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# Triflimide-catalyzed allylsilane annulations of benzylic alcohols for the divergent synthesis of indanes and tetralins†

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The development of a triflimide-catalyzed annulation of benzylic alcohols with allylsilanes for the synthesis of indane or tetralin structures is reported. In this fragment coupling reaction, complexity is built rapidly from readily available starting materials to yield diverse sets of products with up to three contiguous stereocenters. Indanes or tetralins can be generated from common precursors depending on the structure of the allylsilane reagent used. The concise synthesis of several lignan natural products highlights the utility of this newly devised methodology.

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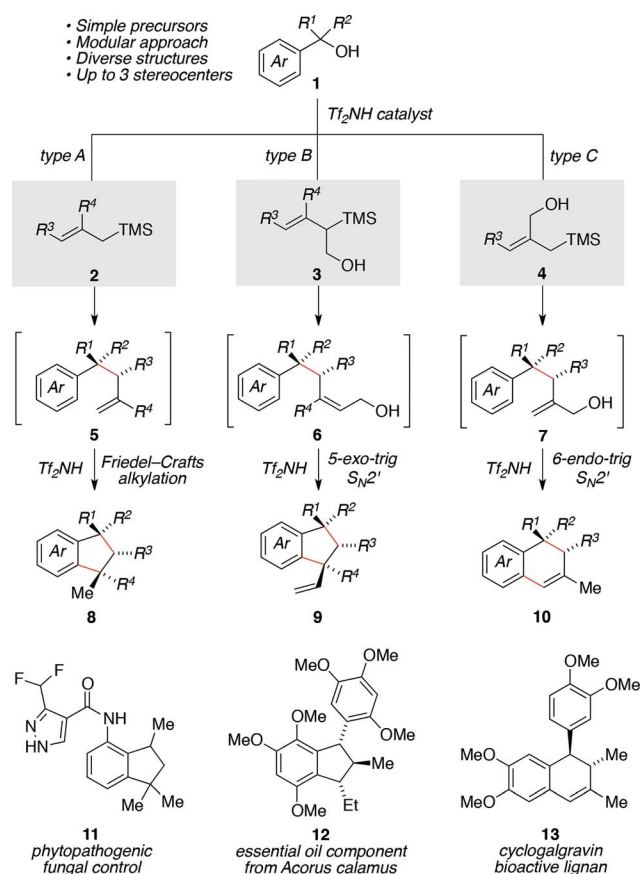
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## Introduction

Fragment coupling reactions that assemble complex products convergently from two or more reaction partners are exceptionally useful in synthesis.<sup>1</sup> This utility is amplified greatly when new stereochemical elements and rings are formed as a consequence of the reaction, allowing the synthesis practitioner to transform simple starting materials into complex cyclic or polycyclic products directly. Within this context, allylsilane reagents have received significant attention due to their capacity to participate in a wide range of complexity-generating annulations leading to the development of efficient methods for the concise synthesis of numerous chemical architectures,<sup>2</sup> including heterocycles<sup>3</sup> and carbocycles.<sup>3a-c,4</sup>

We saw an opportunity to contribute to this field through the development of a Brønsted acid-catalyzed allylsilane annulation that transforms simple benzylic alcohols into a range of indanes<sup>5,6</sup> or tetralins<sup>3c,d,7</sup> depending upon the choice of silane reagent used (Scheme 1). For the case of simple allylsilanes of type A (*i.e.*, 2) we envisioned a scenario where formation of a carbocation from alcohol 1 followed by allylsilane addition would lead to intermediate 5. An ensuing Friedel–Crafts alkylation would then deliver indane 8, whose structure maps onto a variety of useful compounds such as 11. Under the same reaction conditions, type B silanes (*i.e.*, 3) would give rise to an intermediate allylic alcohol 6, which would then undergo an acid-catalyzed 5-*exo*-trig cyclization to afford indane 9, a structure reminiscent of essential oil component 12. Use of the isomeric type C silane (*i.e.*, 4) would yield intermediate 7 in

a similar manner, allowing for a subsequent 6-*endo*-trig cyclization/alkene isomerization en route to 10 and representing a convergent approach to tetralin lignans (*i.e.*, 13).



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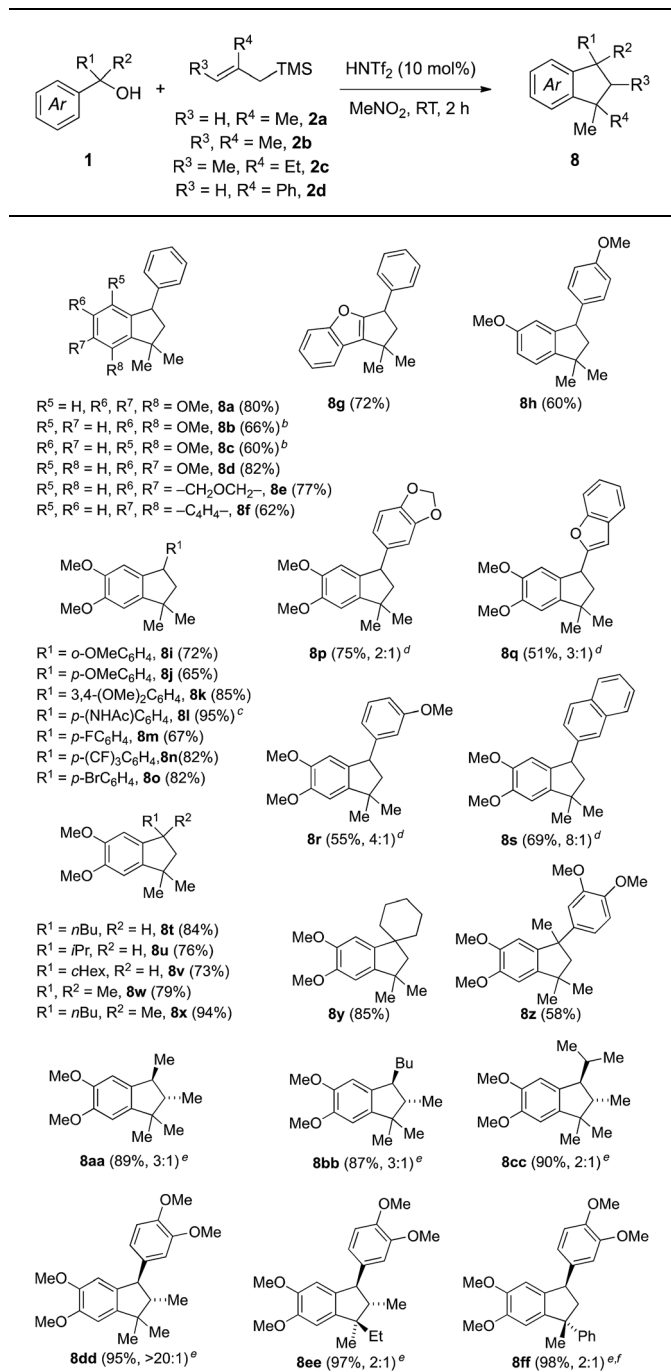
Scheme 1 Divergent access to indanes or tetralin products by way of a tandem allylation/ring-closure sequence catalyzed by triflimide.



## Results and discussion

We initiated our investigations (Table 1) using methallylsilane (**2a**), a commercially available type A silane, and quickly identified bis(trifluoromethanesulfonyl)imide (triflimide) as the

**Table 1** Substrate scope for [3 + 2] annulation reaction with benzhydryl and benzyl alcohols<sup>a</sup>



<sup>a</sup> Isolated yields after column chromatography. <sup>b</sup> Reaction run at 60 °C. <sup>c</sup> Reaction run at 80 °C. <sup>d</sup> Mixture of cyclization regioisomers; major product shown. <sup>e</sup> Diastereomeric ratio determined by <sup>1</sup>H NMR spectroscopy. <sup>f</sup> 0.9 equiv. of silane **2d** used.

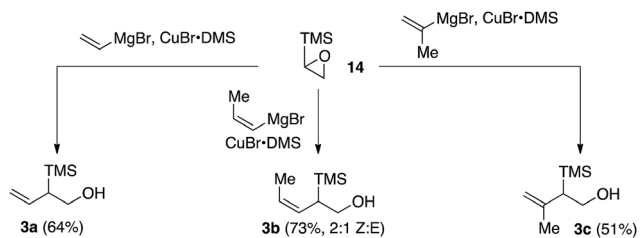
best catalyst, with nitromethane as the optimal solvent (see ESI for more details<sup>†</sup>). Using 10 mol% of triflimide, the reaction proceeded over the course of two hours at room temperature and proved tolerant to a range of benzylic alcohol precursors, thus delivering a diverse set of indane products in good to excellent yields (Table 1). In no cases did we observe products derived from silyl migration. For the case of benzhydryl alcohols where one aromatic ring was a simple phenyl group (**8a–8g**), the reaction proceeded such that cyclization took place on the more electron-rich ring. In some cases, such as **8b** or **8c**, yields were improved by running reactions at a higher temperature (60 °C) to overcome the steric encumbrance of cyclization onto aromatic rings with *ortho*-substituents. Only cyclization to the more electron-rich 1-position, rather than the 3-position, is observed for **8f**. In product **8g**, cyclization has occurred onto a benzofuran ring system to yield a 5,5,6-fused ring system, which while not technically an indane still represents a useful chemotype.<sup>8</sup>

Complete regioselectivity is observed for the cyclization leading to indanes **8h–8o** (Table 1), in line with the expectation that the Friedel–Crafts alkylation would take place *para* to the most electron releasing substituent. For cases where both rings are activated for cyclization, mixtures of regioisomeric products were obtained with modest to good selectivity (Table 1, **8p–8s**). A number of benzyl alcohols with alkyl substituents were employed using the same reaction conditions (Table 1, **8t–8y**). Indanes with two quaternary centers are formed in good yields (**8w–8z**). The efficient construction of spiroindane **8y** is particularly notable since this tricyclic core is found in many bioactive compounds and natural products.<sup>9</sup>

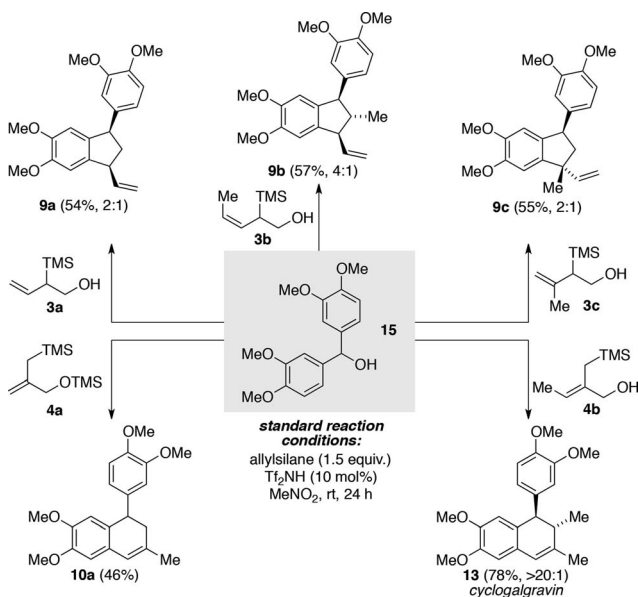
Use of alternative type A allylsilanes allowed access to a range of stereochemically complex indanes (Table 1, **8aa–8ff**). For example, silane **2b** allows for the introduction of two stereocenters within the indane products (**8aa–8cc**) with modest to excellent diastereoselectivity. For the three alkyl substituted products (**8aa–8cc**), the observed anti selectivity was modest as a consequence of low stereoselectivity in the initial addition of silane **2b** into the unsymmetrical benzyl cation intermediate derived from **1** (R<sup>1</sup> = Me, Bu or *i*Pr, R<sup>2</sup> = H). Cyclization in these cases does not generate a new stereocenter. On the other hand, indane **8dd** was generated in >20 : 1 dr due to preferential cyclization on one of the two diastereotopic electron-rich aromatic rings of the intermediate following initial silane addition. This outcome is consistent with related observations we had made during our previously reported synthesis of lignan natural products.<sup>10</sup> Use of silane **2c** gave rise to compound **8ee** that contains three contiguous stereocenters in high yield, but as a 2 : 1 mixture of diastereomers due to poor selectivity during cyclization to form the new quaternary stereocenter. A similar outcome was observed utilizing silane **2d** to produce indane **8ff**. In this last example, it was necessary to reduce the number of equivalents of allylsilane in order to suppress the competitive formation of a 7-membered ring analog formed by double addition of the silane (see ESI<sup>†</sup>).

We next sought to explore the utility of type B and type C silanes that would give rise to indanes or tetralins, respectively (see Scheme 1). While the desired type C silanes (*i.e.*, **4**) have





Scheme 2 Synthesis of allylsilane reagents from trimethylsilyloxypropene 14.

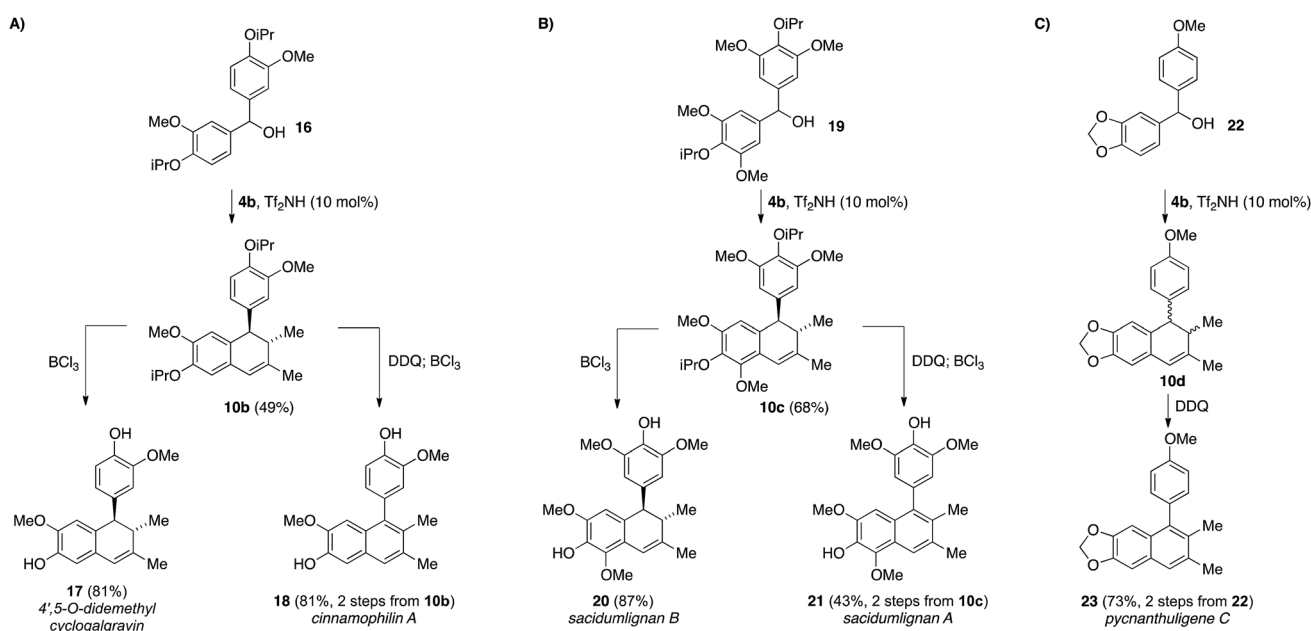


Scheme 3 Divergent synthesis of indane and tetralin compounds.

been reported in the literature,<sup>11</sup> general protocols to access the requisite type B silanes (*i.e.*, 3) were less well developed.<sup>12</sup> We therefore developed an effective protocol for the synthesis of silanes 3a–3c based on the regioselective addition of Grignard reagent-derived vinylcuprates to trimethylsilyloxypropene 14 (Scheme 2).<sup>13</sup>

Utilizing the symmetrical benzhydryl alcohol 15 as a common precursor we next demonstrated the capacity of type B and C allylsilanes to undergo the desired triflimide-catalyzed annulation processes (Scheme 3). The type B silanes 3a–3c gave rise to three different vinyl substituted indane products (9a–9c) in reasonable yield and with modest levels of diastereoselectivity, as observed for the corresponding type A silanes. Type C silane 4a was found to be superior to the corresponding free alcohol derivative, undergoing the desired addition/6-*endo*-trig cyclization/alkene isomerization to provide tetralin 10a in 46% yield. Type C silane 4b was more effective than silane 4a, providing tetralin 13 in 78% yield and with >20 : 1 selectivity for the anti stereochemistry. In this instance the product of the new annulation process is the natural product cyclogalgravin (13), thus establishing a highly efficient two-step total synthesis of this lignan from simple starting materials.<sup>14</sup>

Recognizing the power of this annulation process in accessing cyclolignan natural products,<sup>15</sup> we targeted the synthesis of several other related natural products in order to further demonstrate the usefulness of this methodology (Scheme 4). For example, symmetrical benzhydryl species 16 underwent the triflimide-catalyzed annulation with silane 4b to deliver dihydronaphthalene 10b in 49% yield (Scheme 4A). Selective removal of the two isopropyl ethers from 10b delivered the natural product 4',5-*O*-didemethylcyclogalgravin (17)<sup>16</sup> in 81% yield, while simple oxidation of 10b with DDQ allowed access to cinnamophilin A (18)<sup>17</sup> after isopropyl group cleavage (81%, 2 steps) from 10b in 81% yield, while simple oxidation of 10b with DDQ allowed access to cinnamophilin A (18)<sup>17</sup> after isopropyl group cleavage (81%, 2 steps). Conducting the same reaction sequences on the



Scheme 4 A general approach for accessing tetralin lignan natural products utilizing a triflimide-catalyzed allylsilane annulation.



more highly substituted benzhydryl starting material **19** provided access to the higher oxidation state analogs, sacidum lignan **B** (**20**) and **A** (**21**) with similar levels of efficiency (Scheme 4B).<sup>18</sup> The unsymmetrical benzhydryl **22** delivered the annulated product **10d** as a mixture of *cis* and *trans* stereoisomers, along with some of the naphthalene product **23**. Cyclization only occurred on the more electron-rich aromatic ring, and this mixture could be treated with DDQ without prior purification to deliver pycnanthuligene **C** (**23**) in 73% yield over two steps from **22**.<sup>19</sup>

## Conclusions

In summary, we have developed a Brønsted acid-catalyzed annulation for the divergent synthesis of substituted indanes and tetralins from a set of common precursors. The strategic ability to rapidly build complexity from commercially available or easily prepared starting materials makes this methodology amenable to the concise preparation of various chemotypes, including bioactive natural products. Future work will focus on the development of enantioselective variants of these reactions using chiral strong Brønsted acids, which is an exciting prospect given the recent advancements in that field.<sup>20</sup>

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