Communication

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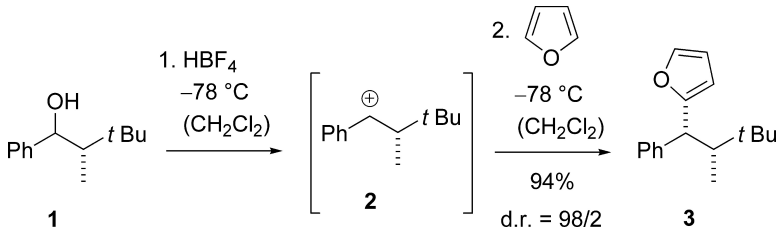

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High Facial Diastereoselectivity in Intra- and Intermolecular Reactions of Chiral Benzylic Cations

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The facial diastereoselectivity of the nucleophilic addition to α-chiral ketones (R = alkyl, aryl) or aldehydes (R = H) of the general structure **A** (Figure 1) is one of the most extensively studied phenomena in stereoselective organic synthesis.[1] The reaction is characterized by the substrate combination weak electrophile/strong nucleophile. It is opposed at the other end of the reactivity scale[2] by the substrate combination strong electrophile/weak nucleophile. In the latter scenario a free carbenium ion of type **B** plays the role of the electrophile. To the best of our knowledge there is no systematic investigation concerning the facial diastereoselectivity of such a transformation.[3,4] There are, however, examples of intramolecular reactions (cyclizations), which show a high degree of diastereoselectivity.[5] In this communication, we report on reactions of chiral benzylic cations with weak nucleophiles. It turned out that both intra- and *inter*molecular reactions of these carbenium ions occur consistently with high levels of stereocontrol.

Benzylic cations were employed because they are known to display a comparatively high stability[6] and because they were considered to provide an advantageous conformational fixation by 1,3-allylic strain (vide infra).[7] In a first set of experiments, Friedel−Crafts-type cyclizations of the appropriate precursors **1**−**3** (Figure 2, Phth = phthaloyl) to tetralines were conducted. Tertiary carbenium ions (**C**, R^2 = Me) were generated by protonation of the styrenes **1**, whereas secondary carbenium ions (**C**, R^2 = H) were obtained either by ring opening of epoxide **2** or by protonation of alcohol **3**. The substrates were synthesized according to known procedures.[8]

The optimized reaction conditions for the cyclization (Scheme 1) are given in Table 1. The reaction proceeded in high yields (91−99%) with excellent diastereoselectivities (dr ≥ 95/5). Solely in the case of epoxide **2**, the semi-pinacol rearrangement was a competing reaction (entry 4), which diminished the yield of product **4d**. The configuration of the tetralines **4** was assigned by NMR studies (^3J, NOESY) and by comparison with known compounds.[9] The *trans* products ***trans*-4** always prevailed. Under the reaction conditions the minor diastereoisomers ***cis*-4** were not converted into the major diastereoisomers ***trans*-4**. A thermodynamic reaction control can consequently be excluded.

Encouraged by these results, we attempted intermolecular Friedel−Crafts alkylation reactions via a putative secondary benzylic cation. Alcohol **5** (Scheme 2) was obtained by reduction of the corresponding ketone, which in turn was accessible by *tert*-alkylation[10] of propiophenone. The alcohol synthesized by this protocol was exclusively *anti* configurated. Contrary to that, Grignard addition to 2,3,3-trimethylbutanal[11] yielded the *syn* diastereoisomer. *Regardless* of the configuration of the starting material, the acid-catalyzed Friedel−Crafts reaction of different arenes ArH with the alcohol **5** afforded the products **6** in almost

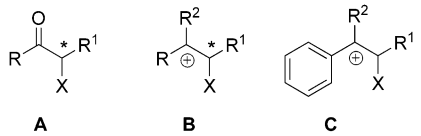

Figure 1. General structure of α-chiral carbonyl compounds **A**, α-chiral carbenium ions **B**, and α-chiral benzylic cations **C**.

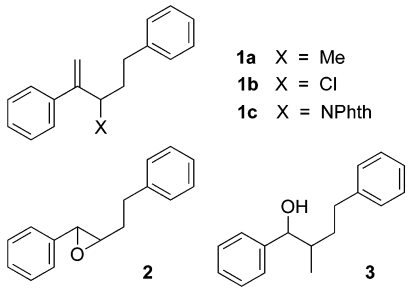

Figure 2. Structures of the starting materials **1**−**3** for the intramoleclar Friedel−Crafts alkylation study.

Scheme 1

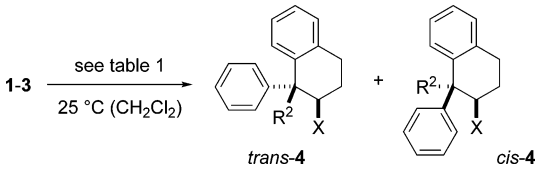

Table 1. Reaction Conditions, Yields, and Diastereoselectivities in the Friedel−Crafts Cyclization of Compounds **1**−**3**

entry	substrate	acid[a]	time[b] [min]	R^2	X	product	dr[c]	yield[d] [%]
1	**1a**	F_3CSO_3H[e]	1	Me	Me	**4a**	98/2	95
2	**1b**	F_3CSO_3H[e]	15	Me	Cl	**4b**	98/2	91
3	**1c**	F_3CSO_3H[e,f]	60	Me	NPhth	**4c**	>95/5	94
4	**2**	$BF_3{\cdot}OEt_2$	180	H	OH	**4d**	>95/5	48
5	**3**	F_3CSO_3H[e]	15	H	Me	**4e**	98/2	99
6	**3**	$HBF_4{\cdot}OEt_2$	15	H	Me	**4e**	99/1	77

[a] One equivalent of the corresponding Brønsted or Lewis acid was used. [b] Time required for complete conversion. [c] The diastereomeric ratio (dr) of the crude product was determined by ^{1}H NMR spectroscopy and GLC analysis. [d] Yield of isolated product. [e] 0.1 M solution in $F_2ClCCFCl_2$. [f] Two equivalents of acid were used.

diastereomerically pure form (Scheme 2). The diastereomeric ratio (dr) was for **6a**, **6b**, **6c**, and **6d**, dr = 98/2, 97/3, 94/6, and 95/5, respectively. These reactions represent the first examples of intermolecular addition reactions to carbocations which proceed with extremely high facial diastereoselectivities.

The assignment of the relative product configuration was based on the crystal structure of compound **6c**, which is depicted in Figure 3. The product configuration suggests an exclusive *re*-face attack

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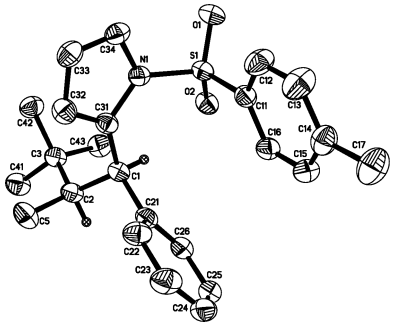


Figure 3. Structure of the Friedel−Crafts alkylation product **6c** in the crystal.

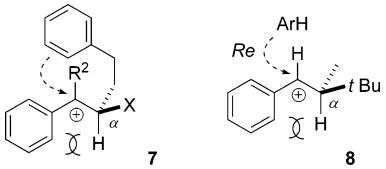
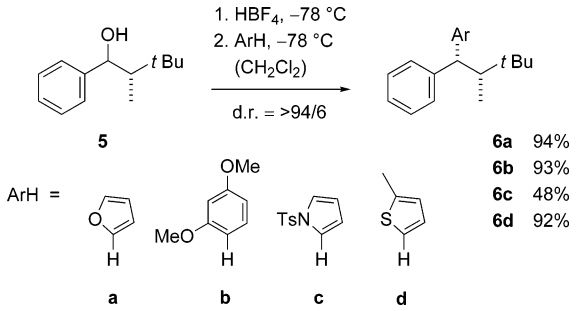


Figure 4. Explanation of the side differentiation in α-chiral benzylic cations **7** and **8** through 1,3-allylic strain.

Scheme 2



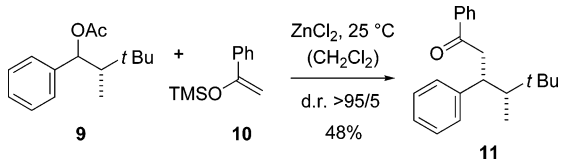
on the intermediate carbenium ion.[12] The other arenes ArH should behave like *N*-tosylpyrrole in their nucleophilic addition reaction to the electrophile and lead to products **6a**, **6b**, and **6d** with the same relative configuration.

For an explanation of the observed facial diastereoselectivity we rely on an analysis of possible conformations accessible to the intermediate carbenium ions, assuming that they live long enough to allow for free rotation around the C−C_α bond. According to the model shown in Figure 4, the selectivity in the cyclization reaction can be accounted for by a preferred conformation of intermediate **7**. Ring closure occurs under kinetic control. With H being significantly smaller than X (X = Me, Cl, OH, NPhth), it is the H atom which resides in the 1,3-allylic position.[7] The phenylalkyl chain is directed to the back of carbenium ion **7**.

The exclusive formation of *syn* products in the reaction of alcohol **5** can also be explained by invoking a carbenium ion as intermediate. The stereoconvergent reaction course (vide supra) supports a trigonal carbenium ion **8** as intermediate. In its preferred conformation (Figure 4) nucleophilic attack occurs from the sterically more accessible *re* face (Me vs *t*-Bu).

In addition to the Friedel−Crafts reactions, the reaction of acetate **9** with the acetophenone-derived silylenolether **10**[13] (Scheme 3) was conducted. It was probed whether the carbenium ion **8** (Figure 4) was also attacked by other weak nucleophiles with high facial

Scheme 3



diastereoselectivity. The best result was achieved with $ZnCl_2$ as Lewis acid. Only a single diastereoisomer **11** was obtained. Further reactions of chiral carbenium ions are currently being studied and will be reported in due course.

Acknowledgment. This work was generously supported by the *Fonds der Chemischen Industrie*.

Supporting Information Available: References for the preparation of **1**−**3**, representative experimental procedures, and NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) At this point in time, the question whether carbenium ion intermediates such as **B** and **C** are formed "free", i.e., without any contact to the counteranion, under the reaction conditions we used, cannot be answered. All reactions we conducted proceeded under kinetic product control and were not stereospecific (no S_N2 pathway). These facts are clear evidence for a trigonal carbenium ion intermediate which is attacked in an irreversible carbon−carbon bond forming step. A memory of chirality effect (cf. Zhao, H.; Hsu, D. C.; Carlier, P. R. *Synthesis* **2005**, 1−16) appears unlikely to us, but cannot be ruled out according to the opinion of a reviewer.
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