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Highly Diastereoselective Friedel–Crafts Alkylation Reactions via Chiral α-Functionalized Benzylic Carbocations

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Dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday

Abstract: A series of chiral 1-aryl-1-alkanols, which carry different functional groups (FGs) at the 2-position, were subjected to an acid (HBF_4)-catalyzed reaction with various arenes. An S_N1 substitution reaction was observed, in the course of which 1,1-diarylalkanes were formed. In most cases (40 out of 51 reactions), yields were very good to excellent (75–99%). The diastereoselectivity of the reaction was heavily dependent on the FG at the 2-position. If the FG was methoxycarbonyl, nitro, hydroxy, cyano, trimethylsilylethynyl, or chloro, the corresponding *anti* products were favored and with a decreasing preference in this order. The methoxycarbonyl-substituted substrates gave the *anti* products with diastereomer ratios (d.r.) that exceeded 92:8 (16 examples). Nitro- and hydroxy-substituted products were obtained in most instances with d.r. $\geq$ 90:10, whereas cyano-, trimethylsilylalkynyl-, or chloro-substituted substrates delivered only with certain arenes products with high selectivity (d.r. $\geq$ 90:10). The sterically more demanding FGs ethylsulfonyl, ethoxysulfonyl, and diethoxyphosphonyl induced diastereofacial selectivity in favor of the corresponding *syn* products, with diethoxyphosphonyl being the most effective. The substrate with FG = $PO(OEt)_2$ delivered, with eight different arenes, the corresponding *syn* substitution products (d.r. = 80:20 – > 95:5). The relative configuration of the products was elucidated by spectroscopic and synthetic methods. On selected examples, the reactions were shown to proceed stereoconvergently, under kinetic control, and without racemization. Depending on the functional group, the onset of the reactions between 2-methylthiophene and some representative alcohols was found to occur at a temperature Θ between −78 and −40 °C. There was no correlation between the selectivity and Θ. A model is suggested to explain the facial diastereoselectivity based on a preferred conformation of the putative intermediate carbocation.

Keywords: aromatic substitution · asymmetric synthesis · carbocations · diastereoselectivity · substituent effects

Introduction

Acyclic Stereocontrol and Carbocations

The discovery that the creation of stereogenic centers can be governed by acyclic stereocontrol elements marks the beginning of a new era in organic synthesis.[1] While it was previously common practice to embed artificially a prostereogenic center into a cyclic array to achieve facial diastereocontrol,[2] it became apparent that conformational and stereoelectronic parameters can deliver sufficient bias for a reaction to proceed diastereoselectively.[3] As carbon–carbon bond-formation reactions between a strong carbon nucleophile and a weak carbon electrophile have dominated organic synthesis in recent times,[4] the facial diastereoselectivity of these processes has been extensively studied.[5] The addition of phenylmagnesium bromide to aromatic ketone **1**, for example, leads to the formation of tertiary alcohol **2** with perfect stereocontrol (Scheme 1).[6]

The selectivity is determined by chelation of the α-methoxy group and the carbonyl group with the nucleophile approaching from the less shielded face (chelation control).[7] In contrast, the related ketone **3** is attacked from the opposite diastereotopic face due to stereoelectronic parameters (Felkin–Anh control[8]). Chelation in this case is clearly impossible, and tertiary alcohol **4** is the major product.[9]

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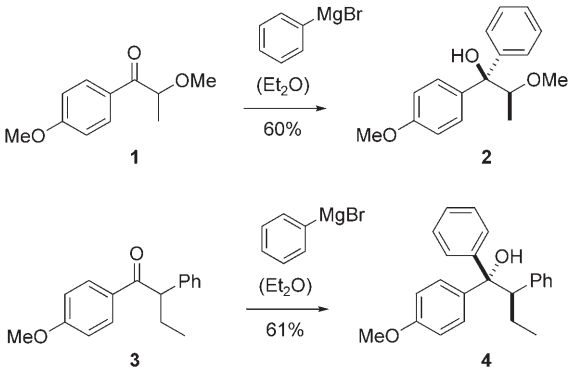


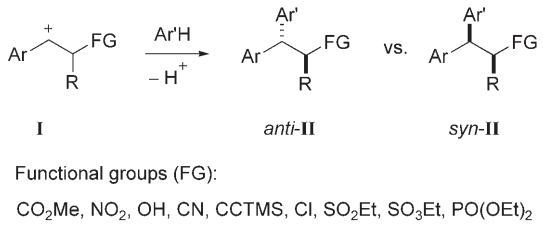
Scheme 1. Diastereoselective addition reactions of the strong nucleophile PhMgBr to two different weakly electrophilic, chiral ketones **1** and **3**.

Abstract in German: Eine Reihe chiraler 1-Aryl-1-alkanole, die eine funktionelle Gruppe (FG) in 2-Position tragen, wurden in einer Säure-katalysierten (HBF_4) Reaktion mit verschiedenen Aromaten umgesetzt. Man beobachtete eine S_N1-artige Substitutionsreaktion, in deren Verlauf 1,1-Diarylalkane gebildet wurden. In den meisten Fällen (40 von 51 Reaktionen) waren die Ausbeuten sehr gut bis hervorragend (75–99%). Die Diastereoselektivität der Reaktion war sehr stark von der funktionellen Gruppe in 2-Position abhängig. Für die Fälle, in denen die funktionelle Gruppe Methoxycarbonyl, Nitro, Hydroxy, Cyano, Trimethylsilylethinyl oder Chlor war, wurden bevorzugt die jeweiligen *anti*Produkte gebildet, wobei die Selektivität in dieser Reihenfolge abnahm. Die Methoxycarbonyl-substituierten Substrate ergaben die jeweiligen *anti* Produkte in Diastereomerenverhältnissen (d.r.), die stets 92:8 überstiegen (16 Beispiele). Die Nitro- und Hydroxy-substituierten Produkte wurden in den meisten Fällen mit einem d.r. $\geq$ 90:10 erhalten, wohingegen die Cyano-, Trimethylsilylethinyl- oder Chlor-substituierten Edukte nur mit bestimmten Aromaten Produkte in hoher Selektivität (d.r. $\geq$ 90:10) lieferten. Die sterisch anspruchsvolleren funktionellen Gruppen Ethylsulfonyl, Ethoxysulfonyl und Diethoxyphosphonyl bewirkten eine Seitendifferenzierung zugunsten der *syn*-Produkte, wobei sich die Diethoxyphosphonyl-Gruppe am effektivsten erwies. Das Substrat mit FG = $PO(OEt)_2$ lieferte mit acht verschiedenen Aromaten die jeweiligen Substitutionsprodukte (d.r. = 80:20 bis >95:5). Die Relativkonfiguration der Produkte wurde durch spektroskopische und synthetische Methoden aufgeklärt. Jeweils an ausgewählten Beispielen wurden gezeigt, dass die Reaktionen stereokonvergent unter kinetischer Kontrolle und ohne Racemisierung stattfinden. Je nach funktioneller Gruppe setzte die Umsetzung von 2-Methylthiophen mit repräsentativen Alkoholen bei einer Temperatur Θ zwischen −78 °C und −40 °C ein. Es gab aber keine Korrelation zwischen der beobachteten Diastereoselektivität und der Temperatur Θ. Ein Modell wird vorgeschlagen, das die faciale Diastereoselektivität auf der Basis einer Vorzugskonformation des mutmaßlichen intermediären Carbokations **I** erklärt.

A reactivity pattern that reverses the common combination of strong nucleophile/weak electrophile, that is, a pattern in which a weak nucleophile attacks a strong electrophile, has received less attention in stereoselective synthesis. Notable exceptions include studies related to the reactivity and selectivity of silyl-based nucleophiles with Lewis acid or Brønsted acid activated electrophiles, such as iminium[10] and oxonium[11] ions. Systematic investigations of other free carbenium ions have not been conducted.[12] We recently began to study the reactivity of chiral benzylic cations more closely.[13] They are generated from the corresponding alcohols upon treatment with strong Brønsted acids, preferably $HBF_4{\cdot}OEt_2$. If the element of chirality is an α-branched aliphatic chain, the diastereoface differentiation would be based on the size of the two alkyl residues. A chiral benzylic cation of this type was observed by NMR spectroscopy, and its preferred conformation was elucidated.[13b]

Scope of This Study

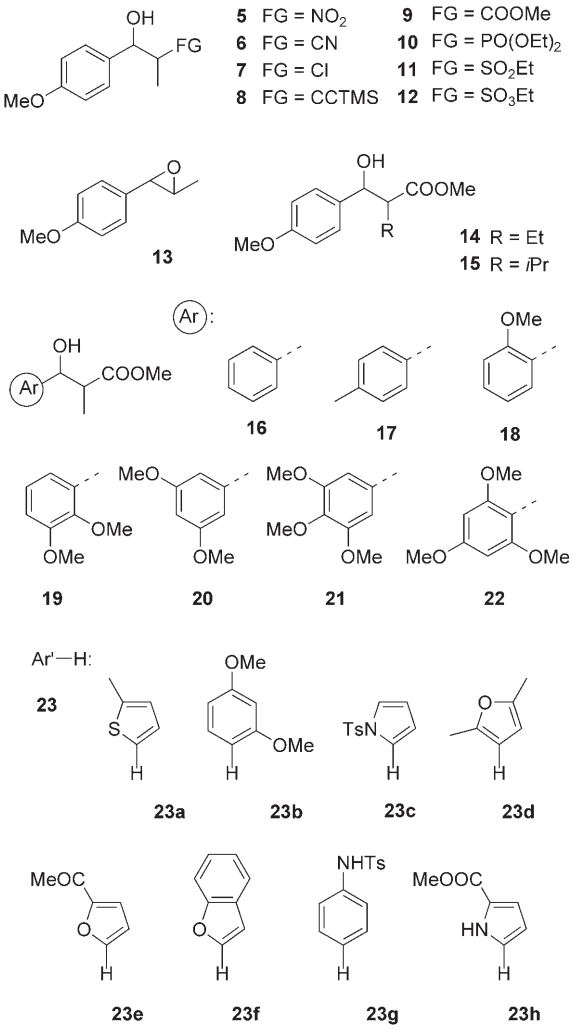
In an ongoing research project, we commenced the study of precursors of benzylic carbenium ions **I** (Scheme 2), which contain a functional group at the α-position. Attack of a



Scheme 2. Putative α-functionalized benzylic carbocation **I** and its reaction with arenes Ar′H to form diastereomeric products *anti*-**II** and *syn*-**II**. TMS = trimethylsilyl.

weak arene nucleophile can lead to two diastereomers, *anti*-**II** and *syn*-**II**, in a Friedel–Crafts alkylation reaction. Preliminary experiments revealed high diastereoselectivities in some reactions of nitro-, hydroxy-, and cyano-substituted cations, which favored the corresponding *anti*(*threo*) diastereomer *anti*-**II**.[13c] We have now studied this issue more comprehensively, including an investigation into cations that contain the functional groups methoxycarbonyl, trimethylsilylethynyl, chloro, ethylsulfonyl, ethoxysulfonyl, and diethoxyphosphonyl. The corresponding alcohols **5**–**12** and epoxide **13**, with an anisyl group as the aryl substituent Ar (Scheme 3), were precursors for the carbenium ions **I**.

Esters **9**, **14**, and **15** were employed to study the facial diastereoselectivity, which depends on the size of the alkyl group R. Further experiments were devoted towards a variation of the aromatic substituent Ar, which again used β-hydroxyesters (**16**–**22**) as cation precursors. Arenes **23** were employed as nucleophiles Ar′H, with **23a**–**c** as the standard nucleophiles tested with all the electrophile precursors **5**–**13**. The complete set of nucleophiles **23** was screened against



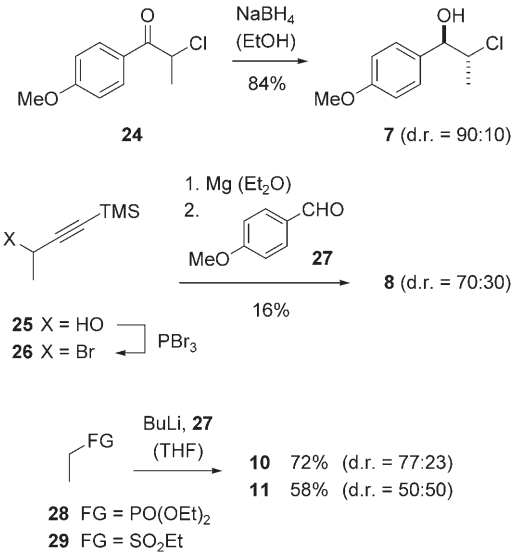
Scheme 3. The alcohols **5**–**22** and arenes **23** employed in this study.

the most selective electrophile precursors, that is, ester **9** and phosphonate **10**, and against chloride **7**. Furthermore, the following questions were addressed: Does the reaction proceed stereospecifically? Is there racemization of enantiomerically enriched compounds? At what temperature do the reactions occur? What are the requirements to be met by the electrophilic and nucleophilic reaction partners for the reaction to be successful? How can the stereochemical outcome of the experiments be interpreted? Details of our comprehensive study are summarized in this full account.

Results and Discussion

Preparation of Starting Materials

Alcohols **5**, **6**, and **8**–**12** were conveniently prepared by the addition of an appropriate nucleophile to anisaldehyde (**27**; Scheme 4). Most syntheses led to mixtures of diastereomers because the simple diastereoselectivity of the aldehyde addition is low.[14] The diastereomer ratio was determined by ^{1}H NMR spectroscopic analysis. Starting from nitroethane (deprotonation with NaOH), the known alcohol **5**[15] was



Scheme 4. Preparation of the 2-substituted 1-methoxyphenyl-1-propanols **7**, **8**, **10**, and **11**.

prepared (d.r. = 62:38). β-Hydroxynitrile **6**[16] was obtained from propionitrile upon deprotonation and subsequent reaction with anisaldehyde (d.r. = 60:40). Reduction of known ketone **24**[17] led to 2-chloroalkanol **7** with the depicted diastereomer predominantly formed (d.r. = 90:10). For the synthesis of propargylic alcohol **8**, the corresponding Grignard reagent was generated from bromide **26**. The bromide in turn was synthesized from alcohol **25**[18] by a straightforward bromodehydroxylation with PBr_3. Addition of the Grignard reagent to anisaldehyde was complicated by competing reactions (S_E2', desilylation). The separation of the reaction product and unreacted anisaldehyde was difficult because both compounds have identical R_f values. Anisaldehyde was reduced by $NaBH_4$ in situ to facilitate separation, but the yield of alcohol **8** remained low. Attempts to form the corresponding lithium reagent from bromide **26** by treatment with butyl lithium or *tert*-butyl lithium remained unsuccessful. The preparation of phosphonate **10** and sulfone **11** paralleled the previously mentioned procedure for the synthesis of nitrile **6**. Deprotonation of the corresponding ethylphosphonate **28** and of diethylsulfone (**29**) with butyl lithium was followed by the reaction with anisaldehyde. Epoxide **13**[19] was formed in either diastereomeric form by treatment of either (*E*)- or (*Z*)-anethol with *meta*-chloroperbenzoic acid (mCPBA).

The deprotonation of an appropriate carbon nucleophile precursor was in several cases conducted with lithium diisopropylamide (LDA). Subsequent addition of an aromatic aldehyde gave the desired alcohol. Alcohols **9** and **12** were thus obtained from anisaldehyde and the corresponding carboxylate or sulfonate. β-Hydroxyalkanoates **14**–**22** were prepared analogously by LDA-mediated aldol addition reactions. Yields and diastereoselectivities are listed in Table 1. In general, yields were in the good to very good range, and the simple diastereoselectivity was expectedly low.[14] The

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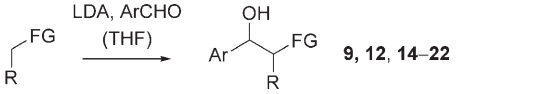
Table 1. Preparation of the 2-substituted 1-aryl-1-propanols **9**, **12**, **14**–**22**.



	9	**12**	**14**	**15**	**16**	**17**
Yield [%]	77	80	87	93	89	80
d.r.	54:46	60:40	55:45	76:24	51:49	53:47
	18	**19**	**20**	**21**	**22**	
Yield [%]	77	74	73	76	66	
d.r.	51:49	54:46	60:40	50:50	62:38	

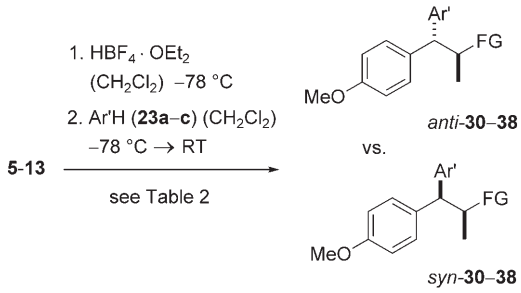
LDA procedure was also applied to the preparation of phosphonate **10**. The yield was slightly higher (77%) than with butyl lithium, and the diastereoselectivity was slightly lower (d.r. = 73:27).

Variation of the Functional Group

In the first set of experiments, 1-anisyl-1-propanols **5**–**12** and epoxide **13** were treated with 2-methylthiophene (**23a**), resorcin dimethyl ether (**23b**), and *N*-tosylpyrrole (**23c**). The reaction conditions were kept constant. A mixture of the Brønsted acid $HBF_4{\cdot}OEt_2$ (1.25 equiv) and the electrophile precursor was stirred at −78 °C for 5 min in CH_2Cl_2. The arene was added (4.0 equiv), and the reaction mixture was subsequently allowed to warm to room temperature. Only silyl-protected alkyne **8** required slightly modified reaction conditions because desilylation was observed with 1.25 equivalents of $HBF_4{\cdot}OEt_2$. With 1.05 equivalents of the Brønsted acid, desilylation could be suppressed. Products **30**–**38** (Scheme 5) were isolated, and the diastereomer ratio was determined by ^{1}H NMR spectroscopy and gas–liquid chromatography (GLC) from the crude product mixture. Whenever possible, the diastereomers were fully separated.

The yields and selectivities of the individual reactions are shown in Table 2. Yields were consistently high in all reactions with very few exceptions (e.g., Table 2, entry 9, product **38c**). Synthetically useful diastereoselectivities were achieved for all products with the functional groups NO_2 (Table 2, entry 1), COOMe (Table 2, entry 5), $PO(OEt)_2$ (Table 2, entry 6), and OH (Table 2, entry 9). The sterically least congested nucleophile 2-methylthiophene (**23a**) led in most cases to the lowest product diastereoselectivity (products **30a**, **31a**, **33a**, **35a**, **37a**, and **38a**). Resorcin dimethyl ether (**23b**) and *N*-tosylpyrrole (**23c**) performed comparably, with the former exhibiting higher or lower selectivity than the latter. With these more selective nucleophiles, notable diastereoface differentiation was observed for substrates with FG = CN (Table 2, entry 2, products **31b** and **31c**), CCTMS (Table 2, entry 4, products **33b** and **33c**), and SO_2Et (Table 2, entry 7, product **36b**). Product **33c** could not be fully separated from minor impurities.

The reactions were fully stereoconvergent, that is, the diastereomeric composition of the substrate did not influence the diastereoselectivity of the reaction, nor did it in any way correspond to it. Thermodynamic reaction control was ruled out by subjecting diastereomeric mixtures with compositions different to that of the reaction product mixture to the reaction conditions. Base-promoted (LDA in THF) epimerization of ester **34a** (d.r. = 96:4) led, for example, to a diastereomeric mixture with an *anti*/*syn* ratio of 45:55. Stirring of this mixture with 1.25 equivalents of $HBF_4{\cdot}OEt_2$ and 4 equivalents of methylthiophene (−78 °C→room temperature) produced no change in the composition of the diastereomeric mixture. Product **34a** was fully recovered with a



Scheme 5. Diastereoselective HBF_4-promoted Friedel–Crafts alkylation of arenes **23a–c** by chiral alcohols **5**–**13**. Yields and selectivities are provided in Table 2.

Table 2. Yields and diastereoselectivities in the reaction of carbon electrophiles **5**–**13** with arenes Ar′H **23a–c**.

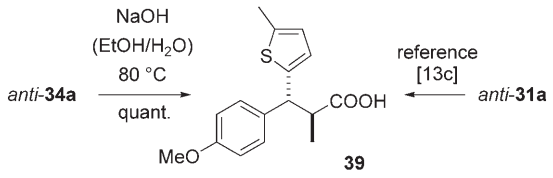
Entry	Substrate[a]	FG	Product	d.r.[b] (*anti*/*syn*)	Yield [%][c]	Product	d.r.[b] (*anti*/*syn*)	Yield [%][c]	Product	d.r.[b] (*anti*/*syn*)	Yield [%][c]
1	**5**	NO_2	**30a**	91:9	73	**30b**	>95:5	78	**30c**	>95:5	78
2	**6**	CN	**31a**	75:25	92	**31b**	87:13	87	**31c**	91:9	67
3	**7**	Cl	**32a**	73:27	97	**32b**	72:28	95	**32c**	85:15	84
4	**8**	C≡CTMS[d]	**33a**	77:23	91	**33b**	90:10	89	**33c**	91:9	90[e]
5	**9**	COOMe	**34a**	96:4	93	**34b**	95:5	85	**34c**	94:6	91
6	**10**	$PO(OEt)_2$	**35a**	12:88	99	**35b**	<5:95	92	**35c**	<5:95	80
7	**11**	SO_2Et	**36a**	26:74	98	**36b**	10:90	90	**36c**	39:61	84
8	**12**	SO_3Et	**37a**	37:63	95	**37b**	17:83	90	**37c**	30:70	88
9	**13**	OH	**38a**	88:12	87	**38b**	>95:5	73	**38c**	89:11	50

[a] All reactions were conducted at a substrate concentration of 50 mM with 1.25 equivalents of $HBF_4{\cdot}OEt_2$ as Brønsted acid and 4 equivalents of Ar′H as the nucleophile. [b] The diastereomer ratio of the crude product was determined by ^{1}H NMR spectroscopy or GC (**34a–c**). [c] Yield of isolated product. [d] 1.05 equivalents of $HBF_4{\cdot}OEt_2$ were used as Brønsted acid. [e] The product was contaminated with **23c**. The yield was calculated by substracting the amount of impurity (^{1}H NMR signal integration) from the total amount of product.

d.r. of 45:55. Similar experiments were conducted with nitro compound **30b** and phosphonate **35a**.

Assignment of Relative Configuration

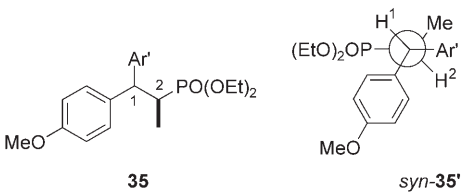
The relative configurations of compounds **30**, **31**, and **38** were determined earlier.[13c] They were based on X-ray crystallographic evidence for **30** and **38** and on the transformation of **31a** into a cyclic compound for **31**. Saponification of compound **34a** yielded carboxylic acid **39** (d.r. = 96:4), which was obtained previously with an *anti*/*syn* d.r. of 75:25 from nitrile **31a**. As the spectroscopic data for the major diastereomer were identical in both instances, the *anti* configuration was assigned to the major diastereoisomer of product **34a** (Scheme 6).



Scheme 6. Configuration assignment of product *anti*-**34a** by synthesis of known carboxylic acid **39**, which in turn was previously prepared[13c] from nitrile *anti*-**31a**.

^{1}H NMR coupling constants $^3J_{H,H}$ in the range 9.5–11.5 Hz for 1-H and 2-H of the 1,1-diaryl-substituted products **30**–**38** indicate an antiperiplanar orientation of the two protons in the major conformer. This conformational preference was corroborated by X-ray crystallographic data.[13] The $^3J_{C,P}$ coupling constants were recorded for the major diastereomers of phosphonates **35**. The $^3J_{C,P}$ values for the phosphorus atom and the *ipso*-carbon atom at the anisyl substituent were small (2.0–4.7 Hz), whereas the values of the coupling constant for the phosphorus atom and the *ipso*-carbon atom of the newly introduced aryl substituent were large (17.3–21.0 Hz), which indicates a synclinal (gauche) arrangement for the former and an antiperiplanar conformation for the latter. With the orientation of the two protons 1-H and 2-H taken into account, only one diastereoisomer (Scheme 7), that is, the *syn* product, can adopt a conformation that is in line with the coupling constants determined.

Further assignments were based on the consistent deshielding and shielding effects for the protons of the methyl group at C2 in the methylthiophene products **30a**–**38b**, which presumably originate from the ring current of the anisyl substituent. The data provided in Table 3 show that all the *anti* diastereomers, for which an antiperiplanar conformation of protons 1-H and 2-H is deduced from their coupling constants, experience a shielding effect for the methyl group at C2 relative to the *syn* diastereomer. The spatial proximity of the anisyl substituent to the methyl group and the fact that the protons of the methyl group are within the ring current of the anisyl substituent are substantiated by X-ray crystallographic evidence.[13]



Scheme 7. Carbon numbering in compound **35** and preferred conformation of its *syn* diastereoisomer *syn*-**35** (Newman projection).

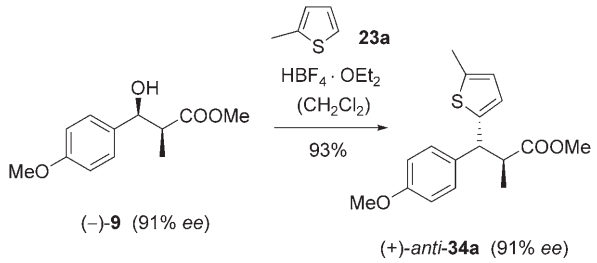
Table 3. $^3J_{H,H}$ coupling constants between 1-H and 2-H and the chemical shift of the methyl group at C2 in the major and minor diastereoisomers of products **30a**–**38a**.

Substrate	FG	$^3J_{major}$ [Hz]	$^3J_{minor}$ [Hz]	$\delta(CH_3)_{major}$ [ppm]	$\delta(CH_3)_{minor}$ [ppm]
30a	NO_2	11.0	–[a]	1.44	1.60
31a	CN	8.9	8.2	1.28	1.33
32a	Cl	8.5	8.7	1.45	1.54
33a	C≡CTMS	7.8	7.8	1.13	1.19
34a	COOMe	11.0	–[a]	1.05	1.22
35a	$PO(OEt)_2$	9.5	9.0	1.22	1.13
36a	SO_2Et	9.1	8.4	1.43	1.33
37a	SO_3Et	8.6	7.2	1.33	1.28
38a	OH	8.2	7.4	1.15	1.24

[a] The ^{1}H NMR coupling constant could not be determined as the signal overlapped with signals of other protons.

Enantiomerically Pure Starting Materials

According to the mechanistic picture of an S_N1-type displacement via free benzylic carbocations, there is no obvious pathway for the racemization of enantiomerically pure starting materials. With α-*tert*-butyl branched aliphatic cation precursors, a slight degree of racemization was observed,[13b] presumably due to the *tert*-butyl cation acting as an electrophilic leaving group.[20] When a functional group is in the α position relative to the putative carbocation, a related mechanism is not feasible because none of the functional groups can act as an electrophilic leaving group. We prepared the chiral alcohol (−)-**9** with 91% *ee* from the corresponding racemate by acetylation and subsequent lipase-catalyzed kinetic resolution.[21] Under the conventional reaction conditions described earlier, the expected product (+)-*anti*-**34a** was isolated in essentially identical yield and with identical diastereoselectivity to the racemate (Scheme 8). Within



Scheme 8. Synthesis of enantiomerically enriched product (+)-*anti*-**34a** (91% *ee*) from alcohol (−)-**9** (91% *ee*).

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the limits of error of HPLC detection (Daicel Chiralcel OJ-H 250×4.6, hexane/isopropanol = 95:5, flow rate = 1 mL min^{-1}), the product exhibited the same enantiomeric purity as the starting material.

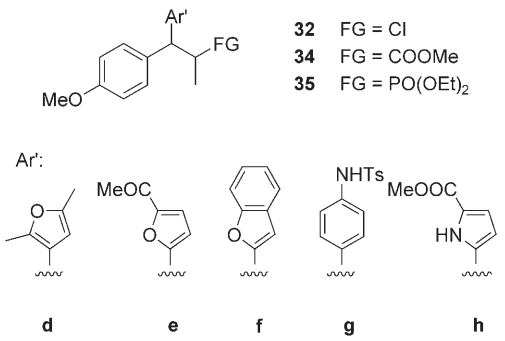
Variation of the Arene Nucleophile Ar′H

Besides the three standard arenes **23a–c**, we employed 2,5-dimethylfuran (**23d**), 2-acetylfuran (**23e**), benzofuran (**23f**), *N*-tosylaniline (**23g**), and methyl 2-pyrrolcarboxylate (**23h**) as nucleophiles. To keep the number of experiments at a reasonable level, we selected three electrophile precursors for treatment with the five additional nucleophiles. All transformations proceeded smoothly, and the results of the reactions are shown in Table 4. Only the reactions of acetylfuran with phosphonate **10** did not give a conclusive result. The structures of the products with the general substituent pattern **32**, **34**, and **35** are depicted in Scheme 9. For the reactions of arenes **23e**, **23g**, and **23h**, a larger amount of Brønsted acid was required to facilitate the reaction, possibly because the arene acts as a competing Brønsted base.

Table 4. Yields and diastereoselectivities in the reaction of carbocation precursors **7**, **9**, and **10** with nucleophiles **23d–h** (Scheme 9).

Entry	Substrate	Arene[a,b]	Product	d.r.[b] (*anti*/*syn*)	Yield [%][d]
1	**7**	**23d**[a]	**32d**	85:15	89
2	**7**	**23e**[b]	**32e**	79:21	74
3	**7**	**23f**[a]	**32f**	90:10	76
4	**7**	**23g**[b]	**32g**	75:25	81
5	**7**	**23h**[b]	**32h**	65:35	90
6	**9**	**23d**[a]	**34d**	93:7	86
7	**9**	**23e**[b]	**34e**	92:8	51
8	**9**	**23f**[a]	**34f**	96:4	74
9	**9**	**23g**[b]	**34g**	92:8	85
10	**9**	**23h**[b]	**34h**	94:6	82
11	**10**	**23d**[a]	**35d**	15:85	95
12	**10**	**23f**[a]	**35f**	20:80	83
13	**10**	**23g**[b]	**35g**	14:86	85
14	**10**	**23h**[b]	**35h**	8:92	88

[a] Reactions were conducted at a substrate concentration of 50 mM with 1.25 equivalents of $HBF_4{\cdot}OEt_2$ as Brønsted acid and 4 equivalents of Ar′H as the nucleophile. [b] Reactions were conducted at a substrate concentration of 50 mM with 4.25 equivalents of $HBF_4{\cdot}OEt_2$ as Brønsted acid and 3 equivalents of Ar′H as the nucleophile. [c] The diastereomer ratio of the crude product was determined by ^{1}H NMR spectroscopy or GC (**34d–h**). [d] Yield of isolated product.



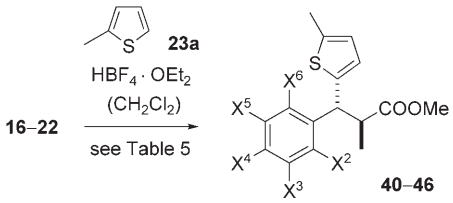
Scheme 9. Structures of the substitution products **32d–h**, **35d–h**, and **36d–h** obtained by the reaction of alcohols **7**, **9**, and **10** with arenes **23d–h**. Yields and selectivites are provided in Table 4. Ts = tosyl.

Compared to the previously used arene nucleophiles **23a–c**, there is neither a major increase nor a decrease in selectivity when the arenes **23d–h** were employed. The general trend for a high *anti* preference with carboxylate **34** (Table 4, entries 6–10) and a high *syn* preference with phosphonate **35** (Table 4, entries 11–14) was corroborated. Benzofuran (**23f**) gave clearly improved *anti* selectivity in the reaction of chloride **7** (Table 4, entry 3).

To summarize these observations, the facial diastereoselectivities in the reaction of carbocation precursors **5–13** are mainly dependent on the given electrophile. The influence of the nucleophile is limited. Although the nucleophile changes the degree of selectivity to some extent, it does not reverse the direction of the face differentiation. The situation is comparable to that of the reactions of strong nucleophiles with weak carbonyl electrophiles, in which, in a series of related organometallic reagents with the same electrophile, identical or at least similar diastereoselectivities were observed.[4c,5a]

Variation of the Aryl Substituent Ar

The electronic influence of the aryl group in the α position relative to the putative carbenium ion was probed by replacing the *para*-methoxy group with other substituents. Alcohols **16–22** were subjected to the reaction with 2-methylthiophene (**23a**) to yield the corresponding diarylpropionates **40–46** (Scheme 10 and Table 5). Most reactions proceeded smoothly (Table 5, entries 2–4, 6, and 7), with the phenyl ring (as Ar) substituted by 4-methyl (Table 5, entry 2), 2-methoxy (Table 5, entry 3), 2,3-dimethoxy (Table 5, entry 4), 3,4,5-trimethoxy (Table 5, entry 6), and 2,4,6-trimethoxy (Table 5, entry 7). Diastereoselectivities were high in most cases and did not differ much from the result obtained with 4-methoxyphenyl (**9**→**34a**), except for the last example (Table 5, entry 7). The reaction with unsubstituted benzylic alcohol **16** failed (Table 5, entry 1), as did the reaction with the 3,5-dimethoxyphenyl-substituted substrate **20** (Table 5, entry 5).



Scheme 10. Diastereoselective HBF_4-promoted Friedel–Crafts alkylation of 2-methylthiophene (**23a**) by chiral substituted phenyl alcohols **16–22**. Yields and selectivites are provided in Table 5.

The low reactivity of alcohols **16** and **20** is presumably due to the fact that carbenium ion formation did not occur

Table 5. Yields and diastereoselectivities in the reaction of alcohols **16–22** with 2-methylthiophene (**23a**) (Scheme 10).

Entry[a]	X^2	X^3	X^4	X^5	X^6	Product	d.r.[b] (*anti*/*syn*)	Yield [%][c]
1	H	H	H	H	H	**40**	–	–
2	H	H	Me	H	H	**41**	92:8	69
3	OMe	H	H	H	H	**42**	93:7	79
4	OMe	OMe	H	H	H	**43**	93:7	72
5	H	OMe	H	OMe	H	**44**	–	–
6	H	OMe	OMe	OMe	H	**45**	97:3	90
7	OMe	H	OMe	H	OMe	**46**	65:35	52

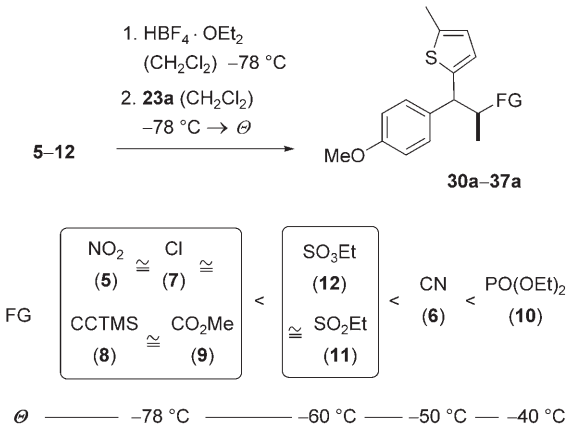
[a] All reactions were conducted at a substrate concentration of 50 mM with 1.25 equivalents of $HBF_4{\cdot}OEt_2$ as Brønsted acid and 4 equivalents of **23a** as the nucleophile. [b] The diastereomer ratio of the crude product was determined by ^1H NMR spectroscopy and GC. [c] Yield of isolated product.

under the acidic conditions employed. The starting material was recovered unchanged. The typical intense color of the benzylic carbenium ion was not observed. The solution remained colorless or slightly yellow even upon warming to room temperature. Alcohols **17–19** and **21** represent substrates in which carbocation formation and subsequent nucleophilic substitution proceeded smoothly. The success of the reaction and its selectivity are not linked to the presence of the methoxy group in the aryl substituent Ar, as proven by the successful conversion of the *para*-tolyl substrate (Table 5, entry 2). They are, rather, linked to a sufficient stabilization of the intermediate carbocation by the aryl group. Apparently, the *para*-tolyl group is still capable of doing so, whereas the phenyl group is too weak an electron donor. The low diastereoselectivity and the decreased yield in the reaction of alcohol **22** could be related to steric effects of the *ortho* substituents. Significant amounts of the elimination product, methyl 3-(2,4,6-trimethoxyphenyl)-2-methylpropenoate, were detected by GLC (29% relative to **46**), which indicates a decreased overlap of the aryl π system with the empty p_z orbital of the cationic center (see below).

Determination of Reaction Temperature

According to our standard procedure, the benzylic alcohol and the Brønsted acid were premixed and stirred at −78 °C for five minutes. Subsequently, the nucleophile was added. After five minutes at −78 °C, the reaction mixture was warmed to room temperature, and the reaction was terminated by addition of saturated aqueous $NaHCO_3$. All preparative reactions were complete when this standard protocol was followed. Data on the progress of the reaction in the range −78 °C to ambient temperature were not collected. We therefore studied the temperature profile of the reactions in a separate set of experiments with alcohols **5–12** and 2-methylthiophene (**23a**) by quenching the reaction mixture at different temperatures. To this end, the reaction was initiated at −78 °C by premixing the corresponding alcohol (0.75 mmol) and $HBF_4{\cdot}OEt_2$ (1.25 equiv) in CH_2Cl_2 (15 mL) for 5 min. After addition of the arene (4 equiv), a first sample (1 mL) was collected after a further 5 min at −78 °C. The reaction was gradually warmed by removing the cooling bath with samples taken at 10 °C intervals starting at −70 °C. Samples of 1 mL were collected directly into a syringe filled with $HNEt_2$ (10 equiv) to assure immediate quenching. The mixture was further diluted with aqueous $NaHCO_3$ in the syringe. The organic layer was separated and analyzed by GLC according to a standardized dilution protocol. The onset of the reaction was indicated by product formation and partial substrate consumption. With nitro (**5**), chloro (**7**), trimethylsilylethynyl (**8**), and methoxycarbonyl (**9**) as functional groups, conversion was already detected at −78 °C, and the reactions went to completion at this temperature. With ethylsulfonyl (**11**) and ethoxysulfonyl (**12**), there was no detectable reaction after 5 min at −78 °C or at −70 °C. Warming to −60 °C, however, was sufficient to induce product formation. The least reactive substrates carried a cyano (**6**) and a diethoxyphosphonyl (**10**) substituent as the functional group, with the reactions starting to progress at −50 and −40 °C, respectively. The results are summarized in Scheme 11.

Products resulting from S_N1-type substitution of the amine at the free carbenium ion were not observed. Clearly, there is no correlation between the diastereoselectivity of the reactions and the reaction temperature. One of the most selective substrates, **10** (FG = $PO(OEt)_2$), reacted at the highest temperature (−40 °C).



Scheme 11. Temperatures required to facilitate the HBF_4-promoted reaction of alcohols **5–12** with 2-methylthiophene (**23a**). Θ = temperature (°C) at which substrate formation was detected.

Mechanistic Considerations

Before the influence of the functional groups on the reaction temperature is discussed any further, a conceivable mechanistic picture for the reactions of the title compounds is provided in Scheme 12. Protonation of the general α-func-

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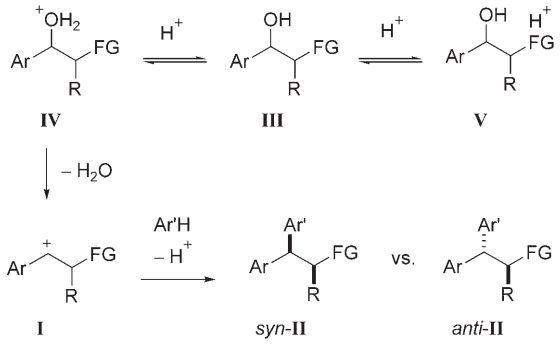
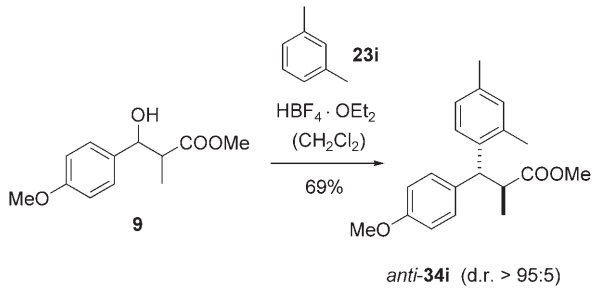


Scheme 12. Mechanistic picture for the reaction of chiral alcohols **III** to form products *anti*-**II** and *syn*-**II**.

tionalized benzylic alcohol **III** leads to onium ion **IV**, from which the benzylic carbocation **I** is formed. The subsequent reaction with arene Ar′H is stereoselectivity-determining and leads to products **II**. If carbocation formation is not possible because of insufficient stabilization by the aryl substituent Ar, there is no reaction (Scheme 10 and Table 5, entries 1 and 5).

Besides protonation at the hydroxy group, protonation of the functional group must be considered. Formation of cation **I** in the equilibrium decreases both the concentration of **III** and the overall rate of the heterolytic bond cleavage **IV**→**I**. Indeed, there is a rough correlation between the reaction temperature and the basicity of the functional group FG. The more basic the functional group, the higher the reaction temperature required for the transformation of **III** into **II** (Scheme 11). If the change in the OH-stretching frequency ($\Delta\nu$) for *para*-fluorophenol upon mixing with representative compounds is taken as a measure of the basicity of a functional group, the trend in the latter would be Cl < COOMe ≤ NO_2 < CCTMS < SO_3Et < SO_2Et < CN.[22] The sequence parallels the reactivity decrease discussed in the previous section and could serve to explain this observation. The argument would only be valid, however, if carbenium ion formation in these series, that is, in the reactions with 2-methylthiophene, was rate-determining.

Carbenium ion **I** can be intercepted by any arene Ar′H with sufficient nucleophilicity. These observations are difficult to quantify as the electrophilicity (e.g., as expressed by its electrophilicity parameter *E*) of **I** is not known; neither is the nucleophilicity (e.g., as expressed by its nucleophilicity parameter *N*) of all the arenes **23a–h**. Known data[23] include those for resorcin dimethyl ether (**23b**; $N=2.48$) and 2-methylthiophene (**23a**; $N=1.36$). It was checked with alcohol **9** whether significantly less reactive arenes as nucleophiles would still react. The reaction with *m*-xylene (**23i**; $N=-3.54$) was successful and gave the expected *anti* product *anti*-**34i** in good chemical yield and with perfect diastereoselectivity (Scheme 13). A further decrease in nucleophile reactivity led to side reactions. The attempted reaction with toluene ($N=-4.47$) gave a GLC ratio of elimination to substitution product of 83:17, with many other products detected by TLC.

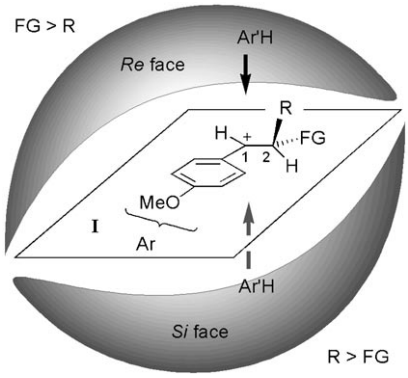


Scheme 13. Diastereoselective HBF_4-promoted Friedel–Crafts alkylation of *meta*-xylene (**23i**) by chiral substituted alcohols **9**.

On the basis of these data, the nucleophilicity range for arenes that are suitable for reacting with alcohols **5–12** covers at least six orders of magnitude and can be estimated to be $N \geq -3.57$, with an upper limit of $N \leq 2.48$; this limit may be higher, but is definitely dictated by the stability of the arene under acidic conditions.

The choice of alcohol electrophile is governed by a subtle balance between the Brønsted acidity of the acid and the Brønsted basicity of the alcohol. The acid must be sufficiently strong and its counterion sufficiently noncoordinating to allow for cation formation. In the current system with $HBF_4{\cdot}OEt_2$ as the acid, a single weak electron donor (methyl) at the *para* positon of the phenyl group provided the required stability (Table 5).

Although the picture is far from complete, the face differentiation in the putative carbocations **I** can be interpreted in an initial explanation attempt by steric arguments. Scheme 14 shows the preferred conformation of a putative *para*-methoxybenzyl-substituted carbocation **I**. Due to the partial-double-bond character of the bond between the cation carbon atom C1 and the aryl group, the stereogenic carbon atom C2 is in a strained 1,3-allylic situation. The hydrogen atom 2-H resides in the plane defined by the trigonal carbenium ion, and the two substituents R and FG point toward different spatial directions relative to this plane. An incoming nucleophile Ar′H will for steric reasons approach the electrophilic center from the less shielded face. The *A* values[24] of the individual substituents can be taken as a



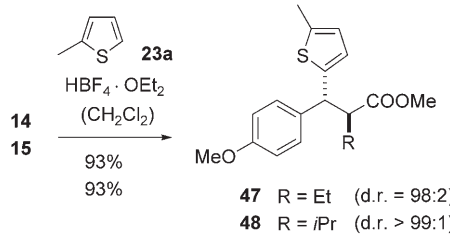
Scheme 14. Model to explain the facial diastereoselectivity in reactions of carbocation **I** based on the size of the two substituents R and FG at C2.

rough measure of their steric bulk. Relative to the methyl group (R = CH_3, $A = 1.74$), the functional groups nitro ($A = 1.1$), hydroxy ($A = 1.0$), cyano ($A = 0.2$), methoxycarbonyl ($A = 1.2$), trimethylsilylethynyl ($A = 0.45$), and chloro ($A = 0.6$) are smaller. The *Si* face is consequently less shielded and invites an approach by the nucleophile, thus leading to the corresponding *anti* products *anti*-**II** preferentially. The ethylsulfonyl ($A = 2.50$),[24] ethoxysulfonyl ($A = 2.50$),[24] and diethoxyphosphonyl ($A = 2.46$)[24] groups are larger than methyl and shield the *Si* face. As a consequence, *Re*-face attack of Ar′H is favored, which leads to the *syn* products *syn*-**II**.

The preferred conformation also explains the low tendency of the carbenium ion to undergo E1 elimination reactions. There is no reasonable trajectory for the elimination of proton 2-H because it is located perpendicular to the empty p_z orbital of the cation center. Only if the cation becomes distorted, for example, due to a twofold *ortho* substitution at the aryl group Ar (Scheme 10 and Table 5, entry 7) or if the arene Ar′H is not sufficiently nucleophilic to attack (e.g., toluene), does elimination set in. In the former case of twofold *ortho* substitution, the conformational preference is less pronounced, which results in low diastereoselectivity of the substitution reaction.

Influence of the Alkyl Substituent R

The model depicted in Scheme 14 is supported by experiments in which the bulk of the alkyl substituent R was increased relative to the methoxycarbonyl group (Scheme 15).



Scheme 15. Diastereoselective reaction of 2-methylthiophene (**23a**) with R-substituted alcohols **14** and **15**.

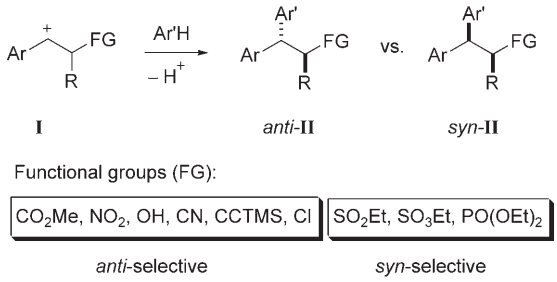
Reactions of substrates **14** and **15** with 2-methylthiophene (**23a**) proceeded in excellent yield (93%). In both cases, the diastereomer ratio in favor of the *anti* diastereomer exceeded the value achieved for substrate **9** (R = Me, d.r. = 96:4; Scheme 5 and Table 2, entry 5); the isopropyl substrate ($A = 2.2$; d.r. > 99:1, product **48**) is expectedly even more selective than the ethyl substrate ($A = 1.8$; d.r. = 98:2, product **47**).

Despite the influence of steric factors, it is obvious that other factors also influence the selectivity. Functional groups of identical size (according to their *A* value) give different diastereoselectivities. A previously reported[13c] example relates to the fluoro-substituted substrate with fluoro ($A = 0.3$) being of roughly identical size to cyano ($A = 0.2$). The diastereoselectivity of the fluoroalcohol reaction with 2-methylthiophene (**23a**), however, was significantly lower (d.r. = 58:42) than that of the analogous reaction with cyanoalcohol **8** (d.r. = 75:25).

Furthermore, our mechanistic understanding of the reaction is still limited, and we need more information about the kinetic parameters involved. Structural information about the intermediate carbocations would be most useful. Studies along these lines are currently underway.

Conclusions

In summary, it was found that the reaction of several precursors for chiral cations of type **I** with arenes Ar′H proceeds with high diastereoselectivity, with the selectivity heavily dependent on the functional group in the α position (Scheme 16). The most striking result was the fact that diastereoselectivities were consistently high with the preparatively useful methyl ester and the phosphonate, the former delivering the *anti* product *anti*-**II**, the latter the *syn* product *syn*-**II**.



Scheme 16. Summary of the dependence of the diastereofacial preference in the reaction of cation **I** on the individual functional groups FG.

Depending on the arene nucleophile, high diastereoselectivities (d.r. ≥ 90:10) were also achieved with the functional groups trimethylsilylethynyl and ethylsulfonyl as well as with the preliminarily studied nitro, hydroxy, and cyano groups.[13c] The reaction is of significant scope with regard to both the electrophile as well as the nucleophile; the latter covers a nucleophilicity range of at least six orders of magnitude.

Experimental Section

General

All reactions that involve water-sensitive chemicals were carried out in flame-dried glassware in dried solvents under argon atmosphere. Common solvents (pentane, EtOAc, THF, Et_2O, CH_2Cl_2) were distilled prior to use. All other reagents and solvents were used as received. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$. Chemical shifts are reported relative to $CHCl_3$ ($\delta = 7.26$ 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). TLC

was performed on aluminum sheets (0.2 mm silica gel 60 F_{254}) with detection by UV (254 nm) or by coloration with ceric ammonium molybdate (CAM). Flash chromatography was performed on silica gel 60 (230–400 mesh, ≈50 g for 1 g of material to be separated) with the indicated eluent. Compounds **5**,[15] **6**,[16] **13**,[19] **24**,[17] and **25**[18] were prepared according to known procedures. The preparation and analytical data of compounds **7**–**12**, **14**–**22**, **26**, **32b**–**h**, **33b**–**c**, **35b**–**h**, **36b**–**c**, **37b**–**c**, **42**, **43**, and **46**–**48** are reported in the Supporting Information.

Representative Experimental Procedures for the Friedel–Crafts Alkylation Reactions

30a: 1-(4′-Methoxyphenyl)-2-nitropropan-1-ol (**5**; 106 mg, 0.5 mmol) was dissolved in dry CH_2Cl_2 (10 mL). The solution was cooled to −78 °C, and $HBF_4{\cdot}OEt_2$ (86 μL, 102 mg, 0.63 mmol) was added. After the mixture was stirred for 5 min at −78 °C, 2-methylthiophene (**23a**; 192 μL, 196 mg, 2.0 mmol) was added. The solution was stirred at −78 °C for a further 5 min and warmed to room temperature over 15 min. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (20 mL), and the mixture was diluted with Et_2O (20 mL). The organic layer was separated, washed with saturated aqueous $NaHCO_3$ (20 mL) and saturated aqueous NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (pentane/Et_2O = 90:10) to give 2-(1′-(4″-methoxyphenyl)-2′-nitropropyl)-5-methylthiophene (**30a**; 107 mg, 73 %) as a colorless oil (d.r. *anti*/*syn* = 91:9). R_f = 0.19 (pentane/Et_2O = 90:10); IR (film): $\tilde{\nu}$ = 2936 (m), 2837 (m), 1610 (s), 1584 (m), 1556 (vs), 1513 (vs), 1387 (s), 1358 (s), 1304 (m), 1254 (vs), 1179 (s) 1110 (m), 869 (m), 833 (s), 736 (w), 666 cm^{-1} (w); ^1H NMR ($CDCl_3$, 360 MHz): δ = 1.44 (d, J = 6.6 Hz, 3H), 2.37 (s, 3H), 3.79 (s, 3H), 4.57 (d, J = 11.0 Hz, 1H), 5.16 (dq, J = 11.0, 6.6 Hz, 1H), 6.50–6.54 (m, 1H), 6.71 (d, J = 3.4 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 7.21 ppm (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 90.6 MHz): δ = 15.3 (q), 19.1 (q), 51.0 (d), 55.4 (q), 88.2 (d), 114.7 (d), 124.8 (d), 125.0 (d), 129.3 (d), 131.1 (s), 139.6 (s), 140.9 (s), 159.3 ppm (s); MS (EI, 70 eV): m/z (%) = 291 (3) $[M]^+$, 244 (58), 229 (14), 217 (100); HRMS: m/z calcd for $C_{15}H_{17}NO_3S$: 291.0929; found: 291.0931.

31a: Reaction of **6** (96 mg, 0.5 mmol) with $HBF_4{\cdot}OEt_2$ (86 μL, 102 mg, 0.63 mmol) and **23a** (192 μL, 196 mg, 2.0 mmol) yielded, after flash chromatography (pentane/Et_2O = 80:20), 3-(4′-methoxyphenyl)-2-methyl-3-(5′-methylthiophen-2′-yl)propanenitrile (**31a**; 125 mg, 92 %) as a colorless oil (d.r. *anti*/*syn* = 75:25). R_f = 0.08 (pentane/Et_2O = 90:10); IR (film): $\tilde{\nu}$ = 3063 (w), 2936 (m), 2836 (m), 2240 (m), 1610 (s), 1512 (vs), 1455 (s), 1252 (vs), 1180 (s), 1033 (s), 801 cm^{-1} (s); ^1H NMR (360 MHz, $CDCl_3$): δ = 1.28 (d, J = 7.1 Hz, 3H), 2.42 (d, J = 1.0 Hz, 3H), 3.23 (qd, J = 8.9, 7.1 Hz, 1H), 3.79 (s, 3H), 4.16 (d, J = 8.9 Hz, 1H), 6.60–6.61 (m, 1H), 6.86–6.91 (m, 3H), 7.22 ppm (d, J = 8.7 Hz, 2H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 15.2 (q), 17.2 (q), 32.8 (d), 49.7 (d), 55.3 (q), 114.3 (d), 122.0 (s), 124.9 (d), 125.2 (d), 128.8 (d), 132.4 (s), 139.3 (s), 141.7 (s), 159.0 ppm (s); MS (EI, 70 eV): m/z (%) = 271 (3) $[M]^+$, 217 (100), 202 (6), 174 (5), 159 (3); elemental analysis: calcd (%) for $C_{16}H_{17}NOS$ (271.38): C 70.81, H 6.31, N 5.16; found: C 70.73, H 6.28, N 5.06.

32a: Reaction of **7** (100 mg, 0.5 mmol) with $HBF_4{\cdot}OEt_2$ (86 μL, 102 mg, 0.63 mmol) and **23a** (192 μL, 196 mg, 2.0 mmol) yielded, after flash chromatography (pentane/Et_2O = 90:10), 2-(2′-chloro-1′-(4″-methoxyphenyl)-propyl)-5-methylthiophene (**32a**; 136 mg, 97 %) as a pale-yellow oil (d.r. *anti*/*syn* = 73:27). R_f = 0.29 (pentane/Et_2O = 95:5); IR (film): $\tilde{\nu}$ = 3062 (w), 2930 (m), 2835 (m), 1609 (s), 1511 (vs), 1442 (m), 1249 (vs), 1179 (s), 1035 (s), 799 cm^{-1} (s); ^1H NMR (360 MHz, $CDCl_3$) δ = 1.45 (d, J = 6.6 Hz, 3H), 2.43 (d, J = 1.0 Hz, 3H), 3.79 (s, 3H), 4.24 (d, J = 8.5 Hz, 1H), 4.51–4.63 (m, 1H), 6.59 (dd, J = 3.4, 1.0 Hz, 1H), 6.78 (d, J = 3.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.22 ppm (d, J = 8.7 Hz, 2H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 15.2 (q), 24.0 (q), 55.4 (q), 60.5 (d), 61.2 (d), 114.0 (d), 124.4 (d), 125.1 (d), 129.1 (d), 133.6 (s), 138.5 (s), 142.9 (s), 158.7 ppm (s); MS (EI, 70 eV): m/z (%) = 282 (1) $[M\{^{37}Cl\}]^+$, 280 (3) $[M\{^{35}Cl\}]^+$, 244 (9), 229 (3), 217 (100), 202 (5), 174 (5), 115 (5), 77 (3); elemental analysis: calcd (%) for $C_{15}H_{17}SOCl$ (280.81): C 64.16, H 6.10; found: C 64.37, H 6.18.

33a: Reaction of **8** (131 mg, 0.5 mmol) with $HBF_4{\cdot}OEt_2$ (72 μL, 86 mg, 0.53 mmol) and **23a** (192 μL, 196 mg, 2.0 mmol) yielded, after flash chromatography (pentane/Et_2O = 98:2), 4-(4′-methoxyphenyl)-3-methyl-4-(5′-methylthiophen-2′-yl)-but-1-ynyl-trimethylsilane (**33a**; 156 mg, 91 %) as a colorless oil (d.r. *anti*/*syn* = 77:23). R_f = 0.25 (pentane/Et_2O = 98:2); IR (film): $\tilde{\nu}$ = 3062 (w), 2957 (s), 2836 (m), 2167 (m), 1610 (s), 1512 (vs), 1453 (m), 1249 (vs), 1179 (s), 1037 (s), 842 cm^{-1} (vs); ^1H NMR (360 MHz, $CDCl_3$): δ = 0.11 (s, 9H), 1.13 (d, J = 6.9 Hz, 3H), 2.41 (s, 3H), 3.08 (qd, J = 7.9, 6.9 Hz, 1H), 3.78 (s, 3H), 4.02 (d, J = 7.9 Hz, 1H), 6.55 (d, J = 3.4 Hz, 1H), 6.78 (d, J = 3.4 Hz, 1H), 6.84 (d, J = 8.7 Hz, 2H), 7.25 ppm (d, J = 8.7 Hz, 2H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 0.0 (q), 15.2 (q), 19.8 (q), 33.8 (d), 52.1 (d), 55.2 (q), 87.1 (s), 110.3 (s), 113.7 (d), 124.1 (d), 125.0 (d), 129.1 (d), 134.8 (s), 138.1 (s), 144.0 (s), 158.4 ppm (s); MS (EI, 70 eV): m/z (%) = 341 (3) $[M]^+$, 217 (100), 202 (5), 174 (3), 159 (2), 141 (2), 97 (2), 59 (2); elemental analysis: calcd (%) for $C_{29}H_{26}OSSi$ (342.57): C 70.12, H 7.65; found: C 70.02, H 7.61.

34a: Reaction of **9** (112 mg, 0.5 mmol) with $HBF_4{\cdot}OEt_2$ (86 μL, 102 mg, 0.63 mmol) and **23a** (192 μL, 196 mg, 2.0 mmol) yielded, after flash chromatography (pentane/Et_2O = 90:10), methyl 3-(4′-methoxyphenyl)-2-methyl-3-(5′-methylthiophen-2′-yl)propanoate (**34a**; 143 mg, 93 %) as a pale-yellow oil (d.r. *anti*/*syn* = 96:4). R_f = 0.32 (pentane/Et_2O = 80:20); IR (film): $\tilde{\nu}$ = 2949 (m), 2836 (w), 1737 (vs), 1610 (m), 1512 (s), 1456 (m), 1252 (vs), 1164 (s), 1035 (s), 835 cm^{-1} (m); ^1H NMR (360 MHz, $CDCl_3$): δ = 1.05 (d, J = 6.9 Hz, 3H), 2.36 (d, J = 1.0 Hz, 3H), 3.15 (dq, J = 11.0, 6.9 Hz, 1H), 3.61 (s, 3H), 3.77 (s, 3H), 4.25 (d, J = 11.0 Hz, 1H), 6.49 (dd, J = 3.3 Hz, J = 1.0 Hz, 1H), 6.64 (d, J = 3.3 Hz, 1H), 6.84 (d, J = 8.7 Hz, 2H), 7.18 ppm (d, J = 8.7 Hz, 2H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 15.2 (q), 16.8 (q), 46.4 (d), 49.3 (d), 51.7 (q), 55.2 (q), 114.0 (d), 123.4 (d), 124.4 (d), 129.0 (d), 134.0 (s), 138.3 (s), 145.1 (s), 158.4 (s), 176.1 ppm (s); MS (EI, 70 eV): m/z (%) = 304 (5) $[M]^+$, 217 (100), 202 (5), 174 (3); elemental analysis: calcd (%) for $C_{17}H_{20}O_3S$ (304.4): C 67.08, H 6.62; found: C 67.06, H 6.67.

34b: Reaction of **9** (112 mg, 0.5 mmol) with $HBF_4{\cdot}OEt_2$ (86 μL, 102 mg, 0.63 mmol) and resorcin dimethyl ether (263 μL, 276 mg, 2.0 mmol, **23b**) yielded, after flash chromatography (pentane/Et_2O = 60:40), methyl 3-(2′,4′-dimethoxyphenyl)-3-(4′-methoxyphenyl)-2-methylpropanoate (**34b**; 146 mg, 85 %) as a colorless oil (d.r. *anti*/*syn* = 95:5). R_f = 0.30 (pentane/Et_2O = 60:40); IR (film): $\tilde{\nu}$ = 2951 (s), 2836 (m), 1736 (vs), 1610 (vs), 1508 (s), 1459 (s), 1252 (vs), 1159 (s), 1036 (s), 83 cm^{-1}7 (m); ^1H NMR (360 MHz, $CDCl_3$): δ = 1.09 (d, J = 6.9 Hz, 3H), 3.32 (dq, J = 11.9, 6.9 Hz, 1H), 3.49 (s, 3H), 3.74 (s, 3H), 3.75 (s, 3H), 3.75 (s, 3H), 4.38 (d, J = 11.9 Hz, 1H), 6.35 (d, J = 2.5 Hz, 1H), 6.42 (dd, J = 8.4 Hz, J = 2.5 Hz, 1H), 6.78 (d, J = 8.7 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H), 7.26 ppm (d, J = 8.4 Hz, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 17.1 (q), 43.9 (d), 46.2 (d), 51.5 (q), 55.1 (q), 55.2 (q), 55.5 (q), 98.9 (d), 104.0 (d), 113.6 (d), 124.8 (s), 127.1 (d), 129.4 (d), 134.7 (s), 157.8 (s), 157.8 (s), 159.2 (s), 176.5 ppm (s); MS (EI, 70 eV): m/z (%) = 344 (5) $[M]^+$, 257 (100), 241 (3), 165 (3), 128 (6), 121 (35); elemental analysis: calcd (%) for $C_{20}H_{24}O_5$ (344.40): C 69.75, H 7.02; found: C 69.79, H 7.09.

34c: Reaction of **9** (112 mg, 0.5 mmol) with $HBF_4{\cdot}OEt_2$ (86 μL, 102 mg, 0.63 mmol) and 1-tosyl-1*H*-pyrrole (433 mg, 2.0 mmol, **23c**) yielded, after flash chromatography (pentane/Et_2O = 60:40), methyl 3-(4′-methoxyphenyl)-2-methyl-3-(1′-tosyl-1*H*-pyrrol-2′-yl)propanoate (**34c**; 195 mg, 91 %) as a colorless oil (d.r. *anti*/*syn* = 94:6). R_f = 0.27 (pentane/Et_2O = 60:40); IR (film): $\tilde{\nu}$ = 2953 (s), 2838 (m), 1735 (vs), 1610 (vs), 1511 (s), 1457 (s), 1252 (vs), 1176 (s), 1036 (m), 812 (m), 673 cm^{-1} (s); ^1H NMR (360 MHz, $CDCl_3$): δ = 1.00 (d, J = 7.0 Hz, 3H), 2.32 (s, 3H), 2.90 (dq, J = 11.4, 7.0 Hz, 1H), 3.48 (s, 3H), 3.75 (s, 3H), 4.69 (d, J = 11.4 Hz, 1H), 6.22 (virt t, J≅3.4 Hz, 1H), 6.35–6.40 (m, 1H), 6.68 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 8.3 Hz, 2H), 7.18 (dd, J = 3.3 Hz, J = 1.6 Hz, 1H), 7.29 ppm (d, J = 8.3 Hz, 2H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 16.9 (q), 21.4 (q), 45.0 (d), 46.1 (d), 51.6 (q), 55.2 (q), 111.4 (d), 112.0 (d), 113.4 (d), 123.2 (d), 126.5 (d), 129.4 (d), 130.0 (d), 132.0 (d), 136.7 (s), 137.3 (s), 144.9 (s), 158.3 (s), 175.9 ppm (s); MS (EI, 70 eV): m/z (%) = 427 (10) $[M]^+$, 340 (100), 272 (23), 185 (34), 170 (19), 137 (21), 91 (21); elemental analysis: calcd (%) for $C_{23}H_{25}NO_5S$ (427.51): C 64.62, H 5.89, N 3.28; found: C 64.63, H 5.85, N 3.18.

34d: Reaction of **9** (112 mg, 0.5 mmol) with $HBF_4{\cdot}OEt_2$ (86 μL, 102 mg, 0.63 mmol) and 2,5-dimethylfuran (214 μL, 192 mg, 2.0 mmol, **23d**) yielded, after flash chromatography (pentane/Et_2O = 90:10), methyl 3-(2′,5′-di-

methylfuran-3′-yl)-3-(4′-methoxyphenyl)-2-methylpropanoate (**34d**; 130 mg, 86%) as a colorless oil (d.r. *anti*/*syn* = 93:7). R_f = 0.62 (pentane/Et_2O = 50:50); IR (film): $\tilde{\nu}$ = 2949 (m), 2836 (w), 1737 (vs), 1610 (m), 1512 (vs), 1457 (m), 1252 (vs), 1165 (s), 1036 (m), 841 (m), 806 cm^{-1} (m); ^1H NMR (360 MHz, $CDCl_3$): δ = 1.04 (d, J = 6.8 Hz, 3H), 2.16 (s, 3H), 2.17 (s, 3H), 3.03 (dq, J = 12.6, 6.8 Hz, 1H), 3.57 (s, 3H), 3.77 (s, 3H), 3.80 (d, J = 12.6 Hz, 1H), 5.94 (s, 1H), 6.83 (d, J = 8.5 Hz, 2H), 7.15 ppm (d, J = 8.5 Hz, 2H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 11.4 (q), 13.5 (q), 16.7 (q), 44.8 (d), 45.3 (d), 51.5 (q), 55.2 (q), 105.2 (d), 114.0 (d), 121.4 (s), 128.8 (d), 134.5 (s), 145.2 (s), 149.3 (s), 158.1 (s), 176.3 ppm (s); MS (EI, 70 eV): m/z (%) = 302 (9) $[M]^+$, 215 (100), 158 (3), 128 (3); elemental analysis: calcd (%) for $C_{18}H_{22}O_4$(302.36): C 71.50, H 7.33; found: C 71.41, H 7.39.

34e: Reaction of **9** (112 mg, 0.5 mmol) with $HBF_4{\cdot}OEt_2$ (292 μL, 347 mg, 2.13 mmol) and 2-acetylfuran (150 μL, 165 mg, 1.5 mmol, **23e**) yielded, after flash chromatography (pentane/Et_2O = 50:50), methyl 3-(5′-acetylfuran-2′-yl)-3-(4′-methoxyphenyl)-2-methylpropanoate (**34e**; 81 mg, 51%) as a colorless oil (d.r. *anti*/*syn* = 92:8). R_f = 0.22 (pentane/Et_2O = 50:50); IR (film): $\tilde{\nu}$ = 2952 (m), 2838 (w), 1735 (vs), 1677 (vs), 1611 (m), 1510 (vs), 1458 (s), 1253 (vs), 1032 (m), 838 (m), 806 cm^{-1} (m); ^1H NMR (360 MHz, $CDCl_3$): δ = 1.04 (d, J = 7.0 Hz, 3H), 2.39 (s, 3H), 3.17 (dq, J = 10.9, 7.0 Hz, 1H), 3.63 (s, 3H), 3.78 (s, 3H), 4.14 (d, J = 10.9 Hz, 1H), 6.21 (d, J = 3.4 Hz, 1H), 6.85 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 3.4 Hz, 1H), 7.18 ppm (d, J = 8.4 Hz, 2H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 16.2 (q), 25.8 (q), 44.0 (d), 47.8 (d), 51.9 (q), 55.2 (q), 108.6 (d), 114.2 (d), 118.2 (d), 129.5 (d), 130.2 (s), 152.0 (s), 158.9 (s), 161.3 (s), 175.6 (s), 186.2 ppm (s); MS (EI, 70 eV): m/z (%) = 316 (13) $[M]^+$, 229 (100), 192 (12), 135 (72); HRMS: m/z calcd for $C_{18}H_{20}O_5$: 316.1311; found: 316.1303.

34f: Reaction of **9** (112 mg, 0.5 mmol) with $HBF_4{\cdot}OEt_2$ (86 μL, 102 mg, 0.63 mmol) and benzofuran (221 μL, 236 mg, 2.0 mmol, **23f**) yielded, after flash chromatography (pentane/Et_2O = 80:20), methyl 3-(benzofuran-2′-yl)-3-(4′-methoxyphenyl)-2-methylpropanoate (**34f**; 120 mg, 74%) as a white solid (d.r. *anti*/*syn* = 96:4). R_f = 0.47 (pentane/Et_2O = 60:40); m.p.: 104 °C; IR (KBr): $\tilde{\nu}$ = 2950 (s), 2836 (m), 1740 (vs), 1610 (s), 1512 (vs), 1455 (vs), 1252 (vs), 1176 (s), 1034 (s), 824 (s), 752 cm^{-1} (m); ^1H NMR (360 MHz, $CDCl_3$): δ = 1.09 (d, J = 7.0 Hz, 3H), 3.24 (dq, J = 10.9, 7.0 Hz, 1H), 3.62 (s, 3H), 3.79 (s, 3H), 4.30 (d, J = 10.9 Hz, 1H), 6.50 (s, 1H), 6.86 (d, J = 8.7 Hz, 2H), 7.13–7.21 (m, 2H), 7.24 (d, J = 8.7 Hz, 2H), 7.37 (d, J = 7.9 Hz, 1H), 7.45–7.48 ppm (m, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 16.3 (q), 43.9 (d), 47.9 (d), 51.9 (q), 55.2 (q), 102.4 (d), 111.0 (d), 114.1 (d), 120.6 (d), 122.5 (d), 123.5 (d), 128.5 (s), 129.6 (d), 130.9 (s), 154.7 (s), 158.8 (s), 159.4 (s), 175.9 ppm (s); MS (EI, 70 eV): m/z (%) = 324 (6) $[M]^+$, 237 (100), 194 (6), 165 (6), 119 (5); elemental analysis: calcd (%) for $C_{20}H_{20}O_4$ (324.27): C 74.06, H 6.21; found: C 73.89, H 6.13.

34g: Reaction of **9** (112 mg, 0.5 mmol) with $HBF_4{\cdot}OEt_2$ (292 μL, 347 mg, 2.13 mmol) and 4-methyl-*N*-phenylbenzenesulfonamide (371 mg, 1.5 mmol, **23g**) yielded, after flash chromatography (pentane/Et_2O = 30:70), methyl 3-(4′-methoxyphenyl)-2-methyl-3-(4′-(4″-methylphenylsulfonamido)phenyl)propanoate (**34g**; 193 mg, 85%) as a white solid (d.r. *anti*/*syn* = 92:8). R_f = 0.31 (pentane/Et_2O = 20:80); m.p.: 66 °C; IR (KBr): $\tilde{\nu}$ = 3254 (m), 2949 (m), 2837 (m), 1734 (s), 1609 (m), 1511 (vs), 1457 (s), 1252 (vs), 1161 (vs), 1034 (m), 815 (m), 665 cm^{-1} (m); ^1H NMR (360 MHz, $CDCl_3$): δ = 1.09 (d, J = 6.8 Hz, 3H), 2.34 (s, 3H), 3.19 (dq, J = 12.6, 6.8 Hz, 1H), 3.40 (s, 3H), 3.75 (s, 3H), 3.95 (d, J = 12.6 Hz, 1H), 6.81 (d, J = 8.7 Hz, 2H), 6.91–6.94 (m, 3H), 7.11 (d, J = 8.7 Hz, 2H), 7.12 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.2 Hz, 2H), 7.60 ppm (d, J = 8.2 Hz, 2H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 16.9 (q), 21.4 (q), 44.8 (d), 51.4 (q), 53.7 (d), 55.2 (q), 114.0 (d), 121.6 (d), 127.2 (d), 128.4 (d), 129.0 (d), 129.5 (d), 133.9 (s), 134.8 (s), 136.2 (s), 140.6 (s), 143.7 (s), 158.3 (s), 176.1 ppm (s); MS (EI, 70 eV): m/z (%) = 453 (6) $[M]^+$, 366 (100), 211 (37); elemental analysis: calcd (%) for $C_{25}H_{27}NO_5S$ (453.55): C 66.20, H 6.00, N 3.09; found: C 65.94, H 5.98, N 2.98.

34h: Reaction of **9** (112 mg, 0.5 mmol) with $HBF_4{\cdot}OEt_2$ (292 μL, 347 mg, 2.13 mmol) and methyl 1*H*-pyrrole-2-carboxylate (188 mg, 1.5 mmol, **23h**) yielded, after flash chromatography (pentane/Et_2O = 50:50), methyl 5-(3′-methoxy-1′-(4″-methoxyphenyl)-2′-methyl-3′-oxopropyl)-1*H*-pyrrole-2-carboxylate (**34h**; 136 mg, 82%) as a colorless oil (d.r. *anti*/*syn* = 94:6). R_f = 0.22 (pentane/Et_2O = 50:50); IR (KBr): $\tilde{\nu}$ = 3311 (m), 2952 (m), 2838 (w), 1733 (vs), 1695 (vs), 1610 (m), 1512 (s), 1485 (s), 1251 (vs), 1038 (m), 765 (m), 737 cm^{-1} (m); ^1H NMR (360 MHz, $CDCl_3$): δ = 1.06 (d, J = 7.0 Hz, 3H), 3.12 (dq, J = 10.4, 7.0 Hz, 1H), 3.62 (s, 3H), 3.78 (s, 3H), 3.79 (s, 3H), 4.14 (d, J = 10.4 Hz, 1H), 6.07 (virt t, $J \cong$ 3.2 Hz, 1H), 6.78–6.80 (m, 1H), 6.84 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H), 9.04 ppm (s, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 17.0 (q), 45.1 (d), 47.4 (d), 51.7 (q), 52.4 (q), 55.7 (q), 108.5 (d), 114.7 (d), 116.0 (d), 122.2 (s), 129.6 (d), 132.3 (s), 139.3 (s), 159.1 (s), 161.8 (s), 176.9 ppm (s); MS (EI, 70 eV): m/z (%) = 331 (15) $[M]^+$, 244 (100), 212 (66), 135 (15), 95 (34); HRMS: m/z calcd for $C_{18}H_{21}NO_5$: 331.1420; found: 331.1422.

34i: Reaction of **9** (112 mg, 0.5 mmol) with $HBF_4{\cdot}OEt_2$ (86 μL, 102 mg, 0.63 mmol) and *m*-xylol (246 μL, 212 mg, 2.0 mmol, **23i**) yielded, after flash chromatography (pentane/Et_2O = 90:10), methyl 3-(2′,4′-dimethylphenyl)-3-(4′-methoxyphenyl)-2-methylpropanoate (**34i**; 108 mg, 69%) as a white solid (d.r. *anti*/*syn* > 95:5). R_f = 0.20 (pentane/Et_2O = 90:10); m.p.: 72 °C; IR (KBr): $\tilde{\nu}$ = 2952 (s), 2836 (m), 1730 (vs), 1607 (m), 1509 (vs), 1459 (s), 1255 (vs), 1154 (vs), 1032 (s), 827 cm^{-1} (m); ^1H NMR (360 MHz, $CDCl_3$): δ = 1.14 (d, J = 6.6 Hz, 3H), 2.26 (s, 3H), 2.30 (s, 3H), 3.26–3.35 (m, 1H), 3.52 (s, 3H), 3.76 (s, 3H), 4.24 (d, J = 11.4 Hz, 1H), 6.82 (d, J = 8.8 Hz, 2H), 6.91 (s, 1H, H-c), 7.01 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 8.8 Hz, 2H), 7.37 ppm (d, J = 7.8 Hz, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 17.3 (q), 19.7 (q), 20.8 (q), 44.8 (d), 49.0 (d), 51.4 (q), 55.1 (q), 113.8 (d), 125.2 (d), 126.5 (d), 129.5 (d), 131.4 (d), 133.7 (s), 135.4 (s), 135.8 (s), 138.6 (s), 158.0 (s), 176.4 ppm (s); MS (EI, 70 eV): m/z (%) = 312 (5) $[M]^+$, 225 (100); elemental analysis: calcd (%) for $C_{20}H_{24}O_3$ (312.40): C 76.89, H 7.74; found: C 76.77, H 7.69.

35a: Reaction of **10** (151 mg, 0.5 mmol) with $HBF_4{\cdot}OEt_2$ (86 μL, 102 mg, 0.63 mmol) and **23a** (192 μL, 196 mg, 2.0 mmol) yielded diethyl 1-(4′-methoxyphenyl)-1-(5′-methylthiophen-2′-yl)propan-2-ylphosphonate (**34a**; 190 mg, 99%) as a colorless oil (d.r. *anti*/*syn* = 12:88). R_f = 0.09 (pentane/Et_2O = 10:90); IR (film): $\tilde{\nu}$ = 3462 (br), 3063 (w), 2978 (m), 2835 (w), 1610 (m), 1512 (vs), 1456 (w), 1246 (vs), 1179 (s), 1027 (vs), 799 cm^{-1} (s); ^1H NMR (360 MHz, $CDCl_3$): δ = 1.05 (t, J = 7.1 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H), 1.22 (dd, $J_{H,P}$ = 17.8 Hz, J = 7.2 Hz, 3H), 2.38 (d, J = 1.1 Hz, 3H), 2.59 (ddq, $J_{H,P}$ = 24.4 Hz, J = 9.9, 7.2 Hz, 1H), 3.75 (s, 3H), 3.79–3.96 (m, 4H), 4.33 (virt t, $J \cong$ 9.5 Hz, 1H), 6.50 (dd, J = 3.4, 1.1 Hz, 1H), 6.68 (d, J = 3.4 Hz, 1H), 6.81 (d, J = 8.7 Hz, 2H), 7.28 ppm (d, J = 8.7 Hz, 2H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 13.4 (dq, $J_{C,P}$ = 4.5 Hz), 15.3 (q), 16.2 (dq, $J_{C,P}$ = 6.1 Hz), 16.2 (dq, $J_{C,P}$ = 6.2 Hz), 37.4 (dd, $J_{C,P}$ = 140 Hz), 47.7 (d), 55.2 (q), 61.3 (dt, $J_{C,P}$ = 6.8 Hz), 61.5 (dt, $J_{C,P}$ = 6.9 Hz), 113.6 (d), 124.3 (d), 124.9 (d), 129.1 (d), 135.4 (d, $J_{C,P}$ = 4.7 Hz), 138.5 (s), 144.2 (d, $J_{C,P}$ = 17.3 Hz), 158.2 ppm (s); MS (EI, 70 eV): m/z (%) = 382 (14) $[M]^+$, 244 (100), 229 (8), 217 (65), 165 (40), 137 (15), 109 (6), 91 (3), 77 (3); HRMS: m/z calcd for $C_{19}H_{27}O_4PS$: 382.1368; found: 382.1364.

36a: Reaction of **11** (129 mg, 0.5 mmol) with $HBF_4{\cdot}OEt_2$ (86 μL, 102 mg, 0.63 mmol) and **23a** (192 μL, 196 mg, 2.0 mmol) yielded, after flash chromatography (pentane/Et_2O = 50:50), 2-(2′-(ethylsulfonyl)-1′-(4″-methoxyphenyl)propyl)-5-methylthiophene (**36a**; 166 mg, 98%) as a colorless oil (d.r. *anti*/*syn* = 26:74). R_f = 0.19 (pentane/Et_2O = 50:50); IR (film): $\tilde{\nu}$ = 2982 (m), 2940 (m), 2836 (w), 1610 (s), 1582 (w), 1511 (vs), 1456 (m), 1300 (s), 1250 (s), 1180 (s), 1129 (s), 1033 (s), 833 (m), 731 (w), 598 cm^{-1} (w); ^1H NMR (360 MHz, $CDCl_3$): δ = 1.16 (virt t, $J \cong$ 7.5 Hz, 3H), 1.43 (d, J = 7.1 Hz, 3H), 2.11 (dq, J = 14.0, 7.3 Hz, 1H), 2.29 (dq, J = 14.0, 7.2 Hz, 1H), 2.41 (s, 3H), 3.63 (dq, J = 9.2, 7.1 Hz, 1H), 3.78 (s, 3H), 4.61 (d, J = 9.2 Hz, 1H), 6.52–6.59 (m, 1H), 6.74 (d, J = 3.4 Hz, 1H), 6.83–6.92 (m, 2H), 7.32–7.39 (m, 2H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 6.4 (q), 12.0 (q), 15.4 (q), 47.4 (t), 47.8 (d), 55.4 (q), 62.5 (d), 114.5 (d), 124.8 (d), 126.0 (d), 129.4 (d), 133.7 (s), 139.6 (s), 141.9 (s), 159.1 ppm (s); MS (EI, 70 eV): m/z (%) = 338 (1) $[M]^+$, 244 (100), 229 (22), 217 (83); HRMS: m/z calcd for $C_{17}H_{23}O_3S_2$: 338.1010; found: 338.1008.

37a: Reaction of **12** (124 mg, 0.5 mmol) with $HBF_4{\cdot}OEt_2$ (86 μL, 102 mg, 0.63 mmol) and **23a** (192 μL, 196 mg, 2.0 mmol) yielded, after flash chromatography (pentane/Et_2O = 70:30), ethyl 1-(4′-methoxyphenyl)-1-(5′-methylthiophen-2′-yl)propane-2-sulfonate (**37a**; 168 mg, 95%) as a colorless oil (d.r. *anti*/*syn* = 37:63). R_f = 0.25 (pentane/Et_2O = 70:30); IR (film): $\tilde{\nu}$ = 2991 (m), 2938 (m), 2837 (w), 1610 (s), 1512 (vs), 1457 (s), 1349 (vs), 1251 (vs), 1166 (vs), 1002 (s), 919 (vs), 802 cm^{-1} (m); ^1H NMR (360 MHz,

$CDCl_3$): $\delta = 1.12$ (t, $J = 7.1$ Hz, 3H), 1.46 (d, $J = 7.0$ Hz, 3H), 2.40 (d, $J = 1.1$ Hz, 3H), 3.78 (s, 3H), 3.80–3.92 (m, 1H), 3.96 (q, $J = 7.1$ Hz, 2H), 4.60 (d, $J = 8.6$ Hz, 1H), 6.54 (dd, $J = 3.4$, 1.1 Hz, 1H), 6.72 (d, $J = 3.4$ Hz, 1H), 6.85 (d, $J = 8.7$ Hz, 2H), 7.30 ppm (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 14.0$ (q), 14.8 (q), 15.2 (q), 47.9 (d), 55.2 (q), 61.4 (t), 65.6 (d), 113.9 (d), 124.6 (d), 125.9 (d), 128.9 (d), 133.8 (s), 139.4 (s), 141.4 (s), 158.6 ppm (s); MS (EI, 70 eV): m/z (%) = 354 (3) $[M]^+$, 244 (18), 217 (100); elemental analysis: calcd (%) for $C_{17}H_{22}O_4S_2$ (354.48): C 57.60, H 6.26; found: C 57.44, H 6.09.

41: Reaction of **17** (104 mg, 0.5 mmol) with $HBF_4{\cdot}OEt_2$ (86 μL, 102 mg, 0.63 mmol) and **23a** (192 μL, 196 mg, 2.0 mmol) yielded, after flash chromatography (pentane/Et_2O = 90:10), methyl 2-methyl-3-(5′-methylthiophen-2′-yl)-3-*p*-tolylpropanoate (**41**; 96 mg, 69%) as a pale-yellow oil (d.r. *anti*/*syn* = 92:8). $R_f = 0.27$ (pentane/Et_2O = 90:10); IR (film): $\tilde{\nu} = 2948$ (m), 2877 (w), 1739 (vs), 1513 (m), 1454 (m), 1262 (vs), 1163 (s), 1051 (s), 799 cm^{-1} (m); ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 1.08$ (d, $J = 6.9$ Hz, 3H), 2.34 (d, $J = 1.0$ Hz, 3H), 2.38 (s, 3H), 3.19 (dq, $J = 11.1$, 6.9 Hz, 1H), 3.64 (s, 3H), 4.28 (d, $J = 11.1$ Hz, 1H), 6.49 (dq, $J = 3.4$, 1.0 Hz, 1H), 6.66 (d, $J = 3.4$ Hz, 1H), 7.07–7.23 ppm (m, 4H); ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 15.6$ (q), 17.3 (q), 21.5 (q), 46.7 (d), 50.3 (d), 52.1 (q), 124.0 (d), 124.9 (d), 128.3 (d), 129.8 (d), 136.9 (s), 138.7 (s), 139.3 (s), 145.3 (s), 176.5 ppm (s); MS (EI, 70 eV): m/z (%) = 288 (5) $[M]^+$, 201 (100); elemental analysis: calcd (%) for $C_{17}H_{20}O_2S$ (288.40): C 70.80, H 6.99; found: C 70.69, H 7.08.

45: Reaction of **21** (142 mg, 0.5 mmol) with $HBF_4{\cdot}OEt_2$ (86 μL, 102 mg, 0.63 mmol) and **23a** (192 μL, 196 mg, 2.0 mmol) yielded, after flash chromatography (pentane/Et_2O = 60:140), methyl 2-methyl-3-(5′-methylthiophen-2′-yl)-3-(3′,4′,5′-trimethoxyphenyl)propanoate (**45**; 164 mg, 90%) as a pale-yellow oil (d.r. *anti*/*syn* = 97:3). $R_f = 0.25$ (pentane/Et_2O = 60:40); IR (film): $\tilde{\nu} = 2939$ (m), 2837 (w), 1735 (vs), 1590 (vs), 1507 (s), 1457 (vs), 1249 (vs), 1164 (s), 1009 (m), 832 cm^{-1} (w); ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 1.08$ (d, $J = 6.9$ Hz, 3H), 2.38 (d, $J = 1.0$ Hz, 3H), 3.14 (dq, $J = 11.2$, 6.9 Hz, 1H), 3.69 (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 4.20 (d, $J = 11.2$ Hz, 1H), 6.48–6.51 (m, 3H), 6.67 ppm (d, $J = 3.4$ Hz, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 15.2$ (q), 16.9 (q), 46.6 (d), 50.6 (d), 51.7 (q), 56.1 (q), 60.8 (q), 105.0 (d), 123.8 (d), 124.5 (d), 136.9 (s), 137.4 (s), 138.4 (s), 144.2 (s), 153.3 (s), 175.9 ppm (s); MS (EI, 70 eV): m/z (%) = 364 (11) $[M]^+$, 277 (100); elemental analysis: calcd (%) for $C_{19}H_{24}O_5S$ (364.46): C 62.61, H 6.64; found: C 62.69, H 6.66.

47: Reaction of **14** (119 mg, 0.5 mmol) with $HBF_4{\cdot}OEt_2$ (86 μL, 102 mg, 0.63 mmol) and **23a** (192 μL, 196 mg, 2.0 mmol) yielded, after flash chromatography (pentane/Et_2O = 90:10), methyl 2-((4′-methoxyphenyl)(5′-methylthiophen-2′-yl)methyl)butanoate (**47**; 148 mg, 93%) as a pale-yellow oil (d.r. *anti*/*syn* = 98:2). $R_f = 0.35$ (pentane/Et_2O = 80:20); IR (film): $\tilde{\nu} = 2963$ (s), 2876 (m), 2836 (w), 1735 (vs), 1610 (m), 1512 (s), 1459 (m), 1249 (vs), 1163 (s), 1036 (s), 836 cm^{-1} (m); ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 0.83$ (virt t, $J \cong 7.4$ Hz, 3H), 1.36–1.52 (m, 2H), 2.36 (d, $J = 1.0$ Hz, 3H), 3.02 (ddd, $J = 11.4$, 10.2, 4.1 Hz, 1H), 3.61 (s, 3H), 3.78 (s, 3H), 4.26 (d, $J = 11.4$ Hz, 1H), 6.49 (dd, $J = 3.5$, 1.0 Hz, 1H), 6.66 (d, $J = 3.5$ Hz, 1H), 6.85 (d, $J = 8.7$ Hz, 2H), 7.19 ppm (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 11.6$ (q), 15.2 (q), 24.7 (q), 48.1 (d), 51.4 (q), 53.9 (d), 55.2 (q), 114.0 (d), 123.4 (d), 124.4 (d), 128.9 (d), 134.3 (s), 138.2 (s), 145.0 (s), 158.4 (s), 175.3 ppm (s); MS (EI, 70 eV): m/z (%) = 318 (3) $[M]^+$, 217 (100); elemental analysis: calcd (%) for $C_{18}H_{23}O_3S$ (318.34): C 67.89, H 6.96; found: C 68.05, H 6.80.

48: Reaction of **15** (126 mg, 0.5 mmol) with $HBF_4{\cdot}OEt_2$ (86 μL, 102 mg, 0.63 mmol) and **23a** (192 μL, 196 mg, 2.0 mmol) yielded, after flash chromatography (pentane/Et_2O = 90:10), methyl 2-((4′-methoxyphenyl)(5′-methylthiophen-2′-yl)methyl)-3-methylbutanoate (**48**; 154 mg, 93%) as a pale-yellow oil (d.r. *anti*/*syn* > 99:1). $R_f = 0.42$ (pentane/Et_2O = 80:20); IR (film): $\tilde{\nu} = 2959$ (s), 2874 (m), 2836 (w), 1733 (vs), 1610 (m), 1511 (s), 1462 (m), 1249 (vs), 1160 (s), 1035 (s), 834 cm^{-1} (m); ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 0.93$ (virt t, $J \cong 6.5$ Hz, 6H), 1.65–1.78 (m, 1H), 2.37 (d, $J = 1.0$ Hz, 3H), 3.17 (dd, $J = 12.0$ Hz, $J = 3.9$ Hz, 1H), 3.61 (s, 3H), 3.79 (s, 3H), 4.43 (d, $J = 12.0$ Hz, 1H), 6.49 (dd, $J = 3.4$, 1.0 Hz, 1H), 6.68 (d, $J = 3.4$ Hz, 1H), 6.86 (d, $J = 8.7$ Hz, 2H), 7.23 ppm (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 15.2$ (q), 16.3 (q), 21.9 (q), 27.9 (q), 46.3 (d), 51.1 (q), 55.2 (q), 57.2 (d), 114.1 (d), 123.2 (d), 124.4 (d), 128.8 (d), 134.3 (s,), 138.1 (s), 145.6 (s), 158.3 (s), 173.5 ppm (s); MS (EI, 70 eV): m/z (%) = 332 (4) $[M]^+$, 217 (100); elemental analysis: calcd (%) for $C_{19}H_{24}O_3S$ (332.56): C 68.64, H 7.28; found: C 68.82, H 7.32.

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