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Carbazole Annulation via Cascade Nucleophilic Addition–Cyclization Involving 2-(Silyloxy)pentadienyl Cation

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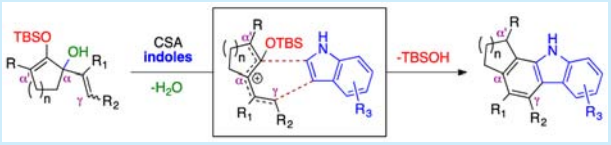
Supporting Information

ABSTRACT: We report a new strategy toward the synthesis of highly functionalized carbazoles via 2-(silyloxy)pentadienyl cation intermediates, which were generated upon ionization of vinyl-substituted α-hydroxy silyl enol ethers under Brønsted acid catalysis. These electrophilic species were found to readily undergo cascade reactions with substituted indoles to generate carbazole molecular scaffolds in good yields via a sequence of regioselective nucleophilic addition, followed by intramolecular dehydrative cyclization.



Carbazoles are a class of nitrogen heterocycles that play a significant role in both chemistry and biology. Due to their structural rigidity and extensive π-conjugation, these aromatic compounds have found vast applications in various organic photoelectronic materials and chromophores.[1] Carbazoles are also highly relevant in drug discovery, as they are commonly found in bioactive natural products and pharmaceutical agents.[2] As illustrated in Figure 1, molecules containing carbazole rings

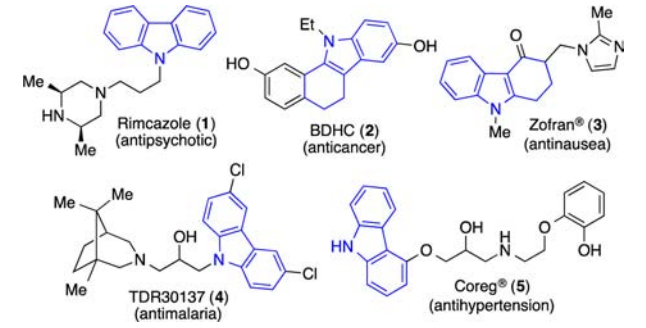
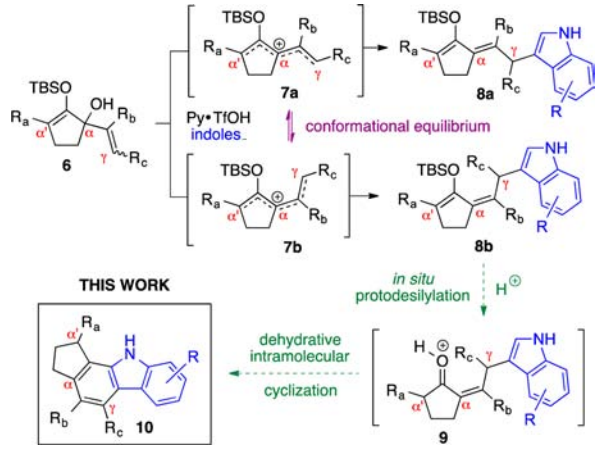


Figure 1. Medicinal activities of carbazole-derived compounds.

are known to exhibit a broad range of therapeutic activities against various human diseases, ranging from psychosis, cancer, nausea, and hypertension to malaria. Due to their widespread significance, the development of synthetic methods to create carbazole molecular scaffolds has remained important.[3] In this report, we detail our novel approach toward carbazole synthesis, highlighted by a novel cascade [4 + 2] bimolecular annulation involving 2-oxypentadienyl cations and unprotected indoles under Brønsted acid catalysis.

Recently, we became interested in exploring the reactivity of 2-oxypentadienyl cations, especially toward nucleophilic addition. Our preliminary studies revealed that vinyl-substituted α-hydroxy silyl enol ethers **6** could be readily ionized with catalytic pyridinium triflate to 2-(silyloxy)pentadienyl cations, which could exist as putative conformational isomers **7a** and **7b** (Scheme 1).[4] These intermediates could be then captured by

Scheme 1. Proposed Strategy in Carbazole Annulation



carbon nucleophiles, including substituted indoles, predictably at the least substituted electrophilic carbon, i.e., the γ-position, in a highly regioselective manner to produce silyldienol ethers **8a** and **8b**.[5] We also observed that the selectivity of the forming alkene geometry in these products was readily controlled by the substituent effect at the β-position.

Our ability to regulate both regioselectivity and the double-bond isomer in these reactions, especially toward formation of (*Z*)-silyldienol ethers **8b**, proved to be highly strategic toward carbazole synthesis. We envisioned that Brønsted acid promoted in situ protodesilylation would produce protonated α,β-unsaturated ketones **9**, leading to spontaneous intramolecular

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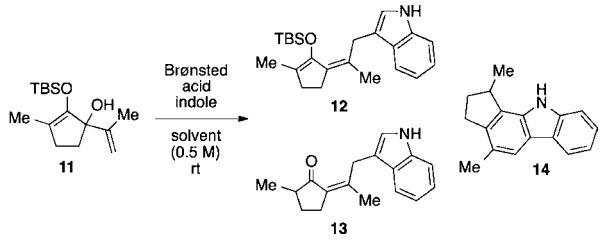
cyclization by the pendant indole ring to the carbonyl moiety. Upon expulsion of water, this nonreversible annulation reaction should generate highly functionalized carbazole core **10**. Recognizing that the formation of γ-indolyl (*Z*)-silyldienol ethers **8b** and the proposed cyclization from these compounds would both require catalytic Brønsted acid, we hypothesized that our carbazole synthesis could be achieved directly from vinyl-substituted α-hydroxy silyl enol ethers **6** through a cascade process, i.e., nucleophilic addition and cyclization. To the best of our knowledge, this strategy would represent the first example of carbazole annulation using 2-silyloxypentadienyl cations as the key intermediate.[6] Moreover, the bimolecular nature of our chemistry would advantageously enable elaboration of the forming carbazole scaffolds in a concise manner.

Our initial investigation is depicted in Table 1, in which α-hydroxy silyl enol ether **11** was employed for proof of concept.

Table 1. Proof of Concept and Reaction Optimization



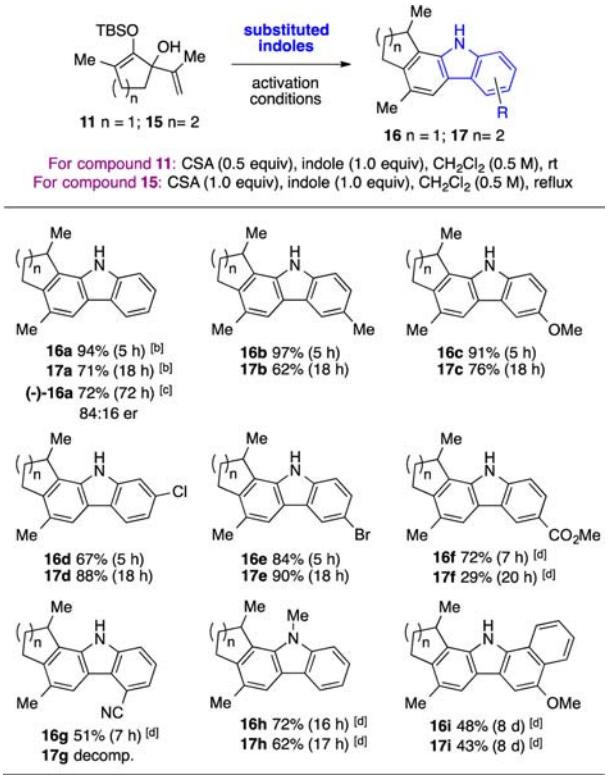
entry	solvent	acid	acid (equiv)	indole (equiv)	time (h)	yield[b] (%) **12:13:14**
1	toluene[a]	Py·TfOH	0.1	1.1	3	99:−:−
2	toluene	CSA	0.1	1.1	73	−:80:8
3	CH_2Cl_2	CSA	0.1	1.1	78	−:52:29
4	CH_2Cl_2	CSA	0.1	1.0	24	−:−:56
5	CH_2Cl_2	CSA	0.2	1.0	24	−:−:85
6	**CH_2Cl_2**	**CSA**	**0.5**	**1.0**	**5**	**−:−:95**

[a]The reaction was carried out in 0.2 M concentration based on starting material **11**. [b]Isolated yields after flash column chromatography.

We demonstrated that the use of catalytic pyridinium triflate in toluene at room temperature furnished γ-indolyl (*Z*)-silyl dienol ethers **12** (entry 1).[4] This control experiment produced neither α,β-unsaturated ketone **13** nor carbazole **14**, signifying that the mild acidity in pyridinium triflate was not enough to induce protodesilylation. As shown in entries 2 and 3, an attempt to activate compound **11** with a stronger Brønsted acid, such as camphorsulfonic acid (CSA) in nonpolar solvents, such as toluene and dichloromethane, generated predominantly α,β-unsaturated ketone **13** and also carbazole **14**, albeit in low yields. We ultimately chose dichloromethane due to the high solubility of CSA in this solvent. In addition, the molar equivalent of indole was reduced to alleviate challenges associated with the chromatographic purification of the desired carbazole from unreacted indole. Upon systematic screenings, the optimal conditions were established through the use of 0.5 equiv of CSA with equimolar amounts of α-hydroxy silyl enol ethers **11** and indole, which successfully produced carbazole **14** in a near-quantitative yield in just 5 h.

With the optimized conditions in hand, we then explored the scope of our chemistry toward various substituted indoles (Scheme 2). Indoles containing both electron-donating groups and halogen atoms were well tolerated to produce substituted carbazoles **16b−e** in excellent yields. Electron-deficient indoles, such as those containing 4-cyano and methyl 5-carboxylate

Scheme 2. Scope of Indoles[a]



[a]Isolated yields after flash column chromatography. [b]The structure of carbazoles **16a** and **17a** was unambiguously confirmed by X-ray crystallography.[7] [c]Conditions: (*R*)-TRIP (0.5 equiv), indole (1.0 equiv), CH_2Cl_2 (0.5 M), rt. [d]These reactions were performed at reflux.

substituents, also afforded the carbazole adducts **16f** and **16g** in 72% and 51% yields, respectively. Nonetheless, these reactions required a slightly elevated temperature to promote cyclization. The use of *N*-methylindole and 5-methoxy-1*H*-benzo[*g*]indole as a coupling partner furnished carbazole-derived compounds **16h** and **16i** in respectable yields. We also attempted to ionize vinyl substituted α-hydroxy silyl enol ethers **11** with 0.5 equiv of a chiral Brønsted acid, such as BINOL-derived phosphoric acid (*R*)-TRIP, in the presence of indole in dichloromethane at room temperature. This asymmetric reaction readily produced (−)-**16a** in 72% yield with an 84:16 enantiomeric ratio.[8]

The compatibility of 6-membered vinyl-substituted α-hydroxy silyl enol ether **15** in this methodology was also examined. Consistent with our previous findings,[5b] this substrate proved to be less reactive than the 5-membered counterpart and required more stringent activation conditions. Upon a short campaign in reaction optimization, we identified that tetrahydrobenzocarbazoles **17** could be prepared using a stoichiometric amount of CSA in dichloromethane at reflux. These conditions appeared to be tolerated by both electron-rich and halogenated indoles, as well as *N*-methylindole and 5-methoxy-1*H*-benzo[*g*]indole, affording the respective functionalized carbazoles **17a−e** and **17h,i** in good yields. Nevertheless, the use of electron-poor indoles only led to significant decomposition, producing ester-containing carbazole **17f** only in 29% yield.

As depicted in Table 2, the substituent effects in starting materials **18** were then investigated. Substrates possessing allyl, *n*-nonyl, phenyl, and indolyl groups at the α′-position (**18a−d**, respectively) were found to be compatible and afforded carbazoles **19a−d** in respectable yields. We also examined the

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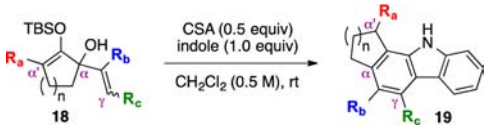
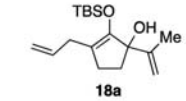
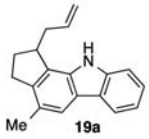
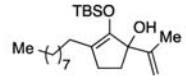
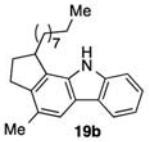
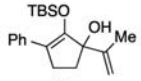
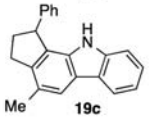
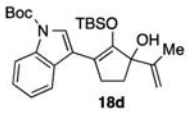
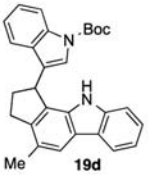
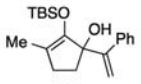
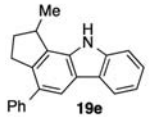
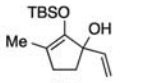
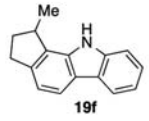
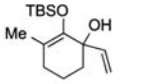
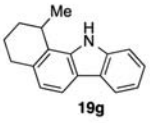
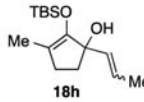
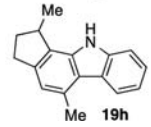
Table 2. Scope of Substrates



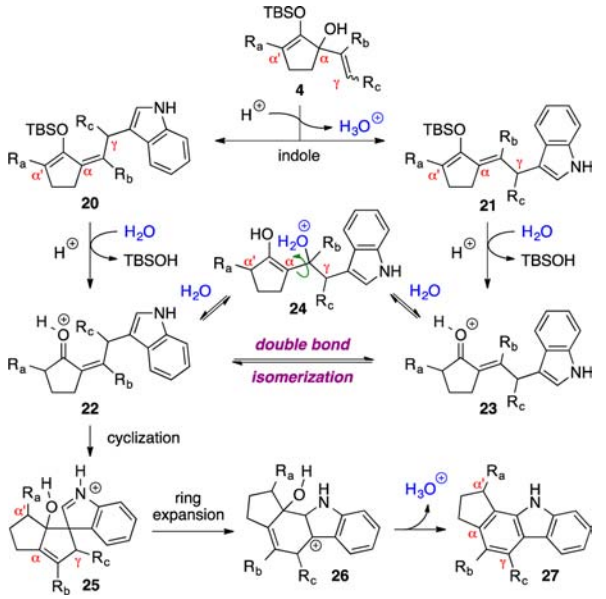
entry	starting material	product	yield (time) [a]
1	 18a	 19a	51% (5 h)
2	 18b	 19b	74% (96 h)
3	 18c	 19c	63% (24 h)
4	 18d	 19d	43% (19 h)
5	 18e	 19e	92% (19 h)
6	 18f	 19f	70% (96 h)
7	 18g	 19g	71% (20 h) [b]
8	 18h	 19h	trace (96 h)

[a]Isolated yields after flash column chromatography. [b]Reaction conditions: CSA (1.0 equiv), indole (1.0 equiv), CH_2Cl_2 (0.5 M), reflux.

β- and γ-positions. Surprisingly, the use of the β-phenyl ring and β-hydrogen atom as exemplified in starting materials **18e–g** readily produced their respective carbazoles **19e–g** in high yields. These results were remarkable, considering the fact that these β-substitution patterns would have generated an incorrect alkene geometry in their corresponding γ-indolyl silyl dienol ether adducts for the ensuing carbazole formation.[4] In contrast, treatment of γ-methyl α-hydroxy silyl enol ether **18h** under the same conditions produced carbazole **19h** only in a trace quantity, even though this substrate would have similarly generated the (*E*)-isomer that, as anticipated, prevented the intramolecular cyclization.

On the basis of these observations, the reaction mechanism of our carbazole synthesis is proposed as follows, which commenced with γ-functionalization of vinyl substituted α-hydroxy silyl enol ethers **4** with indole promoted by CSA (Scheme 3). Through an intermediacy of 2-(silyloxy)pentadienyl

Scheme 3. Proposed Reaction Mechanism



cations **5** and **7** and depending upon the β-substituent effects, this nucleophilic substitution produced γ-indolyl adduct **20** or **21** (or as a mixture). Facilitated by catalytic CSA and trace water generated in the initial ionization step, silyl dienol ethers **20** and **21** then proceeded to protodesilylation, thus unmasking α,β-unsaturated ketones that were further activated to protonated carbonyls **22** and **23** upon proton transfer. These reactive intermediates then underwent a reversible alkene isomerization presumably via enol **24**,[9] produced upon a conjugate addition by water at the β-carbon. This equilibrium would gradually allow for the funneling of the alkene geometry in **22** to the key intramolecular carbonyl addition by the pendant indole ring to generate spirocyclic iminium ion **25**. A subsequent ring expansion, followed by regeneration of aromaticity through the loss of a hydronium ion, then completed the formation of carbazole **27**.

The presumed involvement of water in the alkene isomerization between protonated α,β-unsaturated ketones **22** and **23** was supported by a series of experiments as depicted in Scheme 4, in which we examined the propensity of γ-indolyl (*E*)-silyldienol ether **28** toward carbazole cyclization in two related conditions. Indeed, exposure of this compound to catalytic CSA in the presence of 1.0 equiv of water readily produced carbazole **19f** in 88% yield. In contrast, when water was completely excluded, the reaction only generated a complex mixture of protodesilylated materials. Our proposed mechanism also illuminated the lack of reactivity in substrate **18h**. While this compound produced the (*E*)-geometry upon indole addition,[4] it appeared that the steric congestion imposed by the γ-methyl group seemingly inhibited water addition at the β-position, thus preventing the crucial alkene isomerization.[9] This hypothesis was further supported by the fact that exposure of starting material **18h** to equimolar amounts of CSA and indole in the presence of 5 equiv of water in more forcing conditions, i.e., dichloroethane at reflux, improved the production of carbazole **19h** to 25% yield.

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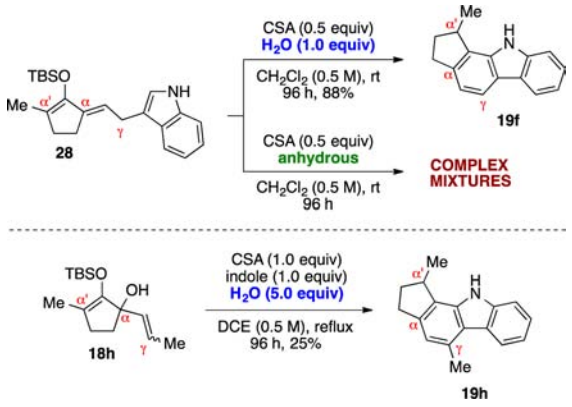
Scheme 4. Supporting Evidence



In summary, we developed a new strategy toward the synthesis of highly functionalized carbazoles under Brønsted acid catalysis. This method was enabled by an intermediacy of 2-(silyloxy)-pentadienyl cations, which were exploited in strategic cascade processes involving a regioselective nucleophilic addition by unprotected indoles, followed by spontaneous intramolecular dehydrative cyclization. We also investigated the plausible reaction mechanism, which suggested the participation of water in the key alkene isomerization, thus enabling carbazole annulation. Efforts toward extending this synthetic methodology to other biologically relevant heterocyclic compounds are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01376.

Experimental procedures and spectral data of new compounds (PDF)
Crystallographic data for compound **16a** (CIF)
Crystallographic data for compound **17a** (CIF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This manuscript is dedicated to Prof. Elis Lee at Glendale Community College, Glendale, CA.

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(7) CCDC 1465143 and 1465144 contains the supplementary crystallographic data for compounds **16a** and **17a**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

(8) This encouraging preliminary result, while not yet optimal, clearly demonstrated proof-of-concept on the possibility to promote enantioselectivity in this chemistry. While the chiral HPLC analyses and optical rotation measurements undoubtedly confirmed enantioenrichment, only racemic crystals have thus far been obtained from enantioenriched carbazole (−)-**16a**. As a result, the absolute configuration of the (−)-enantiomer has not yet been established from X-ray data. Attempts to employ other substituted indoles under these unoptimized conditions proved to be low yielding. Efforts towards improving these asymmetric catalytic conditions are ongoing in our laboratory, and we will report our findings in due course.

(9) At this point, we could not rule out an alternative mechanism for the proposed alkene isomerization involving water-promoted tautomerization of protonated α,β-unsaturated ketones **22** and **23** at the γ-position to their corresponding conjugated dienols.

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