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PAPER

$Sc(OTf)_3$-catalyzed diastereoselective Friedel–Crafts reactions of arenes and hetarenes with 3-phenylglycidates†

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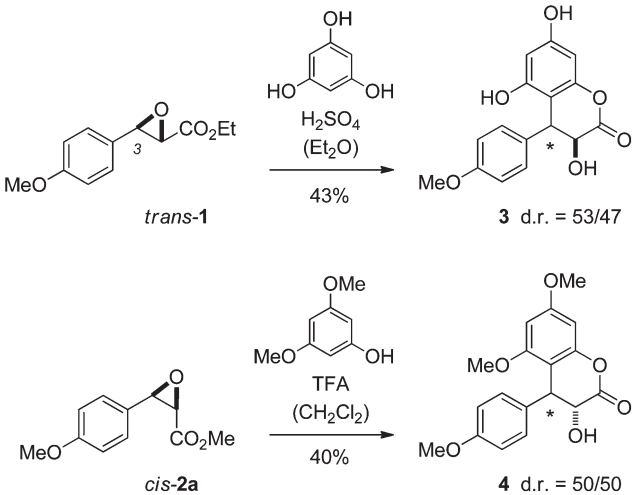
Five different *para*-substituted 3-phenylglycidates (3-phenyloxirane-2-carboxylates) were prepared and subjected to reactions with arenes and hetarenes under Lewis acid catalysis. $Sc(OTf)_3$ was found to effectively (5 mol%) promote a Friedel–Crafts reaction in nitromethane as the solvent. The reaction was shown to proceed stereoconvergently, which makes the intermediacy of a benzylic cation likely. The diastereoselectivities varied depending on the choice of the nucleophile and 3-arylglycidate. Best results were obtained with *tert*-butyl 3-anisylglycidate, which delivered the respective products with high *syn*-preference in diastereomeric ratios (d.r.) between 82 : 18 and >95 : 5. The observed selectivity can be explained by a model, according to which the intermediate benzylic cations adopt a preferred conformation, which allows for diastereoface-differentiation by the adjacent stereogenic center.

Introduction

3-Arylglycidates are readily available compounds,[1] which serve as electrophilic building blocks for introducing appropriate carbon nucleophiles into the β-position of β-aryl-α-hydroxypropionates. If arenes are used as nucleophiles, the reaction with 3-arylglycidates provides Friedel–Crafts reaction[2] products, which exhibit a diarylsubstitution pattern at the β-carbon atom of the resulting propionate. The stereochemical result of the Friedel–Crafts type reactions depends on the reaction conditions. Under acidic conditions the reaction often follows an S_N1-type mechanism, which leads to a (temporary) loss of the stereogenic center at carbon atom C3.

Depending on whether the attack at the resulting carbocation is stereoselective, β,β-diaryl-α-hydroxypropionates are formed either as pure diastereoisomers or as a mixture of diastereoisomers. In Scheme 1 two reactions are depicted, in which the Friedel–Crafts reactions proceeded nonselectively in the presence of Brønsted acids.[3] Starting from glycidates *trans*-**1** or *cis*-**2a** the reactions produced the dihydrocoumarins **3**[3a] and **4**[3b] as essentially a 1 : 1-mixture of diastereoisomers. In these examples the α-hydroxypropionates were not isolated but immediate lactone formation took place.

Reactions in which β,β-diaryl-α-hydroxypropionates are formed from arenes and the respective glycidates[4] have been reported in the literature. However, there is no or little information about the outcome of an S_N1-type displacement. In studies, which were concerned with Lewis acid catalyzed alkylations of pyrrole[5] and indoles,[6] 3-phenylglycidates were used as electrophiles but the diastereoselectivity of the reaction was not mentioned. The reaction of indoles with ethyl 3-phenylglycidate in 2,2,2-trifluoroethanol proceeded with inversion of configuration for the *trans*-isomer while no reaction occurred for the *cis*-isomer.[7] The somewhat related reaction of triarylborates with methyl 3-phenylglycidate also resulted in inversion of configuration but the stereospecificity was incomplete with some substrates.[8] Among possible other methods (which do not start from



Scheme 1 Brønsted-acid promoted, unselective epoxide ring opening reactions of 3-anisylglycinates *trans*-**1** and *cis*-**2a** to the respective dihydrocoumarins **3** and **4**.

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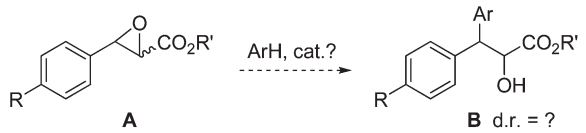


Scheme 2 Key question of the present study: Can compounds **A** be diastereoselectively converted to products **B** in the presence of an appropriate catalyst?

3-arylglycidates), diastereoselective access to β,β-diaryl-α-acetoxypropionates from cyclic *ortho*-esters was reported by Bozell *et al*.[9] They invoked a free carbocation intermediate, which was postulated to be attacked by the nucleophile in a Felkin–Anh type transition state.

We became interested in 3-arylglycidates as potential Friedel–Crafts electrophiles in connection with our studies on stereoselective reactions of benzylic cations, which bear a stereogenic center adjacent to the cationic carbon atom.[10] An acid-catalyzed ring opening of substrates **A** (Scheme 2) under appropriate conditions should lead to chiral benzylic cations, which might be diastereoselectively attacked to form products **B** with significant diastereoselectivity (d.r. = diastereomeric ratio).

In contrast to earlier studies, which were concerned mostly with only one functional group at the stereogenic center,[10] the stereogenic center would carry in this case two functional groups. In this account we summarize the results of our investigations, which led to a protocol for the diastereoselective $Sc(OTf)_3$-catalyzed Friedel–Crafts reaction of arenes and hetarenes with *tert*-butyl 3-anisylglycidate.

Results and conclusions

The *para*-substituted methyl 3-phenylglycidates *trans*-**2** (Fig. 1) were prepared by Darzens reaction of the respective aldehydes with an α-chloroacetate under basic conditions.[11] The previously mentioned *cis*-isomer of compound **2a** (Scheme 1) was synthesised from an appropriate *syn*-α,β-dihydroxypropionate upon tosylation[12,13] and intramolecular nucleophilic substitution.[13] The *tert*-butyl 3-arylglycidate *trans*-**5** was prepared from the corresponding *tert*-butyl ketone by a Baeyer–Villiger oxidation.[14]

Extensive catalyst screening was performed with glycidate *trans*-**2a** and 1,3-dimethoxybenzene as the nucleophile, some results of which are listed in Table 1. Even with the stoichiometrically employed Lewis acid $BF_3{\cdot}OEt_2$, significant diastereoselectivity in favor of the *syn*-product *syn*-**6a** was observed (entry 1). This selectivity increased further when using substoichiometric amounts of metal triflates, with $Bi(OTf)_3$ (entry 3) being slightly superior in selectivity over $Sc(OTf)_3$ (entries 4 and 5) and $Yb(OTf)_3$ (entry 6). The activity of $Bi(OTf)_3$ was low, however, resulting in a decreased yield of only 50%. $FeCl_3$ (entry 2) was less selective than the triflates, whereas $AuCl_3$

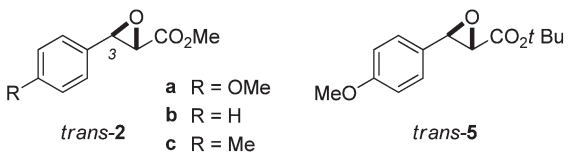
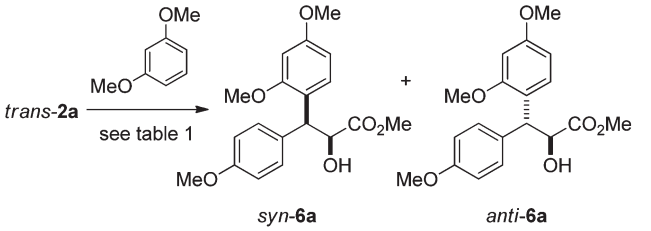


Fig. 1 Structure and substitution pattern of *para*-substituted 3-phenylglycidates *trans*-**2** and *trans*-**5**.

Table 1 Catalyst screening for the diastereoselective conversion of 3-anisylglycidate *trans*-**2a** to the 3,3-diaryl-2-hydroxypropionate **6a**



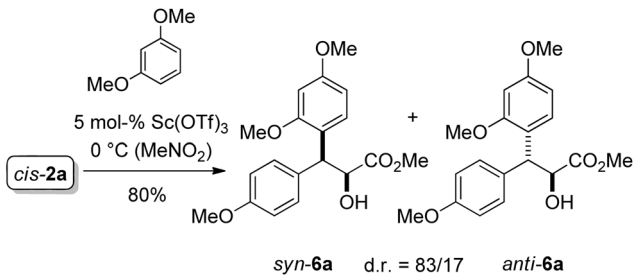
Entry[a]	Catalyst	Cat-loading [mol%]	Temp.	Yield[b] [%]	d.r. (*syn*–*anti*)[c]
1	$BF_3{\cdot}OEt_2$	110	0 °C → r.t.	54	81 : 19
2	$FeCl_3$	10	0 °C → r.t.	29	78 : 22
3	$Bi(OTf)_3$	10	0 °C → r.t.	50	86 : 14
4	$Sc(OTf)_3$	10	0 °C → r.t.	66	83 : 17
5	$Sc(OTf)_3$	5	0 °C	76	83 : 17
6	$Yb(OTf)_3$	5	0 °C	—[d]	83 : 17
7	$AuCl_3$	5	0 °C	80	83 : 17
8	$Sc(OTf)_3$	2	0 °C	43	82 : 18
9	$Sc(OTf)_3$	5	−20 °C	62	83 : 17
10[e]	$Sc(OTf)_3$	5	−20 °C	62	76 : 24

[a] All reactions were conducted with four equivalents of 1,3-dimethoxybenzene at a substrate concentration of 125 mM in nitromethane as the solvent and with a reaction time of 45 min. [b] Yield of isolated product as a diastereomeric mixture. [c] The diastereomeric ratio (d.r.) of the crude product was determined by ^1H NMR spectroscopy. [d] The exact determination of the yield was not possible because the desired product was not obtained free from by-products. [e] The reaction was performed in dichloromethane as the solvent.

(entry 7) showed similar selectivity. Although the performance of $Sc(OTf)_3$ and $AuCl_3$ were under otherwise identical conditions (entries 5 and 7) almost equal, the lower costs for the former catalyst let us employ this Lewis acid in further studies. Lowering the catalyst amount to 2 mol% resulted in an incomplete conversion after 5 hours (entry 8). With 5 mol% of the catalyst, the Friedel–Crafts reaction could be successfully performed even at −20 °C (*vide infra*). A selectivity increase was not observed, however, while the reaction rate expectedly decreased (entry 9). Dichloromethane was an inferior solvent as compared to nitromethane. It did not increase the reaction rate but the diastereoselectivity of the reaction was lower than in nitromethane (entries 9 and 10).

In order to prove that the reaction of glycidate **2a** proceeds *via* a cationic intermediate, the *cis*-isomer of *trans*-**2a**, *cis*-**2a**, was subjected to the reaction conditions, which have been found to be optimal for a rapid and selective conversion of *trans*-**2a** into products **6a** (Table 1, entry 5). Under identical reaction conditions the conversion was equally smooth and the diastereoisomers *syn*-**6a** and *anti*-**6a** were formed in exactly the same diastereoselectivity than with *trans*-**6a** (Scheme 3).

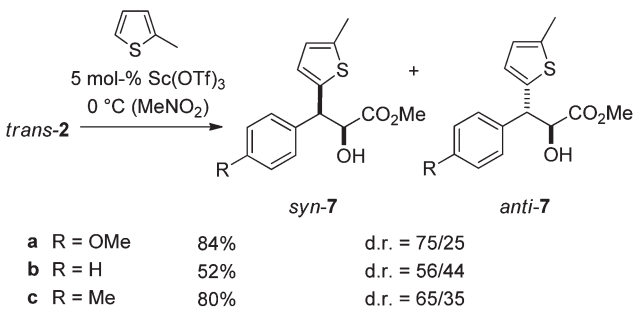
When employing other *para*-substituted 3-phenylglycidates *trans*-**2** we found that the selectivity of the reactions differed significantly from what was observed with glycidate *trans*-**2a**. Reactions with 1,3-dimethoxybenzene became almost completely unselective. The reaction with the *para*-methyl substituted 3-phenylglycidate *trans* **2c** gave the product with a d.r. of 57 : 43 and the unsubstituted 3-phenylglycidate *trans*-**2b** behaved



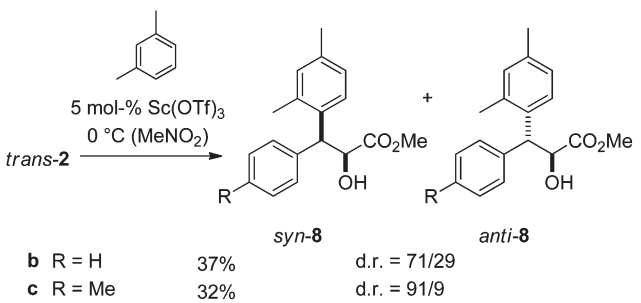
Scheme 3 Stereoconvergent reaction course in the Friedel–Crafts alkylation of 3-phenylglycidates as shown for the reaction of **2a** with 1,3-dimethoxybenzene (*cf.* Table 1, entry 5).

similarly (d.r. = 54 : 46). It could be speculated that the lack of selectivity for less stabilized benzylic cations is due to their higher reactivity, which renders the reaction rate with reactive nucleophiles close to diffusion control. Indeed, 1,3-dimethoxybenzene is a relatively reactive arene, to which an *N* value of *N* = 2.48 was assigned by Mayr *et al.* on their nucleophilicity scale.[15] Reactions with less reactive nucleophiles should retain the selectivity. 2-Methylthiophene (*N* = 1.26) gave with the least reactive cation (R = OMe) derived from *trans*-**2a** a moderate d.r. of 75 : 25, which did not completely vanish when going to higher electrophilicity (Scheme 4). With R = Me (*trans*-**2c**) the d.r. was still 65 : 35 but decreased further to d.r. = 56 : 44 for R = H (*trans*-**2b**).

The effect was more pronounced when using the even less reactive arene *meta*-xylene (*N* = −3.54, Scheme 5). With this nucleophile, the reaction with glycidate *trans*-**2c** proceeded with high diastereoselectivity (d.r. = 91 : 9), which decreased when using the unsubstituted 3-phenylglycidate *trans*-**2b**.



Scheme 4 Diastereoselective Friedel–Crafts reactions of *para*-substituted 3-phenylglycidates *trans*-**2** with 2-methylthiophene.

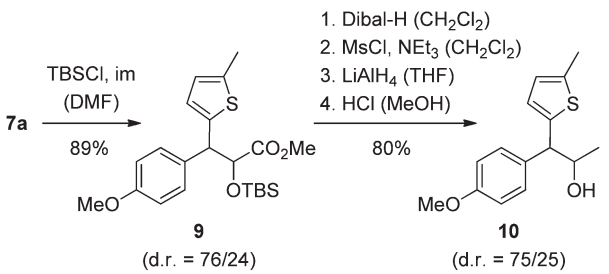


Scheme 5 Diastereoselectivity in the Friedel–Crafts reaction of weakly nucleophilic *meta*-xylene with 3-phenylglycidates *trans*-**2b** and -**2c**.

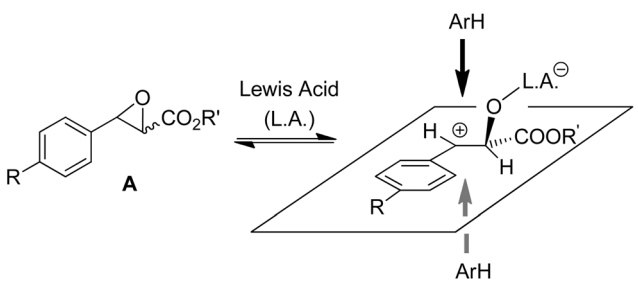
Unfortunately, the chemoselectivity of the reaction was not satisfactory and side reactions of the putative benzyl cations occurred. The more stabilized cation derived from 3-anisylglycidate *trans*-**2a** did not react with *meta*-xylene.

Products **7a** (d.r. = 75 : 25) were used to determine the relative configuration of the major and the minor diastereoisomer. After protection of the secondary alcohol as *tert*-butyldimethylsilyl (TBS) ether **9**, the ester group was completely reduced to the methyl group (Scheme 6). Reduction with Dibal-H delivered the primary alcohol, which was converted into the respective methanesulfonate (Ms = methanesulfonyl). Reductive displacement of the leaving group with $LiAlH_4$ delivered the immediate precursor of alcohol **10**, which was obtained after silyl deprotection under acidic conditions. The whole sequence was performed without purification of the intermediates and proceeded in an overall yield of 80%. The diastereomeric ratio remained unchanged during these transformations. The relative configuration of compound *syn*-**10** has been earlier established by single X-ray crystallography of its 2,4-dinitrobenzoate.[10c] The major diastereoisomer of the reaction sequence **7a** → **10** proved to be identical to *syn*-**10**, while the physical data of the minor diastereoisomer matched the known values of *anti*-**10**.[16] Assignments for the other major products are based on analogy.

For the interpretation of the observed facial diastereoselectivity we invoke our previously suggested[10d] model for the reaction of chiral benzylic cations. The model is based on the preferred conformation of these cations, which is enforced by 1,3-allylic strain and which was substantiated by extensive low temperature NMR studies of these cations in superacidic media.[17] While approaching the electrophilic cation center, nucleophiles encounter less steric strain when passing a small substituent but more strain when passing a large substituent. This fact is reflected by different free energies of the relative transition states (Scheme 7).



Scheme 6 Configuration proof for products **7a** by conversion into the known 1,1-diarylpropanes *syn*-**10** and *anti*-**10**.

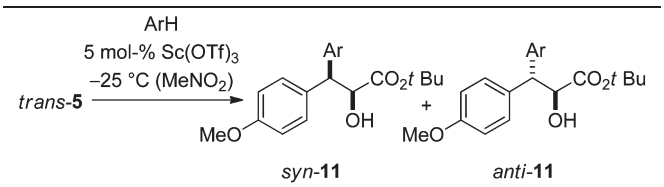


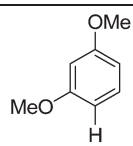
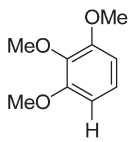
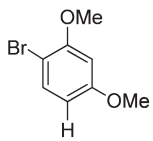
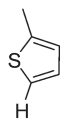
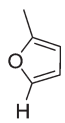
Scheme 7 Model for the diastereoface differentiation in the intermediary cations derived from glycidates of general structure **A**.

In the present case the oxy group is small despite its coordination to a Lewis acid (L.A.) while the ester group is larger. Tabulated *A* values[18] support this notion (A_{OH} = 1.0, A_{COOMe} = 1.2).

The model was supported by the fact that the diastereoselectivity of the reaction increased when increasing the size of the ester substituent R′. An initial experiment with *tert*-butyl ester *trans*-**5** under conditions otherwise identical to those used for the reaction of 1,3-dimethoxybenzene with methyl ester *trans*-**2a** delivered the desired product **11a** in a d.r. of 90 : 10 – as opposed to 83 : 17 for **6a**. However, the lower stability of the *tert*-butyl ester diminished the yield at a reaction temperature of 0 °C. Upon lowering the temperature both diastereo- and chemoselectivity improved and a reaction temperature of −25 °C was found to be optimal to guarantee high conversion with concomitant high diastereoselectivity (Table 2, entry 1).

Table 2 Diastereoselective reaction of *tert*-butyl 3-anisyl-glycidate (*trans*-**5**) with various arenes



Entry[a]	ArH	Product	Yield[b] [%]	d.r. (*syn*–*anti*)[c]
1		**11a**	77	93 : 7
2		**11b**	56	>95 : 5
3		**11c**	66	92 : 8
4		**11d**	71	84 : 16
5		**11e**	58	82 : 18
6		**11f**	37[d]	93 : 7

[a] All reactions were conducted with four equivalents of ArH and 5 mol% of $Sc(OTf)_3$ at a substrate concentration of 75.0 mM in nitromethane as the solvent and with a reaction time of 4 h. [b] Yield of isolated product as a diastereomeric mixture. [c] The diastereomeric ratio (d.r.) of the crude product was determined by ^{1}H NMR spectroscopy. [d] The reaction was performed at 0 °C.

Under these conditions other arenes and hetarenes could be brought to react with 3-anisylglycidate *trans*-**5** to produce the respective products **11** (Table 2, entries 2–6). Diastereoselectivities were consistently high varying between 82 : 18 and >95 : 5. The low solubility of *N*-tosylpyrrole forced us to use a higher reaction temperature (0 °C), which compromised the yield. In all other cases yields were moderate to good (56–77%).

In summary, 3-arylglycidates were employed successfully as electrophiles in $Sc(OTf)_3$-catalyzed Friedel–Crafts reactions with various arenes and hetarenes. A large ester substituent (*tert*-butyl) favorably influences the diastereoselectivity of the reaction and preparatively useful diastereoselectivities were recorded for the 3-arylglycidate *trans*-**5**.

Experimental

General methods

All reactions involving moisture-sensitive chemicals were carried out in flame-dried glassware in dried solvents with magnetic stirring under argon. Diethyl ether (Et_2O) and dichloromethane (CH_2Cl_2) were purified by using an SPS-800 solvent purification system (M. Braun). All other chemicals were used as received. TLC was performed on silica coated glass plates (silica gel 60 F_{254}) with detection by UV (254 nm) or ceric ammonium molybdate (CAM) with subsequent heating. Flash chromatography was performed on silica gel 60 (Merck, 230–400 mesh) with the indicated eluent. All solvents for chromatography [pentane (P) and diethyl ether (Et_2O)] were distilled prior to use. IR-spectra were recorded on a JASCO IR-4100 (ATR), MS/HRMS-measurements were performed on a Finnigan MAT 8200 (EI), a Finnigan MAT 95S (HR-EI), a Finnigan LCQ classic (ESI) and a Thermo Scientific LTQ Orbitrap XL (HRMS-ESI). ^{1}H– and ^{13}C–NMR-spectra were recorded in $CDCl_3$ at 303 K either on a Bruker AV-250, a Bruker AV–360 or a Bruker AV-500 spectrometer. The chemical shifts are reported relative to $CHCl_3$ (δ = 7.26 ppm). Apparent multiplets that occur as a result of the accidental equality of coupling constants to those of magnetically nonequivalent protons are marked as virtual (*virt*). The multiplicities of the ^{13}C–NMR signal were determined by DEPT experiments, assignments (see ESI†) are based on COSY, HMBC and HMQC experiments. Melting points were measured on a Koffler Thermopan and are uncorrected. Elemental analyses were carried out on an Elementar Vario EL in the Department Chemie at the Technische Universität München.

Diastereoselective Friedel–Crafts reactions

Analytical data are provided for representative compounds. A complete set of data for all new compounds can be found in the ESI.†

General procedure I for the Friedel–Crafts reactions with 3-arylglycidates 2. A flame-dried Schlenk flask was purged with argon and charged with the glycidate (250 μmol, 1.00 equiv.) and the aryl nucleophile (1.00 mmol, 4.00 equiv.) in dry nitromethane (2 mL). The solution was cooled to 0 °C and $Sc(OTf)_3$ (6.15 mg, 12.5 μmol, 0.05 equiv.) was added. The resulting

mixture was stirred at 0 °C for 45 min. The reaction was quenched with sat. aqueous $NaHCO_3$ (5 mL) and diluted with CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 7 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography to give the respective product.

Methyl 3-(2,4-dimethoxyphenyl)-2-hydroxy-3-(4–methoxyphenyl)propanoate (6a). Following general procedure I, reaction of **2a** (52.1 mg, 250 µmol, 1.00 equiv.) with 1,3–dimethoxybenzene (138 mg, 132 µL, 1.00 mmol, 4.00 equiv.) and $Sc(OTf)_3$ (6.15 mg, 12.5 µmol, 0.05 equiv.) yielded after flash chromatography (P–Et_2O: 4 : 1 → 2 : 1) **6a** (66.0 mg, 191 µmol, 76%) as a colourless solid (d.r. *syn–anti* 83 : 17). R_f = 0.21 (P–Et_2O: 1 : 1) [UV, CAM]; m.p.: 130–132 °C; IR: $\tilde{\nu}$ = 3556 (br, OH), 2954 (w, $C_{al}H$), 2837 (w, OMe), 2353 (m), 1732 (vs, C═O), 1610 (s), 1584 (s), 1501 (vs), 1473 (m, CH_3), 1246 (vs, COC), 1181 (m), 1112 (vs), 1087 (m), 1028 (s), 841 cm^{-1} (s, $C_{ar}H$).

***syn*-Diastereoisomer (*syn*-6a).** ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 2.76 (bs, 1 H), 3.67 (s, 3 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 3.78 (s, 3 H), 4.82–4.85 (m, 2 H), 6.40–6.44 (m, 2 H), 6.83 (*virt*. d, $J \cong$ 8.4 Hz, 2 H), 7.11 (d, ^3J = 8.4 Hz, 1 H), 7.30 (*virt*. d, $J \cong$ 8.4 Hz, 2 H); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ [ppm] = 45.7 (d), 52.1 (q), 55.2 (q), 55.2 (q), 55.5 (q), 73.2 (d), 98.5 (d), 104.2 (d), 113.6 (d), 119.8 (s), 129.5 (d), 131.2 (d), 134.0 (s), 157.9 (s), 158.0 (s), 159.7 (s), 174.4 (s); MS (EI, 70 eV): *m*/*z* (%) = 346 (1) [M^+], 328 (3) [$(M - H_2O)^+$], 257 (75) [$(M - C_3H_5O_3)^+$], 196 (94), 165 (84), 135 (100); HRMS (EI) *m*/*z* calcd for $C_{19}H_{20}O_5$ [$(M - H_2O)^+$]: calcd: 328.1305, found: 328.1306; CH: calcd for $C_{19}H_{22}O_6$: C: 65.88, H: 6.40, found: C: 65.89, H: 6.61.

Methyl 2-hydroxy-3-(4-methoxyphenyl)-3-(5-methyl-thiophen-2-yl)propanoate (7a). Following general procedure I, reaction of **2a** (52.1 mg, 250 µmol, 1.00 equiv.) with 2–methylthiophene (98.2 mg, 96.8 µL, 1.00 mmol, 4.00 equiv.) and $Sc(OTf)_3$ (6.15 mg, 12.5 µmol, 0.05 equiv.) yielded after flash chromatography (P–Et_2O: 4 : 1 → 1 : 1) **7a** (64.0 mg, 209 µmol, 84%) as a yellow oil (d.r. *syn–anti* 75 : 25). R_f = 0.18 (P–Et_2O: 2 : 1) [UV, CAM]; IR: $\tilde{\nu}$ = 3484 (br, OH), 2928 (w, $C_{al}H$), 2837 (w, OMe), 1735 (vs, C═O), 1610 (m), 1511 (vs), 1439 (m, CH_3), 1246 (vs, COC), 1179 (s), 1113 (m), 1031 (s), 834 (m, $C_{ar}H$), 802 (m), 731 cm^{-1} (m).

***syn*-Diastereoisomer (*syn*-7a).** ^{1}H-NMR (360 MHz, $CDCl_3$): δ [ppm] = 2.41 (d, ^4J = 1.1 Hz, 3 H), 3.03 (d, ^3J = 5.8 Hz, 1 H), 3.73 (s, 3 H), 3.79 (s, 3 H), 4.63 (d, ^3J = 3.6 Hz, 1 H), 4.72 (dd, ^3J = 3.6 Hz, ^3J = 5.8 Hz, 1 H), 6.56–6.58 (m, 1 H), 6.69 (d, ^3J = 3.4 Hz, 1 H), 6.84–6.88 (m, 2 H), 7.36–7.40 (m, 2 H); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ [ppm] = 15.2 (q), 49.5 (d), 52.6 (q), 55.2 (q), 74.2 (d), 113.8 (d), 124.5 (d), 126.1 (d), 129.3 (d), 133.0 (s), 139.0 (s), 139.4 (s), 158.5 (s), 173.7 (s); MS (EI, 70 eV): *m*/*z* (%) = 306 (1) [M^+], 217 (100) [$(M - C_3H_5O_3)^+$], 135 (34), 121 (26); HRMS (EI) *m*/*z* calcd for $C_{16}H_{18}O_4S$ [M^+]: calcd: 306.0920, found: 306.0917.

Methyl 3-(2,4-dimethylphenyl)-2-hydroxy-3-phenyl-propanoate (8b). Following general procedure I, reaction of **2b** (44.5 mg, 250 µmol, 1.00 equiv.) with *m*–xylene (106 mg, 123 µL, 1.00 mmol, 4.00 equiv.) and $Sc(OTf)_3$ (6.15 mg, 12.5 µmol, 0.05 equiv.) yielded after flash chromatography (P–Et_2O: 4 : 1 → 1 : 1) **8b** (26.0 mg, 91.4 µmol, 37%) as a colourless oil (d.r. *syn–anti* 71 : 29). R_f = 0.41 + 0.50 (P–Et_2O 1 : 1) [UV, CAM]; IR: $\tilde{\nu}$ = 3469 (br, OH), 3025 (w, $C_{ar}H$), 2948 (w, $C_{al}H$), 2912 (w, $C_{al}H$), 1733 (vs, C═O), 1557 (m), 1494 (s, C═C_{ar}), 1451 (s), 1438 (s, CH_3), 1228 (vs, COC), 1122 (m), 1091 (vs), 802 (m, $C_{ar}H$), 699 cm^{-1} (vs).

***syn*-Diastereoisomer (*syn*-8b).** ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 2.20 (s, 3 H), 2.28 (s, 3 H), 2.74 (d, ^3J = 5.1 Hz, 1 H), 3.58 (s, 3 H), 4.59 (d, ^3J = 5.9 Hz, 1 H), 4.88–4.91 (m, 1 H), 6.96 (bs, 1 H), 7.02 (d, ^3J = 7.8 Hz, 1 H), 7.18–7.27 (m, 5 H), 7.47 (d, ^3J = 7.8 Hz, 1 H); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ [ppm] = 19.7 (q), 20.9 (q), 50.1 (d), 52.2 (q), 74.0 (d), 126.6 (d), 126.7 (d), 128.0 (d), 128.4 (d), 128.6 (d), 131.6 (d), 134.5 (s), 136.4 (s), 136.5 (s), 140.5 (s), 174.2 (s); MS (ESI): *m*/*z* (%) = 307 [$(M + Na)^+$], 285 [$(M + H)^+$]; HRMS (ESI): $C_{18}H_{21}O_3$ [$(M + H)^+$]: calcd: 285.1485, found: 285.1485.

General procedure II for the Friedel–Crafts reactions with 3-arylglycidate 5. A flame-dried Schlenk flask was purged with argon and charged with glycidate **5** (37.5 mg, 150 µmol, 1.00 equiv.) and the aryl nucleophile (600 µmol, 4.00 equiv.) in dry nitromethane (2 mL). The solution was cooled to −25 °C and $Sc(OTf)_3$ (3.69 mg, 7.50 µmol, 0.05 equiv.) was added. The resulting mixture was stirred at −25 °C for 4 h. The reaction was quenched with sat. aqueous $NaHCO_3$ (5 mL) and diluted with CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 7 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography to give the respective product.

***tert*-Butyl 3-(2,4-dimethoxyphenyl)-2-hydroxy-3-(4–methoxyphenyl)propanoate (11a).** Following general procedure II, reaction of **5** (37.5 mg, 150 µmol, 1.00 equiv.) with 1,3–dimethoxybenzene (82.9 mg, 79.0 µL, 600 µmol, 4.00 equiv.) and $Sc(OTf)_3$ (3.69 mg, 7.50 µmol, 0.05 equiv.) yielded after flash chromatography (P–Et_2O: 4 : 1 → 1 : 1) **11a** (45.0 mg, 116 µmol, 77%) as a colourless solid (d.r. *syn–anti* 93 : 7). R_f = 0.21 (P–Et_2O: 2 : 1) [UV, CAM]; IR: $\tilde{\nu}$ = 3490 (br, OH), 2984 (w, $C_{al}H$), 2939 (w), 2911 (w), 2837 (m, OMe), 1717 (vs, C═O), 1608 (s), 1507 (vs), 1469 (m, CH_3), 1260 (s, COC), 1207 (s), 1157 (vs), 1124 (s), 1034 (s), 834 (m, $C_{ar}H$), 737 cm^{-1} (m).

***syn*-Diastereoisomer (*syn*-11a).** ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 1.25 (s, 9 H), 3.01 (bs, 1 H), 3.76 (s, 3 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 4.70 (d, ^3J = 5.8 Hz, 1 H), 4.77 (d, ^3J = 5.8 Hz, 1 H), 6.43 (d, ^4J = 2.5 Hz, 1 H), 6.46 (dd, ^3J = 8.5 Hz, ^4J = 2.5 Hz, 1 H), 6.80–6.82 (m, 2 H), 7.25–7.27 (m, 2 H), 7.42 (d, ^3J = 8.5 Hz, 1 H); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ [ppm] = 27.7 (q), 45.4 (d), 55.2 (q), 55.3 (q), 55.4 (q), 74.0 (d), 82.0 (s), 98.6 (d), 104.1 (d), 113.6 (d), 121.2 (s), 129.7 (d), 130.2 (d), 133.6 (s), 158.0 (s), 158.0 (s), 159.5 (s), 173.2 (s); MS (ESI): *m*/*z* (%) = 799 (100) [$(2M + Na)^+$], 735 (38), 411 (34) [$(M + Na)^+$], 333 (20), 225 (9); HRMS (ESI): $C_{22}H_{28}O_6Na$ [$(M+Na)^+$]: calcd: 411.1778, found: 411.1776.

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