Pd-Catalyzed $\alpha$-Arylation of Sulfones in a Three-Component Synthesis of 3-[2-(phenyl/methylsulfonyl)ethyl]indoles

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ABSTRACT. A novel four-step domino process for the synthesis of 3-[2-(aryl/alkylsulfonyl)ethyl]indoles starting from readily available 2-iodoanilines is reported. The domino reaction is based on the intramolecular palladium-catalyzed $\alpha$-arylation of sulfones, which was combined with both intermolecular aza-Michael and Michael addition reactions using vinyl sulfones as the electrophile. The domino process produced good yields and tolerated the presence of substituents with different electronic properties on the aniline ring. In addition, Density Functional Theory (DFT) calculations were carried out to gain more insight into the formation of the observed indole derivatives.
KEYWORDS: Palladium-catalyzed, Arylation, Domino reactions, Indoles, Density functional calculations.

1. INTRODUCTION

Indole is a commonly found heterocycle in biologically active natural products and unnatural pharmaceuticals.\(^1\) For this reason, it is not surprising that since Fischer’s pioneering indole synthesis in 1883,\(^2\) numerous methodologies have been reported for the construction and functionalization of the indole skeleton.\(^3\) Besides the vast array of more traditional reactions, recent advances in the area of transition metal-catalyzed transformations have led to the development of several new reliable methods for the synthesis of indoles from simple starting materials.\(^4\) Among the variety of cross-coupling reactions, the palladium-catalyzed arylation of acidic C—H bonds\(^5\) is of particular interest for the synthesis of this heteroaromatic compound from non-aromatic precursors.\(^6,7\)

In the context of our research on palladium-based methodologies for the synthesis of nitrogen heterocycles,\(^8\) we have reported the palladium-catalyzed intramolecular $\alpha$-arylation of $\beta$-(2-iodoanilino) esters\(^9\) and amides\(^10\) to give indole-3-carboxylic acid derivatives. In parallel with these studies, and in order to create more complex and diverse scaffolds from readily accessible starting materials, we have also explored the integration of the palladium-catalyzed $\alpha$-arylation reaction into one-pot sequences.\(^11\) This research allowed us to recently achieve an efficient synthesis of highly functionalized tetrahydroisoquinolines by a domino aza-Michael/$\alpha$-arylation/Michael addition process based on the use of sulfones either as electrophiles or nucleophiles.\(^12\) Continuing these studies, we decided to explore the synthesis of indole derivatives by means of a multistep sequence involving the use of sulfones (Scheme 1). When
starting from 2-haloaniline A, the aforementioned three-step domino process could be expected to generate a 3-(sulfonyl)indoline intermediate (i.e. D), a type of compound known to undergo β-elimination of sulfinic acid to afford indoles.\textsuperscript{13,14} We postulated that this additional step would allow us to prepare 3-[2-(aryl/alkylsulfonyl)ethyl]indoles in a new four-step domino process from readily available 2-haloanilines.

**Scheme 1.** Generic plan for the domino aza-Michael/α-arylation/Michael addition/β-elimination process leading to 3-[2-(aryl/alkylsulfonyl)ethyl]indoles

Among the various substitution patterns of the indole nucleus, compounds bearing the (3-indolyl)ethyl moiety are particularly challenging synthetic targets due to the diversity of biologically active tryptamine analogues.\textsuperscript{15,16} Thus, a general approach to this type of compound using the proposed domino aza-Michael/α-arylation/Michael addition/β-elimination strategy would complement existing methodologies and in some instances provide a more attractive option.\textsuperscript{17}
A successful domino process should occur under conditions that allow the desired sequence of events to take precedence over any undesired competitive reactions. Thus, in our strategy, the starting iodoaniline \( A \) would have to be consumed rapidly by the aza-Michael addition\(^{16} \) to avoid an intramolecular Heck process proceeding as the first step.\(^{19} \) Similarly, the competitive Heck reaction should not interfere with the palladium-catalyzed \( \alpha \)-arylation reaction of intermediate \( B \). Finally, the 3-(sulfonyl)indoline intermediate \( C \) should be immediately trapped\(^{20} \) to prevent a premature \( \beta \)-elimination leading to the non-substituted indole.

The work described herein explores the viability of the proposed palladium-catalyzed \( \alpha \)-arylation of sulfones in a four-step domino process to obtain 3-[2-(phenyl/methylsulfonyl)ethyl]indoles from readily available starting materials. To this end, a detailed joint experimental and computational study was carried out to provide insight into the formation of the target indole through this multicomponent domino reaction.

2. RESULTS AND DISCUSSION

During the optimization of the domino process leading to tetrahydroisoquinolines,\(^{12} \) we realized that the most challenging step of the sequence was the sulfone \( \alpha \)-arylation reaction.\(^{21} \) So, before embarking on the development of a domino process to access 3-substituted indoles, we first examined the palladium-catalyzed \( \alpha \)-arylation of \( \beta \)-(2-iodoanilino) sulfones. Sulfones \( 1\text{a-c} \) were chosen for this purpose (Table 1).

Treatment of \( 1\text{a} \) with the \( \text{Pd}_{2}(\text{dba})_{3}/\text{xantphos} \) couple as the precatalyst and \( \text{K}_{3}\text{PO}_{4} \) as the base in DMF, an effective combination for the domino sequence starting from closely related 2-iodobenzylamines,\(^{12} \) resulted in the decomposition of the starting material (entry 1, Table 1).
When using the same combination of palladium source and ligand, with Cs₂CO₃ as the base in THF, the starting aryl iodide 1a was recovered unchanged (entry 2, Table 1). Substituting the ligand for BINAP resulted, once again, in the formation of a complex reaction mixture (entry 3, Table 1).

**Table 1. Optimization of the α-arylation conditions**

<table>
<thead>
<tr>
<th>entry</th>
<th>sulfone</th>
<th>catalyst (equiv.)</th>
<th>base (equiv.)</th>
<th>solvent</th>
<th>time</th>
<th>¹H NMR ratio</th>
<th>yield (%)&lt;sup&gt;⁵&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>Pd&lt;sub&gt;2&lt;/sub&gt;(dba)&lt;sub&gt;3&lt;/sub&gt; (0.075) xantphos (0.15)</td>
<td>K₃PO₄ (3)</td>
<td>DMF</td>
<td>72 h</td>
<td>---&lt;sup&gt;⁶&lt;/sup&gt;</td>
<td>---&lt;sup&gt;⁶&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>Pd&lt;sub&gt;2&lt;/sub&gt;(dba)&lt;sub&gt;3&lt;/sub&gt; (0.075) xantphos (0.15)</td>
<td>Cs₂CO₃ (3)</td>
<td>THF</td>
<td>72 h</td>
<td>1a&lt;sup&gt;⁴&lt;/sup&gt;</td>
<td>1a&lt;sup&gt;⁴&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>Pd&lt;sub&gt;2&lt;/sub&gt;(dba)&lt;sub&gt;3&lt;/sub&gt; (0.05) BINAP (0.1)</td>
<td>Cs₂CO₃ (3)</td>
<td>THF</td>
<td>72 h</td>
<td>---&lt;sup&gt;⁶&lt;/sup&gt;</td>
<td>---&lt;sup&gt;⁶&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>Pd(PPh₃)&lt;sub&gt;4&lt;/sub&gt; (0.1)</td>
<td>K₃PO₄ (2.5)</td>
<td>DMF</td>
<td>70 h</td>
<td>3a (44%)&lt;sup&gt;⁵&lt;/sup&gt;</td>
<td>3a (44%)&lt;sup&gt;⁵&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>Pd(PPh₃)&lt;sub&gt;4&lt;/sub&gt; (0.1)</td>
<td>K₃PO₄ (2.5)</td>
<td>THF</td>
<td>72 h</td>
<td>2a:3a (1:2): 3a (73%)</td>
<td>2a:3a (1:2): 3a (73%)</td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>Pd(PPh₃)&lt;sub&gt;4&lt;/sub&gt; (0.05)</td>
<td>Cs₂CO₃ (2.5)</td>
<td>THF</td>
<td>72 h</td>
<td>2a:3a (2:1): 3a (68%)</td>
<td>2a:3a (2:1): 3a (68%)</td>
</tr>
<tr>
<td>7</td>
<td>1b</td>
<td>Pd(PPh₃)&lt;sub&gt;4&lt;/sub&gt; (0.1)</td>
<td>K₃PO₄ (3)</td>
<td>DMF</td>
<td>72 h</td>
<td>3b (65%)</td>
<td>3b (65%)</td>
</tr>
<tr>
<td>8</td>
<td>1b</td>
<td>Pd(PPh₃)&lt;sub&gt;4&lt;/sub&gt; (0.1)</td>
<td>K₃PO₄ (3)</td>
<td>THF</td>
<td>72 h</td>
<td>3b (64%)</td>
<td>3b (64%)</td>
</tr>
<tr>
<td>9</td>
<td>1b</td>
<td>Pd(PPh₃)&lt;sub&gt;4&lt;/sub&gt; (0.05)</td>
<td>Cs₂CO₃ (2.5)</td>
<td>THF</td>
<td>72 h</td>
<td>3b (52%)</td>
<td>3b (52%)</td>
</tr>
<tr>
<td>10</td>
<td>1c</td>
<td>Pd(PPh₃)&lt;sub&gt;4&lt;/sub&gt; (0.1)</td>
<td>K₃PO₄ (3)</td>
<td>DMF</td>
<td>120 h</td>
<td>3b (42%)&lt;sup&gt;⁵&lt;/sup&gt;</td>
<td>3b (42%)&lt;sup&gt;⁵&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>1c</td>
<td>Pd(PPh₃)&lt;sub&gt;4&lt;/sub&gt; (0.1)</td>
<td>K₃PO₄ (3)</td>
<td>THF</td>
<td>115 h</td>
<td>2c:3b (5:1)&lt;sup&gt;⁵&lt;/sup&gt;</td>
<td>2c (40%): 3b (41%)</td>
</tr>
<tr>
<td>12</td>
<td>1c</td>
<td>Pd(PPh₃)&lt;sub&gt;4&lt;/sub&gt; (0.1)</td>
<td>Cs₂CO₃ (2.5)</td>
<td>THF</td>
<td>120 h</td>
<td>2c:3b (5:1)&lt;sup&gt;⁵&lt;/sup&gt;</td>
<td>2c (7%): 3b (76%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> The reactions were carried out in a sealed tube at 120 °C.<sup>b</sup> Yields refer to pure products isolated by flash chromatography. <sup>c</sup> Complex mixture. <sup>d</sup> Yield not quantified. <sup>e</sup> Small amounts of the hydrodehalogenation compound (≤10%) were also observed in the crude reaction mixture. Pd<sub>2</sub>(dba)<sub>3</sub>: Tris(dibenzylideneacetone)dipalladium(0). Xantphos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthen. BINAP: 2,2’-Bis(diphenylphosphino)-1,1’-binaphthaleine.
In contrast, the reaction of 1a with Pd(PPh₃)₄ and K₃PO₄ in DMF afforded the product 3a resulting from the elimination of phenylsulfinic acid from the initially formed α-arylation compound 2a (entry 4, Table 1). The use of THF as the solvent, maintaining the same combination of reagents and catalyst, led to the formation of a 1:2 mixture of indoline 2a and indole 3a (entry 5, Table 1), whereas a ratio of 2:1 was observed when the base was changed from K₃PO₄ to Cs₂CO₃ (entry 6, Table 1). However, after column chromatography of these reaction mixtures, only indole 3a was isolated, as a result of the SiO₂-promoted elimination of phenylsulfinic acid from 2a.

Phenyl sulfone 1b, which bears a methyl group at the aniline nitrogen atom, exclusively afforded indole 3b when submitted to the reaction conditions optimized for the α-arylation of 1a (entries 7-9, Table 1). It should be noted that the corresponding indoline intermediate C was not observed in any of the crude reaction mixtures of these runs.

Methyl sulfone 1c was also efficient in the α-arylation reaction, with a similar behavior to phenyl sulfone 1a, although the process was slower. While indole 3b was directly obtained when using DMF as the solvent (entry 10, Table 1), the annulation reaction in THF afforded mixtures of indoline 2c and the indole 3b (entries 11 and 12, Table 1). Interestingly, although 2c partially evolved to indole 3b during the chromatographic purification, in this case the indoline was stable enough to be isolated and characterized.

At this point, the best conditions for the α-arylation of β-(2-iodoanilino) sulfones involved the use of Pd(PPh₃)₄ as the catalyst and either K₃PO₄ or Cs₂CO₃ as the base in THF. On the other hand, the results in Table 1 show that both phenyl and methyl sulfones could a priori be useful to develop the proposed reaction cascade, since the corresponding 3-sulfonyl indolines partially
survived under the α-arylation conditions. However, in the phenylsulfonyl series, changing the substituent at the nitrogen atom from benzyl to methyl resulted in a fast elimination of phenylsulfinic acid, which could hamper the use of N-methyl derivatives in the domino process. With this information in hand, without any further optimization, we then focused on combining the α-arylation reaction with the next steps of the domino process, namely the Michael addition of the 3-sulfonyl indoline intermediate C and the subsequent β-elimination from the resulting alkylated indoline D (Scheme 1 and Table 2).

**Table 2. α-Arylation/Michael addition/β-elimination domino process**

![Scheme 1](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>sulfone</th>
<th>Michael acceptor</th>
<th>base (equiv.)</th>
<th>solvent</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td></td>
<td>K&lt;sub&gt;3&lt;/sub&gt;P&lt;sub&gt;4&lt;/sub&gt; (3)</td>
<td>THF</td>
<td>---&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td></td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (3)</td>
<td>THF</td>
<td>4a (48%)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td></td>
<td>K&lt;sub&gt;3&lt;/sub&gt;P&lt;sub&gt;4&lt;/sub&gt; (3)</td>
<td>DMF</td>
<td>4a (19%)&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td></td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (3)</td>
<td>DMF</td>
<td>4a (27%)&lt;sup&gt;c,e&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td></td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (3)</td>
<td>THF</td>
<td>4d (43%)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>1b</td>
<td></td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (3)</td>
<td>THF</td>
<td>4b (73%)&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>1b</td>
<td></td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (3)</td>
<td>THF</td>
<td>4c (45%)&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>1c</td>
<td></td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (3)</td>
<td>THF</td>
<td>4c (44%)&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>1c</td>
<td></td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (3)</td>
<td>THF</td>
<td>4b (40%)&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 1 (0.2 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (10 mol%), Michael acceptor (2 equiv.), and base (3 equiv.) in the indicated solvent in a sealed tube at 120 ºC for 72 h. <sup>b</sup> Yields refer to pure products isolated by flash chromatography. <sup>c</sup> Complex mixture. <sup>d</sup> N-Benzyl-4-methyl-N-[2-(phenylsulfonyl)ethyl]aniline (5a) was also isolated (17%). <sup>e</sup> Significant amounts of N-benzyl-p-
toluidine were observed in the reaction mixture. 5a (20%) was also isolated. Small amounts of the corresponding hydrodehalogenation product (< 10%) were also observed in the crude reaction mixture. N,4-Dimethyl-N-[2-(methylsulfonyl)ethyl]aniline (5c) was also isolated (20%). 5c (26%) was also isolated.

Treatment of 1a with Pd(PPh₃)₄ and K₃PO₄ in the presence of phenyl vinyl sulfone in THF afforded a complex mixture in which only trace amounts of the desired indole 4a were observed, together with the reduction compound 5a and some products arising from the Heck reaction of the starting aryl iodide (entry 1, Table 2). However, to our delight, changing the base to Cs₂CO₃ resulted in a clean reaction mixture, from which indole 4a (48%) and the reduction compound 5a (17%) were isolated (entry 2, Table 2). When the reactions were performed in DMF using either K₃PO₄ or Cs₂CO₃ as the base, indole 4a was also obtained, although in significantly lower yields (entries 3 and 4, Table 2).

The three-step domino process of 1a with methyl vinyl sulfone afforded indole 4d in 43% yield (entry 5, Table 2). Phenyl sulfone 1b, which bears a methyl group at the nitrogen atom, gave indoles 4b (73%) and 4c (45%) when submitted to the domino reaction with phenyl vinyl sulfone (entry 6, Table 2) and methyl vinyl sulfone (entry 7, Table 2), respectively. This indicates that the Michael addition of the 3-sulfonyl indoline intermediate to the vinyl sulfone is faster than the β-elimination of sulfinic acid, even for those substrates having a methyl substituent at the nitrogen atom (vide supra).

Finally, methyl sulfone 1c also underwent the domino reaction, either with methyl vinyl sulfone (entry 8, Table 2) or phenyl vinyl sulfone (entry 9, Table 2), to afford, respectively, indoles 4c (44%) and 4b (40%).

The promising results obtained in these three-step domino reactions constituted a good starting point to develop the initially proposed four-step domino process, which would simplify the
preparation of 3-[2-(sulfonyl)ethyl]indoles starting from the readily available N-alkyl-2-iodoanilines. N-Benzyl-2-iodoaniline was chosen to test our proposal (Table 3).

**Table 3.** Optimization of the aza-Michael/α-arylation/Michael addition/β-elimination domino process$^a$

![Chemical structure]

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (equiv.)</th>
<th>Michael acceptor</th>
<th>solvent</th>
<th>yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh$_3$)$_4$ (0.1)</td>
<td>$\text{SO}_2$Ph</td>
<td>THF</td>
<td>6a (33%)$^c$</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh$_3$)$_4$ (0.1)</td>
<td>$\text{SO}_2$Ph</td>
<td>DMF</td>
<td>6a (28%)$^d$</td>
</tr>
</tbody>
</table>
| 3     | Pd$_2$(dba)$_3$ (0.075)  
(o-tolyl)$_3$P (0.15) | $\text{SO}_2$Ph | THF     | SM            |
| 4     | Pd$_2$(dba)$_3$ (0.075)  
xantphos (0.15)         | $\text{SO}_2$Ph | THF     | SM            |
| 5     | Pd$_2$(dba)$_3$ (0.075)  
BINAP (0.15)              | $\text{SO}_2$Ph | THF     | 6a (54%)$^e$  |
| 6     | Pd$_2$(dba)$_3$ (0.075)  
dpf (0.15)                  | $\text{SO}_2$Ph | THF     | 6a (69%)      |
| 7     | Pd$_2$(dba)$_3$ (0.075)  
dpf (0.15)                  | $\text{SO}_2$Ph | THF     | 6a (80%)      |
| 8     | Pd$_2$(dba)$_3$ (0.075)  
dpf (0.15)                  | $\text{SO}_2$Ph | THF     | 6a (65%)$^f$  |
| 9     | Pd$_2$(dba)$_3$ (0.075)  
dppp (0.15)                 | $\text{SO}_2$Ph | THF     | 6a (65%)      |
| 10    | Pd$_2$(dba)$_3$ (0.075)  
dpf (0.15)                  | $\text{SO}_2$Ph | THF     | 7$^h$         |
| 11    | Pd$_2$(dba)$_3$ (0.075)  
dppe (0.15)                 | $\text{SO}_2$Ph | THF     | 6a/7 (1:1)$^i$|
| 12    | Pd$_2$(dba)$_3$ (0.075)  
dpf (0.15)                  | $\text{SO}_2$Me | THF     | 6b (33%)$^j$  |
| 13    | Pd$_2$(dba)$_3$ (0.075)  
BINAP (0.15)                | $\text{SO}_2$Me | THF     | 6b (58%)$^k$  |
Reaction conditions: N-Benzyl-2-iodoaniline (0.2 mmol), [Pd] and ligand (see table), Michael acceptor (2.1 equiv.), and Cs$_2$CO$_3$ (3 equiv.) in the indicated solvent in a sealed tube at 120 °C for 72 h. $^b$ Yields refer to pure products isolated by flash chromatography. $^c$ N-Benzylaniline (7) was also isolated (10%). $^d$ 7 was also isolated (17%). $^e$ Michael acceptor (2.4 equiv.). $^f$ The reaction was run at 80 °C. $^g$ N-Benzyl-2-iodoaniline (8%) was recovered. $^h$ Yield not quantified, minor amounts of 6a (≤10%) were also observed in the reaction mixture. $^i$ $^1$H NMR ratio, yields not quantified. $^j$ E-N-Benzyl-2-[2-(methylsulfonyl)ethenyl]aniline (8) was also isolated (14%). $^k$ 8 (13%) was also isolated. dppf: 1,1’-Bis(diphenylphosphino)ferrocene. dtpf: 1,1’-Bis(di-tert-butylphosphino)ferrocene. dppp: 1,3-Bis(diphenylphosphino)propane. dppe: 1,2-Bis(diphenylphosphino)ethane.

When N-benzyl-2-iodoaniline was treated with phenyl vinyl sulfone in the presence of Pd(PPh$_3$)$_4$ and Cs$_2$CO$_3$ in THF, an effective combination to promote the three-step domino process from 1a, indole 6a was obtained in a modest 33% yield, together with N-benzylaniline (7), which resulted from the reduction of the starting 2-iodoaniline (entry 1, Table 3). Although the use of a more polar solvent should facilitate the initial aza-Michael addition, the yield of indole 6a was in fact slightly lower when the reaction was performed in DMF (entry 2, Table 3). In view of these poor results, we decided to optimize the four-step domino reaction by using different commercially available phosphines as the ligand. The use of either (o-tolyl)$_3$P or xantphos resulted in the recovery of the starting material (entries 3 and 4, Table 3). Surprisingly, although BINAP had failed to promote the α-arylation from phenyl sulfone 1a (see Table 1), its use in the present domino process resulted in the formation of 6a in an acceptable 54% yield (entry 5, Table 3).

Using dppf allowed us to obtain indole 6a in 69% yield (entry 6, Table 3), while in the presence of the ligand dppp, 6a was isolated in 65% yield (entry 9, Table 3). We were also able to increase the yield of 6a up to 80% by using dppf and a slightly higher quantity of the Michael acceptor (entry 7, Table 3). Lower reaction temperatures resulted in the recovery of small amounts of the starting material (entry 8, Table 3). Other bidentate ligands were less amenable to promoting the four-step domino process. For instance, the most hindered dtpf mainly resulted in the formation
of the hydrodehalogenation product 7 (entry 10, Table 3), whereas a 1:1 mixture of 6a and 7 was obtained when using dppe (entry 11, Table 3).

The four-step domino process of N-benzyl-2-iodoaniline with methyl vinyl sulfone using dppe as the ligand afforded a complex mixture from which indole 6b was isolated in 33% (entry 12, Table 3). Interestingly, the replacement of the ligand by BINAP allowed us to obtain 6b in an acceptable 58% yield (entry 13, Table 3).

Table 4. Synthesis of 3-[2-(phenyl/methylsulfonyl)ethyl]indoles

<table>
<thead>
<tr>
<th>entry</th>
<th>Michael acceptor</th>
<th>ligand</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SO₂Ph</td>
<td>BINAP</td>
<td>9a, R = Me, R'' = Ph</td>
<td>(71%)</td>
</tr>
<tr>
<td>2</td>
<td>SO₂Ph</td>
<td>dppp</td>
<td>9a, R = Me, R'' = Ph</td>
<td>(50%)</td>
</tr>
<tr>
<td>3</td>
<td>SO₂Me</td>
<td>BINAP</td>
<td>9b, R = Me, R'' = Me</td>
<td>(45%)</td>
</tr>
<tr>
<td>4</td>
<td>SO₂Ph</td>
<td>dppf</td>
<td>10a, R = Pr, R'' = Ph</td>
<td>(69%)</td>
</tr>
<tr>
<td>5</td>
<td>SO₂Me</td>
<td>dppf</td>
<td>10b, R = Pr, R'' = Me</td>
<td>(67%)</td>
</tr>
<tr>
<td>6</td>
<td>SO₂Me</td>
<td>BINAP</td>
<td>10b, R = Pr, R'' = Me</td>
<td>(45%)</td>
</tr>
<tr>
<td>7</td>
<td>SO₂Ph</td>
<td>dppf</td>
<td>11a, R = Et, R'' = Ph</td>
<td>(89%)</td>
</tr>
<tr>
<td>8</td>
<td>SO₂Ph</td>
<td>dppf</td>
<td>4a, R = Bn, R’ = Me, R'' = Ph</td>
<td>(83%)</td>
</tr>
<tr>
<td>9</td>
<td>SO₂Me</td>
<td>dppf</td>
<td>4d, R = Bn, R’ = Me, R'' = Me</td>
<td>(56%)</td>
</tr>
<tr>
<td>10</td>
<td>SO₂Me</td>
<td>BINAP</td>
<td>4d, R = Bn, R’ = Me, R'' = Me</td>
<td>(45%)</td>
</tr>
<tr>
<td>11</td>
<td>SO₂Ph</td>
<td>dppf</td>
<td>12a, R = Bn, R’ = MeO, R'' = Ph</td>
<td>(79%)</td>
</tr>
<tr>
<td>12</td>
<td>SO₂Me</td>
<td>dppf</td>
<td>12b, R = Bn, R’ = MeO, R'' = Me</td>
<td>(57%)</td>
</tr>
<tr>
<td>13</td>
<td>SO₂Ph</td>
<td>dppf</td>
<td>13a, R = Pr, R’ = MeO, R'' = Ph</td>
<td>(45%)</td>
</tr>
<tr>
<td>14</td>
<td>SO₂Ph</td>
<td>dppf</td>
<td>14a, R = Bn, R’ = Cl, R'' = Ph</td>
<td>(85%)</td>
</tr>
<tr>
<td>15</td>
<td>SO₂Me</td>
<td>BINAP</td>
<td>14b, R = Bn, R’ = Cl, R'' = Me</td>
<td>(70%)</td>
</tr>
</tbody>
</table>
As shown in Table 4, a variety of diversely substituted 3-(sulfonylethyl)indoles were prepared through the four-step domino process when using either phenyl vinyl sulfone or methyl vinyl sulfone as the Michael acceptor. The generality and functional group tolerance of the reaction is well illustrated by the fact that both electron-donating and electron-withdrawing groups were perfectly accommodated on the aromatic ring. Overall, the phenyl sulfone afforded better results than the methyl sulfone due to its higher electrophilicity as well as the higher acidity of its α-C-H bonds, which favors both the α-arylation and the Michael addition. In this context, it should be noted that the initial aza-Michael addition took place without any appreciable interference from the competitive Heck reaction. The same behavior was also observed in our previously developed three-step domino process leading to tetrahydroisoquinolines. This absence of competition contrasts with what occurred in a related one-pot aza-Michael addition/α-arylation process using acrylates as the Michael acceptor. In this case, it was impossible to develop a real domino reaction because, in the presence of the Pd catalyst, the Heck coupling with the acrylate took place before the aza-Michael addition.

---

**Table 4**

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SO₂Ph dppf</td>
<td>15a</td>
<td>(65%)</td>
</tr>
<tr>
<td>SO₂Me BINAP</td>
<td>15b</td>
<td>(40%)</td>
</tr>
<tr>
<td>SO₂Ph dppf</td>
<td>16a</td>
<td>(75%)</td>
</tr>
<tr>
<td>SO₂Me dppf</td>
<td>16b</td>
<td>(73%)</td>
</tr>
<tr>
<td>SO₂Ph dppf</td>
<td>17a</td>
<td>(72%)</td>
</tr>
<tr>
<td>SO₂Me BINAP</td>
<td>17b</td>
<td>(56%)</td>
</tr>
<tr>
<td>SO₂Me dppf</td>
<td>17b</td>
<td>(62%)</td>
</tr>
<tr>
<td>SO₂Me dppf</td>
<td>18a</td>
<td>(81%)</td>
</tr>
<tr>
<td>SO₂Me dppf</td>
<td>18b</td>
<td>(60%)</td>
</tr>
</tbody>
</table>

*Note: Reaction conditions: N-Akyl-2-idoaniline (0.2 mmol), Pd₃(dba)₃ (7.5 mol%), ligand (see table, 15 mol%), Michael acceptor (2.1-2.4 equiv.), and Cs₂CO₃ (3 equiv.) in THF in a sealed tube at 120 °C for 72 h. Yields refer to pure products isolated by flash chromatography.*
Some additional comments on the four-step domino reactions described above (Tables 3 and 4) are warranted. In these reactions, the expected reduction products of the initially formed intermediates B (Scheme 1) were never observed, yet they were a common side-product (i.e. 5a-c) in the three-step domino processes starting from sulfones 1a-c (see Table 2). This fact, together with the isolation of significant amounts of N-benzylaniline (7), as well as the apparently contradictory results obtained with BINAP, suggested that a sequence of events different from those depicted in Scheme 1 could be operating in the four-step domino reaction. Indeed, all these results could be easily accommodated by an alternative sequence of reactions (Scheme 2) in which the formation of indoline C begins with the oxidative addition of the iodoaniline to Pd(0). The resulting Pd(II) intermediate E would then undergo deprotonation and aza-Michael addition to the vinyl sulfone to give intermediate F. The latter would evolve to indoline C by means of coordination of the sulfone anion and subsequent reductive elimination.

![Scheme 2. Alternative sequence of events for the domino process](image)

In search of evidence for the proposed aza-Michael/α-arylation/Michael addition/β-elimination sequence, further experiments were performed. Treatment of indole 3b with phenyl vinyl sulfone in the presence of Pd(PPh₃)₄ and Cs₂CO₃ in THF at 120 °C resulted in the recovery of the starting material. On the other hand, the treatment of a 8.3:1 mixture of indoline 2c and indole 3b with
methyl vinyl sulfone and Cs₂CO₃ in THF at 120 °C, both with and without Pd(PPh₃)₄, resulted in 
the formation of a 6.4-6.9:1 mixture of indoles 4c and 3b (Scheme 3). These results therefore 
confirm that indole 4c was generated by the Michael addition of indoline 2c to methyl vinyl 
sulfone followed by β-elimination of sulfinic acid, rather than by the metal-promoted 
nucleophilic addition of indole 3b to the vinyl sulfone.²⁵

\[
\begin{align*}
\text{Me} & \quad \text{Me} & \quad \text{Me} \\
\begin{array}{l}
2c \\
(8.3:1)
\end{array} \\
\text{SO}_{3} \text{Me} & \quad \text{Me} & \quad \text{Me} \\
\text{Cs₂CO₃ (3)} \\
\text{THF, 120 °C} & \quad \text{with or without Pd(PPh₃)₄ (0.1)}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{Me} & \quad \text{Me} \\
\text{4c} & \quad \text{Me} & \quad \text{Me} \\
\text{4c} & \quad \text{3b}
\end{align*}
\]

\[\text{with Pd(PPh₃)₄, 4c:3b, 6.4:1, 4c (36%) without Pd(PPh₃)₄, 4c:3b, 6.9:1, 4c (42%)}\]

**Scheme 3.** Reaction of indoline 2c with methyl vinyl sulfone

More illustratively, the reactions of N-benzyl-2-iodoaniline with the dideuterated phenyl vinyl 
sulfone 19-D₂ under optimized conditions (see for instance Table 3, entry 7) afforded indole 6a-
D₃, bearing deuterium labels at C-2 of the indole nucleus as well as at the β position of the 3-
(phenylsulfonyl)ethyl chain (Scheme 4). This result provides further experimental evidence for 
the proposed aza-Michael/α-arylation/Michael addition/β-elimination sequence of events.
Scheme 4. Reaction of \( N \)-benzyl-2-iodoaniline with sulfone 19-D

Density functional theory (DFT) calculations\(^{26}\) were carried out to gain more insight into the mechanism of the sulfone \( \alpha \)-arylation as well as the other key steps of the domino sequence described above. First, we focused on the \( \alpha \)-arylation process involving an analogous compound of 1c (Table 1), where the methyl group in the aromatic ring was replaced by a hydrogen atom. Our calculations started from species **INT0**, the intermediate formed upon the initial oxidative addition of the 2-iodoaniline derivative to the model Pd(PMe\(_3\))\(_2\) catalyst (Figure 1). In the presence of CO\(_3\)\(^{2-}\) as the base, deprotonation of the slightly acidic hydrogen atom attached to a carbon atom linked to the sulfone group may occur, therefore leading to **INT1** species in a slightly exergonic process (\( \Delta G_R = -4.0 \) kcal/mol). This intermediate would then evolve to complex **INT2** by exergonic coordination of the carbanion to the transition metal (\( \Delta G_R = -14.9 \) kcal/mol) and release of a phosphine ligand. From this species, the \( \alpha \)-arylation would take place directly via **TS1**, a transition state associated with the formation of the new C–C bond. This exergonic step (\( \Delta G_R = -14.2 \) kcal/mol) occurs with an activation barrier of 28.6 kcal/mol, which is fully compatible with a process occurring at 120 °C. Therefore, this reaction mechanism resembles the one we previously proposed for the \( \alpha \)-arylation reaction involving related ketone and ester derivatives.\(^{81}\)

Nevertheless, an alternative reaction pathway involving a key C–H activation step can be also envisaged. Thus, the initial intermediate **INT0** may be readily transformed into complex **INT3** through a highly exergonic (\( \Delta G_R = -26.6 \) kcal/mol) iodide and phosphine ligand replacement promoted by bidentate CO\(_3\)\(^{2-}\). This complex would be then converted into complex **INT4** via **TS2** with an activation barrier of 26.1 kcal/mol in a slightly endergonic transformation (\( \Delta G_R = \))
+2.7 kcal/mol). As depicted in Figure 1, this saddle point is associated with the concerted hydrogen migration from the sulfone to the carbonate ligand and Pd–C bond formation. In this sense, this transformation is analogous to related concerted metathesis-deprotonation (CMD) C–H activations which are assisted by acetate\textsuperscript{27} or carbonate.\textsuperscript{28} From INT4, the final indoline 2M can be directly produced through TS3 in a reductive elimination process associated with the formation of the new C–C bond. Although this reaction is exergonic (\(\Delta G_R = -9.2\) kcal/mol), it proceeds with a relatively high activation barrier of 37.4 kcal/mol. Therefore, INT4 may release the HCO\textsubscript{3}\textsuperscript{−} ligand first and be transformed into INT5, where the reductive elimination reaction via TS4 is computed to be kinetically far more favorable (\(\Delta G^\neq = 13.9\) kcal/mol, from INT5).

Additionally, due to the excess of CO\textsubscript{3}\textsuperscript{2−} in the process, INT2 may alternatively be converted into INT6 through a carbonate/iodide ligand exchange. This transformation seems feasible in view of the high exergonicity (\(\Delta G_R = -18.5\) kcal/mol) computed for this ligand exchange. However, the corresponding reductive elimination via TS5 would proceed with a much higher activation barrier (\(\Delta G^\neq = 42.9\) kcal/mol) than the process involving TS4, which renders this alternative pathway very unlikely. Therefore, based on the computed data, it can be concluded that the INT3 \(\rightarrow\) INT4 \(\rightarrow\) INT5 \(\rightarrow\) 2M pathway, which involves an initial CMD reaction followed by a reductive elimination step, seems to be the most plausible reaction mechanism for the palladium-catalyzed formation of indolines from \(\beta\)-(2-iodoanilino) sulfones.
Figure 1. Computed reaction profiles for the palladium catalyzed $\alpha$-arylation reaction of INT0. Relative free energies ($\Delta G_{298}$, at 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data were computed at the PCM(tetrahydrofuran)-B3LYP-D3/def2-TZVP//PCM(tetrahydrofuran)-B3LYP-D3/def2-SVP level.
As indicated in the reaction profile depicted in Figure 1, the preferred pathway involves the formation of the coordinatively unsaturated palladium(II) complex INT5. We hypothesize that the involvement of the bidentate phosphine ligands used in the experiments must occur from this intermediate. To find computational evidence for this hypothesis, we explored the feasibility of the final reductive elimination reaction from INT5’, the analogous species to INT5 bearing an additional phosphine ligand (i.e. a model bidentate ligand of the dppp ligand, with phenyl groups replaced by methyl groups). As expected, our calculations (Figure 2) indicate that the coordination of the free phosphine leading to the coordinately saturated complex INT7 is highly exergonic (ΔG_R = −18.5 kcal/mol). From this species, the reductive elimination reaction occurs via TS6, the corresponding saddle point associated with the formation of the new C–C bond and release of the Pd(dppp) catalyst. From the data in Figure 2, it becomes clear that the process involving the bidentate ligand proceeds with a much higher activation barrier (ΔG^≠ = 29.5 kcal/mol) and a lower exergonicity (ΔG_R = −9.7 kcal/mol) than the analogous process involving the monodentate ligand (ΔG^≠ = 13.9 kcal/mol and ΔG_R = −19.5 kcal/mol, see Figure 1), which nicely agrees with the experimental findings obtained during the optimization of the α-arylation reaction (see Table 1).
Figure 2. Computed reductive elimination reaction involving INT5'. Relative free energies ($\Delta G_{298}$, at 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data were computed at the PCM(tetrahydrofuran)-B3LYP-D3/def2-TZVP//PCM(tetrahydrofuran)-B3LYP-D3/def2-SVP level.

We then focused on understanding the negligible interference from the competitive Heck coupling reaction in the four-step domino process from N-alkyl-2-iodoanilines (see above, Tables 3 and 4). To this end, we computed the two possible reaction pathways, namely aza-Michael reaction $\text{vs}$ Heck reaction, starting from INT8, the intermediate formed upon the initial oxidative addition of the 2-iodo-N-methylaniline to the model Pd($\text{PMe}_3)_2$ catalyst (Figure 3).

This species, in the presence of $\text{CO}_3^{2-}$ as the base, may deprotonate, leading to the anionic complex INT9 in an exergonic process ($\Delta G_R = -9.9$ kcal/mol). Then, INT9 would react with the corresponding vinyl sulfone to produce INT10 through TS7, a saddle point associated with the
formation of the N–C bond ($\Delta G^\ddagger = 8.2$ kcal/mol) in an aza-Michael type process. Final protonation of $\text{INT10}$ leads to the formation of $\text{INT0}$, the common intermediate in the processes involving both 2-iodoanilines (Tables 3 and 4) and compounds 1 (Table 1 and 2). As clearly seen in Figure 3, the alternative Heck coupling reaction is not competitive in this transformation. This is mainly due to the high endergonicity ($\Delta G_R = 20.2$ kcal/mol) associated with the initial dissociation of a phosphine ligand, which is required to create a vacant coordination to allocate the incoming vinyl sulfone ligand. In addition, the electron-withdrawing effect of the SO$_2$Me group reduces the coordination ability of the attached double bond, which also renders the coordination of the vinyl sulfone to $\text{INT11}$ endergonic ($\Delta G_R = 4.8$ kcal/mol).$^{29}$ Although the subsequent insertion step via $\text{TS8}$ proceeds with a relatively low activation barrier ($\Delta G^\ddagger = 11.5$ kcal/mol), this highly unfavorable phosphine/vinyl sulfone ligand interchange makes the alternative Heck reaction very unlikely, which is fully compatible with the experimental observations.

The beneficial effect of bidentate phosphine ligands observed during the optimization of the four-step domino process (see for instance, Table 3) is also in nice agreement with the expected even higher endergonicity associated with the generation of the coordinatively unsaturated species (i.e. $\text{INT 11}$), which is required for the Heck coupling when using a chelating phosphine.
Figure 3. Computed reaction profiles for competitive aza-Michael and Heck coupling reactions from INT8. Relative free energies ($\Delta G^{298}$, at 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data were computed at the PCM(tetrahydrofuran)-B3LYP-D3/def2-TZVP//PCM(tetrahydrofuran)-B3LYP-D3/def2-SVP level.

Finally, we addressed the last steps of the domino process which involve the transformation of intermediate C (Scheme 1) into the observed 3-[2-(phenyl/methylsulfonyl)ethyl]indoles. Our DFT-calculations began from intermediate 2M, the indoline formed during the palladium-catalyzed $\alpha$-arylation (or CMD-reductive elimination) process described above (see Figure 1). Deprotonation of the highly acidic benzylic hydrogen atom by the base would lead to the formation of carbanion 2M-an, from which a rapid ($\Delta G^\neq = 6.4$ kcal/mol) and exergonic ($\Delta G_R = -3.7$ kcal/mol) Michael addition would take place via TS9. Protonation of intermediate 3M-an
would then produce the 3-(sulfonyl)indoline intermediate 3M, which would be transformed into the final indole 4M through TS10. As depicted in Figure 4, this final five-membered ring transition state is associated with a concerted β-elimination reaction of sulfinic acid. Despite the concomitant rupture of both the S–C and C–H bonds, the process was computed to be highly exergonic ($\Delta G_R = -16.5$ kcal/mol) and to proceed with a feasible activation barrier ($\Delta G^\ddagger = 18.1$ kcal/mol). This can be ascribed to the gain in aromaticity in the final indole derivative which therefore constitutes the thermodynamic driving force of the entire transformation.

**Figure 4.** Final transformation of indoline 2M into indole 4M. Relative free energies ($\Delta G_{298}$, at 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data were computed at the PCM(tetrahydrofuran)-B3LYP-D3/def2-TZVP//PCM(tetrahydrofuran)-B3LYP-D3/def2-SVP level.
In summary, we have developed a set of reaction conditions for a new four-step domino process toward 3-[2-(aryl/alkylsulfonyl)ethyl]indoles from readily available 2-iodoanilines. In this three-component domino process, the crucial intramolecular palladium-catalyzed \( \alpha \)-arylation of sulfones is combined with intermolecular aza-Michael and Michael additions to vinyl sulfones, as well as a highly selective \( \beta \)-elimination of sulfinic acid, avoiding any undesired competitive reactions. A series of diversely substituted 3-[2-sulfonylethyl]indoles were easily synthesized in moderate-to-high yields. According to DFT calculations, after the initial oxidative addition to the palladium catalyst, an aza-Michael reaction occurs without any significant interference from the alternative Heck coupling reaction. The \( \alpha \)-arylation process would then occur through a CMD/reductive elimination process thus leading to indoline derivatives. The latter species are finally converted into the observed 3-[2-(aryl/alkylsulfonyl)ethyl]indoles through two consecutive reaction steps involving an initial rapid Michael addition followed by an exergonic and concerted \( \beta \)-elimination reaction of sulfinic acid.

3. EXPERIMENTAL SECTION

**Representative procedure for the domino reactions (Table 3, Entry 7).** A mixture of \( N \)-benzyl-2-iodobenzylamine (80 mg, 0.26 mmol), \( \text{Pd}_2(\text{dba})_3 \) (18 mg, 0.019 mmol), dppf (21 mg, 0.039 mmol), phenyl vinyl sulfone (104 mg, 0.62 mmol), and \( \text{Cs}_2\text{CO}_3 \) (253 mg, 0.78 mmol) in THF (8 mL) was stirred at 120 °C in a sealed tube for 72 h. The reaction mixture was poured into water and extracted with Et\(_2\)O. The organic extracts were washed with brine, dried, and concentrated. The residue was purified by flash chromatography (\( \text{SiO}_2 \), from hexanes to hexanes-EtOAc 1:4) to give sulfone 6a (78 mg, 80%) as an amorphous brown solid.
4. COMPUTATIONAL DETAILS

All the calculations reported in this paper were obtained with the GAUSSIAN 09 suite of programs. Electron correlation was partially taken into account using the hybrid functional usually denoted as B3LYP in conjunction with the D3 dispersion correction suggested by Grimme and co-workers using the double-\(\zeta\) quality plus polarization def2-SVP basis set for all atoms. Reactants and products were characterized by frequency calculations and have positive definite Hessian matrices. Transition structures (TS’s) show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration using the Intrinsic Reaction Coordinate (IRC) method. Solvents effects were taken into account using the Polarizable Continuum Model (PCM). Single point calculations on the PCM(THF)-B3LYP-D3/def2-SVP geometries were performed to estimate the change in the Gibbs energies at the B3LYP-D3 level using the triple-\(\zeta\) quality plus polarization def2-TZVP basis set for all atoms. This level is denoted PCM(THF)-B3LYP-D3/def2-TZVP//PCM(THF)-B3LYP-D3/def2-SVP.

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, characterization data and copies of NMR spectra for all new compounds, as well as Cartesian coordinates of all species described in the text. This material is available free of charge via the Internet at http://pubs.acs.org.
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Notes

The authors declare no competing financial interest.

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REFERENCES


(22) Significant signals of indoline 2a from a crude reaction mixture containing 2a and 3a (2:1):

\[ ^{1}H \text{NMR (CDCl}_3, \text{ 300 MHz)} \delta \]

2.29 (s, 3H), 3.50 (dd, \( J = 11.7 \) and 9.6 Hz, 1H), 3.78-3.85 (m, 1H), 3.81 (d, \( J = 15.0 \) Hz, 1H), 4.12 (d, \( J = 15.0 \) Hz, 1H), 4.70 (dd, \( J = 9.6 \) and 2.1 Hz, 1H), 6.18 (d, \( J = 8.4 \) Hz, 1H).


(26) All calculations were performed at the PCM(tetrahydrofuran)-B3LYP-D3/def2-TZVP//PCM/tetrahydrofuran)-B3LYP-D3/def2-SVP level. See Computational Details.


(29) Similar endergonicity values have been computed for related Heck couplings involving methyl acrylate. See, for instance, Zhang, S.; Shi, L.; Ding, Y. J. Am. Chem. Soc. 2011, 133, 20218-20229.

(30) The computed free energy difference between TS10 and 3M-an of 35.6 kcal/mol seems unrealistic and can be ascribed to the initial protonation of 3M-an mediated by HCO3−. The high
endergonicity computed for the latter transformation (\(\Delta G = 16.7 \text{ kcal/mol}\)) seems unreliable and is very likely due to the well-known difficulties associated with the calculations involving either highly polar groups or charges species (such as HCO\(_3^-\), CO\(_3^{2-}\) or 3M-an) using continuum models (such as PCM in our case). For a discussion on this issue, see (a) Harvey, J. N. Faraday Discuss. 2010, 145, 487-505. (b) Cheng, G.-J.; Zhang, X.; Chung, L. W.; Xu, L.; Wu, Y.-D. J. Am. Chem. Soc. 2015, 137, 1706-1725. For a related example involving a “computationally intractable” acid-base mechanism, see: (c) Plata, R. E.; Singleton, D. A. J. Am. Chem. Soc. 2015, 137, 3811-3826. See also, (d) Proutiere, F.; Schoenebeck, F. Angew. Chem. Int. Ed. 2011, 50, 8192-8195.


