

## Preview

# Functionalized vinyl diazo compounds: new players in asymmetric catalysis

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In this issue of *Chem Catalysis*, Doyle et al. prepare functionalized vinyl diazoacetates through base-promoted ring opening of 5-alkyl-1,2,3-triazine-1-oxides. These diazo compounds engage in several metal-catalyzed enantioselective transformations. The high degree of functionalization of the products and the excellent enantiocontrol position these new diazo compounds as promising reagents in asymmetric catalysis.

Due to their inherent ability to participate in a broad spectrum of distinct chemical transformations, metal-carbenes occupy a pivotal position as intermediates in organic synthesis and catalysis.<sup>1</sup> While a diverse array of metallocarbene precursors are currently available, stabilized diazo compounds have emerged as the prevailing sources for the catalytic generation of these reactive intermediates.<sup>2</sup> In particular, diazoacetates endowed with a vinyl group attached to the diazo function –referred to as vinyl diazo compounds– have risen in prominence over recent decades as versatile reagents in transition metal-catalyzed transformations (Figure 1A). Their structural framework, comprising two conjugated reactive groups (diazo and vinyl), bestows upon them a diverse and multifaceted reactivity profile. This characteristic feature has been systematically exploited by various groups for a multitude of synthetically valuable transformations. In particular, since the seminal works of the late 1980s,<sup>3</sup> the Davies group has exerted a significant influence in this domain, effectively propelling the rapid expansion and subsequent consolidation of this field. They have achieved this through the development of numerous relevant rhodium-catalyzed transformations involving vinyl diazoacetates. These transformations are proposed to proceed through rhodium vinylcarbene intermediates, which, with a few exceptions, exhibit a typical carbene reactivity transferring the carbene unit to both saturated and unsaturated substrates. Capitalizing on this chemical behavior, an array of synthetic applications have been devised and excellent levels of regio-, diastereo- and enantioselectivity have been accomplished in some of these rhodium-catalyzed transformations of vinyl diazo compounds. More recently, the pursuit of alternative catalysts for transformations of vinyl diazo compounds has led to the identification of novel reactive sites within the corresponding metal vinylcarbene intermediates. Notably, coinage metal catalysts have emerged as attractive alternatives to the extensively used dirhodium catalysts due to the differential reactivity displayed by the generated metal vinylcarbenes. Specifically, most of these coinage metal-catalyzed transformations predominantly involve the C-4 carbon atom (vinylogous reactivity), likely attributed to the enhanced electrophilic character of this position within the corresponding metal vinylcarbene intermediate.<sup>4</sup>

Despite the significant synthetic potential inherent in vinyl diazo reagents, their availability still remains somewhat unsatisfactory. While several efficient methods for the gram-scale

synthesis of vinyl diazo compounds are currently available, in general, these methodologies do not allow extensive structural modification. This limitation arises due to their poor functional group tolerance, thereby permitting facile attachment of only alkyl and aryl groups to the vinyl moiety. With the notable exception of the silyloxy group in enoldiazoacetate derivatives, the straightforward access to vinyl diazo compounds possessing additional functionality –while retaining the ability to partake in well-established metal-catalyzed carbene transformations– remains a challenging synthetic endeavor. In this context, the contribution by Doyle et al. in this issue of *Chem Catalysis* stands as a significant advance within this field.

Very recently, Doyle and co-workers reported an efficient, catalyst-free synthesis of 1,2,3-triazine-1-oxides through treatment of vinyl diazoacetates with alkyl nitrites.<sup>5</sup> Based on this, the chemistry reported in this issue of *Chem Catalysis* delves into the application of these heterocyclic compounds within the realm of diazo chemistry.<sup>6</sup> Specifically, the authors unveil the ability of 1,2,3-triazine-1-oxides featuring an alkyl group containing an  $\alpha$ -C-H bond at the 5-position to undergo a base-catalyzed ring opening reaction leading to new vinyl diazo compounds decorated with an oxime function in their structure (Figure 1B). Employing bases such  $\text{Cs}_2(\text{CO}_3)$  or DABCO in THF as the solvent at room temperature, impressive yields (exceeding 90% in most cases) were attained. This ring-opening process demonstrates a broad scope and, where applicable, providing exclusively the (*Z*)-isomer. Notably, the reaction retained its efficiency even at a gram-scale. Furthermore, the high-yielding silylation of the oxime hydroxyl group within the moderately stable oximido vinyl diazo esters led to the isolation of considerably more stable silyl ether derivatives.

Having established a robust protocol for accessing new functionalized vinyl diazo compounds, the authors proceeded to assess their usefulness in asymmetric catalysis. To this end, a number of well-established metal-catalyzed transformations of vinyl diazoacetates were selected for evaluation.

The study commenced with the intermolecular cyclopropanation of styrene derivatives, arguably one of the most emblematic and widely studied metal-catalyzed transformations of vinyl diazoacetates.<sup>7</sup> Preliminary experiments demonstrated that protection of the OH group of the oxime as *tert*-butyldimethylsilyl (TBS) ether was required. While identifying an optimal set of reaction conditions applicable across the range of available functionalized vinyl diazo compounds proved challenging, the authors succeeded in finding two effective combinations of chiral dirhodium(II) catalysts and solvents. In particular,  $\text{Rh}_2(\text{S-PTTL})_4$  in DCE and  $\text{Rh}_2(\text{S-DOSP})_4$  in toluene provided the corresponding cyclopropanation products in good yields (up to 95%) and with high levels of diastereoselectivity (>20:1 dr) and enantiocontrol (up to 97% ee) in most cases (Figure 1C). Interestingly, while alkyl-substituted alkenes were unsuitable substrates, a representative enoether effectively engaged in this rhodium-catalyzed cyclopropanation reaction.

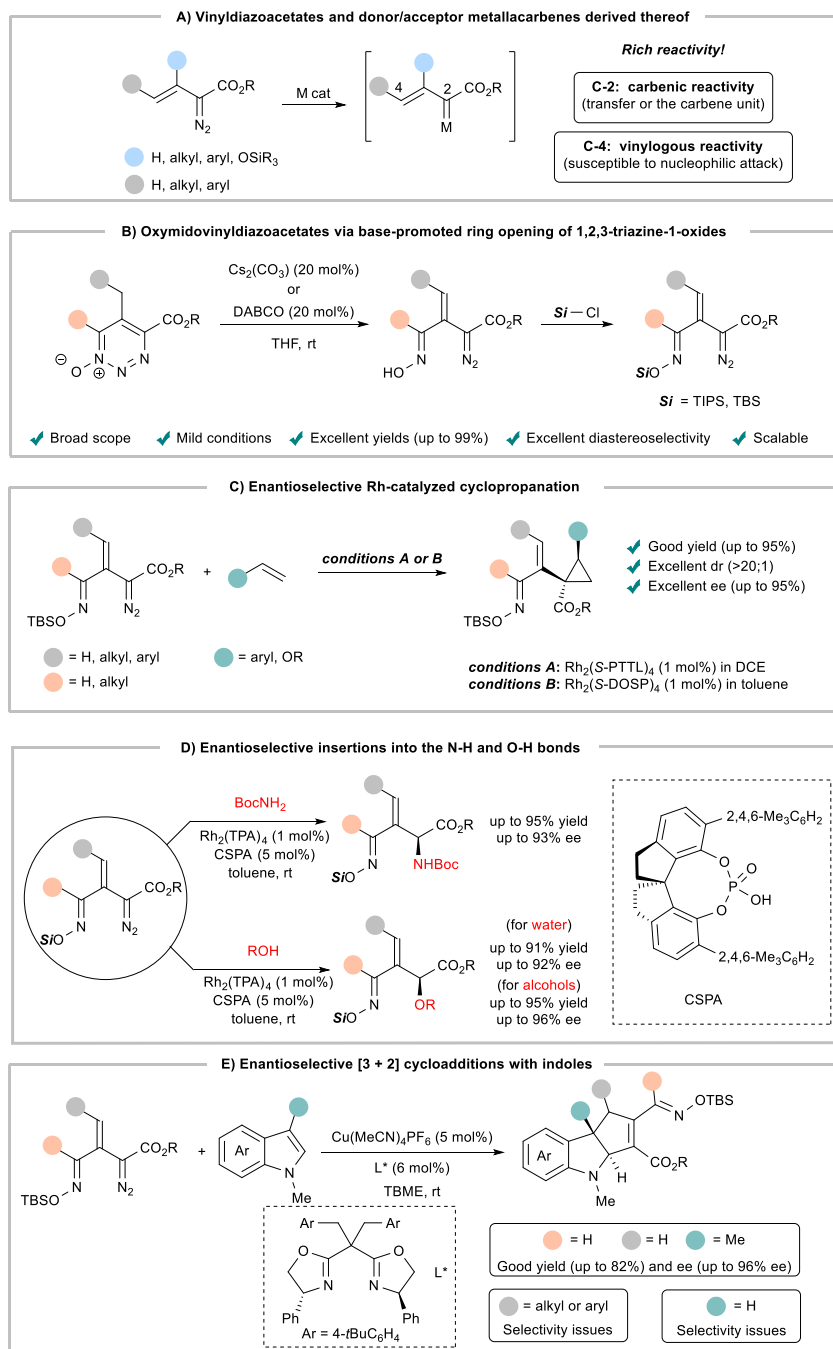
Next, inspired by a report by Zhou and co-workers on the enantioselective synthesis of  $\alpha$ -alkenyl  $\alpha$ -amino acids via N-H insertion reactions,<sup>8</sup> the authors proceeded to evaluate the reactivity of the new functionalized vinyl diazo compounds in this relevant transformation, using *tert*-butyl carbamate ( $\text{BocNH}_2$ ) as the reagent. Employing the Zhou catalytic system, comprising dirhodium tetra(triphenylacetate),  $\text{Rh}_2(\text{TPA})_4$ , in combination with a chiral spiro phosphoric acid catalyst, they achieved high yields (up to 95%) and enantioselectivities (up to 93% ee) (Figure 1C). This insertion reaction occurred with excellent regioselectivity and, under the optimized conditions, vinyllogous N-H insertion was either minimal or not observed. The unprotected oxime function was even tolerated in this insertion reaction. Subsequent hydrolysis of the Boc and ester groups yielded the corresponding enantioenriched  $\alpha$ -alkenyl  $\alpha$ -amino acids.

To further expand the synthetic utility of the new vinyl diazo reagents, the authors explored the catalytic enantioselective insertion into the O-H bond of both water and alcohols. By extrapolating successful conditions developed for simpler vinyl diazoacetates,<sup>9</sup> the authors achieved the corresponding products in good yields and variable enantiocontrol (Figure 1C).

Enantioselectivity ranged from moderate to good (60-92% ee) for water, dependent on the structure of the diazo ester alkyl group, with *tert*-butyl performing better than ethyl. In the case of alcohols, enantioselectivity was notably influenced by the alcohol structure, varying from less than 5% ee for simple alcohols like methanol and ethanol to an exceptional value of 96% ee for *p*-fluorophenol.

Finally, the authors exported previously reported [3+2] annulations of vinyldiazoacetates and indoles to the new functionalized vinyldiazo compounds.<sup>10</sup> Following catalyst screening, copper(I) tetrakis acetonitrile hexafluorophosphate in combination with Sabox ligands emerged as the optimal catalytic system. Good yields (72-85%) and enantioselectivities (81-96% ee) were achieved in reactions of 3-methyl-*N*-methylindole derivatives with the parent TBS-protected oximidovinyldiazoacetate (Figure 1D). Notably, electron-withdrawing group-substituted indole derivatives exhibited superior enantiocontrol compared to those with electron-donating substituents. The authors highlighted that the methyl group at C-3 is paramount for reaction success, as its absence resulted in a less selective process leading to a mixture of the expected [3+2] cycloadduct with low enantioselectivity and a Friedel-Crafts-like product involving the electrophilic vinylogous position of the corresponding metal vinylcarbene intermediate and the C-3 of the *N*-methylindole. On the other hand, the extension to vinyldiazo compounds substituted at the C-4 posed challenges, as their [3+2] annulations with 3-methyl-*N*-methylindole proceeded with low diastereoselectivity, likely due to a stepwise mechanistic pathway.

In summary, the remarkable contribution by Doyle and co-workers in this issue of *Chem Catalysis* describes a simple and efficient approach to vinyldiazo compounds decorated with an oxime function. The preliminary exploration into the reactivity of these novel diazo compounds unveiled their ability to generate donor/acceptor metallacarbene intermediates in the presence of appropriate chiral catalysts. These intermediates readily partake in several established carbene transformations, including additions, insertions into heteroatom-hydrogen bonds or [3+2] cycloadditions. The presence of the oxime function in the reactive species is exceptionally well-tolerated across the demonstrated applications and, from a synthetic perspective, offers great opportunities through subsequent derivatization of the final products. Given the high enantioselectivity achieved in these transformations, this protocol has the potential to serve as a valuable platform for accessing densely functionalized enantiomerically enriched compounds. This contribution could provide new avenues within the domain of asymmetric catalysis, a captivating field in which vinyldiazo compounds and the donor/acceptor metalcarbene intermediates derived thereof are poised to continue playing a pivotal role.



**Figure 1. Synthesis of new functionalized vinyldiazoacetates and preliminary applications in asymmetric catalysis**

- (A) General structure of vinyldiazoacetates and overview of the reactivity of the donor/acceptor metallocarbenes derived from them.
- (B) Synthesis of functionalized vinyldiazoacetates by base-promoted ring opening of 1,2,3-triazine-1-oxides.
- (C) Rh-catalyzed enantioselective cyclopropanation.
- (D) Catalytic enantioselective insertions into N-H and O-H bonds.
- (E) Cu-catalyzed asymmetric [3+2] cycloadditions with indoles.

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## DECLARATION OF INTERESTS

The authors declare no competing interests.

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