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The β-Silyl Effect on the Memory of Chirality in Friedel–Crafts Alkylation Using Chiral α-Aryl Alcohols

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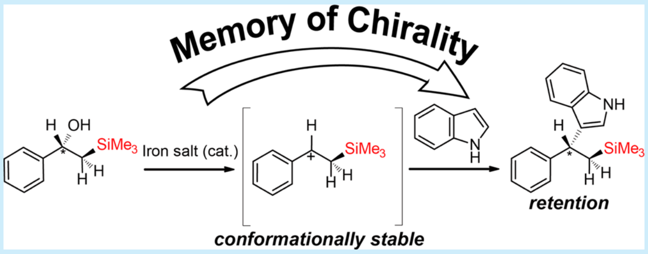
Ⓢ *Supporting Information*

ABSTRACT: Iron salt-catalyzed Friedel–Crafts alkylation of chiral α-aryl alcohols with a trimethylsilyl group was found to proceed with retention of the configuration of the hydroxyl group as a leaving group. The memory of chirality of this system stems from the β-silyl effect of the trimethylsilyl group on the carbocation intermediate.



Asymmetric synthesis based on the memory of chirality (MOC)[1] is quite useful in carbanion chemistry. MOC in carbocation chemistry[2] is rare and there is no general method to achieve it.

During the course of our studies on development of iron salt catalyzed reactions,[3] we were interested in Friedel–Crafts alkylation using α-aryl alcohols as alkylating agents.[4,5] Here, we report a significant effect of a silyl group at the β-position on the MOC in the iron salt catalyzed Friedel–Crafts alkylation of aromatic compounds (Figure 1).

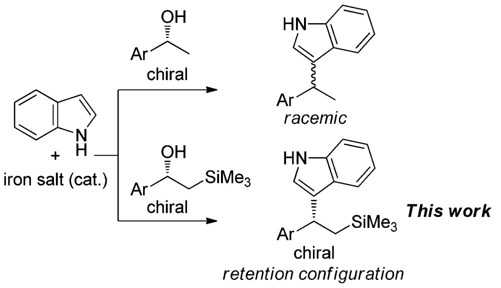


Figure 1. A silyl group effect on the MOC in the Friedel–Crafts type alkylation using chiral α-aryl alcohols as alkylating agents.

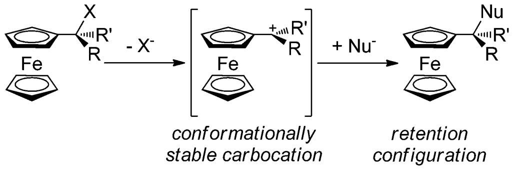


Figure 2. Retentive electrophilic substitution of α-substituted alkylferrocenes.

Electrophilic substitutions of chiral starting materials having a leaving group at the chiral carbon center give racemic products via a carbocation intermediate; however, the reaction of chiral ferrocene derivatives is a known exception (Figure 2). Ugi and co-workers reported the retentive electrophilic substitution of the α-substituted alkylferrocenes.[6] Another example is the electrochemical generation of the N-acyliminium ion and the in situ trap with a nucleophile (Figure 3).[7,8] In both cases, the conformational stability of carbocation intermediates is a crucial property to achieve the MOC.

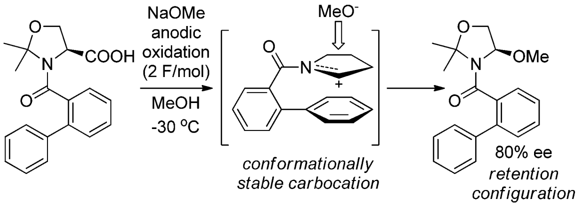


Figure 3. Retentive electrophilic substitution of the electrochemically generated N-acyliminium ion.

We initiated our study from the Friedel–Crafts alkylation of indole (**1**) with β-silyl alcohols **2–4** to optimize an acid catalyst (Table 1). Conventional Lewis acids such as $AlCl_3$ and $FeCl_3$ gave the corresponding alkylation products **5** in moderate yields (entries 1 and 2). Although sulfuric acid, which is a typical Brønsted acid, also catalyzed the reaction, the yield of **5**

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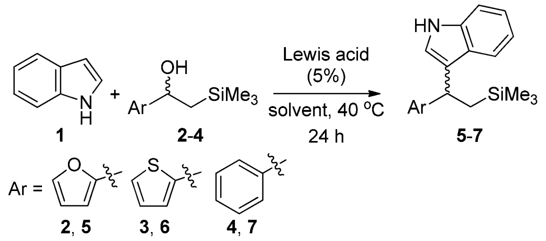
Table 1. Optimization of Reaction Conditions



entry	Ar	acid catalyst	solvent	yield (%)
1	2-furyl	$AlCl_3$	neat	45
2	2-furyl	$FeCl_3$	neat	49
3	2-furyl	H_2SO_4	neat	33
4	2-furyl	$Sc(OTf)_3$	neat	66
5	2-furyl	$Fe(BF_4)_2{\cdot}6H_2O$	neat	96
6	2-furyl	$Fe(ClO_4)_3{\cdot}nH_2O$	neat	49
7	2-furyl	$Fe(BF_4)_2{\cdot}6H_2O$	H_2O	2
8	2-furyl	$Fe(BF_4)_2{\cdot}6H_2O$	CH_3CN	23
9	2-thienyl	$Fe(ClO_4)_3{\cdot}nH_2O$	neat	69
10	2-thienyl	$Fe(BF_4)_2{\cdot}6H_2O$	neat	96
11	phenyl	$Fe(ClO_4)_3{\cdot}nH_2O$	neat	70
12	phenyl	$Fe(BF_4)_2{\cdot}6H_2O$	neat	57

was again moderate (entry 3). $Sc(OTf)_3$ was more effective (entry 4); however, the cationic iron salt $Fe(BF_4)_2{\cdot}6H_2O$[3] was found to be much more effective as a catalyst (entry 5). Further investigation of iron salts and addition of solvents did not improve the yields of **5** (entries 6–8). The choice of iron salts depends on the aryl substituents. With 2-furyl and 2-thienyl derivatives **2** and **3**, $Fe(BF_4)_2{\cdot}6H_2O$ was the best catalyst (entries 9 and 10). On the other hand, $Fe(ClO_4)_3{\cdot}nH_2O$ gave better results with the phenyl derivative of *β*-silyl alcohol **4** (entries 11 and 12).

Next, we investigated chiral *β*-silyl alcohols as alkylating agents to confirm the generation of a carbocation intermediate. The astonishing thing is that chiral alkylation product (+)-**6** (66% ee) was obtained when we subjected chiral *β*-silyl alcohol (+)-**3** (77% ee)[9] to the reaction (Figure 4). Even better chirality transfer was attained in the reaction of chiral *β*-silyl alcohol (*S*)-(+)-**4**:[10,11] the chiral product (*R*)-(+)-**7** (91% ee) was afforded in 67% yield when (*S*)-(+)-**4** (93% ee) was subjected to the reaction with indole in the presence of 5 mol % of $Fe(ClO_4)_3{\cdot}nH_2O$. Fortunately, (+)-**7** was obtained as a pure single crystal (>99% ee, see the Supporting Information for HPLC profiles) after recrystallization from hexane, and the absolute configuration of (+)-**7** was determined by X-ray single crystal structure analysis to be (*R*) (Figure 5).[12,13] These results indicate that the Friedel–Crafts alkylation of chiral *β*-silyl alcohols proceeded with retention of the configuration. The same level of MOC was observed with other conventional Lewis acids such as $AlCl_3$, $FeCl_3$, and $Sc(OTf)_3$, although the yields were lower than those using the best catalyst (see the Supporting Information for details). Thus, the choice of catalyst is not crucial for MOC in this system. We were also surprised that MOC was achieved with retention of the configuration. It is hard to propose a mechanism in which the Lewis acid catalyst activates the hydroxyl group and directs the nucleophile at the same time. Therefore, a reaction mechanism via the carbocation intermediate cannot be ruled out.

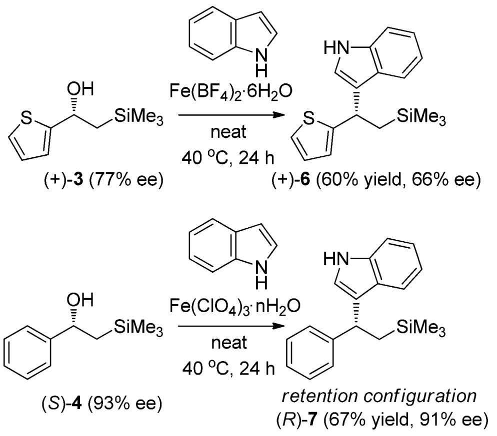


Figure 4. Friedel–Crafts type alkylation using chiral *β*-silyl alcohols (+)-**3** and (*S*)-(+)-**4** as alkylating agents.

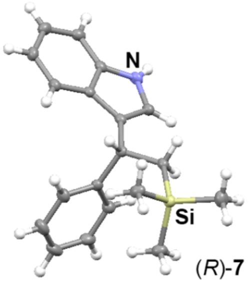


Figure 5. Crystal structure of the alkylation product (*R*)-**7**.

The effect of trimethylsilyl on both reactivity and MOC was significant (Figure 6). (*S*)-1-Phenylethanol ((*S*)-**8**) did not afford the corresponding alkylation product at all under the optimized reaction conditions (Table 1, entry 11). In contrast, (*S*)-1-(thien-2-yl)ethanol ((*S*)-**9**) gave alkylation product (+)-**10** in 60% yield; however, the alkylation product (+)-**10** thus obtained was almost a racemic mixture (3% ee). Therefore, Friedel–Crafts alkylation reactions must proceed via a carbocation intermediate. These results indicate that the trimethylsilyl group plays a crucial role in MOC.

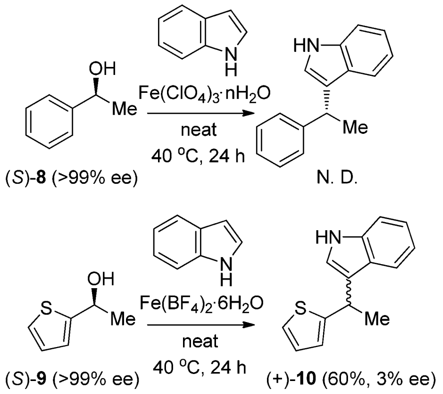


Figure 6. Friedel–Crafts type alkylation using chiral alcohols (*S*)-**8** and (*S*)-**9** as alkylating agents.

Bach and co-workers have reported the *syn*-selective Friedel–Crafts alkylation at the benzylic position of 2,3,3-trimethyl-1-phenylbutan-1-ol via a benzylic carbocation intermediate using a strong Lewis or a Brønsted acid.[5b] They have revealed that the substituent at the *β*-position plays a crucial role in the diastereoselectivity and the steric outcome of the reaction is determined by a conformational restriction in the benzylic carbocation intermediate. Several diastereoselective reactions via carbocation intermediates have also been reported.[14,15]

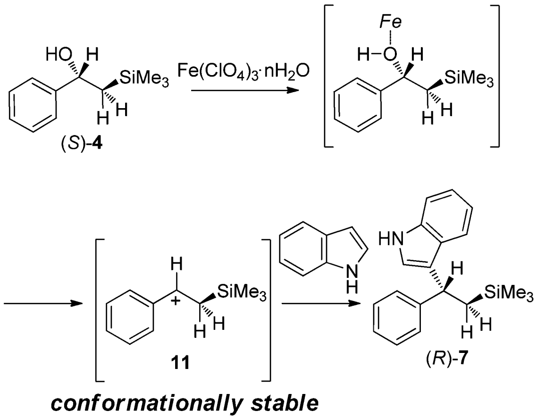


Figure 7. Proposed mechanism of the Friedel–Crafts type alkylation with retention configuration using the chiral β-silyl alcohol (*S*)-**4**.

On the basis of the pioneering works, we assume that the origin of the MOC stems from the carbocation intermediate which is conformationally stable (Figure 7). In the first step, a catalytic amount of iron salt generates conformationally stable carbocation intermediate **11** from chiral β-silyl alcohol (*S*)-**4**. The trimethylsilyl group occupies the opposite face of the leaving hydroxyl group in this carbocation intermediate **11**. In the second step, a nucleophile attacks the cationic carbon from the opposite face of the trimethylsilyl group and affords the alkylation product (*R*)-**7** with retention of configuration.

To support our mechanistic proposal, we investigated the conformational stability of the carbocation intermediate using density functional theory (DFT) calculations.[16] To estimate the possibility of conformational change of carbocation intermediate **11**, the relationship between the free energy and the conformation of the carbocation intermediate was calculated (Figure 8, solid line). We found that the dihedral angle between the plane of the carbocation and the C–Si σ-bond significantly affects the optimized energy of carbocation intermediate **11**.[17] There are two energy maximums at 0° and ±180° in which the carbon (C^3)–silicon (C–Si) bond is located in the same plane as the cationic carbon. Thus, it is hard to change the conformation of the intermediate because there are significant energy barriers for the bond rotation. The energy minimum was observed at ±97° where the C–Si σ-bond is almost perpendicular to the plane of the cationic carbon. For comparison, the methyl analogue of intermediate **12** was also calculated (Figure 8, dashed line). The energy minimum was observed at ±120° where one of the two C–H σ-bonds is perpendicular to the plane of the cationic carbon. In this case, the C–H σ-bond works as an electron donor toward the cationic carbon; however, its ability as an electron donor is much weaker than that of the C–Si σ-bond. This significant difference in the conformational energy can be explained by the hyperconjugation of the C–Si σ-bond to stabilize the carbocation intermediate **11**. Moreover, during the formation of the carbocation intermediate, the leaving hydroxyl group and the trimethylsilyl group are in the antiperiplanar conformation (see the Supporting Information for details). These results support our mechanistic proposal.

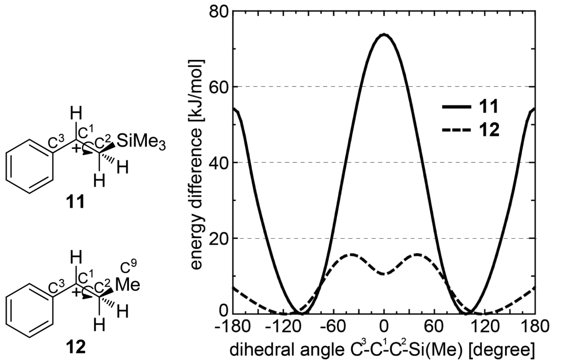


Figure 8. Relationship between energy difference and dihedral angle of the carbocation intermediates **11** and **12**.

In conclusion, we have found that a silyl group has a significant effect on the MOC in Friedel–Crafts alkylations using chiral α-aryl alcohols as alkylating agents. Although Lewis acids do not affect the MOC, the introduction of a silyl substituent at the β-position of the hydroxyl group is crucial. This is the first example of MOC based on the conformational stability of the carbocation intermediate supported by a flexible silyl substituent. Further transformations of the alkylation products including the scope of silyl groups and their application for the synthesis of functional molecules are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, results of DFT calculations, and spectroscopic data of compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01582.

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Notes

The authors declare no competing financial interest.

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(8) Although electrochemical generation of *N*-acyliminium ions was performed in both cases, the major product (39% ee) reported in ref 3a was obtained via the inversion mechanism and the major product (80% ee) reported in ref 3b was obtained via the retention mechanism.

(9) We believe that absolute configuration of (+)-**3** might be (*R*)-form by the specific rotation value, though it has not yet determined. See the Supporting Information for details.

(10) Determination of the absolute configuration of compound (*S*)-(+)-**4** was carried out by the modified Mosher's method. See the Supporting Information for detail.

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(12) Flack parameter shows $x = -0.01$, $u = 0.02$ and the absolute configuration of (+)-7 has been determined to be (*R*). Crystallographic data for compound (*R*)-7 can be obtained free of charge, on application to CCDC as supplementary publication number CCDC 1057845. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax: +44(1223)336033 or e-mail: data_request@ccdc.cam.ac.uk].

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