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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.

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 an 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 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 as 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 (Figure 1).
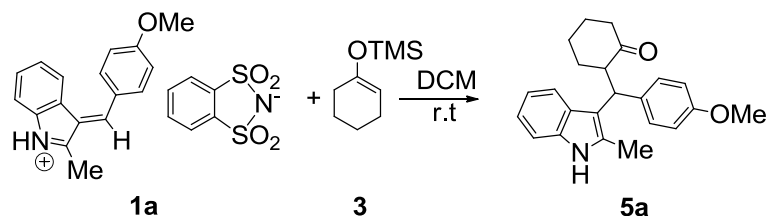

entry	molar ratio 1a : 3 : DTBMP	t (h)		Product 5a yield (%)	d.r.
1	1:1.5:-	24		24	75:25
2	1:1.5:0.5	24		50	nd
3	1:1.5:1	24		82	73:27
4	1:1.5:1	3		50	74:26

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

The reaction was initially carried out in the presence of reactants on their own; a diastereomeric mixture was isolated in a low yield (Figure 1, entry 1). We therefore decided to add 2,6-di-*t*-butyl-4-methylpyridine (DTBMP) to prevent acidic silyl enol ether hydrolysis; one equivalent, 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 hours. 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 the also evaluated via reaction with some arylindolylmethylium tetrafluoroborates **2**[4] and 1-trimethylsilyloxycyclopentene (**4**), respectively (Figure 2).
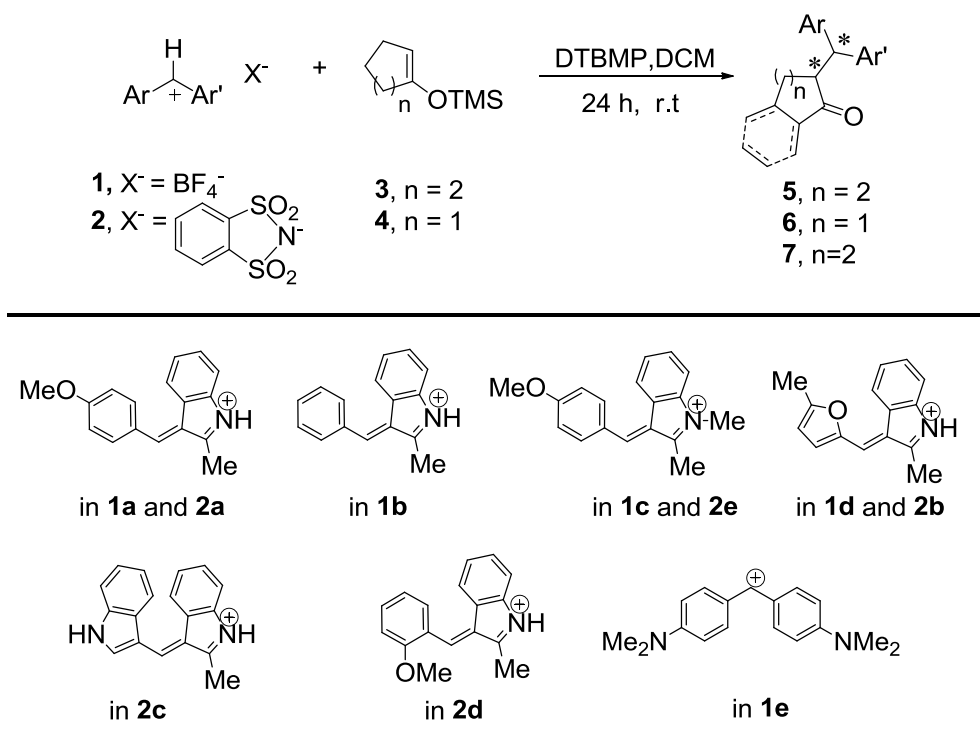
Figure 2: Alkylation of silyl enol ethers 3 and 4 with diarylmethylium salts 1 and 2.

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, while 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, while 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 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.
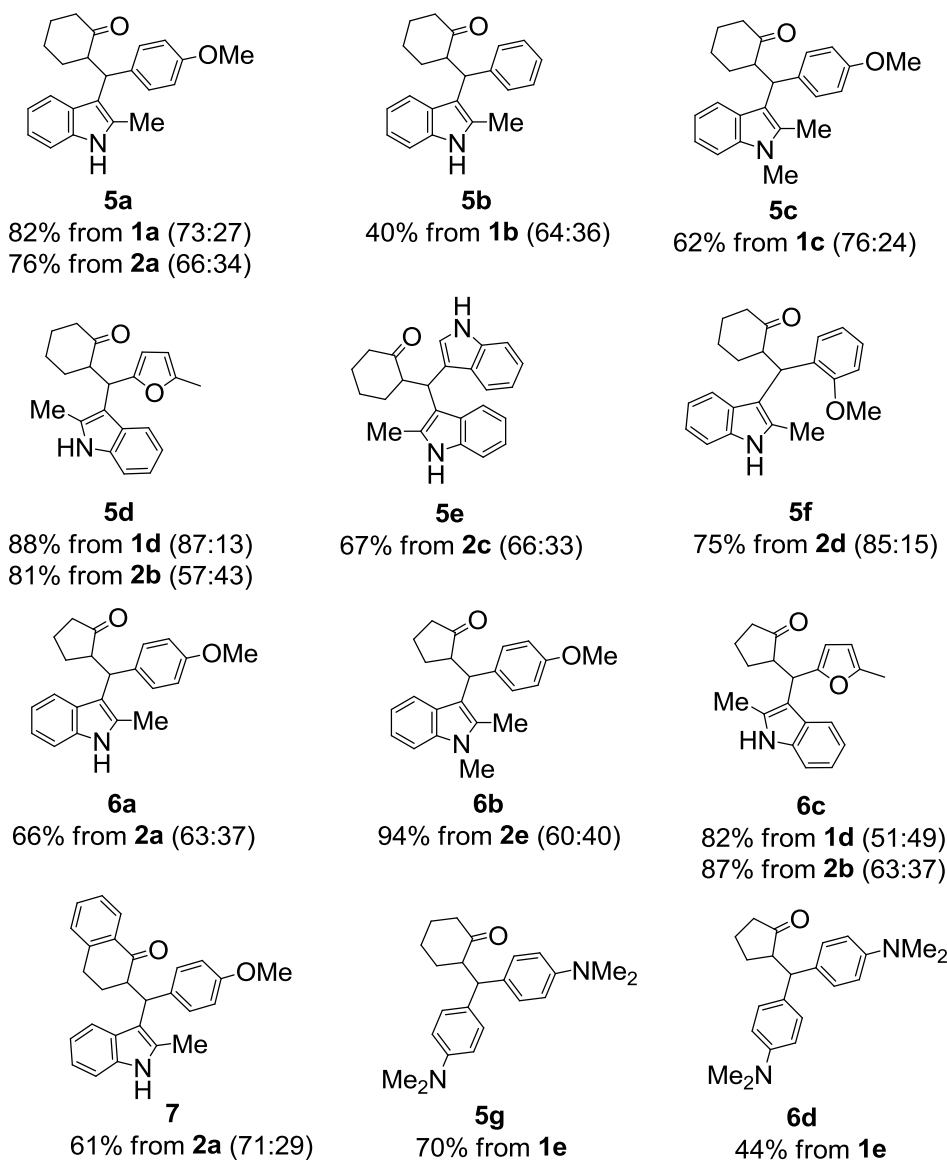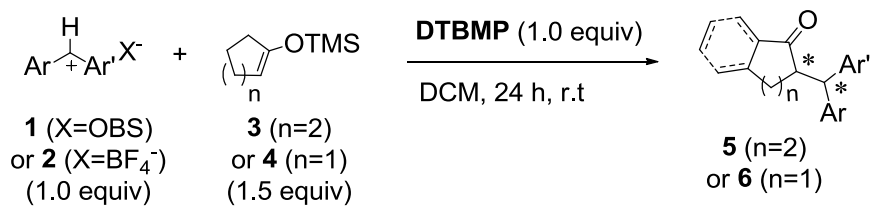
Figure 3. Variation of products **5a–g** and **6a–d.** The reported yields refer to chromatographically purified products. Reactions were performed on a 0.5 mmol scale without exclusion of air or moisture. Diastereomeric ratios (in parentheses) were determined by GC and ^{1}H NMR analyses. For **5c**, **5d** and **5f**, molar ratio was 1:4:1.

Diastereomers were generally purified as inseparable mixtures or only partially separated. It was, however, possible to isolate pure diastereomers of **5d** and **6c** and to assign the relative configurations to **5d** by X-ray diffraction. These products were isolated by column chromatography. The first eluted compound (**5d-A**) was the minor diastereomer, whilst the major one eluted as the

second product (**5d-B**). This order was the same for all adducts **5**. Curiously, the order of elution was the exact opposite for adducts **6**.

The molecular structures and atom labeling of compounds **5d-A** and **5d-B** are reported in Figure 4.
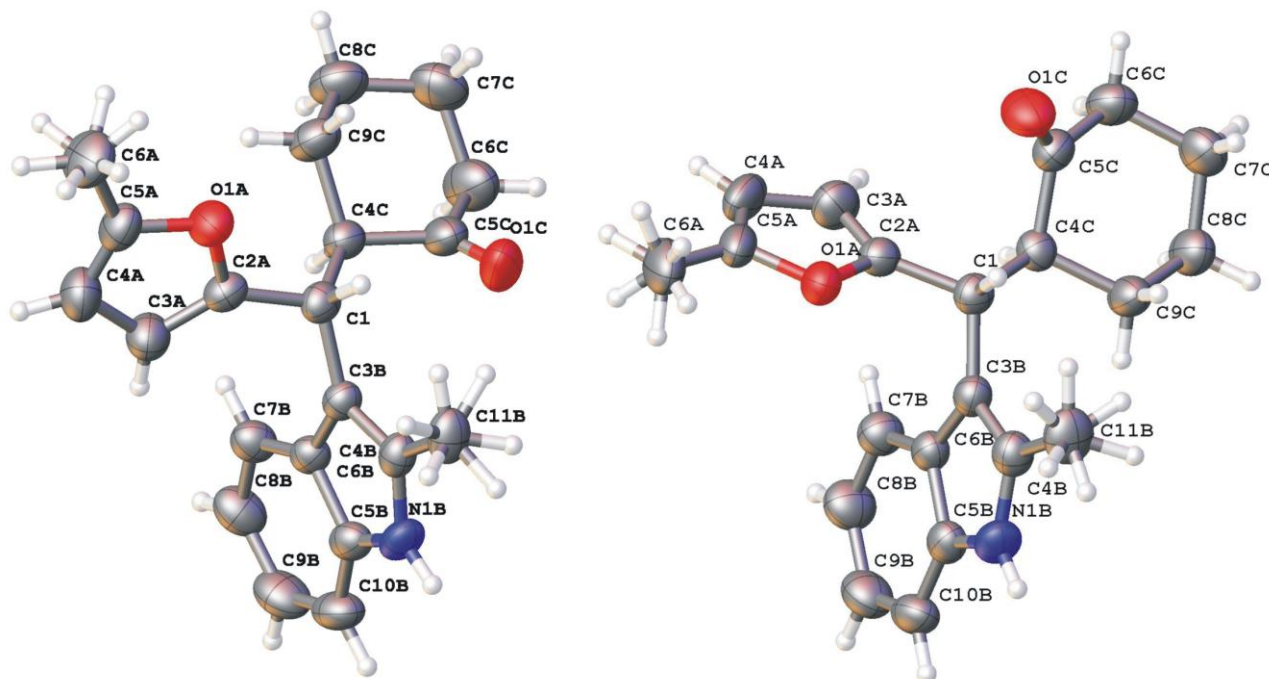

Figure 4: molecular structures and atom labeling of 5d-A (left) and 5d-B (right).

All CH_3 groups in both structures are disordered over two positions; they show rotation around the C4B-C11B and C5A-C6A bonds. The chiral carbon atoms are C1 and C4C. For both compounds, in the asymmetric unit there is only one diastereomer of compound **5d**, but the presence of the inversion centre in both space groups guarantees the presence of the respective enantiomers. As shown in figure 4, the **5d-A** compound is composed of the RR and SS diastereomers, while **5d-B** is composed of the RS and SR ones.

In order to offer an explanation for the partial diastereoselectivity in the formation of product **5d**, we also performed a DFT study of the first key step in the electrophilic addition of diarylmethylium to the silyl enol ether. Details and references for the theoretical method are reported in the Supplementary Material. Firstly, the global reaction free energies for the formation of the two diastereomers RR and SR, were calculated; the poorly exoergic values (see Table 1, ΔG) may well explain the unexceptional final yields. A computational study then focused on the rate determining

step of the reaction, *i.e.* the coupling between the silyl enol ether and diarylmethylium **2b** (the counterion BF_4^- was not included in the model) yielding the OTMS derivative of **5d** (hereafter "precursor" for short). The final product **5d** was expected to be formed quite easily from the hydrolysis of the relative precursor. We have identified 24 different transition structures (TSs): 12 conformations which yield the precursors of the RR diastereomer and 12 which yield the precursor of the SR diastereomer. Figure 5 shows two representative TSs; pictures of all TSs are reported in the Supplementary Material. This large number of TSs is due to the multitude of possible conformations generated by the new C-C bond (3); the position of the TMS group (2 conformations) and the cyclohexadienyl moiety *chair* conformations (2). The 24 mirror images of the cited TSs generate the SS and RS precursors.
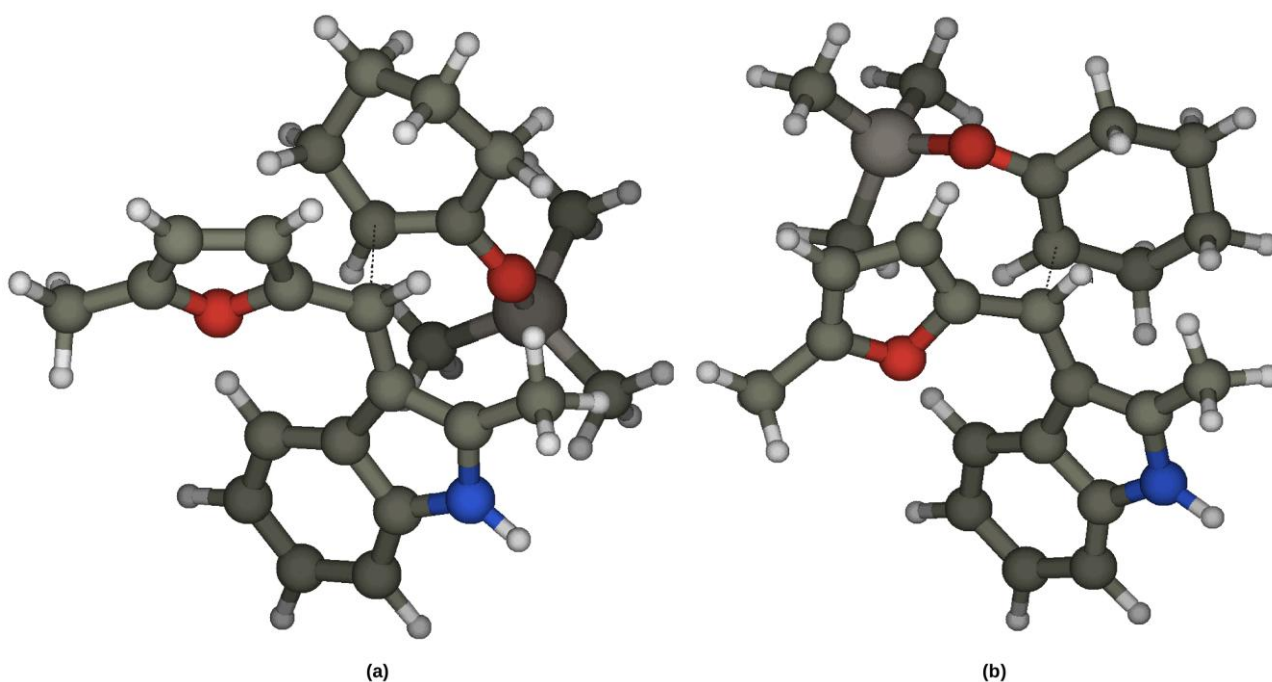
Figure 5: Transition Structures leading to RR (a) and SR (b) precursors of 5d.

The activation free energies ($\Delta G^\ddagger$) (see Table 6 in the Supplementary Material) span between 15.7 and 20.7 kcal mol^{-1}. Both groups of TSs present conformers with $\Delta G^\ddagger$ values of around 16 kcal mol^{-1}, meaning that it is not possible, at first glance, to deduce which diastereomer will be preferred.

However, calculating the reaction rate constants using the Eyring equation and all the activation free energies enables us to estimate the relative yields of the two diastereomers (see Table 1).

	ΔG	k	Y
RR/SS	-4.3	16	23.8
SR/RS	-4.9	52	76.2

Table 1: calculated free reaction energies (ΔG, kcal mol^{-1}), rate constants (k, M^{-1} s^{-1}) and relative diastereomeric yields (Y, %).

We observed that the rate constants are slightly different. This led us to estimate relative yields (24 % for the RR/SS couple and 76 % for the SR/RS couple) which were found to be in good agreement with the experimental findings (13:87 from **1d** and 43:57 from **2b**). We would like to stress that this small difference is partially due to a statistical factor; there are 3 TSs leading to RR with $\Delta G^{\ddagger}$ values of between 15.7 and 16.4 kcal mol^{-1}, but only two TSs that lead to SS are found within this range. All other $\Delta G^{\ddagger}$ are above 17 kcal mol^{-1}. A close inspection of the molecular structures of the TSs (see Figure 2 in the Supplementary Material) does not give any clear explanation as to the differences in energy barriers (a part from the lower barriers for the *antiperiplanar* conformations, "conf. 2" in the Supplementary Material). Factors that are known to affect stereochemistry are either absent (chelation) or, like the presence of the TMS group, do not seem to be determinant for diastereoselectivity. Fleming *et al.*[11a] have already pointed out that the silyl group, although quite large, is attached to the organic framework by a relatively long bond and therefore does not always hinder reactions in its neighbourhood as one might expect. This makes any prediction on other systems hard to perform. However, this is coherent with the limited diastereoselectivity, and with some disagreements in (the present and) other experimental works.

In summary, this work is an initial study into the synthetic potential of new highly stable diarylmethylium salts. Reactivity with the silyl enol ethers of cyclic ketones has been explored. A

library of new products has been obtained in a prevalent diastereoselectivity irrespective of enol ether ring size and cation and anion structures. X-ray analyses on purified diastereomers and DFT calculations have been performed on the same sample adduct.

Supplementary Material

Experimental procedures, compound characterisation (^{1}H and ^{13}C-NMR, IR, MS and elemental analyses for new compounds **1e**, **2d**, **5a–f**, **6a–c** and **7**; ^{1}H and ^{13}C-NMR, IR, MS for known compounds **5g** and **6d**),[12a] CIF files for compounds **5d-A** and **5d-B**, details on the computational method, calculated energies, transition states pictures, and Cartesian coordinates for the formation of compound **5d** associated with this article can be found, in the online version, at http://.....

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