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Diastereoselective Domino Reactions of Chiral 2-Substituted 1-(2′,2′,3′,3′-Tetramethylcyclopropyl)-alkan-1-ols under Friedel−Crafts Conditions

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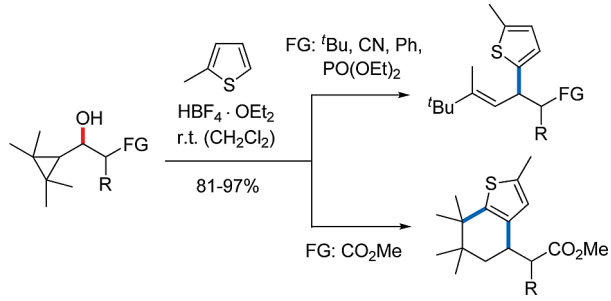

The 2-substituted 1-(2′,2′,3′,3′-tetramethylcyclopropyl)-alkan-1-ols **3**−**7** were prepared by carbonyl addition of tetramethylcyclopropyl lithium to the respective aldehydes or by addition of the respective substituted carbanions to tetramethylcyclopropyl carbaldehyde **16**. Under Brønsted acidic conditions ($HBF_4 \cdot OEt_2$), the alcohols served as substrates in Friedel−Crafts alkylation reactions with 2-methylthiophene (**8**) and *N*-tosylpyrrole (**9**). The alkanols **3**−**6** carrying the groups ^{t}Bu, Ph, CN, $PO(OEt)_2$ in 2-position delivered the rearranged substitution products **17**−**20** in very good chemical yields (9 examples, 81−97%). The products were formed presumably via ring-opening of the tetramethylcyclopropyl-substituted cation, which rearrange by a Wagner−Meerwein shift to allylic cations **I**. The latter cations are eventually attacked by the arene nucleophile. The diastereoselectivity of this process is good (*anti*-preference for Ph, CN, $PO(OEt)_2$) to excellent (*syn*-preference for ^{t}Bu). The esters **7**, carrying a methoxycarbonyl group in 2-position, yielded under the same reaction conditions products **25** and **26**, which are formed by an intermolecular Friedel−Crafts reaction followed by a subsequent intramolecular Friedel−Crafts alkylation (3 examples, 80−93%).

Introduction

Contrary to the relatively stable cyclopropyl-substituted carbocations,[1] the related tetramethylcyclopropyl-substituted carbocations undergo a rapid ring-opening to yield after Wagner−Meerwein rearrangement allylic cations. The behavior is illustrated by the reaction of alcohol **1**, which yields under cation stabilizing conditions even at low temperature the intermediate cation **2** (Scheme 1). The observation of cation **2** by NMR-spectroscopic techniques was reported by Olah et al. as early as 1968.[2] It was speculated that the bisected conformation of the cyclopropyl group relative to the empty p_z-orbital of the cation cannot be adopted due to the bulky methyl groups and that the rearrangement to the allylic cation **2** is consequently facile.[3] Similar observations were made shortly after by Poulter and Winstein.[4] In addition, the latter authors could isolate olefins

(1) (a) Olah, G. A.; Kelly, D. P.; Jeuell, C. L.; Porter, R. D. *J. Am. Chem. Soc.* **1970**, *92*, 2544–2546. (b) Kelly, D. P.; Brown, H. C. *J. Am. Chem. Soc.* **1975**, *97*, 3897–3900. (c) Servis, K. L.; Shue, F.-F. *J. Am. Chem. Soc.* **1980**, *102*, 7233–7240. (d) Friedrich, E. C. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: Chichester, 1987; pp 633−700. (e) Boche, G.; Walborsky, H. M. In *Cyclopropane Derived Reactive Intermediates*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1990; pp 117−173. (f) Olah, G. A.; Prakash, V. R.; Prakash, G. K. S. *Chem. Rev.* **1992**, *92*, 69–95.

(2) Olah, G. A.; Bollinger, J. M. *J. Am. Chem. Soc.* **1968**, *90*, 6082–6086.

(3) One reviewer has raised the question whether the cyclopropylcarbinyl cation and the depicted tertiary cation resulting from alcohol **1** prior to rearrangement to cation **2** are different species or just different Lewis structures representing the same cation. While we have not studied this issue more closely, we feel that the rearrangement is easier to understand in the way it is drawn in Figure 1. However, one could of course accommodate this concern by replacing the reaction arrow with a double-headed arrow (↔) representing mesomeric structures.

(4) (a) Poulter, C. D.; Winstein, S. *J. Am. Chem. Soc.* **1969**, *91*, 3649–3650. (b) Poulter, C. D.; Winstein, S. *J. Am. Chem. Soc.* **1969**, *91*, 3650–3652. (c) Poulter, C. D.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 2297–2305.

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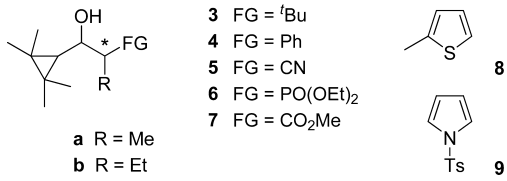
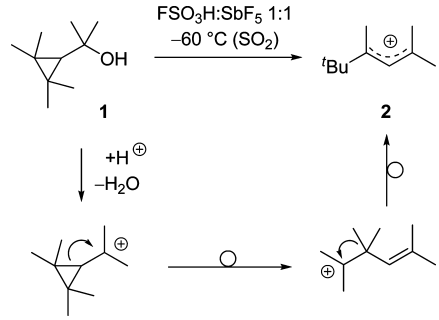


FIGURE 1. Set of starting materials **3**−**7** as cation precursors and arene nucleophiles **8**, **9**.

SCHEME 1. Formation of Cation 2 from Cyclopropyl-Substituted Alcohol 1 under Ionizing Conditions

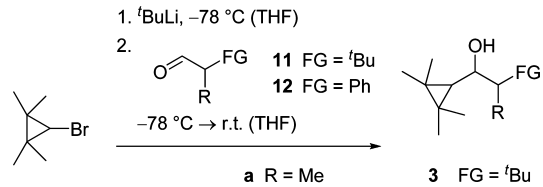


derived from cation **2** upon addition of a methanolic $KHCO_3$-solution to the superacidic solution of **2**. Further synthetic studies were not conducted, however. To the best of our knowledge, there is no precedence for the use of cation **2** and related cations as electrophiles in synthetically relevant transformations.

In connection with our interest in the facial diastereoselectivity of S_N1-type reactions,[5] we considered prochiral cyclopropyl-substituted cations and their respective ring-opening products as valuable intermediates, the reactions of which appeared worthy to be explored. In an initial study, 1-(2′,2′,3′,3′-tetramethylcyclopropyl)-alkan-1-ols **3**-**7** (Figure 1, FG = functional group) were investigated as starting materials. Upon acid treatment it was expected that cation formation would invite the attack of weak nucleophiles with the marked stereogenic center (*) serving as a control element for facial diastereoselectivity. In earlier studies we had shown that high selectivities can be achieved in Friedel−Crafts alkylation reactions, which proceed via benzylic[6] and propargylic cations.[7] For the present study 2-methylthiophene (**8**) was used as arene nucleophile. In some experiments, *N*-toluenesulfonyl(tosyl)-pyrrole (**9**) was also employed.

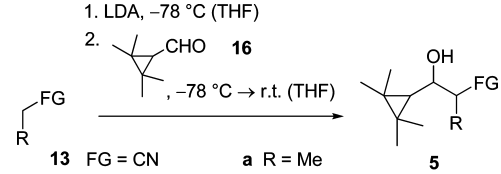
It was found that the intermediate cations derived from alcohols **3**−**7** are intercepted at different stages depending on the substituent FG at the stereogenic center. The most common reaction pathway (for substrates **3**−**6**) proceeded via allylic cations[8] related to **2** and delivered the corresponding substitution products in moderate to good diastereoselectivity. The reactions were shown to proceed stereoconvergently under kinetic product control. Details of our studies are presented in this paper.

TABLE 1. Preparation of Starting Materials 3 and 4



entry	FG	R	product	Yield [%]	d.r. (*anti*:*syn*)
1	tBu	Me	**3a**	48	18:82
2	tBu	Et	**3b**	59	4:96
3	Ph	Me	**4a**	88	16:84
4	Ph	Et	**4b**	70	13:87

TABLE 2. Preparation of Starting Materials 5−7



entry	FG	R	product	Yield [%]	d.r. (*anti*:*syn*)
1	CN	Me	**5a**	99	52:48
2	CN	Et	**5b**	99	82:27
3	$PO(OEt)_2$	Me	**6a**	88	68:32
4	$PO(OEt)_2$	Et	**6b**	46	57:43
5	CO_2Me	Me	**7a**	76	62:38
6	CO_2Me	Et	**7b**	77	57:43

Results and Discussion

Preparation of the Starting Materials. Starting alcohols **3**−**7** were accessible by carbonyl addition reactions either using the respective lithium reagent derived from tetramethylcyclopropyl bromide **10**[9] (Table 1) or an enolate, generated from α-acidic precursors **13**−**15**, as the nucleophile (Table 2).

In the first approach, bromine−lithium exchange was conducted at low temperature employing bromide **10**. The respective aldehyde **11**[6a] (FG = tBu) or **12**[10] (FG = Ph) was added to the solution of the organolithium compound. The products **3** and **4** were isolated as mixtures of diastereoisomers with the *syn*-diastereomer prevailing due to Felkin-Anh control[11] (Table 1). The relative configuration of substrates turned out to be not relevant for the outcome of the subsequent reactions, however (*vide infra*).

Alcohols **5**−**7** were prepared by carbonyl addition of stabilized anions derived from CH-acidic starting materials **13**−**15**. Deprotonation was achieved with LDA in THF solution and upon addition of aldehyde **16**[12] aldol-type addition products **5**−**7** were formed. The simple diastereoselectivity of this transformation was expectedly low.[13] No attempt was made to assign a

(5) (a) Mühlthau, F.; Schuster, O.; Bach, T. *J. Am. Chem. Soc.* **2005**, *127*, 9348–9349. (b) Mühlthau, F.; Bach, T. *Synthesis* **2005**, 3428–3426. (c) Stadler, D.; Mühlthau, F.; Rubenbauer, P.; Herdtweck, E.; Bach, T. *Synlett* **2006**, 2573–2576. (d) Rubenbauer, P.; Bach, T. *Tetrahedron Lett.* **2008**, *49*, 1305–1309. (e) Rubenbauer, P.; Bach, T. *Adv. Synth. Cat.* **2008**, *350*, 1125–1130. (f) Stadler, D.; Bach, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 7557–7559.

(6) (a) Mühlthau, F.; Stadler, D.; Goeppert, A.; Olah, G. A.; Prakash, G. K. S.; Bach, T. *J. Am. Chem. Soc.* **2006**, *128*, 9668–9675. (b) Stadler, D.; Bach, T. *Chem.−Asian J.* **2008**, *3*, 272–284. (c) Stadler, D.; Goeppert, A.; Rasul, G.; Olah, G. A.; Prakash, G. K. S.; Bach, T. *J. Org. Chem.* **2009**, *74*, 312–318.

(7) Rubenbauer, P.; Herdtweck, E.; Strassner, T.; Bach, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 10106–10109.

(8) For previous work in this area, see: Ishikawa, T.; Aikawa, T.; Mori, Y.; Saito, S. *Org. Lett.* **2008**, *10*, 3037–3040.

(9) Hackett, M.; Whitesides, G. M. *J. Am. Chem. Soc.* **1988**, *110*, 1449–1462.

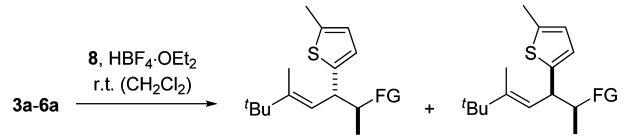
(10) Stratakis, M.; Kalaitzakis, D.; Stavroulakis, D.; Kosmas, G.; Tsangarakis, C. *Org. Lett.* **2003**, *5*, 3471–3474.

(11) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199–2204. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61–70. (c) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145–162.

(12) Laurie, D.; Lucas, E.; Nonhebel, D. C.; Suckling, C. J.; Walton, J. C. *Tetrahedron* **1986**, *42*, 1035–1045.

(13) (a) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066–1081. (b) Tanabe, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1917–1924.

TABLE 3. Diastereoselective Friedel−Crafts Alkylation Reactions with 2-Methylthiophene (8) as the Nucleophile



entry[a]	alcohol	FG	product	yield [%]	d.r.[b] (*anti:syn*)
1	**3a**	^{t}Bu	**17a**	84	3:97
2	**4a**	Ph	**18a**	97	77:23
3	**5a**	CN	**19a**	86	76:24
4	**6a**	$PO(OEt)_2$	**20a**	87	74:26

[a] All reactions were performed with 500 μmol of alcohol **3a**−**6a**, 4 equiv. 2-methylthiophene (**8**) and 1.25 equiv. $HBF_4 \cdot OEt_2$. [b] Diastereomeric ratio of the crude product was determined by NMR-spectroscopy and/or by GLC analysis.

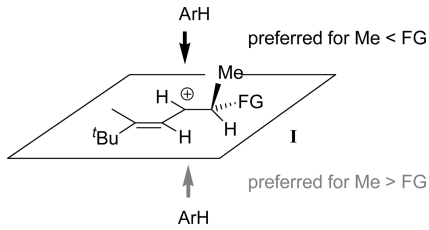


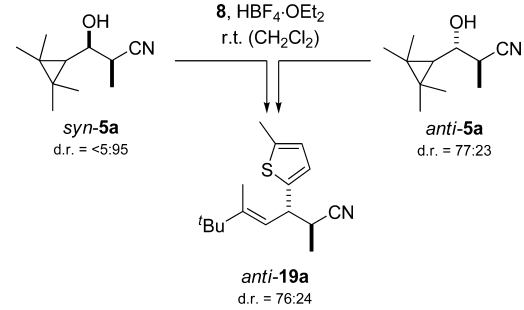
FIGURE 2. Proposed conformation of α-chiral allylic carbocation intermediates.

defined relative configuration to the diastereoisomers, which were not separable and which could be directly used in the subsequent arene alkylation reactions.

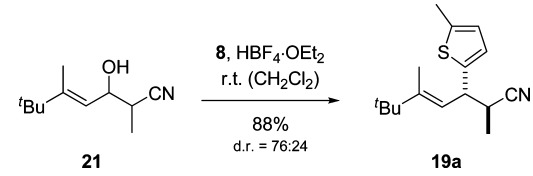
Friedel−Crafts Alkylation Reactions. The alcohols **3a**−**6a** reacted under previously optimized[6a,b] reaction conditions with 2-methylthiophene as the nucleophile in a Friedel−Crafts type alkylation reaction. To this end, the substrates were treated in dichloromethane with 4 equiv of 2-methylthiophene (**8**) at ambient temperature. Subsequently, 1.25 equiv of $HBF_4 \cdot OEt_2$ were added and the mixture was stirred for 15 min. After workup the diastereomeric ratio (d.r.) was determined from the crude reaction mixture either by NMR spectroscopy or by GLC analysis. Purification by column chromatography furnished the products **17a**−**20a** in pure form as a mixture of diastereoisomers. Yields were consistently high (Table 3, entries 1−4). The observed diastereoselectivities were excellent for product **17a** (entry 1, FG = ^{t}Bu) and good for the other products **18a**−**20a** (entries 2−4, FG = Ph, CN, $PO(OEt)_2$) indicating that a facial diastereocontrol was operating in the intermediate allylic cations (*vide infra*).

The occurrence of a cationic intermediate in the domino reactions[14] was supported by the observation that the reactions proceeded stereoconvergently. Irrespective of the relative substrate configuration an identical mixture of diastereomeric products was isolated. As an example the nitrile **5a** was employed in the reaction with 2-methylthiophene (**8**) either as pure *syn*-diastereoisomer *syn*-**5a** or as diastereomerically enriched *anti*-diastereoisomer *anti*-**5a** (Scheme 2). In both experiments, the rearranged alkylation product **19a** was isolated as mixture of diastereoisomers with the *anti*-diastereoisomer *anti*-**19a** prevailing (d.r. = 76:24).

SCHEME 2. Stereoconvergency of Friedel−Crafts Alkylation Reactions



SCHEME 3. Friedel−Crafts Alkylation Reaction with Allylic Alcohol 21



A thermodynamic reaction control was ruled out by subjecting diastereomeric product mixtures with different diastereomeric ratios to the acidic reaction conditions. As an example product *anti*-**19a** (d.r. = 76:24) yielded upon treatment with base (LDA) a 50:50 mixture of diastereoisomers. This ratio remained unchanged under the reaction conditions of the Friedel−Crafts alkylation (1.25 equiv $HBF_4 \cdot OEt_2$, 4 equiv 2-methylthiophene (**8**)).

Further support for the notion that the products **17a**−**20a** were formed by the diastereoselective reaction of an allylic cation was obtained by employing alcohol **21** as a starting material. This substrate was in turn prepared in one step from the aldol-type addition of propionitrile to the corresponding α,β-unsaturated aldehyde.[15] Its reaction with 2-methylthiophene (**8**) delivered product **19a** in the same diastereomeric ratio, which had been previously recorded for the reaction of the cyclopropyl-substituted nitrile **5a** under identical reaction conditions (Scheme 3).

Considering allylic cations of the general structure **I** as intermediates (Figure 2) a model can be suggested, which predicts the stereochemical outcome of the Friedel−Crafts reactions based on the preferred conformation of these cations. The model is analogous to a previously suggested model for the reactions of related benzylic cations.[6]

The partial double bond character of the C−C bond between the cationic carbon atom and the olefinic carbon atom forces the hydrogen atom at the stereogenic center to adopt a position in which it is synperiplanar to the olefin hydrogen atom and antiperiplanar to the hydrogen atom at the cation center. For functional groups larger than methyl (*A* value[16] = 1.7), the model suggests an attack of the arene from the top leading to the *syn*-product. For functional groups smaller than methyl, a bottom attack should be preferred leading to the *anti*-product. Although this static model neglects any stereoelectronic influence of substituents, which may lead to different transition state geometries, it has been found to be of high predictive value for

(14) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006.

(15) Lau, K. S. Y.; Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595–1598.

(16) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; pp 696−697. It should be noted, however, that the conformational *A* value provides only a rough estimate for the size of a functional group.

SCHEME 4. Determination of the Relative Configuration of Nitrile 19a by Chemical Transformation to Ketone 23

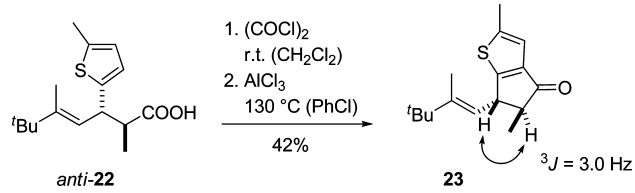
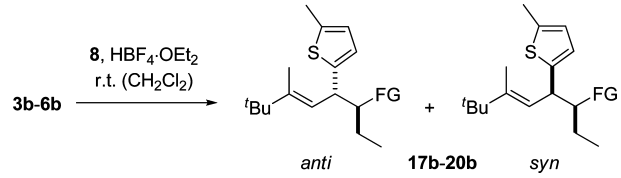


TABLE 4. Reference Experiments with Substrates 3b−6b Bearing an Ethyl Substituent in the α-Position



entry[a]	alcohol	FG	product	yield [%]	d.r.[b] (*anti:syn*)
1	**3b**	^{t}Bu	**17b**	85	15:85
2	**4b**	Ph	**18b**	87	79:21
3	**5b**	CN	**19b**	81	85:15
4	**6b**	$PO(OEt)_2$	**20b**	81	82:18

[a] All reactions were performed with 500 μmol of alcohol **3a**−**6a**, 4 equiv. 2-methylthiophene (**8**) and 1.25 equiv. $HBF_4 \cdot OEt_2$. [b] Diastereomeric ratio of the crude product was determined by NMR-spectroscopy and/or by GLC analysis.

benzylic cations.[6,17] In addition, the fact that the size of the alkyl group can be quickly modified by replacing methyl against ethyl or isopropyl can be usefully exploited for structure assignments (*vide infra*).

The configuration of the major product of the reaction **5a** → **19a**, for which the model suggests an *anti*-configuration (A_{CN} = 0.2) after an approach from the bottom according to Figure 2, was determined unambiguously by further chemical transformations (Scheme 4). Hydrolysis of the nitrile and separation of the minor diastereoisomer by flash chromatography delivered pure carboxylic acid *anti*-**22**, which was cyclized to ketone **23** in a two-step procedure. The *trans*-position of the two hydrogen atoms in the five-membered ring was clearly proven by comparison of the small ^{1}H NMR coupling constant (^3J) with reported values of similar compounds,[5c,18] thus proving the *anti*-configuration of acid **22** and of nitrile **19a**.

The assignment for product **19a** was further supported by the previously mentioned change in size of the substituent R. The consideration is straightforward. If the size of substituent R increases from R = methyl (A = 1.7) to R = ethyl (A = 1.8), an increase of diastereoselectivity in the Friedel−Crafts reaction is expected for any substituent (A < 1.7) that is smaller than methyl. A selectivity decrease is expected if the substituent acts as if it was larger than methyl (A > 1.7). Experiments of this type have been previously used to support assignments in the reaction of benzylic cations.[6b,17] The *anti*-configuration of product **19** was confirmed by an increase in selectivity for the transformation **5b** → **19b** (Table 4, entry 3). The *syn*-configuration of products **17** predicted by the model was corroborated by a decrease of selectivity for the ethyl case (entry 1). Recent studies by Chung et al. have revealed that the phenyl group

(17) Chung, J. Y. L.; Mancheno, D.; Dormer, P. G.; Variankaval, N.; Ball, R. G.; Tsou, N. N. *Org. Lett.* **2008**, *10*, 3037–3040.

(18) Iwasawa, N.; Matsuo, T.; Iwamoto, M.; Ikeno, T. *J. Am. Chem. Soc.* **1998**, *120*, 3903–3914.

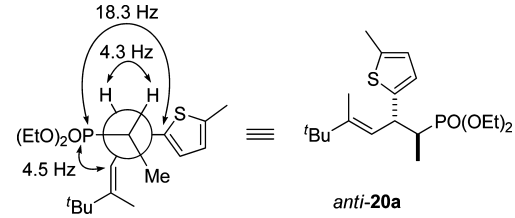
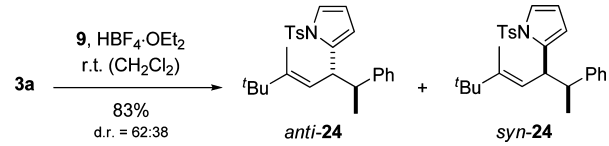


FIGURE 3. Configuration proof of *anti*−**20a** by $^3J_{HH}$- and $^3J_{CP}$-NMR coupling constants.

SCHEME 5. Diastereoselective Friedel−Crafts Alkylation Reaction of 3a with *N*-Tosylpyrrole (9) As the Nucleophile



behaves presumably due to its planarity as a relatively small substituent, its A value (A = 2.8) not fully reflecting its stereochemical properties in diastereoselective Friedel−Crafts reactions.[17] Indeed, it was found that the selectivity increases when comparing the reactions **4a** → **18a** and **4b** → **18b** (entry 3) supporting the *anti*-assignment for the respective major products.

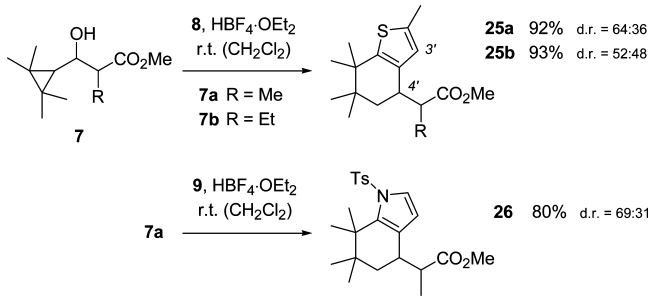
Only phosphonate **6b** delivered an unexpected result (entry 4). The selectivity increased when going from methyl to ethyl, while a decrease was expected based on the size argument for $PO(OEt)_2$ (A = 2.5). In benzyl cations the phosphonate group $PO(OEt)_2$ had behaved as expected, delivering the respective *syn*-products. We therefore sought to obtain independent evidence to support the assignment of products **20**. Careful NMR analysis of compound **20a** furnished not only the $^3J_{HH}$ coupling constants but also the relevant $^3J_{CP}$ coupling constants (Figure 3). Small coupling constants indicate a synclinal (*gauche*) position of substituents in a staggered conformation, large coupling constants indicate an antiperiplanar orientation. The only configuration, which is in line with the determined coupling constants, is the *anti*-configuration *anti*-**20a** (Figure 3).

Explanations for the different behavior of the $PO(OEt)_2$ group in reactions of chiral benzylic cations vs chiral allylic cations are difficult to put forward at this point in time. Recent studies have revealed that stereoelectronic arguments can be more important than static conformation analyses of carbocations in particular if cation conformations of similar energies exist.[7] Further theoretical studies are under way to shed more light on the reactions of cation **I**.

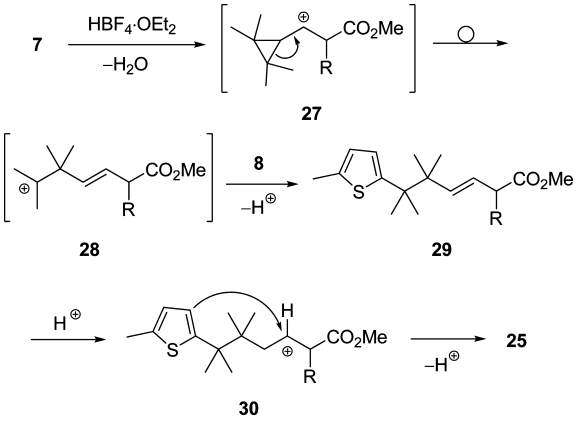
Since the scope of arene nucleophiles was not in the focus of this study and since we have already extensively studied possible nucleophiles in the Friedel−Crafts alkylation of benzylic cations,[5,6] only one experiment was conducted showing that other arenes react similarly to 2-methylthiophene (**8**). Pyrrole **9** was employed as the arene and delivered with substrate **3a** cleanly and in high yield the respective rearrangement/substitution product **24** (Scheme 5). In analogy to the previous assignment (*vide supra*), the *anti*-configuration was assigned to the major product.

Inter- and Intramolecular Friedel−Crafts Reaction. The outcome of the Friedel−Crafts reactions with substrates **7** and 2-methylthiophene (**8**) was different from the reactions conducted with substrates **3**−**6**. The ^{1}H NMR spectrum of products **25** showed four distinct signals of CH_3 groups. In stark contrast

SCHEME 6. Unexpected Reaction Pathway for Substrate 7



SCHEME 7. Proposed Mechanism for the Friedel−Crafts Alkylation Reactions of Cation Precursor 7



to products **17**−**20** there was no ^{1}H NMR signal for an olefinic proton and only one signal for an aromatic proton. Additional two-dimensional NMR-experiments supported the constitution of **25** as shown in Scheme 6. The existence of a $^4J_{HH}$ coupling between the hydrogen atoms at C3′ and C4′ proves the regioselectivity of the thiophene substitution. Yields for the reactions **7** → **25** were high, but the facial diastereoselectivities were relatively low. *N*-Tosylpyrrole (**9**) underwent an analogous reaction with alcohol **7a** to produce the bicyclic product **26** in a slightly better diastereoselectivity.

Mechanistically, the formation of products **25** can be understood if one assumes a cationic intermediate **27**, which rearranges in analogy to Scheme 1 to yield the tertiary cation **28** (Scheme 7). Apparently, this cation is trapped by the arene nucleophile prior to the second rearrangement step delivering intermediate **29**, which undergoes under the reaction conditions an intramolecular Friedel−Crafts reaction via cation **30**. Alternatively, one can envisage a direct nucleophilic displacement leading from cation **27** to intermediate **29** (see also ref 3) or—less likely—a direct nucleophilic displacement of the protonated hydroxy group in a S_N2-type fashion leading directly from alcohol **7** to intermediate **29**. The secondary chiral cation **30** does not exhibit a significant face differentiation. As a consequence the diastereoselectivity remains relatively low in the cyclization step.

Precedence for substitution reactions at 1-(2′,2′,3′,3′-tetramethylcyclopropyl)-propan-1-ols in the sense **7** → **29** exist in the literature for the halo-dehydroxylation of 3-phenyl-1-(2′,2′,3′,3′-tetramethylcyclopropyl)-propan-1-ols[19,20] and for an intramolecular $SnCl_4$-mediated Friedel−Crafts reaction of 3,3-diphenyl-1-(2′,2′,3′,3′-tetramethylcyclopropyl)-propan-1-ol.[21] However, it is not clear what analogy can be drawn to the present reaction and in particular why substrate **7** behaves different as compared to substrates **3**−**6**. Straightforward explanations like a retarded Wagner−Meerwein rearrangement of cation **28** require further theoretical studies, which are under way and which will be reported in due course. A hint might be the fact that methyl β-hydroxycarboxylates were shown to deliver dicationic intermediates under superacidic conditions.[6c]

Conclusions

In summary, the ring-opening and rearrangement of the title compounds **3**−**6** under acidic conditions could be used to synthesize diastereomerically enriched substitution products with arenes deriving presumably from an intermediate allylic cation **I**. This study shows for the first time that significant facial diastereoselectivity can be observed in intermolecular Friedel−Crafts reaction of allylic cations. The stereoconvergent transformation proceeds under kinetic control. Surprisingly, the analogous esters **7** were intercepted by arenes at an earlier stage delivering—presumably via intermediates like **29**—the bicyclic products **25** and **26** of a domino reaction.

Experimental Section

2,3,3-Trimethyl-1-(2′,2′,3′,3′-tetramethylcyclopropyl)-butan-1-ol (3a). 3-Bromo-1,1,2,2-tetramethylcyclopropane (**10**, 1.00 g, 5.65 mmol) was dissolved in tetrahydrofuran (30 mL) and cooled to −78 °C. After slow addition of ^{t}BuLi (7.06 mL, 11.3 mmol, 2.00 equiv, 1.6 M in hexane) the mixture was stirred at −78 °C for aprox. one hour until the yellow color vanished. Aldehyde **11a** (796 mg, 6.21 mmol, 1.10 equiv) was added and the solution was allowed to warm to room temperature over a period of 2 h. The reaction was stopped by addition of saturated aqueous NH_4Cl (20 mL) and diluted with diethylether (40 mL). The separated organic layer was washed with saturated aqueous NH_4Cl (20 mL) and NaCl (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo.The crude product was purified by flash chromatography (3 × 15 cm, pentane:Et_2O = 9:1) to give **3a** (576 mg, 2.71 mmol, 48%) as a colorless oil (d.r. = 18:82). R_f = 0.24 (pentane:Et_2O = 9:1). IR (ATR): $\tilde{\nu}$ = 3478 cm^{-1} (br), 2940 (s), 2866 (m), 1458 (m), 1380 (s), 1242 (m), 1115 (m), 957 (vs). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.50 (d, ^3J = 10.3 Hz, 1 H), 0.88 (s, 3 H), 0.91 (s, 3 H), 0.93 (s, 9 H), 0.96 (d, ^3J = 7.1 Hz, 3 H), 1.01 (s, 3 H), 1.11 (s, 3 H), 1.18−1.24 (m, 1 H), 3.73−3.76 (m, 1 H). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 7.8 (q), 17.1 (q), 17.5 (q), 21.6 (s), 22.4 (s), 23.8 (q), 24.0 (q), 28.4 (q), 33.6 (s), 39.3 (d), 47.5 (d), 70.0 (d). MS (EI, 70 eV), *m*/*z* (%): 194 (2) [(M − H_2O)$^+$], 127 (55), 97 (62), 83 (68), 57 (100).

3-Hydroxy-2-methyl-3-(2′,2′,3′,3′-tetramethylcyclopropyl)-propionitrile (5a). Diisopropylamine (1.22 mL, 874 mg, 8.64 mmol, 1.20 equiv) was dissolved in tetrahydrofuran (20 mL) and cooled to 0 °C. After addition of ^{n}BuLi (3.17 mL, 7.92 mmol, 1.10 equiv, 2.5 M in hexane), the mixture was stirred at 0 °C for 15 min, then cooled to −78 °C and propionitrile (**13a**, 515 μL, 397 mg, 7.20 mmol) was added. Stirring was continued for 30 min, then aldehyde **16** (1.00 g, 7.92 mmol, 1.10 equiv) was added and after additional 15 min at −78 °C, the solution was allowed to warm to room temperature over a period of 2 h. The reaction was stopped by addition of saturated aqueous NH_4Cl (20 mL) and

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(21) Shinzo, S. Japanese Patent 06271484 A 19940927, 1994.

diluted with diethylether (40 mL). The separated organic layer was washed with saturated aqueous NH_4Cl (20 mL) and NaCl (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (3 × 15 cm, pentane: Et_2O = 1:1) to give **5a** (1.29 g, 7.12 mmol, 99%) as a white solid (d.r. = 52:48). R_f = 0.23/0.27 (pentane:Et_2O = 1:1). mp = 34 °C. IR (ATR): $\tilde{\nu}$ = 3433 cm^{-1} (br), 2942 (m), 2871 (w), 1455 (s), 1380 (s), 1132 (s), 1023 (vs). Major diastereoisomer: ^1H NMR (360 MHz, $CDCl_3$): δ = 0.49 (d, ^3J = 10.3 Hz, 1 H), 1.03 (s, 3 H), 1.11 (s, 3 H), 1.13 (s, 3 H), 1.15 (s, 3 H), 1.32 (d, ^3J = 7.2 Hz, 3 H), 1.72 (br s, 1 H), 2.82 (qd, ^3J = 7.2 Hz, ^3J = 5.9 Hz, 1 H), 3.47 (dd, ^3J = 10.3 Hz, ^3J = 5.9 Hz, 1 H). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 13.8 (q), 17.6 (q), 18.0 (q), 22.5 (s), 23.3 (q), 23.6 (q), 24.0 (s), 33.7 (d), 37.4 (d), 71.4 (d), 121.2 (s). Minor diastereoisomer: ^1H NMR (360 MHz, $CDCl_3$): δ = 0.49 (d, ^3J = 10.3 Hz, 1 H), 1.00 (s, 3 H), 1.10 (s, 3 H), 1.12 (s, 3 H), 1.14 (s, 3 H), 1.37 (d, ^3J = 7.3 Hz, 3 H), 1.67 (br s, 1 H), 2.65 (qd, ^3J = 7.3 Hz, ^3J = 4.7 Hz, 1 H), 3.40 (dd, ^3J = 10.3 Hz, ^3J = 4.7 Hz, 1 H). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 14.7 (q), 17.3 (q), 17.6 (q), 22.5 (s), 23.3 (s), 23.4 (q), 23.6 (q), 33.9 (d), 38.1 (d), 71.5 (d,), 121.3 (s). MS (EI, 70 eV), *m/z* (%): 181 (1) [M^+], 127 (44), 109 (20), 97 (100). Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 72.63; H, 10.85, N 7.57.

(*E*)-3-Hydroxy-2,5,6,6-tetramethylhept-4-en-nitrile (21). Diisopropylamine (185 μL, 132 mg, 1.31 mmol, 1.20 equiv) was dissolved in tetrahydrofuran (5 mL) and cooled to 0 °C. After addition of ^{n}BuLi (480 μL, 1.20 mmol, 1.10 equiv, 2.5 M in hexane), the mixture was stirred at 0 °C for 15 min, then cooled to −78 °C and propionitrile (**13a**, 60.0 mg, 1.09 mmol) was added. Stirring was continued for 30 min, then (*E*)-3,4,4-trimethylpent-2-enal (151 mg, 1.20 mmol, 1.10 equiv) was added and after additional 15 min at −78 °C, the solution was allowed to warm to room temperature over a period of 2 h. The reaction was stopped by addition of saturated aqueous NH_4Cl (5 mL) and diluted with diethylether (10 mL). The separated organic layer was washed with saturated aqueous NH_4Cl (5 mL) and NaCl (5 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (1.5 × 15 cm, pentane:Et_2O = 1:1) to give **21** (142 mg, 784 μmol, 72%) as a colorless oil (d.r. = 60:40). R_f = 0.35/0.30 (pentane:Et_2O = 1:1). Major diastereoisomer: ^1H NMR (360 MHz, $CDCl_3$): δ = 1.08 (s, 9 H), 1.26 (d, ^3J = 7.2 Hz, 3 H), 1.74 (d, ^4J = 1.3 Hz, 3 H), 2.86 (qd, ^3J = 7.2 Hz, ^3J = 5.6 Hz, 1 H), 4.44 (dd, ^3J = 8.8 Hz, ^3J = 5.6 Hz, 1 H), 5.37 (dq, ^3J = 8.8 Hz, ^4J = 1.3 Hz, 1 H). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 13.6 (q), 13.8 (q), 28.8 (q), 33.2 (d), 36.6 (s), 69.3 (d), 119.7 (d), 121.0 (s), 150.4 (s). Minor diastereoisomer: ^1H NMR (360 MHz, $CDCl_3$): δ = 1.06 (s, 9 H), 1.31 (d, ^3J = 7.2 Hz, 3 H), 1.73 (d, ^4J = 1.3 Hz, 3 H), 2.66 (qd, ^3J = 7.2 Hz, ^3J = 6.2 Hz, 1 H), 4.42 (dd, ^3J = 8.6 Hz, ^3J = 6.2 Hz, 1 H), 5.28 (dq, ^3J = 8.6 Hz, ^4J = 1.3 Hz, 1 H). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 13.6 (q), 14.3 (q), 28.8 (q), 33.5 (d), 36.5 (s), 69.6 (d), 120.6 (d), 121.2 (s), 150.8 (s). MS (EI, 70 eV), *m/z* (%): 163 (46) [$(M - H_2O)^+$], 148 (63), 127 (31), 109 (100), 93 (72).

Representative Procedure for the Domino Reaction of α-Chiral Tetramethylcyclopropylcarbinols: (*E*)-2-(2′,2′,3′,6′,7′,7′-Hexamethyloct-5′-en-4′-yl)-5-methylthiophene (17a). Cyclopropylcarbinol **3a** (106 mg, 500 μmol) and 2-Methylthiophene (**8**, 192 μL, 196 mg, 2.00 mmol, 4.00 equiv) were dissolved in dichloromethane (10 mL) and $HBF_4 \cdot OEt_2$ (85.0 μL, 101 mg, 625 μmol, 1.25 equiv) was added at room temperature. After stirring for 15 min, the reaction was stopped by the addition of saturated aqueous $NaHCO_3$ (10 mL) and diluted with diethylether (20 mL). The separated organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and NaCl (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (1.5 × 15 cm, pentane) to give **17a** (123 mg, 420 μmol, 84%) as a colorless oil (d.r. = 3:97). R_f = 0.55 (pentane). IR (ATR): $\tilde{\nu}$ = 2960 cm^{-1} (s), 2865 (w), 1465 (m), 1378 (m), 1361 (s), 795 (vs). ^1H NMR (360 MHz, $CDCl_3$): δ = 0.90 (d, ^3J = 7.1 Hz, 3 H), 0.93 (s, 9 H), 1.08 (s, 9 H), 1.63 (d, ^4J = 1.2 Hz, 3 H), 1.79 (qd, ^3J = 7.1 Hz, ^3J = 2.6 Hz, 1 H), 2.42 (s, 3 H), 4.03−4.06 (m, 1 H), 5.52 (dq, ^3J = 9.5 Hz, ^4J = 1.2 Hz, 1 H), 6.48 (dd, ^3J = 3.4 Hz, ^4J = 1.2 Hz, 1 H), 6.53−6.55 (m, 1 H). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 9.8 (q), 13.0 (q), 15.3 (q), 28.5 (q), 28.8 (q), 33.9 (s), 36.5 (d), 39.6 (s), 49.8 (d), 120.7 (d), 122.8 (d), 124.4 (d), 136.8 (s), 143.2 (s), 149.2 (s). MS (EI, 70 eV), *m/z* (%): 292 (1) [M^+], 207 (100), 177 (6), 165 (8), 151 (12). Anal. Calcd for $C_{19}H_{32}S$: C, 78.01; H, 11.03. Found: C, 78.11; H, 11.16.

Methyl 2-(2′,6′,6′,7′,7′-pentamethyl-4′,5′,6′,7′-tetrahydrobenzo[*b*]thiophen-4′-yl)-propanoate (25a). Domino reaction with cyclopropylcarbinol **7a** (107 mg, 500 μmol) gave **25a** (135 mg, 458 μmol, 92%) as a colorless oil (d.r. = 64:36). R_f = 0.49 (pentane: Et_2O = 9:1). IR (ATR): $\tilde{\nu}$ = 2968 cm^{-1} (m), 2871 (w), 1735 (vs), 1455 (m), 1377 (s), 1198 (s), 1173 (s), 826 (m). Major diastereoisomer: ^1H NMR (360 MHz, $CDCl_3$): δ = 0.88 (s, 3 H), 0.94 (s, 3 H), 1.07 (d, ^3J = 7.1 Hz, 3 H), 1.08 (s, 3 H), 1.15 (s, 3 H), 1.16 (dd, ^2J = 13.7 Hz, ^3J = 4.8 Hz, 1 H), 1.77 (dd, ^2J = 13.7 Hz, ^3J = 11.6 Hz, 1 H), 2.41 (d, ^4J = 1.1 Hz, 3 H), 2.89 (qd, ^3J = 7.1 Hz, ^3J = 4.7 Hz, 1 H), 3.36−3.42 (m, 1 H), 3.74 (s, 3 H), 6.50 (*virt.* quint., $^4J \cong$ 1.1 Hz, 1 H). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 11.0 (q), 15.5 (q), 22.9 (q), 23.7 (q), 24.6 (q), 28.2 (q), 35.4 (s), 35.4 (t), 35.9 (d), 38.9 (s), 44.2 (d), 51.7 (q), 124.3 (d), 133.6 (s), 136.9 (s), 146.6 (s), 175.5 (s). Minor diastereoisomer: ^1H NMR (360 MHz, $CDCl_3$): δ = 0.90 (s, 3 H), 0.96 (s, 3 H), 1.09 (s, 3 H), 1.16 (s, 3 H), 1.22 (d, ^3J = 7.1 Hz, 3 H), 1.35 (dd, ^2J = 13.2 Hz, ^3J = 6.0 Hz, 1 H), 1.92 (dd, ^3J = 13.2 Hz, ^3J = 11.7 Hz, 1 H), 2.39 (d, ^4J = 1.1 Hz, 3 H), 2.72 (qd, ^3J = 7.1 Hz, ^3J = 3.8 Hz, 1 H), 3.26−3.33 (m, 1 H), 3.68 (s, 3 H), 6.50 (q, ^4J = 1.1 Hz, 1 H). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 13.1 (q), 15.4 (q), 22.9 (q), 23.7 (q), 24.6 (q), 28.1 (q), 35.6 (s), 38.5 (t), 36.7 (d), 39.0 (s), 44.1 (d), 51.6 (q), 124.0 (s), 132.6 (s), 136.8 (s), 146.3 (s), 175.6 (s). MS (EI, 70 eV), *m/z* (%): 294 (18) [M^+], 207 (100), 191 (14), 151 (25). Anal. Calcd for $C_{17}H_{26}O_2S$: C, 69.34; H, 8.90. Found: C, 69.33; H, 8.81.

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Supporting Information Available: Experimental procedures for the preparation of new compounds and analytical data; ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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