reaction conditions can be adjusted to tailor-make the particular particle size and chemical reactivity desired. Thus, we expect this area of research to be a continuing and fruitful one.

I wish to thank all my co-workers for their enthusiasm, devotion, and skilled contributions to this and ongoing work: P. M. Hudnall, S. E. Bales, S. J. Uhm, L. Chao, K. Ofele, W. Wolf, N. Kujundzic, A. Kavaliunas, and L. I. Rieke. Stimulating discussions with Professor E. O. Fischer and Professor J. P. Collman are acknowledged. Financial support for this work was provided by: Army Research Office, Research Corporation, Petroleum Research Fund (administered by the American Chemical Society), North Carolina Board of Science and Technology, National Science Foundation, and the Alfred P. Sloan Foundation.

Trifyl Activation in Organic Synthesis

James B. Hendrickson,* Daniel D. Sternbach, and Kenneth W. Bair

Department of Chemistry, Brandeis University, Waltham, Massachusetts 02154

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The sulfonyl group is especially valuable in synthetic organic chemistry because of its unusually versatile reactivity. It functions as both an electrophile and as a nucleophile-leaving group. At the same time, the electron-withdrawing power of the sulfonyl group stabilizes adjacent negative charge and activates olefins for nucleophilic addition or cycloaddition. All of these properties (except nucleophilicity) are enhanced as the electronegativity of the sulfonyl substituent is increased. It is this factor that directed our interest to the trifluoromethanesulfonyl group (CF_3SO_2–); hereafter referred to as *trifyl* and symbolized as Tf), which is reported to be one of the strongest neutral electron-withdrawing groups known.[1,2]

The large inductive effect of the trifluoromethyl group is illustrated by comparison of pK_a values (Table I[2-7]) with those of the common benzenesulfonyl derivatives. In general, this strongly enhanced electron withdrawal causes remarkable facilitations of known sulfonyl reactivity and leads to some previously unknown reactions. Furthermore, the trifyl group has the synthetic value of being inert to a wide variety of reaction conditions.

The primary electrophilic trifyl reagent is the very reactive triflic anhydride ($(CF_3SO_2)_2O$), obtained from P_2O_5 dehydration of triflic acid (CF_3SO_2OH). The primary nucleophilic form is triflinate anion ($CF_3SO_2^-$), obtained from iodide reduction of CF_3SO_2Cl.[8,9] Both reagents are easily prepared and stable.[10] In general the reactions cited for these reagents involve initial attachment of the trifyl group to a molecule followed by construction or refunctionalization reactions and finally removal of the trifyl group when no longer needed.

From the outset it was apparent that trifyl activation would involve either or both of the atoms α and β to the trifyl group, i.e., Y and/or Z in the molecular generalization Y–Z–SO_2CF_3. The reactions include making or breaking the Y–Z and Z–SO_2CF_3 single bonds as well as addition or elimination to Y=Z double bonds. The consequent variety of molecular types is illustrated in Table II for the common atoms, and this format is used here to present our initial findings. The dashes in the table imply potentially useful compounds as yet unexplored; some are under current study in our laboratories.

Table I
Comparison of pK_a Values: RSO_2Z

	Z			
R	CH_3[a]	NH_2[a]	OH	H[c]
Ph	29.0[2]	16.7[3]	0.70[4,c]	2.76[6]
CF_3	18.8[2]	9.75[3]	<−11[5,b] (0.31[3,a])	~0[7]

[a] Me_2SO. [b] HOAc. [c] H_2O.

Table II
Permutations of Y-Z-Tf

	Z \ Y	C	N	O	P	S
Triflones	C	*a*	–	–	–	*a*
Triflamides	N	*a*	*a*	*a*	–	–
Triflates	O	*a*	*a*	*a*	*a*	*a*
	P	–	–	–	–	–
	S	–	–	–	–	–

[a] Examples studied to date.

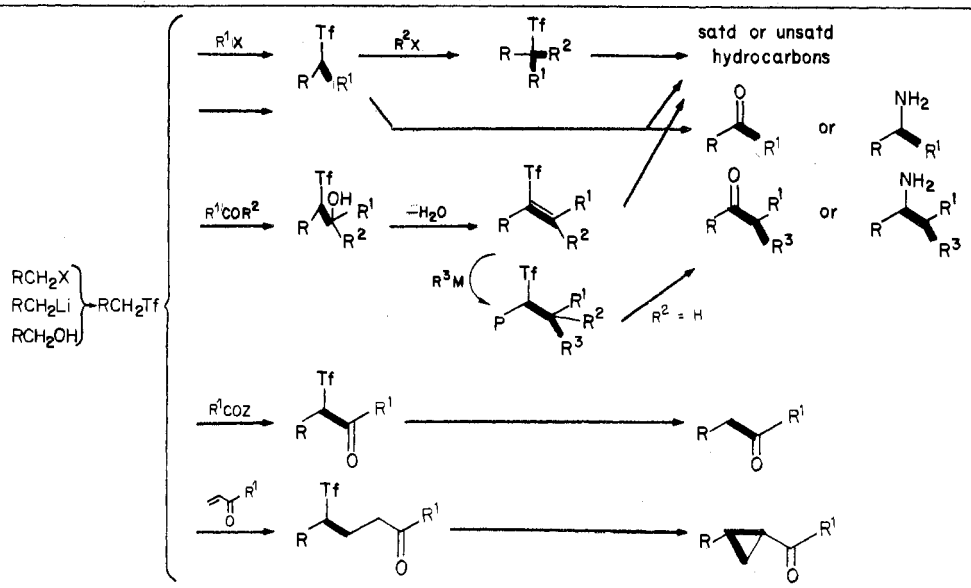
James B. Hendrickson, born in Ohio, received his B.S. degree from California Institute of Technology and the Ph.D. from Harvard in 1955 under R. B. Woodward. Following postdoctoral study with Dr. Woodward and D. H. R. Barton, he spent 5 years on the staff at UCLA, going to Brandeis University in 1963. Recipient of Guggenheim and Sloan Foundation Fellowships, Professor Hendrickson has pursued interests in molecular geometry and organic synthesis.

Daniel Sternbach and Kenneth Bair both completed doctoral work with Professor Hendrickson at Brandeis, and are now engaged in postdoctoral research, Dr. Sternbach at ETH Zurich with A. Eschenmoser, and Dr. Bair at Massachusetts Institute of Technology with J. Baldwin.

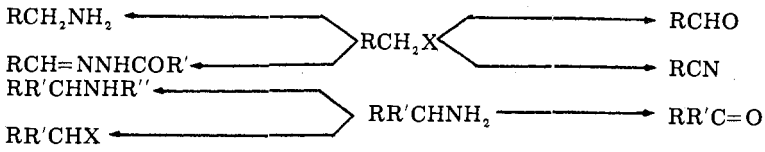
(1) T. Gramstad and R. N. Hazeldine, *J. Chem. Soc.*, 4069 (1957).
(2) F. G. Bordwell, N. R. Vanier, W. S. Matthews, J. B. Hendrickson, and P. L. Skipper, *J. Am. Chem. Soc.*, **97**, 7160 (1975).
(3) F. G. Bordwell, private communication.
(4) "Handbook of Chemistry and Physics", 54th ed, CRC Press, Cleveland, Ohio, 1976, p D-129.
(5) R. L. Hinman and B. E. Hogenboom, *J. Org. Chem.*, **26**, 3461 (1961).
(6) D. De Filipo and F. Momicchioli, *Tetrahedron*, **25**, 5733 (1969).
(7) C. Harzdorf, J. Meussdoerffer, H. Niederprüm, and M. Wechsberg, *Justus Liebigs Ann. Chem.*, 33 (1973).
(8) J. B. Hendrickson, A. Giga, and J. Wareing, *J. Am. Chem. Soc.*, **96**, 2275 (1974).
(9) J. B. Hendrickson and P. L. Skipper, *Tetrahedron*, **32**, 1627 (1976).
(10) Particular laboratory details for these and other related trifyl reagents and general details about their use in practice will be found in J. B. Hendrickson, K. W. Bair, P. L. Skipper, D. D. Sternbach, and J. Wareing, *Org. Prep. Proced. Int.*, in press.

Table III
Synthetic Transformations with Trifyl Activation

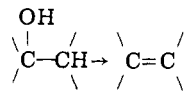
I. Constructions via Triflones



II. Refunctionalizations via Triflamides



III. Refunctionalizations via Triflates



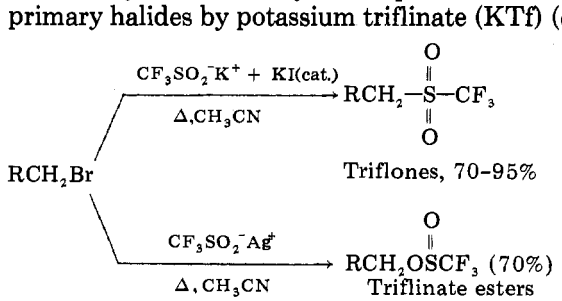
RCH=NOH → RCN
$RCONH_2$ → RCN
RCOOH → RCO-Nu
RCH(OH)R' → RCOR'

A summary of the overall synthetic transformations developed to date is presented in Table III, and organized by the atoms (Z) to which the trifyl group is attached. The exposition that follows is organized in this same format.

Triflones (Y-C-Tf)

The triflones have special interest for the synthetic chemist in the variety of ways they facilitate carbon–carbon bond construction. Their utility, however, depends on their availability and on the ease of removal of the Tf group when its activated constructions are complete. In this section the three operations are separately surveyed, as summarized in Table III: triflone formation, constructions using triflones, and removal of the Tf group.

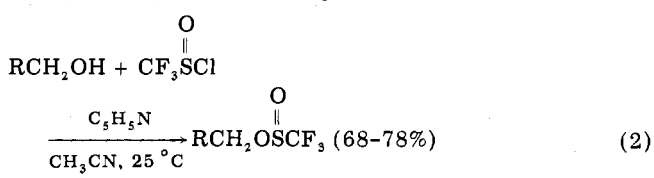
Synthesis of Triflones. Both nucleophilic and electrophilic trifyl sources may be used, although the former has been more widely examined. An ambident anion, triflinate ($CF_3SO_2^-$), can either S- or O-alkylate, S_N2 conditions favoring the former. Thus, alkyl triflones may be formed by nucleophilic substitution of primary halides by potassium triflinate (KTf) (eq 1).[8,9]



(1)

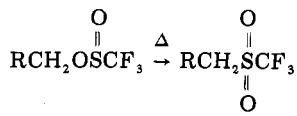
The reaction is slow (due to the low nucleophilicity of triflinate anion) but generally uncontaminated by side reactions.

Alternatively, O-alkylation of triflinate to give triflinate esters ($ROSOCF_3$) occurs when alkyl halides are treated with silver triflinate[11] or when primary nosylates are similarly treated with potassium triflinate.[9,11] Triflinate esters may also be prepared from alcohols using triflinyl chloride (eq 2).[9]



(2)

The triflinate esters, available in good yield from the above routes, are in turn thermally (25–150 °C) convertible to the more stable triflones (eq 3).[9] The re-



(3)

arrangement is much more facile than that of corresponding arenesulfinate esters,[12] and probably occurs via an ionization–recombination mechanism.[9] Only primary triflones are available by these routes since elimination occurs with nonprimary substrates.[9]

The use of electrophilic sources of trifyl in the preparation of triflones has been less successful.

(11) N. V. Kondratenko, V. P. Sambar, and L. M. Yagupol'skii, *Zh. Org. Khim.*, 7, 2382 (1971).

Ditriflation commonly occurs when simple Grignard reagents react with trifyl fluoride.[13] The reactions of triflic anhydride and trifyl chloride with several organometallic reagents were explored with little success,[14] but the less reactive phenyltriflimide ($PhN(Tf)_2$)[15] reacted with primary and secondary alkyllithium reagents or primary cuprates to yield triflones (eq 4).[14]

$$RM + PhN(Tf)_2 \rightarrow RTf + PhNTf^-M^+ \ (70\text{–}90\%) \qquad (4)$$

Methyl, phenyl, and tertiary alkyl organometallic reagents failed here,[14] but some aryl triflones[16] are available by Friedel–Crafts triflation (eq 5), although

$$PhCH_3 + Tf_2O \xrightarrow{AlCl_3} p\text{-}CH_3C_6H_4Tf\ (40\%) + o\text{-}CH_3C_6H_4Tf\ (20\%) \qquad (5)$$

this does not appear to be general.[14]

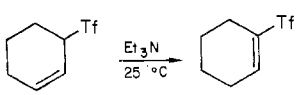
The simplest triflone, methyl triflone, is available most conveniently from *tert*-butyl bromoacetate triflation followed by distillation with thermal decomposition (145–155 °C) (eq 6).[9,10]

$$BrCH_2COO\text{-}t\text{-}Bu + KTf \xrightarrow[\Delta]{CH_3CN} TfCH_2COO\text{-}t\text{-}Bu \xrightarrow{\Delta} CH_3Tf + CO_2 + (CH_3)_2C{=}CH_2 \qquad (6)$$

α,β-Unsaturated triflones are not as generally available. Vinyl triflone itself has been made by a multistep route (eq 7),[17] but could not be prepared by

$$CF_3SCl + CH_2{=}CH_2 \rightarrow CF_3SCH_2CH_2Cl \rightarrow TfCH_2CH_2Cl \rightarrow TfCH{=}CH_2\ (13\%) \qquad (7)$$

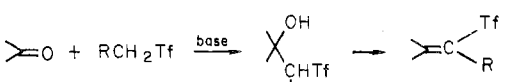
triflinate alkylation of various ZCH_2CH_2Br or thermolysis of the triflinate esters ($ZCH_2CH_2OSOCF_3$).[18] Some allylic triflones tautomerize in base to vinyl triflones (eq 8), but not all. Allyl triflinate itself re-



(8)

arranges thermally first to allyl triflone, which then isomerizes completely to *trans*-1-propenyl triflone, whereas other allylic triflones are completely unchanged in mild base and stronger bases only cause decomposition (compare eq 8).[9]

The most reliable preparation of unsaturated triflones appears to be the condensation of primary triflones with aldehydes and ketones (eq 9),[8,19,20] discussed below.



(9)

Only one acetylenic triflone is known. The thermally very labile phenylacetylene triflone has been prepared by reaction of lithium phenylacetylide with triflic anhydride.[21]

Constructions with Triflones. Although it is largely only primary triflones that are easily available, this is not a serious synthetic limitation since facile α-carbanion alkylation serves to construct new bonds to that primary carbon. There are four major constructions in Table III, distinguished by the nature of the electrophile used. In Table III and below, the bond constructed is identified in boldface. The first construction is simple alkylation. Owing to the marked acidity (Table I) of triflones, alkylations have been carried out with potassium carbonate in hot acetonitrile, but our common practice[10] is the facile, prior formation of the α-carbanion with sodium hydride in ether solvents followed by room-temperature alkylation. Yields are 70–95% in ten cases tried.[8,9,22] Monoalkylation was the exclusive result in virtually every case, even with methyl triflone itself. This property allows clean successive alkylations to build up branched carbon skeletons (eq 10).

$$CH_3Tf \xrightarrow[2.\ R^1X]{1.\ NaH} R^1CH_2Tf \xrightarrow[2.\ R^2X]{1.\ NaH} R^1R^2CHTf \xrightarrow[2.\ R^3X]{1.\ NaH} R^1R^2R^3CTf \qquad (10)$$

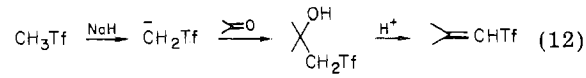
Intramolecular alkylation has been used to construct three- and five-membered rings[8,9,18] as exemplified in the two preparations of cyclopropyl triflone in eq 11.

$$BrCH_2CH_2Br + CH_3Tf \xrightarrow[\text{glyme (31\%)}]{NaH} \text{(cyclopropyl)-Tf} \qquad (11)$$

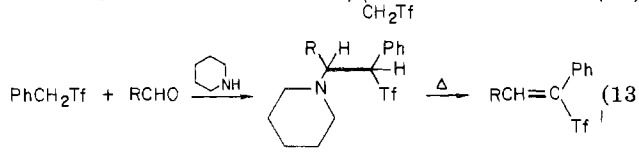
$$TfCH_2CH_2CH_2Tf \xrightarrow[\text{glyme (70\%)}]{NaH} \text{(cyclopropyl)-Tf}$$

The second of these illustrates the displacement of triflone as triflinate anion, a much more active leaving group than sulfinates from other sulfones. Five-membered rings have also been created by internal alkylation with a triflinate leaving group.

With electrophiles at the next oxidation level, trifyl carbanions react generally with aldehydes and ketones. The initial β-hydroxytriflone is readily dehydrated to an unsaturated triflone (eq 12).[19,20] The Mannich reaction variant also proceeds in a parallel manner (eq 13).[8,22]



(12)

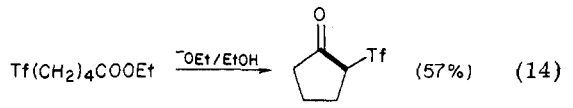


(13)

Acylations of trifyl carbanions have not been as extensively examined, but the simple Claisen condensation of ethyl formate with methyl triflone forms $^-OCH{=}CHTf$, and internal acylation is also facile (eq 14).

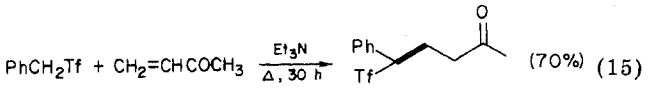
Conjugate additions with triflones can be carried out in two ways, with the triflone acting either as nucleo-

(12) D. Darwish and R. McLaren, *Tetrahedron Lett.*, 1231 (1962), and references therein.
(13) R. J. Koshar and R. A. Mitsch, *J. Org. Chem.*, **38**, 3358 (1973).
(14) J. B. Hendrickson and K. W. Bair, submitted for publication.
(15) J. B. Hendrickson and R. Bergeron, *Tetrahedron Lett.*, 4607 (1973).
(16) L. M. Yagupol'skii and B. E. Gruz, *Zh. Obshch. Khim.*, **31**, 1219 (1961), and references therein.
(17) I. L. Knunyants, I. N. Rozkhov, A. M. Aleksandrov, and L. M. Yagupol'skii, *Zh. Obshch. Khim.*, **37**, 1210 (1967).
(18) Paul L. Skipper, Ph.D. Thesis, Brandeis University, 1976.
(19) L. M. Yagupol'skii and A. G. Panteleimanov, and V. V. Orda, *Zh. Obshch. Khim.*, **36**, 416 (1966).
(20) L. M. Yagupol'skii, A. G. Panteleimanov, and V. V. Orda, *Zh. Obshch. Khim.*, **34**, 3456 (1964).
(21) R. S. Glass and D. L. Smith, *J. Org. Chem.*, **39**, 3712 (1974).
(22) Aziz Giga, Ph.D. Thesis, Brandeis University, 1975.



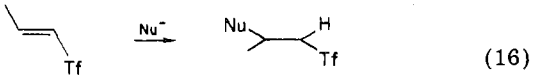
(14)

phile or electrophile. In the first the triflone nucleophile adds to unsaturated ketones or acrylonitrile as in eq 15,



(15)

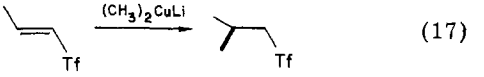
in each case with monalkylation.[8,22] Alternatively, conjugate additions to vinyl triflones are excellent reactions, proceeding with a variety of common nucleophiles under mild conditions (eq 16).[8,9,17] Conjugate



(16)

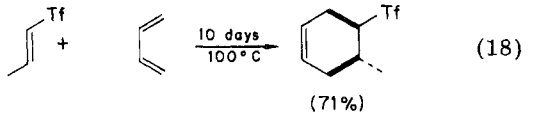
Nu = RO, RNH, RS, etc.
or CN, $CH(COOR)_2$

additions with alkyllithium compounds succeed only when the vinyl triflone has no acidic protons,[8] but the reaction appears to be more general when organocopper reagents are used (eq 17).[9,14] Similarly, vinyl triflones



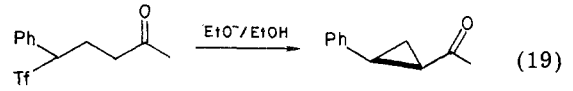
(17)

are active dienophiles for Diels–Alder cycloaddition reactions (eq 18).[8,9]



(18)

Finally, since triflinate anion is an unusually stable sulfinate (Table I), it may act as a leaving group in displacement reactions, thus accomplishing both a construction and final removal of an activating trifyl group. Either of the two kinds of conjugate additions above (eq 15 and 16) create γ-trifyl carbonyls suitable for internal displacement to a cyclopropyl carbonyl compound, and indeed these reactions occur readily at room temperature (eq 19).



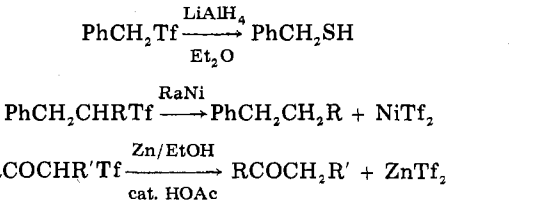
(19)

Triflone Removal. The trifyl group may be removed cleanly in several ways, as summarized in Table IV; all reactions are essentially quantitative. Cleavage usually occurs at the C–Tf bond, and the trifyl group is lost intact as the stable triflinate anion or its acid. The only exception to date is lithium aluminum hydride reduction, which reduces the sulfonyl to thiol in the normal manner.[8] Neither sodium borohydride nor aluminum amalgam reacted with simple triflones, but mild zinc reduction of α-trifyl carbonyls was especially effective. Hydrogenolysis with Raney nickel quantitatively removed the group as nickel triflinate, but platinum-catalyzed hydrogenation of olefinic triflones proceeded smoothly with no loss of triflone as long as it was not benzylic.[8,9]

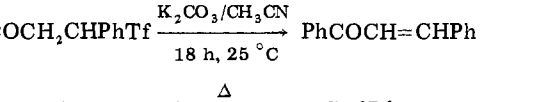
Elimination of trifyl may be effected isohypsically (without oxidation or reduction) either by basic β elimination or by thermolysis.[8] In the latter case, primary triflones were stable, but elimination became

Table IV
Removal of the Trifyl Group from Carbon

A. Reductive

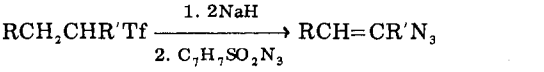


B. Isohypsic (see also eq 11 and 19)



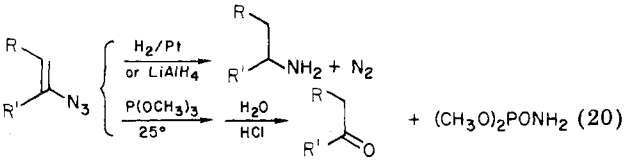
R^1	R^2	R^3	Temp, °C
Ph	H	H	Stable < 300
Ph	H	Ph	200
PhCO	H	Ph	160
Ph	$PhCH_2$	CH_3	180
Ph	CH_3	Ph	70

C. Oxidative



easier with increasing α substitution or with benzylic activation.

α-Oxidation of the trifyl carbanion was sought as a means of functionalizing as well as removal. In particular, the equilibrium between α-hydroxytriflone and carbonyl heavily favors the carbonyl, for triflinate anion was unreactive with simple aldehydes. Brominations of methyl triflone gave only polybromination, however.[18] A smooth oxidation was effected with tosyl azide on the trifyl carbanion, leading directly to elimination of both triflinate and toluenesulfinate and quantitative production of a vinyl azide.[9,14] Unlike many iodine azide additions to olefin,[23] this procedure results in a regiospecific azide, sited at the former triflone carbon. This interesting functionality is synthetically useful in being convertible quantitatively either to saturated primary amine by reduction[9] or to ketone/aldehyde by treatment with trimethyl phosphite and mild hydrolysis, as in eq 20.[14]



(20)

Thus, while no single step discussed in the above sections is especially unusual, the sequence of formation, construction, and removal of the C–Tf group provides overall a powerful tool for the synthetic elaboration of a simple starting materials with clean and facile reactions.

Triflamides (Y–N–Tf)

In contrast to triflones, triflamide reagents are best applied to refunctionalization reactions. The seven reactions of section II, Table III, have been carried out

(23) A. Hassner, E. S. Ferdinandi, and R. J. Isbister, *J. Am. Chem. Soc.*, 92, 1672 (1970); A. Hassner and A. B. Levy, *ibid.*, 93, 5469 (1971).

Table V
Modes of Cleavage of Triflamides

Y–N–Tf (1 2)	
1	2
(a) Y–N–Tf	(a) Y–N–Tf
(b) Y–N–Tf	(b) Y–N–Tf

using these reagents. Of special interest are the applications to amine synthesis (i.e., synthesis of primary amines, monoalkylations, amine protection) which normally occur under mild conditions and in many cases are superior to existing methods. The synthesis and reactivity of triflamides and the various methods for removal of the trifyl group are discussed below.

Synthesis of Triflamides. Triflamides are formed very easily on treatment of amines with triflic anhydride.[1,10,24] Alternatively, the milder, more selective triflating agent, phenyltriflimide,[15] may be used instead of triflic anhydride (eq 4, 21). The by-product of this

$$RR'NH + PhN(Tf)_2 + NEt_3 \xrightarrow[-78\ ^\circ C]{CH_2Cl_2} RR'NTf + Et_3NH^+\ ^-PhNTf \quad (21)$$

reaction, phenyltriflamide (pK_a = 4.4),[25] is readily separated by bicarbonate extraction.[26] Interestingly, secondary aromatic amines do not react with this reagent,[15] providing a useful analytical discrimination. Another mild triflating agent is *N*-trifylimidazolide.[27]

Reactivity of Triflamides. The anions of primary triflamides are easily formed as expected from their low pK_a values (~3–8).[25] These relatively stable triflamide anions undergo alkylation[24,26] and acylation[15] in excellent yields under mild conditions.

The unique advantage of triflamides over other sulfonamides arises from the variety of possible cleavages observed (Table V). Of the four ionic cleavages listed, only 1a has not been observed. Mode 2a represents triflating agents (trifyl electrophiles) with nitrogenous leaving groups as represented by phenyltriflimide or *N*-trifylimidazolide. The same mode (2a) is presumably displayed in the smooth reductive removal of the trifyl group from simple triflamides by aluminum hydrides.[26] Discrimination in reduction of primary and secondary triflamides is provided by different hydrides.[26]

The smooth N-alkylation of triflamides and the subsequent removal of the trifyl group by hydride reduction allowed a new nearly quantitative sequence for the protection and monoalkylation of amines (eq 22).[26]

$$RNH_2 \underset{NaAlH_2(OCH_2CH_2OCH_3)_2}{\overset{Tf_2O}{\rightleftharpoons}} RNHTf \xrightarrow{R'X} RR'NH \underset{LiAlH_4}{\overset{Tf_2O}{\rightleftharpoons}} RR'NTf \quad (22)$$

The relatively stable and crystalline acylating agents RCON(Tf)Ph, somewhat less reactive than acid chlorides, illustrate mode 1b (Y = C). These acyl triflamides acylate amines and alcohols in nearly quantitative yields.[15] The analogous S_N2 displacement of triflamide from *saturated* carbon does not occur with simple triflamides, but such reactions do occur if an additional trifyl group is attached to nitrogen (eq 23).[28,29] This is a rare example of a nitrogen leaving

$$PhCH_2N(Tf)_2 \xrightarrow{X^-} PhCH_2X + {}^-N(Tf)_2 \quad (23)$$
$$X = Br, CN, OMe, CH(COOEt)_2$$

group, made possible by trifyl activation. The reductive cleavage of triflamides α to carbonyl also illustrates mode 1b (eq 24).

$$PhCOCH_2N(CH_2Ph)(Tf) \xrightarrow[CH_3COOH,\ \Delta]{Zn} PhCOCH_3 + PhCH_2NHTf \quad (24)$$

Mode 2b, in Table V, represents the most studied class of reactions. This type of removal is characterized by the loss of triflinate anion from nitrogen, and it is here that the greatest difference of reactivity between triflamides and other sulfonamides is observed. In general these reactions involve alkylation of the triflamide anion followed by elimination of the stable triflinate anion by base-induced removal of an acidic β proton, on either the triflamide or the alkylating agent (eq 25). The proton actually removed first, i.e., (25a)

$$Y{-}\overset{H}{\underset{|}{\bar{N}}}{-}Tf \xrightarrow{RR'CHX} Y{-}\overset{H_a}{\underset{|}{N}}{-}\overset{H_b}{\underset{|}{C}}RR' \quad (Tf)$$

$$-HTf \begin{cases} \xrightarrow{a} Y{=}N{-}CHRR' \xrightarrow{H_3O^+} Y{=}O + RR'CHNH_3^+ & (a) \\ \xrightarrow{b} HY{-}N{=}CRR' \xrightarrow{H_3O^+} HYNH_3^+ + RR'C{=}O & (b) \end{cases} \quad (25)$$

or (25b), and the final position of the double bond before hydrolysis depend largely on the nature of the Y and R groups and the position of the equilibrium of imines.

When HY is a benzyl group, elimination after simple alkylation (eq 25) requires strongly basic conditions.[26] Hydrolysis of the resultant benzaldimine gives benzaldehyde and a primary amine from what was an alkyl halide. This net transformation (eq 25) is equivalent to the classic Gabriel synthesis of primary amines. Seeking more activation of the benzylic proton to facilitate easier elimination of triflinate anion, we added a carbomethoxy group, creating as a Gabriel reagent the methyl ester of phenylglycine triflamide ($CH_3OCOCH(Ph)NHTf$).[26] Indeed, with this reagent elimination occurred under the conditions for alkylation (K_2CO_3/CH_3CN, Δ), and hydrolysis of the resultant imine was facile enough to occur on aqueous workup. Thus the free primary amine could be prepared in one

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(26) J. B. Hendrickson, R. Bergeron, and D. D. Sternbach, *Tetrahedron*, 31, 2517 (1975).
(27) F. Effenberger and K. E. Mack, *Tetrahedron Lett.*, 3947 (1970), and references therein.
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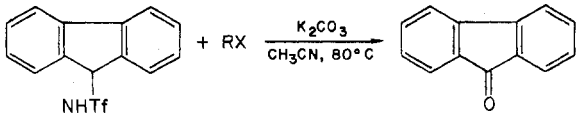
(29) J. B. Hendrickson, R. Bergeron, A. Giga, and D. D. Sternbach, *J. Am. Chem. Soc.*, **95**, 3412 (1973).

operation from phenylglycine ester triflamide and alkyl halide. Imine tautomerization out of conjugation (reaction 25a → 25b) with the ester group did not occur to a significant extent, even when the other imine was stabilized by conjugation.

As an alternative activation of H_a in the amine synthesis, 9-fluorenyltriflamide was examined. This variant considerably reduced the reaction time for alkylation–elimination and appears at present to be the best triflamide adaptation of the Gabriel synthesis, with good yields in the sequence of eq 26.[26]



$$+ RNH_2 + Tf^- + X^- \quad (26)$$

When H_b is more acidic, elimination occurs via path 25b, effecting, after hydrolysis, a net oxidation of the alkyl halide to an aldehyde or ketone, as in alkylation–elimination with a phenacyl bromide (eq 27).[29]

$$p\text{-BrPhCOCH}_2\text{Br} + \text{PhNHTf} \xrightarrow[\text{room temp}]{2K_2CO_3} [p\text{-BrPhCOCH}_2\text{N(Tf)Ph}] \rightarrow p\text{-BrPhCOCH=NPh (90\%)} \quad (27)$$

However, the corresponding oxidation of *n*-butyl bromide does not occur even on refluxing with NaH/DMF.[29]

Seeking to adapt eq 25b to provide a simple oxidation procedure for unactivated halides, we utilized an acidic H_a and a favorable a → b tautomerism. Thus, alkylation of RCONHNHTf was followed spontaneously by elimination and tautomerization to the more stable acyl hydrazone of the desired aldehyde (eq 28), a specific

$$\text{RCONHNHTf} \xrightarrow[K_2CO_3/CH_3CN]{R'CH_2X} \text{RCONHN(Tf)CH}_2\text{R}' \xrightarrow{K_2CO_3} \text{RCON=NCH}_2\text{R}' \longrightarrow \underset{(70\text{-}96\%)}{\text{RCONHN=CHR}'} \quad (28)$$

oxidation procedure without an ordinary oxidant.[30] When R = *t*-BuO the parent hydrazine may be formed with acid.[30] The comparable transformation[24] in the oxime series is a double oxidation of primary halide to nitrile, using an *N*-trifyl-*O*-acylhydroxylamine[31] as reagent (eq 29).

$$\text{PhCH}_2\text{CH}_2\text{ONs} + \text{PhCOONHTf} \xrightarrow[\text{CH}_3\text{CN}]{2K_2CO_3} [\text{PhCH}_2\text{CH=NOCOPh}] \xrightarrow[\Delta]{} \underset{(62\%)}{\text{PhCH}_2\text{CN}} \quad (29)$$

Triflates (Y-O-Tf)

The last group of compounds to be considered contains the Y–O–Tf moiety. As stated in the introduction, the triflate anion is very stable. It is a superb leaving group,[32,33] with solvolysis reaction rates between 10^5 and 10^7 times greater than those of the corresponding tosylates and halides.[34-36]

C–O–Tf. Alkyl, aryl, and vinyl triflates have been synthesized by a variety of methods.[27,32] Most of the procedures involve reaction of an alcohol, phenol, or enol with an electrophilic trifyl source such as triflic anhydride[31] or *N*-trifylimidazolide.[27] We have found phenyltriflimide ($PhN(Tf)_2$) to be an efficient and mild triflating agent for phenols, easily prepared, crystalline, and stable.[10,15] The solvolysis reactions of the triflates of normally unreactive substrates have been investigated by several groups.[34-36] Finally vinyl triflates have been used in the study of bent and linear vinyl cations[37] and in the generation of "free" vinyl carbenes.[32]

N–O–Tf. Compounds containing the N–O–Tf moiety are very labile and not isolable. They exist as intermediates in a useful synthesis of nitriles from aldoximes (eq 30).[38]

$$\text{RCH=NOH} + Tf_2O + 2NEt_3 \xrightarrow[-78\ ^\circ C]{CH_2Cl_2} \text{RCN (88-93\%)} + 2(HNEt_3^{+-}OTf) \quad (30)$$

P–O–Tf. Reasoning that triflate cleavage from phosphorus should produce a potent electrophile for oxygen, capable in turn of removing that oxygen, we examined the compound triphenylphosphine ditriflate ($Ph_3P(OTf)_2$), made by the reaction of triflic anhydride and triphenylphosphine oxide (eq 31). This reagent

$$Ph_3P{=}O + Tf_2O \xrightarrow[CH_2Cl_2/Et_2O]{0\ ^\circ C} Ph_3P(OTf)_2 (\text{or } Ph_3POTf^{+-}OTf) \quad (31)$$

is an effective general oxygen activator which converts the oxygens of various classes of compounds into good leaving groups (eq 32).[39] The reagent works rapidly

$$Ph_3P(OTf)_2 + Z\text{—}OH \rightarrow Ph_3\overset{+}{P}\text{—}O\text{—}Z \rightarrow Z^+ + Ph_3P{=}O \quad (32)$$

and at ambient temperatures. Thus, cyclohexanol and menthol were dehydrated to the corresponding olefins in good yield. The intermediate oxyphosphonium complex (eq 32) from menthol was surprisingly stable at room temperature but eliminated on warming to a mixture of menthenes.[40] Carboxylic acids with this reagent gave a complex which reacted with nucleophiles such as amines and alcohols to give the corresponding amides or esters (eq 33) in good yield at room temperature.[40] Aryl amides may be dehydrated to give nitriles with this reagent, and Bischler–Napieralsky

$$\text{RCOOH} + Ph_3P(OTf)_2 \xrightarrow[CH_2Cl_2]{25\ ^\circ C} \text{RCOOPPh}_3^{+-}\text{OTf} \xrightarrow{\text{Nu:}} \text{RCONu} + Ph_3P{=}O \quad (33)$$

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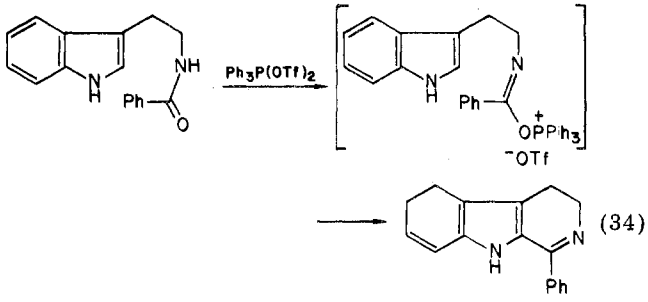
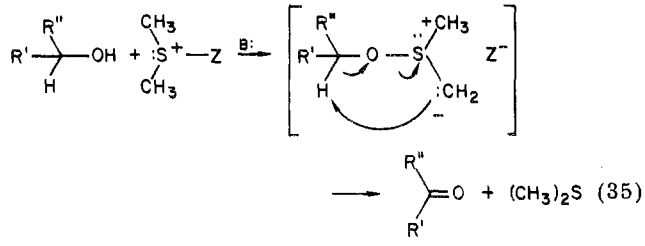
(40) S. M. Schwartzman, Ph.D. Thesis, Brandeis University, 1975.

cyclodehydration has also been effected (eq 34).



(34)

S–O–Tf. In an analogous reaction dimethyl sulfide ditriflate $[(CH_3)_2\ddot{S}(OTf)_2]$ may be prepared by addition of triflic anhydride to dimethyl sulfoxide.[10,41] Dimethyl sulfide derived reagents have a long history as oxidizing agents for alcohols.[42] All the reagents oxidize in a similar manner proceeding through an ylide intermediate (eq 35). Owing to its stability and low nucleophilicity, triflate furnishes a superior Z group for this reaction; the oxidation of alcohols proceeds rapidly to ketones in the presence of various other functional groups.[41]



(35)

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Conclusions

The trifyl group possesses a broad spectrum of reactivity, and yet in most of these transformations it maintains its structural integrity and reacts cleanly. A wide variety of synthetic uses for this reactivity was examined with a view to clarifying its synthetic potential and laying a broad base for further exploration. The results thus far have already demonstrated the utility of trifyl group activation in synthesis. Especially attractive is the variety of applications to construction reactions, formulated in the terms of ref 43 as a B_1 nucleophile with 1_1, 2_1, 3_1, 4_1, $\bar{1}_3$ electrophiles and also as both a 1_1 and $\bar{1}_2$ electrophile. In both construction and refunctionalization reactions the trifyl group is easily attached, broadly stable to undesired reaction, yet easily removed in various ways. The option of both nucleophilic and electrophilic reactivity provides a flexible base for the design of a number of further synthetic reactions to satisfy particular needs. In all these respects the continued development of new reactions activated by the trifyl group appears to have a promising future in synthetic chemistry.[44]

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(44) Since this account was written, another review of the chemistry of the trifyl group has appeared: R. D. Howells and J. D. McCown, *Chem. Rev.*, **77**, 1 (1977).