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Effects of Solvent and Residual Water on Enhancing the Reactivity of Six-Membered Silyloxyallyl Cations toward Nucleophilic Addition

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Supporting Information

ABSTRACT: A new strategy for the generation of six-membered unsymmetrical silyloxyallyl cations using catalytic mild Brønsted acid is reported. These reactive intermediates were found to readily undergo direct nucleophilic addition with a broad range of nucleophiles to produce various α,α'-disubstituted silyl enol ether structural motifs. The findings also highlight the significance of the solvent effect and residual water in enhancing the reaction rate.

The development of synthetic methods that incorporate indole at the α-position of cyclohexanone has recently gained considerable interest. This emerging area of study has largely been inspired by synthetic endeavors from the Baran laboratory, which demonstrated the strategic utility of this type of molecular scaffold toward concise and elegant total syntheses of indole alkaloid natural products such as (−)-fischerindole I, (+)-hapalinole Q, and (+)-ambiguine H (Figure 1), among others.[1] Over the past several years, a particularly interesting strategy to construct α-indolyl cyclohexanone has been exemplified through the generation of zwitterionic oxyallyl cation **2** from the corresponding cyclohexanone precursor **1**, which can then be directly captured by indole at the α-carbon (Figure 1).[2] While generally robust, the scope of this chemistry nonetheless suffers from a lack of regiocontrol when α-branched unsymmetrical oxyallyl cations are used.[2f,g]

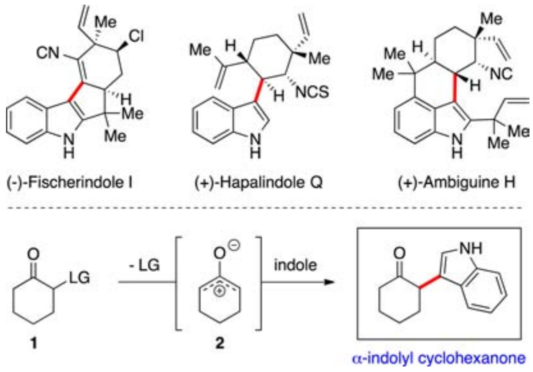
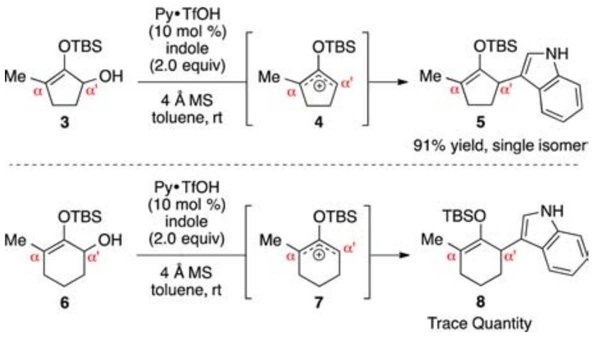


Figure 1. Direct addition of indole to oxyallyl cations.

To address this fundamental issue, we recently demonstrated that simply by "protection" of the forming oxyallyl cation with a silyl group at the oxygen center (viz. **4**), the ensuing addition of indole could be controlled exclusively at the less-substituted electrophilic carbon (i.e., the α'-position), thereby producing α'-indolyl silyl enol ether **5** as a single regioisomer in excellent yield (Scheme 1).[3] This putative unsymmetrical silyloxyallyl cation intermediate was efficiently produced from α'-hydroxy starting material **3** upon ionization with catalytic pyridinium triflate in toluene at room temperature. Surprisingly, exposure of the analogous six-membered starting material **6** to these very mild conditions failed to generate the target product **8**. In fact, this substrate largely remained unreacted. We attributed this profound lack of reactivity to the destabilization of silyloxyallyl cation **7** due to the emerging allylic strain that appeared to be more pronounced in this cationic species compared with that of the five-membered variant **4**.[4]

Scheme 1. Limitation of the Previous Methodology



Given this limitation, we sought to develop a viable solution to further broaden the scope of our chemistry. We hypothesized that the barrier to formation of silyloxyallyl cation **7** could be overcome by applying the Hughes−Ingold rules,[5] which outline the role of polar solvents in accelerating the rate of reactions involving the formation of charged intermediates. In our previous studies, we deliberately employed a nonpolar solvent, such as

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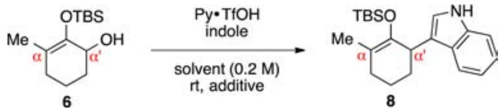
toluene, to maximize the rate of proton transfer between the Brønsted acid catalyst and the α'-hydroxyl group while suppressing protodesilylation. As we embarked on this investigation, we were naturally cognizant that the use of polar solvents could potentially enhance the rate of protodesilylation,[6] thus altering the delicate kinetic balance between these two competitive processes.

Table 1 depicts our reaction optimization. As a starting point, we activated α'-hydroxy silyl enol ether **6** with 0.1 equiv of pyridinium triflate and 1.1 equiv of indole in a slightly polar solvent, dichloromethane (entry 1).[7] To prevent reversibility in the ionization step, 4 Å molecular sieves were introduced to remove water byproduct from the reaction mixtures.[3d] Interestingly, this reaction produced the intended α'-indolyl silyl enol ether **8** in a trace amount despite an extended reaction time.[8] Removal of the molecular sieves resulted in an unexpected improvement in the rate of reaction (entry 2). Nonetheless, when similar conditions were applied in toluene, the starting material never fully disappeared even when the reaction was allowed to run for 2 weeks (entry 3). Astonishingly, ionization of **6** in acetonitrile led to its full consumption in just 26 h, leading to the isolation of the coupling product **8** in 71% yield as a single regioisomer (entry 4).

Table 1. Reaction Optimization[a]



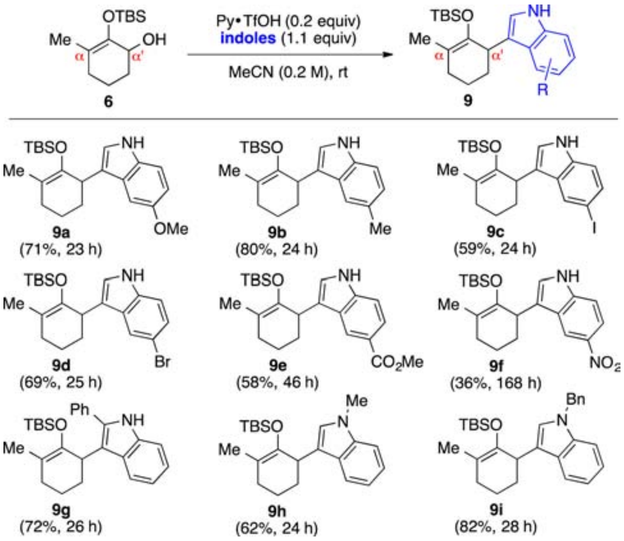
entry	solvent	equiv of acid	additive	equiv of indole	time (h)	yield (%)
1	CH_2Cl_2	0.1	4 Å MS	1.1	>300	trace[b]
2	CH_2Cl_2	0.1	--	1.1	48	52
3	toluene	0.1	--	1.1	>300	40[b]
4	MeCN	0.1	--	1.1	26	71
5	**MeCN**	**0.2**	**--**	**1.1**	**26**	**82**
6	MeCN	0.5	--	1.1	7	80
7	MeCN	1.0	--	1.1	3	85
8	MeCN	0.2	--	1.0	24	76
9	MeCN	0.2	--	2.0	25	81
10	MeCN	0.2	4 Å MS	1.1	>300	18[b]
11	MeCN	0.2	H_2O[c]	1.1	13	60

[a] Isolated yields after flash column chromatography are shown. [b] Starting material **6** was not fully consumed. [c] 0.1 equiv of water was added.

After the solvent screening, the catalyst loading was then investigated through the systematic use of 0.2, 0.5, and 1.0 equiv of pyridinium triflate (Table 1, entries 5−7). While the reaction rate correspondingly accelerated with increasing concentration of the Brønsted acid, the isolated yield of silyl enol ether product **8** only improved to around 80%. Lastly, our attention turned to optimizing the amount of indole (entries 8 and 9). We observed that the use of either 1.0 or 2.0 molar equiv of indole did not particularly affect the yield or reaction rate. Our attempt to perform this reaction in a completely anhydrous environment was again found to be unfruitful (entry 10). In contrast, the addition of catalytic water into the mixture appeared to accelerate the reaction but lowered the isolated yield of **8** (entry 11). Nonetheless, we ultimately established the ionization conditions listed in entry 5 as optimal for the α'-functionalization of silyl enol ether **6** with indole.

With these reaction conditions, we then explored the scope of various substituted indoles (Scheme 2). Unsurprisingly, electron-rich indoles, such as 5-methoxyindole and 5-methylindole, afforded products **9a** and **9b** in 71% and 80% yield, respectively. The use of halogen-containing indoles showed that this methodology readily produced iodinated and brominated silyl enol ethers **9c** and **9d**, which could be further utilized in downstream reactions to introduce more densely functionalized materials. Our reaction also appeared to tolerate electron-deficient methyl indole-5-carboxylate and 5-nitroindole, which furnished α'-indolyl adducts **9e** and **9f**, albeit in lower yields at lower reaction rates. Other substitution patterns, such as sterically hindered 2-phenylindole as well as protected *N*-methylindole and *N*-benzylindole successfully produced silyl enol ethers **9g−i** in good yields. Compounds **9d** and **9g** existed as crystalline materials, thus enabling us to unambiguously confirm their structures by X-ray crystallography.[9]

Scheme 2. Scope of Substituted Indoles[a]



[a] Isolated yields after flash column chromatography are shown. All products were isolated with >20:1 regioselectivity.

Our investigation then continued with the screening of substituent effects at the α-carbon (Table 2). To enable rapid diversification at this position, we designed an alternative starting material in tertiary α-hydroxy silyl enol ether **10** with the hypothesis that ionization of this compound under the typical reaction conditions should produce unsymmetrical silyloxyallyl cations **11**.[7] Similarly, the ensuing nucleophilic addition by indole should then occur at the less-substituted electrophilic α'-carbon and generate the intended coupling product **12**. As a proof of concept, we began with α-methyl silyl enol ether **10a**. Activation of this substrate with catalytic pyridinium triflate and indole under conditions identical to those for ionization of **6** cleanly afforded α-methyl α'-indole adduct **12a** (**8**) with a comparable yield and reaction time (entry 1). A further investigation using *n*-octyl **10b**, allyl **10c**, isobutyl **10d**, and cyclohexyl **10e** revealed the tolerance of various aliphatic groups at the α-carbon, as the respective α'-indolyl products **12b−e** were readily isolated in high yields (entries 2−5). Interestingly, we observed a substantial enhancement in the reaction rate associated with substrates **10d** and **10e**. Although the exact origin of this behavior is currently unclear, we speculated that steric congestion at the α-carbon might have affected the extent of ionization of these starting materials, which was presumed to be reversible and rate-determining.

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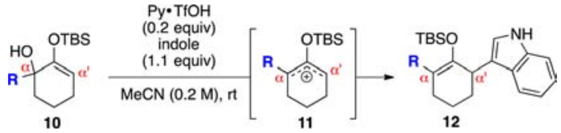
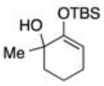
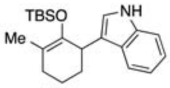
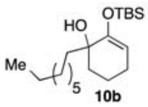
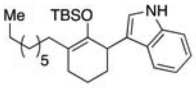
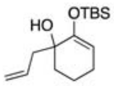
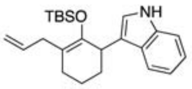
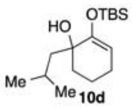
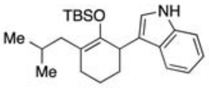
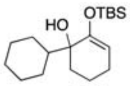
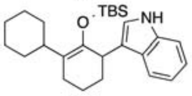
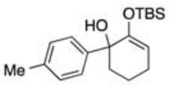
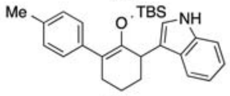
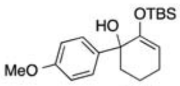
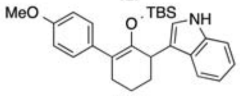
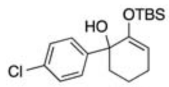
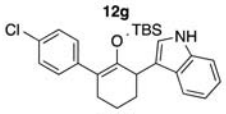
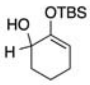
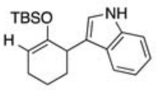
Table 2. Scope of Substrates[a]



10 11 12

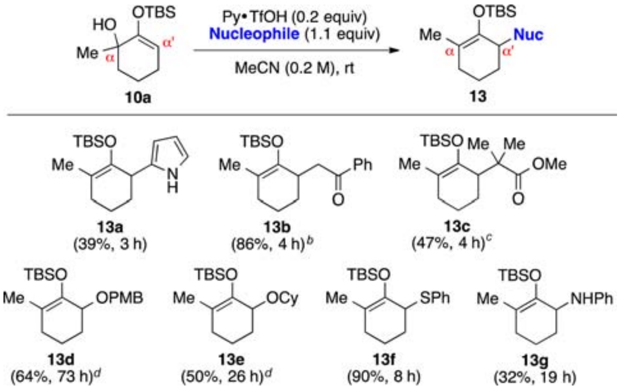
entry	starting material	product	time (h)	yield (%)
1	 **10a**	 **12a**	24	73
2	 **10b**	 **12b**	16	79
3	 **10c**	 **12c**	24	72[b]
4	 **10d**	 **12d**	5	83
5	 **10e**	 **12e**	6	76
6	 **10f**	 **12f**	168	82
7	 **10g**	 **12g**	22	75
8	 **10h**	 **12h**	>500	50[c]
9	 **10i**	 **12i**	no reaction	

[a]Isolated yields after flash column chromatography are shown. All products were isolated with >20:1 regioselectivity. [b]A prolonged reaction time resulted in the decomposition of the product. [c]The starting material **10h** was not fully consumed.

As illustrated in Table 2, entries 6–8, the effect of aromatic substituents was then examined, starting with α-tolyl substrate **10f**. While exposure of this compound to the typical indolylation conditions produced the corresponding α,α'-diaryl silyl enol ether **12f** in 82% yield, the reaction was extremely sluggish. We believed that this surprisingly longer reaction time was most likely attributable to the unfavorable 1,3-allylic strain inherent in the emerging silyloxyallyl cation **11** due to the presumed planarization between the tolyl group and the oxyallyl cation moiety, enabling delocalization of π electrons. This stereoelectronic trade-off appeared to be readily controlled by the substituent on the aromatic ring. For instance, the introduction of an electron-rich *p*-methoxyphenyl substituent in **10g** cleanly afforded silyl enol ether **12g** in merely 22 h. The proposed participation of putative silyloxyallyl cation **11** as an intermediate in our methodology was supported by the experiments depicted in entries 8 and 9. Treatment of starting material **10h** with catalytic pyridinium triflate and indole led to an extremely sluggish reaction, implying that the weakly deactivating *p*-chlorophenyl substituent readily impeded the formation of the cationic species. Similarly, the unsubstituted substrate **10i** failed to react, thus indicating that (1) the alternative S_N2' mechanism is unlikely to be responsible for the formation of observed substitution products, especially since both starting materials **6** and **11a** yielded the same product, and (2) substitution effects at the α-position are crucial to help stabilize the silyloxyallyl cation intermediate.

We also investigated the suitability of other carbon and heteroatom nucleophiles beyond substituted indoles using tertiary α-hydroxy silyl enol ether **10a** as the substrate (Scheme 3). While benzothiophene and benzofuran failed to capture the putative silyloxyallyl cation **7**, the use of pyrrole readily furnished coupling product **13a** in a modest yield. To underscore the mildness of our reaction conditions, we demonstrated the compatibility of acid-labile π nucleophiles, such as 1-phenyl-1-trimethylsiloxyethylene and methyl trimethylsilyl dimethylketene acetal. Such nucleophiles produced the corresponding 1,4-dicarbonyl-derived products **13b** and **13c** in good yields. Our ability to selectively differentiate the two carbonyl groups in these compounds while creating a new carbon–carbon connectivity in one single synthetic operation clearly highlights the novelty of our chemistry. With regard to heteroatom-centered nucleophiles, applications of both primary and secondary alcohols in *p*-methoxybenzyl alcohol and cyclohexanol proceeded to afford their corresponding α'-alkoxy silyl enol ethers **13d** and **13e** in 64% and 50% yield, respectively. We also tested thiophenol and aniline, which yielded products **13f** and **13g** in 90% and 32% yield, respectively.

Scheme 3. Scope of Nucleophiles[a]



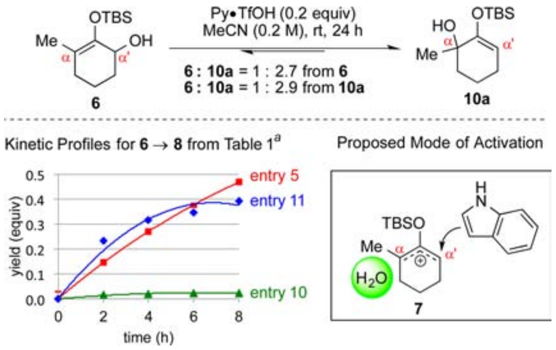
10a **13**

13a (39%, 3 h)
13b (86%, 4 h)[b]
13c (47%, 4 h)[c]
13d (64%, 73 h)[d]
13e (50%, 26 h)[d]
13f (90%, 8 h)
13g (32%, 19 h)

[a]Isolated yields after flash column chromatography are shown. All products were isolated with >20:1 regioselectivity. [b]2.0 equiv of 1-phenyl-1-trimethylsiloxyethylene was employed. [c]3.0 equiv of methyl trimethylsilyl dimethylketene acetal was employed. The reaction was carried out at −10 °C and then warmed to rt. See the Supporting Information. [d]2.0 equiv of alcohols was employed.

In the course of reaction optimization, we observed the significance of residual water in enhancing the reaction rate. In fact, kinetic measurements on three sets of activation conditions (Table 1, entries 5, 10, and 11) unambiguously established this reactivity pattern (Scheme 4).[10] To further probe the role of water in our methodology, we treated secondary and tertiary α'-hydroxy silyl enol ethers **6** and **10a** individually with 0.2 equiv of

Scheme 4. Probing the Role of Water



[a]The reaction progress was monitored by HPLC analyses of the crude reaction mixtures using 0.1 equiv of naphthalene as an internal standard. These compounds were assumed to elicit identical LC responses at 254 nm.

pyridinium triflate in acetonitrile. Upon equilibration for 24 h, each sample was found to produce a mixture of isomers **6** and **10a**, favoring the tertiary alcohol **10a** in a roughly 3:1 ratio as determined by NMR analyses of the crude materials. From these results, in conjunction with the solvation effect provided by the subtle polarity in acetonitrile, we proposed that silyloxyallyl cation **7** is perhaps further stabilized by residual water via a noncovalent interaction at the tertiary electrophilic center, en route to nucleophilic addition with indole at the α'-position. This hypothesis was supported by the fact that the introduction of catalytic water (entry 11) appeared to induce substantial rate acceleration during the initial progression of the reaction where the amount of water generated from the ionization of starting material **6** was essentially negligible. Whether this underlying intermolecular force involves solvent separation or more intimate pairing is unclear at this juncture, and further studies are currently ongoing.

In conclusion, we have successfully developed a new strategy that addresses the lack of reactivity of six-membered unsymmetrical silyloxyallyl cations toward direct nucleophilic addition. Given the mildness of the activation conditions, our methodology was readily tolerated by a broad scope of substrates and nucleophiles. While our initial mechanistic investigation revealed the significance of acetonitrile and residual water in enhancing the rate of reaction, we are now pursuing in-depth studies to further probe the mechanism, including the origin of the regioselectivity. Our results will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02194.

Experimental procedures and spectral data (PDF)
Crystallographic data for **9d** (CIF)
Crystallographic data for **9g** (CIF)

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Notes

The authors declare no competing financial interest.

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(4) While six-membered oxyallyl cations can be generated under base-promoted activation conditions (see ref 2f–i), the use of milder catalytic protocols was shown to be ineffective (see ref 2j)

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(6) (a) Schubert, M.; Metz, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 2954. (b) Fischer, D.; Nguyen, T. X.; Trzoss, L.; Dakanali, M.; Theodorakis, E. A. *Tetrahedron Lett.* **2011**, *52*, 4920. (c) O'Connor, P. D.; Del Signore, G.; McLachlan, M. M. W.; Willis, A. C.; Mander, L. N. *Aust. J. Chem.* **2010**, *63*, 1477. (d) Spivey, A. C.; Martin, L. J.; Grainger, D. M.; Ortner, J.; White, A. J. P. *Org. Lett.* **2006**, *8*, 3891.

(7) Compounds **6**, **10**, and **13** were readily prepared in just a few steps from commercially available materials. See the Supporting Information.

(8) Interestingly, ionization of substrate **6** with 0.1 equiv of CSA in dichloromethane at −78 °C in the presence of indole and 4 Å molecular sieves, following a protocol described in ref 3a, failed to produce the target α'-indolyl silyl enol ether **8**.

(9) CCDC 1493044 and 1493045 contain the supplementary crystallographic data for compounds **9d** and **9g**, respectively. These data can be obtained from The Cambridge Crystallographic Data Centre.

(10) The lower product yield in Table 1, entry 11 was most likely caused by competitive water-promoted decomposition of starting material **6** under the reaction conditions.