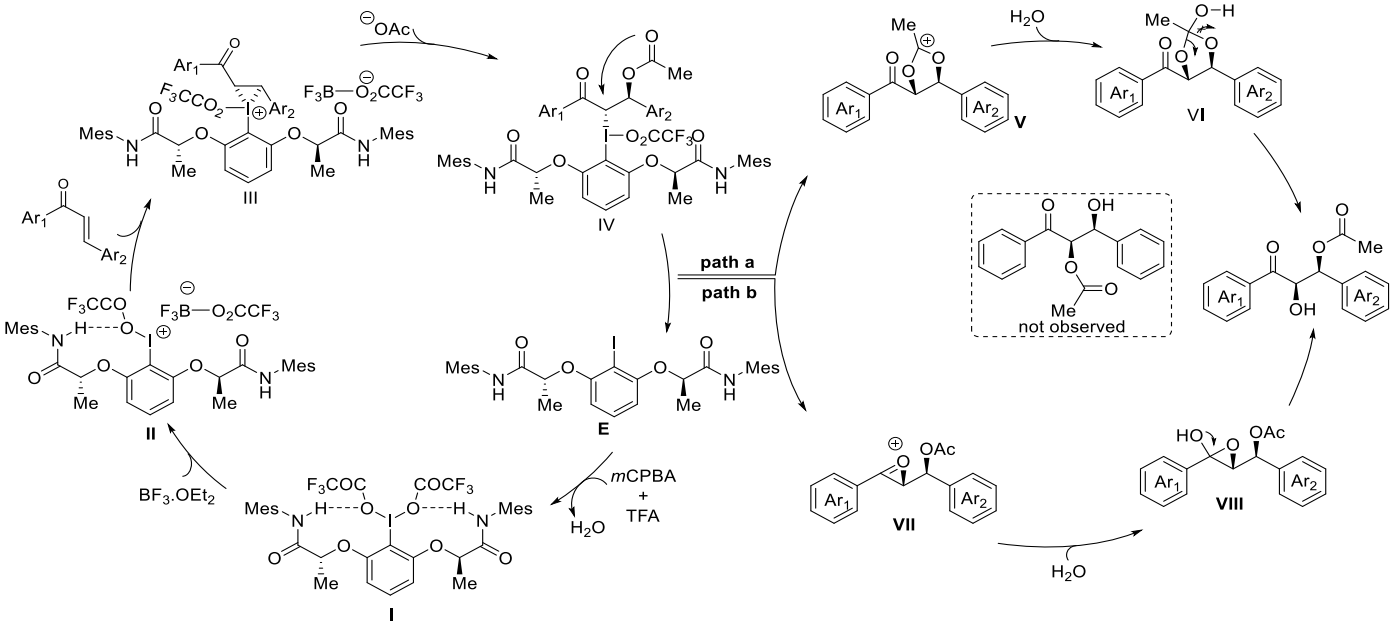


**2ac**, 60%, 90% ee

[a]HPLC separation for 2z was not achieved, see SI for further details.

like Me, Et, OMe, $^i$Pr; and EWGs like flouro, chloro, bromo on the aryl ring $Ar_1$ gave the desired products in good to excellent yields and high enantioselectivity. Substitution patterns on the *β*-aryl ring ($Ar_2$) were also compatible with the optimized reaction condition producing the desired products in good yields and excellent ee.[16] Switching from acetic acid to higher analogues also furnished **2ab** and **2ac** in good yields without any loss in enantioselectivity.

**Scheme 3. Proposed Reaction Mechanism**




Our proposed reaction mechanism for this transformation is detailed in Scheme 3. The catalytic cycle begins with the *in situ* oxidative generation of I(III) in presence of *m*CPBA/TFA that reacts with $BF_3.OEt_2$ to produce intermediate **II**. This intermediate coordinates with the chalcones **1** to give adduct **III**. A regioselective substitution by an acetate generates intermediate **IV**. The regeneration of catalyst **E** takes place *via* reductive elimination to give either intermediate **V** (path a) or intermediate **VII** (path b). Subsequent regioselective hydrolysis of intermediate **VI** or **VIII** generates the desired product with excellent regio- and stereoselecvity. A detailed DFT calculation is underway to ascertain the preferred reaction pathway among the path a and path b.

In conclusion, we have achieved the first enantioselective *syn*-hydroxy-oxyacylation of electron deficient olefins using hypervalent iodine(III) catalysis. This method furnished the orthogonally protected *syn*-diols from alkenes with a wide substrate scope and excellent enantiocontrol. Further studies towards selective transformation of the products is under progress in our laboratory.

## ASSOCIATED CONTENT

### Supporting Information

Experimental procedure, characterization data and spectra (PDF)

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### Notes

The authors declare no competing financial interests.

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15. CCDC 1946629 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/daa_request/cif.
16. HPLC separation for **2z** was not achieved, see SI for further details.