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Diverse Reactions of Vinyl Diazo Compounds with Quinone Oxonium Ions, Quinone Imine Ketals, and Eschenmoser's Salt

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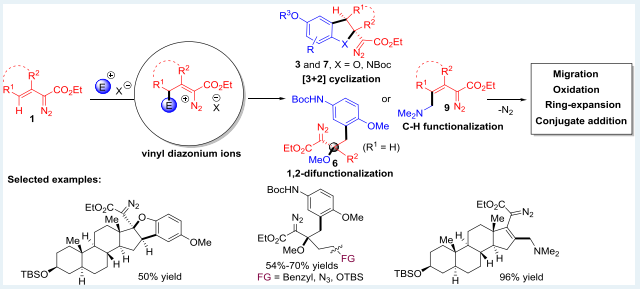
ABSTRACT: Metal-free electrophile addition to vinyl diazo compounds reveals highly selective formal [3 + 2] cyclization, 1,2-difunctionalization of alkenes, and C−H functionalization. The success of these methodologies is based on electrophilic addition to the vinylogous position of vinyl diazo compounds, forming vinyl diazonium ion intermediates. By using diverse electrophilic reagents, these highly reactive intermediates show diverse reactivities, affording β-benzohydrofuran-, β-methoxy-β-benzyl-, and γ-aminoallyl-substituted α-diazo esters in high yields and selectivities. Further transformations that include migration, oxidation, ring-expansion, and conjugate addition highlight the potential utility of this method.



KEYWORDS: *Brønsted acid catalysis, vinyl diazo compounds, electrophile addition, vinyl diazonium ions, β- and γ-functionalized diazo compounds*

Diazo compounds are versatile reagents that are easily accessible and have provided an attractive platform for a variety of metal carbene transformations, including diverse cycloadditions,[1] rearrangement,[2] insertions,[3] ylide formation,[4] and others.[5] Meanwhile, their dipolar nature makes them susceptible to addition by different electrophilic reagents, affording diazonium ion intermediates (Scheme 1a-i)[6] that undergo substitution or migration reactions. The homologation (Scheme 1a-ii)[7] or epoxidation (Scheme 1a-iii)[8] of aldehydes or ketones with diazo compounds is an example of this process. Their asymmetric versions have been extensively investigated and used in the synthesis of biologically active compounds and complex natural products.[9] However, the reactions of vinyl diazo compounds in which the alkene is directly attached to the diazo functional group with electrophilic reagents have rarely been explored.[10]

In 2011, Barluenga, López, and co-workers reported a copper(II) catalyzed oxidative rearrangement of vinyl diazo compounds with iodosyl benzene which resulted in the formation of β-oxo diazo compounds in moderate to good yields, indicating the suitability of vinyl diazo compounds to nucleophilic addition and further transformations (Scheme 1b).[11] Very recently, we reported that bis(trifluoromethanesulfonyl)imide ($HNTf_2$) serves as a uniquely efficient Brønsted acid that selectively protonates the vinylogous position of vinyl diazo compounds forming vinyl diazonium ions, which could be captured by indole nucleophiles to give β-indole-substituted diazo esters, or releases dinitrogen to form vinyl carbocation ions for further transformations.[12] A similar discovery, the Lewis acid-mediated dehydroxylation of β-hydroxy-α-diazo carbonyl compounds to vinyl diazonium ions, was reported by the Brewer group.[13] These investigations illustrate that vinyl diazo compounds as nucleophiles have the potential to offer complementary processes to those of metal carbenes. The stability of vinyl diazonium ions appears to lie between their alkyl and aryl counterparts. The use of suitable electrophiles could restrain the loss of dinitrogen, providing alternative strategies to prepare structurally complex diazo-containing compounds that would be beneficial to the synthetic community. However, compared with known transformations of alkyl- and aryldiazonium ions, those of vinyl diazonium ions are still in their infancy.

Herein, we report that vinyl diazo compounds react with three types of electrophiles (from quinone oxonium ions, quinone imine ketal, and Eschenmoser's salt), separately realizing formal [3 + 2] cyclization, 1,2-difunctionalization of alkenes, and C−H functionalization reactions via vinyl diazonium ion intermediates. In these metal free strategies, β-benzohydrofuran-, β-methoxy-β-benzyl-, and γ-aminoallyl-substituted α-diazo esters are obtained in good to excellent yields and selectivities (Scheme 1c). In addition, the enhanced

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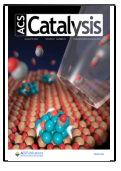

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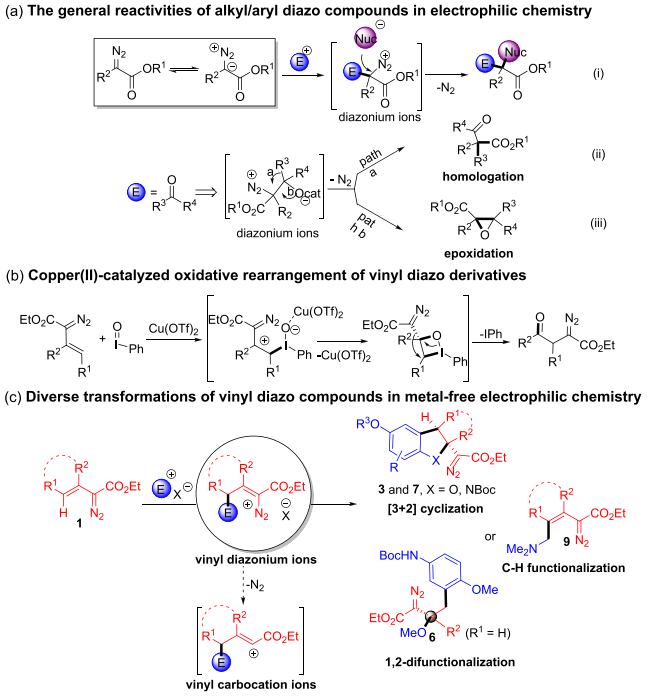
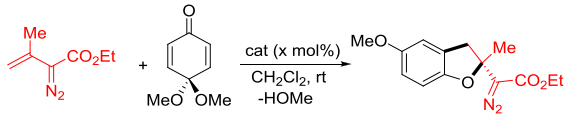
Scheme 1. Electrophile Addition Reactions of Diazo Compounds and This Work



structural complexity of these diazo esters allows further transformations that include migration, oxidation, ring-expansion, and conjugate addition.

Initially, quinone ketal **2a**, which is the precursor of quinone oxonium ions in acid-catalyzed reactions,[14] was selected as the model substrate to investigate the viability of its reaction with vinyl diazo compound **1a**. We anticipated that acid would convert **2a** to its quinone oxonium ion in competition with formation of the vinyl diazonium ion from **1a**,[12] whereby the oxonium ion could then undergo electrophilic addition to **1a**. A variety of commercially available Lewis acids and Brønsted acids were employed as catalysts (Table 1). Interestingly, the use of strong acid catalysts gave the formal [3 + 2] cyclization product **3aa** in reasonable yield (Table 1, entries 2−4 and 7−8), and the superacid $HNTf_2$, with the low nucleophilicity and low coordinating ability of its conjugate base (Tf_2N^-), was the most effective catalyst; product **3aa** was obtained in 32% yield. Attempts to optimize the yield of **3aa** by varying the solvent and decreasing the temperature were unsuccessful (for details, see the Supporting Information). Fortunately, reducing the catalyst loading and increasing the amount of quinone ketal **2a** lessened the competing decomposition of vinyl diazo compound **1a** and provided the best results with an isolated yield of product **3aa** of 55% (Table 1, entry 9).

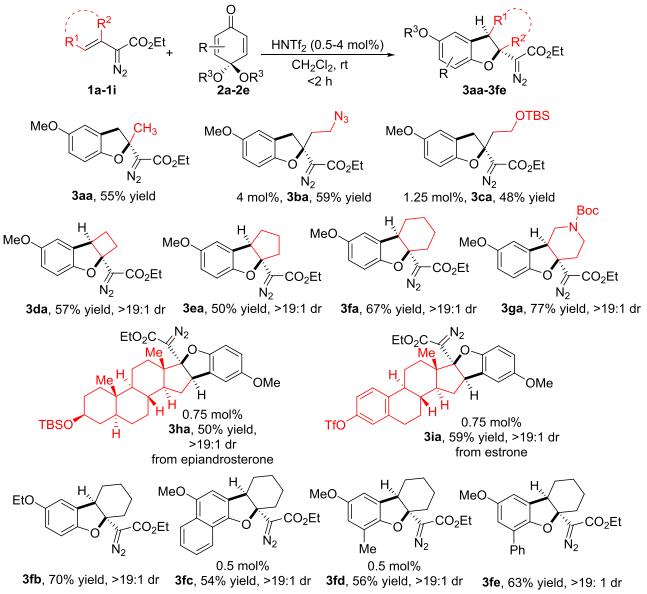
Table 1. Optimization of Reaction Conditions for Cyclization of 1a and 2a[a]



entry[a]	cat.	conditions	yield of **3aa** (%)[b]
1	$B(C_6F_5)_3$	5 mol %, 24 h	trace
2	$BF_3{\cdot}Et_2O$	5 mol %, 2 h	12
3	$Sc(OTf)_3$	5 mol %, 2 h	26
4	$Fe(OTf)_3$	5 mol %, 2 h	15
5	$Zn(OTf)_2$	5 mol %, 24 h	no reaction
6	CF_3COOH	5 mol %, 24 h	no reaction
7	TfOH	5 mol %, 2 h	17
8	$HNTf_2$	5 mol %, 2 h	32
9[c]	$HNTf_2$	1 mol %, 2 h	55

[a]Reactions were performed by adding cat. (*x* mol %) to **1a** (0.25 mmol) and **2a** (0.25 mmol) in CH_2Cl_2 (2.5 mL) at rt. [b]Isolated yield. [c]4 equiv of **2a** (1.0 mmol) was used.

Scheme 2. Scope of the $HNTf_2$-Catalyzed Formal [3 + 2] Cyclization Reaction of β-Alkyl-Substituted Vinyl Diazo Compounds 1 and Quinone Ketals 2[a]



[a]Reactions were performed by adding $HNTf_2$ (0.5−4 mol %) to **2** (1 mmol) and **1** (0.25 mmol) in CH_2Cl_2 (2.5 mL) at rt for 2 h. Unless otherwise noted, 1 mol % $HNTf_2$ was used.

With optimized conditions in hand, we examined the scope of the $HNTf_2$-catalyzed formal [3 + 2] cyclization reaction of quinone ketal **2a** and β-alkyl-substituted vinyl diazo compounds **1** (Scheme 2). The results show that functional groups, including azide (N_3) and *tert*-butyldimethylsilyl ether (OTBS), were tolerated in this reaction; the corresponding products **3ba** and **3ca** were obtained in 59% and 48% yields, respectively. Furthermore, vinyl diazo compounds bearing different cyclic rings (**1d**−**1g**) were suitable substrates, giving the desired products (**3da**−**3ga**) in 57%−77% yields with excellent diastereoselectivities. More importantly, vinyl diazo compounds (**1h** and **1i**) derived from natural products epiandrosterone and estrone participated in the reaction, delivering products **3ha** and **3ia** in 50% yield (>19:1) dr and 59% yield (>19:1 dr), respectively.

Subsequently, our investigations were focused on the scope of quinones **2** (Scheme 2). Ethyl ether-substituted quinone ketal **2b** was able to give product **3fb** in 70% yield with >19:1 dr. In addition, naphthoquinone ketal **2c** reacted with vinyl diazo compound **1f**, affording the corresponding [3 + 2]-cycloaddition product **3fc** in 54% yield and >19:1 dr. Furthermore, 2-methyl- and 2-phenyl-substituted quinone ketals (**2d** and **2e**) were suitable substrates, and the

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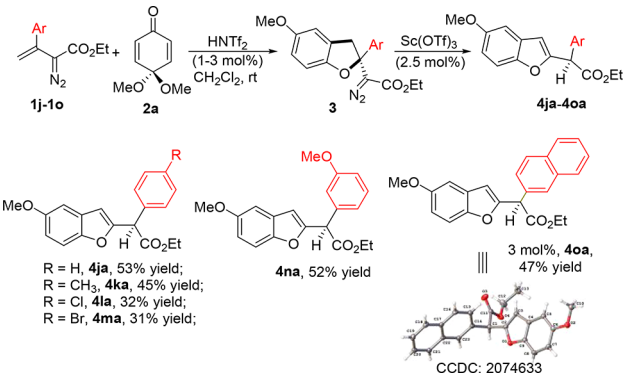
corresponding products **3fd** and **3fe** were obtained in 56% and 63% yield, respectively. However, attempts with other electron-withdrawing-substituted quinone ketal substrates did not give any cycloaddition products (for details, see the Supporting Information).

Based on the successful cyclization of quinone ketal **2a** with *β*-alkyl substituted vinyl diazo compounds, we investigated their use with the less reactive *β*-aryl-substituted vinyl diazo compounds (**1j**−**1o**). The desired [3 + 2]-cycloaddition products **3** were obtained, accompanied by dedinitrogen/aryl migration products **4**, but the addition of a catalytic amount of $Sc(OTf)_3$ fully converted products **3** to **4** in a one-pot reaction (Scheme 3). Both electron-withdrawing and electron-donating

Scheme 3. Scope of Catalyzed Formal [3 + 2] Cyclization/Migration Reaction of *β*-Aryl-Substituted Vinyl Diazo Compounds 1 and Quinone Ketal 2a[a]



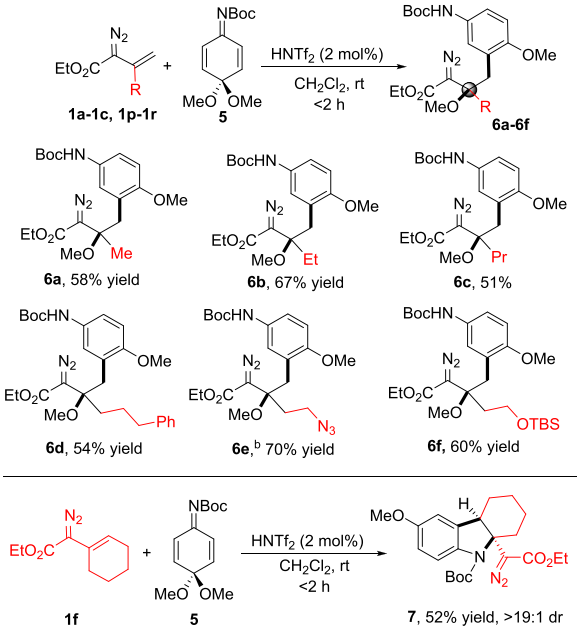
[a]Reactions were performed by adding $HNTf_2$ (1−3 mol %) to **2a** (0.25 mmol) and **1** (0.5 mmol) in CH_2Cl_2 (2.5 mL) at rt for 2 h. After that, $Sc(OTf)_3$ (2.5 mol %) was added, and the reaction was continued for 1 h. Unless otherwise noted, 1 mol % $HNTf_2$ was used.

substituents on the phenyl ring produced the corresponding products (**4ja**−**4na**, 31%−52% yield) in moderate yields due to the decomposition of quinone ketal **2a** with $HNTf_2$. The *β*-naphthyl-substituted vinyl diazo compound **1o** underwent the reaction, giving product **4oa** in 47% yield. The structure of **4oa** was confirmed by X-ray diffraction.[15]

To better understand the properties of vinyl diazo compounds as nucleophiles, we synthesized quinone imine ketal **5**[16] and investigated its reactivity with vinyl diazo compounds (**1a**−**1c**, **1f**, and **1p**−**1r**). Interestingly, with $HNTf_2$ catalysis a formal 1,2-difunctionalization reaction occurred instead of cycloaddition, and the corresponding products **6** were obtained in good yields (Scheme 4). *β*-Methyl- (**1a**), ethyl- (**1p**), and *n*-propyl- (**1q**) substituted vinyl diazo compounds were tolerated, giving products **6a**−**6c** in 51%−67% yield. In addition, other vinyl diazo compounds bearing R = 2-phenethyl (**1r**), 2-azidoethyl (**1b**), and 2-*tert*-butyldimethylsiloxyethyl (**1c**) groups also reacted with quinone imine ketal **5**, and the functionalized diazo ester products **6d**−**6e** were obtained in good yields (54−70%). However, the less nucleophilic *β*-aryl-substituted vinyl diazo compounds were not suitable substrates. Furthermore, due to steric and conformational effects, the reaction between cyclic vinyl diazo compound **1f** and imine ketal **5** gave the formal [3 + 2] cyclization product **7** in 52% yield and >19:1 dr.

Eschenmoser's salt, dimethylmethylideneammonium iodide **8**, is a strong dimethylaminomethylating agent that has been

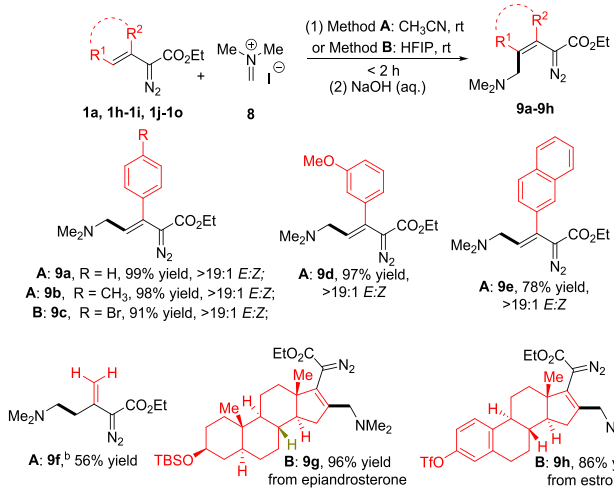
Scheme 4. Scope of the $HNTf_2$-Promoted 1,2-Difunctionalization of Vinyl Diazo Compounds 1 with Quinone Imine Ketal 5[a]



[a]Reactions were performed by adding $HNTf_2$ (2 mol %) to **1** (0.25 mmol) and **5** (1.0 mmol) in CH_2Cl_2 (2.5 mL) at rt. [b]Catalyst loading is 3 mol %.

widely used to prepare derivatives of the type $RCH_2N(CH_3)_2$.[17] When applied to reactions with vinyl diazo compounds, Eschenmoser's salt underwent a formal C−H functionalization reaction yielding *E*-substituted vinyl diazo compounds in high yields and stereoselectivities (Scheme 5). Both electron-withdrawing and electron-donating substituents on the phenyl ring of *β*-aryl-substituted vinyl diazo compounds (**1j**−**1n**) were tolerated, and the products **9a**−**9d** were isolated in 91%−99% yield and >19:1 *E*:*Z*. In addition, *β*-naphthyl-

Scheme 5. Scope of the C−H Functionalization of Vinyl Diazo Compounds 1 with Eschenmoser's Salt 8[a]



[a]Reactions were performed by adding **1** (0.25 mmol) to Eschenmoser's salt (1.0 mmol) in CH_3CN (**A**) or HFIP (**B**) (4 mL). [b]1.5 equiv of **1a** was used.

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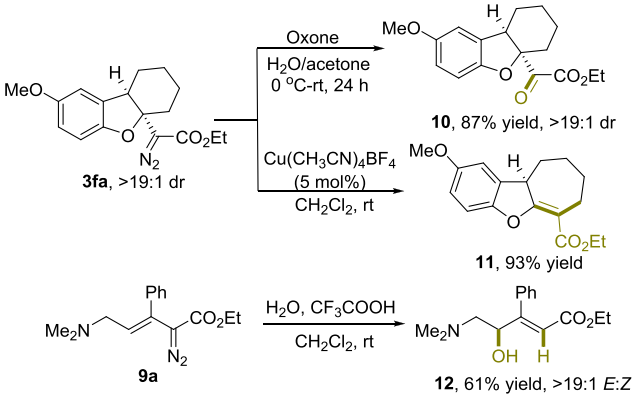
substituted vinyl diazo compound **1o** gave **9e** in 78% yield. Interestingly, for the β-methyl-substituted vinyl diazo compound **1a**, the addition−elimination product **9f** was isolated in 57% yield. Furthermore, natural products epiandrosterone and estrone derived vinyl diazo compounds (**1h** and **1i**) participated in this reaction, delivering products **9g** and **9h** in 96% yield and 86% yield, respectively.

To illustrate the utility of these processes, further transformations of diazo compounds **3fa** and **9a** were performed (Scheme 6). Oxone oxidation of **3fa** occurred under mild

Scheme 6. Further Transformations of Products 3fa and 9a



conditions, affording product **10** in 87% yield and >19:1 dr. In addition, $Cu(CH_3CN)_4BF_4$ effected ring-expansion of **3fa**, and **11** was isolated in 93% yield. Furthermore, with CF_3COOH, vinyl diazo compound **9a** reacted with water, delivering conjugated addition product **12** in 61% yield and >19:1 *E*:*Z*.

Based on the experimental data, a probable reaction mechanism for electrophile-induced transformations of vinyl diazo compounds is proposed in Figure 1. For the formal [3 + 2] cyclization, the selective addition of the quinone oxonium ion, generated in situ by $HNTf_2$ catalysis, on the vinylogous position of vinyl diazo compounds **1** gives the vinyl diazonium ion intermediate **int-I**. Subsequently, vinyl diazonium intermediate **int-I** is captured by the oxygen of phenol or by an imine nitrogen (in the case of **1f**) to afford the final cyclization products **3** or **7** (path a). In addition, the $HNTf_2$ catalyzed Michael addition of vinyl diazo compounds **1** with quinone imine ketal **5** forms intermediate **int-II**, and then methoxy group transfer and proton loss resulting in aromatization occurs, providing the 1,2-difunctionalization products **6** (path b). Furthermore, Eschenmoser's salt **8** reacts with vinyl diazo compounds **1** to provide vinyl diazonium intermediate **int-III**, and subsequent deprotonation by nitrogen delivers the formal C−H functionalization products **9** (path c).

In summary, we have realized formal [3 + 2] cyclization, 1,2-difunctionalization of alkenes, and C−H functionalization reactions of vinyl diazo compounds via metal-free strategies. The success of these methodologies is based on the selective electrophilic addition to the vinylogous position of vinyl diazo compounds forming vinyl diazonium ions. By using different electrophilic reagents, the vinyl diazonium ion intermediates show diverse reactions. These results demonstrate the intriguing reactivity of vinyl diazo compounds as nucleophiles in electrophilic chemistry and provide a fascinating methodology for the selective synthesis of β-benzohydrofuran-, β-methoxy-β-benzyl-, and γ-aminoallyl-substituted α-diazo esters. Furthermore, migration, oxidation, ring-expansion, and conjugated addition transformations of the product diazo esters were performed to demonstrate the utility of these processes.

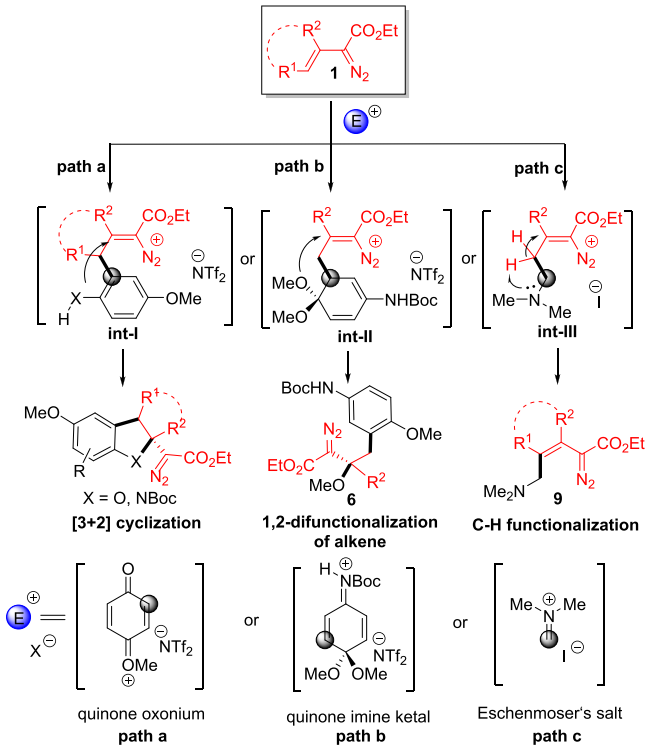


Figure 1. Proposed mechanism for vinylogous electrophilic additions to vinyl diazo compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c02674.

Experimental procedure and spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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