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A conjugate addition approach to diazo-containing scaffolds with β quaternary centers

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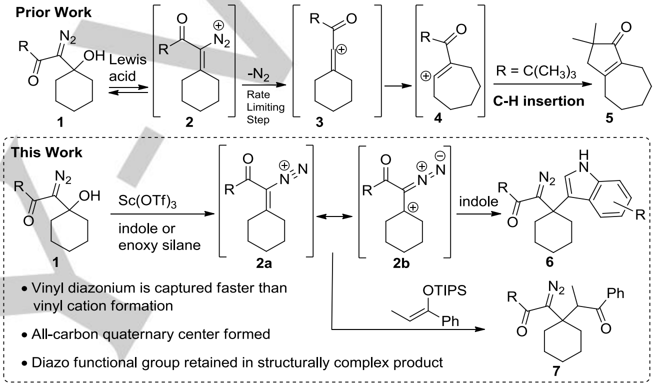
Abstract: Structurally complex diazo-containing scaffolds are formed by conjugate addition to vinyl diazonium salts. The electrophile, a little studied α-diazonium-α,β-unsaturated carbonyl compound, is formed at low temperature under mild conditions by treating β-hydroxy-α-diazo carbonyls with $Sc(OTf)_3$. Conjugate addition occurs selectively at the 3-position of indole to give α-diazo-β-indole carbonyls, and enoxy silanes react to give 2-diazo-1,4-dicarbonyl products. These reactions result in the formation of tertiary and quaternary centers, and give products that would be otherwise difficult to form. Importantly, the diazo functional group is retained within the molecule for future manipulation. Treating a α-diazo ester indole addition product with $Rh_2(OAc)_4$ caused a rearrangement to occur to give a 2-(1*H*-indol-3-yl)-2-enoate. In the case of diazo ketone compounds, this shift occurred spontaneously on prolonged exposure to the Lewis acidic reaction conditions.

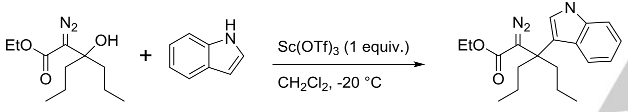


Scheme 1. Reactions of vinyl cations and vinyl diazonium salts

The diazo group is one of the most versatile functional groups in synthetic chemistry.[1–5] Apart from being reactive 1,3-dipoles in their own right,[6–8] the diazo group is a progenitor to several important reactive intermediates including cations, vinyl cations,[9] and both free and metal bound carbenes.[10–12] Chemists have taken advantage of diazo compounds to develop a variety of important synthetic transformations (for example, C-H and X-H insertions,[13–17] cyclopropanation,[18] the Buchner reaction,[19,20] the Wolff rearrangement,[21] and cycloadditions based on ylide formation[22–24]) that are frequently used in complex molecule synthesis.[25] However, the high reactivity of diazo compounds also makes them fairly labile and they are incompatible with many reaction conditions including protic and Lewis acids, strong nucleophiles, reductive conditions, and some metal catalysts. α-Diazo carbonyl compounds are more stable than alkyl diazos, but the diazo functional group is typically not carried through long synthetic sequences due to reactivity concerns. Incorporating a diazo group into a complex molecule is not always trivial, and is most often achieved by diazo transfer to a carbonyl enolate,[26,27] or the oxidation of hydrazine-based precursor.[28–37] In view of their synthetic utility, alternative strategies to prepare structurally complex diazo-containing compounds would be beneficial to the synthetic community.

The addition of a metalated α-diazo carbonyl compound to a ketone or aldehyde via an aldol-type addition is another way of incorporating a diazo group into a molecule.[38] We have taken advantage of this strategy to prepare a variety of β-hydroxy-α-diazo carbonyls (e.g. **1**, Scheme 1), which we have studied in ring fragmentation,[39] C-H insertion,[40] and other intramolecular cyclization reactions.[41,42] These intramolecular reactions proceed via a vinyl cation intermediate (e.g. **3**) which is formed from a vinyl diazonium precursor (e.g. **2**) as shown in Scheme 1. As part of our studies into the mechanism of the vinyl cation C-H insertion reaction,[43] we modeled the reaction pathway computationally, which showed that the Lewis acid mediated dehydroxylation step was reversible, and that the rate limiting step of this sequence is formation of the vinyl cation by loss of N_2 from the vinyl diazonium intermediate. This led us to consider that it might be possible to intercept vinyl diazonium intermediate **2** with a nucleophile other than OH prior to N_2 dissociation to give a more complex product that still retains the diazo fragment. Despite early recognition that vinyl diazonium ions might serve as useful synthetic intermediates,[44] very few studies have emerged to realize this potential.[45–50] Structurally simple β,β-dialkoxyethenediazonium salts that are stable and isolable because of strongly contributing dialkoxycarbenium resonance forms have received the most attention, and these are electrophilic at the alkoxycarbenium carbon.[45–48] Crich and coworkers[50] recently showed that vinyl diazonium ions react with phenols to give complex 2,3-dihydrobenzofurans through an addition cyclization process with loss of N_2. However, other than their use as vinyl cation precursors, no general and useful synthetic transformations have been developed that take advantage of vinyl diazonium ions. In this paper we show that vinyl diazonium ions such as **2** can react with carbon nucleophiles to give tertiary and all-carbon quaternary centers, while retaining the diazo functional group within the molecule for future manipulation. All-carbon quaternary centers are found in a number of biologically active molecules.[51–53] Many natural products containing these motifs have been shown to be excellent medicinal leads if not potent drugs themselves.[54–56] Although advances in methods to form all-carbon quaternary centers have been made in recent years[53,57–62] there is still need for new strategies to prepare these challenging motifs.

To begin our studies, we chose indole as the nucleophile because indole scaffolds are privileged structural subunits in drug discovery programs,[63,64] and are present in a large number of biologically active natural products.[65,66] In addition, indole is fairly non-basic and is known to react in Lewis acid catalyzed conjugate addition reactions.[67,68] In our earlier fragmentation and C-H insertion work, we showed that $SnCl_4$ and $(C_6F_5)_3B$ were effective Lewis acids and we began our current studies by treating diazo **8** (Scheme 2) with $SnCl_4$ in the presence of indole at -20 °C. These conditions led to a complex mixture of products that contained indole addition product **9,** albeit in only 5% yield. This addition is noteworthy because it results in the formation of a new all-carbon quaternary center under mild conditions. While indole is known to add to β,β-disubstituted ketones,[67] we are not aware of any example of indoles reacting with a β,β-disubstituted ester due to their weaker electrophilicity.[69] Changing the Lewis acid to $(C_6F_5)_3B$ gave no desired product. However, under identical reaction conditions, $Al(OTf)_3$ returned **9** in 83% yield, and $Sc(OTf)_3$ gave **9** in 90% yield. In prior work, we had noted that gas evolution typically occurs around -20 °C, and we thought that keeping the reaction cold might be critical to increase the lifetime of the vinyl diazonium intermediate. We were surprised to observe that running the reaction at 20 °C still gave the addition product in 79% yield, which shows that addition is faster than vinyl cation formation even at this higher temperature.



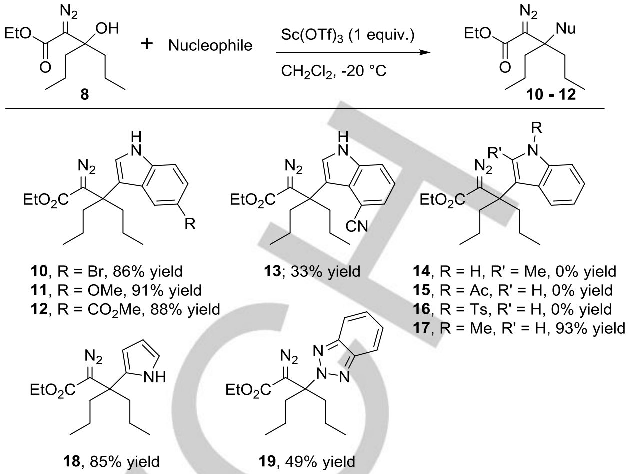
8 **9**; 90% yield

Scheme 2. Conjugate addition of indole to a vinyl diazonium ester

We examined a small series of substituted indoles to assess their ability to act as nucleophiles in this reaction (Table 1). Electron withdrawing or releasing substituents at the indole's 5 position were well tolerated and had little effect on the reaction outcome (**10-12**). A nitrile substituent at the 4 position, on the other hand, attenuated reactivity significantly and product **13** was formed in only 33% yield. This lower yield is likely due to unfavorable steric interactions. Similarly, 2-methyl indole failed to add, which again indicates that sterics play an important role in the reaction. Capping the indole nitrogen with the electron withdrawing acetyl and tosyl groups also prevented the reaction from occurring, presumably because these compounds are less nucleophilic. However, a free indole N-H is not necessary since N-methyl indole gave the expected addition product **17** in 93% yield.

Other aromatic nucleophiles were also assessed for their ability to add to the vinyl diazonium intermediate. Pyrrole proved to be a willing reaction partner and returned diazo **18** in 85% yield (Table 1). An nOe NMR spectroscopic study confirmed that the reaction took place at the 2-position of pyrrole. Substituted phenyl rings, including phenol, anisole, *N*-phenylacetamide and furan failed to add. According to Mayr's reactivity scales, these systems have lower nucleophilicity parameters than indole derivatives, which provides another indication that there is a lower limit to how weak the nucleophile can be.[70,71] 1H-Benzotriazole was a moderately effective nucleophile providing 2-substituted benzotriazole **19** in 49% yield. The 1-substituted benzotriazole regioisomer was not observed.

Table 1. Conjugate addition of substituted indoles, pyrrole and benzotriazole with a vinyl diazonium ester.



10, R = Br, 86% yield
11, R = OMe, 91% yield
12, R = CO_2Me, 88% yield

13; 33% yield

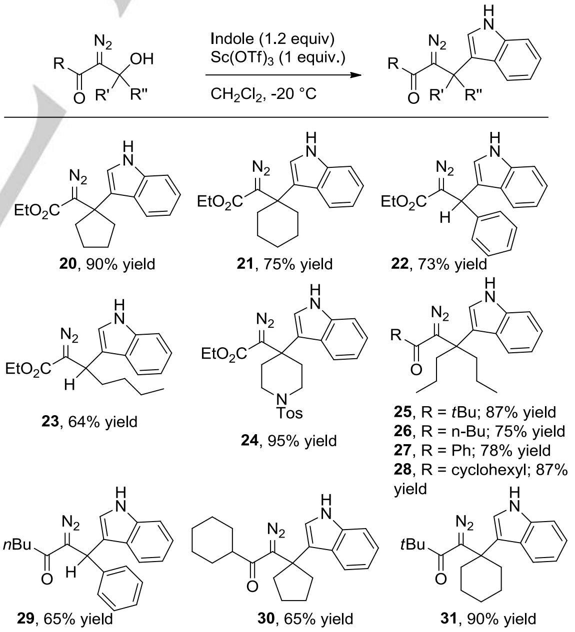
14, R = H, R' = Me, 0% yield
15, R = Ac, R' = H, 0% yield
16, R = Ts, R' = H, 0% yield
17, R = Me, R' = H, 93% yield

18, 85% yield

19, 49% yield

As shown in Table 2, a variety of structurally different β-hydroxy-α-diazo carbonyl compounds gave the expected 1,4-conjugate addition reaction with indole in good to excellent yields. It is noteworthy that starting materials that had a 2° alcohol at the β position react productively to give addition products with new tertiary centers (e.g. **22** and **23**). It is also noteworthy that a distal N-tosyl protected amine was compatible with the conditions, and addition product **24** was formed in 95% yield. Importantly, changing the diazo fragment from a diazo ester to a diazo ketone did not affect the outcome of the reaction and β-hydroxy-α-diazo ketones provided the expected conjugate addition products in generally high yield (**25**-**31**). Again, both tertiary and quaternary centers were formed in comparable yields.

Table 2. Conjugate addition of indole to various vinyl diazonium intermediates.



20, 90% yield

21, 75% yield

22, 73% yield

23, 64% yield

24, 95% yield

25, R = *t*Bu; 87% yield
26, R = n-Bu; 75% yield
27, R = Ph; 78% yield
28, R = cyclohexyl; 87% yield

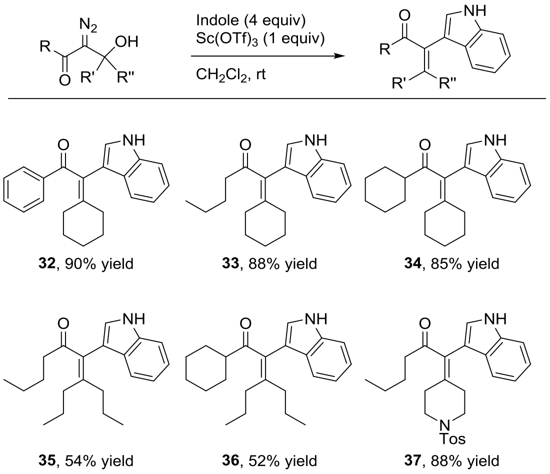
29, 65% yield

30, 65% yield

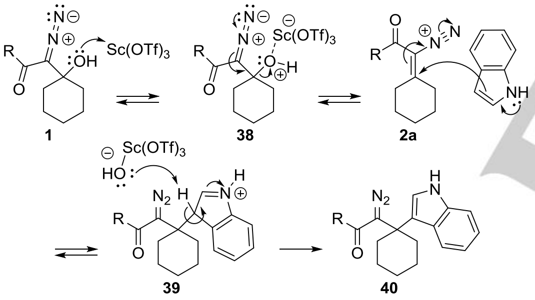
31, 90% yield

For the diazo ketone series we noted a strong temperature dependence on the outcome of the reaction. Whereas β-hydroxy-α-diazo esters gave the expected conjugate addition products at room temperature, β-hydroxy-α-diazo ketones gave enone products instead (Table 3). These products were also formed when low temperature reactions that had formed conjugate addition products (as determined by TLC) were warmed to room temperature. Treating isolated diazo **28** with $Sc(OTf)_3$ also gave enone **36**, confirming that the enone products are the result of a Lewis acid mediated rearrangement of the 1,4-addition products. This same transformation could be effected on ester derivatives by treatment with $Rh_2(OAc)_4$. [72]

Table 3. Diazo ketone rearrangement products.

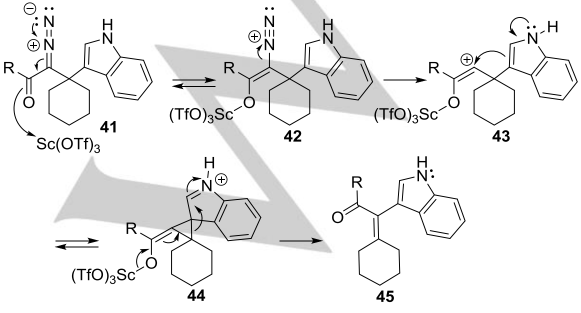


Plausible mechanisms for the formation of **40** and **45** are shown in Schemes 3 and 4. Scandium mediated dehydroxylation of β-hydroxy-α-diazo carbonyl **1** would provide vinyl diazonium intermediate **2a**, which has a carbocation resonance form (**2b**, Scheme 1) that is indicative of the electrophilicity of the β position. Addition of indole followed by rearomatization of the indole ring by proton abstraction would give the addition product (**40**). The irreversible addition of indole occurs faster than loss of N_2, which explains why including the nucleophile in the reaction mixture changes the course of the reaction.



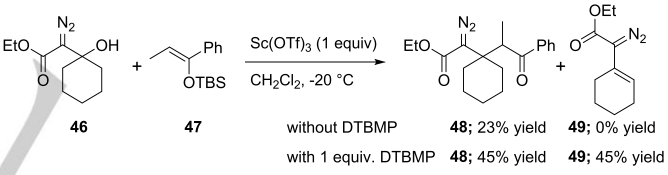
Scheme 3. Mechanism for the formation of addition products

Diazo ketones participate in Lewis acid catalyzed intramolecular cyclizations with pendent nucleophiles.[73] It is not clear whether these reactions proceed via complexation of the Lewis acid with the oxygen or carbon atom of the diazo ketone functionality, and either could be used to explain the formation of **45** from **41**. Scheme 4 shows the oxygen coordination pathway. Warming diazo ketone **41** to room temperature with the Lewis acid would give vinyl cation **43**, and addition of the adjacent indole would give spirocyclopropane intermediate **44**. Ring opening would provide the observed enone product **45**.



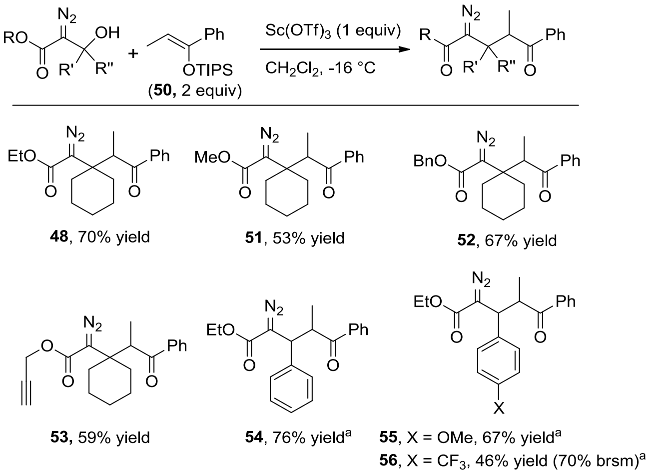
Scheme 4. Mechanism for the formation of enone products

To further expand the utility of this conjugate addition reactivity, we were interested to see if non-aromatic nucleophiles could add to the diazonium intermediate. Substituting allyl trimethyl silane in place of indole did not give any desired addition product. However, we have found that enoxy silanes are effective nucleophiles. In our initial attempt, we reacted diazo ester **46** with the TBS enoxy silane of propiophenone (**47**) in the presence of $Sc(OTf)_3$, which gave the desired Michael addition product in 23% yield (Scheme 5). A substantial amount of propiophenone was formed in this reaction, indicating decomposition of the enoxy silane under the reaction conditions. In an attempt to suppress decomposition of the nucleophile, we added 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) to the reaction as a buffer. While this increased the product yield to 45%, it also resulted in the formation of an equal quantity of an elimination product (**49**), which presumably forms via deprotonation of the vinyl diazonium intermediate. Future work will tell if deprotonation is a general problem that limits what nucleophilic partners can be used in this reaction, but it is noteworthy that pyridine and aniline also promoted this elimination. To prevent decomposition of the nucleophile, we looked toward using a more robust enoxy silane. To date, our best results came from treating diazo ester **46** with two equivalents of the TIPS enoxy silane of propiophenone (**50**, Table 4) and one equivalent of $Sc(OTf)_3$ at -16 °C, which gave the Michael addition product (**48**) in 70% yield. A fuller study of the scope of this Mukaiyama-Michael-like reaction is currently underway, but our preliminary results (Table 4) show that this conjugate addition forms a tertiary center adjacent to either a quaternary (**48**, **51-53**) or tertiary (**54-57**) center in good yield. This reaction is noteworthy because the Michael addition of enolates resembling **50** to unsaturated esters is known to be difficult.[74] Importantly, while systems that form adjacent tertiary centers could react to give two diastereomers, keto esters **54** to **57** were formed as single diastereomers. Efforts to rigorously establish the relative configuration of these products are on-going.



Scheme 5. Michael addition of a TBS enoxy silane nucleophile.

Table 4. Michael addition of a TIPS enoxy silane nucleophile to various vinyl diazonium esters.



a) isolated as a single diastereomer

This work demonstrates that α-diazonium-α,β-unsaturated carbonyl compounds, which are little studied reactive species, are potent electrophiles. Indole and enoxy silanes are effective nucleophiles in these reactions, leading to the formation of tertiary and quaternary centers in good to excellent yields. Importantly, the products of these reactions, which are non-trivial and would be difficult to form by other means, retain the diazo functional group, which could be taken advantage of in a variety of subsequent synthetic transformations. As the indole motif is present in numerous biologically active natural products, the reaction described here may enable new strategies for the synthesis of indole alkaloids. We envision that more structurally complex enoxy silanes could be employed to form products which would enable the rapid assembly of chemically rich polycyclic scaffolds. Further studies are ongoing to establish the full scope of these conjugate addition reactions, and efforts to render the conjugate addition enantioselective are being assessed.

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Keywords: Conjugate addition • Michael addition • Diazo • quaternary center • Indole

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Entry for the Table of Contents

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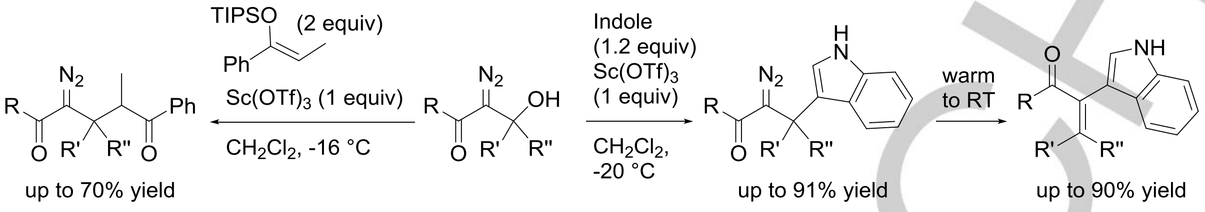

Indole and enoxy silanes readily act as nucleophiles in conjugate addition reactions with vinyl diazonium ions that are formed in situ by the Lewis acid mediated dehydroxylation of β-hydroxy-α-diazo carbonyls. These reactions, which occur under very mild conditions, can generate a new quaternary center while the products of these reactions retain the diazo functional group for further synthetic manipulation.