The Use of Tosylhydrazone Salts as a Safe Alternative for Handling Diazo Compounds and Their Applications in Organic Synthesis

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Keywords: Diazo compounds / Hydrazones / Bamford–Stevens reaction / Epoxidation / Aziridination / Cyclopropanation / Olefination / Pyrazoles / Homologation / Ether synthesis

Diazo compounds are useful synthetic intermediates in organic synthesis but, due to their toxicity and unpredictable explosive behaviour, their unique reactivity has not been fully exploited and their use on large scale has been avoided. We have developed a reliable method that generates diazo compounds in situ. Our approach is based on the Bamford–Stevens reaction, which utilizes tosylhydrazone salts as diazo precursors. In the presence of phase-transfer-catalysts (PTC), we found that tosylhydrazone salts can be cleanly converted to diazo compounds under mild reaction conditions and in a wide range of solvents. These diazo compounds can then be induced to react directly with alkenes or alkynes to synthesize pyrazoles or with aldehydes to generate ketones. Alternatively, diazo compounds can react with transition metals capable of carbene transfer reactions. We have shown the usefulness of this chemistry in a number of different transformations, such as Wittig olefination reactions and the sulfur ylide mediated epoxidation, as well as aziridination and cyclopropanation chemistry as applied toward the synthesis of more complicated molecules.

Introduction

Diazo compounds are inherently dangerous.[1–3] Their toxicity and tendency to explode are indeed serious hazards to be taken into account when synthesising and working with them.[4] The toxicity of diazo compounds is due to their acid-catalyzed decomposition to form carbocations, which are able to alkylate deoxynucleic acids. This is especially acute when handling volatile diazo compounds. For instance, diazomethane is reported to be a strong respiratory irritant that can cause asthmatic symptoms as well as pulmonary edema.[5] There has been one reported fatality of diazomethane poisoning in humans and the high acute

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Varinder K. Aggarwal was born in Kalianpur in North India in 1961 and emigrated to the United Kingdom in 1963. He received his B.A. (1983) and Ph.D. (1986) from Cambridge University, the latter under the guidance of Dr. Stuart Warren. He was subsequently awarded a Harkness Fellowship and carried out postdoctoral work with Professor Gilbert Stork at Columbia University, NY (1986–1988). He returned to a lectureship at Bath University and in 1991 moved to Sheffield University, where in 1997, he was promoted to Professor of Organic Chemistry. In 2000, he moved to the University of Bristol to take up the Chair of Synthetic Chemistry. He is recipient of the AstraZeneca award, Pfizer Awards, GlaxoWelcome award, Novartis lectureship, RSC Hickinbottom Fellowship, Nuffield Fellowship, RSC Corday Morgan Medal the Liebigs Lectureship, RSC Green Chemistry Award, and AstraZenecaDistinguished Lecturer award.

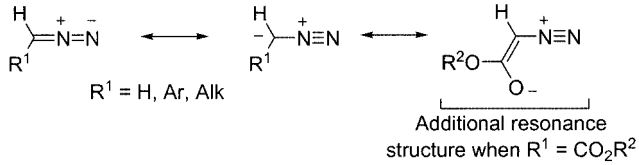
Javier de Vicente was born in Madrid in 1974. He studied chemistry at the Autonoma University of Madrid, receiving his B.S. degree in 1997 and his MS degree in 1999 under the supervision of Professor Juan Carlos Carretero. For his Ph.D. degree, he studied with Professor. Varinder K. Aggarwal at the University of Bristol, developing user-friendly synthetic processes using diazo compounds generated in situ. He is currently conducting postdoctoral studies with Professor Scott D. Rychnovsky at the University of California, Irvine, and his work focuses on the synthesis of natural polyhydroxy structures.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

toxicity to cats has also been described. The potentially violent behaviour of diazomethane has also been well documented. Several researchers have reported diazomethane explosions resulting from contact with sharp surfaces, such as etched or scratch flasks or upon warming on ambient to elevated temperatures.[6] De Boer and Backer also reported that most explosions occur during distillation. In addition, diazomethane has been reported to react exothermically with Drierite® (calcium sulfate).

Trimethylsilyldiazomethane is remarkably more stable than diazomethane and has led to investigations on its use in synthesis as a stable and safe substitute of diazomethane.[7] Diazoesters are considered to be much safer than diazomethane due to the resonance stabilization of the ester functional group (although only estimated to be around 16 kJ/mol) (Scheme 1).[8] These compounds can still detonate, albeit under much more forcing conditions, such as exposure to heat or concentrated sulfuric acid.[9] In addition, the health hazards associated with ethyl diazoacetate are much reduced, partially due to its significantly higher boiling point. The toxicity of aliphatic and aromatic diazo compounds has not been studied in the same detail; however, these compounds are assumed to be toxic (due to the pathways previously discussed) and are also explosive. On a personal account, one of the authors' co-workers experienced an explosion during a distillation of phenyldiazomethane. Fortunately, the impact of the explosion was minimal as the reaction vessel was placed behind a glass shield.

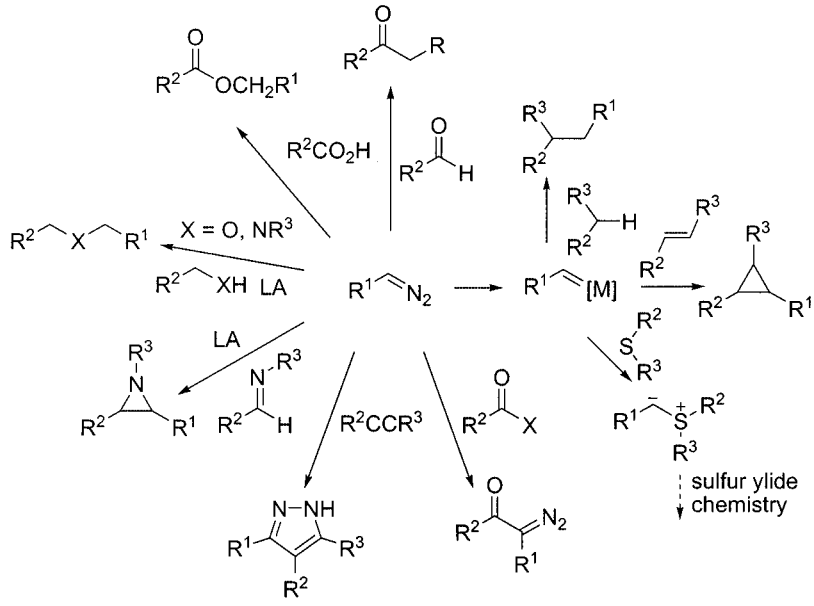
Despite their danger, the synthetic utility of diazo compounds cannot be overlooked.[10–12] Diazo compounds have an unique reactivity due to their 1,3-dipole and ylide nature.[13] They can react directly with organic substrates, such as in the alkylation of acidic alcohols and carboxylic acids, homologation of carbonyl compounds, 1,3-dipolar addition onto alkynes and preparation of diazoketones from acyl halides (Scheme 2). In the presence of a Lewis-acid, diazo



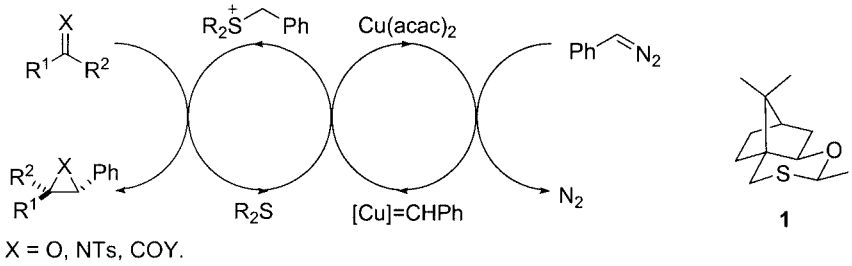
Scheme 1. Resonance structures of aliphatic and ester substituted diazo compounds.

compounds will alkylate amines and aziridinate imines.[14,15] Diazo compounds are also the preferred precursors of metallocarbenes and carbenoids.[13,16–19] They can react with a wide number of transition metal complexes capable of transferring carbenes, and such diazo compounds can be used for a variety of different transformations, including carbene insertion reactions into C–H,[20] Si–H, N–H, O–H, and S–H bonds,[13] sulfur ylide mediated epoxidation, aziridination or cyclopropanation reactions (the latter can also occur directly) in addition to Wittig-type transformations.[21,22] Despite diverse reactivity, diazo compounds are generally avoided in an industrial setting due to their unpredictable explosive behaviour. Only recently has the thermo-chemistry and the detonation properties of ethyl diazoacetate have been studied and large scale chemistry of ethyl diazoacetate has shown limited use.[9,23–25] With regards to diazomethane, only one patent has described the production of diazomethane on a large scale[26] and methods for the continuous process of diazomethane have also been described.[27,28] To the best of our knowledge, there has been no large scale production of more complex aliphatic non-diazocarbonyl compounds.

The synthetic utility of diazo compounds and their limited use in industry has evolved a recent drive to develop safer alternative methods for using diazo compounds; either generating them in situ or using an alternative source of carbene equivalents and precursors. This review will focus



Scheme 2. Some of the most useful transformations of diazo compounds (LA = Lewis acid).



Scheme 3. Catalytic epoxidation (X = O), aziridination (X = NTs), and cyclopropanation (X = CH_2COY) mediated by sulfur ylides.

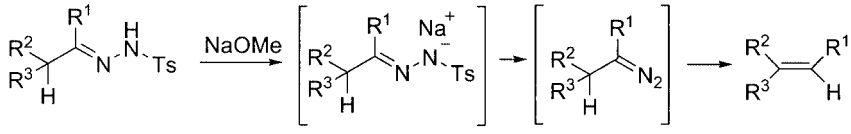
on the in situ generation of diazo compounds from tosylhydrazone compounds. It is noteworthy that other alternatives such as the use of phenyliodonium ylides, *N*-aziridinylimines and amino ester hydrochloride derived diazo compounds have been developed, although they will not be discussed in this article. The use of phenyliodonium ylides has recently been reviewed by Müller,[29] *N*-aziridinylimines cannot be regarded as safer than diazo compounds due to the explosive nature of its precursor, 1-amino-2-phenyl-aziridinium acetate.[30,31] Amino ester hydrochlorides have found limited use as they are only used to generate diazoacetates by diazotization.[32,33] Interestingly, Myers has recently reported a new method for the in situ generation of diazo compounds by oxidation of *N*-*tert*-butyldimethylsilylhydrazones.[34]

Origin of the In Situ Process for the Generation of Diazo Compounds from Tosylhydrazone Salts: History and Scope

The impetus for developing a safer alternative for using diazo compounds within our group arose from the desire to expand the scope of current chemistry under investigation. We had been using phenyldiazomethane as a carbene source for sulfur ylide mediated epoxidation,[35,36] aziridination[35,37] or cyclopropanation reactions (Scheme 3).[38] The presence of both a transition metal capable of transferring a carbene (such as rhodium acetate, $Rh_2(OAc)_4$, or copper actylacetonate, $Cu(acac)_2$) as well as a sulfide was required for the desired transformation. Presumably, the diazo compound reacts directly with the copper complex to form a copper carbene intermediate.[39] The carbene is then transferred to the sulfide to generate a sulfur ylide, which is directly responsible for the transformation of aldehydes, imines or alkenes into epoxides, aziridines, or cyclopropanes, respectively (Scheme 3).

These reactions were initially explored using tetrahydrothiophene and then chiral sulfides (such as **1**), resulting in high enantioselective formation of epoxides,[40] aziridines[41] or cyclopropanes (Scheme 3).[42] Unfortunately, further applicability and potential commercial success of this new methodology was thwarted by the need to handle diazo compounds as the use of diazo compounds in the laboratory was very cumbersome for several reasons. Firstly, solutions of phenyldiazomethane could not be synthesized in large quantities due to the hazards associated with it and therefore had to be freshly prepared and titrated. Moreover, there is some inherent risk to the temperatures required for their synthesis.[43] Secondly, slow addition of the diazo compound required the use of syringe pumps and continual monitoring with the inconvenience associated with storing the diazo compound on the syringe pump during the addition period. Finally, the scope of the reaction was very limited due to the number of diazo compounds that could be used. For instance, electron-rich diazo compounds, such as *p*-methoxy substituted phenyldiazomethane, are unstable to the point that they decompose at –80 °C.[44] Thus, we were inspired to find a user friendly methodology that would allow us to generate a wide variety of diazo compounds yet minimize the risk associated with them. This seemingly contradictory wish was addressed by investigations into the Bamford–Stevens reaction.

The Bamford–Stevens Reaction: The base mediated decomposition of substituted arylhydrazones to form diazo compounds was firstly reported by W. R. Bamford and T. S. Stevens in 1952 (Scheme 4).[45] A few diazo compounds could be isolated if mild temperatures were employed; however, in most examples, the diazo compound thermally decomposed to form alkenes, the net result of loss of dinitrogen followed by a 1,2-hydrogen shift. The mechanism for alkene formation was extensively studied and was found to be dependent upon the reaction conditions.[46] For instance, in protic media, the diazo compound can be protonated to form a diazonium ion, resulting in the formation of a carbocation upon loss of dinitrogen. This pathway does not occur in the absence of protons, and in aprotic media, dinitrogen loss results in the formation of carbene intermediates.



Scheme 4. The Bamford–Stevens reaction.

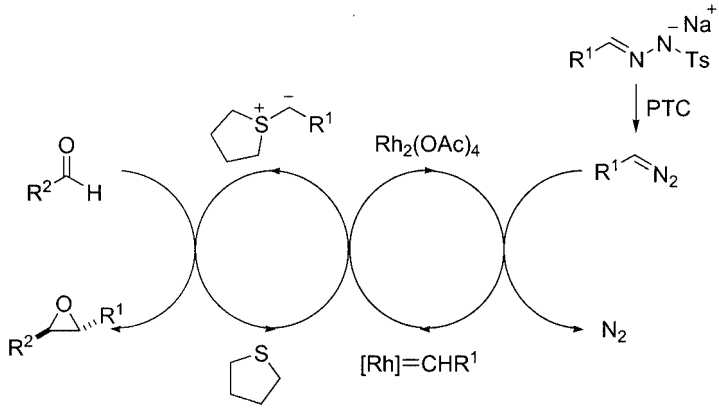
The decomposition of tosylhydrazones with base (and variations thereof) was subsequently used as a preparative procedure to synthesize a series of aryldiazomethanes and is still a standard method for their generation.[43,47] This procedure initially involves deprotonation of the tosylhydrazone to form the corresponding anion. When the reaction is performed cold, the tosylhydrazone salt can sometimes be isolated. Upon heating (generally 60 °C or higher), the tosylate anion will dissociate, generating the diazo compound. This reaction must be performed in either a polar media such as pyridine or methanol, or in a basic aqueous two-phase system.

Development of the in situ Technology: We found that we could generate diazo compounds under mild conditions and in non-polar media by gently warming (30–40 °C) a suspension of the isolated tosylhydrazone salt in the presence of a phase-transfer catalyst (PTC). As the salt is not very soluble in highly non-polar solvents, the PTC is necessary to aid the passage of the anion from the solid to the liquid phase where decomposition (diazo formation) occurs. As every component in the reaction mixture, except for the diazo compound, is fairly inert, we realized that we could add to this mixture substrates that could react directly with the in situ generated diazo compounds without the worry of these substrates reacting with the reagents promoting the decomposition of the tosylhydrazone salts. Thus, as the diazo compound is formed, it can immediately be "trapped out" in a subsequent reaction. This in situ generation of diazo compounds would not only keep the diazo concentration low and minimize the hazards associated with the more concentrated diazo solutions, but it would also prevent dimerization of the diazo compounds to form azines or alkenes through common decomposition pathways for these molecules.

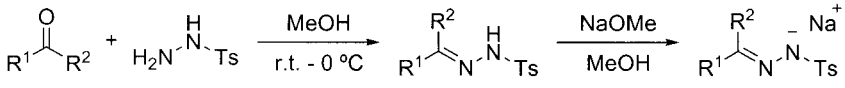
Our in situ concept was initially tested on the sulfur ylide mediated epoxidation of aldehydes (Scheme 5).[48] In this reaction, a transition metal catalyst would "trap out" the diazo compound as it was slowly generated, resulting in the formation of a metal carbene complex. Since the diazo decomposition or metal carbene formation is a fast reaction and the concentration of diazo is small, the metal carbene would presumably only react with the sulfide and not with another equivalent of the diazo compound. To our delight, this hypothesis proved correct, and epoxides were obtained in good yields.[48] As such, the scope of the sulfur ylide mediated epoxidation reaction increased dramatically. Diazo compounds that were initially considered to be too dangerous, such as *p*-methoxyphenyldiazomethane, could now be used as a coupling partner. Moreover, since tosylhydrazone salts were initially prepared by treatment of an aldehyde or ketone with tosylhydrazide (vide infra), the number of tosylhydrazone salts, and hence diazo compounds, that could be utilized is in principle limitless.

The in situ technology was applied to other reactions (vide infra), such as the aziridination of imines,[49] aldehyde homologation,[50] cyclopropanation of alkenes,[49] 1,3-dipolar additions to alkynes,[51] and Wittig olefination.[52] Most of our knowledge of the stability and properties of tosylhydrazone salts, including the optimal reaction conditions, was obtained during our studies on the epoxidation of aldehydes. However, as the decomposition pathway presumably does not change, the knowledge we gained is applicable to all systems.

Synthesis and Stability of Tosylhydrazone Salts: A wide range of tosylhydrazone salts were examined, all of which were easily synthesized by treating the analogous aldehyde with *p*-tolylsulfonylhydrazide (Scheme 6). This general procedure involves dropwise addition of the aldehyde (or solution thereof) into a suspension of sulfonylhydrazide in a minimal amount of methanol followed by the cold isolation of the precipitate.[53] The sodium tosylhydrazone salt is formed by treating this precipitate with a freshly prepared 1 M sodium methoxide solution in methanol. In some instances, care must be taken as to the amount of base added;



Scheme 5. Catalytic epoxidation of aldehydes using tosylhydrazone salts.



Scheme 6. Preparation of tosylhydrazone salts.

anything greater than 1.08 equivalents of base could result in decreased yields in subsequent metal-catalyzed reactions, presumably due to inhibition of the metal catalyst by the excess base. If necessary, the salts were titrated to determine the excess base content.[53] Tosylhydrazones contaminated with more than 0.1 equiv. of base were discarded. Analogous lithium salts were generated upon treatment of the corresponding hydrazone with a commercial 1 M solution of LiHMDS and potassium salts were made using home solutions of *t*BuOK.[52] The choice of counterion was system dependent and will be discussed in the relevant sections.

To prevent thermal and photochemical decomposition, all of the salts were stored in the dark at –20 °C (freezer). The stability of the tosylhydrazone salts depended upon the electronic nature of the salt. Electron-rich salts could be kept indefinitely at –20 °C without evidence of decomposition. However, electron-poor salts decomposed readily even at –20 °C and had to be prepared just prior to use. Note that the opposite is true with the corresponding diazo compounds: electron-withdrawing groups stabilize and electron-donating groups destabilize the diazo functionality. This again highlights the unique properties of tosylhydrazone salts as they are a stable source of unstable diazo compounds.

Reaction Conditions: The process for generating diazo compounds in situ from tosylhydrazone salts is compatible with a large number of reaction conditions. The optimal reaction conditions are, in part, dictated by their compatibility with the conditions that will be coupled to this user-friendly process. However, we have always found that the best conditions for metal-catalyzed reactions arise from keeping the concentration of the diazo compound as low as possible. The most important variables to be considered for the optimal reaction conditions are solvent, PTC and temperature.

a) *Solvent.* A wide range of solvents can be used including ethereal, nitrile, protic chlorinated and aromatic solvents. The reaction media should be optimized for each reaction type considering that more polar solvents will increase the rate of generation of the diazo compound in the reaction mixture.

b) *Phase-transfer catalyst.* The presence of a PTC is necessary when the reactions are performed at temperatures below 50 °C as the PTC facilitates the dissolution and subsequent decomposition of the tosylhydrazone salt to the corresponding diazo compound. When polar solvents such as acetonitrile or 1,4-dioxane were used, the PTC can be benzyltriethylammonium chloride. However, as benzyltriethylammonium chloride exhibited limited solubility in less polar media such as toluene, a greasier PTC, such as tri-*n*-octylmethylammonium chloride (Aliquat® 336), was sometimes necessary.[52]

c) *Temperature.* The optimal temperatures and amount of PTC used generally reflected the thermal stability of the tosylhydrazone salt. The more stable salts required a higher concentration of PTC (up to 20 mol-%) and 40 °C for adequate decomposition whereas the less stable salts decompose at lower temperatures (30 °C) and required very little, if any, PTC (0–5 mol-%). Non metal-catalyzed reactions can be performed at 50 °C whereas the temperature limit when metal catalyst was used was generally 40 °C.

An optimal set of reaction conditions will promote the desired diazo reaction and inhibit side reactions. The most common side products obtained using this in situ process arise from the reaction of eletrophilic metallo carbenes and diazonium salts intermediates with nucleophiles present in the reaction mixture such as the diazo compound leading to azine **2** or alkene **3**, *p*-toluenesulfinic acid sodium salt providing sulfone **4** and the tosylhydrazone starting material giving hydrazone **5** (Figure 1).

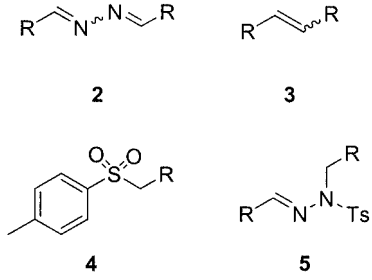
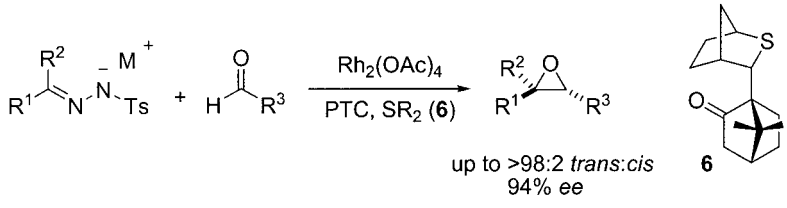


Figure 1. Side-products obtained under unoptimized reaction conditions.

Nevertheless, the formation of these side-products can be suppressed by choosing the optimal combination of reaction conditions as discussed in the following section. In contrast, the formation of these side-products, such as symmetrical dienes,[18] can be promoted which leads to new synthetic methodology.

Applications of the In Situ Process for Generating Diazo Compounds to Synthetic Methods

Application in the Sulfur-Mediated Epoxidation of Aldehydes. A Model Reaction for Exploring the Scope of the in situ Process: The epoxidation of aldehydes with tosylhydra-



Scheme 7. Asymmetric sulfur ylide mediated expoxidation of aldehydes using diazo compounds generated in situ.

zone salts has been our most comprehensively investigated reaction (Scheme 5 and Scheme 7).[48,54–57] This transformation relies on a series of events involving the decomposition of the tosylhydrazone salt to the diazo compound, reaction of the diazo compound with the metal catalyst to create a metal-carbene complex, transfer of the carbene to the sulfide, and finally reaction of the resulting sulfur ylide with the aldehyde. As such, the epoxide yields depend upon all of these events occurring very efficiently and a variety of different reaction conditions had to be optimized. The factors controlling selectivity, including diastereoselectivity and enantioselectivity (when chiral sulfide **6** was utilized) have been comprehensively described elsewhere[53,56,58] including our efforts into designing chiral sulfides compatible with the in situ process.[59–61] Thus, only the factors that influence the decomposition of the salt will be discussed.

a) *Choice of catalyst.* Even though copper acetylacetonate ($Cu(acac)_2$) was the catalyst of choice when phenyldiazomethane was used directly, rhodium acetate ($Rh_2(OAc)_4$) was significantly more efficient in the in situ reactions. For instance, control experiments in which benzaldehyde-derived tosylhydrazone salt was coupled with *p*-chlorobenzaldehyde, the maximum yield obtained when the copper catalyst is utilized is 73% with a 5 mol-% catalyst loading. In contrast, an 86% yield is obtained when the rhodium catalyst is used, even though the catalyst loading was 1 mol-%. The reason for this difference in catalyst behaviour is unclear but it is entirely plausible that copper is more sensitive to the presence of salts (either tosylate or chloride from the PTC).

b) *Choice of counterion*. In addition, the choice of counterion to the tosylhydrazone salt is also important, with the sodium tosylhydrazone salt outperforming the analogous lithium, potassium and tetrabutylammonium salts in terms of both yields and conditions. This could be either due to the initial decomposition of the salt; however, the later steps could also be affected and we have yet to the controlling factors in this observation.

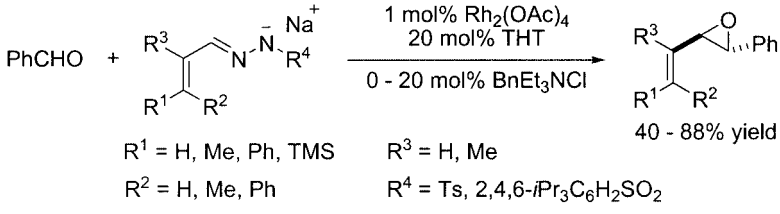
c) *Optimal conditions.* Although the epoxide yield greatly depended on the coupling partner, sulfide, and solvent, we could optimize the reaction conditions such that a 98% yield of epoxide was obtained when *p*-methoxybenzaldehyde was used as the coupling partner with the benzaldehyde derived tosylhydrazone salt and 20 mol-% of tetrahydrothiophene (THT) was used. This kind of result indicates *decomposition of the tosylhydrazone salt and transfer to the rhodium metal species is a clean reaction and is not be a factor in determining the success of a reaction*. The lower yields observed are generally due to subsequent reactions, such as the carbene transfer from rhodium to sulfide or the reaction between the sulfur ylide and aldehyde.

The optimal reaction conditions using achiral sulfides were generally 1 mol-% of $Rh_2(OAc)_4$, 20 mol-% of THT, and 0–20 mol-% of benzyltriethylammonium chloride in acetonitrile at 40 °C. When chiral sulfides were used, a higher concentration of sulfide was sometimes necessary to generate epoxide in good yields due to the lower ability of hindered chiral sulfides to trap the metal carbene. However, this again was not due to the decomposition of the tosylhydrazone salt.

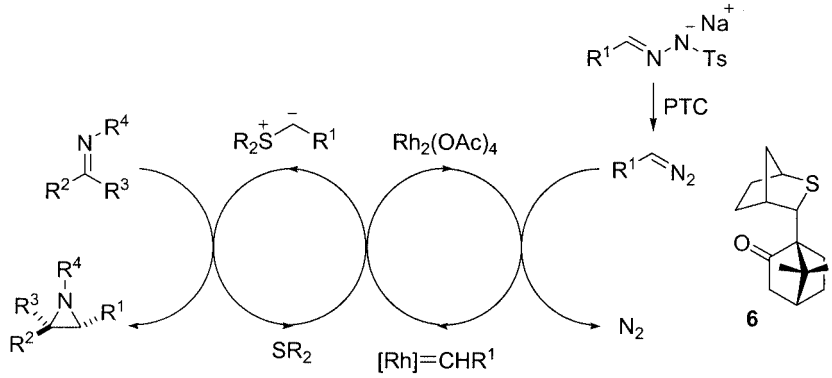
These optimized conditions were subsequently applied to a wide range of tosylhydrazone salts derived from both aryl and α,β-unsaturated aldehydes. We were unable to use the *p*-nitrobenzaldehyde derived tosylhydrazone salt as it decomposed upon formation to give a deep red solution of the corresponding diazo compound. Similarly, the *p*-fluorobenzaldehyde-derived tosylhydrazone salt was capricious and variable yields of epoxide were obtained from the same batch of starting materials, although the *o*-fluorobenzaldehyde tosylhydrazone salt gave high and consistent yields (when coupled with benzaldehyde). Other notable examples include tosylhydrazone salts derived from 2- and 3-furyl aldehydes. The corresponding diazo compounds have been reported to decompose readily and without the in situ technology, we would not have been able to use such compounds. In addition, α,β-unsaturated tosylhydrazone salts could also be employed in the epoxidation reaction (Scheme 8). This reaction was particularly effective in terms of yields when the tosylhydrazone was substituted at both the α and β positions. The epoxide yields could sometimes be improved by using the (2,4,6-triisopropylphenylsulfonyl) hydrazone salt instead of the tosylhydrazone salt. Presumably, the bulkier sulfonyl group facilitated the decomposition of the salt at lower temperatures thus preventing the salt from undergoing side reactions.

Application in the Sulfur Ylide-Mediated Aziridination of Imines: The in situ technology was also applied to the sulfur ylide mediated aziridination of imines (Scheme 9).[41,49,62] We had been encouraged by our earlier aziridination results using phenyldiazomethane as very high levels of enantioselectivity and diastereoselectivity (up to 10:1 *trans*:*cis*) had been achieved.[37]

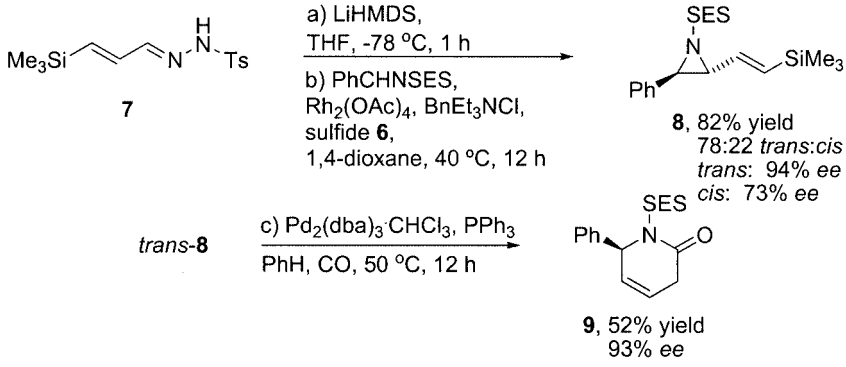
When the in situ process was applied towards the aziridination reaction, an increase in both yield and scope were observed. By using the chiral sulfide **6**, reasonable yields (50–82%) and very high enantioselectivities of aziridines



Scheme 8. Epoxides formed from benzaldehyde and substituted vinylsulfonylhydrazones.



Scheme 9. Asymmetric sulfur ylide mediated aziridination of imines using diazo compounds generated in situ (R^1 = Ph; R^2 = alkyl, aryl, vinyl; R^3 = Ph, H).



Scheme 10. Synthesis of an unsaturated aziridine and subsequent converstion to a lactam.

were achieved. The reaction was sensitive to the nitrogen protecting group on the imine with TcBoc-protected imines giving the highest yields whereas the Boc-protected imine partially hydrolyzed under the reaction conditions (in contrast to the non in situ case).[49] Even though the TcBoc-protected imines resulted in a slightly higher yields than the *N*-SES-protected imines, the *N*-SES-protected imines were easier to prepare and used in most studies [TcBoc = 1,1-dimethyl-2,2,2-trichloroethoxycarbonyl, Boc = *tert*-butoxycarbonyl, SES = 2-(trimethylsilyl)ethylsulfonyl].

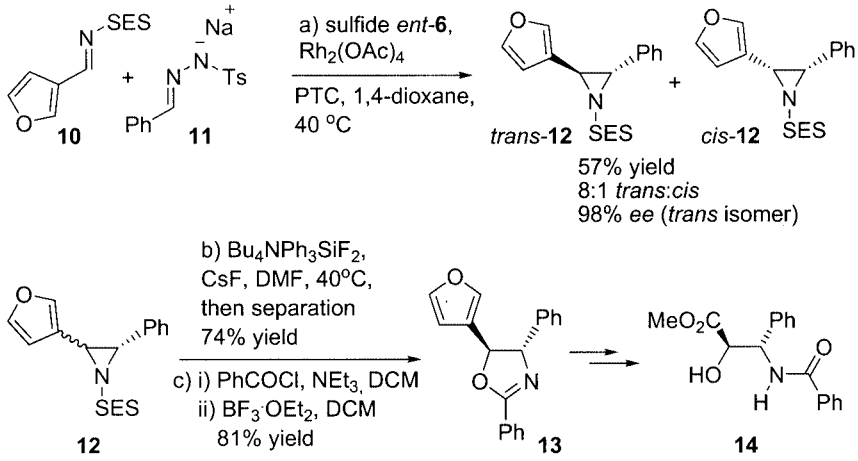
This methodology was extended to the synthesis of unsaturated aziridines by generating alkenyldiazomethanes in the presence of an *N*-SES-activated imines.[49] The resultant aziridines were formed in good yields with moderate to good selectivities. This reaction was particularly attractive as unsaturated aziridine *trans*-**8** could undergo rearrangement to form δ-lactam **9** (Scheme 10).

In order to highlight the usefulness of the in situ technology as a synthetic tool, we applied our technology to the synthesis of the side chain of Taxol **14**, a *syn*-α-amino alcohol (Scheme 11).[62] *trans*-Aziridines can be useful intermediates in the synthesis of these functionalized alcohols as aziridines can be readily converted to either *syn*- or *anti*-α-amino alcohols depending upon the reaction conditions. Thus, *N*-SES imine **10** reacted with tosylhydrazone salt **11** in the presence of a PTC, $Rh_2(OAc)_4$ and catalytic quantities of chiral sulfide *ent*-**6** affording satisfactorily aziridine **12** in 57% yield as a 8:1 *trans*/*cis* diastereomeric ratio in 98% *ee* (*trans* isomer). The diastereomeric mixture of aziridines **12** was desulfonylated and separated and the *trans* isomer was converted into the corresponding benzoyl aziridine and treated with $BF_3 \cdot OEt_2$ resulting in regioselective ring-expansion/isomerization. The oxazoline protected amino alcohol **13** was then transformed into the side chain of Taxol (**14**) by a sequence involving hydrolysis and furan oxidation.

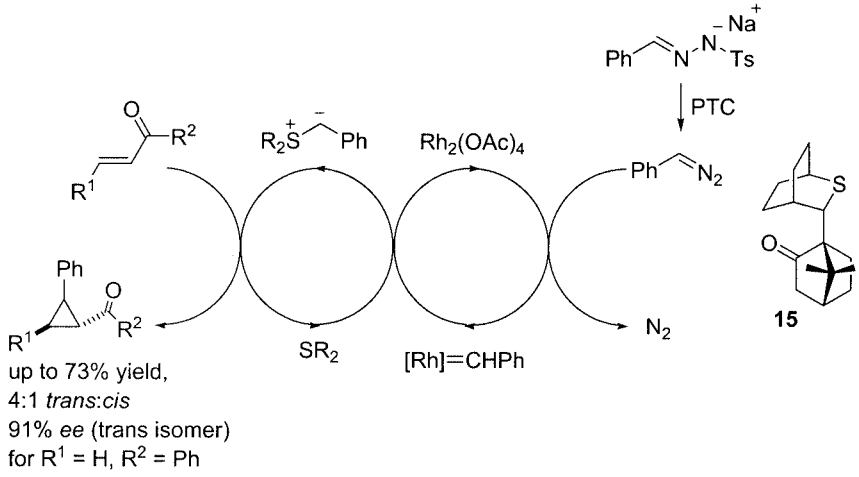
Application in the Sulfur-Mediated Cyclopropanation of Electron Deficient Alkenes: The in situ technology can also be used for the cyclopropanation of alkenes (Scheme 12).[49] We initially investigated tosylhydrazone salts derived from benzaldehyde or an α,β-unsaturated aldehyde (**7**).[49] When chiral sulfide **15** was used, good yields and high enantioselectivities were obtained. The less than perfect yields were not a result of incomplete decomposition of the tosylhydrazone salt, but a consequence of subsequent reactions.

We have also found that α-amino-substituted acrylates are excellent substrates providing cyclopropanes in high yields as exemplified in Scheme 13.[49] The cyclopropanes derived from the amino acrylates could be converted in one step to the corresponding amino acids providing the most efficient asymmetric route to this important class of conformationally locked amino acids.

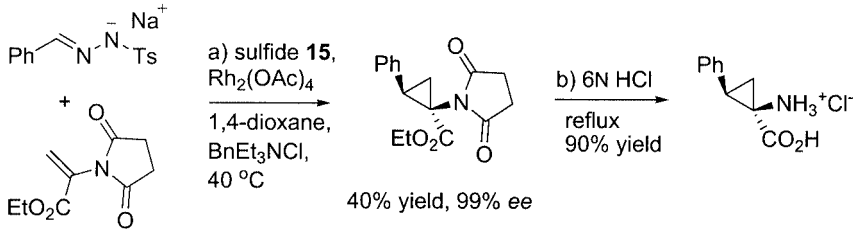
Applications in the Transition Metal Catalyzed Cyclopropanation of Electron-Rich Alkenes: Transition metal catalyzed cyclopropanation of alkenes is one of the most efficient methods for the preparation of cyclopropanes.[17] A



Scheme 11. Asymmetric synthesis of the Taxol side chain (**14**) using diazo compounds generated in situ.



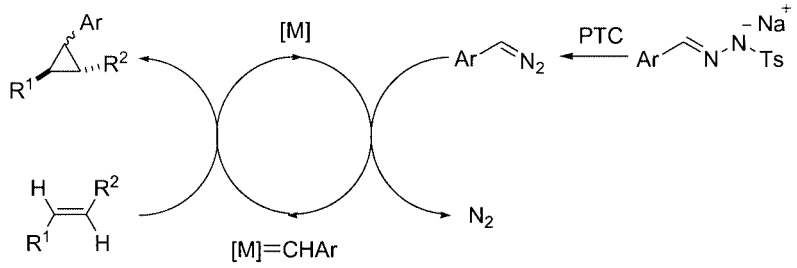
Scheme 12. Catalytic sulfur ylide mediated cyclopropanation of electron-deficient alkenes using tosylhydrazone salts (R^1 = H, CH_3, Ph; R^2 = O-alkyl, alkyl, aryl).



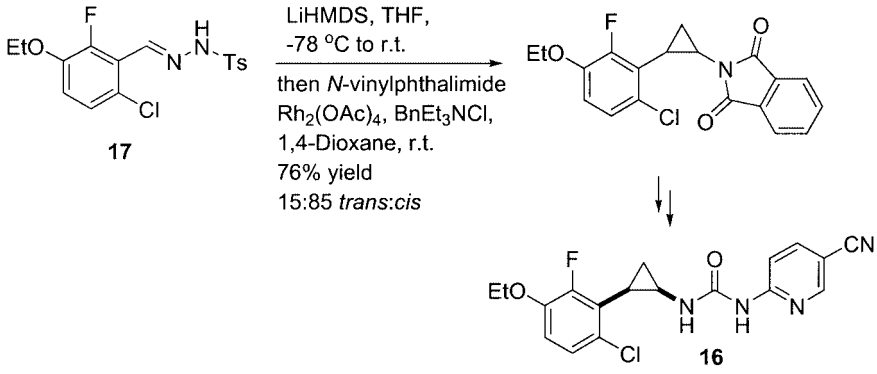
Scheme 13. Synthesis of cyclopropane amino acids using diazo compounds generated in situ.

variety of transition metal catalysts can directly transfer carbenes from diazo compounds to alkenes, thus forming cyclopropanes. However, up until this point, the only diazo compounds that had been regularly utilized were diazocarbonyl analogues presumably due to the inherent instability of aryl-, alkenyl-, or alkynyl diazomethanes and their propensity to undergo metal-catalyzed dimerization.[63]

The in situ technology was used in the synthesis of an assortment of functionalized cyclopropanes (Scheme 14).[64] We screened a variety of different transition metal catalysts including commonly used cyclopropanation catalysts such as copper salts, iron porphyrin complexes, and rhodium and palladium complexes. The copper salts gave only traces of the cyclopropanated product even though it is one of the most common catalysts for the cyclopropanation of alkenes. This is in line with what we observed in our epoxidation chemistry and lends more support that the copper is somehow inhibited in the presence of either a tosylate anion or a PTC. The best catalyst in terms of both yield and diastereoselectivity was the iron porphyrin complex ClFeTPP (TPP = tetraphenylporphyrin), which gave a 91:9 *trans*:*cis* selectivity when the benzaldehyde-derived tosylhydrazone salt was coupled with styrene. Interestingly, when rhodium acetate was used as the catalyst, similar yields were



Scheme 14. Transition metal catalyzed cyclopropanation of alkenes by using tosylhydrazone salts.



Scheme 15. Synthetic route into HIV-1 reverse transcriptase inhibitor **16**.

achieved, but an opposite diastereoselectivity (23:77 *trans*:*cis*) was observed.

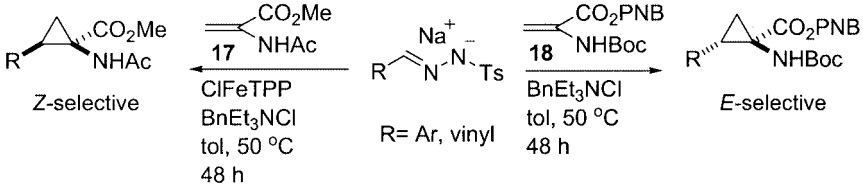
A variety of tosylhydrazone salts could be utilized in this process. Unfortunately, the yields for the *p*-fluoro- substituted and *p*-methoxy- substituted aromatic rings were less than desirable when rhodium acetate was used as the catalyst. It should be noted that this is not due to the actual decomposition of the tosylhydrazone salt to form the diazo compound as these salts have been quite successfully used in the epoxidation chemistry. Contrary to the epoxidation chemistry, the moderate yields often obtained in these cyclopropanation reactions are due to the lower nucleophilicity of alkenes in comparison with sulfides, which limits the use of the tosylhydrazone salts in these reactions.

We further demonstrated the utility of the in situ technology by applying it towards the synthesis of HIV-1 reverse transcriptase inhibitor **16** (Scheme 15).[64] This urea was prepared via cyclopropanation of *N*-vinylphthalimide with a highly substituted aromatic tosylhydrazone salt generated from hydrazone **17**. The phthalimide unit was then readily converted in two steps to the desired urea **16**. This efficient synthesis of HIV-1 inhibitor **16** (6 steps, 18% overall yield) is also notable in that it demonstrates the first direct use of enamides in cyclopropanation reactions.

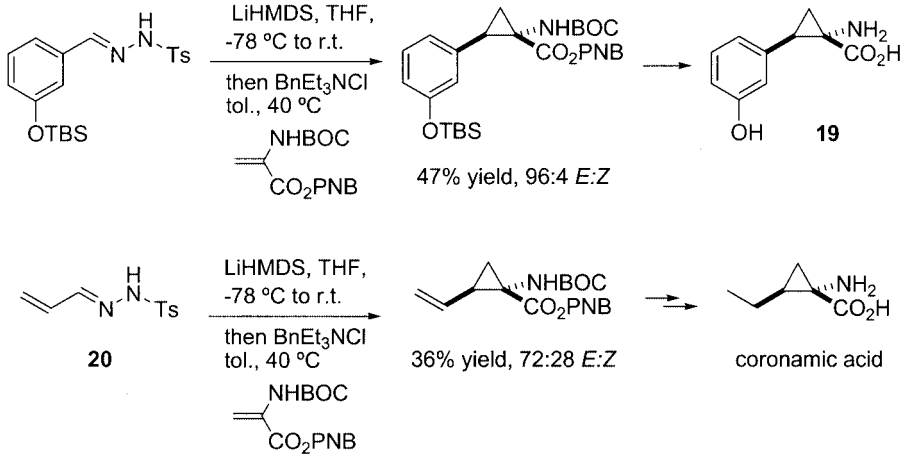
The in situ technology was also used to prepare cyclopropane amino acids from dehydroamino acids and tosylhydrazone salts (Scheme 16).[65] In this system, we found that the reaction conditions could be varied to favour either the *E* or *Z* isomers. The reaction was *Z* selective when dehydroamino acid **17** was employed in the presence of ClFeTPP. In contrast, the *E* isomer was favoured when dehydroamino acid **18** was employed and no catalyst was present. The mechanism of the cyclopropane formation of non-metal-catalyzed reactions was postulated to go by a diastereoselective construction of a pyrazoline followed by extrusion of nitrogen.

The utility of the in situ technology in the synthesis of cyclopropane amino acids was exemplified in the synthesis of the dopa decarboxylase inhibitor (±)-(*E*)-2,3-methano-*m*-tyrosine (**19**) and the natural product (±)-coronamic acid (Scheme 17).[65] With regards to the former, the cyclopropanation step was uncatalyzed and resulted in a 47% yield and very good diastereoselectivity (96:4 *E*:*Z* ratio). The *E* cyclopropane was then fully deprotected under acidic conditions providing *anti*-Parkinson agent **19**. The key cyclopropanation step involved in the synthesis of coronamic acid was low yielding (36% yield, 72:28 *E*:*Z* ratio) due to the use of a problematic α,β-unsaturated hydrazone **20** (vide supra). However, the *E* isomer could be isolated and easily converted into the carboxylic acid upon exposure to an atmosphere of hydrogen in the presence of $Pd(OH)_2$ on carbon, and then treated with concentrated hydrochloric acid to provide coronamic acid.

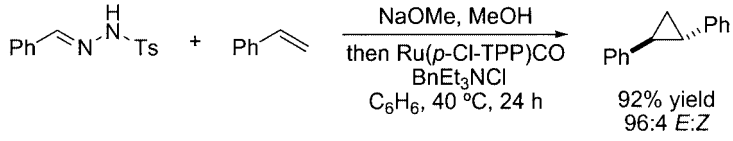
Che's and Doyle's research groups have also explored the use of tosylhydrazone salts for the cyclopropanation of alkenes. Che and co-workers utilized a ruthenium-porphyrin catalyst for the transformation and up to 92% yields and 95:4 *trans*:*cis* selectivity could be obtained (Scheme 18). This is a significant improvement over our catalyst screening results using similar reaction conditions.[66] Che's ruthenium catalyst is more efficient than any of the commercially available catalysts that we screened using similar reaction conditions. Contrary to the rhodium acetate system, the ruthenium porphyrin catalyst failed to provide good dia-



Scheme 16. Cyclopropanation of dehydroamino acids by using tosylhydrazone salts.



Scheme 17. Synthetic routes into (±)-(*E*)-2,3-methano-m-tyrosine (**19**) and (±)-coronamic acid.



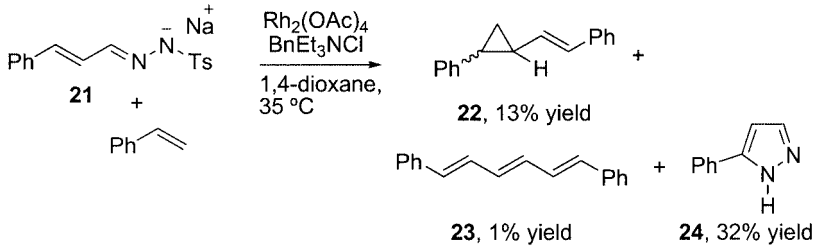
Scheme 18. Cyclopropanation of styrene-catalyzed Che's ruthenium catalyst using benzaldehyde-derived tosylhydrazone.

stereoselectivities when *N*-vinyphthalimide was employed and the diastereoselectivities were similar to those obtained with ClFeTPP in our previous studies.[64]

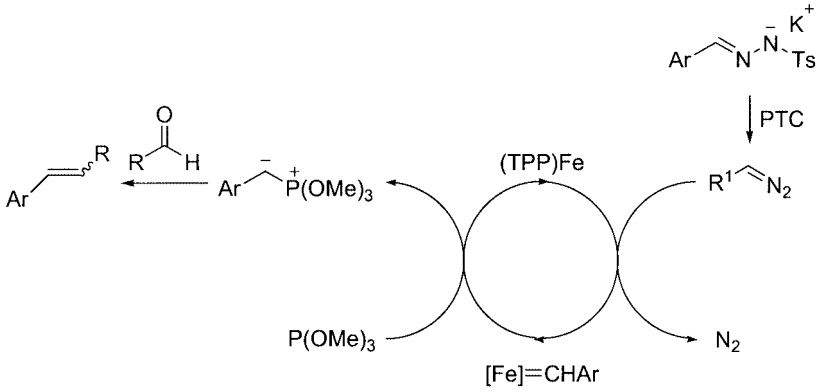
Doyle's group have also explored the utility of tosylhydrazones salts as diazo precursors in the synthesis of cyclopropanes possessing an unsaturated substituent.[18] To this end, they generated the tosylhydrazone salt of cinnamaldehyde (**21**) and treated it with styrene in the presence of a PTC and a metal catalyst at elevated temperatures (Scheme 19). The results were disappointing in terms of yields of cyclopropane **22** as both triene **23** formed by diazo dimerization and pyrazole **24** produced by electrocyclization were major side products. Nevertheless, we have demonstrated that unsaturated tosylhydrazone salts can be used as diazo precursors for the cyclopropanation of dehydroamino acids catalyzed by ClFeTPP.[65]

Applications in the Synthesis of Alkenes via Wittig-Type Transformations: The metal-catalyzed Wittig olefination of aldehydes with diazo compounds in the presence of triphenylphosphane was discovered in 1998 by Fujimura and Honma.[22] Diazo compounds are able to generate phosphorus ylides from phosphanes in the presence of a transition metal catalyst via carbene transfer as in the previously described sulfur ylide mediated reactions. In addition to the typical problems associated with using diazo compounds, this methodology had additional limitations due to the direct reaction between diazo compounds and phosphanes to form phosphazines.[67] Thus, the in situ technology is ideal for this type of Wittig olefination reaction.

Our in situ technology was successful employed in the Wittig olefination chemistry (Scheme 20).[52] The iron porphyrin complex, ClFeTPP, was found to be the most efficient catalyst we tested. This is presumably due to the ability of phosphane to bind and inhibit other carbene-transfer catalysts such as $Rh_2(OAc)_4$ and $Cu(acac)_2$. The base-free conditions used for generating phosphorus ylides by simple carbene transfer chemistry encourage us to test phosphites for the first time in the Wittig reaction. Phosphoranes derived from phosphites had never been used in such chemistry due to their propensity to undergo the Arbuzov rearrangement under standard Wittig reaction conditions.[68] Our approach was successful and we were able to obtain alkenes in good yields. Interestingly, when trimethylphosphite was used we were able to obtain significantly better *E*/*Z* selectivity than when triphenylphosphane was used. Optimization of the reaction conditions resulted in alkene yields of around 90% for most substrates examined. For instance, when benzaldehyde-derived tosylhydrazone was coupled with *p*-chlorobenzaldehyde, the resulting stilbene was formed in 92% yield and an *E*/*Z* selectivity of 97:3.



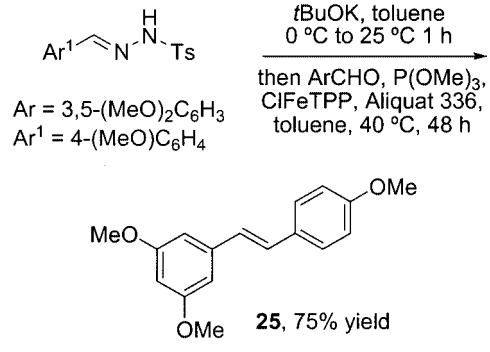
Scheme 19. Doyle's cyclopropanation results using unsaturated tosylhydrazones.



Scheme 20. Wittig olefination reaction using phosphoranes generated from tosylhydrazone salts and trimethylphosphite.

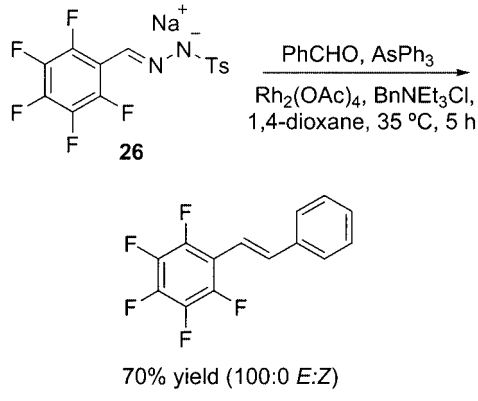
The advantage of the tosylhydrazone salt methodology was further illustrated when we tried this reaction using a solution of purified phenyldiazomethane. The resulting alkene was obtained in yield of 30%, with the corresponding stilbenes (diazo dimer) and phosphazine (Staudinger reaction product) as the major by-products.

In contrast to our epoxidation chemistry, tosylhydrazone potassium salts gave the best results in terms of both yields and selectivity. In addition, as toluene was our optimal solvent, we conveniently changed the PTC from benzyltriethylammonium chloride to the greasier Aliquat® 336. We applied our optimal reaction conditions towards the synthesis of anticancer compound **25** (Scheme 21). Substituted stilbene **25** was generated in 75% yield with an *E*/*Z* selectivity of 97:3 leading to the most direct route to this biologically active molecule.



Scheme 21. Synthesis of anticancer agent **25** by using diazo compounds generated in situ.

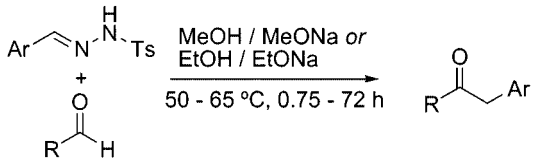
Zhu and co-workers have also utilized a tosylhydrazone salt for use in the synthesis of fluorinated *E*-stilbenes via a Wittig-type transformation as exemplified in Scheme 22.[69] In their studies, arsines were found to give excellent selectivity (*E*/*Z* = 100:0) and yields (up to 70%) than analogous phosphanes (trimethylphosphite was not examined). In addition, rhodium acetate was found to be the most efficient catalyst whereas ClFeTPP gave only moderate to low yields of the desired stilbenes.



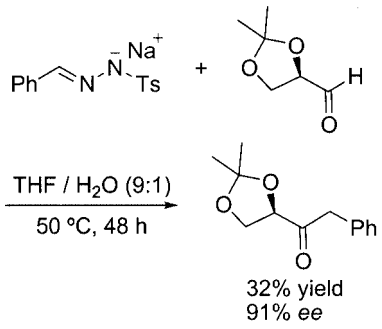
Scheme 22. Representative olefination of benzaldehyde using arsenium ylides derived from polyfluorinated tosylhyrazone salts.

Applications in the Homologation of Aldehydes to Ketones: The majority of studies on the in situ use of tosylhydrazone salts have been focused on the generation of diazo compounds in the presence of a metal catalyst capable of transferring carbenes. In the absence of such a catalyst, other diazo reactivity can be exploited. For instance, diazo compounds can react directly with aldehydes to form ketones. Both the Angle group (Scheme 23)[69] and our group (Scheme 24)[50] have applied the in situ technology

towards this reaction. It should be noted that PTC is not necessary in this transformation due to the solubility of the salt under the polar reaction media. Additionally, additives commonly required for a successful transformation, such as LiBr, were not necessary.[70]



Scheme 23. Angle's conditions for the homologation of aldehydes by using tosylhydrazones.



Scheme 24. Homologation of a chiral aldehyde using benzaldehyde-derived tosylhydrazone salt.

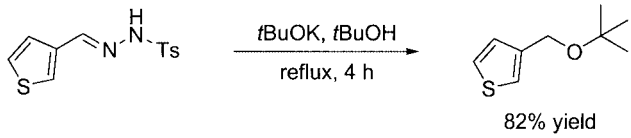
The Angle group methodology varied from ours in that they did not isolate the tosylhydrazone salt prior to use whereas we examined both the in situ generated tosylhydrazone and the isolated tosylhydrazone salt. In addition, the Angle group favoured methanol or ethanol solvents. In contrast, we found that 9:1 mixture of THF and water gave the best results.

Two different studies carried out by both groups did reveal the importance of isolating tosylhydrazone salts when sensitive substrates were used. Both the Angle group and ours investigated the homologation of enantiomerically pure glyceraldehyde acetonide with the benzaldehyde-derived tosylhydrazone. With our isolated tosylhydrazone salt, we were able to obtain a 91% *ee* for the homologated product; however, the Angle group noted complete racemization in albeit higher yield (66%). These results can probably be attributed to a small amount of excess base present in Angle's system, which would readily catalyze the racemization process.

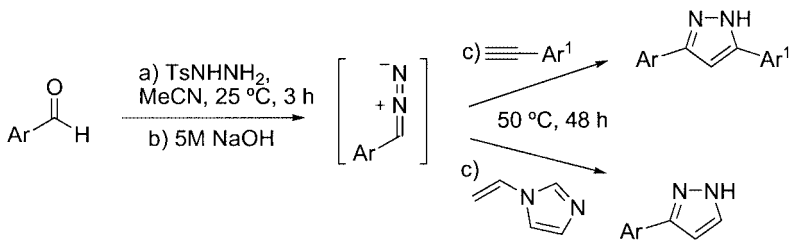
Applications in the Synthesis of Pyrazoles by 1,3-Dipolar Cycloadditions: The 1,3-dipolar cycloaddition of diazo compounds onto multiple bonds is one of the most straightforward methods for the preparation of pyrazoles.[71] We decided to expand the utility of the in situ process towards a new user-friendly method for the synthesis of pyrazoles from tosylhydrazone derivatives (Scheme 25). The 1,3-dipole reactivity of diazo compounds generated in situ was tested with the intermolecular reaction of alkynes and alkenes bearing a leaving group.[51] For both reactions, we generated the tosylhydrazone directly from the aldehyde precursor, treated the resulting solution with a 5 M NaOH solution, then added the alkyne or alkene to the tosylhydrazone salt solution and heated the reaction mixture to 50 °C. In the former reaction, we utilized either phenylacetylene or 3-ethynylpyridine as the alkyne in addition to a variety of different aryl tosylhydrazone salts providing the desired pyrazoles with excellent regioselectivity (*re* = 90–99.6%) in favour of the 3,5-regioisomer. The yields of the reaction varied from 19 to 67%, depending upon the coupling partners (aldehyde and alkyne). However, these yields could be increased if the tosylhydrazone salt was isolated prior to treatment with the alkyne.

N-Vinylimidazole was utilized in the coupling of the tosylhydrazone salts with alkenes. This reaction initially forms a non-isolable cycloadduct intermediate that loses imidazole to form the desired 3-substituted pyrazole product. Again, moderated to good yields (32–79%) were obtained for all tosylhydrazone salts investigated. Additionally, if isolated tosylhydrazone salt was used, then greater pyrazole yields can be obtained.

Synthesis of *tert*-Butyl Ethers: The in situ technology has also been applied to the synthesis of *tert*-butyl ethers.[72] In protic solvents, diazo compounds can be protonated by a protic media forming diazonium intermediates, which losses nitrogen providing a carbocation that can be trapped with alcohols, such as *t*BuOH. Chandrasekhar and co-workers expanded this reaction and generated a wide range of *tert*-



Scheme 26. Chandrasekhar's synthesis of *tert*-butyl ethers using tosylhydrazone salts.



Scheme 25. Synthesis of pyrazoles using diazo compounds generated in situ.

butyl ethers in good yields by treating tosylhydrazones with *t*BuOK in refluxing *t*BuOH (Scheme 26).

Summary and Outlook

The in situ generation of diazo compounds from tosylhydrazone salts is a safe alternative for the use of diazo compounds in synthesis. This safer way of handling diazo compounds has several advantages in addition to the obvious safety benefit. Firstly, the tosylhydrazone salts can be prepared well in advance and on fairly large scales, negating the need to prepare the diazo compound just prior to use. Secondly, the number of tosylhydrazone salts, and the resulting diazo compounds, is immense and diazo chemistry is no longer limited to electron-poor substituted diazo compounds. Finally, this process is user friendly as it forgoes the use of syringe pumps which are necessary for the slow addition of diazo solutions. Factors influencing the decomposition pathway of the tosylhydrazone salt have been determined, as well as factors controlling their stability. Our group and others have demonstrated that this methodology can be utilized in the synthesis of a wide variety of substrates, including several natural products and medicinally relevant compounds. We are currently working on determining the scalability of this process and have obtained several good results towards that end.

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Received: October 5, 2004
Published Online: February 16, 2005

