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Efficient alkylation of cyclic silyl enol ethers by diarylmethylium salts

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ABSTRACT

Isolated, bench-stable, non-symmetric diarylmethylium salts have been reacted with cyclic silyl enol ethers. Products have been easily obtained in a prevalent diastereoselectivity irrespective of salt counter-anion, aromatic ring substitution and silyl enol ether ring size. X-ray analyses on two purified diastereomers have been performed; the observed diastereoselectivity has been confirmed and rationalised using DFT calculations.

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The synthesis of complex molecules that contain the indole moiety is the focus of many organic syntheses, for the simple reason that indole is a scaffold commonly found in molecules of interest in a variety of applications.[1] 3-Substituted indoles, a building block for biologically active compounds and natural products, are generally regioselectively prepared via electrophilic alkylation because of the greater reactivity of the 3-position.[2]

We have recently reported the synthesis of non-symmetric diarylmethylium salts via the direct coupling of aryl (or heteroaryl) aldehydes and *N*-heteroarenes in the presence of stoichiometric amounts of a strong Brønsted acid. The acid was chosen in order to provide a non-nucleophilic anion. *o*-Benzenedisulfonimide was successfully employed in the initial 12 examples, using either 2-methylindole or 1,2-dimethylindole and electron-rich aromatic and heteroaromatic aldehydes; it was not possible to replace the indole with the pyrrole ring.[3] The synthetic methodology was then extended and a tetrafluoroboric acid diethyl ether complex was found to be an economically valid and complementary alternative in another 12 examples. 2-Methyl- or 1,2-dimethylindole and 2,5- or 2,4-dimethylpyrrole were successfully reacted with aromatic and heteroaromatic aldehydes.[4] In the light of the obtained results, we inferred that the presence of an azole moiety (whether isolated or benzene-fused) is needed to stabilize the positive charge and to allow carbocation isolation to occur; this was supported by X-ray analyses of two representative diarylcarbenium *o*-benzenedisulfonimide and tetrafluoroborate, which bare the indole and pyrrole core respectively.

Carbocations are well-known highly reactive key intermediates. They are usually prepared in situ and immediately reacted, but some exhibit high stability which allows for easy isolation and use. A huge number of symmetric and non-symmetric benzhydrylium tetrafluoroborates have been prepared and reacted by professor Herbert Mayr's research group within their systematic study of electrophilicity and nucleophilicity scales.[5] Meanwhile, a wide variety of mono- and dicarbenium hexafluorophosphates (or tetrafluoroborates) have been reported on by Takekuma's group.[6]

Their great stability and easy preparation procedure has led us to study the reactivity of our benzhydrylium salts which are bench-stable, ready to use and storable for long periods. It is worth noting that, recently, some of these salts have been used in a direct organocatalyzed asymmetric alkylation of aldehydes by prof. P.G. Cozzi;[7] new aryl 3-indolyl tetrafluoroborates have been reacted with a rich series of silylated enol ethers and ketene acetals[8a] and their Lewis acidity has been investigated by H. Mayr.[8b]

Cyclic silyl enol ethers were chosen as the reference nucleophiles with which to test the synthetic potential of our diarylmethylium salts as reagents thanks to their nucleophilicity values and the electrophilicity values of comparable indolylmethylium ions.[8] Indeed, these values follow Mayr's rule of thumb that electrophile–nucleophile combinations may take place at room temperature if the inequation $E + N > -5$ is satisfied.[9]

Silyl enol ethers nucleophiles have been widely explored in many fundamental reactions and there are a number of reports

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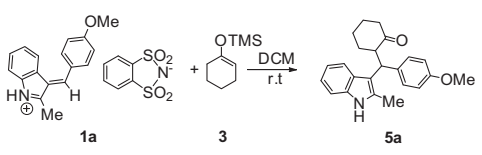
concerning the direct α-alkylation of both simple carbocyclic ketones or their enol ethers by isolated (or in situ generated) carbocations.[10] Furthermore, the stereoselectivity of silyl nucleophile reactions has been reviewed.[11] However, the number of reported examples of the synthesis of 2-(diarylmethyl- or arylheteroarylmethyl)cycloalkanones by means of diaryl- or arylheteroarylmethylium ions is limited. The electrophiles have been generated in situ or isolated and the results concerning observed diastereoselectivity are not always in agreement each other.

The direct alkylation of cyclic ketones has been carried out using diarylmethylium ions generated from symmetric benzhydryl alcohols in the presence of a Brønsted acid[12] or functionalized ionic liquids[13] under organocatalytic conditions with dr 2:1[12a] and 2:1,[13] respectively, for cyclohexanone derivatives. The same reaction has been reported using *N*-benzhydrylic sulfonamides through carbon–nitrogen bond cleavage (dr 59:41 for cyclohexanone)[14] and from α-phenyl-*nor*-gramine under basic catalysis (only one diastereomer for tetralone or 1-indanone, dr 96:4 for cyclopentanone and 50:50 for cyclohexanone).[15] In the second case, the high diastereoselectivity was explained as a result of the planar structure of both reagents and the coordination of a metal cation with the indole ring and the oxygen atom of the enolate ring, whilst the lack of diastereoselectivity for the cyclohexanone derivative was ascribed to isomerization through the enolic form of the ketone in the product.[15] The authors ascribed the diastereoselectivity to kinetic control. Most examples of alkylation with isolated benzhydrylium salts comes from Mayr's research: a high number of symmetric benzhydrylium tetrafluoroborates, both isolated and not, have been reacted with (trimethylsiloxy)cyclopentene and cyclohexene (along with several oxygenated rings).[16] When non-symmetric benzhydrylium salts were used in these case, no diastereoselectivity was observed.[8]

The first reaction we taken into consideration was between (2-methyl-3-indolyl)(4-methoxyphenyl)methylium *o*-benzenedisulfonimide (**1a**)[3] and 1-trimethylsilyloxycyclohexene (**3**) using a molar ratio of **1a:3** = 1:1.5 at rt and DCM as the solvent (Fig. 1).

The reaction was initially carried out in the presence of reactants on their own; a diastereomeric mixture was isolated in a low yield (Fig. 1, entry 1). We therefore decided to add 2,6-di-*t*-butyl-4-methylpyridine (DTBMP) to prevent acidic silyl enol ether hydrolysis; 1 equiv, with respect to salt **1**, was found to be the optimal amount (entries 2–3). An 82% yield was obtained when the reaction was run at a molar ratio of **1:3**:DTBMP = 1:1.5:1 at room temperature in DCM for 24 h. A reduction in reaction time was detrimental (entry 4). Furthermore, the product was always obtained in a virtually identical diastereomeric ratio (entries 1, 3–4), which was determined by GC and ^{1}H NMR analyses.

Encouraged by these results and by the dr value, reaction conditions were extended to different arylindolylmethylium *o*-benzenedisulfonimide **1** in order to investigate reaction scope. The role of the counter-anion and the ring size of the enol ether were also evaluated via reaction with some arylindolylmethylium tetrafluoroborates **2**[4] and 1-trimethylsilyloxycyclopentene (**4**), respectively (Fig. 2).



entry	molar ratio 1a : 3 : DTBMP	t (h)		Product 5a yield (%)	d.r.
1	1:1.5:-	24		24	75:25
2	1:1.5:0.5	24		50	nd
3	1:1.5:1	24		82	73:27
4	1:1.5:1	3		50	74:26

Figure 1. Alkylation of silyl enol ether **3** by salt **1a**.

Results are summarised in Figure 3. Aryl 2-methyl-3-indolylcarbenium *o*-benzenedisulfonimides **1a–c** gave modest to good yields of alkylation products **5a–c**. Products were isolated and purified using column chromatography, whilst the diastereomeric ratio was determined by GC analysis and ^{1}H NMR spectra. Although the diastereoselectivity was lower for **5b** than for **5a** and **5c**, it was, nevertheless, appreciable.

Heteroaryl indolylmethylium salt **1d** gave product **5d** in good yields and very good diastereoselectivity.

In order to evaluate the possible anion effect, selected tetrafluoroborates **2a–c** were reacted with **3**. Analogous results were obtained in terms of yield (products **5a, d–e**), although some differences in diastereoselectivity were noticed in **5a** and **5d**. The good diastereoselectivity observed in **5d**, starting from salt **1d**, unfortunately dropped off when we started from salt **2b**.

A steric effect was noticed when using salt **2d**; product **5f** was obtained in good yield and dr. In order to confirm this finding, salt **2a** was reacted with (3,4-dihydro-1-naphthyloxy)trimethylsilane under the same conditions. Product **7** was isolated, although in a modest yield and a sufficiently good dr (71:29). However, efforts to react salt **2d** with the same enol ether were unsuccessful: only traces of the expected adduct were detected by ^{1}H NMR spectra.

We then tested the effect of ring size by reacting **1d** and **2a–b,e** with enol ether **4**. Alkylation products **6a–c** were obtained in modest to high yields, whilst diastereoselectivity deteriorated. In the case of **6c**, both dr were lower than in **5d**. Furthermore we observed the opposite anion effect to that observed for **5a** and **5d**.

To further evaluate reaction scope, products **5g** and **6d** were prepared from symmetric salt **1e** in good and modest yields respectively.

It is worth noting that these reactions were carried out several times, occasionally in slightly modified conditions, in order to ascertain the observed diastereoselectivity and find a possible experimental explanation. In the reported reagent combinations, as well as in others that we decided to not describe here, small differences in terms of yields and diastereoselectivity were observed, although in a quite restricted range. Despite the observed diastereoselectivities generally not being very high, a clear general trend was confirmed irrespective of ring size. This is in contrast with results reported in the literature.[13] We feel that, in our reaction conditions, it was not possible to observe a clear anion or ring size effect, but some prevalence in diastereoselectivity was always observed.

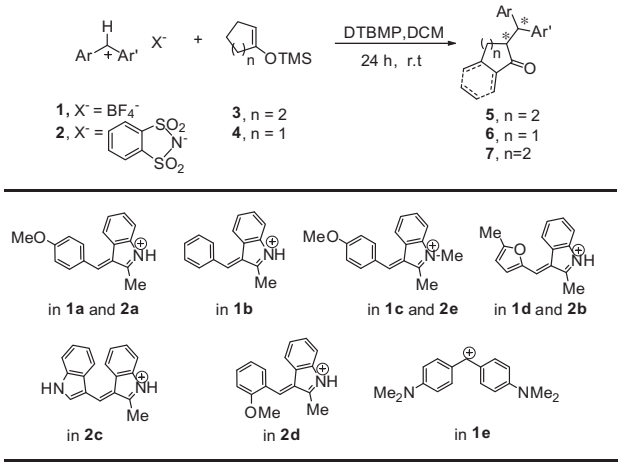


Figure 2. Alkylation of silyl enol ethers **3** and **4** with diarylmethylium salts **1** and **2**.

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