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Enantioselective Synthesis of Dialkylated *N*-Heterocycles by Palladium-Catalyzed Allylic Alkylation

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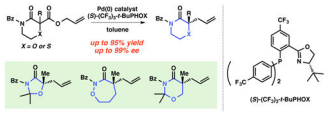
Abstract

The enantioselective synthesis of α-disubstituted *N*-heterocyclic carbonyl compounds has been accomplished using palladium-catalyzed allylic alkylation. These catalytic conditions enable access to various heterocycles, such as morpholinone, thiomorpholinone, oxazolidin-4-one, 1,2-oxazepan-3-one, 1,3-oxazinan-4-one and structurally related lactams, all bearing fully substituted α-positions. Broad functional group tolerance was explored at the α-position in the morpholinone series. We demonstrate the utility of this method by performing various transformations on our useful products to readily access a number of enantioenriched compounds.

Graphical Abstract



N,O-heterocycles such as morpholine, oxazolidine, and isoxazolidine are important pharmacophores in medicinal chemistry (figure 1).[1–11] Notable morpholine-containing pharmaceuticals include edivoxetine[2], an antidepressant and a treatment for ADHD; linezolid[5], a synthetic antibiotic; and gefitinib[4], an EGFR inhibitor used to treat certain breast, lung and other cancers. 5-Membered isoxazolidinone is the core structure of cycloserine[8], an antibiotic for the treatment of tuberculosis. Quinocarcin[7], possessing an oxazolidine ring in the 3,8-diazabicyclo[3.2.1]octane framework, has shown remarkable

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Supporting Information

Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

Notes

The authors declare no competing financial interest.

antiproliferative activity against lymphocytic leukemia. An antibiotic, FR-66979[9], isolated from *Streptomyces sandaensis* No. 6897, contains a 1,2-oxazinane moiety.

In addition to a wide variety of biological activity, *N*,*O*-heterocycles shown in Figure 2 are commonly used as synthetic intermediates, which provide various hydroxy acid moieties after acetal removal or N-O bond cleavage. Oxazolidin-4-ones have been reported as good platforms to α-hydroxyacids.[12] For example, Ye et al.[12a] reported that the formal [3+2] cycloaddition between ketenes and oxaziridines could be applied in an enantioselective fashion to synthesize oxazolidin-4-one derivatives, which could be converted into the corresponding α-hydroxy acids. 1,2-Oxazinan-3-ones have proved to be excellent precursors to γ-hydroxy acid and γ-butyrolactone derivatives.[13]

Our group has a sustained interest in the enantioselective synthesis of α-quaternary carbonyl compounds,[14 – 16] which offers a novel solution for these challenging chiral centers in natural product synthesis. Influenced by our results, the Lupton group[17a] and the Shao group[17b] simultaneously reported that carbazolones are suitable substrates under our allylic alkylation conditions and applied the resulting chiral building blocks to total syntheses of indole alkaloids. Significant work in our laboratory has identified conditions for the enantioselective allylic alkylation to provide α-quaternary lactams in exceptional yields and enantioselectivities.[14b] As part of that endeavor, we reported that 2-allyl-2-methylmorpholin-3-one **2a** was obtained in a similar manner in high yield (91% yield) and outstanding enantioselectivity (99% ee). We sought to extend the substrate scope to morpholine derivatives and postulated that a broadly expanded array of chiral *N*,*O*-heterocyles might be readily accessible using our palladium-catalyzed allylic alkylation. Herein, we describe enantioselective allylic alkylation of heterocycles, including morpholin-3-one, thiomorpholine-3-one, oxazolidin-4-one, 1,2-oxazepan-3-one and 1,3-oxazinan-4-one.[18] Furthermore, the enantioenriched products obtained were successfully converted into useful asymmetric building blocks containing quaternary and tetrasubstituted tertiary chiral centers.

We prepared a collection of racemic morpholinone substrates **1a**-**e**[19] and performed palladium-catalyzed decarboxylative allylic alkylation with $Pd_2(dba)_3$ (5 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX ligand[20] (12.5 mol %, PHOX = phosphinooxazo-line) in a 0.033 M solution of toluene (Figure 3). Simple α-benzyl substitution performed well in this chemistry; the desired 2-benzyl α-tetrasubstituted morpholinone **2b** was obtained in 95% yield and 99% ee. Gratifyingly, other functionalized substrates (benzyl ether, methyl ester, nitrile) are well tolerated, affording α-functionalized morpholinones **2c**, **2d** and **2e** in uniformly excellent enantioenrichment (99% ee), although the yield of **2d** was moderate (60%). Having demonstrated a broad functional group tolerance within the side chain, we explored other ring sizes and frameworks. Replacement of oxygen with sulfur gave thiomorpholinone **2f** in good yield, but slightly decreased enantioselectivity (79% yield, 86% ee). Like morpholinone, benzomorpholinone is also a good substrate class, delivering allylated product **2g** in 76% yield and 95% ee. Additionally, α-tetrasubstituted oxazolidin-4-one **2h** is produced in 82% yield and 96% ee with higher temperature applied (60 °C).[21] Benzyloxazolinone **2i** is also produced in good yield and enantioselectivity.

With excellent results on α,α-dialkyl 2-oxa- and thia-linked lactams in hand, we started to investigate allylic alkylation using cyclic hydroxamic acid derivatives to obtain a-quaternary *N,O*-heterocycles (Table 1). Isoxazolidin-3-one **3a** (R = Bz), **3b** (R = Boc) and **3c** (R = CO_2Ph) produced the desired alkylated compounds **4a-c** in excellent yields (95–98%), but with modest enantioselectivities (72–73% ee) (entries 1–3). Benzoyl protected 1,2-oxazinan-3-one **3d** underwent an unexpected side reaction, and produced only small amounts of **4d** (entry 4).[24] Despite of the low yield, the enantioselectivity of **4d** is still satisfactory (88% ee), which encouraged us to identify an effective *N*-protecting group to circumvent the undesired reaction. A bulky pivaloyl group somehow suppresses the side reaction, but decreases the enantioselectivity (entry 5). An electron-rich *N*-benzylated **3f** was a poor substrate for decarboxylative alkylation (entry 6).[25] Finally, we discovered that carbamates **3g-i** produced the desired products in good yields (67–89%) and acceptable enantioselectivities (84–87% ee) (entries 7–9), with little or none of the undesired side reactivity observed. We were delighted to find that 7-membered **3j** is an excellent substrate in this class, furnishing **4j** in a good yield and excellent enantioselectivity (entry 10, 81% yield, 93% ee).

As shown in Scheme 1, we have also demonstrated allylic alkylation with 1,3-oxazinan-4-one **5** as an alternative β-hydroxy acid synthon of **3a**. To our delight, **5** was successfully converted into **6** in 90% yield and 94% ee.

We anticipate that our newly developed heterocycles could play important roles in medicinal agent discovery and also serve as useful chiral building blocks. To demonstrate the value and versatility of this new class of α-tetrasubstituted heterocycles, we implemented a number of product transformations (Scheme 2). For example, removal of the benzoyl group followed by reduction using $LiAlH_4$ can readily convert morpholinone **2c** into N-H morpholine **7**. Acid treatment of **2h** in methanol provided α-tertiary-hydroxy ester **8** in 71% yield without erosion of enantiopurity.[26] a-Quaternary δ-lactone **9** was synthesized from **4j** in a good yield by zinc mediated reduction of the N-O bond followed by acid catalyzed cyclization.

In conclusion, we have developed a variety of new classes of substrates for catalytic enantioselective allylic alkylation to generally form α,α-disubstituted 2-keto heterocycles, such as morpholinones, oxazolidinones, cyclic hydroxamic acid derivatives, and 1,3-oxazinanones. The asymmetric products formed in this communication are envisioned to be valuable pharmacophores in medicinal chemistry and their transformations afford a variety of important structures such as chiral hydroxy acid derivatives. Studies utilizing this method toward the synthesis of complex natural products and other bioactive small molecules are ongoing in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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(21). The substrate 1h can be readily prepared from commercially available lactamide in three steps.[19]

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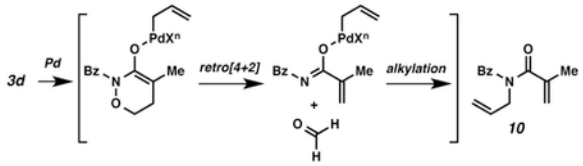
(24). We isolated 10 presumably due to retro [4+2] cycloaddition followed by palladium-catalyzed alkylation.



(25). We also observed that electron-rich N-alkyl protection of amides decreased the reactivity under our conditions, see ref 14b.

(26). For an alternative preparation of a-tertiary-hydroxy carbonyl compounds , see ref 23.

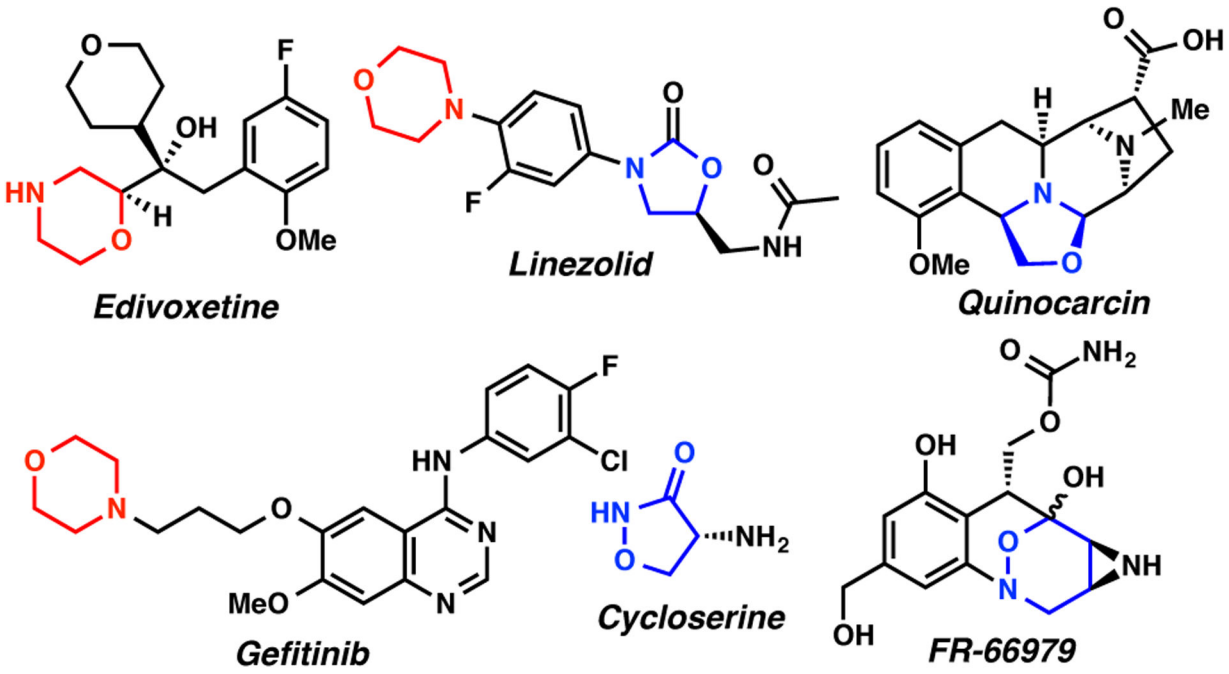
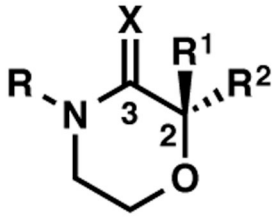
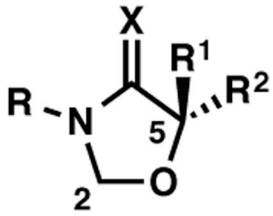


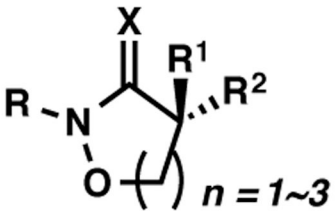
Figure 1.
Representative *N,O*-heterocyclic-containing pharmaceuticals and natural products



morpholine (X = H_2)
morpholin-3-one (X = O)



oxazolidine (X = H_2)
oxazolidin-4-one (X = O)



isoxazolidine (*n* = 1, X = H_2)
isoxazolidin-3-one (*n* = 1, X = O)
1,2-oxazinan-3-one (*n* = 2, X = O)
1,2-oxazepan-3-one (*n* = 3, X = O)

Figure 2.
α-Tertiary and quaternary *N,O*-heterocycles

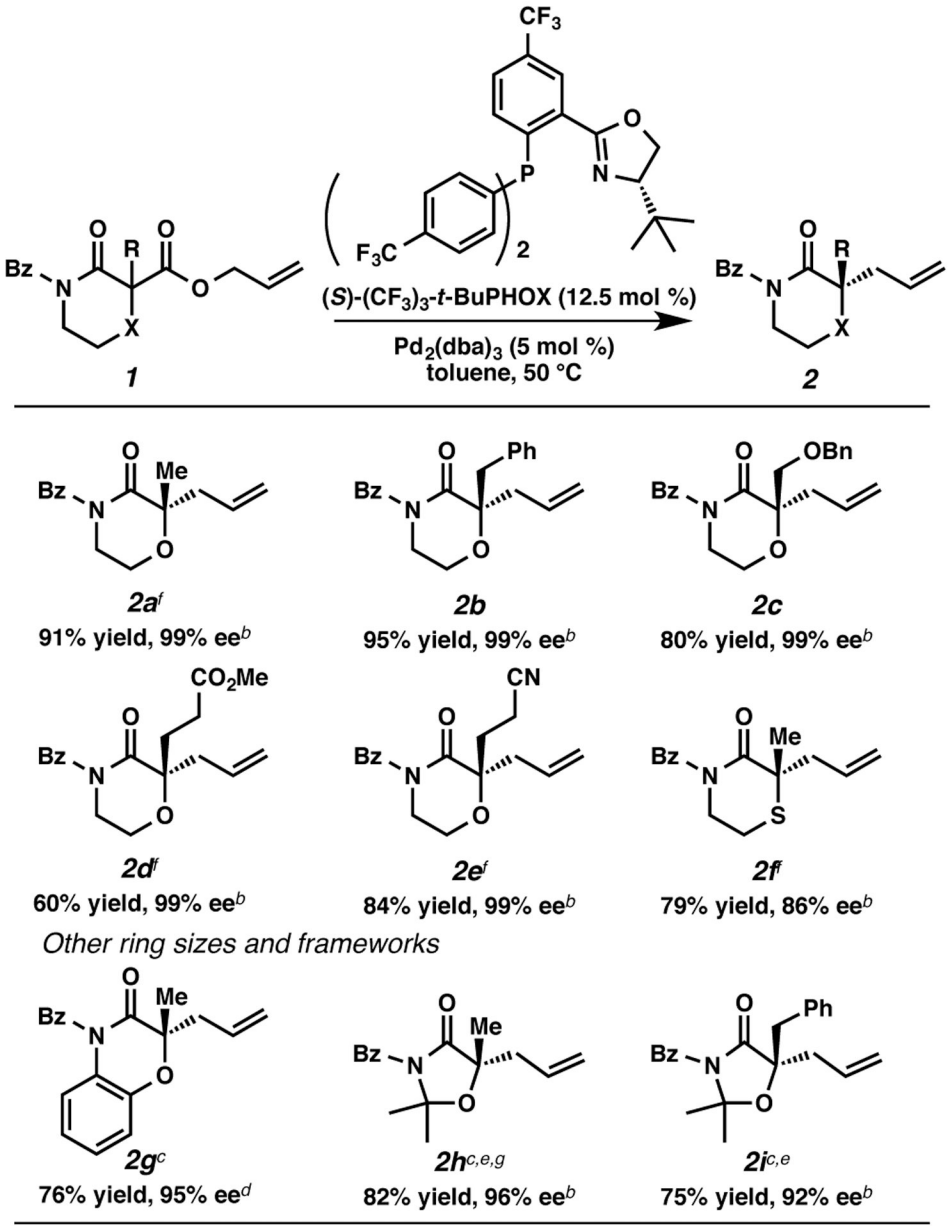
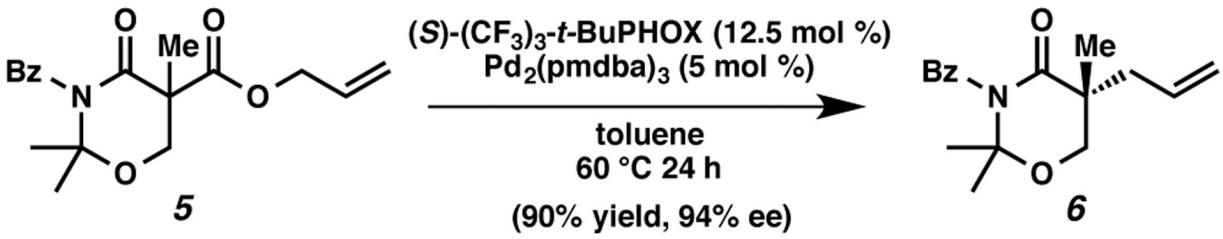
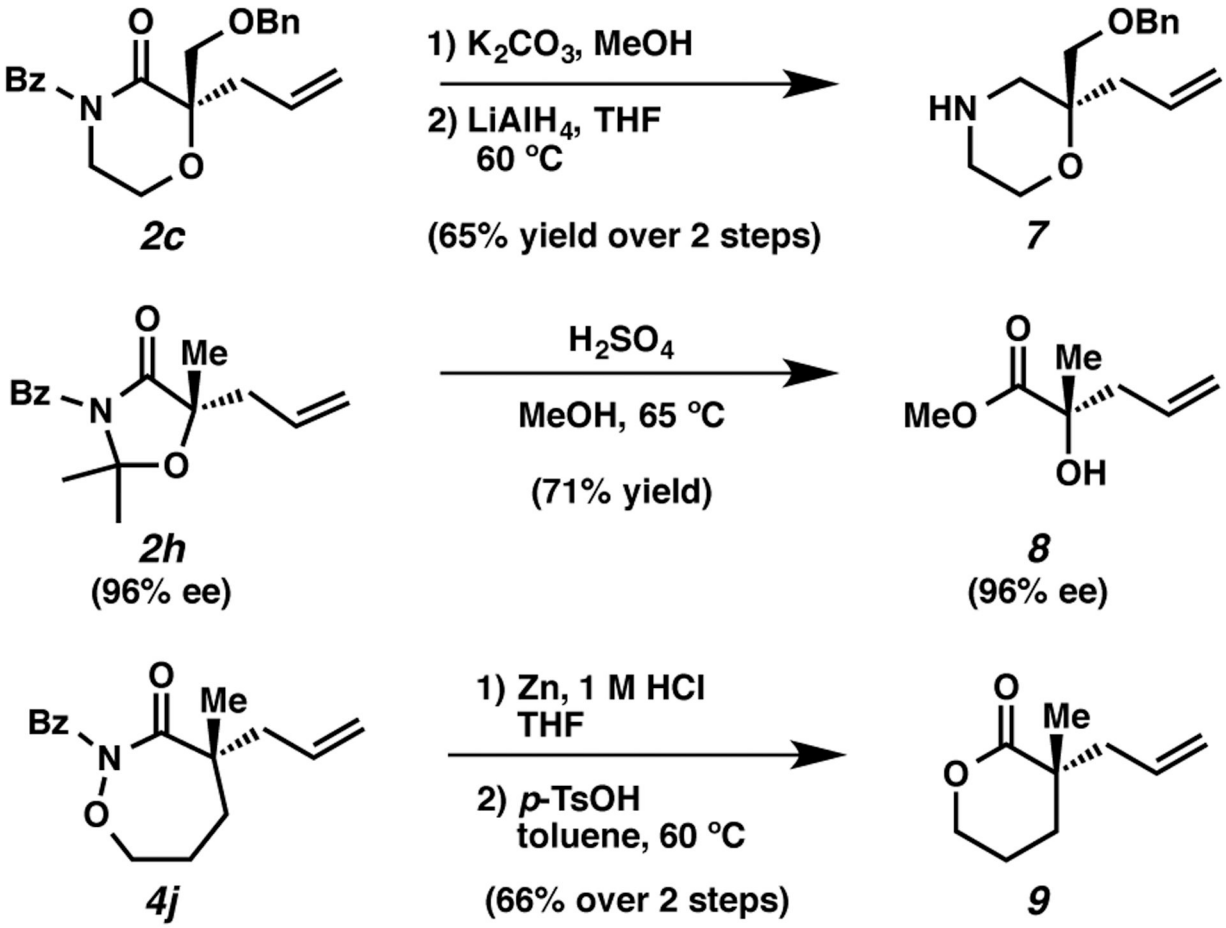


Figure 3. Substrate Scope of α-Tertiary Heterocycles[a]

[a]Reaction performed with 0.1 mmol of **1**, 5 mol % of Pd2(dba)3, 12.5 mol % of (*S*)-(CF3)3-*t*-BuPHOX at 0.033 M in toluene at 50 °C *b*Determined by chiral SFC analysis. *c*Reactions were performed on **1g**, **1h** and **1i** at 60 °C. *d*The ee of **2g** was determined by chiral SFC analysis after Bz removal (see supporting information). *e*Pd2(pmdba)3 (pmdba = bis(4-methoxybenzylidene)acetone) was used instead of Pd2(dba)3. *f*Absolute configuration was assigned by vibrational circular dichroism (VCD) spectroscopy[22] supported by theoretical calculations (see supporting information). *g*Absolute stereochemistry assigned by conversion into (–)-methyl 2-hydroxy-2-methylpent-4-enoate.[23]



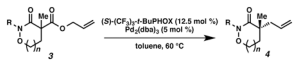
Scheme 1.
Synthesis of 1,3-oxazinan-4-one 6

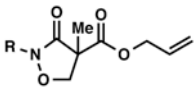
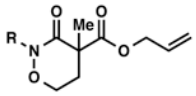
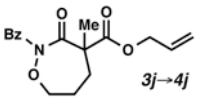


Scheme 2.
Derivatization of Allylic Alkylation Products

Table 1.

Substrate Scope of α-Quaternary Cyclic Hydroxamic Acid Derivatives[a]



entry	substrate	R	yield (%)[b]	ee (%)[c]
1		Bz (***3a*→*4a***)[d]	98	73
2		Boc (***3b*→*4b***)	95	72
3		PhO(CO) (***3c*→*4c***)	95	73
4		Bz (***3d*→*4d***)	29	88
5		Piv (***3e*→*4e***)	48	73
6		Bn (***3f*→*4f***)	trace	ND
7		Boc (***3g*→*4g***)	67	85
8		Cbz (***3h*→*4h***)	89	84
9		PhO(CO) (***3i*→*4i***)	70	87
10			81	93

[a] Reaction performed under the conditions of Figure 3 at 60 °C.

[b] All reported yields are for isolated products.

[c] Enantiomeric excesses were determined by chiral SFC analysis.

[d] Absolute configuration was assigned by VCD spectroscopy22 supported by theoretical calculations (see supporting information).