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Chiral α-Branched Benzylic Carbocations: Diastereoselective Intermolecular Reactions with Arene Nucleophiles and NMR Spectroscopic Studies

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Abstract: The chiral benzylic alcohols **1**−**6** were prepared and subjected to S_N1-type displacement reactions with various arene nucleophiles in acidic medium. Under optimized conditions (HBF_4·OEt_2, CH_2Cl_2, −78 °C → r.t.) the corresponding 1,1-diarylalkanes **11**−**18** and **20** were obtained in good chemical yields (48−99%). The facial diastereoselectivity of the reaction is high (d.r. = 91/9−97/3) when the substrate bears a stereogenic carbon center −CH*t*BuMe in the α-position to the electrophilic carbon atom. If the starting material was enantiomerically pure, no significant racemization was observed (94% ee → 92% ee). The reactions proceed stereoconvergently as demonstrated by the conversion of the separated diastereoisomers *syn*-**1a** and *anti*-**1a** in separate reactions to the same product *syn*-**11** (d.r. = 97/3). Further evidence for long-lived chiral benzylic carbocations as reaction intermediates was obtained from NMR studies in superacidic medium. The chiral cation **24** was generated in SO_2ClF as the solvent at −70 °C employing SbF_5 as the Lewis acid and characterized by its ^1H and ^{13}C NMR spectra. NOE measurements suggest a preferred conformation in which the diastereotopic faces of the cation are differentiated by the two carbon substituents R and Me at the stereogenic carbon center in the α-position. The hypothesis is further supported by the observation that the diastereoselectivity of the substitution reaction decreases if the bulky *tert*-butyl (R = *t*Bu) substituent in the substrate **1a** is replaced by a smaller ethyl group (**2a**, R = Et).

Introduction

The cationic carbon atom in a trivalent carbocation (carbenium ion) is prostereogenic if its three substituents are different. In the absence of any chiral information, nucleophilic addition reactions to free carbenium ions occur stereorandomly, leading to the known racemization commonly observed in S_N1 reactions.[1] In this scenario, the plane defined by the three substituents at the cationic carbon atom exhibits two faces, which are enantiotopic. If the carbocation is chiral and its cationic carbon atom center is prostereogenic, the two faces are diastereotopic (Figure 1). A nucleophilic addition reaction consequently leads to diastereoisomers which may be formed in nonequal amounts. In this paper we address the question of facial diastereoselectivity in chiral α-branched benzylic carbocations of the general structure **A**. The study includes intermolecular Friedel−Crafts reactions, in which ions **A** are generated as intermediates,[2] and NMR experiments, which aimed at structural information on cations of type **A**.

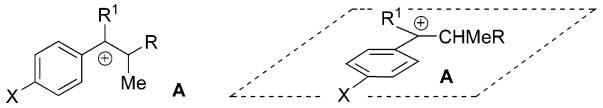

Figure 1. Chiral benzylic carbocation of type **A** and its two diastereotopic faces defined by the depicted plane (---).

Diastereoselective intramolecular reactions (cyclizations) have been previously reported in which intermediates of type **A** are possibly involved.[3] Cyclic 5-substituted 2-methyladamant-2-yl cations have been studied to elucidate the electronic factors determining facial selectivity in sterically unbiased substrates.[4]

[†] Technische Universität München.
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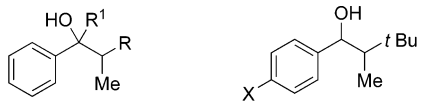


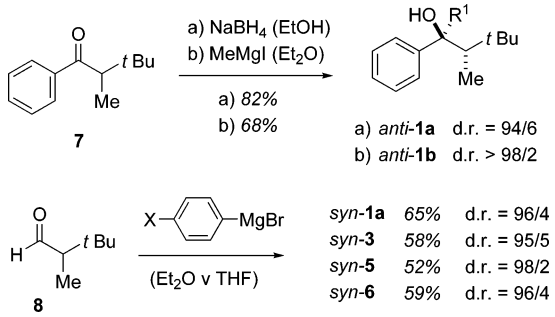
1 R = *t* Bu **a** R^1 = H **3** X = MeO **5** X = Cl
2 R = Et **b** R^1 = Me **4** X = Me **6** X = CN

Figure 2. Molecular formula of the secondary and tertiary alcohols **1**−**6** which served as precursors for the corresponding chiral benzylic carbocations.

In addition, there is a host of information about diastereoselective intermolecular reaction of chiral iminium[5] and chiral oxonium[6] ions. This issue is further related to the addition of strong nucleophiles to weak chiral carbonyl electrophiles, such as ketones and aldehydes, which has been extensively studied.[7] Earlier, one of us has investigated the highly enantioselective addition of indoles to trifluoropyruvates under catalysis by cinchona alkaloids.[8] Despite the synthetic importance acyclic stereocontrol has gained in organic synthesis,[9] it is remarkable that the intermolecular reaction of weak nucleophiles with strongly electrophilic carbocations has not been systematically explored.[10] We have started our own investigations with the chiral alcohols **1**−**6** (Figure 2), which were used as starting materials for diastereoselective Friedel−Crafts reactions.[11] Treatment of these substrates with various arenes under acidic conditions should lead to chiral 1,1-arylphenylmethanes.

Previous studies on similar reactions[12] had not given a hint on a possible diastereoselective reaction course.[13] However, the ring opening of a chiral oxazoline under acidic conditions in *o*-dichlorobenzene had generated a major diastereomeric arylation product (d.r. = 93/7), the configuration of which was not elucidated.[14] Some stereoselective cyclizations of biomimetic type have been carried out under either Lewis or Brønsted acid catalysis.[15]

Scheme 1



In our studies, the *tert*-butyl-substituted substrates **1a**, **3**, **4**, and **5** reacted diastereoselectively with various arene nucleophiles. The reaction was shown to be stereoconvergent. The stereochemical integrity of the α-stereogenic center was evaluated and the product configuration was established. A previously postulated hypothesis,[2] which explains the diastereoselective reaction course, has now been confirmed by NMR studies on a chiral carbocation of type **A**.[16] Full details on this work are provided in the following account.

Results and Discussion

Preparation of Starting Materials. Most of the required alcohols were synthesized by nucleophilic addition reactions to a given carbonyl compound. The two starting materials **7** and **8** most commonly used for this purpose are depicted in Scheme 1. Reduction ($NaBH_4$) or methyl addition (MeMgI) to ketone **7**[17] furnished the chiral alcohols **1a**[18] and **1b**. The *anti*-products were formed as major diastereoisomers due to Felkin-Anh control.[19] Arylmagnesium bromide addition to aldehyde **8**[20] yielded the *syn*-configurated benzylic alcohols **1a**,[21] **3**,[22] **5**, and **6**. The related *p*-tolyl-substituted alcohol **4**[22] was prepared in an anti/syn ratio of 65/35 by a Wittig rearrangement. The ethyl derivatives **2** (R = Et) were obtained by addition of *sec*-butyllithium to benzaldehyde (for **2a**) or acetophenone (for **2b**). The simple diastereoselectivity in the addition was expectedly low. The diastereomeric ratio for **2a**[23] was 50/50 and for **2b**[24] 60/40.

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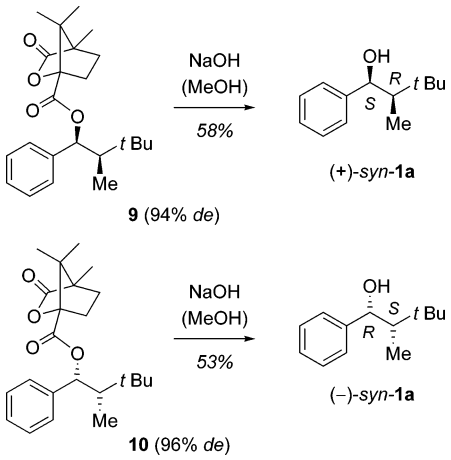
Scheme 2



Compound *syn*-**1a** was prepared in enantiomerically pure form by a conventional resolution (Scheme 2). To this end, the free racemic alcohol was converted into the corresponding diastereomeric esters **9** and **10** by treatment with (−)-camphanyl chloride in pyridine. The diastereoisomers could be separated by flash column chromatography and their diastereomeric excess (de) was determined by HPLC. Saponification of the esters led to the enantiomerically enriched alcohols (+)-*syn*-**1a** and (−)-*syn*-**1a**. The separation of the enantiomeric alcohols *syn*-**1a** on various analytical HPLC columns was not feasible. Their enantiomeric purity (ee) was therefore deduced from the de of the starting materials under the reasonable assumption that saponification does not lead to a racemization of *both* stereogenic centers. The specific rotation $[\alpha]_D$ of the enantiomers was indeed almost identical in value and opposite in sign ($[\alpha]_D = +45.7$ and $[\alpha]_D = -45.1$, $c = 1$, CH_2Cl_2). The configuration assignment was based on the specific rotation. The isopropyl analogues of the *tert*-butyl compounds *syn*-**1a** are known.[25] Their configuration has been established and the specific rotation has been assigned to either enantiomer. The (1*S*,2*R*)-enantiomer was found to be dextrorotatory ($[\alpha]_D = +32.3$, $c = 1$, $CHCl_3$) and the (1*R*,2*S*)-enantiomer levorotatory ($[\alpha]_D = -33.6$, $c = 1$, $CHCl_3$).

N-Tosylpyrrole, which was used as one of the arene nucleophiles, was prepared from pyrrole by *N*-tosylation under phase transfer conditions.[26]

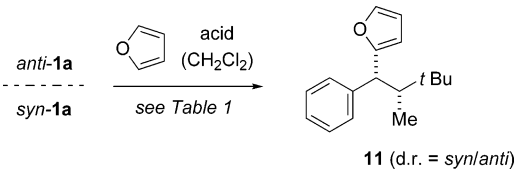
Intermolecular Reactions with Arene Nucleophiles. Optimization experiments for the addition reactions were conducted with alcohol **1a** and with the most sensitive arene nucleophile employed, i.e., with furan. Some of the results are listed in Table 1 (cf. Scheme 3). In all cases (entries 1−6) a major diastereoisomer, *syn*-**11**, was formed with high selectivity. The three depicted acids, F_3CSO_3H, $BF_3{\cdot}OEt_2$,[27] and $HBF_4{\cdot}OEt_2$, were best suited to promote the reaction. The reaction was somewhat slower in the presence of $BF_3{\cdot}OEt_2$ (entry 4) as compared to the two Brønsted acids. The temperature (entries 1 and 3) and nucleophile concentration (entries 1 and 2) had a minor influence on the selectivity and yield of the F_3CSO_3H-catalyzed reaction.

Table 1. Reaction Conditions, Yields, and Diastereoselectivities in the Friedel−Crafts Alkylation of Furan with Substrate **1a** (see Scheme 3)

entry	**1a**[a]	acid[a]	furan (equiv)	temp (°C)	time[b] (min)	d.r.[c]	yield[d] (%)
1	anti	F_3CSO_3H[e]	4	25	15	96/4	60
2	anti	F_3CSO_3H[e]	10	25	15	96/4	68
3	anti	F_3CSO_3H[e]	4	0	15	97/3	63
4	anti	$BF_3{\cdot}OEt_2$	4	25	75	95/5	69
5	anti	$HBF_4{\cdot}OEt_2$	10	25	15	96/4	59
6	anti	$HBF_4{\cdot}OEt_2$	4	−78 → 25[f]		97/3	94
7	syn	$HBF_4{\cdot}OEt_2$	4	−78 → 25[f]		97/3	91

[a] All reaction were conducted at a substrate concentration of 50 mM and 1.25 equiv of the corresponding Brønsted or Lewis acid was used; anti refers to *anti*-**1a** (d.r. = 94/6) as starting material and syn to *syn*-**1a** (d.r. = 96/4). [b] Time required for complete conversion. [c] The diastereomeric ratio of the crude product was determined by ^1H NMR spectroscopy. [d] Yield of isolated product. [e] 0.1 M solution in $F_2ClCCFCl_2$. [f] The acid was added to **1a** at −78 °C. After 5 min, furan was added and the mixture was warmed to room temperature within 15 min.

Scheme 3



11 (d.r. = *syn*/*anti*)

Still, it became evident that side reactions occurred both at 0 °C and at ambient temperature. Yields remained moderate to good (entries 1−5, 59−68%). With F_3CSO_3H a significant decrease of the reaction temperature was impossible, however, as the solution of F_3CSO_3H solidified at −35 °C. The handling of $HBF_4{\cdot}OEt_2$ at low temperature turned out to be much more convenient. The reaction could be initiated at −78 °C and went to completion upon warming to room temperature (entry 6). This procedure gave superior yields and facilitated the isolation of clean product simply after workup. The pretreatment of alcohol **1a** with $HBF_4{\cdot}OEt_2$ and the subsequent addition of the nucleophile do not necessarily imply a complete carbocation formation at −78 °C. The protocol allows, however, for the immediate trapping of any carbocation formed at the lowest possible temperature (vide infra).

A key issue relevant for further discussion is the observation that the product distribution did not change upon replacing the starting material *anti*-**1a** by its diastereoisomer *syn*-**1a** (entry 7, Table 1). In other words, the epimeric composition *anti*-**1a**/*syn*-**1a** did not influence the stereoselectivity (stereoconvergent reaction). A S_N2-type displacement can be clearly ruled out and the result is in line with the intermediacy of a carbocation of type **A**.

Under optimized conditions ($HBF_4{\cdot}OEt_2$, CH_2Cl_2, −78 °C → r.t.) several other arene nucleophiles were employed in the reaction of alcohol **1a**. The diastereoselectivity was extremely high in all cases investigated (Figure 3). The diastereomeric ratio exceeded 94/6 and product yields were satisfactory to excellent. All arenes (furan, 2-methylthiophene, *N*-tosylpyrrole, resorcindimethyl ether, and benzofuran) are comparably nucleophilic. The *N* value for three of the five arenes is tabulated on Mayr's scale of nucleophilicity[28] with resorcindimethyl ether

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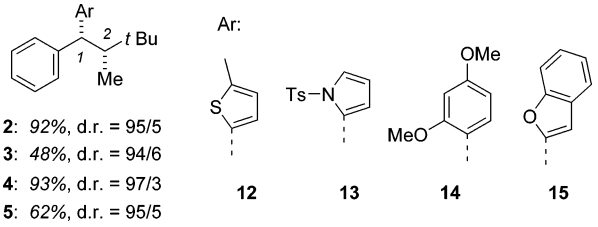


Figure 3. Structure and yield of the arylation products **12**−**15** obtained in diastereoselective reactions of alcohol **1a**.

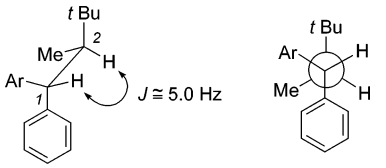


Figure 4. Preferred conformation (according to a crystal structure[2]) of compounds *syn*-**11**−**15** in sawhorse representation (left) and in Newman projection (right).

($N = 2.48$) being the most nucleophilic followed by furan ($N = 1.36$) and 2-methylthiophene ($N = 1.26$). The two arenes (*N*-tosylpyrrole, benzofuran) not tabulated should exhibit similar nucleophilicity ($N > 1$). Less nucleophilic arenes such as mesitylene or thiophene ($N = -1.01$) failed to undergo a reaction with **1a**. Elimination products were observed, indicating that the carbocation was formed but not trapped effectively to avoid the intramolecular side reaction.

The configuration assignment for compounds **11**−**15** rests on an X-ray crystallographic study conducted with single crystals of product **13**.[2] The synclinal relationship (Figure 4) between H-1 and H-2, which was established by the crystal structure, was corroborated for all compounds in solution by a coupling constant $^3J_{HH} \cong 5.0$ Hz. In the major syn diastereoisomers the hydrogen atom H-1 and the protons at the C-2 methyl group are deshielded by 0.10−0.32 ppm relative to the ^{1}H NMR signals of the minor diastereoisomers. The observation is in line with the crystal structure data, which revealed that the deshielding is likely due to the spatial proximity of the phenyl group and the relevant hydrogen atoms (H-1, Me). Vice versa, the configuration assignment for related products can be based on the ^{1}H NMR chemical shifts provided that the coupling constant $^3J_{HH}$ (H-1/H-2) confirms a preferred synclinal conformation.

Thermodynamic product control was ruled out by subjecting diastereomeric mixtures of compound **12** (d.r. = syn/anti = 75/25 to 80/20) to the optimized reaction conditions previously mentioned (4 equiv of 2-methylthiophene, 1 equiv of HBF_4·OEt_2, CH_2Cl_2, −78 °C → r.t.). There was no indication for a change of the d.r. in favor of the major diastereoisomer *syn*-**12**. In other words, while the syn compound *syn*-**12** was formed with excellent diastereoselectivity in the intermolecular Friedel−Crafts reaction (d.r. = 95/5), this diastereomeric ratio was not observed upon attempted thermodynamic equilibration. The diastereomeric mixtures with low d.r. (d.r. = 75/25 to 80/20) had been isolated from reactions conducted under nonoptimized conditions using other acids and running the reactions at higher temperature [e.g., $Yb(OTf)_3$ at 100 °C]. The results indicate a kinetic product control in the currently studied Friedel−Crafts reactions.

The influence of a para substituent in the benzyl alcohol substrate was probed by the reaction of alcohols **3**−**6** with 2-methylthiophene (Scheme 4, Table 2). With the reaction that took place (entries 1−3), yields and diastereroselectivities were

Scheme 4

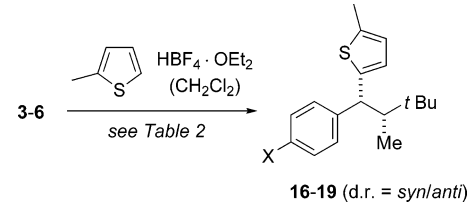
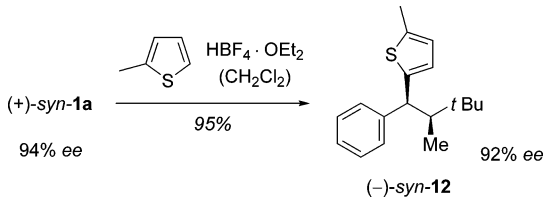


Table 2. Yields and Diastereoselectivities in the Friedel−Crafts Alkylation of 2-Methylthiophene with Substrates **3**−**6** (See Scheme 4)

entry[a]	substrate	X	product	d.r.[b]	yield[c] (%)
1	**3**	MeO	**16**	91/9	99
2	**4**	Me	**17**	94/6	87
3	**5**	Cl	**18**	97/3	91
4	**6**	CN	**19**	−	−

[a] HBF_4·OEt_2 was added to the corresponding alcohol **3**−**6** at −78 °C. After 5 min, 2-methylthiophene was added and the mixture was warmed to room temperature within 15 min. [b] The diastereomeric ratio (d.r.) of the crude product was determined by ^{1}H NMR spectroscopy. [c] Yield of isolated product.

Scheme 5



excellent. The electron-withdrawing cyano group ($\sigma_{para} = 0.71$)[29] precluded a reaction presumably because the formation of the carbocation cannot be promoted by the comparably weak Brønsted acid HBF_4·OEt_2. The minor diastereoselectivity increase that was detected going from X = MeO to X = Cl can be rationalized by the most reactive carbocation (X = Cl) reacting at a lower temperature than the more stable carbocations (X = Me < X = MeO). The syn configuration was assigned to the major products **16**−**18** obtained in these experiments based on analogy and based on the NMR data for major and minor diastereoisomer. As for the major diastereoisomers obtained in the reaction of **1a**, the major products *syn*-**16**−**18** exhibited a coupling constant $^3J_{HH} \cong 5.0$ Hz (H-1/H-2) and the ^{1}H NMR signals for H-1 and for the methyl group in the major diastereoisomer were deshielded relative to the minor diastereoisomer.

The question whether the stereogenic α-carbon atom retains its stereochemical integrity was addressed by subjecting the enantiomerically enriched alcohols (+)-*syn*-**1a** and (−)-*syn*-**1a** to the reaction conditions of the arylation (Scheme 5). A slight decrease of enantiomeric excess (94% ee → 92% ee) was observed for the corresponding product (−)-*syn*-**12** in the reaction of alcohol (+)-*syn*-**1a**. Similar observations were made for the other enantiomer (−)-*syn*-**1a**. The product ee was determined by chiral HPLC. While the slight ee change may be associated with uncertainties in the determination of the substrate ee (vide supra), it became evident that racemization of starting material is indeed an issue by monitoring the pretreatment of the alcohol *syn*-**1a** with HBF_4·OEt_2. The ee decrease became more significant (<80% ee for product

(29) Exner, O. *Correlation Analysis of Chemical Data*; Plenum Press: New York, 1988.

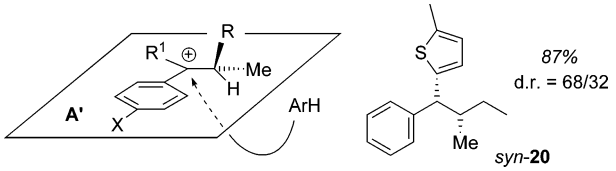
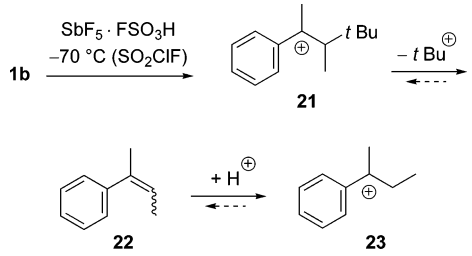


Figure 5. Diastereoselective attack of an arene nucleophile ArH at the preferred conformation **A′** of cation **A** and structure of product *syn*-**20** obtained by arylation of alcohol **2a**.

Scheme 6



(−)-*syn*-**12**) upon prolonging the time for the pretreatment. The results strongly suggest an addition of the arene nucleophile immediately after addition of HBF_4·OEt_2 if enantiomerically pure starting materials are employed.

Since we speculated that the racemization occurs by α-deprotonation and subsequent reprotonation of the carbocation, we used the putative intermediate, *β*-*tert*-butyl-*β*-methyl styrene, as starting material in the Friedel−Crafts reaction. Under identical conditions no reaction was observed with 2-methylthiophene, which clearly proves that this styrene is *not* an intermediate in the racemization process. The alternative hypothesis, namely, that the release of a *tert*-butyl cation and its subsequent reaction[30] with *β*-methyl styrene causes the racemization, was later supported by NMR studies (see Scheme 6).

Carbocation Conformation and NMR Studies. The high facial diastereoselectivity of the reactions discussed in the previous chapter has been explained by a kinetic product control in addition to a chiral carbocation of type **A**.[2] The carbocation conformation should be determined by 1,3-allylic strain[31] and the preferred conformation should therefore resemble structure **A′** (Figure 5). Attack from a nucleophile ArH at the prostereogenic center occurs from the bottom face of the plane defined by the α-substituent, by the aryl (XC_6H_4−) substituent, and by the substituent R^1. For the carbocation derived from alcohol (−)-*syn*-**1a** this face is the "re" face. The preferred transition state for this attack should correlate to the preferred conformation of the carbocation. According to this model, if the size of substituent R is reduced, the diastereoselectivty of the arylation should decrease. Indeed, benzyl alcohol **2a** which differs from **1a** by the smaller ethyl substituent (R = Et) at the α-carbon atom furnished in the reaction with 2-methylthiophene the corresponding product **20** in a diastereomeric ratio syn/anti = 68/32. The diastereoselectivity for R = *t*Bu was 95/5.

Studies were undertaken to elucidate the conformation of carbocations **A** by ^{1}H NMR spectroscopy (NOE). Generating a chiral carbocation under superacidic conditions was attempted, which in turn should stabilize the short-lived intermediate to allow for NOE studies at low temperature.[32] The experiments

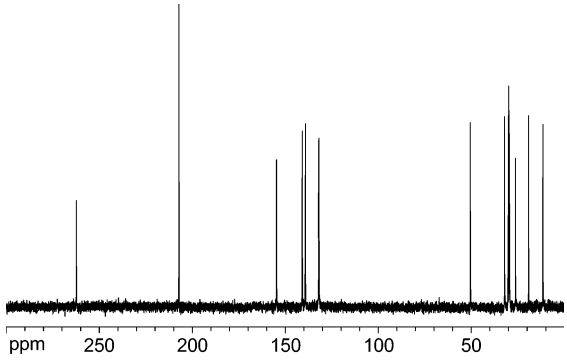


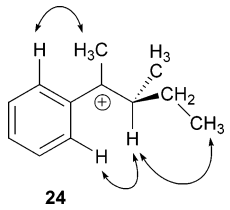
Figure 6. ^{13}C NMR spectrum of carbocation **24** (acetone-d_6 as external standard).

were conducted at −70 °C with SbF_5 or with FSO_3H·SbF_5 in SO_2ClF as the solvent. The secondary carbocations derived from the alcohols **1a** and **2a** were not sufficiently stable under these conditions. Decomposition was observed and both ^{1}H and ^{13}C NMR spectra were not conclusive. Similarly, the tertiary carbocation derived from alcohol **1b** did not live sufficiently long enough for meaningful NOE experiments. In this case, however, the formation of the stable carbocation **21** (Scheme 6) was clearly indicated at low temperature and a peak assignment was possible in the ^{13}C NMR spectrum (see Experimental Section). In addition, the decomposition process could be followed by ^{13}C NMR spectroscopy. Both the *tert*-butyl cation[33] and the tertiary benzylic cation **23**[34] were detected, proving that a *β*-elimination is the dominating consecutive reaction. Release of the *tert*-butyl cation leads to styrene **22** which upon protonation provides the observed carbocation **23**. The observation lends support to the earlier mentioned hypothesis that the reversible *β*-elimination of a *tert*-butyl cation is responsible for the racemization observed in the formation of 1,1-diarylalkane (−)-*syn*-**12**.

Since the *β*-elimination of the ethyl cation should occur with a significantly lower rate than the elimination of the *tert*-butyl cation, the chances to observe the tertiary cation **24** derived from alcohol **2b** appeared to be good. With SbF_5 as the Lewis acid and SO_2ClF as the solvent, clean NMR spectra were recorded at −70 °C. The ^{13}C NMR spectrum is depicted in Figure 6. It exhibits 12 carbon signals, the most deshielded signal being observed at 262.2 ppm relative to acetone-d_6 as the external standard. The aromatic region shows all six carbon atoms of the phenyl ring. They are magnetically nonequivalent because the rotation around the phenyl−carbocation bond is restricted. The ^{13}C NMR chemical shift values for the four carbon atoms of the *sec*-butyl group and for the methyl group are in line with the expected values.

The ^{1}H NMR spectrum of carbocation **24** was equally well-resolved and allowed for the projected NOE experiments. Significant information with regard to its confirmation was expected from the isolated pseudo sextet (3.41 ppm, $^3J \cong 6.4$ Hz) of the hydrogen atom at the stereogenic center and from the isolated doublet (0.72 ppm, $^3J = 6.4$ Hz) of the methyl group

(30) The addition of a *tert*-butyl cation to an olefin is known to be reversible: Saunders, M.; Lloyd, J. R. *J. Am. Chem. Soc.* **1977**, *99*, 7090−7091.
(31) Review: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.
(32) For reviews, see: (a) Olah, G. A., Prakash, G. K. S., Eds. *Carbocation Chemistry*; Wiley: Hoboken, NJ, 2004. (b) Saunders, M.; Jiménez-Vázquez, H. A. *Chem. Rev.* **1991**, *91*, 375−397.
(33) Olah, G. A.; Kuhn, S. J.; Tolgyesi, W. S.; Baker, E. B. *J. Am. Chem. Soc.* **1962**, *84*, 2733−2740.
(34) Olah, G. A.; Spear, R. J.; Forsyth, D. A. *J. Am. Chem. Soc.* **1977**, *99*, 2615−2621.



24

Figure 7. Major nonvicinal ^{1}H NMR NOE contacts observed in carbocation **24**.

at the same position. The most important NOE connections are summarized in Figure 7.

Diagnostic NOE contacts were observed between the methyl group at the cationic carbon atom and an aromatic ortho proton as well as between the hydrogen atom at the stereogenic center and an ortho proton. The spatial proximity of these atoms is perfectly in line with a conformationally restricted intermediate such as **A′** and it is support for the model presented earlier. To the best of our knowledge, cation **24** is the first acyclic chiral carbocation, the preferred conformation of which has been elucidated.

It was not possible to trap the carbocation under the conditions of stable ion formation with carbon nucleophiles. Side reactions were predominant. Methyl ether formation was feasible upon quenching the superacidic solution of cation **24** with methanol. In line with the preparative Friedel−Crafts experiment leading to **20**, the reaction proceeded with low diastereoselectivity (d.r. = 60/40). In the latter case, however, a thermodynamic equilibration cannot be ruled out.

Conclusion

In summary, chiral benzylic cations have been shown to be useful intermediates in S_N1 reactions proceeding with acyclic stereocontrol. Facial diastereoselectivities can be high (d.r. = >91/9) despite the fact that the chiral electrophile is highly reactive. The steric outcome of the reactions can be rationalized by a conformational restriction in the benzylic cation, which makes the two diastereotopic faces of the prostereogenic cationic carbon atom distinguishable. Evidence for such a conformational preference was provided by NMR studies on a stable chiral benzylic cation under superacidic conditions. The reaction medium and the nucleophilic strength of the carbon nucleophile have to be adjusted to comply with the reactivity of the intermediate and to avoid side reactions. Nonetheless, given the variety of weak nucleophiles available and given the number of structural parameters to be altered at a chiral benzylic cation, there is extensive room for further work in this area. From a synthetic point of view, the method appears to be extremely well-suited for the construction of chiral 1,1-diarylalkanes.

Experimental Section

Representative Procedure for the Diastereoselective Friedel−Crafts Alkylation. A solution of 96.2 mg (500 μmol) of the alcohol **1a** in 10 mL of dry dichloromethane was cooled to −78 °C. After addition of 102 mg (630 μmol) of HBF_4·OEt_2 and stirring of the solution for 5 min, 136 mg (2.00 mmol) of furan was added and the solution was warmed to ambient temperature over 15 min. The reaction was stopped by adding 10 mL of saturated aqueous $NaHCO_3$ after 1 min at room temperature. The reaction mixture was diluted with 20 mL of diethyl ether. The organic layer was washed with 10 mL of saturated aqueous $NaHCO_3$ and with 10 mL of saturated aqueous NaCl. After drying with $NaSO_4$ concentration in vacuo yielded 114 mg (470 μmol, 94%) of product **11**, which was obtained as a yellowish oil in a diastereomeric ratio of syn/anti = 97/3. In cases in which the product was not sufficiently pure, a subsequent flash column chromatography was conducted.

R_f 0.19 (pentane). IR (film): $\tilde{\nu}$ 3084 cm^{-1} (w), 3024 (w), 2960 (s), 1803 (m), 1450 (s), 798 (m), 729 (s), 710 (s). ^{1}H NMR (360 MHz, $CDCl_3$, 297 K): δ 0.83 (s, 9 H), 0.94 (d, ^3J = 7.2 Hz, 3 H), 1.93 (qd, ^3J = 7.2 Hz, ^3J = 4.4 Hz, 1 H), 4.39 (d, ^3J = 4.4 Hz, 1 H), 6.08 (d, ^3J = 3.1 Hz, 1 H), 6.30 (dd, ^3J = 3.1 Hz, ^3J = 1.5 Hz, 1 H), 7.13−7.30 (m, 5 H), 7.37 (d, ^3J = 1.5 Hz, 1 H). ^{13}C NMR (90 MHz, $CDCl_3$, 297 K): δ 11.5 (q), 28.2 (q), 34.2 (s), 45.9 (d), 49.5 (d), 107.9 (d), 110.3 (d), 126.0 (d), 128.3 (d), 140.9 (d), 144.6 (s), 156.5 (s), two aromatic carbon signals are superimposed. MS (EI): *m*/*z* (%) 242 (4), 157 (100). Anal. Calcd for $C_{17}H_{22}O$ (242.356): C, 84.25; H, 9.55. Found: C, 84.20; H, 9.10.

*syn-2-(Methyl-5-2,3,3-trimethyl-1-phenylbutyl)thiophene (**12**).* The compound was prepared from benzylic alcohol **1a** (96.2 mg, 500 μmol) and 2-methylthiophene (196 mg, 2.00 mmol) in CH_2Cl_2 (10 mL). Column chromatography (pentane as eluent) yielded 125 mg (459 μmol, 92%) of the desired product **12** as colorless liquid in a diastereomeric ratio of syn/anti = 95/5: R_f 0.26 (pentane). IR (film): $\tilde{\nu}$ 3058 cm^{-1} (w), 3022 (w), 2959 (s), 1493 (s), 1449 (s), 794 (m), 698 (s). ^{1}H NMR (500 MHz, $CDCl_3$, 297 K): δ 0.87 (s, 9 H), 0.99 (d, ^3J = 7.1 Hz, 3 H), 2.02−2.10 (m, 1 H), 2.43 (s, 3 H), 4.45 (d, ^3J = 5.0 Hz, 1 H), 6.54−6.59 (m, 1 H), 6.65−6.68 (m, 1 H), 7.17 (t, ^3J = 7.2 Hz, 1 H), 7.28 (t, ^3J = 7.6 Hz, 2 H), 7.35 (d, ^3J = 7.7 Hz, 2 H). ^{13}C NMR (90 MHz, $CDCl_3$, 297 K): δ 12.7 (q), 15.4 (q), 28.6 (q), 34.6 (s), 48.8 (d), 49.0 (d), 124.4 (d), 125.8 (d), 125.9 (d), 128.2 (d), 128.3 (d), 138.1 (s), 144.5 (s), 146.5 (s). MS (EI): *m*/*z* (%) 272 (2), 215 (2), 187 (100). Anal. Calcd for $C_{18}H_{24}S$ (272.448): C, 79.35; H, 8.88. Found: C, 79.37; H, 8.90.

Enantiomerically enriched product (−)-*syn*-**12** (92% ee) was obtained in a similar fashion from starting material (+)-*syn*-**1a**. The enantiomeric excess (ee) was determined by HPLC (Chiralcel-OJ-H, 250 × 4.6, t_R = 14.7 min; *n*-hexane/2-propanol = 70/30, flow rate = 1 mL/min; 254 nm). $[\alpha]_D^{20}$: +0.2 (*c* = 0.89, CH_2Cl_2). (+)-*syn*-**12** (90% ee) was obtained from (−)-*syn*-**1a**. HPLC: t_R = 11.6 min (Chiralcel-OJ-H, 250 × 4.6, *n*-hexane/2-propanol = 70/30, flow rate = 1 mL/min). $[\alpha]_D^{20}$: −0.7 (*c* = 1.23, CH_2Cl_2).

*syn-2-(2,3,3-Trimethyl-1-phenylbutyl)-1-tosyl-1H-pyrrole (**13**).* The compound was prepared from benzylic alcohol **1a** (96.2 mg, 500 μmol) and tosyl-1*H*-pyrrole (221 mg, 1.00 mmol) in CH_2Cl_2 (10 mL). Column chromatography (pentane/Et_2O 90/10 as eluent) yielded 94.0 mg (238 μmol, 48%) of the desired product **13** as white solid in a diastereomeric ratio of syn/anti = 94/6: R_f 0.34 (pentane/Et_2O 90/10). mp 118 °C. IR (KBr): $\tilde{\nu}$ 3148 cm^{-1} (w), 2974 (m), 2866 (w), 1491 (s), 1362 (vs), 1174 (vs), 1058 (m), 738 (s), 671 (vs). ^{1}H NMR (360 MHz, $CDCl_3$, 297 K): δ 0.81 (d, ^3J = 7.2 Hz, 3 H), 0.83 (s, 9 H), 1.84−1.94 (m, 1 H), 2.24 (s, 3 H), 5.02 (d, ^3J = 5.0 Hz, 1 H), 6.27 (t, ^3J = 3.5 Hz, 1 H), 6.37−6.41 (m, 1 H), 6.84−6.96 (m, 4 H), 6.99−7.06 (m, 3 H), 7.24 (d, ^3J = 8.4 Hz, 2 H), 7.34−7.39 (m, 1 H). ^{13}C NMR (90 MHz, $CDCl_3$, 297 K): δ 12.0 (q), 21.6 (q), 28.7 (q), 34.5 (s), 42.4 (d), 51.6 (d), 111.4 (d), 115.2 (d), 122.6 (d), 125.3 (d), 126.8 (d), 127.9 (d), 128.7 (d), 129.4 (d), 136.0 (s), 136.1 (s), 144.1 (s), 144.3 (s); MS (EI): *m*/*z* (%) 395 (2), 310 (100), 154 (23). Anal. Calcd for $C_{24}H_{29}NO_2S$ (395.558): C, 72.87; H, 7.39; N, 3.54; S, 8.11. Found: C, 72.84; H, 7.35; N, 3.39; S, 8.00.

*syn-1-(1-(2,4-Dimethoxyphenyl)-2,3,3-trimethylbutyl)benzene (**14**).* The compound was prepared from benzylic alcohol **1a** (96.2 mg, 500 μmol) and 1,3-dimethoxybenzene (276 mg, 2.00 mmol) in CH_2Cl_2 (10 mL). Column chromatography (pentane/Et_2O 95/5 as eluent) yielded 145 mg (464 μmol, 93%) of the desired product **14** as colorless oil in a diastereomeric ratio of syn/anti = 97/3: R_f 0.30 (pentane/Et_2O 95/5). IR (film): $\tilde{\nu}$ 3054 cm^{-1} (w), 2957 (s), 1611 (s), 1586 (s), 1504 (s), 1292 (s), 1038 (s), 924 (w), 834 (m), 756 (m), 700 (s). ^{1}H NMR (500 MHz, $CDCl_3$, 297 K): δ 0.79 (d, ^3J = 6.9 Hz, 3 H), 0.84 (s, 9 H),

2.32−2.42 (m, 1 H), 3.77 (s, 3 H), 3.81 (s, 3 H), 4.52−4.64 (m, 1 H), 6.40−6.46 (m, 2 H), 7.08−7.16 (m, 2 H), 7.23 (t, ^3J = 7.6 Hz, 2 H), 7.37 (d, ^3J = 7.6 Hz, 2 H). ^{13}C NMR (90 MHz, $CDCl_3$, 297 K): δ 14.4 (q), 29.0 (q), 34.8 (s), 45.4 (d), 55.3, 55.5, 98.5 (d), 104.2 (d), 125.3 (d), 126.7 (s), 128.1 (d), 128.8 (d), 130.3 (d), 147.5 (s), 157.8 (s), 158.5 (s), one aliphatic signal is superimposed. MS (EI): *m*/*z* (%) 312 (2), 255 (2), 227 (100). HRMS (EI) calcd for $C_{21}H_{28}O_2$, 312.2089; found, 312.2084.

*syn-2-(2,3,3-Trimethyl-1-phenyl-butyl)-benzofuran (**15**).* The compound was prepared from benzylic alcohol **1a** (96.2 mg, 500 μmol) and benzofuran (236 mg, 2.00 mmol) in CH_2Cl_2 (10 mL). Column chromatography (pentane as eluent) yielded 90.0 mg (308 μmol, 62%) of the desired product **15** as white solid in a diastereomeric ratio of syn/anti = 95/5: R_f 0.10 (pentane). mp 68 °C. IR (KBr): $\tilde{\nu}$ 2961 cm^{-1} (s), 2868 (m), 2359 (w), 1581 (m), 1493 (m), 1454 (s), 1380 (m), 1257 (s), 946 (m), 803 (s), 7411 (vs), 700 (vs). ^{1}H NMR (500 MHz, $CDCl_3$, 297 K): δ 0.91 (s, 9 H), 1.06 (d, ^3J = 7.2 Hz, 3 H), 2.12 (qd, ^3J = 7.2 Hz, ^3J = 4.9 Hz, 1 H), 4.46 (d, ^3J = 4.9 Hz, 1 H), 6.48 (s, 1 H), 7.16−7.25 (m, 3 H), 7.30 (t, ^3J = 7.7 Hz, 2 H), 7.38 (d, ^3J = 7.7 Hz, 2 H), 7.45−7.52 (m, 2 H). ^{13}C NMR (90 MHz, $CDCl_3$, 297 K): δ 12.3 (q), 28.4 (q), 34.4 (s), 46.9 (d), 49.1 (d), 104.8 (d), 111.1 (d), 120.5 (d), 122.6 (d), 123.3 (d), 126.3 (d), 128.4 (d), 128.8 (s), 144.0 (s), 154.7 (s), 160.2 (s), one aromatic carbon signal is superimposed. MS (EI): *m*/*z* (%) 292 (4), 208 (23), 207 (100), 178 (39). HRMS (EI) calcd for $C_{21}H_{24}O$, 292.1827; found, 292.1828.

*syn-2-[1-(4-Methoxy-phenyl)-2,3,3-trimethyl-butyl]-5-methylthiophene (**16**).* The compound was prepared from benzylic alcohol **3** (111 mg, 500 μmol) and 2-methylthiophene (196 mg, 2.00 mmol) in CH_2Cl_2 (10 mL). Column chromatography (pentane as eluent) yielded 150 mg (496 μmol, 99%) of the desired product as a colorless oil in a diastereomeric ratio of syn/anti = 91/9: R_f 0.08 (pentane). IR (film): $\tilde{\nu}$ 2958 cm^{-1} (s), 1609 (m), 1583 (w), 1510 (vs), 1463 (m), 1301 (w), 1247 (vs), 1179 (s), 1047 (s), 822 (m), 797 (s). ^{1}H NMR (360 MHz, $CDCl_3$, 297 K): δ 0.86 (s, 9 H), 0.96 (d, ^3J = 7.2 Hz, 3 H), 2.00 (qd, ^3J = 7.2 Hz, ^3J = 5.3 Hz, 1 H), 2.41 (s, 3 H), 3.77 (s, 3 H), 4.38 (d, ^3J = 5.3 Hz, 1 H), 6.52−6.56 (m, 1 H), 6.63 (d, ^3J = 3.4 Hz, 1 H), 6.81 (d, ^3J = 8.7 Hz, 2 H), 7.24 (d, ^3J = 8.7 Hz, 2 H). ^{13}C NMR (90 MHz, $CDCl_3$, 297 K): δ 12.7 (q), 15.4 (q), 28.6 (q), 34.6 (s), 48.0 (d), 49.1 (d), 55.3 (q), 113.7 (d), 124.4 (d), 125.6 (d), 129.1 (d), 138.0 (s), 138.8 (s), 145.0 (s), 157.8 (s). MS (EI): *m*/*z* (%) 302 (<1), 245 (2), 217 (100). Anal. Calcd for $C_{19}H_{26}OS$ (302.47): C, 75.45; H, 8.66; S, 10.60. Found: C, 75.40; H, 8.45; S, 10.64.

*syn-2-Methyl-5-(2,3,3-trimethyl-1-p-tolyl-butyl)thiophene (**17**).* The compound was prepared from benzylic alcohol **4** (103 mg, 500 μmol) and 2-methylthiophene (196 mg, 2.00 mmol) in CH_2Cl_2 (10 mL). Column chromatography (pentane as eluent) yielded 124 mg (433 μmol, 87%) of the desired product as a colorless oil in a diastereomeric ratio of syn/anti = 94/6: R_f 0.31 (pentane). IR (film): $\tilde{\nu}$ 3047 cm^{-1} (w), 2960 (s), 1512 (vs), 1479 (s), 1469 (s), 1396 (m), 1378 (s), 1364 (s), 1233 (m), 1118 (w), 1034 (m), 796 (vs), 728 (w). ^{1}H NMR (500 MHz, $CDCl_3$, 297 K): δ 0.86 (s, 9 H), 0.98 (d, ^3J = 7.2 Hz, 3 H), 2.03 (qd, ^3J = 7.2 Hz, ^3J = 5.3 Hz, 1 H), 2.31 (s, 3 H), 2.42 (s, 3 H), 4.41 (d, ^3J = 5.3 Hz, 1 H), 6.53−6.58 (m, 1 H), 6.64 (d, ^3J = 3.3 Hz, 1 H), 7.09 (d, ^3J = 8.0 Hz, 2 H), 7.23 (d, ^3J = 8.0 Hz, 2 H). ^{13}C NMR (90 MHz, $CDCl_3$, 297 K): δ 12.7 (q), 15.4 (q), 21.1 (q), 28.7 (q), 34.6 (s), 48.4 (d), 49.0 (d) 124.4 (d), 125.7 (d), 128.1 (d), 129.0 (d), 135.4 (s), 138.0 (s), 143.6 (s), 144.9 (s). MS (EI): *m*/*z* (%) 286 (1), 229 (2), 201 (100). Anal. Calcd for $C_{19}H_{26}S$ (286.47): C, 79.66; H, 9.15. Found: C, 79.68; H, 9.02.

*syn-2-[1-(4-Chlorophenyl)-2,3,3-trimethyl-butyl]-5-methylthiophene (**18**).* The compound was prepared from benzylic alcohol **5** (113 mg, 500 μmol) and 2-methylthiophene (196 mg, 2.00 mmol) in CH_2Cl_2 (10 mL). Column chromatography (pentane as eluent) yielded 139 mg (453 μmol, 91%) of the desired product as a colorless oil in a diastereomeric ratio of syn/anti = 94/6: R_f 0.36 (pentane). IR (film): $\tilde{\nu}$ 3060 cm^{-1} (w), 2961 (vs), 2867 (m), 1490 (vs), 1396 (m), 1365 (m), 1232 (w), 1091 (s, C−Cl), 1014 (s), 813 (m), 796 (s), 740 (w). ^{1}H NMR (360 MHz, $CDCl_3$, 297 K): δ 0.85 (s, 9 H), 0.96 (d, ^3J = 7.2 Hz, 3 H), 1.99 (qd, ^3J = 7.2 Hz, ^3J = 5.4 Hz, 1 H), 2.42 (s, 3 H), 4.40 (d, ^3J = 5.4 Hz, 1 H), 6.53−6.57 (m, 1 H), 6.64 (d, ^3J = 3.4 Hz, 1 H), 7.20−7.29 (m, 4 H). ^{13}C NMR (90 MHz, $CDCl_3$, 297 K): δ 12.6 (q), 15.3 (q), 28.6 (q), 34.6 (s), 48.3 (d), 49.0 (d), 124.5 (d), 125.9 (d), 128.5 (d), 129.6 (d), 131.7 (s), 138.4 (s), 143.9 (s), 145.0 (s). MS (EI): *m*/*z* (%) 308 (<1), 306 (<1), 223 (36), 221 (100). Anal. Calcd for $C_{18}H_{23}ClS$ (306.89): C, 70.45; H, 7.55; Cl, 11.55. Found: C, 70.46; H, 7.49; Cl, 11.64.

*syn-2-Methyl-5-(2-methyl-1-phenyl-butyl)thiophene (**20**).* The compound was prepared from benzylic alcohol **2a** (82.1 mg, 500 μmol) and 2-methylthiophene (196 mg, 2.00 mmol) in CH_2Cl_2 (10 mL). Column chromatography (pentane as eluent) yielded 106 mg (434 μmol, 87%) of the desired product as a colorless oil in a diastereomeric ratio of syn/anti = 68/32: R_f 0.26 (pentane). IR (film): $\tilde{\nu}$ 3061 cm^{-1} (w), 3026 (w), 2961 (s), 2919 (m), 2873 (m), 1600 (w), 1494 (m), 1452 (s), 1379 (m), 1032 (w), 793 (m), 740 (m), 700 (vs), 635 (w). ^{1}H NMR (360 MHz, $CDCl_3$, 297 K): δ 0.79 (d, ^3J = 6.6 Hz, 0.9 H, [anti]), 0.84 (t, ^3J = 7.3 Hz, 2.1 H, [syn]), 0.91 (t, ^3J = 7.4 Hz, 0.9 H, [anti]), 0.95 (d, ^3J = 6.6 Hz, 2.1 H, [syn]), 0.94−1.06 (m, 0.7 H, [syn]), 1.06−1.19 (m, 0.3 H, [anti]), 1.32−1.46 (m, 0.7 H, [syn]), 1.53−1.66 (m, 0.3 H, [anti]), 2.03−2.20 (m, 1 H), 2.40 (s, 3 H), 3.71−3.79 (m, 1 H), 6.50−6.54 (m, 1 H), 6.61−6.67 (m, 1 H), 7.13−7.22 (m, 1 H), 7.23−7.32 (m, 4 H). ^{13}C NMR (90 MHz, $CDCl_3$, 297 K), *syn*-**20**: δ 11.3 (q), 15.4 (q), 17.7 (q), 27.5 (t), 40.3 (d), 54.4 (d), 124.0 (d), 124.4 (d), 126.3 (d), 128.2 (d), 128.5 (d), 137.9 (s), 144.4 (s), 146.6 (s). ^{13}C NMR (90 MHz, $CDCl_3$, 297 K), *anti*-**20**: δ 11.4 (q), 15.4 (q), 17.6 (q), 27.8 (t), 40.4 (d), 54.1 (d), 123.9 (d), 124.5 (d), 126.3 (d), 128.3 (d), 128.5 (d), 137.8 (s), 144.4 (s), 146.7 (s). MS (EI): *m*/*z* (%) 244 (5), 187 (100). Anal. Calcd for $C_{16}H_{20}S$ (244.39): C, 78.63; H, 8.25. Found: C, 78.53; H, 8.14.

NMR Studies. *2-Phenyl-3,4,4-trimethyl-pentane-2-carbeniumion (**21**).* The benzylic alcohol **1b** (22.0 mg, 106 μmol) was mixed with SO_2ClF at −78 °C in a NMR tube. A solution of SbF_5 in SO_2ClF precooled to −78 °C was added and the deep green solution was properly mixed. After addition of the precooled external standard acetone-d_6 the mixture was inserted into the NMR, which was already cooled to −90 °C. ^{13}C NMR (100 MHz, SO_2ClF, external standard acetone-d_6, 183 K): δ 13.8 (q, $^1J_{C-H}$ = 130.0 Hz), 27.4 (q, $^1J_{C-H}$ = 125.4 Hz), 28.9 (q, $^1J_{C-H}$ = 144.1 Hz), 42.2 (s), 58.2 (d, $^1J_{C-H}$ = 133.0 Hz), 131.1 (d, $^1J_{C-H}$ = 173.3 Hz), 131.7 (d, $^1J_{C-H}$ = 174.0 Hz), 138.9 (d, $^1J_{C-H}$ = 165.5 Hz), 139.2 (d, $^1J_{C-H}$ = 167.9 Hz), 141.1 (s), 154.0 (d, $^1J_{C-H}$ = 169.1 Hz), 262.7 (s).

*3-Methyl-2-phenyl-pentane-2-carbeniumion (**24**).* The benzylic alcohol **2b** (30.0 mg, 168 μmol) was added to SO_2ClF at −78 °C in a test tube and mixed to yield a homogeneous solution. The solution of the alcohol was added quickly at −78 °C to an analogously prepared solution of SbF_5 in SO_2ClF. The deep red mixture was transferred to a NMR tube at −78 °C and a precooled external acetone-d_6 standard was inserted. The sample was than transferred into the precooled NMR (−70 °C). ^{1}H NMR (400 MHz, SO_2ClF, external standard acetone-d_6, 203 K): δ 0.20 (t, ^3J = 7.6 Hz, 3 H), 0.72 (d, ^3J = 6.4 Hz, 3 H), 1.00−1.26 (m, 2 H), 2.55 (s, 3 H), 3.41 (virt sext, $^3J \cong$ 6.4 Hz, 1 H), 7.10 (virt q, $^3J \cong$ 7.7 Hz, 2 H), 7.69 (t, ^3J = 7.1 Hz, 1 H), 7.91 (virt t, $^3J \cong$ 9.8 Hz, 2 H). ^{13}C NMR (100 MHz, SO_2ClF, external standard acetone-d_6, 203 K): δ 11.5 (q, $^1J_{C-H}$ = 128.5 Hz), 19.2 (q, $^1J_{C-H}$ = 131.1 Hz), 26.2 (q, $^1J_{C-H}$ = 131.6 Hz), 32.1 (t, $^1J_{C-H}$ = 131.5 Hz), 50.4 (d, $^1J_{C-H}$ = 135.8 Hz), 131.8 (dd, $^1J_{C-H}$ = 170.0 Hz, $^2J_{C-H}$ = 7.0 Hz), 132.0 (dd, $^1J_{C-H}$ = 171.5 Hz, $^2J_{C-H}$ = 6.8 Hz), 139.1 (d, $^1J_{C-H}$ = 166.7 Hz), 139.3 (s), 140.8 (d, $^1J_{C-H}$ = 167.3 Hz), 154.7 (d, $^1J_{C-H}$ = 166.1 Hz), 262.2 (s).

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Supporting Information Available: Complete analytical data for the yet unreported starting materials (+)-*syn*-**1a**, (−)-*syn*-**1a**, **1b**, **5**, and **6** and procedures for their preparation. ^{1}H and ^{13}C NMR data for the known starting materials *syn*-**1a**, *anti*-**1a**, **2a**, **2b**, **3**, and **4**. ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org. See any current masthead page for ordering information and Web access instructions.

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