Carbocations

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Stereoselective Reactions with Stabilized Carbocations**

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S_N1-type reactions are ubiquitous in modern organic synthesis. Organic chemists are introduced to well-established S_N1-type reactions in undergraduate courses, and the accompanying message of these lessons is the elusive stability and the high reactivity of carbocations.[1]

By taking advantage of the stability of particular carbocations, the use of carbocations in selective reactions has recently become increasingly important. Highly diastereoselective reactions involving carbocations have been recently reported in the literature, and can be considered as guides for further developments.

From the pioneering studies of Olah, the knowledge of carbocations has increased tremendously.[2] Although carbocations are generally believed to be unstable and highly reactive, there is a ≥ 7 orders of magnitude in the stability and reactivity of carbocations. The precise and meticulous work of Mayr has helped to shed light on this topic. Several S_N1-type reactions can be now be rationally designed through the use of the Mayr scales of reactivity.[3] What is very important when designing stereoselective reactions of carbocations is to consider the combination of the parameters of the electrophile and nucleophile partners. In fact, Mayr has established a useful "rule of thumb"[4] for such reactions. Choosing an incorrect combination of reactants will result in a reaction than can occur only in months! It can be expected that electrophiles will react with all nucleophiles located below themselves in the general Mayr scales (Figure 1). Benzylic carbocations are positioned in the electrophilicity scale as a function of the substituents. Strong electron-donating substituents enhance the stability of the carbocations.

Benzylic carbocations have moderate stability and high reactivity, (mesitylbenzylic carbocation is positioned at $+6$ on the Mayr scale) and are capable of reacting with a large variety of possible nucleophiles. Benzylic carbocations could be easily generated from the corresponding alcohols or acetates by stoichiometric[5] or catalytic[6] amounts of Lewis or Brønsted acids. Only a few examples of intramolecular attack on chiral benzylic cations have been published,[7] and the intermolecular version of the reaction was investigated recently by Bach and co-workers.[8a] Chiral benzylic alcohol, which carries a functional group in the stereogenic position, reacts with various arenes (weak nucleophiles) in a highly selective fashion.[8] Diastereoselective Friedel–Crafts reactions, producing diarylated *anti* and *syn* products (Scheme 1; Ar′ = arene, heteroarene), were performed with $HBF_4{\cdot}OEt_2$ in CH_2Cl_2 at low temperature. Chiral benzylic cations are likely intermediates in these reactions, and to explain the high *anti* selectivity of these reactions, the energetic and geometric properties of the carbocationic intermediates were investigated more closely by DFT calculations.

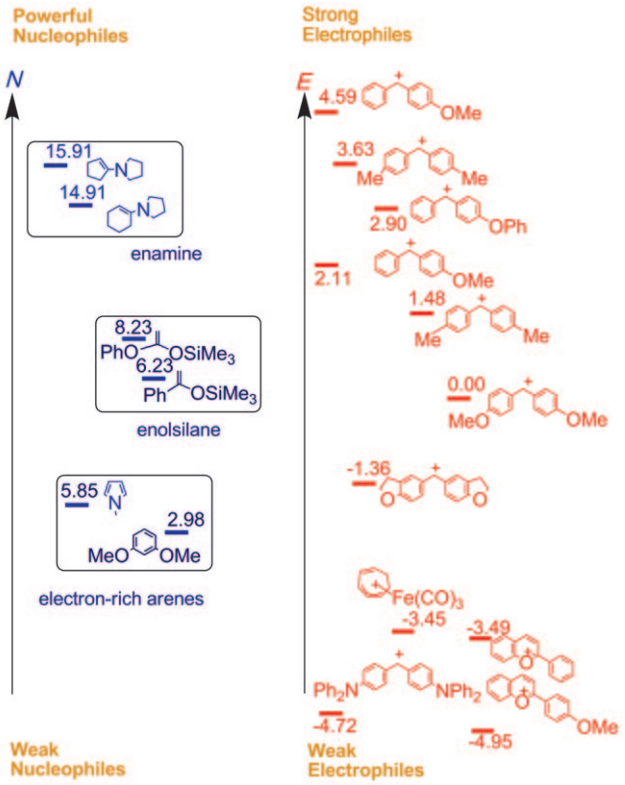

Figure 1. Powerful nucleophiles (blue) and stable electrophiles (red) according to Mayr. E/N = electrophilicity/nucleophilicity parameter.

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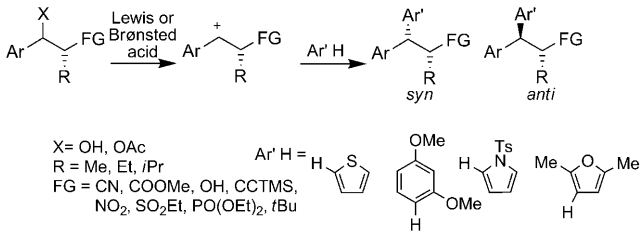


Scheme 1. Functionalization of a benzylic carbocation to form *anti* and *syn* diastereoisomeric products. FG = functional group.

Evidence collected from DFT calculations and experiments[8e] suggest that cations exist in a preferred conformation that is determined by the 1,3-allylic strain. Substituents of the stereogenic center are shielding one diastereotopic face in a preferential manner (Figure 2). The diastereoselectivity results from a preferred conformation, in which the two faces of the cationic center are shielded differently by the R and FG substituents. The two substituents R and FG point in different directions relative to the plane containing the carbocation. An incoming nucleophile will, for steric reasons, approach the electrophilic center from the less shielded face. The A value[9] of the individual substituents can be taken as an indication of their steric bulk. Relative to the methyl group (A = 1.74), the nitro (A = 1.1), hydroxy (A = 1.0), cyano (A = 0.2), methoxycarbonyl (A = 1.2), trimethylsilylethynyl (CCTMS, A = 0.45), and chloro (A = 0.6) groups are smaller, and the *Si* face of the carbocation is less shielded thereby favoring the approach by the nucleophile from this direction, which leads to the corresponding *anti* product. When the FG are ethylsulfonyl (A = 2.50), ethoxysulfonyl (A = 2.50), and diethoxyphosphonyl ($PO(OEt)_2$, A = 2.46) groups, they are larger than methyl and therefore they shield the *Si* face. As a consequence, attack of the *Re*-face is favored and leads to the *syn* products. The exclusive formation of the *syn* product was observed when the *tert*-butyl functional group (*A* = 4.7–4.9, Scheme 1) was utilized, regardless of the configuration of the starting material.[8a,b]

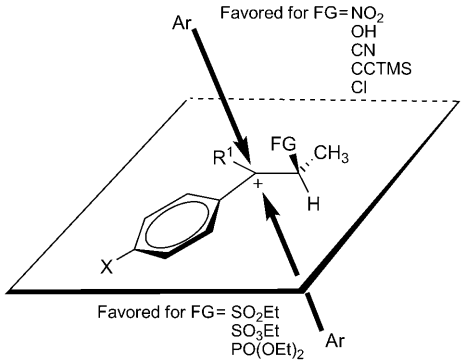
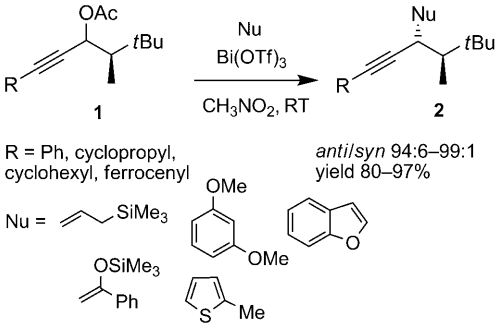


Figure 2. Diastereoselective attack of an arene to a preferred conformation of a carbocation.

Rubenbauer and Bach have also reported examples of *syn* products in the reaction of various chiral acetates with resorcinol dimethyl ether as a reference electrophile and $AuCl_3$ as the catalyst.[10] In their paper, the extension of the diastereoselective methodology was realized with other nucleophiles such as allyltrimethylsilane, trimethylsilylcyanide, and acetylacetone, thereby showing the wide scope of this chemistry—which is not limited to Friedel–Crafts-type reactions. In all these cases the reaction afforded good yield and high selectivity (d.r. 91:9–97:3). Enolsilane was also investigated in the presence of catalytic $AuCl_3$,[10] or stoichiometric amounts of $ZnCl_2$.[8a] In both cases an outstanding level of diastereoselection was obtained, even when the reactions were carried out at room temperature.

As the stabilization effect of the propargyl group on a carbocation is well established, the investigation of propargylic cations was also undertaken. Propargylic cations can be easily generated from the corresponding propargylic acetate **1** in the presence of Lewis acids. Interestingly, Bach and coworkers reported further developments in the area.[11] The first compelling observation is the number of Lewis acids that are able to produce the desired transformation when they are used in catalytic amounts. The list includes $FeCl_3$, $InCl_3$, $AuCl_3$, $Cu(OTf)_2$, $[Au(PPh_3)]SbF_6$, and BF_3. $Bi(OTf)_3$, which proved to be the most effective for the transformation (Scheme 2), and with TMSOTf being nearly as effective



Scheme 2. Stereoselective addition of nucleophiles to propargylic cation promoted by $Bi(OTf)_3$.

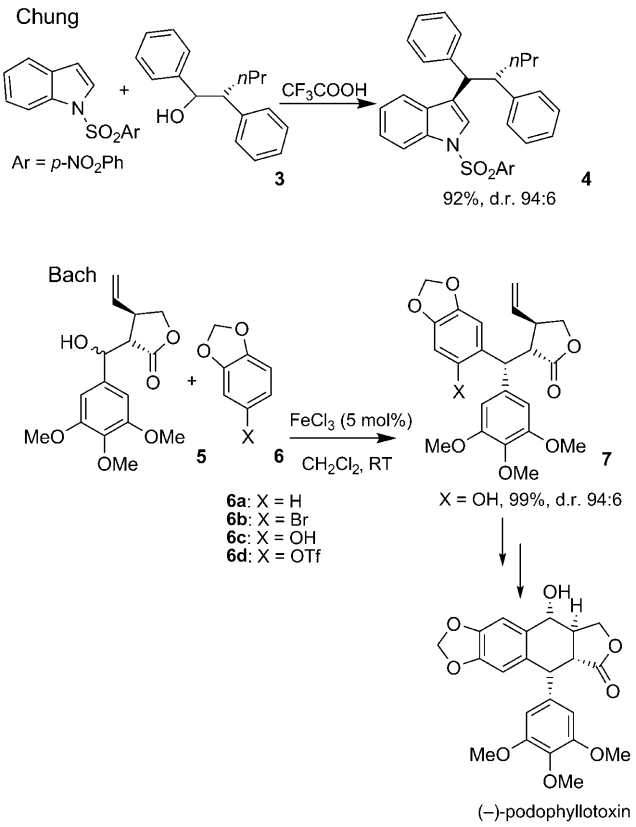
(TMSOTf = trimethylsilyltriflate). The generation of the carbocation could be coupled with various processes mediated by the same Lewis acid, and in this perspective, the recent chemistry displayed by gold salts could be investigated further.[12] More interesting is the high level of simple diastereoselection obtained irrespective of the Lewis acid employed. The fact that the transformation is not observed in the presence of the propargylic alcohol could be related to the stability of the generated carbocation, its position in the Mayr scale, and its fast reaction with water.[3] The *anti* versus *syn* ratio obtained in these reactions depends on the *tert*-butyl group, which adopts a favored orientation, thus stabilizing the incipient antiperiplanar bond as postulated in the Felkin–Anh model—where the nucleophile approaches from the bottom side.

As nucleophiles, electron-rich aromatic compounds also showed good levels of diastereoselectivity. Although the exact electrophilicity of the chiral carbocation used by Bach was not

determined, recent studies on the reaction of methoxybenzyl cation with π-nucleophiles were reported by Mayr and coworkers.[13] On the basis of the experimental data, the inferior limit of nucleophilicity of arenes which are suitable for reacting with benzylic alcohols investigated by Bach (covering at least six orders of magnitude) can be estimated to have $N = -3.57$, but this value is definitely dictated by the stability of the carbocation. Side reactions started to appear when less reactive nucleophiles (e.g. toluene) were employed. The choice of alcohol electrophile is governed by a subtle balance between the Brønsted acidity of the acid used for promoting the formation of the carbocation and the Brønsted basicity of the alcohol. The acid must be sufficiently strong and its counterion sufficiently noncoordinating to allow for cation formation. When formation of the carbocation does not occur through the use of the alcohol and Lewis or Brønsted acids, then replacing the alcohol with the corresponding acetate may allow the reaction to occur.

Optically pure starting materials for the chemistry described by Bach are readily accessible by standard stereoselective aldol reactions or by lipase-catalyzed kinetic resolution.[8e] Diastereoselective attack of nucleophiles on the generated carbocation occurs, in general, with no racemization.[8e] This option was fully exploited in the synthesis of natural products and by the pharmaceutical industry. Using the concepts developed by Bach, Chung et. al have developed a highly diastereoselective reaction to solve a synthetic problem connected to the development of a drug containing a 1,1,2-triarylalkane fragment, which was achieved by the addition of indole to a benzylic carbocation (Scheme 3).[14] The reaction was carried out on optically active chiral benzylic alcohol **3** obtained by asymmetric hydrogenation through a dynamic kinetic resolution. The alcohols were subjected to an intermolecular Friedel–Crafts reaction with tosyl-protected indole. BF_3 or neat CF_3COOH at room temperature gave the desired alkylated product **4** in a diastereoselectivity of up to 16:1. Interestingly, the major diastereoisomer obtained in the reaction was the *anti* product, in complete contrast to what was reported by Bach for similar reactions. In these reactions, the phenyl ring played the role of the small group. However, as the nucleophile is indole, arene–arene interactions between the incoming indole and the phenyl ring could be responsible for the observed selectivity. This hypothesis was also correlated to the scope of this chemistry.

Furthermore, Stadler and Bach have recently completed the total synthesis of (−)-podophyllotoxin by a diastereoselective addition of sesamol (**6c**) to the benzylic carbocation generated in situ with $FeCl_3$ (Scheme 3).[15] The reaction of **6a** with **5** proceeded smoothly under the reaction conditions developed by Bach ($HBF_4{\cdot}OEt_2$ in CH_2Cl_2), and gave good diastereoselectivity to give product **7a** (d.r. 85:15)—even though the analogous reactions of the substituted derivatives **6b** (X = Br), **6d** (X = OTf), and sesamol (**6c**, X = OH) failed. Interestingly, the various Lewis acids tested ($Bi(OTf)_3$, $AuCl_3$, and $FeCl_3$) catalyzed the reaction of sesamol in good diastereoselectivity, while no conversion was observed with **6b** and **6d**. Further studies led to the identification of $FeCl_3$ as the optimal Lewis acid,[16] and was able to form the product



Scheme 3. Diastereoselective Friedel–Crafts alkylation in the synthesis of biologically active products.

with high diastereoselectivity in nearly quantitative yield (d.r. 94:6).

In summary, acyclic stereocontrol can be realized with chiral carbocations by exploiting conformational and stereoelectronic parameters able to deliver sufficient bias for a reaction to proceed diastereoselectively. The generation of chiral carbocation appears to be quite facile, by the use of various Lewis acids in catalytic amounts. Alcohols or even olefins could be considered to be the precursors of carbocations, thereby diminishing functional group manipulations and operating under greener and more economical reaction conditions. In these reactions, a reversal of the common combination of strong nucleophile/weak electrophile, is realized. Such a pattern, in which a weak nucleophile attacks a strong electrophile, has received less attention in stereoselective synthesis. Carbocations generated by Brønsted or Lewis acids can be considered a new frontier for approaching stereoselective reactions. In the near future, the employment of chiral nucleophiles generated in situ under catalytic conditions, anionic binding principles, or chiral counterions will be explored in highly enantioselective and diastereoselective reactions with cationic precursors.

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