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Introduction

Cycloaddition reactions have become powerful transformations for the construction of carbocyclic and heterocyclic compounds with structural diversity.¹ Among these, major contributions have come from transition metal catalytic reactions of vinyl-diazo compounds which generated metalvinylcarbenes that serve as 1,3-dipoles in various types of [3 + *n*]-cycloadditions or annulations (Scheme 1A, path a).² In the course of these investigations, stable donor-acceptor cyclopropenes were found to be generated from enoldiazocarbonyl compounds under catalytic and thermal conditions, and these cyclopropenes serve as metal carbene precursors³ or could undergo cycloaddition reactions (Scheme 1A, path b).⁴ However, cyclopropenes bearing a hydrogen atom at the C-3 position often undergo alder-ene dimerization to give 3-cyclopropylcyclopropenes.⁵ Because cyclopropenes that can undergo the ene reaction are often unstable,⁶ the scope of their cycloaddition applications have been limited to cyclopropenes that can be stabilized.⁴ Limited attempts have been made for *in situ* generation of these unstable intermediates *via* elimination reactions of cyclopropyl halides,⁷ but they are highly restricted

Photoinduced [4 + 2]-cycloaddition reactions of vinyl-diazo compounds for the construction of heterocyclic and bicyclic rings†

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Highly selective formal [4 + 2]-cycloaddition of vinyl-diazoacetates with azoalkenes from α -halohydrazone, as well as with cyclopentadiene and furan, occurs with light irradiation at room temperature, producing highly functionalized heterocyclic and bicyclic compounds in good yields and excellent diastereoselectivity. Under blue light these vinyl-diazoacetate reagents selectively form unstable cyclopropenes that undergo intermolecular cycloaddition reactions at a faster rate than their competitive ene dimerization. [4 + 2]-cycloaddition of vinyl-diazoacetates with *in situ* formed azoalkenes produces bicyclo[4.1.0]tetrahydropyridazine derivatives and, together with their cycloaddition using cyclopentadiene and furan that form tricyclic compounds, they occur with high chemoselectivity and diastereocontrol, good functional group tolerance, and excellent scalability. Subsequent transformations portray the synthetic versatility of these structures.

in their scope and applications. Thus, the development of a more general methodology for their *in situ* generation and applications for cycloaddition reactions remains a challenge.

We have recently shown that “unstable” cyclopropenes from a broad spectrum of vinyl-diazo compounds can be generated photochemically in the presence of 1,3-dipoles to produce [3 + 2]-cycloaddition products in generally high yields and diastereocontrol.⁸ The propensity of stable cyclopropenes to undergo [4 + 2]-cycloaddition reactions is well known,⁹ but these transformations have been limited to cyclopropenes that do not undergo the ene reaction. This manuscript reports how previously inaccessible cyclopropene intermediates from diverse vinyl-diazoacetates can be conveniently generated photolytically to undergo [4 + 2]-cycloaddition reactions with α -halohydrazone, cyclopentadiene, and furan for the synthesis of heterocyclic and bicyclic compounds (Scheme 1B). Furthermore, the cycloaddition products formed from oximidovinyl-diazoacetates undergo convenient copper(II) acetate catalyzed oxidative conversion to nitriles that, in some cases, is accompanied with highly structural isomerization under mild thermal conditions.

Results and discussion

Initially, α -halohydrazone **2a**, which is the precursor of azoalkenes in base-catalyzed reactions,¹⁰ was selected as the model substrate to investigate the viability of its reaction with vinyl-diazoacetate **1a**.¹¹ Tetrahydropyridazines, as an important class of six-membered heterocycles, are widely found in many natural products and pharmaceutically active compounds;¹² but there has only been one report of the synthesis of bicyclo[4.1.0]

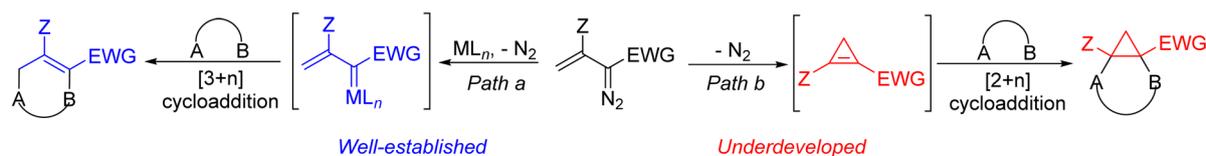
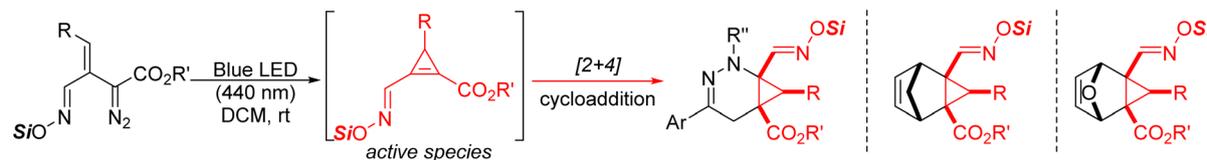
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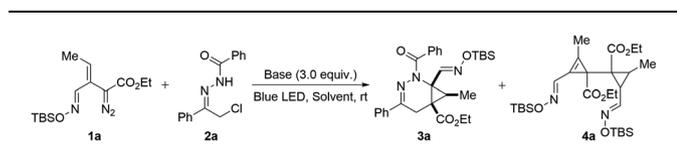
† Electronic supplementary information (ESI) available. CCDC 2346068 and 2346069. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4sc03558e>



A) Transformations of vinyl diazo compounds: cycloaddition via metal carbene or cyclopropene

B) **This work:** [2+4]-cycloaddition reaction of vinyl diazo compounds via cyclopropene with light irradiation

Scheme 1 Catalytic transformations of vinyl diazo compounds.

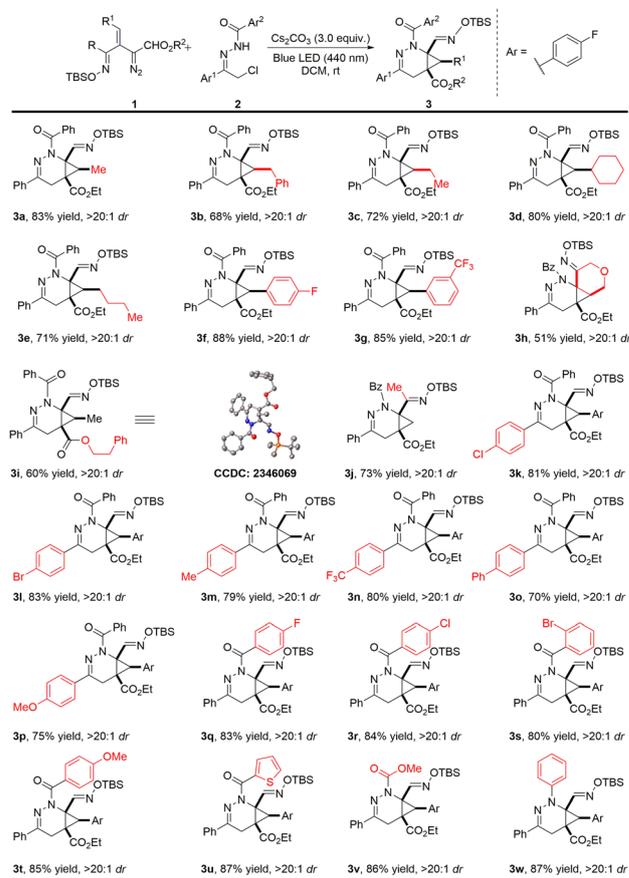
Table 1 Optimization of the reaction conditions^a

Entry	Solvent	Base	$h\nu$ [nm]	3a/4a yields ^b [%]
1	DCM	Cs ₂ CO ₃	440	67/25
2	THF	Cs ₂ CO ₃	440	<5/86
3	Toluene	Cs ₂ CO ₃	440	15/74
4 ^c	DCM	Cs ₂ CO ₃	440	83/10
5 ^c	DCM	K ₂ CO ₃	440	79/12
6 ^c	DCM	Cs ₂ CO ₃	467	40/50
7 ^c	DCM	Cs ₂ CO ₃	400	70/22

^a Unless otherwise noted, the reaction was carried out on a 0.1 mmol scale: **2a** (23.6 mg, 0.15 mmol, 1.5 equiv.), base (0.3 mmol, 3.0 equiv.) in 1.0 mL solvent and stirred over 2 h at room temperature, then **1a** (31.1 mg, 0.1 mmol) in 1.0 mL solvent was added to the solution *via* a syringe pump over 2.0 h with irradiation by 440 nm blue LED. ^b Isolated yields of **3a** and **4a**. ^c **1a** in 1.0 mL solvent was added to the solution *via* a syringe pump over 3.0 h.

tetrahydropyridazines, which occurred with crotonate-derived sulfur ylides and offered only monosubstitution on the cyclopropane ring.¹³ Generally, the intermolecular [4 + 2] reaction between 1,2-diazo-1,3-dienes and alkenes is one of the most effective and economic approaches for the synthesis of tetrahydropyridazines.¹⁴ Thus, we anticipated that mild base would convert **2a** to its azoalkene species, which could then undergo cycloaddition to the active cyclopropene generated *in situ* from oximido vinyl diazo acetates **1a** with light irradiation. A variety of common solvents were employed using Cs₂CO₃ as the base with blue LED light sources (40 W) (Table 1). Interestingly, the desired [4 + 2]-cycloaddition product **3a** was obtained in 67% yield with DCM as the solvent (Table 1, entry 1), while the use of THF and toluene mainly gave the Alder-ene dimer **4a** of the cyclopropene (Table 1, entries 2 and 3). Fortunately, reducing the addition rate of vinyl diazo compound **1a** lessened the competing ene reaction and provided better results with an

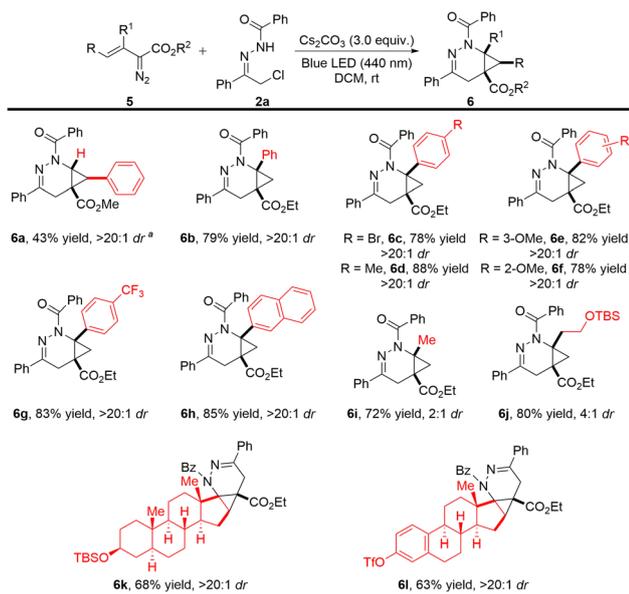
isolated yield for **3a** of 83% (Table 1, entry 4). Attempts to optimize the yield of **3a** by varying the base and using a different wave length of blue light were unsuccessful (Table 1, entries 5–7).



Scheme 2 Photoinduced [4 + 2]-cycloaddition of diverse oximido vinyl diazo esters with α -halohydrazone. Reaction conditions: **2** (0.15 mmol, 1.5 equiv.), Cs₂CO₃ (0.3 mmol, 3.0 equiv.) in 1.0 mL DCM and stirred over 2 h at room temperature, then **1** (0.1 mmol) in 1.0 mL DCM was added to the solution *via* a syringe pump over 3.0 h with irradiation by 440 nm blue LED. Isolated yields are given.



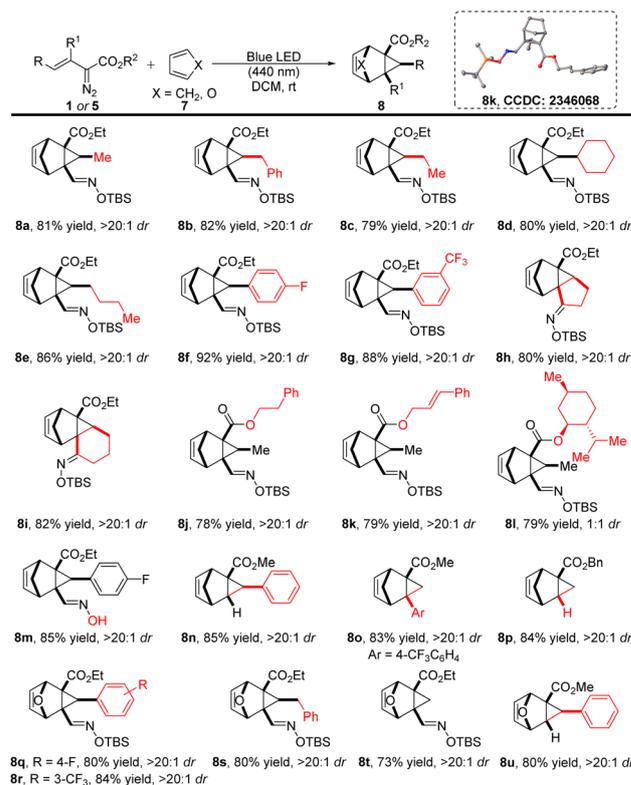
With the optimal reaction conditions established, the substrate scope with respect to the oximidovinylidiazooacetate was first investigated (Scheme 2). Various alkyl substitutions at the β -position of oximidovinylidiazoo compounds **1** were all well tolerated, delivering the bicyclo[4.1.0]tetrahydropyridazine products **3a–3e** in 68–83% yields with high diastereoselectivity ($>20:1$ dr). Moreover, these reactions proceeded smoothly with fluoro and trifluoromethyl substituents on the aryl ring of oximidovinylidiazoo compounds (**3f–3g**). The reaction could also be applied to a cyclic vinylidiazooacetate derivative and a phenethyl ester analogue with excellent dr values, although some deterioration in product yield was observed (**3h–3i**, 51–60% yields). Notably, the methyloximidovinylidiazoo compound **1j** also performed well under optimal conditions, furnishing the corresponding product **3j** in 73% yield with $>20:1$ dr. The impact of aryl group substitution in α -halohydrazone **2** was then evaluated. The electronic effect of the substituents at the *para*-position on the Ar¹ had little influence on the reaction outcomes, generating **3k–3p** in 70–83% yields with $>20:1$ dr. In addition, the effect of the substituents on the Ar² group was also investigated. For Ar² with electron-withdrawing or electron-donating groups at the *para*-position and with the 1-thienyl substituent (**3q–3u**) product yields were at least 80% with $>20:1$ dr. It is worth mentioning that the *N*-carboxylate and *N*-phenyl derived α -halohydrazone also underwent the reaction smoothly, leading to the products **3v–3w** in high yields and diastereocontrol. The structure of product **3i** was confirmed by single-crystal X-ray diffraction analysis, and other products were assigned by analogy.



Scheme 3 Photoinduced [4 + 2]-cycloaddition of 3-substituted vinylidiazoo compounds with α -halohydrazone. Reaction conditions: **2a** (23.6 mg, 0.15 mmol, 1.5 equiv.), Cs₂CO₃ (0.3 mmol, 3.0 equiv.) in 1.0 mL DCM and stirred over 2 h at room temperature, then **5** (0.1 mmol) in 1.0 mL DCM was added to the solution via a syringe pump over 3.0 h with irradiation by 440 nm blue LED. ^a Methyl 3-phenyl-1*H*-pyrazole-5-carboxylate was obtained in 40% yield. Isolated yields are given.

Encouraged by the above promising results, we further investigated the reaction scope by employing other types of vinylidiazoo compounds beyond oximidovinylidiazooacetates (Scheme 3). In the case of methyl styryldiazooacetate, the cycloaddition product **6a** was obtained under the established conditions with a high dr value in moderate yield due to competitive intramolecular pyrazole formation (40% yield).¹⁵ By contrast, cycloaddition occurred smoothly with β -arylvinyldiazoo compounds having different substituents on the aryl ring, producing **6b–6g** in high yields with $>20:1$ dr without competing pyrazole formation. In addition, β -alkylvinyldiazoo compounds gave the corresponding heterocyclic products **6i** and **6j** in good yields, but with low diastereocontrol (**6i** and **6j** in 2:1 and 4:1 dr, respectively). Surprisingly, vinylidiazoo compounds (**5k** and **5l**) derived from natural products epianthrosterone and estrone were also suitable, generating cycloaddition products **6k** and **6l** smoothly and selectively as signal enantiomers in synthetically useful yields.

Considering that cyclopentadiene and furan are relatively reactive C₄ synthons that are well known to undergo [4 + 2]-cycloaddition reactions with various dipoles to form diverse bicyclic compounds,¹⁶ we turned our attention to use cyclopentadiene and furan as carbon synthons for cycloaddition with *in situ* generated unstable cyclopropanes. As anticipated, under photolysis with blue light, in the presence of cyclopentadiene



Scheme 4 Photoinduced [4 + 2]-cycloaddition of vinylidiazoo compounds with cyclopentadiene and furan. Reaction conditions: **1** (0.1 mmol) in 1.0 mL DCM was added to the solution of **7** (0.15 mmol, 1.5 equiv.) in 1.0 mL DCM via a syringe pump over 3.0 h with irradiation by 440 nm blue LED. Isolated yields are given.



and furan (7), the cyclopropene intermediate undergoes rapid [4 + 2]-cycloaddition effectively using only a 50% molar excess of 7 (Scheme 4). Oximidovinylidiazacetates with various substitutions, including alkyl (**1a–1e**), aryl (**1f–1g**), cyclic (**1h–1i**), and ester (**1j–1l**) groups, all reacted with cyclopentadiene smoothly to form corresponding bicyclic products in high yields and diastereoselectivities. Use of the unprotected oximidovinylidiazacetate also gave the desired product **8m** in 85% yield with >20 : 1 dr. Notably, comparably high yields were obtained in the cases of methyl styryldiazoacetate, 3-aryl-2-diazo-3-butenolate, and unsubstituted benzyl 2-diazo-3-butenolate (**8n–8p**). Furthermore, the reaction proceeded smoothly with furan as the C4 synthon, delivering the cycloaddition products **8q–8u** in good yields and diastereoselectivities. The structure of these generated bicyclic products was confirmed by single-crystal X-ray diffraction analysis of compound **8k**.

To demonstrate the synthetic utility of the current method, further transformations with these generated products were conducted (Scheme 5). Epoxidation of **8n** with *m*-CPBA in DCM produced **9** as a single isomer in 88% yield (Scheme 5a). Notably, the oximido functional group was conveniently converted to nitriles with catalysis by copper(II) acetate,¹⁷ and corresponding products **10f** and **10q** were obtained in 70% and 72% yields, respectively (Scheme 5b), while with **8a**, **8f**, **8g** and **8j** this functional group transformation was accompanied by valence isomerization to tetracyclic derivatives **11** in 79–82% yields (Scheme 5c). In a control experiment without copper(II) acetate under the same conditions, the reactant was recovered

unchanged. Related to the conversion of norbornadiene to quadricyclane,¹⁸ this homologous vinylcyclopropane rearrangement is rare but has been reported to occur at temperatures as low as 80 °C with a nickel catalyst, suggesting a free radical process.¹⁹

Conclusions

In summary, we have developed a photoinduced selective [4 + 2]-cycloaddition of vinylidiazacetates with azoalkenes from α -halohydrazone, cyclopentadiene, and furan that provides an expeditious synthesis of highly functionalized bicyclo[4.1.0]tetrahydropyridazines and tricyclic compounds in good to high yields with excellent diastereoselectivity at room temperature. The reactive cyclopropene generated selectively from vinylidiazacetates by blue-light photolysis is the key intermediate in this cycloaddition transformation. This [4 + 2]-cycloaddition features high chemoselectivity and diastereocontrol, good functional group tolerance, and excellent scalability. Further functionalization adds additional value, including catalytic dehydration of the oximido group that can occur with structural isomerization.

Data availability

Further experimental details, synthetic procedures, characterization data, copies of NMR spectra and X-ray crystallographic data are available in the ESI.†

Author contributions

MB carried out the experiments. MB and ARRB prepared the starting material. HA performed the X-ray crystallography studies. MPD and MB conceived the project, wrote the manuscript, and co-wrote the ESI.†

Conflicts of interest

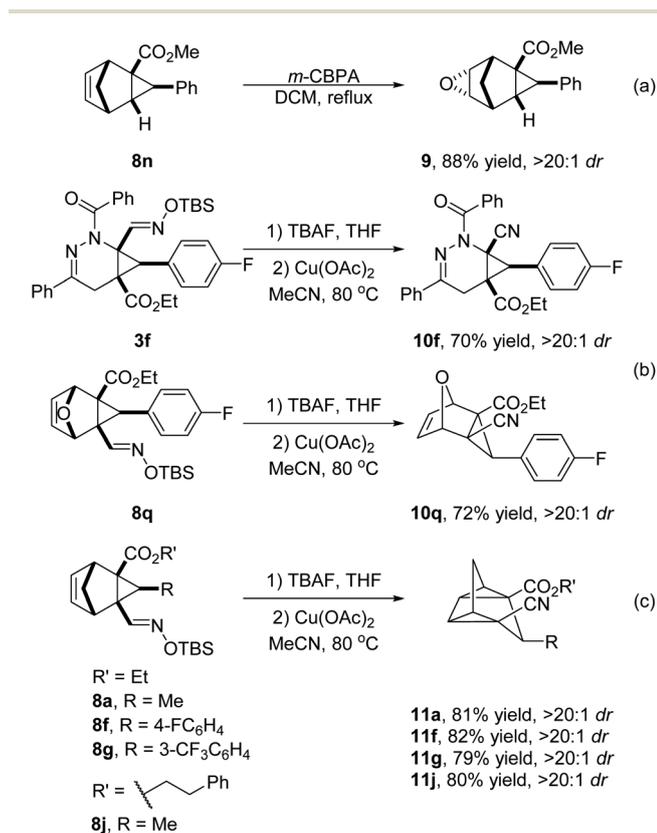
There are no conflicts to declare.

Acknowledgements

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Scheme 5 Synthetic transformations.



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