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# Leveraging long-lived arenium ions in superacid for *meta*-selective methylation

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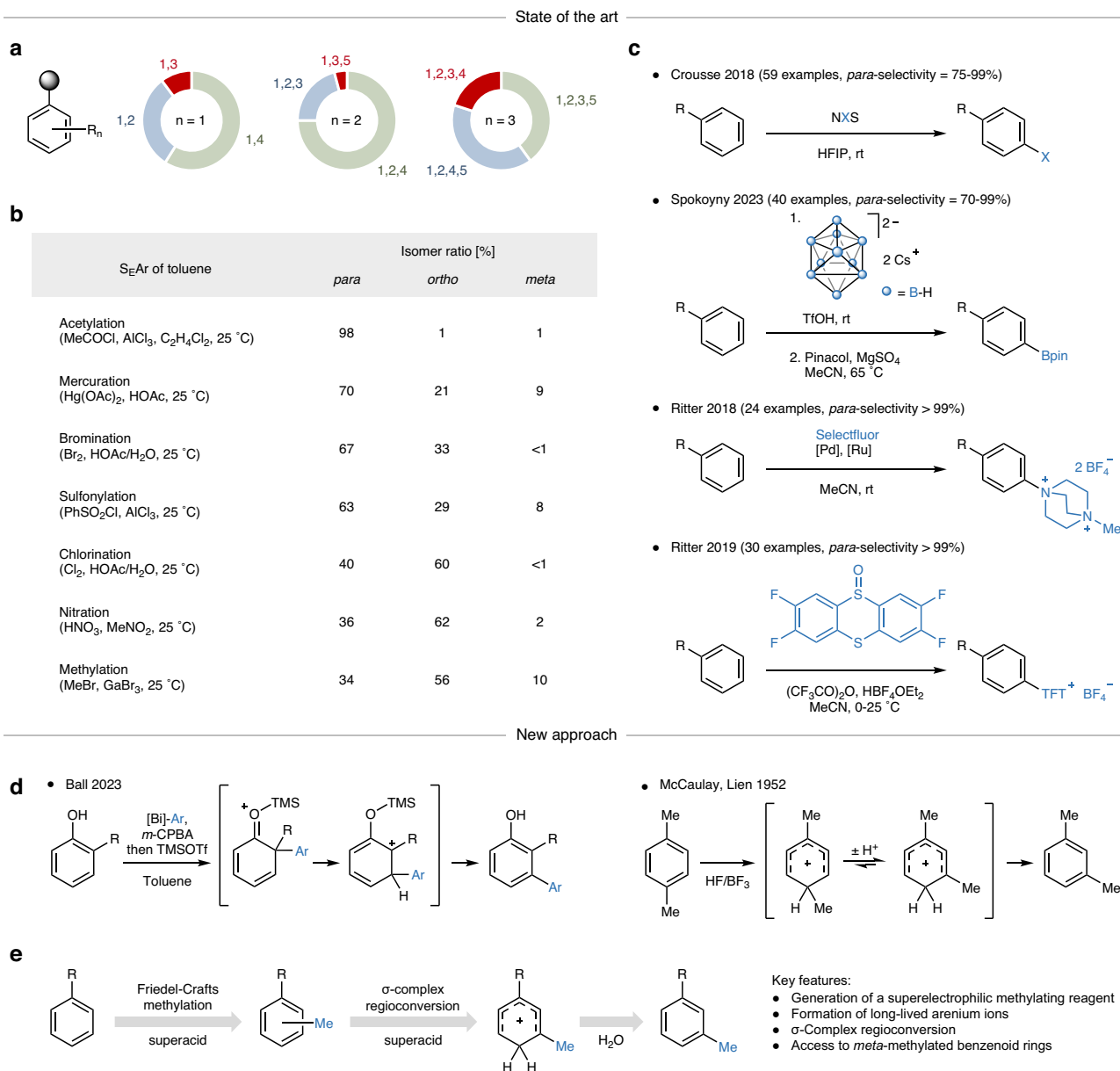
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Electrophilic aromatic substitution is one of the most mechanistically studied reactions in organic chemistry. However, precluded by innate substituent effects, the access to certain substitution patterns remains elusive. While selective C–H alkylation of biorelevant molecules is eagerly awaited, especially for the insertion of a methyl group whose magic effect can boost lead molecules potency, one of the most obvious strategies would rely on electrophilic aromatic substitution. Yet, the historical Friedel–Crafts methylation remains to date poorly selective and limited to activated simple aromatics. Here, we report the development of a selective electrophilic methylation enabling the direct access to highly desirable 1,3-disubstituted arenes. This study demonstrates that this reaction is driven by the generation of long-lived arenium intermediates generated by protonation in superacid and can be applied to a large variety of functionalized (hetero)aromatics going from standard building blocks to active pharmaceutical ingredients.

Transformation of aromatic rings is the cornerstone of many large-scale industrial processes with an evident relevance in drug discovery which relies extensively on aromatic scaffolds<sup>1</sup>. Analysis of benzenoid rings in small molecule active pharmaceutical ingredients (APIs) reveals however a very heterogeneous distribution of substitution patterns (Fig. 1a)<sup>2</sup>. New synthetic strategies that target under-represented substitution patterns are therefore eagerly awaited. One of the oldest and most straightforward strategy to substitute an aromatic C–H bond with a functional group is electrophilic aromatic substitution (S<sub>E</sub>Ar)<sup>3</sup>. However, the level of site-selectivity of a S<sub>E</sub>Ar for a given arene differs widely depending on the nature of the electrophile (Fig. 1b)<sup>4</sup>. More specifically, it is accepted that the level of *para* vs. *ortho* selectivity is mostly dominated by steric effects while the level of *para* vs. *meta* selectivity depends on the position of the transition state on the reaction coordinate for the formation of the Wheland intermediates<sup>5–7</sup>. To face this discrepancy, one strategy relies on S<sub>E</sub>Ar methods that allows selective installation of a functional group which can serve as a synthetic handle for further functionalization (e.g., halogenation<sup>8</sup>, borylation<sup>9</sup>, TEDAylation<sup>10</sup> or thianthrenation<sup>11</sup> (Fig. 1c)). However, while these approaches improve

the level of *para*-selectivity, the selective access to intrinsically-disfavored positions still remains a highly challenging task<sup>12</sup>. The *meta*-selective arylation of phenols via the regioconversion of an *ortho* σ-complex to the S<sub>E</sub>Ar-inconsistent *meta* σ-complex through 1,2-aryl migration was recently reported (Fig. 1d, left)<sup>13</sup>. Although this method is necessarily limited to the functionalization of *ortho*-alkylated phenols, it demonstrates that controlling rearrangement of cyclohexadienyl cation intermediates can be synthetically relevant. Such rearrangement is reminiscent of uncontrolled methyl shifts which are known to occur under Friedel–Crafts conditions on toluene derivatives<sup>14–16</sup>. Referred as Baddeley isomerization<sup>17</sup> or Friedel–Crafts isomerization<sup>14</sup>, this reaction has been explored as a piece of exoticism<sup>18</sup> but has never been exploited for the regioconvergent methylation of aromatics. Long-lived cyclohexadienyl cations (σ-complexes) can be generated by protonation or alkylation of arenes in weakly-nucleophilic superacid media<sup>19–21</sup>. In an insightful report, McCaulay and Lien have demonstrated that complete isomerization of *para*-xylene to *meta*-xylene can be achieved when excess of BF<sub>3</sub> Lewis acid is used in combination with HF (Fig. 1d, right)<sup>22</sup>. Here, the high concentration of H[BF<sub>4</sub>] superacid allows the

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**Fig. 1 | Toward a new approach for the *meta*-selective Friedel–Crafts methylation.** **a** Distribution of di-, tri- and tetra-substituted benzenoid substitution patterns in small molecule active pharmaceutical ingredients; 1,2-, 1,4-, and 1,2,4-substituted rings dominate this chemical space<sup>2</sup>. **b** Comparison of the regioisomeric distribution of different electrophilic aromatic substitutions of toluene reveals a large discrepancy on regioselectivity depending on the nature of the electrophile<sup>4</sup>. **c** Representative examples of the late efforts for the development of *para*-selective

S<sub>E</sub>Ar for the introduction of a synthetic handle. **d** Conceptual backgrounds: regioversion of  $\sigma$ -complexes as an alternative approach toward S<sub>E</sub>Ar-inconsistent benzenoid ring diversification. **e** Reaction design: our strategy for *meta*-methylation relies on consecutive Friedel–Crafts type alkylation with a superelectrophilic methylating reagent followed by  $\sigma$ -complex regioconversion through the generation of long-lived arenium ions in superacid.

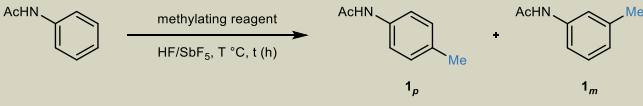
full protonation of the arene thereby shifting the equilibrium to the more stable *meta*-xylene-derived  $\sigma$ -complex. Considering the relevancy to selectively install a methyl group on substituted arenes<sup>23,24</sup> and the fact that the Friedel–Crafts methylation<sup>25</sup> is arguably one of the least selective S<sub>E</sub>Ar reactions<sup>26,27</sup>, we designed a superacid-mediated *meta*-selective electrophilic methylation of arenes based on these conceptual backgrounds.

In this work, we show that under superacid weakly-nucleophilic conditions, after Friedel–Crafts methylation, the resulting product can successively react with superacidic protons to trigger isomerization in favor of the most stable *meta*- $\sigma$ -complexes, thus furnishing *meta*-methylated products after aqueous work-up (Fig. 1e).

## Results and discussion

### Reaction development

To test our hypothesis, we decided to start our investigations by submitting acetanilide as a model substrate to HF/SbF<sub>5</sub> superacid ( $H_0 \approx -23$ )<sup>28</sup> (Table 1). Using a stoichiometric amount of methyl triflate as alkylating reagent, we observed the formation of a *meta/para* regioisomers mixture (**1<sub>m</sub>/1<sub>p</sub>** = 57/43) of the expected methylated acetanilide **1** in 61% yield after 2 h at  $-40$  °C (Table 1, entry 1). Gratifyingly, raising the temperature favored the selective formation of the targeted *meta* product **1<sub>m</sub>** and only traces of **1<sub>p</sub>** was observed after 2 h at 0 °C (Table 1, entries 2 and 3). This is in striking contrast to other S<sub>E</sub>Ar reactions of the same substrate in similar conditions which favor *para*-functionalization<sup>29–33</sup>. Screening of a large selection of

**Table 1 | Summary of the reagents and conditions tested for the superacid-mediated Friedel–Crafts methylation of acetanilide**


Entry	Methylating reagent	T (°C)	t (h)	Yield (%) <sup>a</sup>	Isomer ratio (%) <sup>b</sup>	
					para	meta
1	MeOTf (1 equiv.)	-40	2	61	43	57
2	MeOTf (1 equiv.)	-20	2	79	25	75
3	MeOTf (1 equiv.)	0	2	83	<5	>95
4	Me <sub>3</sub> PO <sub>4</sub> (0.33 equiv.)	0	2	81	<5	>95
5	Me <sub>2</sub> SO <sub>4</sub> (1 equiv.)	0	2	90	<5	>95

Key experiments for the optimization of the title reaction (full description of methylating reagents and conditions screening in SI). Reactions performed in an equivolumetric mixture of HF/SbF<sub>5</sub>.  
<sup>a</sup>Yield of **1** determined by <sup>1</sup>H NMR analysis using *p*-anisaldehyde as internal standard.

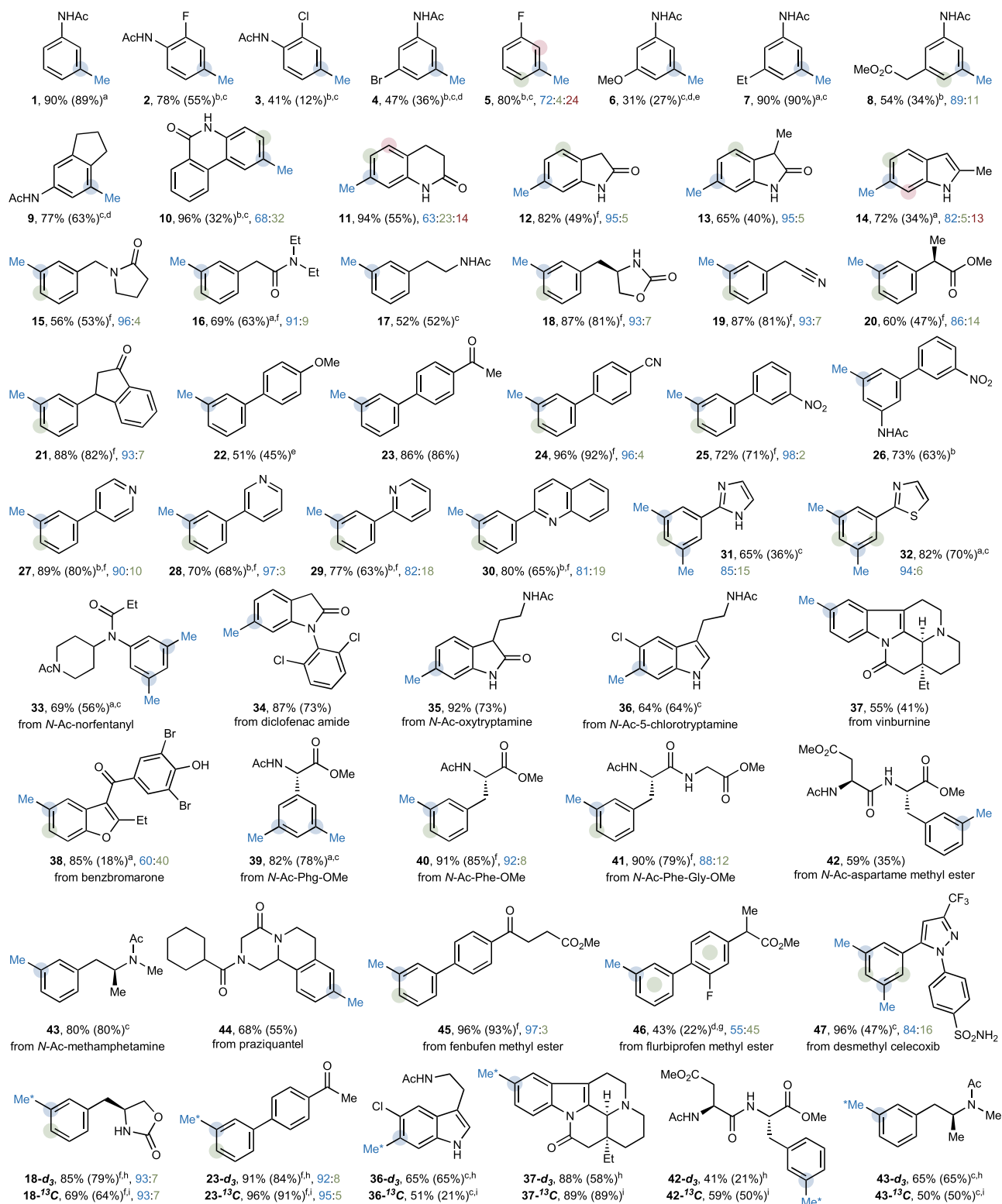
<sup>b</sup>Determined by <sup>1</sup>H NMR analysis of crude product.

methylating reagents (full description in SI) eventually allowed us to identify trimethyl phosphate and dimethyl sulfate as convenient electrophilic methyl sources under these conditions, also affording **1<sub>m</sub>** in very good yield (Table 1, entries 4 and 5).

### Scope of application

With these optimized conditions in hand, we next explored the scope of application of this transformation (Fig. 2). 2-Haloacetanilides were exclusively methylated at position 4 (**2**, **3**) while 3-bromoacetanilide afforded the 1,3,5-trisubstituted derivative **4** albeit in moderate yields due to the deactivating nature of the halogen atoms. S<sub>E</sub>Ar reactions of haloacetanilides under similar conditions usually favor *para*- or *ortho*-selectivity with respect to the halo-substituent<sup>29–33</sup>. In comparison, the reaction of fluorobenzene under the same conditions afforded mostly *meta*-fluorotoluene (**5**). This result is noteworthy as superelectrophile-promoted methylation of the same substrate was recently reported to give a 38:11:51 mixture of *ortho*-, *meta*- and *para*-fluorotoluenes<sup>25</sup>. 3-Methoxy- and 3-alkylacetanilides were converted into their *meta*-methylated analogues **6–9**. The low yield obtained for the methoxy derivative (**6**) can be explained by the protonation of the alkoxy substituent under these conditions which considerably lowers the nucleophilicity of the protonated substrate in equilibrium with non-protonated 3-methoxyacetanilide. The methylation of phenanthridinone afforded compound **10** in very high yield although the regioselectivity of the reaction was significantly lower in this case probably due to the dissonant directing effect of the amide and aryl substituents. Methylation of dihydroquinolinone and indolinones favored the less hindered *meta*-position to the amide moiety (products **11–13**). The non-innate site selectivity of this transformation is even more striking starting from the 2-methylindole. While indoles are known to be excellent nucleophiles at C3 position, the methylation occurred exclusively on the benzene ring under these conditions affording mostly the C6-methyl derivative **14**. This unusual regioselectivity can be attributed to the formation of an iminium ion after protonation of the pyrrole ring in superacid. Next, we probed the compatibility of the transformation with common functional groups installed on the side chain of alkylbenzene derivatives. The reaction proceeded equally well with substrates bearing amide (**15–17**), cyclic carbamate (**18**), nitrile (**19**), ester (**20**) or ketone (**21**) functionalities with good to excellent *meta*-selectivity. Noteworthy, chiral products **18** and **20** were obtained from their enantiopure precursors with no sign of racemization. The reaction of 4-methoxybiphenyl afforded the *meta*-methylated compound **22** with exclusive functionalization of the phenyl ring, the electron-richer anisyl moiety being most likely protonated under these conditions and thus less reactive toward S<sub>E</sub>Ar. Similarly,

biphenyls bearing an electron-withdrawing group reacted selectively at *meta* position of the less deactivated benzene ring as exemplified with products **23–26**. In comparison, acetophenone was fully recovered when subjected to optimized methylation conditions. Phenylpyridines could be efficiently methylated on the phenyl moiety despite the deactivating nature of the pyridyl group (most likely in equilibrium with its protonated form under the reaction conditions) with good to excellent *meta*-selectivity (**27–30**). Intermolecular S<sub>E</sub>Ar on phenylpyridines are very scarce in the literature and rare examples of acid-promoted nitration show the preferential functionalization of the *para* position with low level of selectivity (*p/m* = 1.2–1.4 for the nitration of 2- and 4-phenylpyridine)<sup>34,35</sup>. On the other hand, the strongly deactivated 4-phenylpyrimidine did not react, even at room temperature on prolonged reaction time. An important feature is that under these conditions, the electron-richer methylated products react slower than the parent arenes—thereby limiting the formation of overalkylated byproducts—as they must be easily protonated to arenium ions. The dimethylation could not be avoided only with 2-phenylimidazole and 2-phenylthiazole (even with a lower amount of methylating reagent) but the *meta*-dimethylated products **31** and **32** could be isolated in good yields. In these cases, protonation of the azole moiety presumably disfavors the arenium ion formation by protonation after the first methylation allowing further alkylation. We next focused on the late-stage methylation of substrates derived from natural or synthetic drug-like molecules<sup>36</sup>. Satisfyingly, the aromatic amides derived from norfentanyl (**33**), diclofenac (**34**) and tryptamine (**35**) were selectively methylated in high yields under optimized conditions. *N*-Ac-5-chlorotryptamine, precursor of serotonin-like molecules, and the natural alkaloid vinburnine reacted both selectively on the benzene ring of their indole subunit in reasonable yields (**36**, **37**). The reaction was also found very efficient with the benzofuran-derived benzbromarone (**38**) although the C5/C6 selectivity was somewhat lower in this case. The reaction was also amenable to the methylation of aromatic amino acids as exemplified with phenylglycine- and phenylalanine-derived product **39** and **40**, both obtained enantiomerically pure. The preferential dimethylation observed for compound **39** might be explained by the protonation of both acetamide and ester functions which might hamper aromatic protonation by repulsive effect, thereby increasing its propensity to overreact with the alkylating reagent. Similarly, phenylalanine-derived dipeptides were selectively methylated (**41**, **42**). The superacid-mediated methylation was also found very efficient on phenethylamine derivatives with very high level of selectivity as exemplified with the formation of products **43** and **44**. Derivatives of the nonsteroidal anti-inflammatory drugs fenbufen (**45**) and flurbiprofen (**46**) were methylated with moderate to excellent efficiency on the



**Fig. 2 | Scope of application of the superacid-mediated Friedel-Crafts methylation.** Overall yield and regioselectivity determined by NMR or HPLC analysis of the crude product (isolated yield of pure major regioisomer in parenthesis). Reaction conditions: arene (1 equiv.), Me<sub>2</sub>SO<sub>4</sub> (1 equiv.), HF/SbF<sub>5</sub> (v/v = 1/1), 0 °C, 4 h. <sup>a</sup> After 2 h. <sup>b</sup> Using Me<sub>3</sub>PO<sub>4</sub> (0.37 equiv.). <sup>c</sup> At room temperature. <sup>d</sup> After 16 h. <sup>e</sup>

Using Me<sub>3</sub>PO<sub>4</sub> (1 equiv.). <sup>f</sup> Isolated as mixture of regioisomers (calculated yield of major regioisomer in parenthesis). <sup>g</sup> Yield of major regioisomer only; estimated by HPLC analysis of the crude product (isolated yield in parenthesis). <sup>h</sup> Using (CD<sub>3</sub>)<sub>2</sub>SO<sub>4</sub> (1 equiv.). <sup>i</sup> Using (CD<sub>3</sub>)<sub>2</sub>SO<sub>4</sub> (1 equiv.).

less-substituted phenyl ring albeit with modest selectivity in the case of **46**. Finally, as observed for products **31** and **32**, desmethyl celecoxib underwent dimethylation under the optimized conditions to afford a *meta*-dimethylated analogue of celecoxib **47**.

Importantly, this method is also efficient to install isotopically-labeled methyl groups owing to the ready availability of dimethyl sulfate isotopologues. Since 2017 and the first FDA approval of a CD<sub>3</sub>-containing drug (deutetrabenazine)<sup>37</sup>, the development of new methods to introduce a trideuteromethyl group has received a considerable attention<sup>38,39</sup>. By using either (CD<sub>3</sub>)<sub>2</sub>SO<sub>4</sub> or (<sup>13</sup>CH<sub>3</sub>)<sub>2</sub>SO<sub>4</sub> under the optimized conditions, six selected representative molecules were efficiently methylated with consistent degree of selectivity to afford the corresponding isotopically-labeled products adorned with a CD<sub>3</sub> or a <sup>13</sup>CH<sub>3</sub> group (Fig. 2, bottom). Noteworthy, no sign of hydrogen isotope exchange was detected from the deuterated products.

### Nature of the reactive methylating reagents

The original Friedel–Crafts alkylation relies on the polarization of an alkyl halide by complexation of a Lewis acid such as AlCl<sub>3</sub> to generate an alkylating species whose carbocationic character depends on the stabilizing effect of its substituents. Formation of free CH<sub>3</sub><sup>+</sup> is very unlikely and the Friedel–Crafts methylation with MeCl has been suggested to proceed via the formation of a dimethylchloronium cation<sup>40–43</sup>. On the other hand, dimethyl sulfate and trimethylphosphate are convenient reagents for heteroatom methylation under neutral or basic conditions but their use as Friedel–Crafts reagents in acidic conditions has never been reported. Therefore, the behavior of dimethyl sulfate and trimethylphosphate in HF/SbF<sub>5</sub> solution was explored by low-temperature NMR spectroscopy to gain some information on the nature of the reactive species in superacid (Table 2, see SI for full analysis). The clean <sup>1</sup>H NMR spectrum obtained at –50 °C from dimethyl sulfate displays a singlet slightly shielded to 3.11 ppm (compared with a singlet at 3.98 ppm for Me<sub>2</sub>SO<sub>4</sub> in acetone-*d*<sub>6</sub>). This can be attributed to O-protonation of dimethyl sulfate although no proton on oxygen could be directly observed due to fast exchange as previously suggested<sup>44</sup>. Olah et al. reported a δ <sup>1</sup>H of 4.85 ppm in the FSO<sub>3</sub>H/SbF<sub>5</sub>/SO<sub>2</sub>ClF superacid system<sup>44</sup>. The difference of chemical shift with our value might be explained by solvent effect which strongly influences <sup>1</sup>H NMR analysis. The <sup>13</sup>C NMR spectrum shows a single signal at 66.4 ppm deshielded by 7 ppm compared to that of dimethyl sulfate in acetone-*d*<sub>6</sub> accounting for the strong electron-withdrawing effect induced on the methyl group. Importantly, no sign of the MeF·SbF<sub>5</sub> complex<sup>45</sup> was detected by <sup>1</sup>H, <sup>13</sup>C or <sup>19</sup>F NMR analysis precluding its role as an active species in this transformation<sup>46</sup>. No major changes in the <sup>1</sup>H and <sup>13</sup>C NMR spectra were observed at 0 °C suggesting that the reactive species in the reaction conditions is a protonated form of dimethyl sulfate, although exact structural assignment remains elusive on this sole basis (see below for the proposition from DFT calculations). Similarly, <sup>1</sup>H NMR spectrum of a solution of trimethyl phosphate in HF/SbF<sub>5</sub> at –50 °C shows a slight shielding of the doublet corresponding to the three methyl groups while the <sup>13</sup>C NMR signal is deshielded by 3.3 ppm compared to the signal of the parent molecule in acetone-*d*<sub>6</sub>. Moreover, the <sup>31</sup>P NMR spectrum displays a signal at 0.81 ppm slightly shielded compared to the signal observed in acetone-*d*<sub>6</sub> (2.30 ppm). All these data are in agreement with a protonation on the phosphoryl oxygen atom (also confirmed by the computed protonation energies and δ <sup>13</sup>C, see below) although fast exchange with surrounding excess acid prevents its direct observation by <sup>1</sup>H NMR analysis<sup>47</sup>. <sup>1</sup>H, <sup>13</sup>C and <sup>31</sup>P NMR analysis of this solution at 0 °C reveals the presence of the same species but accompanied with several other organophosphorus compounds which we could not precisely identified. The presence of three sets of signals centered at 0.9, –5.2 and –11.6 ppm in the <sup>31</sup>P NMR spectrum could however indicate the formation of polyphosphate derivatives<sup>48</sup> over time which might also act as methylating reagents. The case of

methyl triflate is slightly more complicated. In superacid, we observed the formation of three species amongst which we could readily identify TfOH (δ <sup>13</sup>C: 116.9 ppm, q, *J* = 319.2 Hz/δ <sup>19</sup>F: –76.2 ppm; see SI), most likely under its protonated form CF<sub>3</sub>SO<sub>3</sub>H<sub>2</sub><sup>49</sup>. The remaining two set of signals observed in the <sup>1</sup>H, <sup>13</sup>C and <sup>19</sup>F spectra are very similar and could be attributed to a protonated form of TfOME and to a dimethylated oxonium salt arising from the disproportionation of TfOME in superacid (along with TfOH). Both species display a singlet around 3.5 ppm in the <sup>1</sup>H NMR spectrum, slightly shielded compared to that of TfOME in CD<sub>2</sub>Cl<sub>2</sub>. The <sup>13</sup>C NMR spectrum consists of two deshielded singlets around 71 ppm, both accounting for methyl groups, and two quartets around 117 ppm (*J* = 321 and 324 Hz) which fit very well with the <sup>13</sup>C NMR signature of a trifluoromethylsulfonium salt<sup>50</sup>. Also, the observed <sup>19</sup>F NMR signals (–71.3 and –74.0 ppm) are very close to the signal reported for [CF<sub>3</sub>SO<sub>3</sub>(SiMe<sub>3</sub>)<sub>2</sub>]<sup>+</sup>[B(C<sub>6</sub>F<sub>5</sub>)<sub>4</sub>]<sup>–</sup> in benzene-*d*<sub>6</sub> (δ <sup>19</sup>F: –74.1 ppm)<sup>50</sup>. From this NMR study, we could propose structures for the methylating reagents in superacid (Table 2, bottom). In each case, the preferred site of protonation was further confirmed by DFT calculations at the ωB97xD/def2-TZVP + PCM level of theory (see SI for full detail) also supported by computed <sup>13</sup>C NMR shifts (B3LYP/cc-pvTZ//ωB97xD/def2-TZVP). Thus, the main reactive species from dimethylsulfate and trimethylphosphate would consist in a protonated form of these reagents while methyl triflate would generate a mixture of [CF<sub>3</sub>SO<sub>3</sub>HMe]<sup>+</sup> and [CF<sub>3</sub>SO<sub>3</sub>(Me)<sub>2</sub>]<sup>+</sup>, both acting as superelectrophilic methylating reagents.

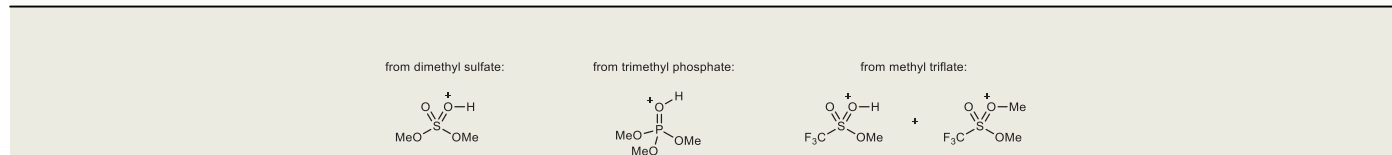
### Rationalization of the observed regioselectivity

According to literature and our own experimental observations, we supposed that the non-innate selectivity observed for this electrophilic methylation might come, at least in part, from the rearrangement of methylated products in superacid. Monitoring the methylation of acetanilide under the optimized conditions showed the initial formation of a mixture of **1<sub>p</sub>** and **1<sub>m</sub>** within the first minutes which rapidly evolved in favor of **1<sub>m</sub>** to reach full conversion after 2 h (Fig. 3a). Moreover, when **1<sub>p</sub>** was submitted to HF/SbF<sub>5</sub> at 0 °C, it was fully converted into **1<sub>m</sub>** after 1 h thus supporting our hypothesis (Fig. 3b). This rearrangement was much slower at –20 °C and almost inoperative at –40 °C. This indicates that the large proportion of *meta*-methylated product observed at –40 °C with TfOME (Table 1, entry 1) does not come from the isomerization of **1<sub>p</sub>** but is rather the consequence of the poor intrinsic selectivity of the Friedel–Crafts methylation. The absence of isomerization with other acid promoters revealed the necessity to use strong superacidic media to promote the rearrangement of acetanilide **1<sub>p</sub>** (Fig. 3b). The generality of this process was then evaluated on four representative examples (Fig. 3c). The *para* isomers of compounds **19**, **23** and **29** and the C5-methylated compound **14** were thus submitted to the optimized conditions affording the corresponding rearranged products with the same degrees of selectivity than those observed from the direct methylation of their parent arenes. Importantly, when pure *meta* regioisomer **29<sub>m</sub>** was submitted to HF/SbF<sub>5</sub>, compound **29** was recovered as a *meta/para* isomer mixture (*m/p* = 82:18) similar to the one obtained from the rearrangement of **29<sub>p</sub>**, suggesting a thermodynamically-controlled isomerization.

To gain a deeper understanding of the bond cleavage/bond formation event occurring during the methyl shift, we next explored deuterium kinetic isotope effects (KIE). We first set up an intramolecular competition experiment from the partially-labeled compound **1<sub>p-d</sub>** (Fig. 3d). However, this compound readily undergoes full hydrogen isotope exchange even at –40 °C preventing any success in measuring an eventual KIE. Nevertheless, this experiment demonstrates that C3 protonation of **1<sub>p</sub>** under these conditions is a fast and reversible process. KIE study through intermolecular competition and by separate experiments between two isotopologues **1<sub>p</sub>** and **1<sub>p-d</sub>** was next examined. No appreciable secondary kinetic isotope effect (SKIE) could be

**Table 2 | In situ NMR analysis of methylating reagents**

Entry	Reagent (conditions)	Experimental $\delta^1\text{H}$ (ppm)	Experimental $\delta^{13}\text{C}$ (ppm)	DFT calculated <sup>a</sup> $\delta^{13}\text{C}$ (ppm)	
1	Me <sub>2</sub> SO <sub>4</sub> (HF/SbF <sub>5</sub> , -50 °C)	3.11	66.4	64.8	
2	Me <sub>2</sub> SO <sub>4</sub> (Acetone- <i>d</i> <sub>6</sub> , 20 °C)	3.98	59.4	54.8	
3	Me <sub>3</sub> PO <sub>4</sub> (HF/SbF <sub>5</sub> , -50 °C)	2.66 (d, <i>J</i> = 11.5 Hz)	57.7 (d, <i>J</i> = 7.5 Hz)	58.5 (d, <i>J</i> = 7.2 Hz)	
4	Me <sub>3</sub> PO <sub>4</sub> (Acetone- <i>d</i> <sub>6</sub> , 20 °C)	3.71 (d, <i>J</i> = 11.0 Hz)	54.4 (d, <i>J</i> = 5.9 Hz)	53.4 (d, <i>J</i> = 6.4 Hz)	
5	MeOTf (HF/SbF <sub>5</sub> , -50 °C)	3.56	71.8	71.1 <sup>b</sup>	127.4 (q, <i>J</i> = 370 Hz) <sup>b</sup>
		3.48	70.4	69.8 <sup>c</sup>	127.3 (q, <i>J</i> = 369 Hz) <sup>c</sup>
6	MeOTf (CD <sub>2</sub> Cl <sub>2</sub> , 20 °C)	4.22	62.6	60.2	127.1 (q, <i>J</i> = 366 Hz)

Proposed structures of methylating reagents in HF/SbF<sub>5</sub>

<sup>a</sup>Computed at the B3LYP/cc-pVTZ//ωB97xD/def2-TZVP level with a PCM solvent model, either acetone, dichloromethane or HF (using the dielectric constant of HF:  $\epsilon = 83.6$  at 273 K) and using TMS as reference (see SI for full detail).

<sup>b</sup>Calculated for [CF<sub>3</sub>SO<sub>3</sub>HMe]<sup>+</sup>.

<sup>c</sup>Calculated for [CF<sub>3</sub>SO<sub>3</sub>(Me)<sub>2</sub>]<sup>+</sup>.

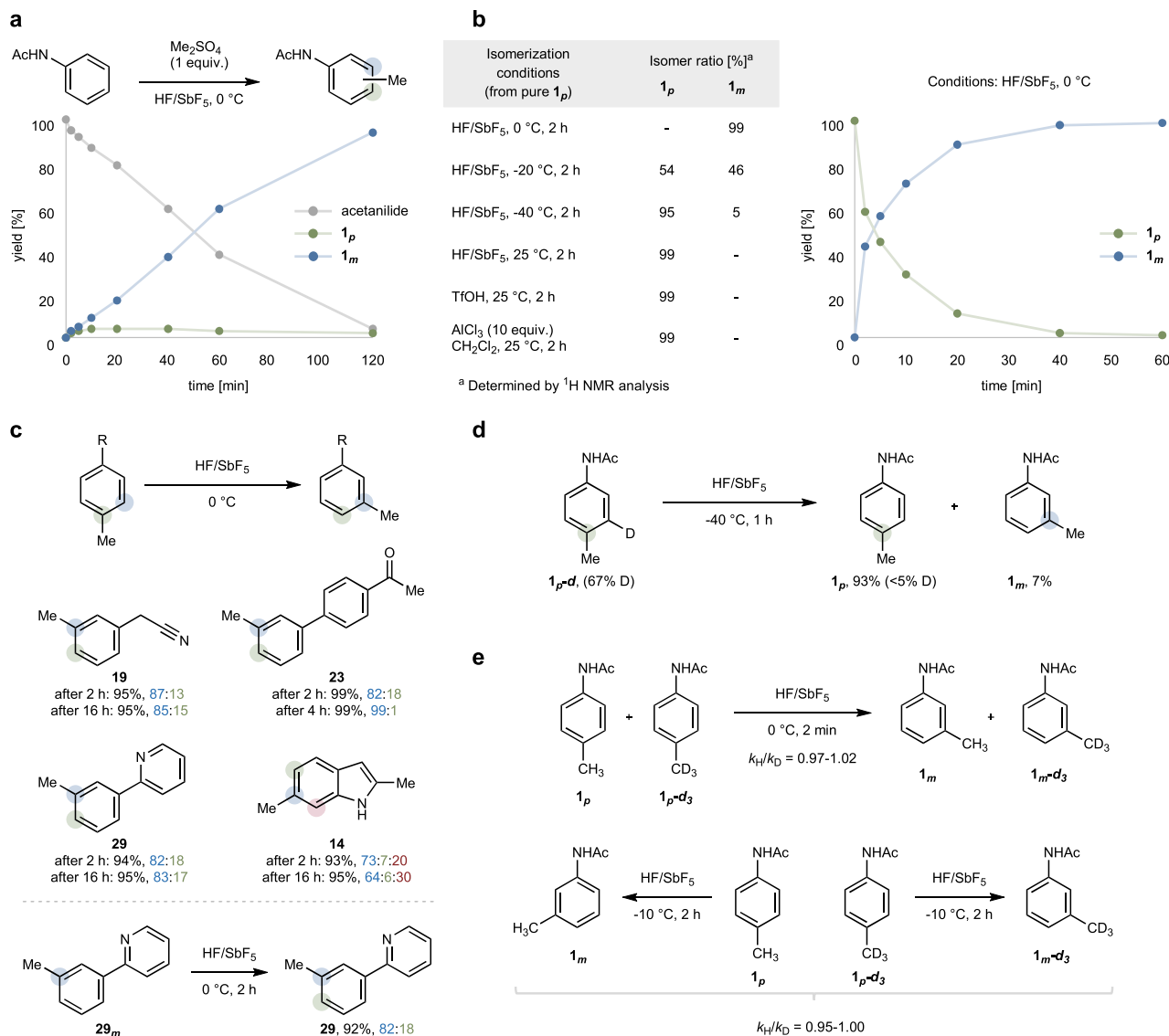
observed from these experiments (Fig. 3e). A positive SKIE would have been expected if a positive charge was developed at C4 during the selectivity-determining step due to hyperconjugative effect<sup>51</sup>. This absence of normal SKIE also discards a carbocationic character of the methyl group during the selectivity-determining step as a positive  $\alpha$ -SKIE would have also been expected if change in hybridization from sp<sup>3</sup> to sp<sup>2</sup> was taking place<sup>52</sup>. This contrasts severely with related rate-controlling methyl shifts for which a substantial amount of positive charge is born by the migrating methyl group, decreasing C–H stretching and bending force constants, which is reflected by normal SKIE values ( $k_{\text{H}}/k_{\text{D}} = 1.1$ – $1.2$ )<sup>53,54</sup>. On the other hand, the small inverse SKIE observed for the Wagner-Meerwein rearrangement of neopentyl brosylate ( $k_{\text{H}}/k_{\text{D}} = 0.98$ ) has been interpreted as the consequence of methyl migration occurring after the rate-controlling step<sup>53</sup>. Accordingly, we propose that the superacid-mediated aromatic methyl shift takes place after a rate-controlling arenium ion formation through C4 protonation.

To explore the transient formation of such arenium ions, we next studied the behavior of methylated arenes in superacid by low-temperature NMR spectroscopy (Fig. 4a). We started our investigations by submitting compound **1<sub>p</sub>** to HF/SbF<sub>5</sub> at -40 °C to prevent any isomerization. However, no clean <sup>1</sup>H or <sup>13</sup>C NMR spectra could be collected from this experiment. Upon prolonged reaction time, signals corresponding to dication **1<sub>A</sub>** started to appear. The structure of **1<sub>A</sub>** was confirmed by submitting pure **1<sub>m</sub>** to HF/SbF<sub>5</sub> under similar conditions which gave the same spectrum. This species **1<sub>A</sub>** is characterized by a broad singlet at  $\delta^1\text{H} = 3.56$  ppm correlating with  $\delta^{13}\text{C} = 42.1$  ppm in the HSQC spectrum which was attributed to the methylene moiety resulting from aromatic protonation *para* to the acetamido group. This is also evidenced in the <sup>13</sup>C NMR spectrum by the presence of two strongly deshielded signals at 170.2 and 204.3 ppm consistent with the formation of a cyclohexadienyl cation with a delocalized positive charge<sup>55</sup>. The observation of this arenium ion is particularly noteworthy considering that the acetamide moiety is also protonated as confirmed by the signal at 11.30 ppm in the <sup>1</sup>H NMR spectrum. Similar analysis performed on other representative methylated products allowed the characterization of **19<sub>A</sub>**, **23<sub>A</sub>**, **29<sub>A</sub>** and **14<sub>A</sub>** which represent rare examples of long-lived arenium dications in solution<sup>56</sup>. Collectively, these data

suggest that the isomerization is thermodynamically driven by the relative stability of arenium ions under superacidic conditions.

To obtain more information on this aspect, we then computed the relative free energies of arenium ions derived from compounds **1**, **19**, **23** and **29** by DFT calculations at the ωB97xD/def2-TZVP + PCM (HF)<sup>57</sup> level of theory (Fig. 4b). For this, we considered four arenium isomers (**A–D**) in their monocationic and dicationic forms (aromatic functional group R either protonated or not). We furthermore conducted full conformer search using the CREST methodology developed by Grimme et al.<sup>58</sup> to ensure the lowest energy conformers were systematically considered (see SI for the full details of the methodology). In the monocationic series, *meta*-methylated arenium isomers **A** were found the most stable ones in each case (by at least 2.6 kcal/mol). As anticipated, similar results were obtained from control computational analysis of xylene-derived arenium ions (**48**). On the other hand, *para*-methylacetophenone-derived arenium ion **49<sub>B</sub>** was found more stable in comparison with **49<sub>A</sub>**. This can be directly related to the strong electron-withdrawing effect of the ketone functionality which prevents the development of any cationic charge in *meta* position of the acetyl group. In fact, any tentative of isomerization failed in our hand when *para*-methylacetophenone **49<sub>p</sub>** was subjected to HF/SbF<sub>5</sub> at 0 °C for 2 h. Considering the ability to generate dications in these superacidic conditions, we next studied the influence of the protonation of the aromatic functional groups on the relative stability of arenium ions. The dicationic forms of **1<sub>A</sub>** and **23<sub>A</sub>** were found more stable than **1<sub>B</sub>** and **23<sub>B</sub>** respectively by 2.1 and 1.2 kcal/mol despite the protonation of the amide and ketone functionalities. On the other hand, *para*-methylated **19<sub>B</sub>** and **29<sub>B</sub>** were found the most stable isomers in their dicationic forms (by 0.7 and 1.2 kcal/mol compared with **19<sub>A</sub>** and **29<sub>A</sub>**). In these cases, the dicationic forms must be in a disfavored equilibrium with their monocationic forms which would mostly dictate the orientation of the  $\sigma$ -complex regioconversion. This is also in accordance with the constant ratio of *meta* and *para* isomers of **29** observed after isomerization of either pure **29<sub>m</sub>** or **29<sub>p</sub>** (Fig. 3c). This equilibrium would also account for the lower resolution of <sup>1</sup>H and <sup>13</sup>C NMR spectra obtained from compounds **19<sub>m</sub>** and **29<sub>m</sub>** in superacid (Fig. 4a).

To conclude, we have developed a direct and selective method for the *meta*-methylation of arenes. Although inefficient with electron-



**Fig. 3 | Experimental investigations of the isomerization of Friedel–Crafts products.** **a** Monitoring of the Friedel–Crafts methylation of acetanilide (monitored by <sup>1</sup>H NMR analysis of aliquot samples of the reaction mixture). **b** Control experiments for the isomerization of **1<sub>p</sub>** to **1<sub>m</sub>** (monitored by <sup>1</sup>H NMR analysis of aliquot samples of the reaction mixtures). **c** Isomerization of compounds **14**, **19**, **23**, **29** (overall yield of the mixture of regioisomers; regioselectivity determined by

NMR analysis of the crude product). **d** Attempt of intramolecular competition between the methylation of a C–H or a C–D bond after methyl migration from **1<sub>p-d</sub>**. **e** KIE study through intermolecular competition and by separate experiments between two isotopologues **1<sub>p</sub>** and **1<sub>p-d3</sub>** ( $k_H/k_D$  average values obtained from three experiments, see SI).

deficient arenes, this transformation exhibits a broad substrate scope, tolerating synthetically useful functionalities, and is also efficient to functionalize biorelevant molecules at a later stage of a synthetic plan. The weakly nucleophilic superacid solution is crucial for the selectivity of the process that is controlled by the stabilization of  $\sigma$ -complex intermediates generated after methylation/isomerization. Additional kinetic, spectroscopic and computational investigations provide insights into this mechanism. We believe that this study will pave the way for the emergence of new synthetic strategies exploiting long-lived cyclohexadienyl cations.

## Methods

### General procedure for superacid-mediated Friedel–Crafts methylation

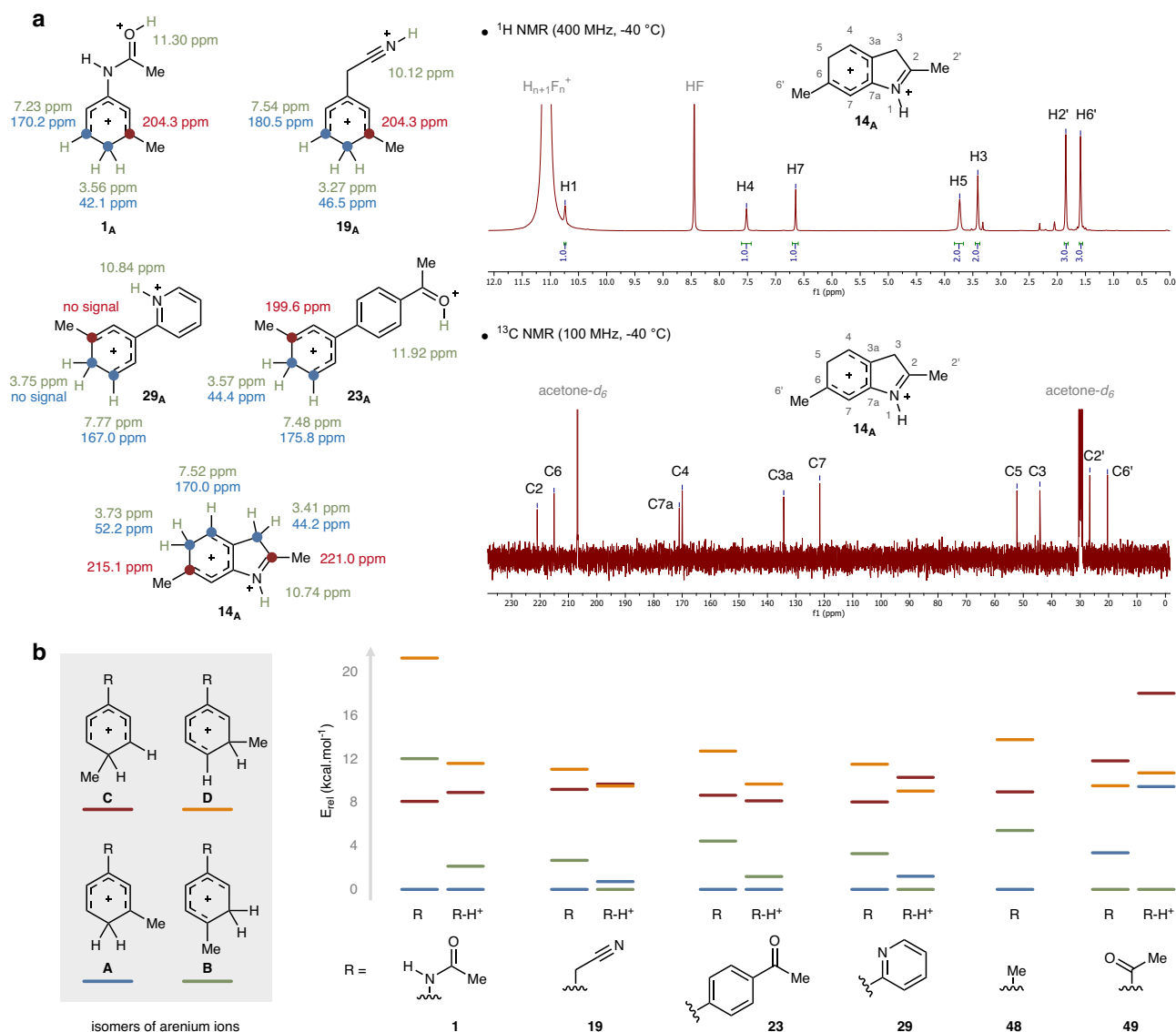
To a solution of HF/SbF<sub>5</sub> (v/v 1/1, 1–2 ml) was added aromatic starting material (0.2–0.5 mmol) at 0 °C unless stated otherwise. The methylating reagent (Me<sub>2</sub>SO<sub>4</sub> or Me<sub>3</sub>PO<sub>4</sub> as indicated in Fig. 2) was added and

the reaction mixture was stirred at the same temperature for 2–16 h (as indicated in Fig. 2). The reaction mixture was then poured onto an ice-cold saturated aqueous solution of Na<sub>2</sub>CO<sub>3</sub>. The aqueous phase was extracted thrice with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude residue was then purified by flash column chromatography over silica gel using the eluent system described for each compound in the Supplementary Information.

### Caution

HF/SbF<sub>5</sub> is highly toxic and corrosive. Handling of hydrogen fluoride and antimony pentafluoride must be done by experienced chemists with all the necessary safety arrangements in place. Direct exposure must be avoided. Use calcium gluconate gel to treat the affected skin area in case of skin exposure. Reactions performed in superacid were carried out in a screw-capped Teflon® flask with a magnetic stirrer. No further precautions have to be taken to prevent mixture from moisture.





**Fig. 4 | Experimental and computational investigations on the formation of arenium ions.** **a** Left: key NMR signals of cationic intermediates obtained from a representative panel of products in HF/SbF<sub>5</sub> at -40 °C using acetone-*d*<sub>6</sub> as external standard. <sup>1</sup>H NMR signals in green, <sup>13</sup>C NMR signals in blue or red. Right: <sup>1</sup>H and <sup>13</sup>C NMR spectra of dication **14**<sub>A</sub> as a representative example. **b** Relative free energies of

arenium isomers derived from compounds **1**, **19**, **23**, **29** and control compounds **48** and **49** in their monocationic and dicationic forms computed at the ωB97xD/def2-TZVP + PCM (using the dielectric constant of HF: ε = 83.6 at 273 K) level of theory. Only the lowest energy conformers were considered in each case for the sake of clarity (see SI for full computational details).

## Data availability

All data generated and analyzed during this study, which include experimental, spectroscopic and computational data, are included in this article and its Supplementary Information. The relative free energies data and the Cartesian coordinates are available as a Supplementary dataset. Should any raw data files be needed in another format they are available from the corresponding author upon request.

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## Author contributions

Conceptualization: B.M. and S.T.; Methodology: B.M. and S.T.; Investigation: P.B., K.V., A.M.M., H.G., F.G. and B.M.; Writing: B.M. and S.T.; Review & editing: B.M. and S.T.; Funding acquisition: S.T.; Supervision: A.M.M., B.M. and S.T.

## Competing interests

The authors declare no competing interests.

## Additional information

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