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Development of a Friedel–Crafts Triflation

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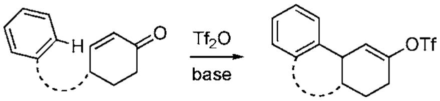
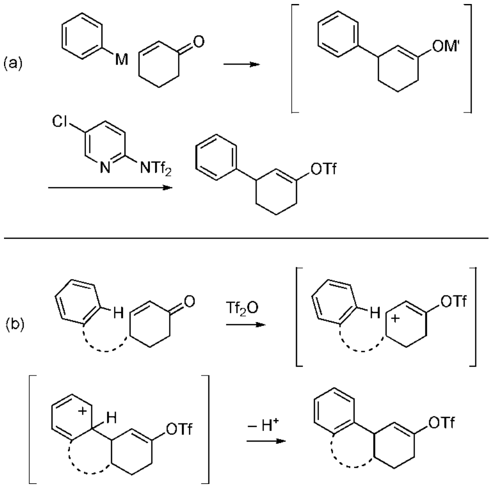
ABSTRACT



The development of a new variant of the Friedel–Crafts reaction that yields 3-aryl enol triflates is described. The reaction is practical, is atom-economical, and works well with electron-rich arene substrates.

The conjugate addition of an organocuprate to an enone followed by trapping of the resulting enolate as an enol triflate is a powerful strategy for the regioselective installation of double bonds (Scheme 1a).[1] Although it has been widely used in synthesis, this sequence is largely limited to *inter*molecular cases. In the *intra*molecular sense, the generation of the organometallic species is normally incompatible with the presence of an enone; in other words, Barbier conditions cannot be easily applied. Radical additions, on the other hand, which are compatible, do not lend themselves well to triflation. In addition, the formation of the organometallic species or radical usually requires prior functionalization as a halide, which is undesirable from an atom-economical point of view.

Scheme 1. Regioselective Formation of Enol Triflates



A solution to this problem could consist of the activation of an enone with the highly electrophilic reagent triflic anhydride, followed by reaction of the resultant allylic cation with a suitable nucleophile (Scheme 1b).[2] The use of triflic anhydride for the electrophilic activation of simple carbonyl compounds is indeed well documented.[3] Somewhat surprisingly, however, the ability of this reagent to activate *enones* toward reaction with carbon nucleophiles remains largely unexplored. If the attacking nucleophile was an arene, the overall reaction would amount to a Friedel–Crafts alkylation with concomitant formation of an enol triflate.

Our interest in this reaction initially came from a need in total synthesis (Scheme 2). During our synthetic study toward the haouamines, we found that treatment of enone **1** with triflic anhydride and a sterically hindered base gave com-

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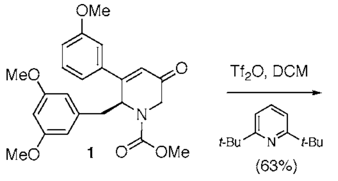
[1] Perlmutter, P. In *Conjugate Addition Reactions in Organic Synthesis*; Baldwin, J. E., Magnus, P. D., Eds.; Tetrahedron Organic Chemistry Series; Pergamon Press: Oxford, 1992; Vol. 9.

[2] For activation of enones with other anhydrides, see: (a) Cooper, J. L.; Harding, K. E. *Tetrahedron Lett.* **1977**, *18*, 3321. (b) Harding, K. E.; Cooper, J. L.; Puckett, P. M.; Ryan, J. D. *J. Org. Chem.* **1978**, *43*, 4363. (c) Amupitan, J.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1980**, 398.

[3] (a) Baraznanok, I. L.; Nenajdenko, V. G.; Balenkova, E. S. *Synthesis* **1997**, 465. (b) Baraznanok, I. L.; Nenajdenko, V. G.; Balenkova, E. S. *Tetrahedron* **2000**, *56*, 3077. (c) Liang, G.; Xu, Y.; Seiple, I. B.; Trauner, D. *J. Am. Chem. Soc.* **2006**, *128*, 11022.

10.1021/ol061980g CCC: \$33.50

Scheme 2. Discovery of the Reaction

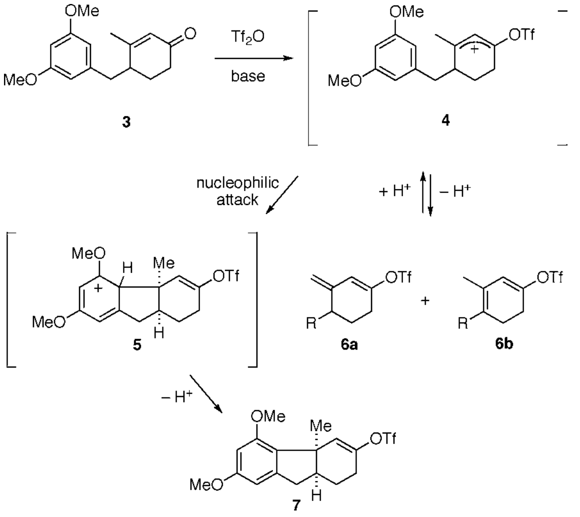


pound **2**, representing the indeno-tetrahydropyridine core of the natural products.[4]

Concerned that this reaction represented a specialized case due to the very electron-rich nature of the enone moiety and the arene, which would benefit electrophilic activation and nucleophilic attack, respectively, we decided to map its scope and limitations. We now report the further development of the reaction, which proved useful for the synthesis of polycyclic ring systems with regio-defined double bonds but appears to be limited to relatively electron-rich arenes. We call this reaction "Friedel−Crafts triflation" because it can be viewed as a new variant of this venerable electrophilic aromatic substitution.

To identify optimal conditions for the reaction and gain insight into its mechanism, we chose dimethoxybenzyl cyclohexenone **3** as a standard substrate (Scheme 3). This

Scheme 3. Optimization of the Friedel−Crafts Triflation



compound was prepared in a short sequence via Stork−Danheiser alkylation (see Supporting Information).[5]

Treatment of **3** with triflic anhydride in different solvents and in the presence of a variety of bases gave the desired product **7** in variable yields. In less polar solvents, we only isolated trifloxy dienes **6a**,**b** (Table 1, entries 1−3). These compounds presumably stem from deprotonation of the cationic intermediate **4** competing with an interceding intramolecular nucleophilic attack of the arene. Resubjection of **6a**,**b** to triflic acid led to clean cyclization to afford **7**. This means that trifloxy dienes can undergo protonation by triflic acid (pK_a = −14) to afford allylic cations of type **4**.

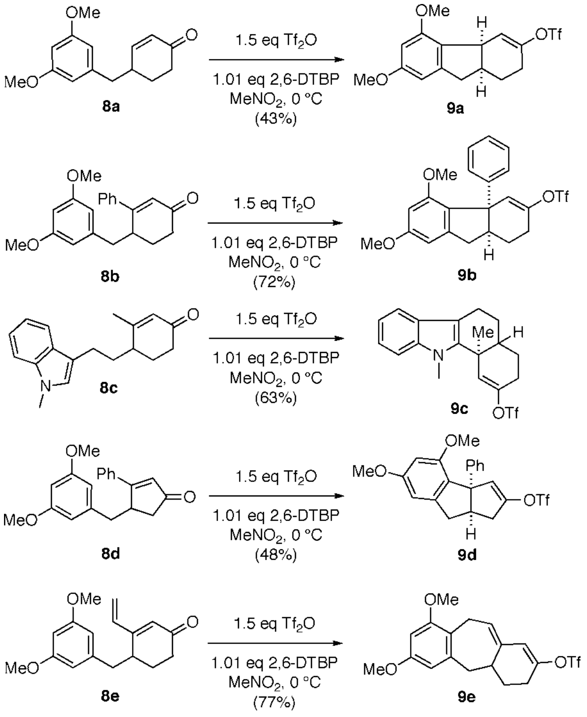
Table 1. Optimization Conditions

entry	solvent	base	**6a**	**6b**	**7**
1	DCM	2,6-DTBP	54%	31%	–
2	PhH	2,6-DTBP	42%	30%	–
3	Et$_2$O	2,6-DTBP	59%	28%	
4	MeCN	2,6-DTBP	–	–	64%
5	MeNO$_2$	2,6-DTBP	–	–	70%
6	MeNO$_2$	*i*-Pr$_2$NEt	–	–	44%
7	MeNO$_2$	Et$_3$N	–	–	47%
8	MeNO$_2$	–	–	–	45%

With highly polar solvents (MeCN or MeNO$_2$), substrate **3** underwent fast cyclization to afford only the desired cyclization product **7**. Polar solvents presumably stabilize the allylic cation, allowing it to undergo ring closure rather than loss of a proton. Systematic variation of the base showed that the reaction worked best with sterically demanding, non-nucleophilic bases such as 2,6-di-*tert*-butyl pyridine (2,6-DTBP). Accordingly, the combination of nitromethane or acetonitrile as a solvent and 2,6-DTBP as a base was subsequently used as our standard set of conditions.

Having optimized the reaction, we proceeded to explore the substrate scope and limitations of related intramolecular reactions (Scheme 4). To this end, substrates **8a**−**h** were prepared using Stork−Danheiser chemistry (see Supporting Information).

Scheme 4. Intramolecular Cyclizations



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(4) Grundl, M. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 23.

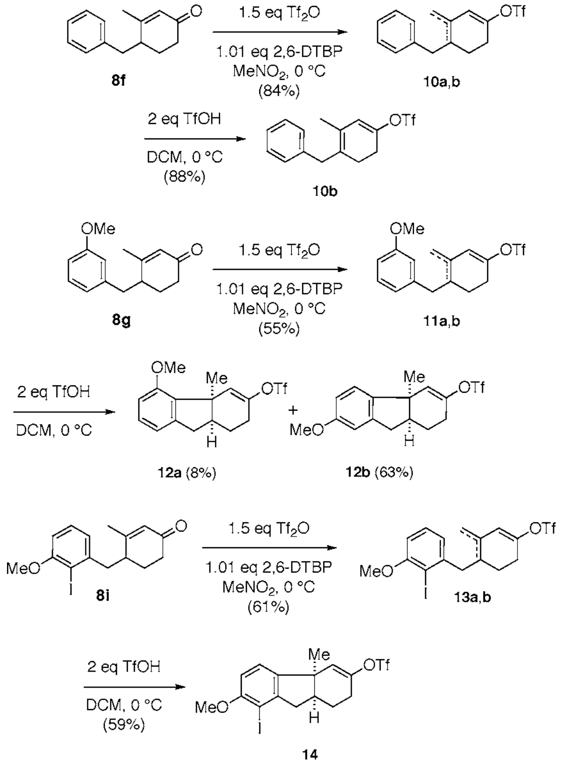
(5) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.

Generally, we observed that the Friedel−Crafts triflation proceeded well with highly nucleophilic arenes. Dimethoxybenzenes **8a**,**b** reacted rapidly to afford the cis-fused products **9a**,**b**. Within the cyclohexenone series, yields increased with the electron-donating nature of the enone substituent. This trend presumably reflects the stability of intermediary allylic cations of type **4**.

Other ring systems were investigated as well. Substrate **8c** gave indole **9c** as a single diastereomer, whose relative stereochemistry could not be determined by NMR spectroscopy. Dimethoxybenzyl cyclopentenone **8d** afforded benzobicyclo[3.3.0]octadiene **9d**. Vinyl cyclohexenone **8e** cleanly underwent 7-endo trig instead of 5-endo trig attack to afford the diene triflate **9e**. Related [6-7-6] ring systems are relatively rare but are found in several natural products.[6]

Electronically less-activated substrates failed to undergo direct cyclization under our standard conditions (Scheme 5). Benzyl cyclohexenone **8f**[7] afforded trifloxy dienes **10a** and **10b**. Resubjection of this mixture to triflic acid did not afford a cyclized product but resulted in almost full conversion of the mixture to **10b**. By contrast, *m*-methoxybenzyl cyclohexenone **8g** and iodomethoxybenzyl cyclohexenone **8h** initially gave a mixture of dienes, which could be cyclized to afford tricyclic enol triflates **12a**,**b** and **14**, respectively.

Scheme 5. Two-Step Procedures



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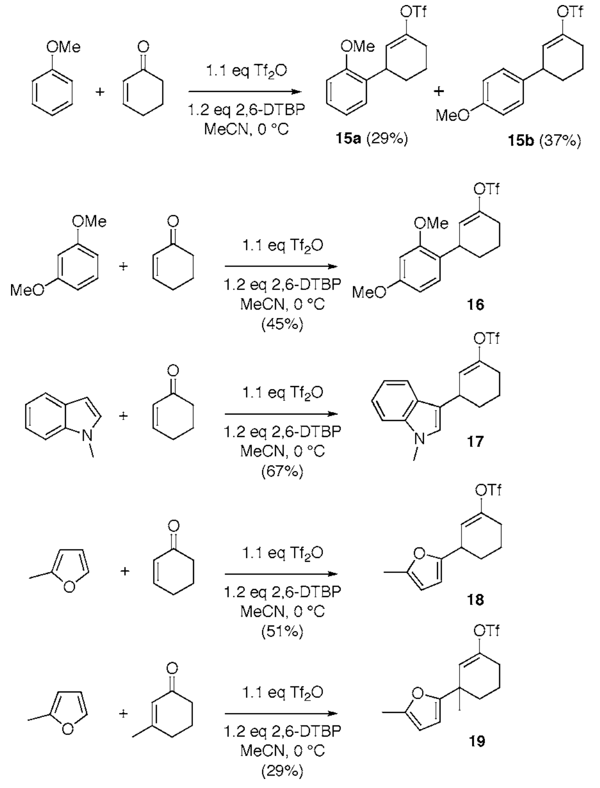
(6) For synthetic approaches toward the [6-7-6] ring system, see: (a) Majetich, G.; Zhang, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4979. (b) Majetich, G.; Hicks, R.; Zhang, Y.; Tian, X.; Feltman, T. L.; Fang, J.; Duncan, S. *J. Org. Chem.* **1996**, *61*, 8169. (c) Simmons, E. M.; Sarpong, R. *Org. Lett.* **2006**, *8*, 2883.

(7) Kim, S.; Jon, S. Y. *Bull. Korean Chem. Soc.* **1995**, *16*, 472.

In addition to intramolecular reactions, we explored intermolecular cases (Scheme 6). These were found to work in slightly better yields with acetonitrile as a solvent. Anisole reacted with cyclohexenone to afford a mixture of regioisomeric enol triflates **15a**,**b** in synthetically useful yields. Resorcinol dimethyl ether cleanly gave enol triflate **16**. Methyl indole gave the corresponding 3-substituted enol triflate **17**. Sylvan reacted with cyclohexenone and 3-methyl cyclohexenone to give enol triflates **18** and **19**, respectively. The formation of a quaternary center in the latter reaction is remarkable, despite its low yield. It should be noted though that sterically congested quaternary carbons were routinely formed in the intramolecular reactions (Scheme 4).

Scheme 6. Intermolecular Reactions



In summary, we have described a new variant of the Friedel−Crafts reaction that generates enol triflates through triflic anhydride promoted conjugate addition of an arene to an enone. The reaction appears to work well if three conditions are met: (a) a substituted enone that yields a stabilized allylic cation after activation with triflic anhydride is present; (b) a polar solvent that further increases the lifetime of this cation is used; and (c) the arene is nucleophilic enough to compete with deprotonation.

The Friedel−Crafts triflation is operationally simple and atom-economical because triflic acid is the only byproduct. It provides a useful alternative to cuprate conjugate additions followed by interception of the resulting metal enolate with phenyl triflimide or Commins' reagent. The method does not require prior functionalization of the arene and could be especially advantageous in cases where the organometallic species cannot be generated easily in the presence of the enone, as is generally the case in intramolecular reactions.

The extension of the method toward other unsaturated carbonyl compounds, nucleophiles, and electrophilic activators is currently under investigation.

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Supporting Information Available: Spectroscopic and analytical data for compounds **3**, **7**−**9**, **10b**, **12a**,**b**, **14**−**19**, and **22a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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