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 β - and Z-selective metal-free cyanation of ynamides: a direct approach to piperidines fused to arenes

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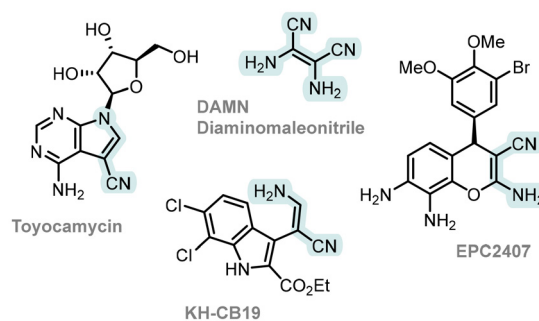
Metal-free β - and Z-selective hydrocyanation of terminal ynamides using TMS-CN and TBAF is described. The transformation proceeds with excellent regio- and stereoselectivity, delivering exclusively Z-configured tertiary enamides. Treatment with TMSOTf promotes clean Z to E isomerization. Simultaneous activation of the nitrile moiety by TMSOTf in the presence of an internal nucleophile induces intramolecular cyclization, yielding piperidine frameworks. The reaction accommodates a range of nucleophiles, enabling the synthesis of structurally diverse and previously inaccessible heterocyclic scaffolds.

Introduction

Acrylonitriles are privileged intermediates in synthetic chemistry, finding widespread applications in pharmaceuticals, agrochemicals, and materials science.¹ Among them, aminoacrylonitriles serve as versatile building blocks for the synthesis of heterocycles.² In particular, β -cyanoenamides exhibit a characteristic “push-pull” electronic nature, where the amino group acts as an electron donor and the cyano group as an acceptor on adjacent carbons.³ A representative example is diaminomaleonitrile (DAMN), a key substance for the prebiotic synthesis of nucleobases and is increasingly employed in industrial applications.⁴ Beyond DAMN, β -enamionitriles are key intermediates in polymer chemistry, for instance, in thermally robust polyenaminonitriles⁵ and serve as essential precursors to numerous bioactive natural products and pharmaceuticals, including the antibiotic toyocamycin,⁶ the selective kinase inhibitor KH-CB19,⁷ and the anticancer agent grobulin (EPC2407) (Chart 1).⁸

In recent years, ynamides have emerged as powerful synthetic platforms due to the distinctive polarization of their triple bond, enabling the efficient construction of complex molecular frameworks.⁹ Carbon-centered nucleophiles typically add to ynamides at the α -position upon activation of the ynamide.¹⁰ In contrast, heteroatom nucleophiles such as indoles¹¹ or phosphines¹² have been reported to undergo a more unusual β -addition, enabled by delocalization of the

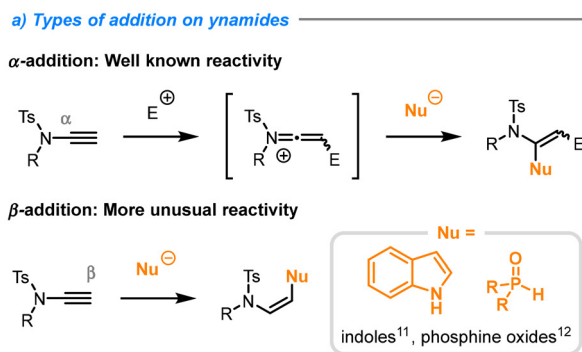
nitrogen lone pair into the electron-withdrawing group (Scheme 1a). However, β -hydrocyanation of ynamides has not been reported to date and remains underexplored. Donnard *et al.* reported a palladium-catalyzed silylcyanation, where β -substituents dictated the stereoselectivity but required elevated temperatures.¹³ They subsequently developed a zinc-catalyzed hydrocyanation with improved functional-group tolerance.¹⁴ More recently, Sun *et al.* disclosed a silylium-ion-catalyzed heterodifunctionalization of ynamides with broad substrate compatibility (Scheme 1b).¹⁵ However, these methods have been limited to the formation of α -cyanoenamides with a preferred E-stereoselectivity, and no examples of β -cyanoenamide synthesis have been reported to date. Herein, we describe a mild, metal-free hydrocyanation of ynamides that delivers Z- β -cyanoenamides exclusively. We also demonstrate that β -cyanoenamides serve as ideal platforms for the construction of various piperidines fused to arenes (Scheme 1c).

**Chart 1** Representative bioactive molecules containing the β -cyanoenamide motif.

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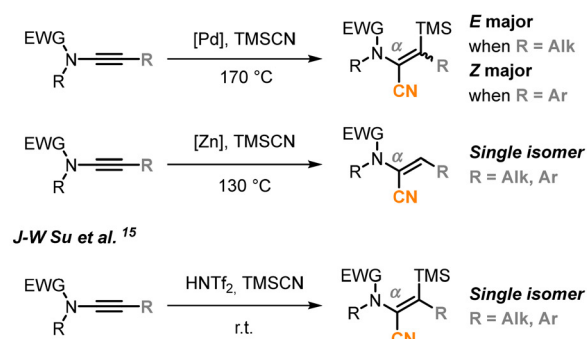
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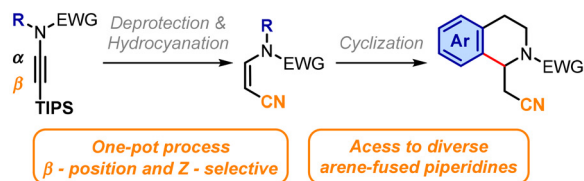


b) State of the art: Cyanation of ynamides

M. Donnard *et al.*^{13,14}



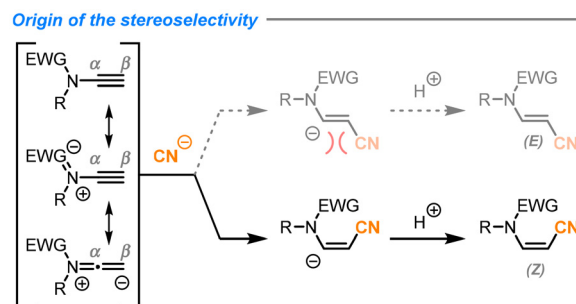
c) This work



Scheme 1 Types of ynamide addition and cyanation reactions.

Results and discussion

During the study of the reactivity of activated *N*-allenamides, we demonstrated that (trimethylsilyl cyanide) TMSCN in the presence of (tetra-*n*-butylammonium fluoride) TBAF led to enamido-nitriles regio- and stereoselectively.¹⁶ Inspired by this result, our aim was to evaluate the hydrocyanation of ynamides. When we treated ynamide **1a** with a mixture of TMSCN and TBAF, *Z*- β -cyanoenamide **2a** was obtained regio- and stereoselectively. X-ray analysis confirmed the structure of the *Z*-configured alkene **2a** obtained (CCDC 2499446).¹⁷ A *trans*-selective β -addition of cyanide to the ynamide was observed, overriding the classical α -addition predicted by the intrinsic polarization of the ynamide. A plausible reaction mechanism is proposed to rationalize the β -cyanation of ynamides (Scheme 2). Ynamides can be described by two resonance forms allowing nucleophilic attack at either the α - or β -position. However, previous calculations (Dodd *et al.*)¹¹ revealed a polarized LUMO in terminal ynamides with a significant orbital coefficient at the β -carbon, rendering this posi-



Scheme 2 Plausible mechanism for ynamide β -cyanation.

tion electrophilic. Likewise, an approach of the cyanide anion may induce π -electron redistribution toward C_{α} , generating a nascent α -carbanion and lowering electron density at C_{β} , thereby enabling nucleophilic attack at C_{β} . coulombic repulsion between the emerging lone pair at C_{α} and the CN substituent favors a *trans* relationship, accounting for the exclusive formation of the *Z*-isomer. At the outset, ynamide **1a** was selected as the model substrate to optimize the formation of the corresponding β -cyanoenamides. Screening various fluoride sources revealed that any deviation from the standard conditions was detrimental to the transformation. Specifically, the use of potassium fluoride (KF), KF in combination with crown ether and cesium fluoride (CsF) resulted in no detectable product formation (Table 1, entries 2–4). Similarly, replacing the ammonium counterpart with Tetrabutylammonium bromide (TBAB) failed to promote the reaction (Table 1, entry 5). Subsequent efforts focused on varying the cyanide source. Although potassium cyanide (KCN) proved competent, the reaction proceeded with marked erosion of stereoselectivity (Table 1, entry 6). Without TBAF, the starting material was recovered (Table 1, entry 7). Likewise, replacing TBAF with cesium carbonate (Table 1, entry 8) led to the same result.

Table 1 Optimization of the reaction conditions^a

Entry	R=	Additives	Yield ^b (%)
1	H	TBAF	66
2	H	KF	0
3	H	KF, 18-Crown-6	0
4	H	CsF	0
5	H	TBAB	0
6 ^c	H	TBAF	55 (<i>Z/E</i> 86 : 14)
7	H	—	0
8	H	Cs ₂ CO ₃	0
9 ^d	H	TBAF (0.2 equiv.)	38
10 ^d	TIPS	TBAF	92

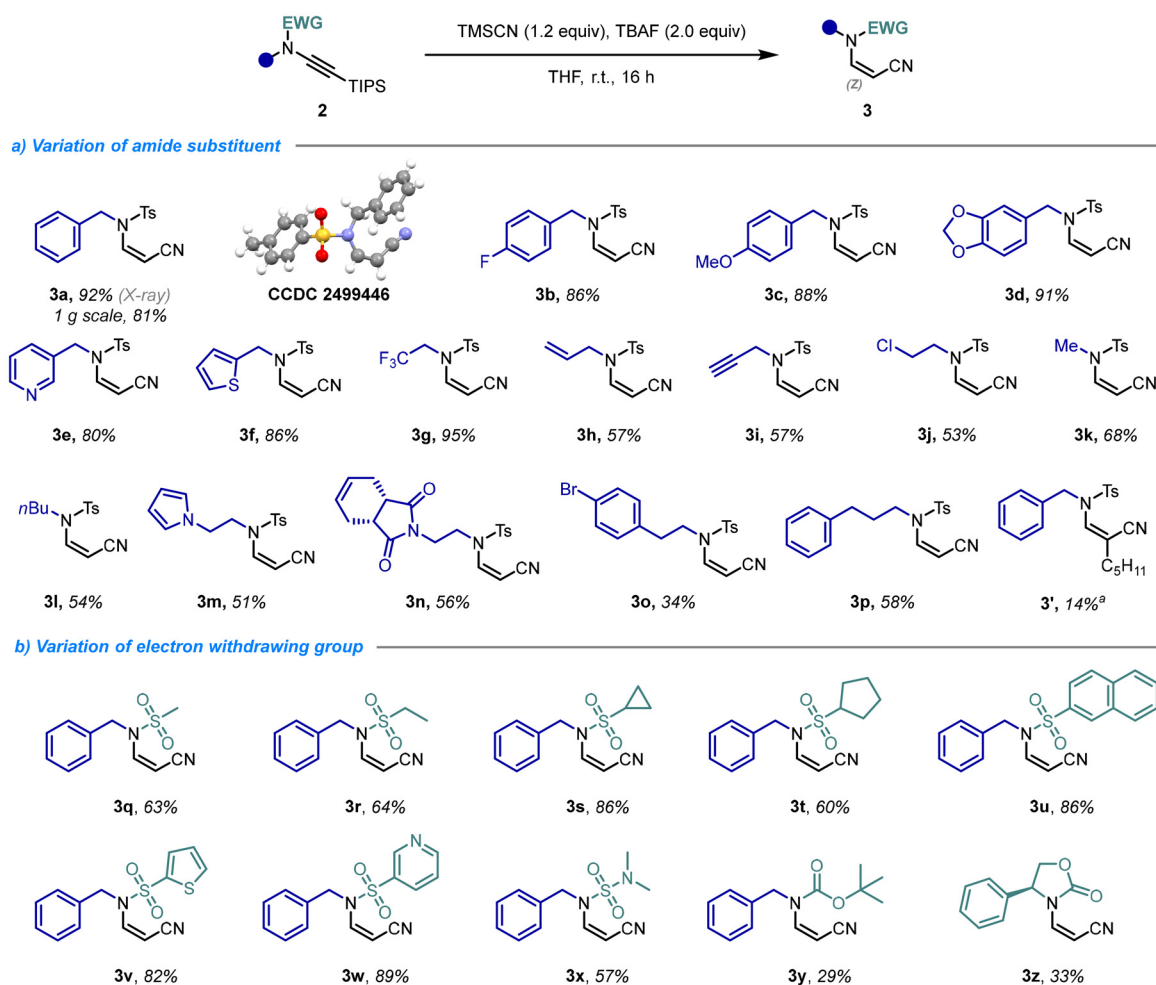
^a General reaction conditions: **1a** or **2a** (0.1 mmol), TMSCN (0.12 mmol), additive (2 equiv.), THF (0.1 M). ^b Isolated yields. ^c KCN was used instead of TMSCN. ^d Reaction time was 16 h.



When treating **2a** in the presence of a catalytic amount of TBAF, the β -cyanoamide **3a** was obtained, albeit in a modest 38% yield (Table 1, entry 9). Alternatively, when employing directly the (TIPS)-substituted ynamide, the optimal conditions were identified. The combination of 1.2 equivalents of TMSCN and 2.0 equivalents of TBAF exclusively delivered the desired *Z*-configured β -cyanoamide **3a** in 92% isolated yield with complete stereoselectivity (Table 1, entry 10). TBAF serves a dual role by promoting *in situ* TIPS deprotection and fluoride-promoted cyanide release from TMSCN. The one-pot process avoids isolation of the unstable terminal ynamide affording the β -cyanoamide in improved yield.

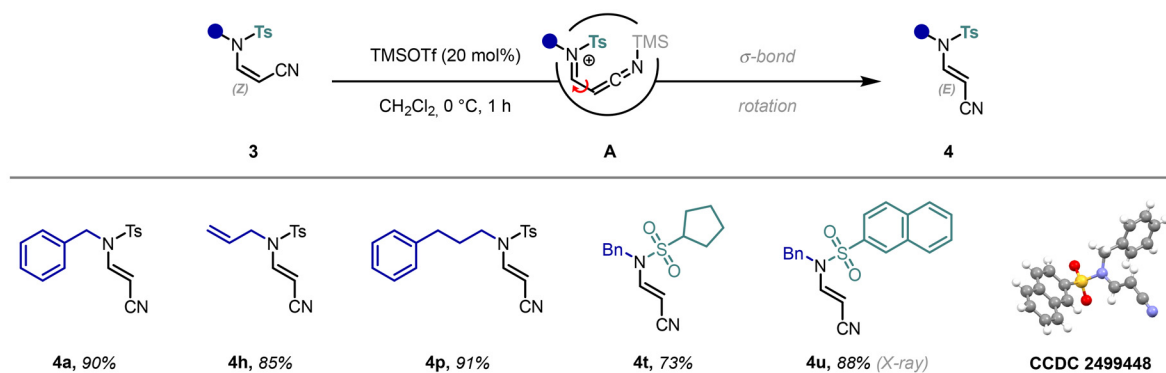
With the optimized reaction conditions established, we next examined the substrate scope (Scheme 3). A broad range of benzyl derivatives bearing electron-withdrawing (**3b**) or electron-donating substituents (**3c**), as well as heteroaryl groups (**3d–3f**), were well tolerated. Linear alkyl substrates (**3g–3l**) also proved compatible. Importantly, the reaction proceeded efficiently in the presence of various functionalized side chains (**3m–3p**). Although β -cyanation also occurs with

internal ynamides (**3'**), the yield is significantly reduced, while the *Z* stereochemistry is preserved. Modification of the electron-withdrawing group on the nitrogen atom delivered the products in good yields. Notably, various sulfonyl derivatives (**3q–3w**) could be adapted, but also sulfamoyl derivatives (**3x**), as well as carbamates (**3y**) and Evans's chiral auxiliary (**3z**) were compatible, albeit the yields were lower. We then investigated whether it was possible to achieve a selective isomerization of the electron-deficient enamides with a Lewis acid. Interestingly, only silylating agents promoted this transformation, and the reaction proceeded with complete stereoselectivity affording exclusively the *E*-isomer (optimization details are provided in Table S1 in the SI). We propose that the trimethylsilyl (TMS) group activates the cyano moiety toward a ketene imine intermediate **A**,¹⁸ favoring formation of the thermodynamically preferred *E*-configured amidoacrylonitrile **4a**. We next explored the scope of this stereoselective isomerization (Scheme 4). Various functionalized side chains (**4h**, **4p**) on the nitrogen atom and different electron-withdrawing substituents (**4t**, **4u**) were compatible, affording the desired pro-

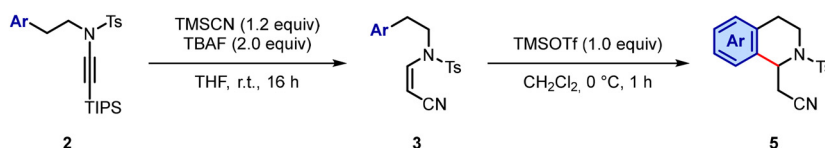


Scheme 3 Substrate scope for one pot deprotection and β -cyanation of ynamide. Reaction conditions **2** (0.1 mmol), TMSCN (0.12 mmol), TBAF (0.2 mmol), THF (0.1 M). Isolated yields. ^aReaction was performed at 60 °C.

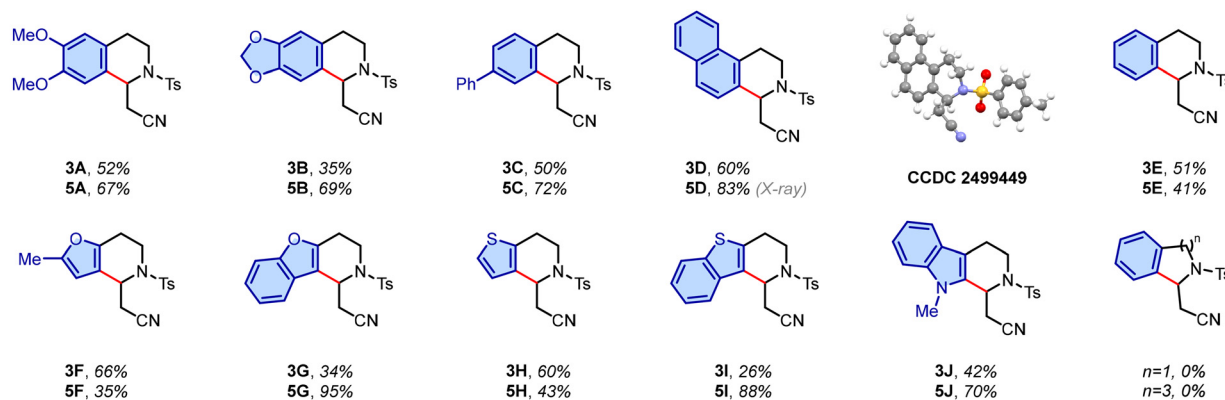




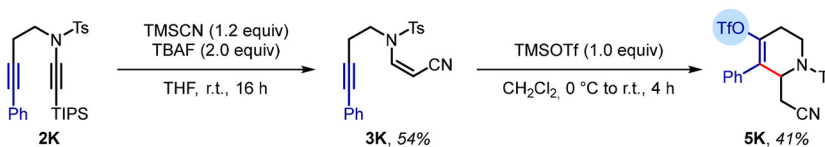
Scheme 4 Substrate scope for isomerization of β -cyanoenamides. Reaction conditions **3** (0.1 mmol), TMSOTf (0.02 mmol), CH_2Cl_2 (0.1 M). Isolated yields.



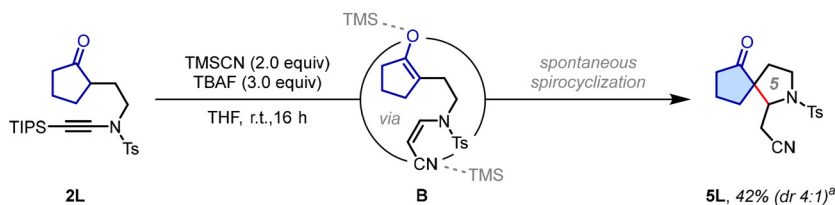
a) Substrate scope for arene-fused piperidines



b) Extension to alkynes - addition of triflate



c) Domino reaction - spirocyclization



Scheme 5 Substrate scope for TMS-activation of CN and cyclization. Reaction conditions for cyanation: **2** (0.3 mmol), TMSCN (0.36 mmol), TBAF (0.6 mmol), THF (0.1 M). Isolated yields. For cyclizations: **3** (0.1 mmol), TMSOTf (0.1 mmol), CH_2Cl_2 (0.1 M). Isolated yields. ^aObtained as 2 separable diastereoisomers.



ducts in good yields. The *E*-configuration of alkene **4a** was unambiguously confirmed by single-crystal X-ray diffraction (CCDC 24499448).¹⁹ Leveraging the CN-TMS activation, we questioned whether an internal nucleophile could trigger intramolecular cyclization, granting access to heterocyclic frameworks. In particular, we envisioned that electrophilic aromatic substitution ($S_{\text{E}}\text{Ar}$) might enable direct access to tetrahydroisoquinolines, a class of privileged and synthetically challenging scaffolds that are ubiquitous in bioactive natural products and central to modern drug design.²⁰

Gratifyingly, treatment of the 3,4-dimethoxyphenyl derivative **3A** with TMSOTf delivered the corresponding tetrahydroisoquinoline **5A** in 67% yield. The transformation proved to be notably general, tolerating biphenyl (**3C**) and naphthalene-based substrates (**3D**). The structure of the naphthalene-fused piperidine **5D** was unambiguously confirmed by X-ray crystallographic analysis (CCDC 2499449).²¹ Importantly, even substrates bearing an unsubstituted arene exhibited sufficient nucleophilicity to undergo cyclization, affording tetrahydroisoquinoline **5E**. Furthermore, a range of heteroaryl substrates successfully participated in the reaction to furnish products **5F–5I**, thereby significantly expanding the chemical space accessible through this methodology. Amongst them, thiophene-derivatives **5H** and **5I** display a tetrahydrothienopyridine scaffold, a heterocyclic motif highly prevalent in nature.²² Compounds **5E**, **5F**, **5H** were obtained in lower yields compared to their more electron rich congeners (**5D**, **5G**, **5I**), consistent with decreased nucleophilicity of the arene moiety which makes the attack on the iminium ion more difficult.

Encouraged by these results, we next explored alternative nucleophiles, including Pictet–Spengler-type substrates. Remarkably, exposure of indole derivative **3J** to TMSOTf directly furnished the corresponding tetrahydro- β -carboline **5J**. Tetrahydro- β -carbolines (THBCs) constitute a prominent family of indole alkaloids widely distributed in nature and are known to display a broad range of pharmacological activities, making them highly attractive scaffolds for drug discovery and medicinal chemistry.²³ In contrast, substrates featuring either a one-carbon or three-carbon linker between the tosylsulfonamide and the arene underwent exclusive isomerization to **4a** and **4p**, underscoring the importance of tether length for productive cyclization (Scheme 5a). Beyond aromatic nucleophiles, the methodology also proved compatible with alkynes, enabling efficient access to piperidine frameworks. Piperidines rank among the most prevalent nitrogen heterocycles in small-molecule drugs, reflecting their exceptional importance in medicinal chemistry and pharmaceutical development.²⁴ In this transformation, the triflate anion adds to the alkyne, generating a vinylic anion that subsequently undergoes nucleophilic addition to the TMS-activated acrylonitrile **3K**. This cascade affords piperidine **5K** bearing a vinyl triflate moiety, which constitutes a highly versatile functional handle for downstream diversification *via* cross-coupling or other late-stage functionalization strategies (Scheme 5b).

Finally, ketone substrates **2L** bearing an ynamide tether were successfully activated using a TMSCN/TBAF combination

to deliver spiro-tosyl pyrrolidines **5L** featuring a nitrile-substituted side chain. In this domino process, TBAF plays a critical role, mediating TIPS deprotection of the ynamide, generating cyanide anions, and promoting formation of the silyl enol ether nucleophile **B**, which initiates spirocyclization (Scheme 5c).

Conclusions

In summary, we have developed a regio- and stereoselective hydrocyanation of ynamides, the CN-moiety being exclusively installed at the β -position to the nitrogen atom, to afford *Z*-configured cyanoenamides. These β -cyanoenamides could be efficiently isomerized to the corresponding *E*-isomers *via* treatment with TMSOTf. Extension to a broad range of nucleophiles, including indoles, alkynes, and enols, underscored the versatility of this strategy, demonstrating excellent functional group tolerance and enabling significant expansion of chemical space through efficient access to tetrahydroisoquinolines, tetrahydro- β -carbolines, piperidines, and spirocyclic heterocycles.

Author contributions

All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: all experimental data and detailed procedures, including computational details. See DOI: <https://doi.org/10.1039/d6qo00022c>.

CCDC 2499446 (**3a**), 2499448 (**4u**) and 2499449 (**5D**) contain the supplementary crystallographic data for this paper.^{17,19,21}

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