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Diastereoselectively Complementary C−H Functionalization Enables Access to Structurally and Stereochemically Diverse 2,6-Substituted Piperidines

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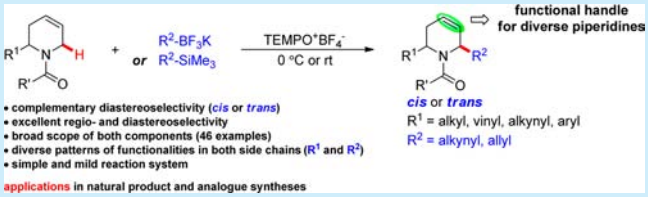
Supporting Information

ABSTRACT: The preparation of 2,6-substituted piperidine derivatives through diastereoselective C−H functionalization of corresponding nitrogen heterocycles represents an appealing protocol and yet remains a formidable challenge. Here, we describe a stereochemically complementary oxidative C−H functionalization of *N*-carbamoyl tetrahydropyridines with a wide variety of building blocks, providing either the *cis*- or *trans*-2,6-substituted piperidines with diverse patterns of functionalities. The mild metal-free process exhibits excellent regio- and diastereoselectivities as well as functional group tolerance. The synthetic utilities in natural product and analogue syntheses are also described.



Cis- or *trans*-2,6-substituted tetrahydropyridines and piperidines are key units spread across numerous bioactive natural products and synthetic pharmaceuticals.[1] Their prevalent syntheses mainly focus on the diastereoselective heterocycle construction strategy that relies on functional group transformations.[2] On the other hand, the method through the direct stereocontrolled C−H functionalization of easily accessible α-substituted piperidine derivatives represents a more economical and topologically obvious alternative.[3] Important progress has been achieved in the diastereoselective C−H functionalization of α-substituted piperidines through the α-amino anion and C−H activation pathways.[4,5] However, the former always requires more than a stoichiometric amount of strongly basic organolithium reagents, and the latter often suffers from modest stereocontrol, extra efforts to remove heterocyclic directing groups, limited functionality (aryl group) introduced into the α-position, and the prerequisite metal catalyst. Moreover, both approaches always provide *trans*-2,6-substituted products as the major isomer, with no direct access to the *cis*-isomer.

Metal-free oxidative C−H functionalization of nitrogen heterocycles through an α-amino cation pathway is an attractive alternative.[6] However, the overwhelming majority of these studies have focused on cyclic and benzylic amines, especially on *N*-arylated tetrahydroisoquinolines, and thus, the intermolecular diastereoselective approach has been rarely established.[7] To our knowledge, the diastereoselective bimolecular oxidative C−H functionalization of simplified carbamates has never been established to date. Therefore, identifying a practical, predictable, and stereochemically complementary C−H functionalization method to rapidly prepare structurally and stereochemically diverse 2,6-substituted piperidine derivatives is highly desirable.

We envisioned that the direct oxidative C−H functionalization of *N*-acyltetrahydropyridines would be an attractive solution for the objective because the alkene moiety would act not only as an activating group for the oxidative C−H cleavage but also as an outstanding functional handle for structurally diverse piperidines. As part of our ongoing interest in developing a practical synthetic method through oxidative C−H functionalization strategy,[7f] we now report the first stereochemically complementary intermolecular C−H functionalization of *N*-carbamoyl tetrahydropyridines with a wide variety of building blocks, providing either *cis*- or *trans*-2,6-substituted piperidine derivatives with excellent diastereocontrol.

Initially, the alkynylation of tetrahydropyridine **1a** with potassium trifluoroborate **2a** was chosen as the model reaction for optimization (Table 1). No expected **3a** was observed when common oxidants including DDQ, TBHP, Ph_3CBF_4, and $PhI(OAc)_2$ were used (entry 1, Table 1). Gratifyingly, $TEMPO^+OTf^-$ (TEMPO oxoammonium trifluoromethanesulfonate) can promote the reaction, giving the 2,6-substituted **3a** in 50% yield with a *cis*/*trans* ratio of 7:1, together with the undesired bis-functionalized **3′a** in 25% yield (entry 2).[8] Subjecting **3a** to the reaction system did not give any **3′a**, indicating that **3′a** should not originate from the overoxidation of **3a**. While the potential 1,4-adduct **3″a** was not detected, we still envisioned that **3a′** might derive from the overoxidation of **3″a** because enamide **3″a** possesses lower oxidation potential than allylic amides **1a** and **3a**.[2k] Therefore, once the **3″a** was formed, it might further undergo a second C−H oxidation

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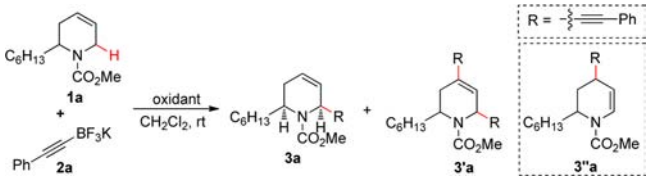
Table 1. Reaction Condition Optimization[a]



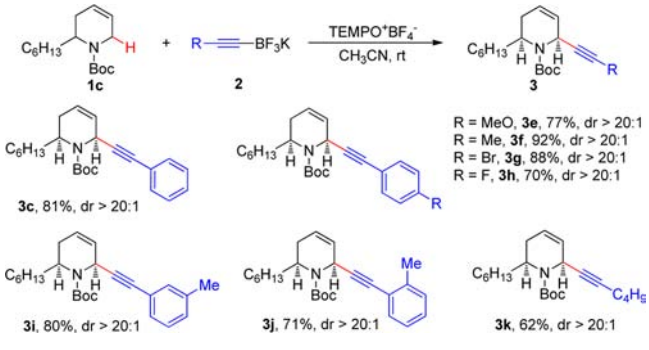
entry	oxidant	yield (%)[b] of 3a/3″a	dr[c]
1[d]	oxidant	<5	n.a.
2	$TEMPO^+OTf^-$	50/25	7:1
3	$TEMPO^+ClO_4^-$	66/12	10:1
4	$TEMPO^+BF_4^-$	76/<5	12:1
5[e]	$TEMPO^+BF_4^-$	73/13	16:1
6[f]	$TEMPO^+BF_4^-$	68/17	>20:1
7[g]	$TEMPO^+BF_4^-$	55/21	11:1
8[f,h]	**$TEMPO^+BF_4^-$**	**81/<5**	**>20:1**

[a] **1a** (0.1 mmol), **2a** (0.15 mmol), and oxidant (0.13 mmol) in CH_2Cl_2 (1.0 mL) at rt. [b] Yield of isolated product. [c] Determined by ^1H NMR spectroscopy. [d] DDQ, TBHP, Ph_3CBF_4, or $PhI(OAc)_2$ as an oxidant. [e] Cbz as the amine protecting group (**3b**). [f] Boc as the amine protecting group (**3c**). [g] SO_2Me as the protecting group (**3d**). [h] CH_3CN as the solvent.

followed by 1,2-addition to give bis-functionalized **3′a**. The counterions of the TEMPO oxoammonium salt were screened, and when $TEMPO^+BF_4^-$ was employed, the undesired 1,4-addition process was supremely suppressed, with **3a** isolated in 76% yield with a dr of 12:1 (entries 2−4).[9] Increasing the size of the amide protecting groups proved to have a beneficial effect on the dr (entries 4−7). Solvent optimization identified CH_3CN as the ideal choice in terms of the regioselectivity (entry 8).

The scope of the stereoselective C−H alkynylation was then explored (Scheme 1). A wide range of electronically varied aryl

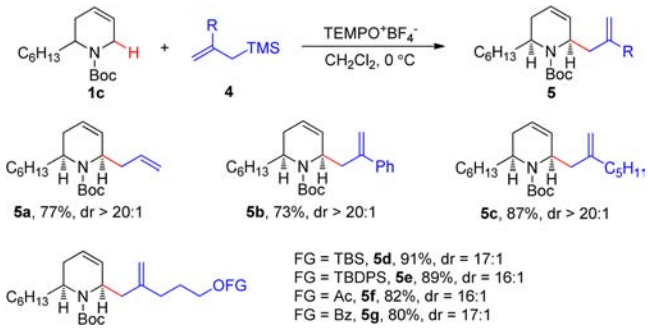
Scheme 1. Scope of C−H Alkynylation



alkynyl trifluoroborate salts with different substituent patterns participated in the stereoselective C−H alkynylation of **1c**, giving *cis*-2,6-substituted **3c−j** in good to excellent yields as a single stereoisomer. Simple alkyl-substituted alkynyl boronate **3k** was also well tolerated. Notably, such excellent *cis*-2,6-stereoselectivity has never been achieved in the existing C−H functionalization studies for piperidine derivatives.[3−5] Aryl, alkenyl, and benzyl trifluoroborates did not give any desired product.

The scope of the diastereoselective C−H allylation of **1c** with allyltrimethylsilanes **4** was then explored (Scheme 2). Simple allyltrimethylsilane **4a** together with phenyl- and alkyl-substituted **4b** and **4c** were suitable components, affording

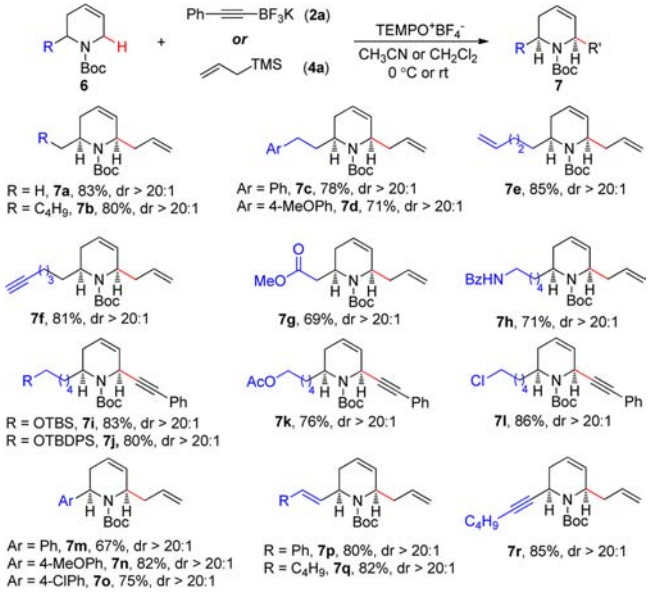
Scheme 2. Scope of C−H Allylation



cis-2,6-substituted **5a−c** as a single isomer. Common functional groups such as silyl ethers (**5d** and **5e**), acetates (**5f**), and benzoates (**5g**) were well tolerated in high stereocontrol for further manipulations. The ability to deliver diverse functionalities into the core skeleton indicates that the C−H functionalization approach should be applicable to complex molecule synthesis and library construction.

The scope of tetrahydropyridines was next explored (Scheme 3). The efficiency and dr were not sensitive to the length of the

Scheme 3. Scope of Tetrahydropyridines



alkyl side chain (**7a** and **7b**). The highly stereoselective C−H functionalization exhibited excellent compatibility with a broad range of unsaturations in the alkyl side chain, such as aryls (**7c** and **7d**), terminal alkenes (**7e**), and terminal alkynes (**7f**). The process was also well tolerated with diverse oxygen- and nitrogen-containing moieties, such as esters (**7g**), amides (**7h**), silyl ethers (**7i** and **7j**), acetates (**7k**), and halides (**7l**) as additional functional handles. The substrates with unsaturated side chains such as aryls (**7m−o**), alkenyls (**7p** and **7q**), and alkynyls (**7r**) were also well tolerated with overwhelming selectivity at the less sterically hindered secondary C−H bond.

The facile access to *cis*-2,6-substituted tetrahydropyridines prompted us to further explore the direct preparation of *trans*-isomers through the oxidative C−H functionalization method. Excitedly, the stereoselective C−H allylation and alkynylation of bicyclic tetrahydropyridine **8** went smoothly, generating

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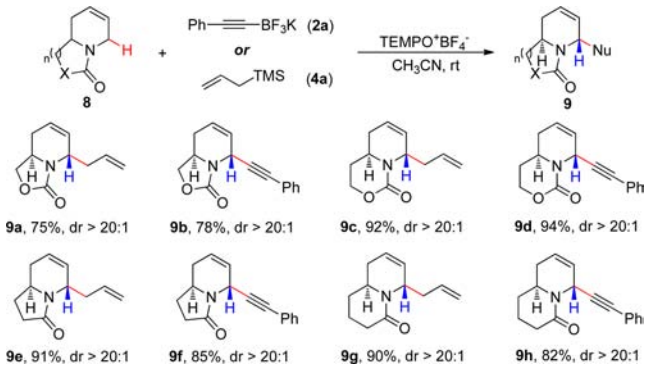
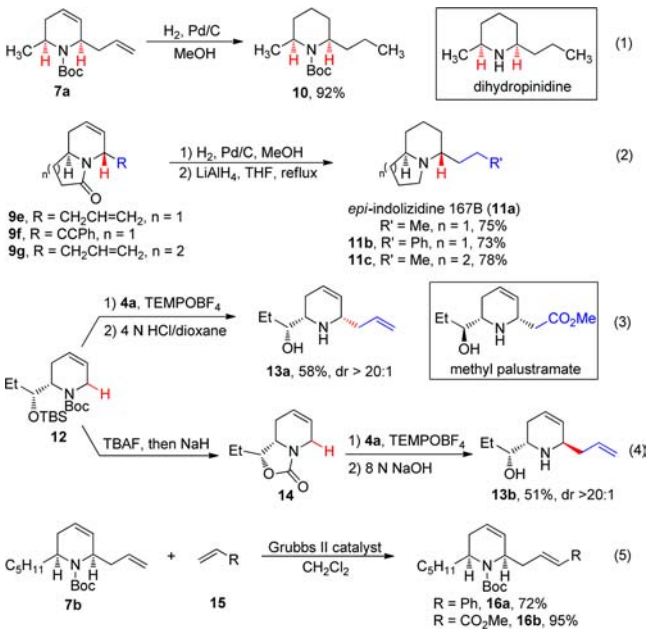
trans-2,6-substituted **9a–h** in excellent yields as a single diastereomer (Scheme 4). The completely inverted stereoselectivity will not only allow for pharmaceutically important bicyclic indolizidine- and quinolizidine-type alkaloid synthesis but also provide a route to access simple *trans*-2,6-substituted piperidine derivatives simply by cleaving the amide bond.

Scheme 4. Stereoselective Access to *Trans*-2,6-Substituted Tetrahydropyridines[a]



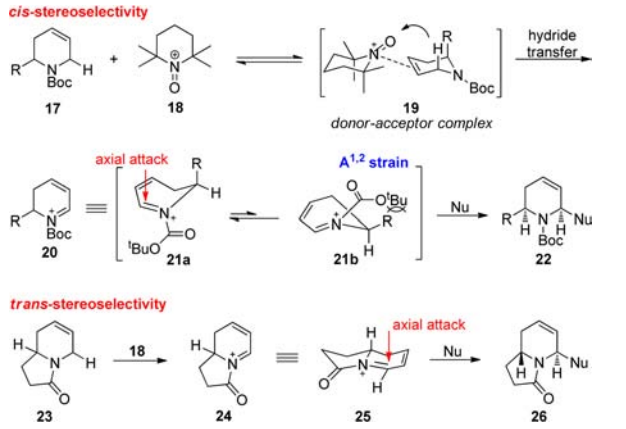
The diastereoselectively complementary C–H functionalization method can facilely provide diverse *cis*- or *trans*-2,6-substituted piperidine derivatives. For example, hydrogenation of **7a** afforded *cis*-dialkyl-substituted piperidine **10**, a known precursor for natural product dihydropinidine (Scheme 5, eq 1). *trans*-Bicyclic **9e–g** were sequentially reduced by H_2 and $LiAlH_4$, respectively, affording *epi*-indolizidine 167B (**11a**) and its analogues **11b** and **11c** as a single diastereomer (eq 2). The diastereoselectively divergent synthesis of the *cis*-analogue **13a** and *trans*-analogue **13b** of natural product methyl palustramate was also accomplished starting from a common substrate **12** in two and three steps, respectively (eqs 3 and 4). The terminal olefin in tetrahydropyridine **7b** can also act as a powerful handle for diversity-oriented synthesis, as exemplified by the efficient formation of diversely functionalized alkenes **16a** and **16b** through the cross metathesis with the unsaturation in tetrahydropyridine ring intact (eq 5).

Scheme 5. Synthetic Applications



The oxidative C–H functionalization was not affected by addition of stoichiometric radical inhibitors such as TEMPO or BHT, thus indicating that a radical process might not be involved. Such observation coincides with the mechanistic study on TEMPO oxoammonium salt mediated oxidative cleavage of benzylic ethers.[10] Therefore, we envisioned that the *N*-acyliminium **19** might be generated through a direct hydride transfer from tetrahydropyridine **17** to the oxygen of the oxoammonium salt **18**, perhaps involving prior complexation of **17** with **18** to form an electron donor–acceptor (**19**) (Scheme 6).[10,11] The excellent *cis*-selectivity observed for the C–H functionalization of simple tetrahydropyridines could be explained in the following manner. The α,β-unsaturated *N*-acyliminium **20** would exist as a flat chair (**21a**) with the R group in the pseudoaxial orientation to avoid the allylic 1,2-strain between the R group and the acyl moiety.[12] Stereoelectronically preferred axial attack of the nucleophile at C_2 of **21a** provides the observed *cis*-2,6-substituted tetrahydropyridine **22** as the major product. With respect to the bicyclic tetrahydropyridines like **23**, a completely inverted stereoselectivity was observed, which might also be ascribed to the stereoelectronically preferred axial attack to C_2 of *N*-acyliminium **24** through **25**, leading to *trans*-2,6-substituted **26** as the major isomer.

Scheme 6. Proposed Mechanism and Explanation on the Complementary Diastereoselectivity



In summary, a predictable and diastereoselectively complementary oxidative C–H functionalization of *N*-carbamoyl tetrahydropyridines with a wide assortment of components at ambient temperature has been established, stereoselectively providing either *cis*- or *trans*-2,6-substituted tetrahydropyridines and piperidines with diverse patterns of functionalities. The practical metal-free method has excellent regio- and diastereoselectivity and is well tolerated for diverse functional groups. The synthetic utilities in structurally and stereochemically diverse 2,6-substituted piperidine derivatives were also demonstrated. We envision that the practical method outlined herein will have broad applications in natural product and library synthesis for drug discovery.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental details and spectral data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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