Organic Syntheses

Discussion Addendum for:

Detrifluoroacetylative Diazo Group Transfer: (*E*)-1-Diazo-4-phenyl-3-buten-2-one

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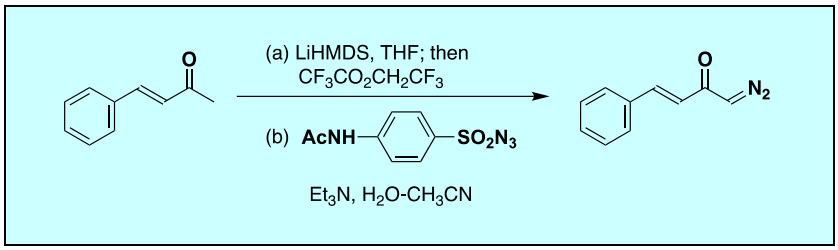
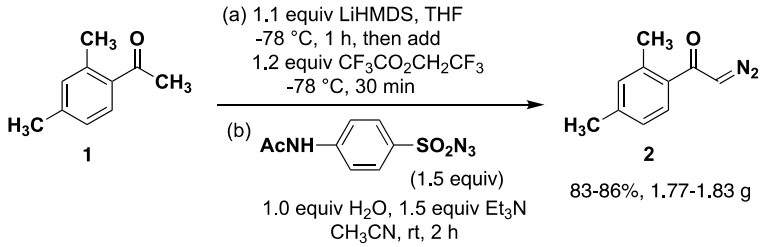


α-Diazo ketones have numerous applications in organic synthesis, serving as key synthetic intermediates in a number of important processes such as cyclopropanation, the Wolff rearrangement, and various C–H and heteroatom–H insertion reactions.[2]

The most widely used methods for the synthesis of α-diazo ketones[3] employ the acylation of diazo alkanes and "diazo group transfer"[4] involving the base-promoted reaction of sulfonyl azides with β-dicarbonyl and other active methylene compounds. Direct diazo transfer to ketone enolates usually is not feasible,[5] but diazo transfer to simple ketones can be achieved in two steps by an indirect "deformylative diazo transfer" strategy pioneered by Regitz[4] in which the ketone is first formylated and then treated with a sulfonyl azide reagent.

Unfortunately, several important classes of α-diazo ketones cannot be prepared in good yield by these standard methods. α'-Diazo derivatives of α,β-unsaturated ketones generally cannot be prepared by deformylative diazo transfer in good yield, and acylation of diazomethane with α,β-unsaturated acid chlorides and anhydrides generally is not successful because of the facility of dipolar cycloaddition to conjugated double bonds which leads to the formation of mixtures of isomeric pyrazolines. Also problematic are diazo transfer reactions involving base-sensitive substrates such as certain α,β-enones and heteroaryl ketones. Finally, the relatively harsh conditions and lack of regioselectivity associated with the thermodynamically controlled Claisen formylation step in the "deformylative" diazo transfer procedure limit the utility of this method when applied to the synthesis of diazo derivatives of many enones and unsymmetrical saturated ketones.

In 1990 we described the utility of a *detrifluoroacetylative* diazo transfer strategy involving the trifluoroacetylation of kinetically generated lithium ketone enolates.[6] This procedure has been illustrated in two *Organic Syntheses* procedures from our lab[7] (e.g., Scheme 1). In the general procedure, reaction of the ketone substrate with 1.1 equiv of lithium hexamethyldisilazide in THF produces the corresponding lithium enolate, which is acylated by exposure to 1.2 equiv of trifluoroethyl trifluoroacetate (TFETFA) at –78 °C. The resulting α-trifluoroacetyl ketone is then treated at room temperature with a sulfonyl azide in acetonitrile containing 1.0 equiv of water and 1.5 equiv of triethylamine. Column chromatography on silica gel furnishes the desired α-diazo ketone in good to excellent yield.



Scheme 1. Detrifluoroacetylative diazo transfer (*Org. Synth.* 2016 procedure)[7b]

The key feature of the new procedure is the activation of the ketone starting material as the corresponding α-trifluoroacetyl derivative. The use of TFETFA to activate ketones in this fashion had not previously been reported, although Doyle employed a similar strategy to achieve diazo transfer to a base sensitive *N*-acyloxazolidone derivative.[8] We found TFETFA to be superior to other trifluoroacetylating agents [e.g., CF_3CO_2Et, $(CF_3CO)_2O$] and the reaction of ketone enolates with this ester takes place essentially instantaneously at −78 °C. By contrast, the formylation of ketone enolates with ethyl formate is usually carried out using sodium hydride or sodium ethoxide as base and generally requires 12 to 48 h at room temperature for complete reaction.

Only one equivalent of base is required for the trifluoroacetylation step; apparently the chelated tetrahedral intermediate is stable at −78 °C and the β-dicarbonyl product is not generated until workup. Interestingly, in some cases the choice of LiHMDS for the generation of the ketone enolate proved superior to the use of LDA; however, in other cases no significant difference in the yield of diazo ketone was observed.

In this Discussion Addendum we describe recent experimental developments and review selected examples of the application of the protocol in the synthesis of natural products and other compounds.

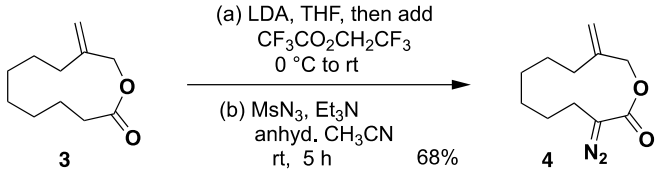
Experimental Developments

Close to 100 papers have appeared reporting on the application of the detrifluoroacetylative diazo transfer reaction since our original communication (1990) and *Organic Syntheses* article (1996). For the most part, these applications have employed the standard procedure described in our original papers, but there have been some developments with regard to the experimental procedure and these are reviewed in this section.

Choice of Trifluoroacetylating Agent

As mentioned above, a central feature of our method is the activation of the carbonyl compound substrate by acylation with trifluoroethyl trifluoroacetate at low temperature. The advantage of this approach over the classic diazo transfer procedure has been confirmed in a number of subsequent reports. For example, Sampson found that attempted application of the classic Regitz deformylative diazo transfer procedure to lactone **3** led to oligomeric products and none of the desired α-diazo lactone.[9] Presumably,

opening of the lactone by ethoxide ion generated in the initial formylation initiates oligomerization under these Claisen condensation type conditions. Detrifluoroacetylative diazo transfer, on the other hand, provided the desired α–diazo lactone in good yield since the less nucleophilic trifluoroethoxide ion is not reactive enough to attack the lactone under the conditions of the reaction (Scheme 2).



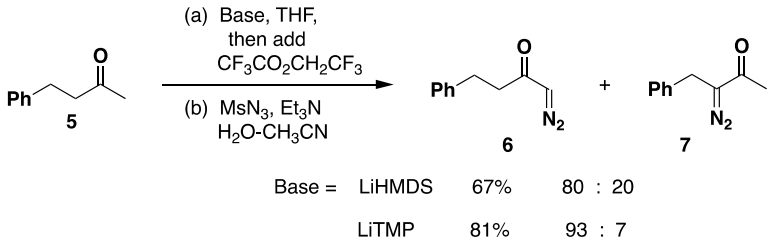
Scheme 2. Diazo transfer with lactone 3

Method of Enolate Generation

Several amide bases have been employed for generation of the enolate in the initial trifluoroacetylation step. In our original study we found that LDA and LiHMDS gave similar results in the case of many ketones including acetophenone and acetylcyclohexene. NaHMDS and KHMDS also appear to function similarly to LiHMDS in these diazo transfer reactions. On the other hand, as we reported previously, we observed dramatic improvements in the yield of diazo transfer product when LiHMDS rather than LDA was used in the case of several aryl and heteroaryl ketones including 2-acetylfuran and 3-acetylthiophene.[6]

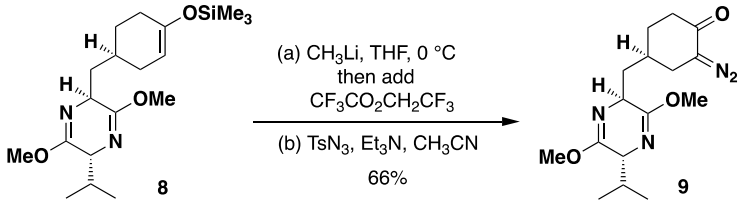
Sampson has reported that LDA is a superior base for detrifluoroacetylative diazo transfer in the case of esters and lactones.[9] For example, less than 10% of **4** was obtained using LiHMDS, possibly due to slow or incomplete deprotonation of **3** with this base which is significantly weaker than LDA.

Finally, it is worth noting that the application of LiTMP as base can prove advantageous in reactions involving unsymmetrical ketones. For example, as illustrated in Scheme 3, improvements in both yield and regioselectivity were observed using LiTMP in the case of methyl ketone **5**.[10]



Scheme 3. Effect of base on diazo transfer with unsymmetrical ketone 5

As reported in our original study, TMS enol ethers can also be deployed as enolate precursors for detrifluoroacetylative diazo transfer reactions. As shown in Scheme 4, Wild exploited this version of the diazo transfer strategy in his synthesis of the antimycotic natural product chlorotetaine.[11] Silyl enol ether **8** was first generated by diastereoselective deprotonation of the corresponding ketone using the chiral base lithium (*R,R*)-bis(phenethyl)amide followed by silylation. Exposure of the silyl enol ether to CH_3Li then liberated the lithium enolate which was subjected to trifluoroacetylation and diazo transfer with tosyl azide to furnish the desired diazo ketone **9**.

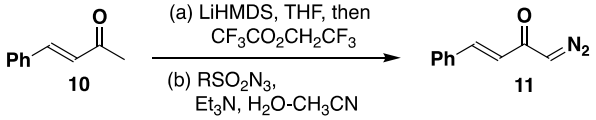


Scheme 4. Detrifluoroacetylative diazo transfer via a silyl enol ether

Choice and Stoichiometry of Sulfonyl Azide Reagent

Although tosyl azide has traditionally been the reagent of choice for effecting diazo transfer reactions, we found methanesulfonyl azide to be a more convenient and in some cases superior reagent. As pointed out by Taber,[12] the use of this reagent has the advantage that excess mesyl azide as well as methanesulfonamide byproducts are easily separated from the desired diazo ketone product by extraction into dilute aqueous base during workup.

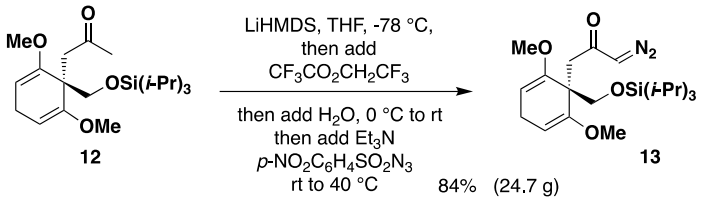
Unfortunately, both tosyl and mesyl azide pose safety hazards that restrict their use in many laboratories and for industrial applications. The thermal stability and explosion hazard associated with various diazo transfer reagents have been evaluated and compared in an excellent recent study.[13] In our published *Organic Syntheses* procedures[7] we employed 4-dodecylbenzenesulfonyl azide[14] and 4-acetamidobenzenesulfonyl azide ("*p*-ABSA")[15] as safer alternatives to mesyl azide. In our experience, all three sulfonyl azides are equally effective for detrifluoroacetylative diazo transfer, as shown in Scheme 5 for the case of enone **10**, the substrate in our original *Organic Syntheses* procedure.[7a] Although mesyl azide has advantages with respect to atom economy and facility of product separation, on the basis of safety considerations, we generally recommend the use of *p*-ABSA, especially for larger scale preparative work.



$CH_3SO_2N_3$	86%[7a]
p-$C_{12}H_{25}(C_6H_4)SO_2N_3$	81-83%[7a]
p-$AcNH(C_6H_4)SO_2N_3$	83%[16]

Scheme 5. Comparison of diazo transfer reagents

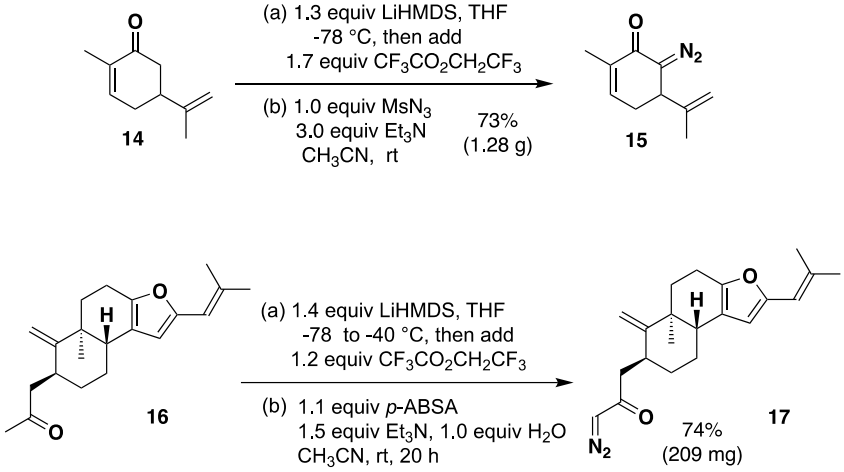
In 1990 Evans and coworkers investigated how the ratio of azide formation vs. diazo transfer is affected by the choice of sulfonyl azide reagent and enolate counterion and found that diazo transfer is favored by the use of *p*-nitrobenzenesulfonyl azide.[17] Although we obtained α-diazoacetophenone in only 21% yield using this reagent,[6] other groups have reported successful diazo transfer using *o*-[18] and *p*-nitrobenzenesulfonyl azide[19,20,21] as the sulfonyl azide reagent with our protocol. Nakada, for example, reported the preparation of diazo ketone **13** using this modification of our method in a key step in their total synthesis of the polyprenylated acylphloroglucinol nemorosone (Scheme 6).[20c]



Scheme 6. Application of *p*-nitrobenzenesulfonyl azide in the diazo transfer reaction

Finally, Brown has reported on the use of a polymer-bound sulfonyl azide reagent in our procedure,[21a] and Kumar has described the application of an "ionic liquid-supported" sulfonyl azide for the diazo transfer step.[22]

With regard to stoichiometry, our original protocol called for the use of 1.5 equiv of sulfonyl azide for the diazo transfer step. Besides being wasteful, the use of excess reagent can lead to complications in the isolation and purification of the desired diazo transfer product. It is therefore noteworthy that several groups have reported successful diazo transfer employing our protocol but with only 1.0–1.1 equiv of reagent (Scheme 7).[23,24]



Scheme 7. Application of 1.0-1.1 equiv of sulfonyl azide reagent in the diazo transfer reaction

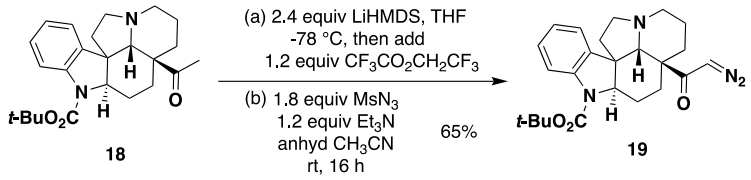
In the case of our *Organic Syntheses* substrate **1** (Scheme 1), we found that when only 1.0 rather than 1.5 equiv of *p*-ABSA is used (under otherwise identical conditions) the desired product is obtained in ca. 10% lower yield and is difficult to separate from the ketone starting material.

It must be noted that while the great majority of laboratories have employed 1.0 to 1.5 equiv of sulfonyl azide for the diazo transfer, in some cases the use of a large excess of reagent (3 to 6 equiv) has been reported. We can imagine that the use of a large excess of reagent may be advisable in the case of diazo transfer reactions carried out in the late stages of a total synthesis where the reaction is performed on a relatively small scale and the yield of product is of paramount importance.

In summary, in our experience the optimal amount of sulfonyl azide must be evaluated on a case-by-case basis. For some applications 1.0 to 1.1 equiv of reagent can be used, while for valuable substrates we recommend using 1.5 equiv of the sulfonyl azide to maximize yield and to facilitate the separation of product from any possible unreacted starting carbonyl substrate.

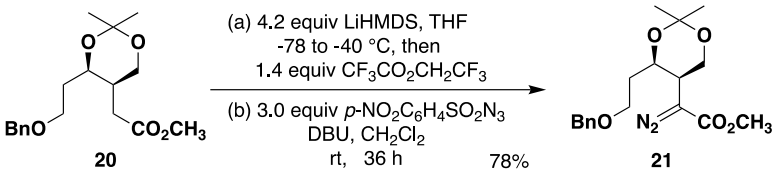
Choice of Solvent, Base, and Inclusion of Water in the Diazo Transfer Step

The use of 1.0 equiv of water in the diazo transfer step does not appear to be essential since a number of reports describe the use anhydrous acetonitrile in reactions producing the desired diazo carbonyl compound in good yield (e.g., see Schemes 2, 7 (**14** to **15)**, and 8[25]). Unfortunately, none of these reports provide a comparison of the results of the reaction with and without the presence of water. We have found in the case of several aryl and heteroaryl ketones that the yield of diazo ketone generally differs by no more than 10% when the reaction is carried out under anhydrous conditions rather than in the presence of water. We conclude that the addition of water may not always be necessary and should be evaluated on a case-by-case basis.



Scheme 8. Diazo transfer under anhydrous conditions

The great majority of researchers have followed our original protocol and used triethylamine as the base in the diazo transfer step. Taber, however, obtained better results by using DBU in place of Et_3N in a diazo transfer reaction involving an ester and using *p*-nitrobenzenesulfonyl azide as the sulfonyl azide reagent (Scheme 9).[19]



Scheme 9. Diazo transfer with DBU as base

Other Experimental Aspects

Another variation on our original protocol involves "telescoping" the two steps of the original procedure and carrying out the detrifluoroacetylative diazo transfer as a one-pot operation. In this case, the intermediate trifluoroacetyl derivative is not isolated and the reaction mixture from the trifluoroacetylation step is treated directly with base and the sulfonyl azide reagent (e.g., Scheme 6). We have found that this "one pot" procedure frequently gives comparable results to reactions carried out with isolation of the intermediate β-dicarbonyl compound.

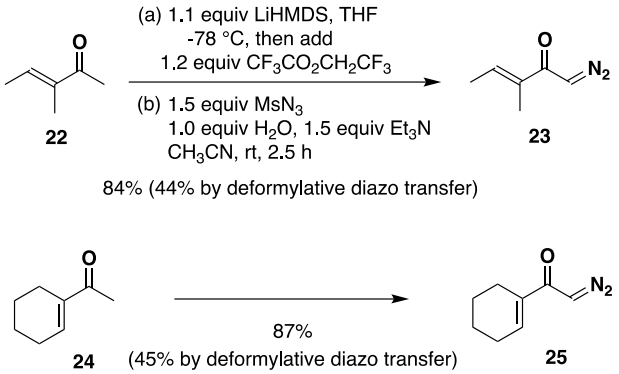
Scope and Applications of the Detrifluoroacetylative Diazo Transfer

The application of the detrifluoroacetylative diazo transfer method to several important classes of compounds is highlighted in this section.

Diazo Transfer with α,β-Enones

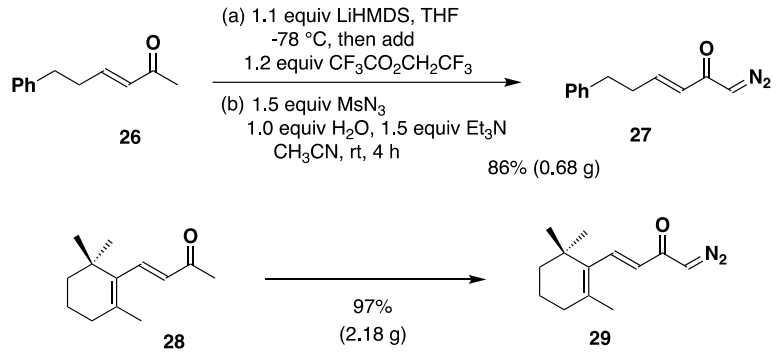
As noted earlier, α,β-unsaturated carbonyl compounds generally do not undergo diazo transfer in good yield under the conditions of the classical deformylative diazo transfer procedure. Our need for an efficient method for accessing α'-diazo derivatives of α,β-unsaturated ketones motivated the development of the detrifluoroacetylative diazo transfer procedure and its

application to α,β-enones was highlighted in our original report (e.g., Scheme 10).[6]



Scheme 10. Diazo transfer with α,β-unsaturated ketones

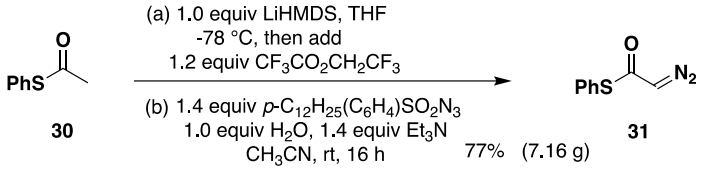
Detrifluoroacetylative diazo transfer has proven to be a general and efficient method for synthesizing a variety of α'-diazo-α,β-unsaturated ketones beginning with both methyl and cyclic unsaturated ketones. In particular, we have employed this chemistry extensively for the preparation of precursors to (trialkylsilyl)vinylketenes (e.g., Scheme 11).[26] Along with the Horner-Wadsworth-Emmons reaction of diethyl 3-diazo-2-oxopropylphosponate pioneered by Burtoloso,[27] this constitutes the most useful method for the synthesis of this valuable class of synthetic building blocks.



Scheme 11. Diazo transfer with α,β-unsaturated ketones

Diazo Transfer with Carboxylic Acid Derivatives

In 2000 we reported the extension of detrifluoroacetylative diazo transfer to the preparation of α′-diazo derivatives of thiol esters and an example was subsequently published as an *Organic Syntheses* procedure (Scheme 12).[28] As illustrated earlier, the detrifluoroacetylative diazo transfer method has also proven to be applicable to a wide range of lactones (e.g., Scheme 2)[9] and carboxylic esters (e.g., Scheme 9).[19,29]

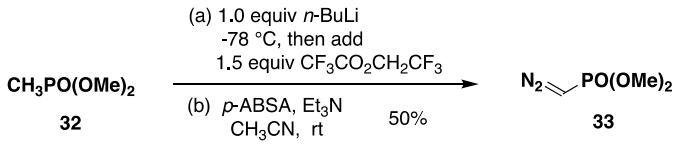


Scheme 12. Diazo transfer for the synthesis of α-diazo thiol esters

Diazo Transfer with Miscellaneous Substrates

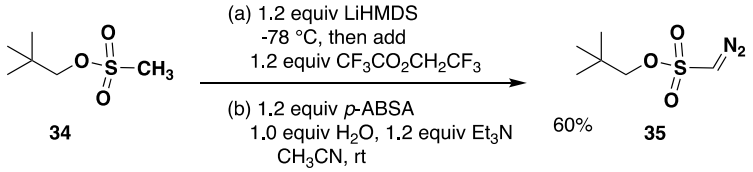
Since our original publication detrifluoroacetylative diazo transfer has been applied for the synthesis of α-diazo derivatives of phosphonate and sulfonate esters.

As shown in Scheme 13, Brisbois applied the detrifluoroacetylative diazo transfer protocol to dimethyl methylphosphonate and obtained the Seyferth-Gilbert reagent ("DAMP") in 50% yield.[30]



Scheme 13. Synthesis of DAMP via detrifluoroacetylative diazo transfer

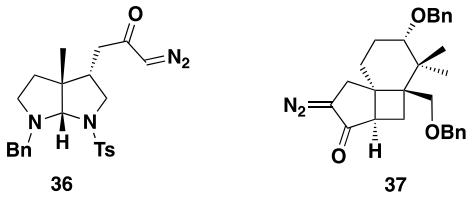
In 2005, Ye and Zhou reported the synthesis of a series of α-diazo sulfonate esters as cyclopropanating agents using the detrifluoroacetylative diazo transfer protocol (Scheme 14).[31]



Scheme 14. Synthesis of α-diazo sulfonate esters via detrifluoroacetylative diazo transfer

Examples of Inefficient Detrifluoroacetylative Diazo Transfer

Although the detrifluoroacetylative diazo transfer procedure has proven to have broad scope, several cases of unsuccessful reactions have been reported (Scheme 15). Attempts by Porter and coworkers to prepare diazo ketone **36** were not successful due to a failure to obtain the intermediate trifluoroacetyl ketone in good yield.[32] Trauner recently reported that diazo ketone **37** could only be obtained in low yield under the conditions of the detrifluoroacetylative diazo transfer protocol.[33]



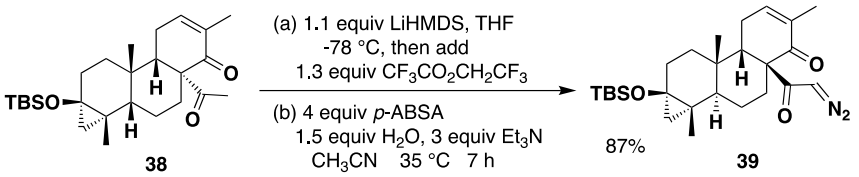
Scheme 15. Diazo ketones not available via detrifluoroacetylative diazo transfer in good yield

Applications of Detrifluoroacetylative Diazo Transfer in Natural Product Synthesis

We close with several examples of the application of the detrifluoroacetylative diazo transfer reaction in the synthesis of key intermediates for the synthesis of natural products, illustrating the application of the method in the context of highly functionalized substrates.

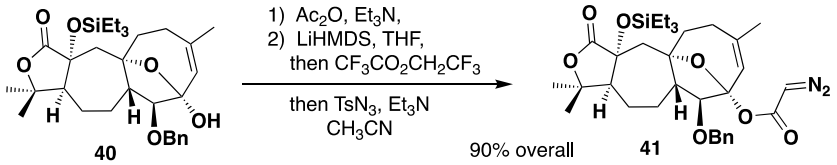
As shown in Scheme 16, Abad and coworkers were able to achieve diazo

transfer to the sterically congested diketone **38** as a key step in their total synthesis of antiquorin and several other atisane diterpenes.[34]



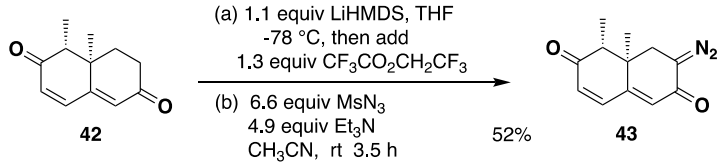
Scheme 16. Diazo transfer in the synthesis of diterpenes

Acetylation of the hydroxy group in **40** followed by detrifluoroacetylative diazo transfer on the resultant ester provided **41** in excellent yield; this diazo ester served as an intermediate in the synthesis of (+)-19-dehydoxyl arisandilactone A (Scheme 17).[35]



Scheme 17. Diazo transfer in the synthesis of nortriterpenoids

Detrifluoroacetylative diazo transfer of the diene dione **42** served as a key step in the total synthesis of the sesquiterpene periconianone A by Reddy and coworkers (Scheme 18).[36]



Scheme 18. Diazo transfer in the synthesis of periconianone A

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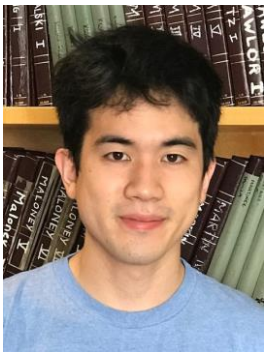

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