Synthesis T. H. Wöste, K. Muñiz Feature

Enantioselective Vicinal Diacetoxylation of Alkenes under Chiral Iodine(III) Catalysis

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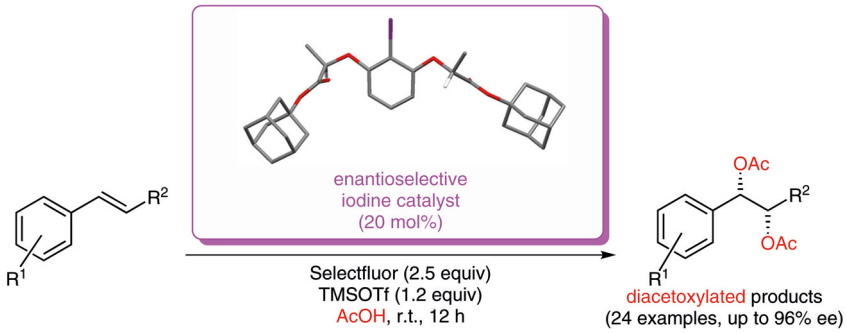

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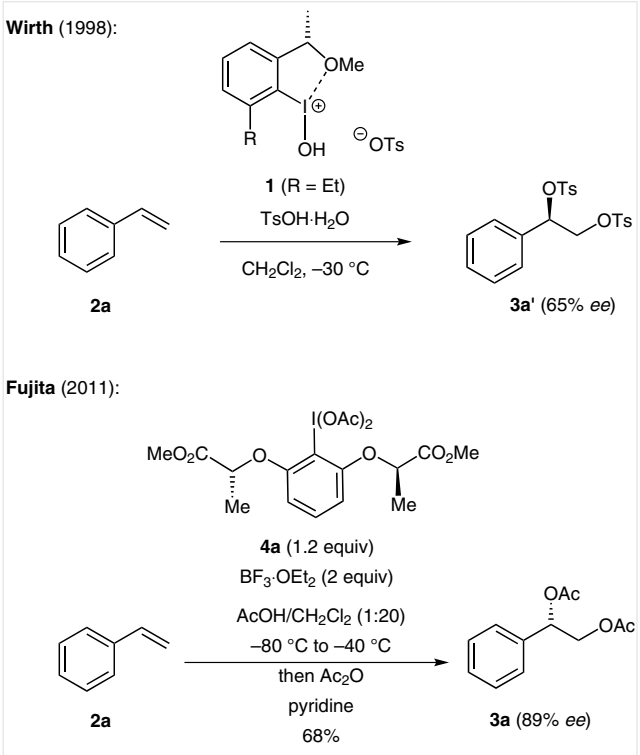
Abstract A procedure for the intermolecular enantioselective dioxygenation of alkenes under iodine(III) catalysis has been developed. This protocol employs Selectfluor as the terminal oxidant together with a defined C_2-symmetric aryl iodide as the organocatalyst. This enantioselective reaction proceeds under mild conditions and converts a series of terminal and internal styrenes into the corresponding vicinal diacetoxylation products with up to 96% *ee*.

Key words alkenes, chirality, diacetoxylation, hypervalent iodine, oxidation, Selectfluor

As a synthetic concept, the vicinal difunctionalization of alkenes allows for a rapid structural and functional diversification of simple alkene moieties within a single operation.[2] Among the many examples of this type of reactions, the development of processes that proceed entirely under intermolecular reaction control is of particular challenge. While this field has been largely dominated by enantioselective transition metal catalysis such as the seminal osmium-based dihydroxylation and aminohydroxylation processes developed by Sharpless,[3] chiral nonracemic iodine(III) reagents[4] have recently emerged as potentially versatile alternatives.[5] Based on earlier work on defined iodine(III) reagents for selective dioxygenation of alkenes,[5c,6] the development of the corresponding enantioselective dioxygenation reactions was pioneered and extensively investigated by Wirth.[7] These reactions made use of defined chiral iodine(III) reagents such as **1**, and the oxidation of styrene **2a** led to the formation of the corresponding ditosylation product **3a'** with up to 65% *ee* (Scheme 1). The appearance of the chiral bislactate derived iodine(III) oxidant **4a** has greatly advanced the inherent synthetic possibilities,[5,8] and, based on this reagent, an enantioselective diacetoxylation of **2a** subsequently led to the formation of the corresponding diacetoxylated product **3a** in up to 89% *ee* (Scheme 1).[9] A related diamination[10] was also developed using stoichiometric amounts of **4a**. Moreover, an amide derivative of **4a** promoted an oxygenative rearrangement reaction,[11a] an Umpolung functionalization of silylated enol ethers,[11b] and asymmetric Kita-spirolactonization reac-



Scheme 1 Intermolecular vicinal dioxygenation reactions of styrene with stoichiometric amounts of hypervalent iodine(III) promoters

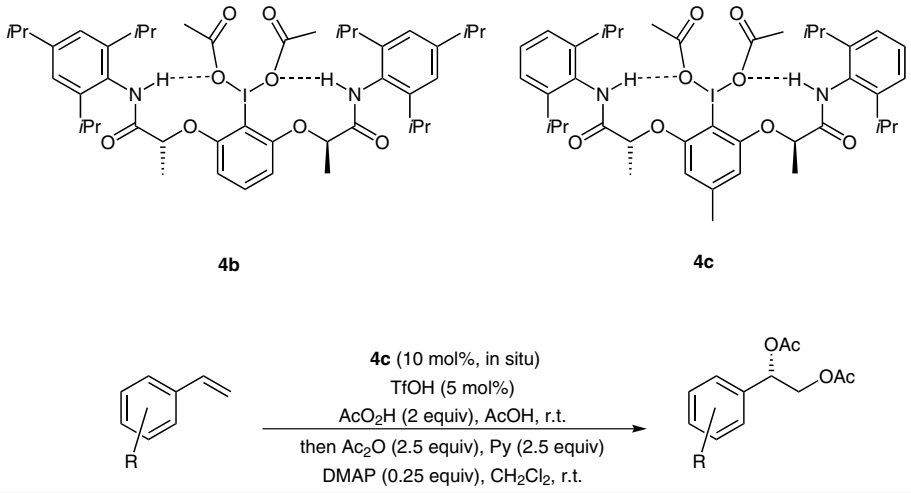
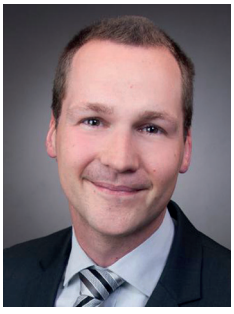


Figure 1 Intramolecular hydrogen bonding properties of chiral hypervalent iodine compounds **4b**,**c** and catalytic enantioselective diacetoxylation of styrenes

tions.[11c–e] In addition, important contributions were also achieved in the field of related intramolecular enantioselective reactions of alkene oxidation.[5,12,13] In the case of the latter, Fujita recently reported that such oxidations could also be conducted with catalytic amounts of **4a** in the presence of *m*-CPBA as terminal oxidant.[5,14,15]

However, despite the fact that dioxygenation belongs to the most extensively investigated reactions in iodine(III)-mediated oxidation of alkenes,[16] the development of corresponding reaction conditions for strictly intermolecular difunctionalization under iodine(III) catalysis represents an ongoing challenge.[17]

Biographical Sketches



Thorsten H. Wöste was born in 1983 in Sögel, Germany. He received his Diploma degree under the supervision of Prof. Dr. Martin Oestreich at the Westfälische Wilhelms-Universität Münster, Germany in 2009 and his Ph.D. in 2012. He was involved in catalytic asymmetric (Mizoroki–)Heck reactions in Münster as well as at the Technische Universität Berlin. In December 2012, Thorsten joined the group of Prof. Dr. Kilian Muñiz as a postdoctoral fellow, funded by the Deutsche Forschungsgemeinschaft (DFG). His research was focused on metal-free, hypervalent iodine catalyzed difunctionalization of alkenes. Currently, Thorsten is working as R & D Manager at Convertec GmbH, Germany.

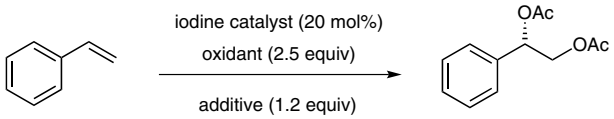
Kilian Muñiz was born in 1970 in Hildesheim, Germany. He studied Chemistry at the Universities of Hannover (Germany) and Oviedo (Spain), and at the Imperial College London (UK). He received a Doctorate in Chemistry from the RWTH Aachen in 1998 for work with Professor Carsten Bolm and was an Alexander von Humboldt/JSPS-postdoctoral associate with Professor Ryoji Noyori at Nagoya University (Japan). From 2001–2005 he was a Liebig fellow at Bonn University associated with Professor Karl Heinz Dötz, before accepting a full professorship at Strasbourg University (France). He was elected as a junior member of the Institute Universitaire de France in 2008. He moved to his present position at ICIQ in Tarragona (Spain) in 2009. Since 2010 he has also been an ICREA research professor. He received a 2015 Award for Excellence in Research from the Royal Spanish Chemical Society (RSEQ). His research throughout the past decade has dealt with the development of new processes in the area of vicinal difunctionalization, in particular with the oxidative diamination of alkenes.

This is a noteworthy observation, in particular when taking into account the potential that a metal-free process would have for applications in fields such as biological and medicinal synthesis, where the avoidance of metal contamination is of major importance. We have recently introduced new derivatives of chiral hypervalent iodine reagents of the Ishihara motif, which led to catalyst structures based on effective hydrogen bonding (Figure 1).[18]

These compounds indeed enabled the catalytic enantioselective diacetoxylation of styrenes under intermolecular reaction control with up to 94% *ee*. Despite the success of these new catalysts, we remained curious to explore whether the parent diesters such as **4a** could be employed as catalysts as well. We report here the development of suitable conditions for such an enantioselective diacetoxylation of alkenes using catalytic amounts of an iodine(I/III) catalysis with **4a** and related derivatives.

Although different oxygen sources such as perchlorate, trifluoroacetate, and tosylate have become available,[16] we were particularly drawn to the development of a dioxygenation reaction using the more common acetate as nucleophile. Such a process would be based on chiral derivatives of the fundamental $PhI(OAc)_2$ reagent. Its notoriously low reactivity towards alkenes is usually attributed to the diminished electrophilicity of the central iodine(III) atom. In an elegant study, Gade and Kang demonstrated that Brønsted activation of $PhI(OAc)_2$ with triflic acid represents a powerful tool to accelerate the overall diacetoxylation process.[19,20] Attempts to devise conditions for diacetoxylation reactions that are catalytic in iodine reagent have met with certain success,[21] however, the potential contribution of background reactivity to the overall product formation[22] remains an issue. Obviously, the use of a chiral iodine reagent would provide the possibility to employ enantioselectivity

Table 1 Optimization of the Catalytic Enantioselective Diacetoxylation



2a **3a**

Entry	I_2 cat.	Oxidant	Additive	Solvent	Yield (%)[a]	*ee* (%)[b]
1	**4a**	*m*-CPBA	–	$AcOH/CH_2Cl_2$	n.c.[c]	–
2	**4a**	*m*-CPBA	TFA	CH_2Cl_2	n.c.	–
3	**4a**	AcO_2H	–	AcOH	n.c.	–
4	**4a**	AcO_2H	TMSOTf	AcOH	n.c.	–
5	**4a**	NaOCl	TMSOTf	AcOH	n.c.	–
6	**4a**	Selectfluor	–	AcOH	n.c.	–
7	**4a**	Selectfluor	TfOH	AcOH	63	0
8	**4a**	Selectfluor	MsOH	AcOH	38	0
9	**4a**	Selectfluor	TMSOTf	AcOH	67	68
10	**4a**	Selectfluor	TMSOAc	AcOH	n.c.	–
11	**4a**	Selectfluor	TMSOAc, TfOH	AcOH	69	72
12	**4a**	Selectfluor	TMSOTf	$AcOH/CH_2Cl_2$	n.c.	–
13	**4a**	Selectfluor	TMSOTf	$AcOH/CHCl_3$	n.c.	–
14	**4a**	Selectfluor	TMSOTf	$AcOH/(CH_2Cl)_2$	n.c.	–
15	**4a**	Selectfluor	TMSOTf	$AcOH/CCl_4$	n.c.	–
16	**5a**	Selectfluor	TMSOTf	AcOH	64	74
17	**5e**	Selectfluor	TMSOTf	AcOH	67	52
18	**5b**	Selectfluor	TMSOTf	AcOH	47	78
19	**5c**	Selectfluor	TMSOTf	AcOH	63	78
20	**5d**	Selectfluor	TMSOTf	AcOH	66	80

[a] Isolated yield after treatment with Ac_2O.
[b] Determined by chiral HPLC analysis (OD-H column).
[c] n.c.: No conversion to **3a** was observed.

as a tool to unambiguously prove the catalytic performance of the aryl iodine. Our approach to develop an enantioselective diacetoxylation of alkenes was started from **4a** as the catalyst source and with styrene as the standard alkene (Table 1). Our initial attempts on the use of peracids as terminal oxidants[15] for the present case of an intermolecular dioxygenation were quickly abandoned. In agreement with the earlier conclusion from Gade and Kang on achiral iodines,[22] that due to similar kinetics, iodine(III) catalysis and stoichiometric oxidation by the stoichiometric oxidant itself compete for the alkene oxidation, aldehyde formation and other degradation products were observed. For the chiral reagent **4a**, reactions in the presence of *m*-CPBA, peracetic acid, or sodium hypochlorite lead to no diacetoxylation of styrene (**2a**) to the expected product **3a**, regardless whether potential activating additives were added (Table 1, entries 1–5).

We thus changed our approach and employed Selectfluor, which is known for its ability to promote stoichiometric iodine(III) formation from the corresponding aryl iodides.[8c,23] While reagent **4a** itself cannot promote a catalytic diacetoxylation of styrene in the sole presence of Selectfluor (Table 1, entry 6), addition of triflic acid demonstrated that turnover can be achieved, although the desired product **3a** was formed as a racemate (entry 7). Less acid strength as with methylsulfonic acid results in a decrease in yield (entry 8). Finally, addition of TMS triflate gave a catalytic reaction that formed a product with 68% *ee* (entry 9). Changing the additive to TMS acetate shut down the reaction (entry 10), while the additional presence of triflic acid reactivated the enantioselective catalysis (entry 11). Attempts to carry out the reaction in solvent mixtures were not successful (entries 12–15). The reaction was then further developed exploring the potential of different in situ generated hypervalent iodine compounds. When starting the reaction from the corresponding iodine(I) compound **5a** (Figure 2), an efficient catalysis was observed (entry 16). A related catalyst **5e** with a single lactate side chain gave similar yield, but decreased *ee* (entry 17). A useful increase in enantioselectivity to 78% *ee* was observed for the *tert*-butyl ester **5b**, although the chemical yield decreased. The latter was attributed to a potential incompatibility of the *tert*-butyl ester with the TMS additive. Consequently, the new adamantyl derivatives **5c** and **5d** were synthesized and structurally characterized (Figure 3).[24]

The adamantyl-substituted catalysts were demonstrated to be efficient, giving the diacetoxylation product in up to 80% *ee* (entries 19, 20). In particular, compound **5d** displayed significantly higher stability than the *tert*-butyl ester **5b**, and could be recovered in over 95% isolated yield after the oxidation catalysis. In all these cases, in order to account for a uniform product, the crude reaction mixtures were treated with acetic anhydride prior to analysis of product **3a** (cf. footnote a, Table 1).

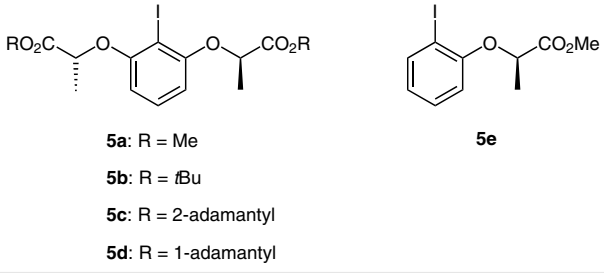


Figure 2 Chiral iodine(I) catalysts: structures

The reaction is general for a range of styrenes. Scheme 2 displays 17 examples of different styrenes **2a**–**q** that could be converted into the corresponding diacetoxylation products **3a**–**q** in an enantioselective manner. These examples demonstrate a higher substrate scope than reported for the stoichiometric reaction.[9] The high robustness of the reaction conditions was further demonstrated for a 24 mmol scale diacetoxylation of **2a**, which provided 2.99 g of the corresponding product **3a**.

Apart from styrene itself, several *para*-substituted arenes **2b**–**g** underwent diacetoxylation in good yields and with 64–86% *ee*. An exception was encountered in the case of 4-methoxystyrene, which suffered from degradation under the present conditions. Other successful examples in-

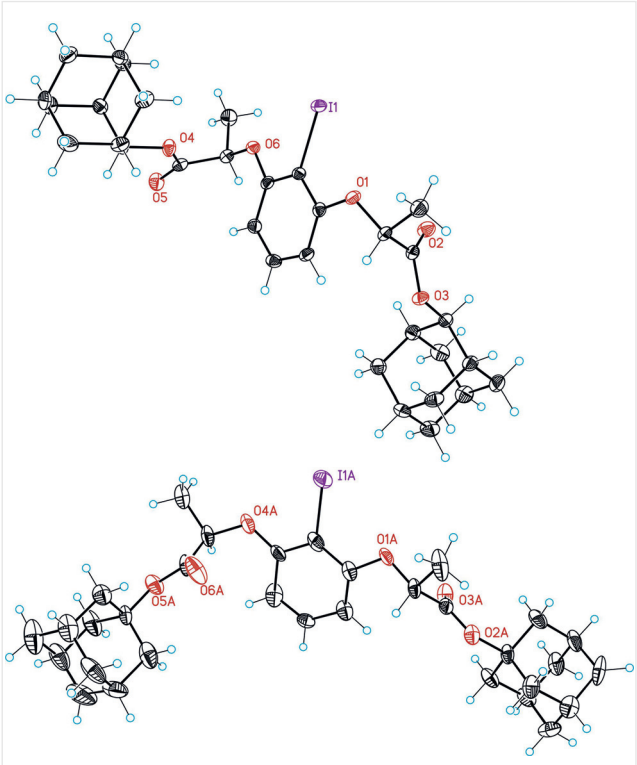
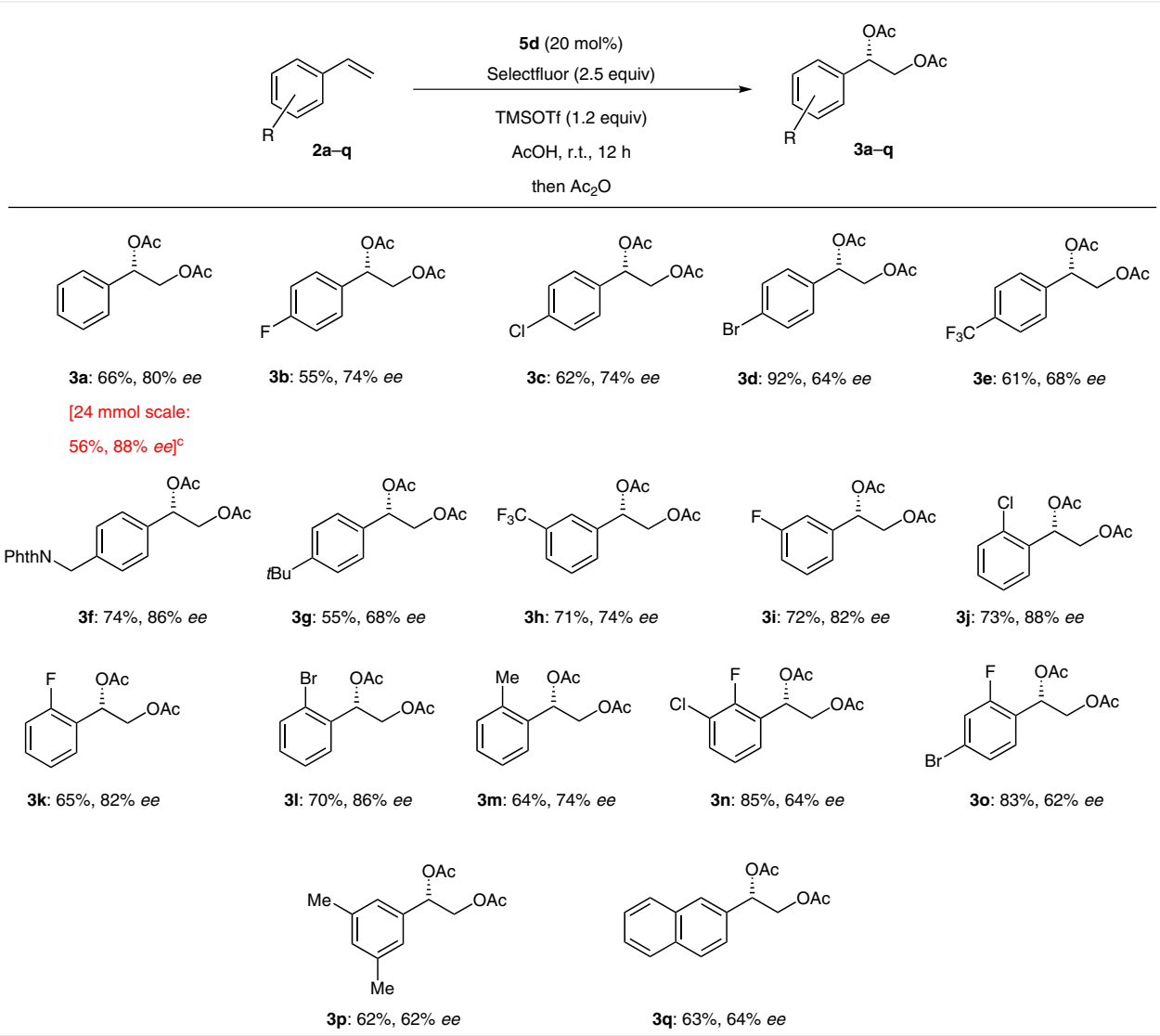


Figure 3 Solid state structures of compounds **5c** (top) and **5d** (bottom)

clude the *meta*- and *ortho*-substituted products **3h**–**m**, which formed with up to 88% *ee*. Higher-substituted styrenes **2n**–**q** led to the formation of the corresponding diacetoxylation products **3n**–**q** with good enantioselectivities of 62–64% *ee*. The enantioselectivity values obtained from such room temperature catalyses are noteworthy when compared to the outcome of the parent stoichiometric reaction, which was conducted at a temperature range between –80 and –40 °C.[9] They are only slightly lower than the ones for the presently best enantioselective catalysis based on compounds **4b**,**c**.[18]

A mechanistic context for this intermolecular enantioselective iodine(III)-catalyzed dioxygenation reaction is discussed in Figure 4. The reaction starts with the Selectfluor-mediated oxidation of the iodine(I) species Ar*I to the corresponding cationic iodine(III) catalyst state **A**, which in the presence of trimethylsilyl acetate and triflic acid generates the catalyst state **B**. Since the reaction proceeds in acetic acid as solvent, this pathway could initially proceed through the formation of the corresponding diacetoxyiodine(III) species, which upon protonolysis by triflic acid will ultimately generate **B**. In any case, the presence of both the TMS group for removal of the fluoride and HOTf for the formation of a cationic catalyst state are required. In agreement with the data from Gade on the achiral reaction,[19] **B** should represent the active catalyst involved in the alkene oxidation. This was corroborated by a stoichiometric control experiment on diacetoxylation of styrene (**2a**) with **4a** together with 1.2 equivalents of TMS triflate in acetic acid at room temperature (Scheme 3), which gave **3a** (56% yield,



Scheme 2 Scope of the iodine(III)-catalyzed enantioselective diacetoxylation of styrenes.[a,b] [a] Isolated yield after purification. [b] Determination of *ee* values carried out at the stage of free diols by HPLC on chiral stationary phase. [c] 24 h reaction time.

73% *ee*) in a comparable outcome to the results from catalysis (Table 1, entry 11: 69% yield, 72% *ee*). Upon oxidation of the styrene, the iodo-oxygenated intermediate **C** is formed, from which the iodine(I) catalyst is regenerated upon an intramolecular reductive displacement by the acetyl group forming the resulting dioxolonium derivative **D**. It had previously been discussed[16] that such an intermediate **D** can undergo ring opening by acetate through a Prévost mechanism[25] or through water addition to form a hydroxyacetate **6** within a Woodward pathway.[26] It should also be noted that both pathways from **D** release one equivalent of HOTf. However, the reaction does not proceed with catalytic amounts of HOTf, which should be the result of neutralization through the tertiary quinuclidinium amine that is generated from Selectfluor within the oxidation step.

To gain further insight on the involved intermediates in the dioxygenation, we isolated the direct reaction products

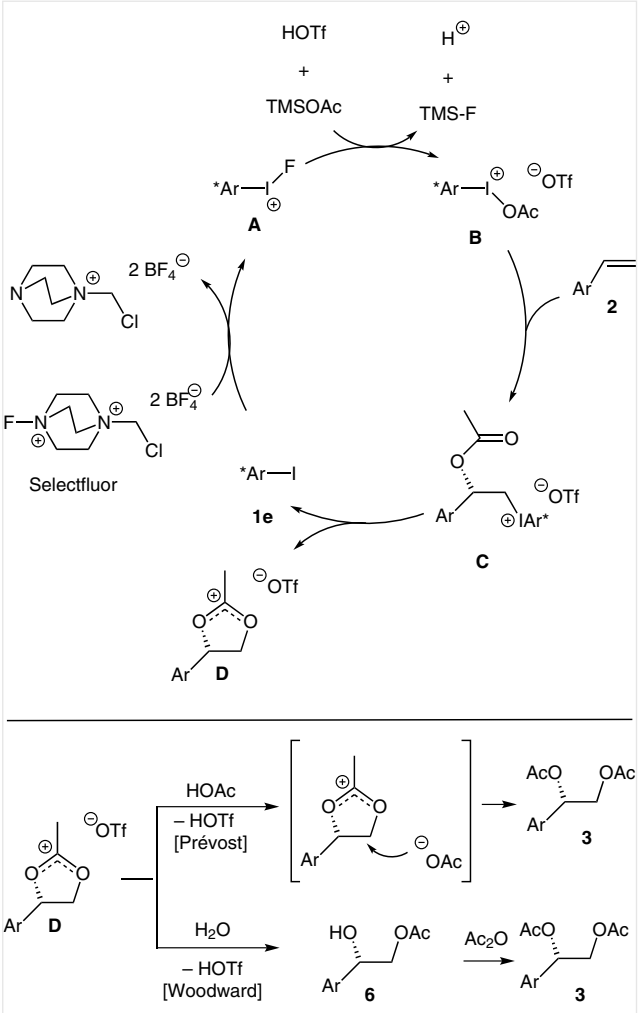
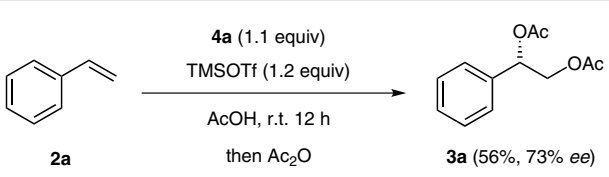
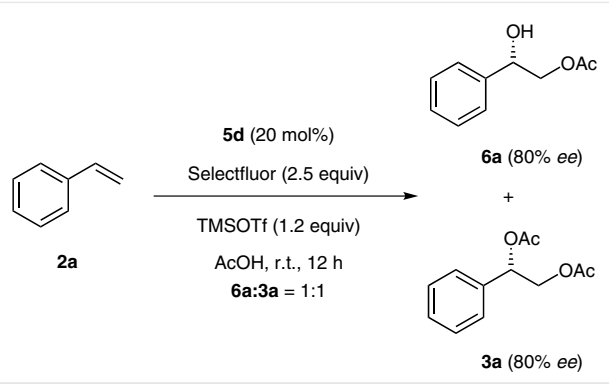


Figure 4 Catalytic cycle for the enantioselective diacetoxylation of styrenes



Scheme 3 Stoichiometric control experiment

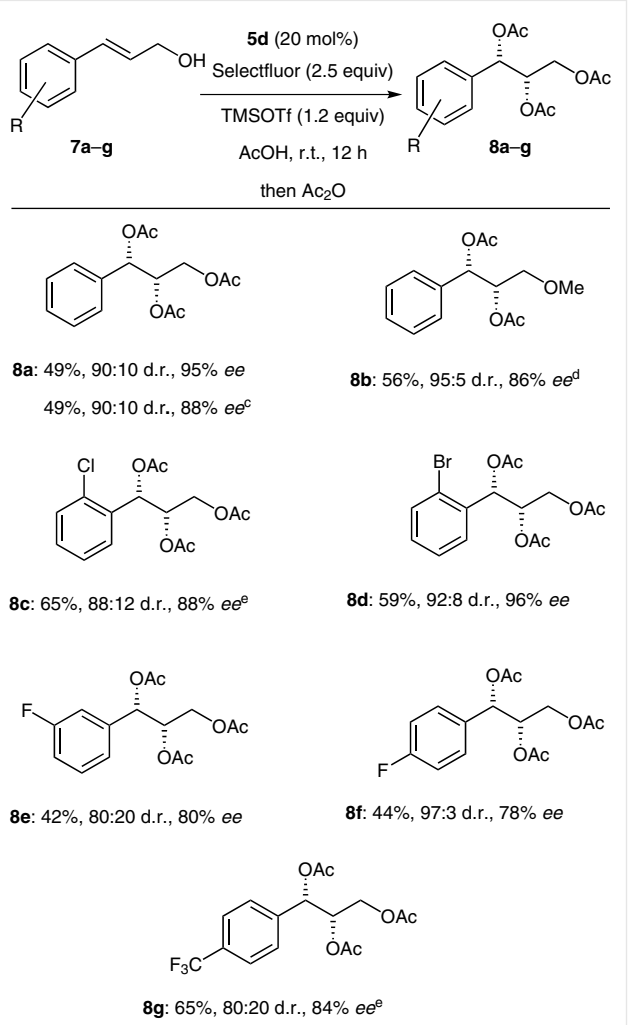
from catalytic dioxygenation of styrene (**2a**) (Scheme 4). In this case, the crude reaction mixture contained both the diacetoxylation product **3a** as well as the regioselectively formed 1-hydroxy-2-acetoxy product **6a**, indicating that two different pathways are competent under the reaction conditions. The diacetate **3a** was isolated as the *S*-enantiomer in 42% yield with 80% *ee*, while the equally *S*-configured hydroxyacetate **6a** was formed in 40% yield and with 80% *ee* as determined after conversion to the diacetate **3a**.



Scheme 4 Control experiment on the initial product distribution for terminal alkene oxidation

The fact that the two compounds **3a** and **6a** form with identical absolute configuration and identical enantiomeric excess is important. To account for the observed *S*-configuration of the diacetoxylation product through a Prévost pathway, an opening of intermediate **D** at the homobenzylic position is required. While this is not entirely impossible, it appears highly improbable. In fact, a Prévost mechanism was suggested to be involved in the stoichiometric dioxygenation, which provided the expected *R*-stereochemistry.[9] The present observation on the stereochemical outcome suggests that a Prévost mechanism is not involved in this transformation and product **3a** should form through a different pathway (vide infra).

The present conditions for catalytic enantioselective diacetoxylation reaction could also be extended to the substrate class of internal alkenes, which are beyond the scope of our earlier catalysts **4b**,**c**. While β-methylstyrene did not display any reactivity under the present standard catalytic conditions, cinnamic alcohol and its derivatives were found



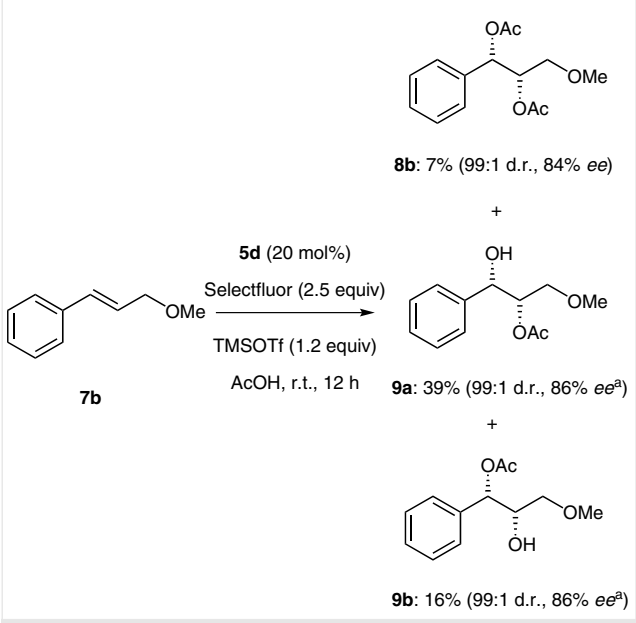
Scheme 5 Scope of the iodine(III)-catalyzed enantioselective diacetoxylation of styrenes.[a,b] [a] Isolated yield after purification. [b] Determination of ee was carried out by HPLC on chiral stationary phase.[21] [c] From cinnamyl acetate **7a′**. [d] From cinnamyl methyl ether **7b**. [e] With **5b** as catalyst.

to be suitable substrates (Scheme 5). This observation is reminiscent of the earlier report on stoichiometric reactivity[9] and appears to be the consequence of an electronic effect of the allylic oxygen. For example, cinnamyl alcohol (**7a**) gave the corresponding oxidation product **8a** with a 90:10 diastereomeric ratio in favor of the *like*-product **8a**, which formed with 95% *ee*. The same product could be obtained from the acetoxylated alcohol leading to an identical product formation with 88% *ee*. This somewhat lower induction may be the result of the presence of a sterically more demanding acetoxy substituent retarding the face selection. The corresponding cinnamyl methyl ether led to a 95:5 diastereomeric ratio in favor of the *like*-product **8b**, which formed with 86% *ee*. From this observation, possible hydrogen bonding from the free OH in **8a** appears not to play an essential role in the reaction. Finally, substituted free cinnamyl alcohols **7c**–**g** gave the corresponding *like*-diacetoxylation products **8c**–**g** in good to very good diastereoselectivities and with 78–96% *ee*.

While the crude product was usually directly transformed by treatment with acetic anhydride to furnish single diacetate products **8** in all cases as shown in Scheme 5, we also investigated again the initial formation of different dioxygenation products for cinnamyl methyl ether (**7b**) (Scheme 6). After direct workup, the crude reaction product was identified to consist of a mixture of the diacetoxylation product **8b** in 7% and with 84% *ee*, together with 55% of the two hydroxylated products **9a** and **9b** in a 70:30 ratio. After separation of the two compounds and their conversion into **8b** by acetoxylation with acetic anhydride, an identical 86% *ee* was determined for both samples. This outcome confirms a *like*-configuration for products **9a**,**b** and suggests the dominance of a Woodward pathway in the cases of internal alkenes **7a**–**g** and **7a′**.

In addition, the observed *like*-configuration for product **8b** is inconsistent with the potential involvement of a Prévost mechanism, as the underlying opening of the corresponding cationic dioxolanyl intermediate should generate the opposite diastereoisomer of an *unlike*-configuration.

As a result, it must be concluded that Prévost pathways are entirely absent in the present oxidative difunctionalization of styrenes. Instead, a direct reductive elimination of the iodine(III) moiety in intermediate **C′** appears to be taking place (Figure 5). Such a process involves an intermolecular S_N2-displacement **E** of the iodine(III) nucleofuge[27]



Scheme 6 Control experiment for the reaction outcome in the dioxygenation of internal alkenes. [a] Determination of *ee* was carried out after conversion into **8b**.

through acetate or acetic acid at stage **C′**, which competes with the intramolecular displacement that forms the dioxolonium intermediate **D′**. Such a direct nucleophilic substitution at the alkyl-iodine(III) group is in agreement with related investigation on ditosylation reactions.[6,7a,16d,28] In these cases, the tosyl group does not engage in an intramolecular iodine displacement leading to a stereochemical outcome that perfectly resembles the one from the present diacetoxylation.[28]

For steric reasons, such direct iodine for acetate exchange at stage **E** has a higher chance to proceed for styrene derivatives, where the S_N2 reaction proceeds at a primary center (R = H). In contrast, for cinnamyl derivatives, the Woodward pathway is largely dominating. Since both path-

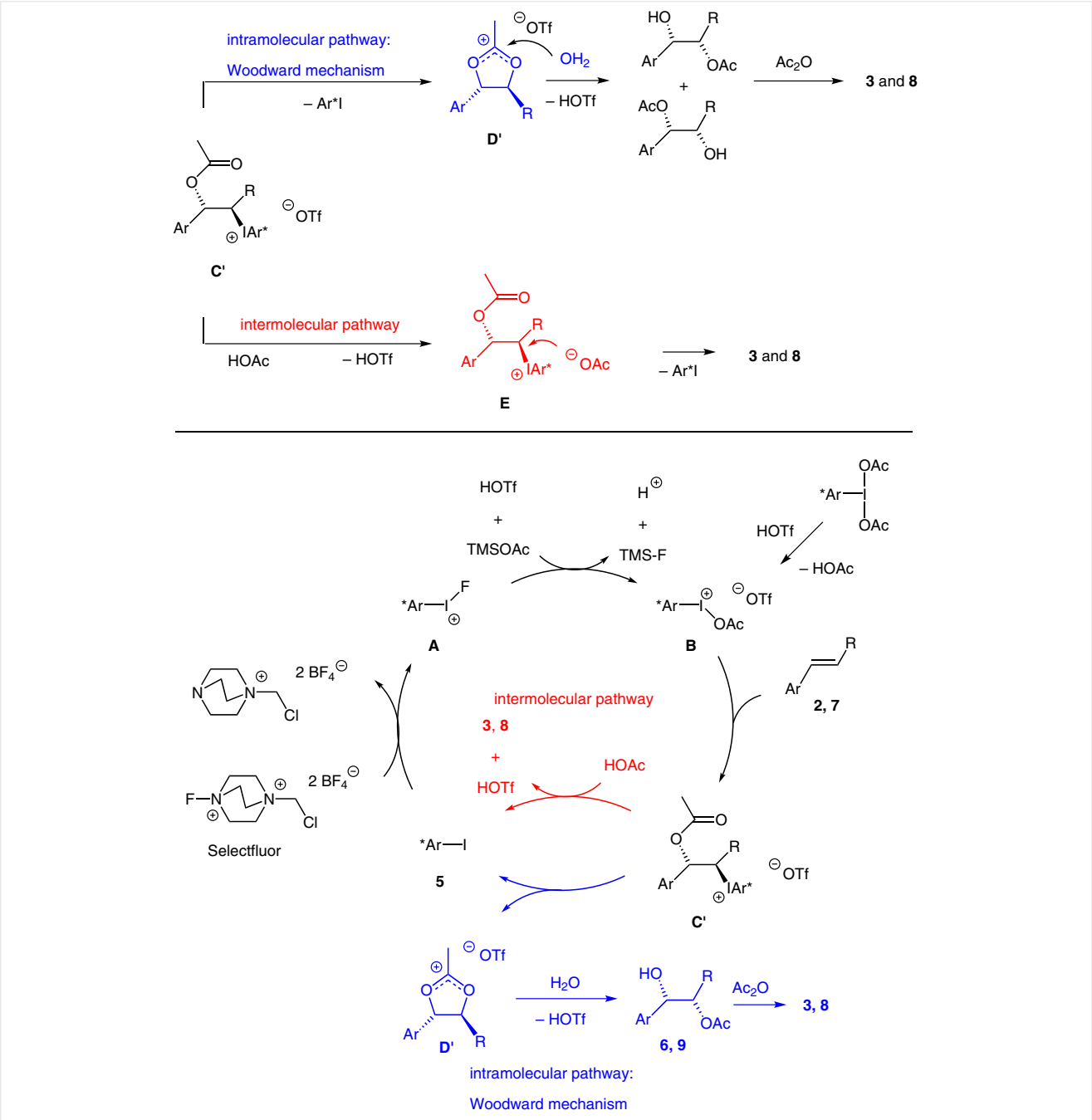


Figure 5 Mechanistic conclusion: Competing pathways in the enantioselective catalytic diacetoxylation of alkenes and overall catalytic cycle for diacetoxylation of terminal (R = H) and internal alkenes

ways lead to stereochemically uniform products, the relative participation of each of the enantioconvergent pathway does not alter the overall enantiomeric excess of the product. Figure 5 displays the full catalytic cycle based on all data including control experiments and stereochemical conclusions.

In summary, we have developed a second protocol for an iodine(III)-catalyzed enantioselective vicinal dioxygenation of alkenes under intermolecular reaction control. The reaction proceeds under mild conditions, extends the substrate class to β-substituted styrenes and provides the corresponding oxidation products with up to 96% *ee*. The two successful realizations of catalytic dioxygenation with **4b**,**c** and now **5d** should be instructive for the development of similar iodine(I/III)-catalyzed enantioselective difunctionalization reactions of alkenes.[29]

All solvents, reagents, and all deuterated solvents were purchased from Aldrich and Acros. Column chromatography was performed with silica gel Merck type 60 (0.063–0.20 mm). NMR spectra were recorded on a Bruker Avance 300 MHz, 400 MHz, or 500 MHz spectrometer, respectively. All chemical shifts in NMR experiments are reported in ppm downfield from TMS. The following calibrations were used: $CDCl_3$ δ = 7.26 and 77.16; DMSO-d_6 δ = 2.50 and 39.52. MS (ESILCMS) experiments were performed using an Agilent 1100 HPLC with a Bruker micro-TOF instrument (ESI). Unless otherwise stated, a Supelco C8 (5 cm × 4.6 mm, 5 µm particles) column was used with a linear elution gradient from 100% H_2O (0.5% HCO_2H) to 100% MeCN in 13 min at a flow rate of 0.5 mL/min. MS (EI) and HRMS experiments were performed on a Kratos MS 50 within the service departments at ICIQ. Melting points were determined with a Büchi Melting Point B-540 apparatus. IR spectra were taken with a Bruker Alpha instrument in the solid state. Specific optical rotation values were measured with a Polarimeter JascoP1030 equipped with a 100 mm cell. HPLC measurements were carried out on a Knauer Wellchrome (injection valve A0258, pump K-100, solvent organizer K-1500, UV detector K-2600). The respective chiral stationary phase and exact conditions are specified for each individual compound within the compound characterization section. Diastereomeric ratios were determined by achiral gas chromatography on an Agilent Technologies 7890A gas chromatograph equipped with an Agilent J & W HP-5 column.

Synthesis and availability of styrenes **2a**–**q**, diacetoxylation products **3a**–**q**, and the corresponding free diols were reported previously.[18] (*E*)-1-Phenyl-3-methoxypropene (**7b**),[30] (*E*)-3-(2-chlorophenyl)prop-2-en-1-ol (**7c**),[31a] (*E*)-3-(2-bromophenyl)prop-2-en-1-ol (**7d**),[31b] (*E*)-3-(3-fluorophenyl)prop-2-en-1-ol (**7e**),[31c] (*E*)-3-(4-fluorophenyl)prop-2-en-1-ol (**7f**),[31d] (*E*)-3-(4-trifluoromethylphenyl)prop-2-en-1-ol (**7g**)[31e] were synthesized according to a literature protocol.[32] Products **8a**,**b** were reported previously.[33]

Diacetoxylation of Alkenes Catalyzed by Hypervalent Iodine Reagents; General Procedure

A Pyrex tube equipped with a stir bar was charged with the respective iodine(I)- or iodine(III)-compound (0.040 mmol, 20 mol%) and AcOH (4 mL). The addition of the respective alkene (0.20 mmol, 1.0 equiv) was followed by subsequent addition of Selectfluor (0.50 mmol, 2.5 equiv) and TMSOTf (0.24 mmol, 1.2 equiv). The tube was sealed and the reaction mixture was stirred at r.t. for 12 h. The reaction mixture was poured into a separating funnel containing CH_2Cl_2 and H_2O. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 ×). The combined organic layers were washed with H_2O (1 ×) and brine (1 ×). Drying the organic phase over Na_2SO_4 and filtration was followed by removal of the solvents under reduced pressure. The residue was dissolved in CH_2Cl_2 (0.35 mL) and, depending on whether a styrene- or a cinnamyl alcohol derivative was used as the starting material, DMAP (0.050–0.070 mmol, 0.25–0.35 equiv), pyridine (0.50–0.70 mmol, 2.5–3.5 equiv), and Ac_2O (0.50–0.70 mmol, 2.5–3.5 equiv) were added. After stirring at r.t. for 5 h, aq 1 M HCl and H_2O were added and the aqueous phase was extracted with CH_2Cl_2 (3 ×). After drying over Na_2SO_4 and removing the solvent under reduced pressure, the crude product was purified by flash column chromatography on silica gel using hexane/EtOAc mixtures. In order to determine the enantiomeric excesses in the cases of styrene derivatives as starting materials, the pure product was dissolved in MeOH (0.1 M). Addition of K_2CO_3 (1.5 equiv) was followed by stirring at r.t. for 4 h. MeOH was removed under reduced pressure after acidification with aq 1 M HCl. Extraction of the aqueous layer with CH_2Cl_2 (3 ×), drying the combined organic layers over Na_2SO_4, and evaporation of the solvent yielded the corresponding diol, which was submitted to HPLC analysis. In the case of cinnamyl alcohol derived starting materials, enantiomeric excesses were determined at the stage of the acetoxylated products.

(*S*)-1-Phenylethane-1,2-diol-1,2-diacetate (3a)

Isolated yield: 29.4 mg (66%). HPLC-conditions for free diol: OD-H, hexane/*i*-PrOH = 95:5, 0.7 mL/min, t_R = 24.9 (minor), 27.3 (major): 80% *ee*.

(*S*)-1-(4-Fluorophenyl)ethane-1,2-diol-1,2-diacetate (3b)

Isolated yield: 26.4 mg (55%). HPLC-conditions for free diol: OD-H, hexane/*i*-PrOH = 95:5, 1 mL/min, t_R = 17.1 (minor), 18.5 (major): 74% *ee*.

(*S*)-1-(4-Chlorophenyl)ethane-1,2-diol-1,2-diacetate (3c)

Isolated yield: 32 mg (62%). HPLC-conditions for free diol: OD-H, hexane/*i*-PrOH = 95:5, 1 mL/min, t_R = 18.2 (minor), 19.8 (major): 74% *ee*.

(*S*)-1-(4-Bromophenyl)ethane-1,2-diol-1,2-diacetate (3d)

Isolated yield: 55.4 mg (92%). HPLC-conditions for free diol: OD-H, hexane/*i*-PrOH = 95:5, 0.5 mL/min, t_R = 39.9 (minor), 43.2 (major): 64% *ee*.

(*S*)-1-(4-Trifluoromethylphenyl)ethane-1,2-diol-1,2-diacetate (3e)

Isolated yield: 35.4 mg (61%). HPLC-conditions for free diol: OD-H, hexane/*i*-PrOH = 95:5, 0.5 mL/min, t_R = 34.8 (minor), 36.5 (major): 68% *ee*.

(*S*)-4-(Phthaloylmethylenephenyl)ethane-1,2-diol-1,2-diacetate (3f)

Isolated yield: 56.4 mg (74%). HPLC-conditions for free diol: IA, hexane/*i*-PrOH = 93:7, 1 mL/min, t_R = 90.3 (major), 101.6 (minor): 86% *ee*.

(*S*)-1-(4-*tert*-Butylphenyl)ethane-1,2-diol-1,2-diacetate (3g)

Isolated yield: 30.6 mg (55%). HPLC-conditions for free diol: OD, hexane/*i*-PrOH = 98:2, 0.8 mL/min, t_R = 48.7 (minor), 52.6 (major): 68 *ee*.

(*S*)-1-(3-Trifluoromethylphenyl)ethane-1,2-diol-1,2-diacetate (3h)

Isolated yield: 41.3 mg (71%). HPLC-conditions for free diol: OD-H, hexane/*i*-PrOH = 95:5, 0.7 mL/min, t_R = 19.8 (minor), 22.3 (major): 74 *ee*.

(*S*)-1-(3-Fluorophenyl)ethane-1,2-diol-1,2-diacetate (3i)

Isolated yield: 34.6 mg (72%). HPLC-conditions for free diol: OD-H, hexane/*i*-PrOH = 95:5, 1 mL/min, t_R = 16.0 (minor), 17.7 (major): 82% *ee*.

(*S*)-1-(2-Chlorophenyl)ethane-1,2-diol-1,2-diacetate (3j)

Isolated yield: 37.5 mg (73%). HPLC-conditions for free diol: OD-H, hexane/*i*-PrOH = 95:5, 1 mL/min, t_R = 13.4 (minor), 17.5 (major): 88% *ee*.

(*S*)-1-(2-Fluorophenyl)ethane-1,2-diol-1,2-diacetate (3k)

Isolated yield: 31 mg (65%). HPLC-conditions for free diol: OD-H, hexane/*i*-PrOH = 95:5, 1 mL/min, t_R = 12.7 (minor), 15.2 (major): 82% *ee*.

(*S*)-1-(2-Bromophenyl)ethane-1,2-diol-1,2-diacetate (3l)

Isolated yield: 42.2 mg (70%). HPLC-conditions for free diol: OD-H, hexane/*i*-PrOH = 95:5, 0.7 mL/min, t_R = 21.3 (minor), 27.9 (major): 86% *ee*.

(*S*)-1-(2-Methylphenyl)ethane-1,2-diol-1,2-diacetate (3m)

Isolated yield: 30.2 mg (64%). HPLC-conditions for free diol: OD-H, hexane/*i*-PrOH = 95:5, 0.7 mL/min, t_R = 21.9 (minor), 27.9 (major): 74% *ee*.

(*S*)-1-(3-Chloro-2-fluorophenyl)ethane-1,2-diol-1,2-diacetate (3n)

Isolated yield: 46.7 mg (85%). HPLC-conditions for free diol: OD-H, hexane/*i*-PrOH = 95:5, 0.7 mL/min, t_R = 20.0 (minor), 25.8 (major): 64% *ee*.

(*S*)-1-(4-Bromo-2-fluorophenyl)ethane-1,2-diol-1,2-diacetate (3o)

Isolated yield: 53 mg (83%). HPLC-conditions for free diol: OD-H, hexane/*i*-PrOH = 95:5, 0.7 mL/min, t_R = 20.1 (minor), 22.8 (major): 62% *ee*.

(*S*)-1-(3,5-Dimethylphenyl)ethane-1,2-diol-1,2-diacetate (3p)

Isolated yield: 31 mg (62%). HPLC-conditions for free diol: OD-H, hexane/*i*-PrOH = 95:5, 0.7 mL/min, t_R = 19.2 (minor), 22.3 (major): 62% *ee*.

(*S*)-1-(2-Naphthyl)ethane-1,2-diol-1,2-diacetate (3q)

Isolated yield: 34.3 mg (63%). HPLC-conditions for free diol: OD-H, hexane/*i*-PrOH = 90:10, 0.95 mL/min, t_R = 14.6 (minor), 17.7 (major): 64% *ee*.

(1*S*,2*S*)-1,2,3-Propanetriol-1-phenyl-1,2,3-triacetate (8a)

Isolated yield: 28.8 mg (49%). HPLC-conditions: OJ, hexane/*i*-PrOH = 85:15, 1.0 mL/min, t_R = 23.2 (major), 32.9 (minor): 88% *ee*.

(1*S*,2*S*)-3-Methoxy-1-phenyl-1,2-propanediol-1,2-diacetate (8b)

Isolated yield: 30 mg (56%). HPLC-conditions: IC, hexane/*i*-PrOH = 95:5, 0.5 mL/min, t_R = 23.7 (minor), 27.3 (major): 86% *ee*.

(*R*,*R*)-1,3-Bis[1-(2-adamantoxycarbonyl)ethoxy]-2-iodobenzene (5c)

According to the procedure of Breit,[34] a solution of *N*,*N*-dicyclohexylcarbodiimide (706 mg, 3.42 mmol, 2.60 equiv) in CH_2Cl_2 (4.4 mL) was added to a suspension of (2*R*,2′*R*)-2,2′-(2-iodo-1,3-phenylene)bis(oxy)dipropanoic acid (500 mg, 1.32 mmol), 2-adamantanol (881 mg, 5.79 mmol, 4.40 equiv), and DMAP (106 mg, 0.870 mmol, 0.660 equiv) in CH_2Cl_2 (6.6 mL) at 0 °C. Stirring was continued for 12 h, while the reaction mixture was allowed to warm to r.t. slowly. A small amount of silica gel was added to the reaction mixture, the solvent was removed under reduced pressure, and the crude product was submitted to flash column chromatography using hexane/EtOAc (12:1) as eluent. Washing the obtained compound with pentane yielded the pure product (604 mg, 71%) as a white crystalline solid; mp 136 °C; $[\alpha]_D^{25}$ –39.1 (*c* = 0.115, $CHCl_3$).

IR (ATR): 2989, 2903, 2852, 2673, 2119, 1736, 1719, 1587, 1458, 1374, 1344, 1277, 1252, 1217, 1200, 1182, 1135, 1098, 1067, 1041, 1016, 977, 964, 933, 903, 860, 817, 798, 764, 753, 703, 675, 647, 626, 607, 575, 508, 456, 412 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.37–2.01 (m, 28 H), 1.71 (d, *J* = 6.5 Hz, 6 H), 4.80 (q, *J* = 4.6 Hz, 2 H), 4.94–4.97 (m, 2 H), 6.39 (d, *J* = 8.6 Hz, 2 H), 7.10 (t, *J* = 8.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.8, 27.0, 27.2, 31.6, 31.8, 31.8, 32.0, 36.3, 36.4, 37.4, 74.4, 78.3, 80.6, 106.7, 129.5, 158.4, 171.2.

HRMS: *m*/*z* calcd for $C_{32}H_{41}INaO_6^+$: 671.1840; found: 671.1846.

(*R*,*R*)-1,3-Bis[1-(1-adamantoxycarbonyl)ethoxy]-2-iodobenzene (5d)

According to the procedure described above for compound **5c**,[21] the title compound was obtained as a white crystalline solid (76%); mp 153 °C; $[\alpha]_D^{25}$ –27.9 (*c* = 0.1, $CHCl_3$).

IR (ATR): 2985, 2907, 2852, 2117, 1746, 1586, 1458, 1374, 1349, 1315, 1288, 1250, 1201, 1180, 1126, 1101, 1069, 1046, 1021, 966, 940, 916, 899, 876, 831, 761, 752, 725, 701, 642, 606, 589, 525, 467, 453, 407 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.62–1.64 (m, 12 H), 1.66 (d, *J* = 6.8 Hz, 6 H), 2.03–2.09 (m, 12 H), 2.12–2.16 (m, 6 H), 4.63 (q, *J* = 6.5 Hz, 2 H), 6.37 (d, *J* = 8.2 Hz, 2 H), 7.12 (t, *J* = 7.9 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.7, 31.0, 36.2, 41.3, 74.6, 80.6, 82.1, 106.7, 129.3, 158.5, 170.7.

HRMS: *m*/*z* calcd for $C_{32}H_{41}INaO_6^+$: 671.1840; found: 671.1840.

(1*S*,2*S*)-1,2,3-Propanetriol-1-(2-chlorophenyl)-1,2,3-triacetate (8c)

Synthesized according to the general procedure; colorless oil; isolated yield: 43 mg (65%). HPLC conditions: OJ, hexane/*i*-PrOH = 85:15, 0.5 mL/min, t_R = 35.3 (major), 45.7 (minor).

IR (ATR): 2958, 2926, 2854, 1742, 1475, 1442, 1370, 1209, 1126, 1042, 960, 865, 760, 741, 710, 689, 602, 568, 546, 475, 459, 415 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.99 (s, 3 H), 2.05 (s, 3 H), 2.12 (s, 3 H), 4.04 (dd, *J* = 11.8, 6.6 Hz, 1 H), 4.27 (dd, *J* = 11.8, 4.5 Hz, 1 H), 5.55 (ddd, *J* = 6.6, 5.3, 4.5 Hz, 1 H), 6.41 (d, *J* = 5.3 Hz, 1 H), 7.23–7.29 (m, 2 H), 7.35–7.40 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.8, 20.8, 21.0, 62.2, 70.6, 71.1, 127.1, 128.3, 129.9, 130.0, 133.0, 134.1, 169.5, 169.9, 170.6.

HRMS: *m*/*z* calcd for $C_{15}H_{17}ClNaO_6^+$: 351.0606; found: 351.0602.

(1*S*,2*S*)-1,2,3-Propanetriol-1-(2-bromophenyl)-1,2,3-triacetate (8d)

Synthesized according to the general procedure; colorless oil; isolated yield: 44 mg (59%). HPLC conditions: IB, hexane/*i*-PrOH = 95:5, 0.3 mL/min, t_R = 28.6 (major), 30.3 (minor).

IR (ATR): 3423, 2961, 1744, 1470, 1438, 1370, 1210, 1122, 1043, 1021, 961, 865, 759, 737, 686, 603, 567, 545, 470, 453 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.99 (s, 3 H), 2.05 (s, 3 H), 2.12 (s, 3 H), 4.07 (dd, *J* = 11.8, 6.6 Hz, 1 H), 4.27 (dd, *J* = 11.8, 5.0 Hz, 1 H), 5.55 (ddd, *J* = 6.7, 5.0, 5.0 Hz, 1 H), 6.37 (d, *J* = 5.0 Hz, 1 H), 7.15–7.19 (m, 1 H), 7.28–7.32 (m, 1 H), 7.36–7.39 (m, 1 H), 7.54–7.56 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7, 20.9, 20.9, 62.2, 71.1, 72.8, 122.9, 127.6, 128.6, 130.2, 133.3, 135.8, 169.5, 169.8, 170.6.

HRMS: *m*/*z* calcd for $C_{15}H_{17}BrNaO_6^+$: 395.0101; found: 395.0110.

(1*S*,2*S*)-1,2,3-Propanetriol-1-(3-fluorophenyl)-1,2,3-triacetate (8e)

Synthesized according to the general procedure; colorless oil; isolated yield of a 4:1 diastereomeric mixture: 26.2 mg (42%). HPLC conditions: IB, hexane/*i*-PrOH 0 95:5, 0.5 mL/min, t_R = 16.0 (minor), 18.3 (major).

IR (ATR): 3441, 2962, 1742, 1617, 1593, 1490, 1450, 1371, 1210, 1145, 1079, 1044, 969, 947, 912, 872, 792, 768, 732, 702, 648, 602, 522, 485, 448, 409 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.05 (s, 3 H), 2.05 (s, 3 H), 2.10 (s, 3 H), 3.82 (dd, *J* = 12.1, 5.7 Hz, 1 H), 4.28 (dd, *J* = 12.1, 4.0 Hz, 1 H), 5.39 (ddd, *J* = 6.6, 5.7, 3.9 Hz, 1 H), 5.94 (d, *J* = 6.6 Hz, 1 H), 6.99–7.09 (m, 2 H), 7.12–7.14 (m, 1 H), 7.30–7.35 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 20.8, 21.0, 62.1, 72.2, 73.3 (d, *J* = 1.8 Hz), 114.3 (d, *J* = 23.0 Hz), 116.0 (d, *J* = 20.0 Hz), 122.9 (d, *J* = 3.1 Hz), 130.5 (d, *J* = 8.3 Hz), 138.7 (d, *J* = 7.3 Hz), 163.0 (d, *J* = 246.9 Hz), 169.8, 170.0, 170.5.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –112.1.

HRMS: *m*/*z* calcd for $C_{15}H_{17}FNaO_6^+$: 335.0901; found: 335.0912.

(1*S*,2*S*)-1,2,3-Propanetriol-1-(4-fluorophenyl)-1,2,3-triacetate (8f)

Synthesized according to the general procedure; white solid; mp 103 °C; isolated yield: 27.5 mg (44%). HPLC conditions: IB, hexane/*i*-PrOH = 95:5, 0.5 mL/min, t_R = 16.6 (minor), 19.0 (major).
IR (ATR): 2959, 1740, 1607, 1512, 1434, 1371, 1211, 1160, 1044, 961, 837, 788, 730, 689, 647, 603, 544, 501, 435 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.05 (s, 3 H), 2.05 (s, 3 H), 2.08 (s, 3 H), 3.80 (dd, *J* = 12.1, 5.8 Hz, 1 H), 4.26 (dd, *J* = 12.1, 3.8 Hz, 1 H), 5.40 (ddd, *J* = 7.1, 5.7, 3.7 Hz, 1 H), 5.94 (d, *J* = 7.1 Hz, 1 H), 7.02–7.08 (m, 2 H), 7.32–7.37 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 20.9, 21.1, 62.2, 72.3, 73.3, 115.9 (d, *J* = 21.7 Hz), 129.2 (d, *J* = 8.4 Hz), 132.0 (d, *J* = 3.3 Hz), 163.0 (d, *J* = 248.4 Hz), 169.8, 170.1, 170.5.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –112.5.

HRMS: *m*/*z* calcd for $C_{15}H_{17}FNaO_6^+$: 335.0901; found: 335.0900.

(1*S*,2*S*)-1,2,3-Propanetriol-1-(4-trifluoromethylphenyl)-1,2,3-triacetate (8g)

Synthesized according to the general procedure; white solid; isolated yield of a 4:1 diastereomeric mixture: 47 mg (65%). HPLC conditions: IB, hexane/*i*-PrOH = 95:5, 0.5 mL/min, t_R = 16.3 (minor), 26.8 (major).

IR (ATR): 2958, 1742, 1622, 1422, 1372, 1324, 1212, 1164, 1122, 1066, 1044, 1017, 962, 839, 765, 749, 697, 602, 531, 454, 432 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.04 (s, 3 H), 2.04 (s, 3 H), 2.11 (s, 3 H), 3.82 (dd, *J* = 12.2, 5.7 Hz, 1 H), 4.30 (dd, *J* = 12.2, 4.2 Hz, 1 H), 5.42 (ddd, *J* = 6.5, 5.8, 4.1 Hz, 1 H), 6.00 (d, *J* = 6.6 Hz, 1 H), 7.47–7.49 (m, 2 H), 7.61–7.63 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 20.8, 21.0, 62.0, 72.0, 73.3, 123.9 (q, *J* = 272.6 Hz), 125.8 (q, *J* = 3.8 Hz), 127.6, 131.2 (q, *J* = 32.8 Hz), 140.2 (q, *J* = 1.3 Hz), 169.7, 169.9, 170.5.

^{19}F NMR (282 MHz, $CDCl_3$): δ = – 62.9.

HRMS: *m*/*z* calcd for $C_{16}H_{17}F_3NaO_6^+$: 385.0869; found: 385.0876.

(1*S*,2*S*)-3-Methoxy-1-phenyl-1,2-propanediol-2-acetate (9a) and (1*S*,2*S*)-3-Methoxy-1-phenyl-1,2-propanediol-1-acetate (9b)

These compounds were synthesized from **7b** according to the general procedure, but without acetoxylation using Ac_2O. Separation by column chromatography from the corresponding diacetate **8b** afforded the pure compounds as colorless liquids; combined isolated yield: 27.8 mg (55%).

IR (ATR, both regioisomers): 3455, 3033, 2927, 1737, 1495, 1453, 1372, 1231, 1197, 1127, 1081, 1025, 985, 952, 916, 871, 850, 762, 732, 701, 622, 540, 495, 448 cm^{-1}.

Major Regioisomer

^1H NMR (400 MHz, $CDCl_3$): δ = 2.12 (s, 3 H), 2.33 (br s, 1 H), 3.17 (dd, *J* = 9.8, 5.6 Hz, 1 H), 3.30–3.34 (m, 1 H), 3.31 (s, 3 H), 4.00 (ddd, *J* = 7.3, 5.6, 3.3 Hz, 1 H), 5.84 (d, *J* = 7.5 Hz, 1 H), 7.28–7.40 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 59.3, 72.8, 73.3, 76.8, 127.3, 128.6, 128.7, 137.5, 170.4.

Minor Regioisomer

^1H NMR (400 MHz, $CDCl_3$): δ = 2.08 (s, 3 H), 2.33 (br s, 1 H), 3.33 (s, 3 H), 3.38 (dd, *J* = 10.8, 4.1 Hz, 1 H), 3.55 (dd, *J* = 10.7, 4.1 Hz, 1 H), 5.00 (d, *J* = 5.9 Hz, 1 H), 5.14 (ddd, *J* = 5.7, 4.4, 3.8 Hz, 1 H), 7.28–7.40 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 59.5, 71.7, 73.7, 75.9, 126.7, 128.3, 128.7, 140.2, 170.8.

HRMS: *m*/*z* (both regiosisomers) calcd for $C_{12}H_{16}NaO_4^+$: 247.0946; found: 247.0941.

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Supporting Information

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