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Olefin Synthesis via Organometallic Coupling Reactions of Enol Triflates

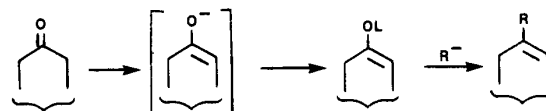
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The carbonyl group has been called the most versatile functionality available to the synthetic organic chemist. One major reason is the ability to convert a carbonyl compound into the corresponding olefin, a result normally achieved by addition of a nucleophile followed by dehydration of the intermediate alcohol. Neither of the two steps is necessarily straightforward, however. For example, sterically hindered ketones are often inert to nucleophilic addition. Similarly, sterically hindered nucleophiles either will not add to, or can act as reducing agents toward, ketones. Even more troublesome is the fact that dehydration of the intermediate alcohol is rarely regioselective. A mixture of olefin products often results from alcohol dehydration, lessening the value of the procedure for synthesis. Because of these problems, much research has been directed at the development of new methods for the regioselective synthesis of olefins from ketones.

An attractive alternative to the nucleophilic addition/dehydration route would be to take advantage of known methods¹ for regioselectively generating an enolate ion. Thus, formation and trapping of an enolate ion, followed by substitution of the enol derivative with a nucleophile, would lead to regiospecific formation of an olefin.



The key step, displacement of a leaving group from an enol derivative, requires a nucleophilic substitution reaction at an sp^2 center. Although similar substitution reactions at the sp^2 centers of vinylic halides have been known since 1968,² it was not until 1976 that Blaszcak demonstrated the replacement of an enolate oxygen by reaction of an enol diphenyl phosphate with lithium dibutylcopper.³ Unfortunately, use of the less reactive lithium dimethylcopper led to low product yields.

Since sulfonates are often used as leaving groups in nucleophilic substitution reactions, it occurred to us that trapping of an enolate ion as its enol sulfonate, followed by displacement, might constitute a general scheme for olefin synthesis. Enol *p*-toluenesulfonates (tosylates) are not easily prepared, but the corresponding enol trifluoromethanesulfonates (triflates) are well-known and have been much studied as a source of vinylic cations.⁴ Thus, the conversion of ketones into olefins via the corresponding enol triflates was investigated.

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A short biography of John E. McMurry appeared previously in *Acc. Chem. Res.* **1983**, *16*, 405.

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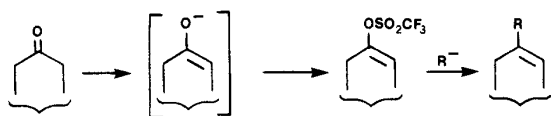
[‡]Cornell University.

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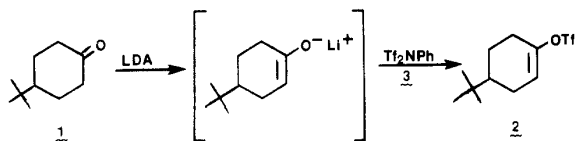


Synthesis of Enol Triflates

The first step of the projected transformation involves conversion of a ketone into its enol triflate, a reaction that has been accomplished in two general ways. The most common method is the reaction of a ketone with trifluoromethanesulfonic anhydride (triflic anhydride) in the presence of a mild nonnucleophilic base.⁵ The enol triflate is thought to be formed by initial reaction of triflic anhydride with the ketone, followed by loss of a proton, and the reaction normally leads to production of the more thermodynamically stable product. For example, treatment of 2-methylcyclohexanone (4) with triflic anhydride and base gives 2-methyl-1-cyclohexenyl triflate (5) as the major product.⁶

The second general method of enol triflate synthesis is by conversion of a ketone into its enolate ion followed by trapping. Although stable enolate ions derived from highly acidic ketones can be trapped with triflic anhydride in good yield,⁷ the more reactive enolates derived from monoketones tend to C-sulfonate, affording α -keto sulfone products.⁸

In order to find a more general method of enolate trapping, we initiated a comparative study of a number of potential sulfonating agents. Using as our test system the enolate ion prepared by deprotonation of 4-*tert*-butylcyclohexanone (1) with lithium diisopropylamide (LDA), we found that reaction with triflic anhydride failed to yield any of the desired product 2, but that reaction with (trifluoromethanesulfonyl)imidazole⁹ provided 2 in 48% yield and reaction with *N*-phenyltriflimide¹⁰ (3) gave 2 in 82% isolated yield.¹¹



One of the most important features of the enolate-trapping method is its ability to define the regiochemistry of the enol triflate, as exemplified by the selective conversion of 2-methylcyclohexanone (4) into either its thermodynamic (5) or kinetic (6) enol triflate by choice of reaction conditions. Treatment of 4 with LDA, followed by trapping, gives enol triflates 6 and 5 in a 19:1 ratio,¹¹ whereas treatment with bromomagnesium diisopropylamide¹² followed by trapping gives the two products in a 1:19 ratio.¹³ By contrast, treatment of

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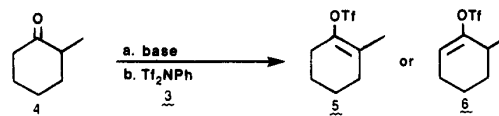
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Table I
Preparation of Enol Triflates from Ketones

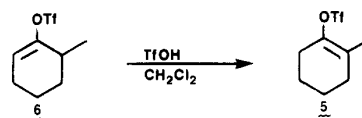
entry		yield, %	ref
1		80	11
2		65	11
3		97	11
4		65	11
5		65	11
6		65	11
7		93	14

4 with triflic anhydride and sodium carbonate gives 6 and 5 in a 1:3 ratio.⁶



N-Phenyltriflimide was also found to be effective for trapping a variety of enolates generated in a number of different ways (Table I).^{11,14} Enolate ions prepared by treatment of silyl enol ethers with methyllithium, by addition of diorganocuprate reagents to conjugated ketones, and by reduction of conjugated ketones with either sodium in liquid ammonia or with *L*-Selectride, can all be converted into the corresponding enol triflate by reaction with *N*-phenyltriflimide.

Finally, enol triflates can be equilibrated under anhydrous acidic conditions in a manner similar to that used for silyl enol ethers.^{15,16} Thus, treatment of 6-methyl-1-cyclohexenyl triflate (6) with a catalytic amount of anhydrous triflic acid yields the thermodynamically more stable 2-methyl-1-cyclohexenyl triflate (5).^{17,18}



Coupling Reactions of Enol Triflates with Diorganocuprates

With efficient methods for the regioselective preparation of enol triflates available, we turned our attention to reactions of the triflates with organometallic reagents. We found in short order that, although alkylolithiums effect sulfur-oxygen bond cleavage with enol triflates, diorganocuprates effect carbon-oxygen cleavage and

(14) Crisp, G. T.; Scott, W. J. *Synthesis* 1985, 335-337.

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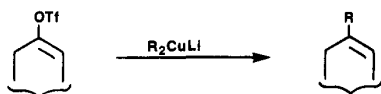
(17) Scott, W. J., unpublished results.

(18) Cacchi, S.; Morera, E.; Ortari, G. *Tetrahedron Lett.* 1980, 21, 4313-4316.

Table II
Coupling Reactions of Enol Triflates with Organocopper Reagents

entry	triflate	organocopper reagent	product	isolated yield, %	ref
1		Me ₂ CuLi		75	19
2		(CH ₂) ₂ CuMgBr		62	19
3		(C ₃ H ₅) ₂ CuMgBr		68	19
4		Ph ₂ CuLi		75	19
5		Me ₂ CuLi		95	19
6		Me ₂ CuLi		95	19
7		(CH ₂) ₂ CuMgBr		71	19

convert the triflate into the corresponding olefin.¹⁹ Thus, our initial hope of devising a regioselective olefin synthesis complementary to the standard nucleophilic addition/dehydration scheme had been realized.



As shown in Table II, yields of olefin products are high for a wide variety of diorganocuprates, including *n*-butyl, phenyl, vinyl, and cyclopropyl. Particularly noteworthy is the fact that yields remain high even when dimethylcuprate is used, in contrast to the result previously observed for reactions of enol diphenyl phosphates.³

The stereospecificity of the coupling reactions was demonstrated by treatment of pure (*Z*)-5-((trifluoromethanesulfonyl)oxy)-5-decene with lithium dimethylcopper to give (*E*)-5-methyl-5-decene of greater than 99% stereochemical purity (Table II, entry 5). Similarly, reaction of (*E*)-5-((trifluoromethanesulfonyl)oxy)-5-decene gave (*Z*)-5-methyl-5-decene of greater than 99% purity. Although a preliminary result suggested that a small amount of isomerization occurred during the coupling reaction, subsequent analysis has indicated this not to be the case.²⁰

Palladium-Catalyzed Coupling Reactions of Enol Triflates with Organostannanes

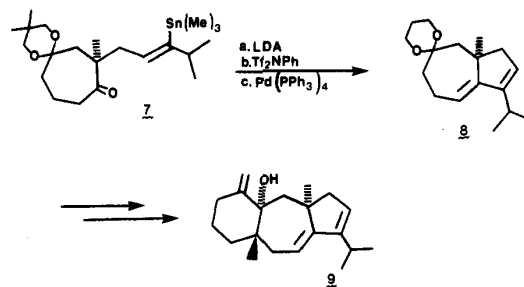
Transition metals have recently been found to catalyze the coupling reactions of a number of enol derivatives with carbon nucleophiles.²¹ For example, zero-

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Scheme I
An Intramolecular Enol Triflate/Organostannane Coupling Route to Dolastane Sesquiterpenes



valent nickel complexes catalyze the coupling of Grignard reagents with methyl enol ethers^{22,23} and silyl enol ethers²⁴ to yield alkene products. Similarly, palladium complexes have been shown to catalyze the coupling of enol phosphates with alanes.²⁵

Enol triflates are also capable of undergoing transition-metal-catalyzed coupling with nucleophiles. Thus, treatment of 4-*tert*-butyl-1-cyclohexenyl triflate (3) with an organostannane²⁶ in the presence of 2 mol % of tetrakis(triphenylphosphine)palladium(0) and an excess of LiCl gives the coupled alkene product in high yields.^{13,27} The coupling can be carried out in most polar solvents except for chloroform. Even some water or air can be tolerated, but the reaction will not take place unless added salt is present. The reaction is general for a variety of organostannanes, including alkyl, vinyl, acetylenic, and allyl (Table III). Aryl- and benzylstannanes yield only traces of coupled products, however.

One of the more important results shown in Table III is that palladium-catalyzed coupling of an enol triflate with hexamethyldistannane gives the corresponding vinylic stannane in good yield. Such regioselectively formed vinylic stannanes can then be further converted into vinylic iodides by reaction with I₂²⁸ or into vinylic lithium reagents by reaction with methyllithium.²⁹ Surprisingly, however, attempts to form vinylic stannanes by palladium-catalyzed coupling of enol triflates with hexabutylstannane,^{13,29} or diethyl(trimethylstannyl)aluminum were unsuccessful.³⁰

Both the organocopper reaction and the palladium-catalyzed coupling of enol triflates with organostannanes are compatible with the presence of severe steric hindrance about both the electrophilic and the nucleophilic sites. Hindrance in the enol triflate affects

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Table III
Palladium-Catalyzed Coupling of Enol Triflates with Organostannanes

entry	triflate	organostannane	product	isolated yield, %	ref
1		Bu ₃ SnCH=CH ₂		91	13
2		Bu ₃ SnCH=CHCH ₃		96	13
3		Bu ₄ Sn		80	13
4		Me ₃ SnSnMe ₃		73	13
5		Bu ₃ SnCH=CH ₂		80	13
6		Me ₃ SnCH=CHSiMe ₃		90	13
7				75	13

Table IV
Palladium-Catalyzed Reduction of Enol Triflates

entry	triflate	hydride source	product	isolated yield, %	ref
1		Bu ₃ SnH		78	13
2		-[(Me)-HSiO] _n -		75	13
3		HCO ₂ H		79	35
4		DCO ₂ D		87	35

neither reaction rate nor yield.¹³ Thus, coupling of 4-*tert*-butyl-1-cyclohexenyl triflate with vinyltributyltin proceeds only 1.5 times as fast as the analogous reaction with 2,5,5-trimethyl-1-cyclopentenyl triflate. Hindrance in the organostannane appears to affect rate but not yield.

The reaction has already been put to good use in synthesis, most notably by Piers, who has used an intramolecular variant of the palladium-catalyzed coupling to synthesize five- and six-membered rings.³¹ This annulation served as the key step in a synthetic approach to the dolastane diterpenes (Scheme I).³² Surprisingly, LiCl was found to hinder, rather than help, the intramolecular reaction. The coupling has also been used in a stereospecific synthesis of peraplysellin-1 (Table III, entry 7)¹³ and in an approach to vitamin D metabolites.³³

Palladium-Catalyzed Reduction of Enol Triflates

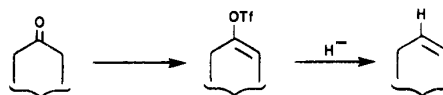
As previously mentioned, the conversion of a ketone into an enol triflate, followed by coupling with a carbon

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nucleophile, is a regioselective alternative to the standard nucleophilic addition/dehydration scheme for olefin synthesis. In the same way, conversion of a ketone to an enol triflate, followed by reduction, would be a regioselective alternative to the standard reduction/dehydration scheme.



In practice, reduction of enol triflates with standard hydride reducing agents such as LiAlH₄ or (*i*-Bu)₂AlH results only in sulfur-oxygen bond cleavage, regenerating the enolate ion.^{13,34} The desired reaction can be accomplished smoothly, however, when tributylstannane,^{13,27} various organosilanes, or formic acid³⁵ is used in the presence of a palladium catalyst (Table IV). The overall sequence represents an extremely mild method for preparing olefins and should find use in natural-products synthesis. Of particular importance is the fact that dienol triflates reduce smoothly to yield dienes, a conversion that is difficult or impossible to achieve cleanly by other methods.

Palladium-Catalyzed Olefination of Enol Triflates

In addition to their ability to undergo coupling reactions with organocuprates and organostannanes, enol triflates also react with olefins and alkynes in a palladium-catalyzed Heck olefination reaction (Table V).^{18,36} No added salt is necessary, and the reaction takes place in most common solvents, although dimethylformamide is normally chosen. The best yields are obtained when the olefin reactant is substituted by an electron-with-

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Table V
Palladium-Catalyzed Olefination of Enol Triflates

entry	triflate	olefin	product	isolated yield, %	ref
1				89	36
2				86	36
3				95	36
4				89	36
5				92	36
6				77	18
7				60	18

Table VI
Palladium-Catalyzed Carbonylative Couplings of Enol Triflates

entry	triflate	organostannane	product	isolated yield, %	ref
1		$\text{Me}_3\text{Sn}-\text{CH}=\text{CH}_2$		76	37
2 ^a		$\text{Me}_3\text{Sn}-\text{CH}=\text{CH}-\text{CH}=\text{CH}_2$		95	37
3 ^a		Me_4Sn		73	37
4 ^a		Me_3SnPh		93	37
5		$\text{Me}_3\text{Sn}-\text{C}\equiv\text{C}-\text{SiMe}_3$		95	37
6		$\text{Me}_3\text{Sn}-\text{CH}=\text{CH}-\text{SiMe}_3$		77	37

^a One equivalent of ZnCl_2 added.

drawing group, as in a conjugated ketone or ester. Steric hindrance about the enol triflate has little effect on the reaction rate, and double-bond stereochemistry of the final product is normally the result of a palladium-catalyzed equilibration. Thus, only the more thermodynamically stable *E* product is formed when either methyl acrylate or methyl vinyl ketone is used.

Palladium-Catalyzed Carbonylations of Enol Triflates

Still another kind of coupling process occurs when enol triflates are allowed to undergo palladium-catalyzed reaction with vinylic or acetylenic stannanes in the presence of LiCl and 1 atm of carbon monoxide.³⁷

Although the reaction conditions must be carefully controlled, high yields of divinyl ketones can result from carbonylative coupling (Table VI). No reaction takes place at low temperatures, and direct noncarbonylative coupling can be competitive at high temperature. Optimal conditions vary with the organostannane, although most react best at a temperature just below the boiling point of the solvent. Vinylic stannanes appear to retain their stereochemical integrity during the carbonylative coupling process, but the cross-conjugated ketone products must be purified carefully to prevent acid-catalyzed equilibration of *Z*-enones to their more stable *E* isomers.

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