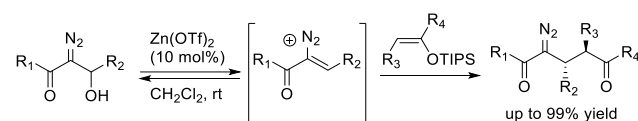


# A Lewis acid catalyzed diastereoselective synthesis of functionalized 2-diazo-1,5-dicarbonyl compounds

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**KEYWORDS:** Conjugate addition, vinyl diazonium, diastereoselective, vinyl cation, 1,4-addition, Mukaiyama Michael, furan, cation

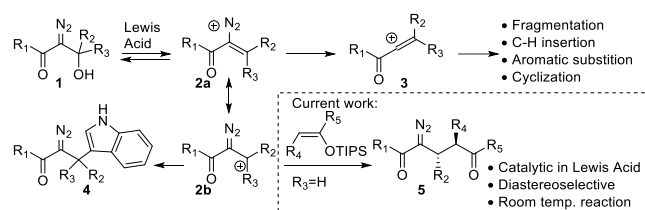


**ABSTRACT:** A diverse array of 2-diazo-1,5-dicarbonyl compounds were formed by the Lewis acid catalyzed reaction of enoxy silanes with  $\beta$ -hydroxy- $\alpha$ -diazo carbonyls. This reaction proceeds via the  $\text{Zn}(\text{OTf})_2$  catalyzed dehydroxylation of the  $\beta$ -hydroxy- $\alpha$ -diazo carbonyl to form a vinyl diazonium ion intermediate that is intercepted by the enoxy silane nucleophile to give diazo-containing scaffolds with increased molecular complexity. The reaction appears to be general and a variety of functional groups, including common protecting groups, are well tolerated. The 2-diazo-1,5-dicarbonyl products are formed in yields of up to 99% with diastereoselectivity up to >20:1.

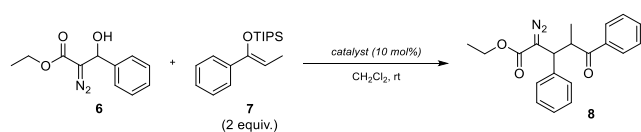
The conjugate addition of carbon nucleophiles to  $\alpha,\beta$ -unsaturated carbonyl compounds is one of the most important ways to form C-C bonds. Michael additions, wherein enolates serve as the nucleophile, are particularly useful and noteworthy examples of this reactivity.<sup>1-4</sup> Mukaiyama and co-workers discovered an important variant of this reaction wherein a Lewis acid activates the  $\alpha,\beta$ -unsaturated carbonyl compound and facilitates the conjugate addition of an enoxy silane nucleophile.<sup>5-7</sup> The Mukaiyama-Michael addition is more mild and selective and can circumvent undesired side reactions observed in traditional Michael additions giving 1,5-dicarbonyl compounds in high yields.<sup>8-12</sup>

We have studied Lewis acid mediated reactions of  $\beta$ -hydroxy- $\alpha$ -diazo carbonyls and have shown that they participate in a variety of mechanistically distinct reactions, including ring fragmentation,<sup>13-16</sup> C-H insertion,<sup>17-19</sup> electrophilic aromatic substitution,<sup>20</sup> and intramolecular cyclization.<sup>21</sup> Our computational work on the C-H insertion of vinyl cations<sup>18-19</sup> revealed that these reactions proceed through a reversible Lewis acid mediated dehydroxylation step that gives a vinyl diazonium ion such as **2a** (Scheme 1). Aside from their use as vinyl cation progenitors,<sup>22</sup> vinyl diazonium salts have not received much attention from synthetic chemists, and little is known about their synthetic utility. However, limited studies suggest that these systems are promising reactive intermediates.<sup>23-25</sup> For example, they are known to undergo electrophilic aromatic substitution at the  $\beta$  carbon,<sup>24</sup> and they can participate in cycloaddition-type reactions with loss of  $\text{N}_2$ .<sup>24, 26</sup>

## Scheme 1. Formation and reactions of vinyl diazonium ions.



Vinyl diazonium **2a** contains an  $\alpha,\beta$ -unsaturated carbonyl motif and has a resonance structure with a carbenium ion at the  $\beta$ -position (**2b**). We reasoned that these species would be excellent electrophiles and would react with nucleophiles to formally give the conjugate addition product while retaining the diazo group which is one of the most versatile functional groups for organic synthesis.<sup>27-28</sup> In addition to participating in 1,3-dipolar cycloadditions giving useful heterocycle products,<sup>29</sup> the diazo group is a progenitor to more reactive intermediates including carbenes and carbenium ions through loss of molecular nitrogen. Very recently we reported that indoles added to vinyl diazonium ions in high yield to give tertiary and all-carbon quaternary centers while retaining the diazo functional group within the molecule (Scheme 1).<sup>30</sup> A complementary and concomitant study by Doyle and co-workers demonstrated a similar reactivity stemming from vinyl diazo compounds in the presence of  $\text{Tf}_2\text{NH}$ .<sup>31</sup> We also provided a limited set of examples showing that enoxy silanes were competent nucleophiles in these reactions.<sup>30</sup> However, while the addition of indole generally proceeded in high yield, the yield of enoxy silane additions

**Table 1. Lewis acid catalyst screening.**

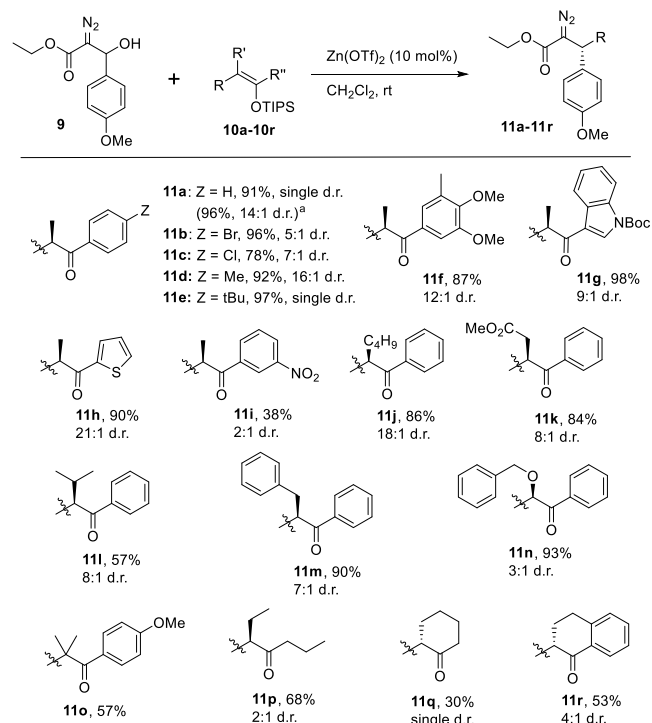
	Catalyst	Time <sup>a</sup>	Yield <sup>b</sup>
1	La(OTf) <sub>3</sub>	48 h	48%
2	Dy(OTf) <sub>3</sub>	1.5 h	87%
3	Sc(OTf) <sub>3</sub>	1 h	64%
4	Al(OTf) <sub>3</sub>	1 h	86%
5	AlCl <sub>3</sub>	2 h	< 12%
6	FeCl <sub>3</sub>	1 h	72%
7	Cu(OTf) <sub>2</sub>	45 min	38%
8	In(OTf) <sub>3</sub>	30 min	61%
9	Mg(OTf) <sub>2</sub>	- <sup>c</sup>	0%
10	Zn(OTf) <sub>2</sub>	3 h	99%
11	BiCl <sub>3</sub>	30 min	85%
12	Ag(OTFA)	15 min	0% <sup>d</sup>
13	TfOH	10 min	0% <sup>d</sup>

<sup>a</sup>Until **6** was consumed by TLC; <sup>b</sup>Determined by <sup>1</sup>H NMR using 4-nitrobenzaldehyde as an internal standard, single diastereomer observed in all cases; <sup>c</sup>No reaction. <sup>d</sup>**6** fully consumed, **8** not detected.

were modest, in part due to the incompatibility of the enoxy silane with the Lewis acid that was used in stoichiometric quantity. In addition, these reactions required precise temperature control (-16°C) to allow an appropriate reaction rate and prevent degradation of the products. Here we report a method for the conjugate addition of enoxy silanes to vinyl diazonium salts that overcomes these barriers and uses catalytic quantities of Lewis acid to give excellent yields of a variety of 2-diazo-1,5-dicarbonyl compounds.

We began our studies by screening Lewis acid catalysts for their ability to promote the reaction of β-hydroxy-α-diazoester **6** and enoxy silane **7**. The results are summarized in Table 1; it is worth noting that Sc(OTf)<sub>3</sub> did function as a catalyst but the product yield was lower than when the Lewis acid was used in stoichiometric quantities (64% vs 76% respectively). Interestingly, although Al(OTf)<sub>3</sub> and AlCl<sub>3</sub> differ only in their counterions, the former was an efficient catalyst (86% yield) whereas the latter almost completely failed to promote the reaction (<12% yield). No reaction occurred with Mg(OTf)<sub>2</sub> as a catalyst, and while complete consumption of the diazoester occurred when Ag(OTFA) and TfOH were used, vigorous gas evolution was observed and none of the desired product was seen in <sup>1</sup>H NMR spectrum of the crude reaction mixture. Although it is not yet clear to us why, it is interesting to note that weaker Lewis acids<sup>32</sup> tended to give better yields. Ultimately the most effective Lewis acid catalyst for this transformation proved to be Zn(OTf)<sub>2</sub> which at 10 mol% loading provided addition product **8** in nearly quantitative yield as a single diastereomer by <sup>1</sup>H NMR.

We turned our attention to examining the scope of enoxy silanes that would productively react with 4-methoxy diazoester **9** under these conditions. The results of these studies are summarized in Table 2. As expected, the TIPS-enoxy silane of propiophenone reacted smoothly to give **11a** in 91% yield as a single diastereomer. This reaction proved to be scalable and on 1.2 mmol scale **11a** was formed in similar yield (96%, 0.422 g). On this larger scale we observed a minor diastereomer in the

**Table 2. Substrate scope for addition of enoxy silanes to **9**.**

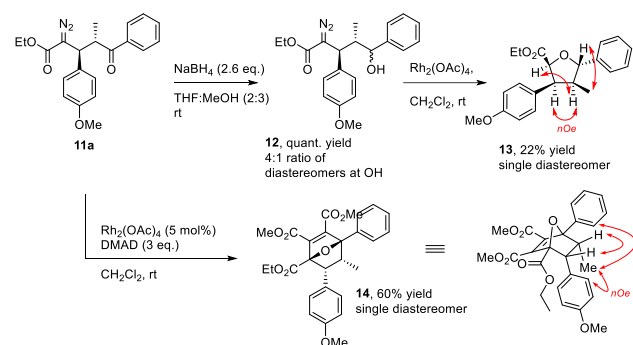
<sup>a</sup>Yield and d.r. on 1.2 mmol scale

<sup>1</sup>H NMR spectrum in a ratio of 14:1. Aware of the possibility of “hidden Brønsted” acid catalysis (i.e., *in situ* generation of trace TfOH), we also ran this reaction in the presence of 1 equiv. K<sub>2</sub>CO<sub>3</sub>; **11a** was still formed in 93% yield as a single diastereomer, thereby ruling out this possibility. To determine the relative configurations of the newly formed stereocenters we subjected **11a** to the reaction sequence shown in Scheme 2. Treating **11a** with NaBH<sub>4</sub> resulted in selective reduction of the ketone to give alcohol **12** in quantitative yield as an inseparable mixture of diastereomers. Treating this mixture with Rh<sub>2</sub>(OAc)<sub>4</sub> resulted in intramolecular O-H insertion. Tetrahydrofuran **13**, which notably has four contiguous stereocenters, was isolated as a single diastereomer in 22% yield. Attempts to increase this yield have not been successful. A NOESY NMR experiment was used to assign the 4-methoxyphenyl and methyl groups as *cis* on the tetrahydrofuran ring, which corresponds to them being oriented *anti* in the addition product. To corroborate this assignment, we also subjected **11a** to Rh<sub>2</sub>(OAc)<sub>4</sub> in the presence of dimethyl acetylenedicarboxylate (DMAD). 1,3-dipolar cycloaddition product **14** was formed in 60% yield as a single diastereomer, and its stereochemistry was assigned using

NOESY (Scheme 2). Based on these outcomes, we tentatively assign the major diastereomer of the remaining addition products as *anti*.

As shown in Table 2, electronically neutral and electron-rich 1-arylenoxy silanes tended to add well, giving the addition products **11a-11h** in excellent yields. Incorporating a nitro group onto the aryl ring of the enoxy silane gave **11i** in low yield with little diastereoselectivity. It is not clear if the low yield is due to a lack of nucleophilicity, or detrimental interaction between the nitro group and the Lewis acid. Increased steric hindrance at the 2-position of the enoxy silane was tolerated but decreased the product yields (**11j-11o**). Importantly, product **11o**, which is derived from a tetrasubstituted enoxy silane and contains an all-carbon quaternary center was isolated in 57% yield. N-Boc and O-benzyl protecting groups were also well tolerated and products **11g** and **11n** were formed in 98% and 93% yields, respectively. This latter example also shows that an enediol derivative is a competent nucleophile in this reaction. Enoxy silanes derived from aliphatic ketones were also competent nucleophiles giving **11p** and **11q**, albeit in lower yields than their aryl counterparts.

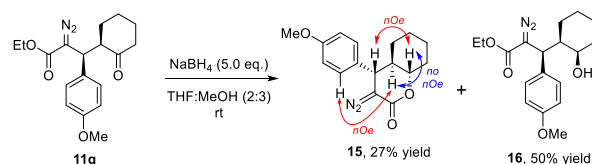
### Scheme 2. Determination of stereochemistry of 11a.



The diastereomeric ratios of the products in Table 2 were typically high, although electron-poor arylenoxy silanes gave products with lower diastereomeric ratios (**11b**, **11c**, **11i**) than the more electron-rich ones (**11d-f**, **11h**). We considered that the initially formed products might epimerize under the Lewis acidic conditions, however we monitored the formation of **11b** over a 24-hour period and the 5 to 1 diastereomeric ratio did not change over time. The enoxy silanes used to make **11a-11p** were prepared as mixtures of alkene diastereomers that in all cases favored the *Z* isomer. This, of course, is not the case for the enoxy silanes used to form **11q** and **11r**, which are by necessity *E* isomers. It is noteworthy that the reactions leading to **11q** and **11r** were significantly slower than the reactions leading to **11a-11p**. To establish if the stereochemical outcome of the reaction was affected by the stereochemistry of the enoxy silane we attempted to subject the diastereomerically pure **11q** to the same reduction/cyclization sequence shown in Scheme 2 (Scheme 3). Upon reduction, one alcohol diastereomer spontaneously cyclized to give *trans*-diazolactone **15**. NOESY NMR of **15** indicates that **11q** is the *syn* addition product. These data appear to indicate that *Z*-enoxy silanes react more quickly than the *E*-isomers and preferentially give the *anti*-addition products, while the slower reacting *E*-

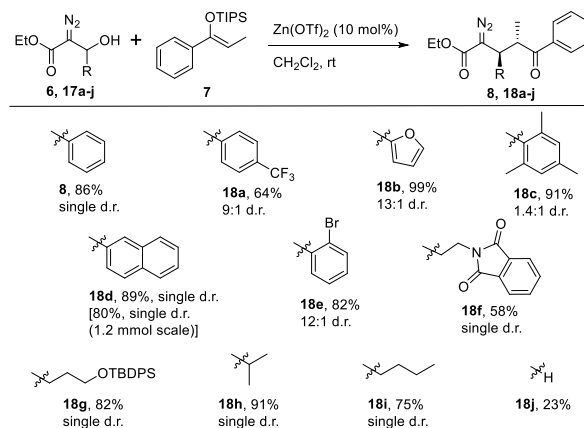
enoxy silanes give the *syn*-addition products. This difference in reaction rate, and the fact that in reactions leading to **11a-11p** the faster reacting *Z*-isomer of the enoxy silane was always present in super stoichiometric quantity,<sup>33</sup> explains why the *anti*-diastereomer is formed preferentially in these reactions.

### Scheme 3. Determination of stereochemistry of 11q.



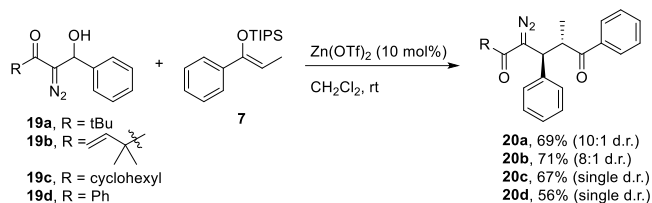
A variety of  $\beta$ -hydroxy- $\alpha$ -diazooesters bearing a range of functionalized R groups were also synthesized and subjected to the reaction conditions. The results are summarized in Table 3. Substrates bearing aryl and simple aliphatic groups performed equally well. We were also pleased to find that the normally acid-sensitive TBDPS group remained intact over the course of the reaction, and product **18g** was formed in 82% yield as a single diastereomer. Only the unsubstituted ethyl 2-diazo-3-hydroxypropanoate performed poorly in this series, giving product **18j** in 23% yield. **18d** was also prepared on 1.2 mmol scale (0.369g, 80% yield) as a single diastereomer.

Table 3. Substrate scope for addition of enoxy silane 7 to various  $\beta$ -hydroxy- $\alpha$ -diazooesters.



Finally, we sought to extend this reactivity to  $\beta$ -hydroxy- $\alpha$ -diazoketones. To this end, we prepared a small series of benzaldehyde-derived  $\beta$ -hydroxy- $\alpha$ -diazoketones (**19a-19d**) bearing different R groups (Scheme 4). Although these types of compounds were previously demonstrated by us to be more prone to loss of  $N_2$  in Lewis acidic reaction media, we were delighted to find that these substrates performed as well as their ester analogues, albeit requiring longer reaction times. In these cases, we noted that a bulkier R group on the diazoketone resulted in reduced diastereoselectivity. **20a** and **20b** were formed as mixtures of two diastereomers, whereas **20c** and **20d** were isolated as single diastereomers.

### Scheme 4. Conjugate addition of 7 to $\beta$ -hydroxy- $\alpha$ -diazoketones.



In summary, we have described a mild and efficient method to synthesize highly functionalized 2-diazo-1,5-dicarbonyls in short order from simple starting materials. This represents an improvement over our previously reported method, as only 10 mol% of Zn(OTf)<sub>2</sub> is required to achieve excellent yields of the products. The use of catalytic Lewis acid opens the possibility for catalytic enantioselective transformations, which we are pursuing. The reaction tolerates a wide variety of functional groups including acid-sensitive ones. The active electrophile in this reaction is the little-studied vinyl diazonium ion, thus the results presented here add valuable insight into the reactivity patterns of these highly reactive intermediates.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and compound characterization data (PDF).

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### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

## ACKNOWLEDGMENT

Financial support from the National Science Foundation (CHE-1665113 and CHE-2102229) is gratefully acknowledged. Mass spectrometry data was acquired by Bruce O'Rourke at The University of Vermont with support from the National Institutes of Health (NIH) grants S10-OD018126 and P30-GM118228.

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