



Cite this: *RSC Adv.*, 2020, 10, 20264

Received 26th March 2020

Accepted 19th May 2020

DOI: 10.1039/d0ra03726e

rsc.li/rsc-advances

Site-selective, catalytic, and diastereoselective sp^3 C–H hydroxylation and alkoxylation of vicinally functionalized lactams†

Timothy K. Beng, * Victoria Shearer, Rachel Davey and Ivianne Redman

The C–H bond functionalization of sp^3 carbon centres presents a significant challenge due to the inert nature of hydrocarbons as well as the need to selectively functionalize one of the numerous aliphatic C–H bonds embodied in organic molecules. Here, we describe catalytic, diastereoselective, and site-selective sp^3 C–H hydroxylation/alkoxylation protocols featuring dihydroisoquinolones, γ -, and δ -lactams, which bear vicinal stereocenters. The hydroxylation strategy utilizes oxygen, a waste-free oxidant and affords attractive fragments for potential drug discovery. Fe-catalyzed dehydrative coupling of the resulting tertiary alcohols with simple primary alcohols has led to the construction of highly versatile unsymmetrical dialkyl ethers.

Introduction

Site-selective functionalization of C–H bonds continues to provide chemists with transformative tools for editing and constructing complex molecular architectures. Indeed, nature is endowed with several enzymes that achieve direct and selective oxygenation of organic molecules.¹ Benzylic C–H bonds are often the target of most of these enzymes in part due to their relatively low bond dissociation energy (BDE ~ 90 kcal mol^{−1}).² Fittingly, functionalized benzylic cyclic amino tertiary alcohols constitute the core of several alkaloid natural products and pharmaceuticals, including anti-inflammatory agent Homocrepidine B,³ anti-HIV agent Nifedipine,⁴ antipsychotic agent Haloperidol,⁵ and anticancer agent Donaxaridine⁶ (Fig. 1). Meanwhile, alcohol-bearing dihydroisoquinolones are resident in several natural products, including 6-oxocorynoline.⁷ We have therefore identified the development of a catalytic and stereoselective methodology for the site-selective hydroxylation and alkoxylation of tertiary C–H bonds in readily affordable dihydroisoquinolones (DHIQs) of type 1 and vicinally functionalized lactams such as 4 as an important research objective (Fig. 2A). Central among our objectives was the prospect of developing a protocol that enables the sp^3 C–H hydroxylation of DHIQs while obviating the need for expensive metal catalysts, cryogenic conditions, and the reliance on directing groups. Such an efficient and selective sp^3 C–H oxidation method would undeniably streamline the synthesis of drug metabolites, natural products, and fine chemicals.⁸

Despite rapid advances in the development of metal-catalyzed reactions,⁹ synthetically useful C(sp^3)–H oxygenation chemistry is still in great demand.¹⁰ To the best of our knowledge, only a single report exists on the construction of reduced DHIQs (*i.e.*, tetrahydroisoquinolines) bearing a tertiary alcohol motif at the C4 position of the azaheterocycle.¹¹

Remarkable progress has been made using transition-metal catalysis with molecular O₂ for selective sp^3 C–H hydroxylation.¹² The use of O₂ for the synthesis of quaternary α -hydroxyl carbonyl compounds was first described by Ritter and co-workers using dinuclear palladium complexes.¹³ Herein, we report a site-selective, Cu-catalyzed, and diastereoselective approach to hydroxylated DHIQs with excellent functional group compatibility, which uses oxygen as the sole oxidant (see

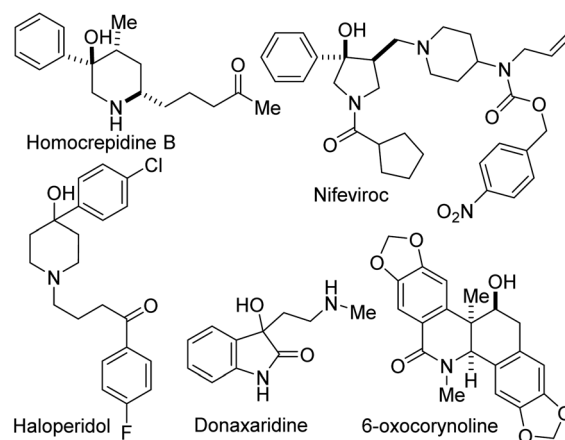


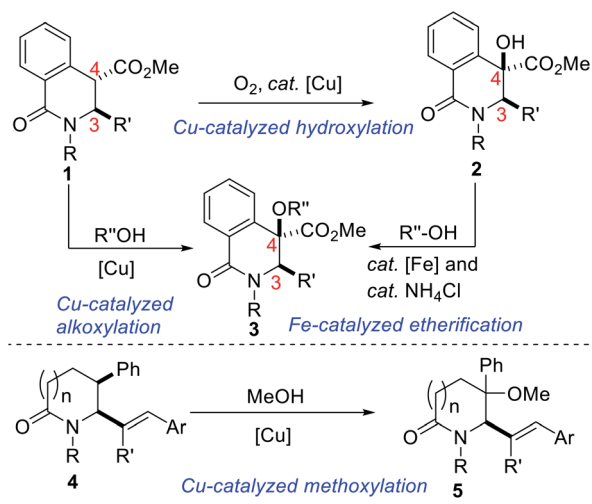
Fig. 1 Examples of biologically active benzylic cyclic amino tertiary alcohols and hydroxylated dihydroisoquinolones.

Department of Chemistry, Central Washington University, Ellensburg, WA 98926, USA.
E-mail: Timothy.beng@cwu.edu

† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data. See DOI: 10.1039/d0ra03726e



A: Catalytic, site-selective, and diastereoselective hydroxylation and alkoxylation of vicinally functionalized lactams (*this work*)



B: Prior work on site- and stereoselective benzylation of DHIQs

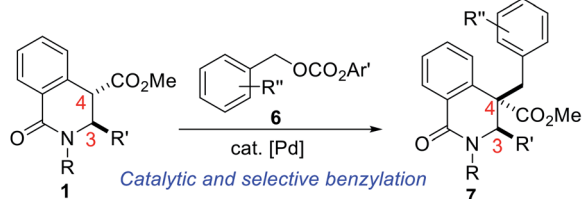


Fig. 2 (A) Proposed plan for the construction of C4 hydroxylated dihydroisoquinolones and subsequent alkoxylation, (B) selective and catalytic benzylation of DHIQs.

2). Fe-catalyzed dehydrative coupling of these sterically congested alcohols has led to the synthesis of unsymmetrical alkyl ethers (see 3). Direct Cu-catalyzed sp^3 C–H methoxylation of vicinally functionalized γ - and δ -lactams has also been accomplished (see 5). These selective C–O bond-forming reactions nicely complement our recently disclosed C–C bond-forming tactic (Fig. 2B).¹⁴

Results and discussion

The substitution of noble metals by earth-abundant, inexpensive and relatively less toxic metals is one of the most beneficial aspects of modern day transition metal-catalyzed processes. Accordingly, copper-catalyzed oxidative C–H functionalization protocols have emerged as alternatives to well-heeled but less practical Pd-catalyzed processes.¹⁵ Seeking to take advantage of the aforementioned merits of Cu-catalysis and inspired by the ubiquity of cyclic amine-bearing tertiary alcohols in bioactive compounds, the amenability of DHIQ **1** to diastereoselective and site-selective hydroxylation, with O_2 as the oxidant, was explored. After surveying several conditions (Table 1), we were pleased to find that model DHIQ **1a** undergoes efficient hydroxylation to furnish product **2a** in 92% yield. Magnesium-mediated (entry 9), potassium-mediated (entry 10), and organocatalytic conditions (entry 11) were also evaluated, but they did not perform as well as these Schoenebeck-inspired,¹⁶ Cu-

Table 1 Optimization of the diastereoselective and site-selective hydroxylation of DHIQ **1a**

Entry	Deviation from condition A	% yield
1	Acetonitrile (MeCN) as solvent	52
2	<i>N,N</i> -Dimethylformamide (DMF) as solvent	57
3	DMSO as solvent	69
4	hphH in place of CS_2CO_3	63 ^a
5	Cu_2O in place of CuF_2	84
6	$Cy(OTf)_2$ in place of CuF_2	49
7	Conditions B in place of conditions A	69
8	Conditions C in place of conditions A	57
9	Conditions D in place of conditions A	68
10	Conditions E in place of conditions A	37
11	Conditions F in place of conditions A	31

Conditions B

$CuCl$ (5 mol%)

NHTPPI (1 mol%)

O_2 (1 atm), MeCN

40 °C, 12 h

Conditions C

MsOOMs (1.5 equiv.)

$CuOAc$ (20 mol%)

TMSOAc (3 equiv.)

CH_2Cl_2 (0.2 M), rt, 18 h

then 5% NaOMe in MeOH

Conditions D

$Mg(NO_3)_2 \cdot 6H_2O$ (2 equiv.)

Diphenylphosphine oxide (4 equiv.)

1,4-Dioxane, 80 °C, 4 h

Conditions E

$KOtBu$ (1 equiv.)

air, PhMe, 40 °C, 6 h

hphH

NHTPPI

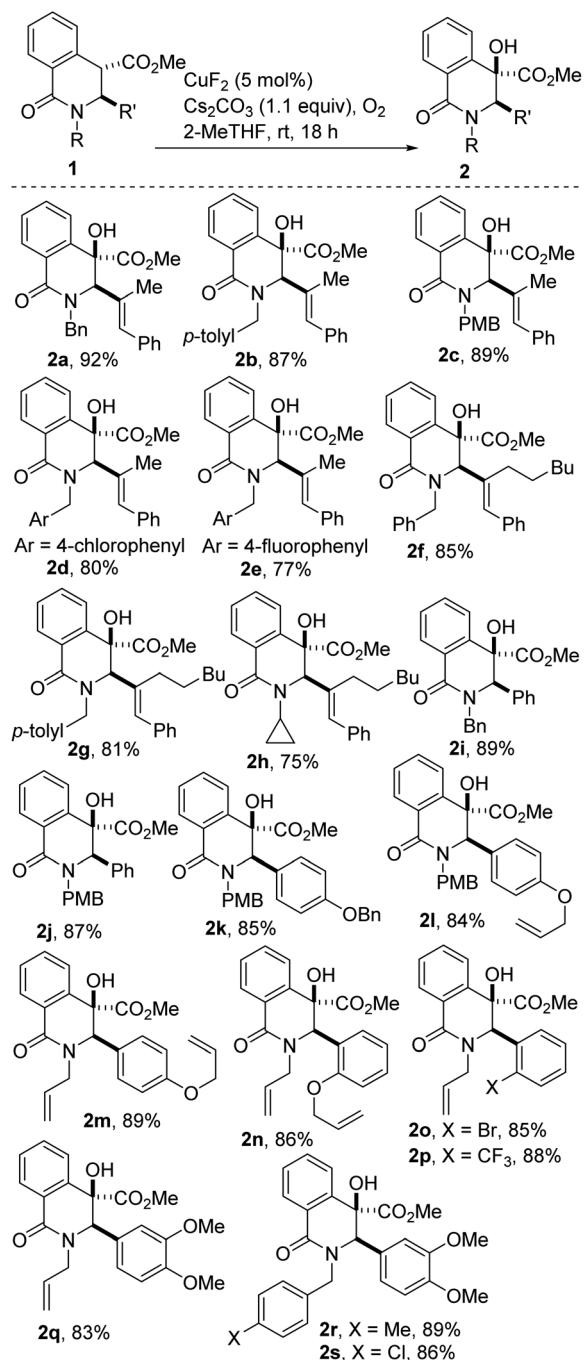
HDQ

^a Epimerization observed (down to 80 : 20 dr.).

catalyzed conditions. Control experiments in the absence of base or oxygen revealed that both components are necessary.

With efficient conditions for site-selective and catalytic hydroxylation of DHIQs in hand, the scope of the transformation with respect to the stereoelectronics of the DHIQ was next explored (Scheme 1). DHIQs bearing *N*-benzyl, alkyl, and allyl substituents were surveyed. Pleasingly, the hydroxylated DHIQs are obtainable in synthetically attractive yields when a wide range of diversely functionalized lactam esters are exposed to the identified reaction conditions (see **2a–s**). The transformation fully tolerates C3 alkenyl substituents (entries **2a–h**), which bodes well for late-stage diversification given that the alkenyl motif could pave the way for harnessing several reactivity modes, including hydroarylation,¹⁷ oxoamination,¹⁸ trifluoromethylation,¹⁹ oxacyclopropanation,²⁰ and





PMB = *para*-methoxybenzyl; Isolated yields are reported. Performed on 1.0 mmol scale using 5 mL 2-MeTHF. Reaction times ranged from 10 to 18 h. Diastereomeric ratios were determined by GC-MS analysis. Relative configurations were established using coupling constant analyses and NOESY analyses in some cases.

Scheme 1 C4 hydroxylation of dihydroisoquinolones.

aziridination.²¹ Owing to the continuing emergence of C3-arylated dihydroisoquinolones and tetrahydroquinolines with medicinal potential, DHIQs bearing benzylic α -amino stereocenters were surveyed. In the event, we find that this site-selective oxygenation protocol proceeds with great tolerance

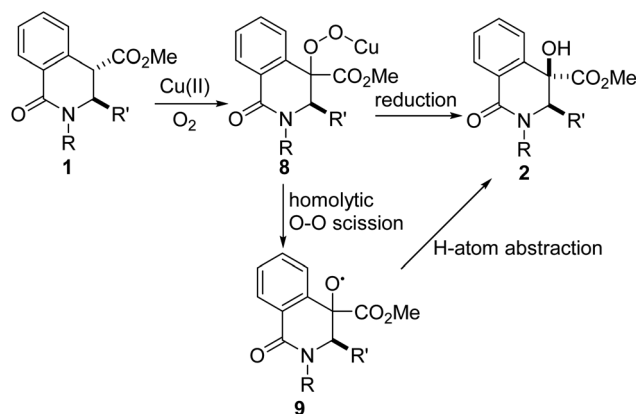


Fig. 3 Possible mechanism for the formation of **2**.

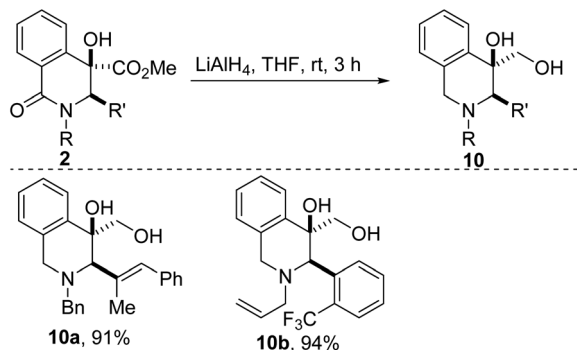
for electron-neutral, electron-rich, and electron-deficient arenes. Of note, site-selective hydroxylation still occurs even when potentially problematic benzyloxy and allyloxy groups are employed (see **2k–n**). Notably, *ortho*-substituted arenes are amenable to this hydroxylation reaction, which converts sp^3 α -C–H bonds of hindered esters to C–O bonds (see **2n–p**).

A hydroxylated DHIQ harboring a requisite halogen group for potential cross-coupling is obtainable in synthetically useful yield (see **2o**). The incorporation of a fluorinated moiety into organic molecules generally increases the solubility, lipophilicity and metabolic stability of the parent molecules, thus, explaining why ~25% of existing preclinical drugs and 40% of agrochemicals contain at least one fluorine atom.²² Specifically, the CF_3 group enjoys a privileged role because its incorporation often enhances efficacy by promoting electrostatic interactions with targets, improving cellular membrane permeability, and increasing robustness toward oxidative metabolism of the drug.²³ It is therefore noteworthy that DHIQs **2e** (fluorine-containing) and **2p** (CF_3 -containing), are obtainable in good yields.

Gleaning from prior detailed mechanistic studies on Cu-catalyzed hydroxylation or scission of enolizable and branched ketones,¹⁶ we propose that **2** arises from **1** via a sequence involving enolization and oxygenation of the ester enolate to peroxide **8**, which either undergoes reduction or homolytic O–O cleavage (see **9**) and concomitant hydrogen atom abstraction (Fig. 3). The diastereoselectivity of the hydroxylation is presumably governed by substituent effects, especially the vicinal C3 substituent.

Post-diversification strategies that enable the step-economical incorporation of new latent functionality often provide an efficient strategy for rapidly accessing structural analogues of pharmaceutical candidates with a diverse array of chemical and biological properties. Fittingly, reduction of the ester and lactam groups resident in **2a/p** affords tetrahydroisoquinolines (THIQs) of type **10** (Scheme 2). The reliable synthesis of THIQs bearing a hydroxymethyl group such as **10**, is noteworthy given that this substructure constitutes the core of a few alkaloids, including calycotomine.²⁴





Scheme 2 Synthesis of C4 hydroxylated tetrahydroisoquinolines.

Iron-catalyzed dehydrative etherification of 2

The development of effective coupling methods that rely on the cleavage of unactivated C(sp³)-O bonds is synthetically and theoretically appealing. However, formidable challenges remain to be addressed given that carbon-oxygen bonds are strong (~95 kcal mol⁻¹).²⁵ Thus, forcing conditions are typically required to achieve useful conversions and even these are subject to limitations. Direct intermolecular dehydrative coupling of two alcohols to form unsymmetrical ethers is attractive from the standpoint of atom economy.²⁶ This is all the more relevant since unsymmetrical alkyl ethers have widespread applications as solvents, plasticizers, disinfectants, herbicides, drug intermediates, fragrances, and as precursors for polymers.²⁷ Moreover, in the realm of medicinal chemistry, hindered and unsymmetrical ethers are highly desirable given that extensive substitution about the ether bond prevents unwanted metabolic processes that can lead to rapid degradation *in vivo*. However, due to the poor departing ability of the hydroxyl functionality, hydroxide activation is challenging, particularly for nucleophilic substitution. These challenges notwithstanding, the construction of unsymmetrical ethers directly from two different alcohols, under transition-metal catalysis continues to garner attention from the synthesis community.²⁸ However, Fe-catalyzed dehydrative etherification of two different alcohols has scarcely been investigated,²⁹ which is unfortunate since iron is an earth abundant, less toxic, and environmentally benign metal that is capable of emulating or surpassing the catalytic activities of noble transition metals.³⁰

Inspired by our prior success on Fe-catalyzed dehydrative intramolecular coupling of alkenols,³¹ and seeking to further demonstrate the synthetic utility of the catalytic hydroxylation protocol described herein, we interrogated the hindered benzylic alcohols depicted in Scheme 1 in an intermolecular, Fe-catalyzed cross-coupling protocol with simple alcohols. Pleasingly, we have found that these lactam-bearing alcohols are amenable to efficient Fe(OTf)₃-catalyzed dehydrative coupling (Table 2 and Scheme 3). No reaction is observed in the absence of the iron catalyst and minimal coupling is observed when Fe(OTf)₃ is replaced by FeCl₃·6H₂O. An excess of methanol is necessary to compensate for the formation of small amounts of dimethylether. Indeed, the homocoupling product

Table 2 Optimization of the catalytic dehydrative etherification of 2i

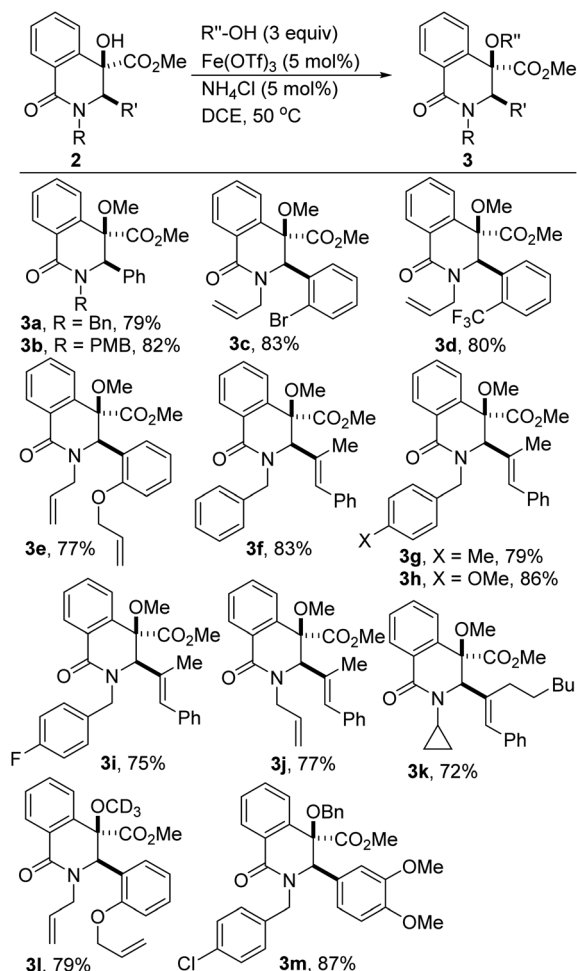
2i, 95:5 dr conditions A: yield of 3a = 79% 3a, 95:5 dr		
Entry	Deviation from conditions A	% yield as solvent
1	PhMe as solvent	0
2	CH ₂ Cl ₂ as solvent	67
3	2-MeTHF as solvent	48
4	FeCl ₃ ·6H ₂ O in place of Fe(OTf) ₃	39
5	Fe(NO ₃) ₃ (5 mol%) in place of Fe(OTf) ₃	0
6	No Fe(OTf) ₃	0
7	No NH ₄ Cl	0
8	Conditions B in place of conditions A	57
9	Conditions C in place of conditions A	Trace
Conditions B		Conditions C
Mg(NO ₃) ₂ ·6H ₂ O (2 equiv.)		KOtBu (1 equiv.)
Diphenylphosphine oxide (4 equiv.)		air, PhMe, 40 °C, 6 h
1,4-Dioxane, 80 °C, 4 h		

was suppressed only when ammonium chloride was introduced. Several hydroxylated DHIQs react satisfactorily with methanol (see 3a-k). Isotopically labelled methanol reacts prudently and affords deuterated ether 3l. Benzyl alcohol is also a suitable alcohol for this etherification process (see 3m), which is noteworthy since organic and medicinal chemists routinely employ benzyl ethers as protecting/directing groups as they tackle synthetic targets of increasing complexity. The use of ligand-free, simple, cheap, and readily available Fe(OTf)₃ as a catalyst makes this protocol highly attractive and endows it with a practical advantage over existing methodologies. This carbocation-driven process should in principle tolerate hindered nonbenzylic alcohols as reactive partners. Accordingly, the amenability of hindered secondary as well as tertiary alcohols to this intermolecular etherification process is currently under investigation and the results will be disclosed later.

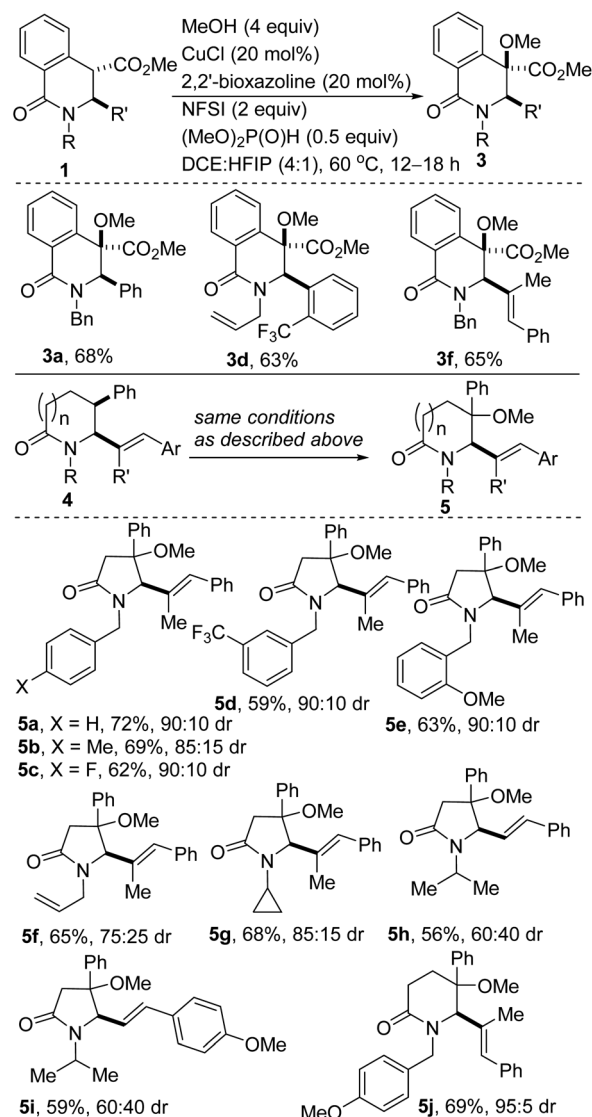
Copper-catalyzed site-selective dehydrogenative etherification of vicinally functionalized lactams

The direct alkoxylation of sp³-hybridized C-H bonds (especially those that are not adjacent to a heteroatom) remains attractive, particularly in the context of late-stage modification of pharmaceutically-pertinent fragments.³² Specifically, the installation of a methoxy group is quite appealing given that in addition to introducing a potential hydrogen bond acceptor site, it has minimal impact on the overall lipophilicity (*i.e.*, log *P*).³³ Accordingly, we sought a one-step protocol for the conversion of vicinally functionalized lactams such as 1 to unsymmetrical methyl ethers. We reasoned that the successful implementation of this mode of reactivity would obviate the need for pre-installation of the hydroxyl functionality resident





Scheme 3 Fe-catalyzed intermolecular dehydrative coupling of tertiary dihydroisoquinolins with simple alcohols.



Scheme 4 Site-selective methoxylation of vicinally functionalized lactams.

in **2**. Importantly, we desired to achieve direct sp^3 α -C–H methoxylation of lactams of type **4** (Scheme 4) which resisted sp^3 α -C–H hydroxylation under the conditions described in Scheme 1. We were however not oblivious to the challenges associated with realizing such an atom-economical transformation in sterically congested environments and with substrates that bear many active/labile sp^3 C–H bonds.

In keeping with our interest in Cu-catalyzed direct sp^3 α -C–H oxygenation, these studies have revealed that DHIQs of type **1** undergo site-selective benzylic C–H methoxylation with methanol to afford benzyl methyl ethers (Scheme 4, see **3a/d/f**). Importantly, these Stahl-inspired conditions³⁴ allow for direct site-selective benzylic methoxylation of sp^3 C–H bonds resident in vicinally functionalized γ -lactams (see **5a–i**). Remarkably, site-selective benzylic methoxylation of the heterocycles occurs even when potentially active side-chain α -amino-benzyl (see **5a–e**), allyl (see **5f**), and tertiary (see **5g–i**) C–H bonds are present. A vicinally functionalized δ -lactam is also amenable to this site-selective dehydrogenative methoxylation (see **5j**). The relative configuration of **5** has not been fully established at this point but the diastereomeric ratios of most of the products are synthetically useful.

Conclusions

In summary, Cu-catalyzed and site-selective conversion of sp^3 α -C–H bonds of hindered benzylic esters to C–O bonds in vicinally functionalized dihydroisoquinolones has been accomplished. Environmentally benign molecular oxygen is employed as the sole oxidant. The reaction shows compatibility with alkenes, which are typically sensitive to oxidative conditions and not tolerated in most aliphatic C–H oxidations. Substrates bearing multiple benzylic positions, including α -amino and α -alkoxy benzylic positions, undergo site-selective hydroxylation only at the benzylic position alpha to the ester. Post-diversification of the tertiary alcohols to unsymmetrical alkyl ethers by Fe-catalyzed dehydrative coupling with simple primary alcohols has also been achieved. Dehydrogenative methoxylation of vicinally functionalized lactams has led to the rapid construction of a small library of benzylic lactam ethers. The application



of this strategies to simplify the synthesis of medicinally important entities and the extension of the Fe-catalyzed dehydrative coupling protocol to primary and tertiary alcohols are ongoing and the results will be disclosed in due course.

Experimental

All experiments involving air and moisture sensitive reagents were carried out under an inert atmosphere of nitrogen and using freshly distilled solvents. Column chromatography was performed on silica gel (230–400 mesh). Thin-layer chromatography (TLC) was performed using Silicycle Siliaplate™ glass backed plates (250 μ m thickness, 60 Å porosity, F-254 indicator) and visualized using UV (254 nm) or KMnO₄ stain. Unless otherwise indicated, ¹H, ¹³C, and DEPT-135 NMR, and NOESY spectra were acquired using CDCl₃ solvent at room temperature. Chemical shifts are quoted in parts per million (ppm). HRMS-EI⁺ data were obtained using either electrospray ionization (ESI) or electron impact (EI) techniques. High-resolution ESI was obtained on an LTQ-FT (ion trap; analyzed using Excalibur). High resolution EI was obtained on an Autospec (magnetic sector; analyzed using MassLynx). Representative GC-MS traces are provided to substantiate the diastereomeric ratios.

General procedure A: conversion of 1 to 2

To a solution of lactam ester **1** (1 mmol) and CuF₂ (5 mol%) in anhydrous 2-methyltetrahydrofuran (5 mL) was added cesium carbonate (1.1 mmol, 1.1 equiv.). The reaction vessel was sealed, evacuated, refilled with oxygen gas, and stirred at room temperature for the desired time period (TLC and GC-MS monitoring) under oxygen atmosphere (which was maintained with an O₂-filled balloon). The reaction mixture was diluted with an aqueous solution of hydrochloric acid (0.50 M, 10 mL) and extracted with ethyl acetate (3 \times 20 mL). The combined organic phases were dried (MgSO₄), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with hexanes/EtOAc to give the pure alcohol.

General procedure B: conversion of 2 to 8

To a 10 mL round-bottomed flask equipped with a magnetic stir bar under a N₂ atmosphere, in a 0 °C ice/water bath, was added the lactam (0.25 mmol) and THF (10 mL). LiAlH₄ (44 mg, 1.12 mmol) was then added portion-wise. The reaction mixture was allowed to warm to room temperature for 3 h (as judged complete by GC-MS analysis). After this time, the reaction mixture was cooled to 0 °C and quenched by slow addition of a solution of 2 N NaOH(aq.) (1 mL). The organic layer was decanted and the aqueous layer was extracted with EtOAc (3 \times 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to yield the crude tertiary aminodiol, which was purified by flash chromatography on silica.

General procedure C: conversion of 2 to 3

To the hydroxylated dihydroisoquinolone **2** (0.5 mmol), dissolved in 1,2-dichloroethane (2 mL), was added the primary

alcohol (1.5 mmol, 3 equiv.), ammonium chloride (1.3 mg, 0.025 mmol), and Fe(OTf)₃ (12.6 mg, 5 mol%) in a vial equipped with a magnetic stir bar, under open atmosphere. The reaction mixture was stirred at 50 °C. After completion of the reaction (TLC and GC-MS monitoring), the mixture was cooled to room temperature. The solvents were removed *in vacuo* and the crude mixture was dissolved in ethyl acetate and subjected to flash column chromatography on silica gel.

General procedure D: conversion of 4 to 5

To an oven-dried vial equipped with a stir bar was added copper(I) chloride (10.0 mg, 0.100 mmol, 20 mol%), 4,4',5,5'-tetrahydro-2,2'-bioxazole (14 mg, 0.100 mmol, 10 mol%), and NFSI (315.2 mg, 1.0 mmol, 2.0 equiv.). The capped vial was placed under nitrogen followed by addition of 5 mL of a mixture of 1,2-dichloroethane and HFIP (4 : 1). Lactam **4** (0.50 mmol, 1.0 equiv.) dissolved in 1 mL DCE, methanol (84 μ L, 2.0 mmol, 4.0 equiv.) and dimethyl phosphonate (24 μ L, 0.25 mmol, 0.5 equiv.) were added to the septum-capped vial under nitrogen. The contents were then heated to 60 °C under stirring for the desired length of time. After completion of the reaction (TLC and GC-MS monitoring), the mixture was cooled to room temperature and triethylamine (0.5 mL) was added to quench any unreacted NFSI. The solvents were removed *in vacuo* and crude product **5** was dissolved in ethyl acetate and subjected to flash column chromatography on silica gel.

Synthesis of C4 hydroxylated DHIQ 2a

Prepared from ester **1a** (411.5 mg, 1.0 mmol) using general procedure A. Purification: flash chromatography on silica eluting with hexane/EtOAc (80 : 20). Oily substance. Yield = 393 mg, 92%. ¹H NMR (400 MHz, CDCl₃) δ 8.26 (dd, *J* = 6.9, 2.1, 1H), 7.52–7.40 (m, 2H), 7.39–7.13 (m, 11H), 6.36 (s, 1H), 5.56 (d, *J* = 15.1 Hz, 1H), 4.17 (s, 1H), 4.08 (d, *J* = 15.1 Hz, 1H), 3.85 (br s, 1H), 3.64 (s, 3H), 1.47 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 172.96, 163.16, 136.58, 136.41, 135.82, 134.07, 132.36, 132.07, 129.57, 129.22, 129.04, 129.01, 128.99, 128.77, 128.70, 128.67, 128.65, 128.59, 128.48, 128.43, 128.40, 128.37, 127.61, 127.38, 127.06, 76.97, 74.27, 53.32, 48.18, 13.60. HRMS calc. for C₂₇H₂₅NO₄ 427.1784, found 427.1788. FTIR (KBr): 3384.5506, 2924.8333, 1642.2515, 1494.9545, 1448.8548, 1427.0419, 1393.4602, 1361.6968, 1328.7144, 1289.7737, 1223.6425, 1198.9141, 1130.0001, 1074.1578, 1030.4745, 988.561, 966.1662, 925.5022, 741.6755, 693.4562.

Note: All other hydroxylated products depicted in Scheme 1 were prepared as described above. Spectroscopic data can be found in the ESI.†

Synthesis of alcohol 10a

Prepared from ester **2a** (0.5 mmol) using general procedure B. Purification: flash chromatography on silica eluting with hexane/EtOAc (50 : 50). Oily substance. Yield = 175.4 mg, 91%. ¹H NMR (400 MHz, CDCl₃) δ 7.66 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.49–7.29 (m, 12H), 7.05 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.47 (s, 1H), 4.30 (d, *J* = 10.7 Hz, 1H), 4.06 (d, *J* = 13.3 Hz, 1H), 3.98 (d, *J* = 16.0 Hz, 1H), 3.80–3.65 (m, 3H), 3.62 (s, 1H), 3.56 (d, *J* = 13.3 Hz, 1H),



3.30 (s, 1H), 1.93 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 138.05, 138.04, 137.11, 134.37, 133.12, 132.46, 129.30, 128.77, 128.34, 127.80, 127.63, 127.32, 127.05, 125.99, 125.22, 75.30, 72.14, 67.80, 60.19, 53.60, 18.48. HRMS calc. for $\text{C}_{26}\text{H}_{27}\text{NO}_2$ 385.2042, found 385.2047.

Note: All other alcohols depicted in Scheme 2 were prepared as described above. Spectroscopic data can be found in the ESI.†

Synthesis of ether 3a

Prepared in 0.5 mmol scale using general procedure C. Purification: flash chromatography on silica eluting with hexane/EtOAc (25 : 75). Oily substance. Yield = 158.6 mg, 79%. ^1H NMR (400 MHz, CDCl_3) δ 8.49 (d, J = 7.7 Hz, 1H), 7.65 (td, J = 7.6, 1.3 Hz, 1H), 7.57 (td, J = 7.6, 1.3 Hz, 1H), 7.45 (d, J = 7.3 Hz, 1H), 7.32–7.27 (m, 8H), 6.85 (d, J = 7.2 Hz, 2H), 5.54 (d, J = 15.2 Hz, 1H), 4.85 (s, 1H), 3.82 (d, J = 15.2 Hz, 1H), 3.44 (s, 3H), 3.02 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 169.57, 162.56, 136.33, 135.27, 131.18, 131.12, 130.18, 129.81, 129.79, 129.24, 128.93, 128.67, 128.54, 128.30, 127.98, 127.44, 83.35, 68.62, 52.89, 52.30, 48.76. HRMS calc. for $\text{C}_{25}\text{H}_{23}\text{NO}_4$ 401.1627, found 401.1633. FTIR (KBr): 2976.0754, 2927.2335, 1721.7979, 1650.1792, 1492.0415, 1438.4625, 1362.2698, 1320.5399, 1290.1484, 1206.364, 1180.3512, 1146.7618, 1132.397, 995.8166, 918.8793, 700.1334.

Note: All other ethers depicted in Scheme 3 were prepared as described above. Spectroscopic data can be found in the ESI.†

Synthesis of ether 5j

Prepared in 0.5 mmol scale using general procedure D. Purification: flash chromatography on silica eluting with hexane/EtOAc (75 : 25). Oily substance. Yield = 152.3 mg, 69%, 95 : 5 dr. ^1H NMR (400 MHz, CDCl_3) δ 7.30–7.17 (m, 10H), 6.90–6.85 (m, 4H), 6.12 (s, 1H), 5.22 (d, J = 17.1 Hz, 1H), 4.67 (s, 1H), 3.85–3.76 (m, 4H), 3.59 (s, 3H), 2.79–2.70 (m, 2H), 2.62–2.42 (m, 2H), 1.06 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 169.08, 158.13, 136.41, 135.58, 134.11, 132.29, 131.94, 129.89, 129.58, 129.35, 129.02, 128.78, 128.47, 128.38, 127.35, 126.92, 114.10, 72.84, 67.90, 55.35, 53.34, 48.43, 29.59, 23.59, 17.32. HRMS calc. for $\text{C}_{29}\text{H}_{31}\text{NO}_3$ 441.2304, found 441.2309.

Note: All other methyl ethers depicted in Scheme 4 were prepared as described above. Spectroscopic data can be found in the ESI.†

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

We are grateful to Central Washington University for financial support to T. K. B. The School of Graduate Studies and Research is thanked for partial support of this work through a Faculty Research Award to T. K. B. V. S. thanks the McNair Scholars Program for a research fellowship.

Notes and references

- 1 P. R. Ortiz de Montellano, Substrate Oxidation by Cytochrome P450 Enzymes, in *Cytochrome P450: Structure, Mechanism, and Biochemistry*, Springer International Publishing, Cham, 2015, pp. 111–176.
- 2 T. N. Thompson, *Med. Res. Rev.*, 2001, **21**, 412–449.
- 3 (a) C. Decker, N. T. Viet, D. Decker and E. WeberKoehl, *Polymer*, 2001, **42**, 5531; (b) Y. Hu, C. Zhang, Z. Zhao, Y. Wang, D. Feng, M. Zhang and H. Xie, *J. Nat. Prod.*, 2016, **79**, 252–256.
- 4 D. Ma, S. Yu, B. Li, L. Chen, R. Chen, K. Yu, L. Zhang, Z. Chen, D. Zhong, Z. Gong, R. Wang, H. Jiang and G. Pei, *ChemMedChem*, 2007, **2**, 187–193.
- 5 M. W. Tyler, J. Zaldivar-Diez and S. J. Haggarty, *ACS Chem. Neurosci.*, 2017, **8**, 444–453.
- 6 H. B. Rasmussen and J. K. Macleod, *J. Nat. Prod.*, 1997, **60**, 1152–1154.
- 7 M. Cushman, A. Abbaspour and Y. P. Gupta, *J. Am. Chem. Soc.*, 1983, **105**, 2873.
- 8 (a) T. Newhouse and P. S. Baran, *Angew. Chem., Int. Ed.*, 2011, **50**, 3362; (b) M. C. White, *Science*, 2012, **335**, 807; (c) J. Genovino, D. Sames, L. G. Hamann and B. B. Toure, *Angew. Chem., Int. Ed.*, 2016, **55**, 14218; (d) P. A. Wender, M. K. Hilinski and A. V. W. Mayweg, *Org. Lett.*, 2005, **7**, 79; (e) K. Chen and P. S. Baran, *Nature*, 2009, **459**, 824; (f) E. M. Stang and M. C. White, *Nat. Chem.*, 2009, **1**, 547.
- 9 (a) D. Yang, M.-K. Wong, X.-C. Wang and Y.-C. Tang, *J. Am. Chem. Soc.*, 1998, **120**, 6611; (b) B. H. Brodsky and J. Du Bois, *J. Am. Chem. Soc.*, 2005, **127**, 15391; (c) K. Chen, J. M. Richter and P. S. Baran, *J. Am. Chem. Soc.*, 2008, **130**, 7247; (d) N. D. Litvinas, B. H. Brodsky and J. Du Bois, *Angew. Chem., Int. Ed.*, 2009, **48**, 4513; (e) S. Kasuya, S. Kamijo and M. Inoue, *Org. Lett.*, 2009, **11**, 3630; (f) A. M. Adams and J. Du Bois, *Chem. Sci.*, 2014, **5**, 656.
- 10 (a) X. Li, X. Che, G.-H. Chen, J. Zhang, J.-L. Yan, Y.-F. Zhang, L.-S. Zhang, C.-P. Hsu, Y. Q. Gao and Z.-J. Shi, *Org. Lett.*, 2016, **18**, 1234; (b) J. Ozawa, M. Tashiro, J. Ni, K. Oisaki and M. Kanai, *Chem. Sci.*, 2016, **7**, 1904; (c) A. Hollister, E. S. Conner, M. L. Spell, . Deveaux, L. Maneval, M. W. Beal and J. R. Ragains, *Angew. Chem., Int. Ed.*, 2015, **54**, 7837.
- 11 D. W. Low, G. Pattison, M. D. Wiczyzsty, G. H. Churchill and H. W. Lam, *Org. Lett.*, 2012, **14**, 2548–2551.
- 12 (a) M. T. Rahman and H. Nishino, *Org. Lett.*, 2003, **5**, 2887; (b) H. Wang, Y. Wang, D. Liang, L. Liu, J. Zhang and Q. Zhu, *Angew. Chem., Int. Ed.*, 2011, **50**, 5678; (c) Z.-Q. Wang, W.-W. Zhang, L. B. Gong, R.-Y. Tang, X.-H. Yang, Y. Liu and J.-H. Li, *Angew. Chem., Int. Ed.*, 2011, **50**, 8968; (d) C. Zhang and N. Jiao, *J. Am. Chem. Soc.*, 2010, **132**, 28; (e) C. Zhang, Z. Xu, L. Zhang and N. Jiao, *Angew. Chem., Int. Ed.*, 2011, **50**, 11088; (f) L. Zhang, X. Bi, X. Guan, X. Li, Q. Liu, B.-D. Barry and P. Liao, *Angew. Chem., Int. Ed.*, 2013, **52**, 11303; (g) J. M. Hoover, B. L. Ryland and S. S. Stahl, *J. Am. Chem. Soc.*, 2013, **135**, 2357; (h) A. N. Campbell and S. S. Stahl, *Acc. Chem. Res.*,



- 2012, **45**, 851; (i) E. Boess, C. Schmitz and M. Klussmann, *J. Am. Chem. Soc.*, 2012, **134**, 5317.
- 13 G. J. Chuang, W. Wang, E. Lee and T. Ritter, *J. Am. Chem. Soc.*, 2011, **133**, 1760.
- 14 T. K. Beng and A. Moreno, *RSC Adv.*, 2020, **10**, 8805–8809.
- 15 S. Thapa, B. Shrestha, S. K. Gurung and R. Giri, *Org. Biomol. Chem.*, 2015, **13**, 4816–4827.
- 16 A. S.-K. Tsang, A. Kapat and F. Schoenebeck, *J. Am. Chem. Soc.*, 2016, **138**, 518.
- 17 K. Brak and J. A. Ellman, *Org. Lett.*, 2010, **12**, 2004–2007.
- 18 B. Ye and N. Cramer, *Acc. Chem. Res.*, 2015, **48**, 1308–1318.
- 19 P. K. Prasad, R. N. Reddi and A. Sudalai, *Org. Lett.*, 2016, **18**, 500–503.
- 20 A. Deb, S. Manna, A. Modak, T. Patra, S. Maity and D. Maiti, *Angew. Chem., Int. Ed.*, 2013, **52**, 9747–9750.
- 21 D. T. Smith and J. T. Njardarson, *Angew. Chem., Int. Ed.*, 2014, **53**, 4278–4280.
- 22 T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214–8264.
- 23 K. Muller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881–1886.
- 24 A. Chatterjee and N. Adityachaudhury, *J. Org. Chem.*, 1962, **27**, 309–310.
- 25 J. B. Pedley, R. D. Naylor and S. B. Kirby, *Thermochemical Data of Organic Compounds*, 2nd edn, Chapman and Hall, New York, 1986.
- 26 (a) P. A. Wender and B. L. Miller, *Nature*, 2009, **460**, 197–201; (b) B. M. Trost, *Acc. Chem. Res.*, 2002, **35**, 695; (c) B. M. Trost, *Science*, 1991, **254**, 1471.
- 27 (a) S. Mandal, S. K. Ghosh, P. Sar, A. Ghosh and R. Saha, *RSC Adv.*, 2016, **6**, 69605–69614; (b) M. Pagliaro, R. Ciriminna, H. Kimura, M. Rossi and C. D. Pina, *Angew. Chem., Int. Ed.*, 2007, **46**, 4434–4440; (c) W. H. Miles and K. B. Connell, *J. Chem. Educ.*, 2006, **83**, 285–286.
- 28 (a) R. M. P. Veenboer and S. P. Nolan, *Green Chem.*, 2015, **17**, 3819–3825; (b) A. B. Cuenca, G. Mancha, G. Asensio and M. Medio-Simón, *Chem.–Eur. J.*, 2008, **14**, 1518–1523; (c) J. Kim, D.-H. Lee, N. Kaluntharage and C. S. Yi, *ACS Catal.*, 2014, **4**, 3881–3885; (d) G. V. M. Sharma and A. K. Mahalingam, *J. Org. Chem.*, 1999, **64**, 8943–8944; (e) Z. Zhu and J. H. Espenson, *J. Org. Chem.*, 1996, **61**, 324–328; (f) O. V. Khazipov, D. V. Nykytenko, T. V. Krasnyakova, A. N. Vdovichenko, D. S. F. Frias and S. A. Mitchenko, *J. Mol. Catal. A: Chem.*, 2017, **426**, 490–498; (g) Q. Xu, H. Xie, P. Chen, L. Yu, J. Chen and X. Hu, *Green Chem.*, 2015, **17**, 2774–2779.
- 29 (a) B. N. Moghadam, B. Akhlaghinia and S. Rezazadeh, *Res. Chem. Intermed.*, 2016, **42**, 1487–1501; (b) L. Busetto, R. Mazzoni, M. Salmi, S. Zacchini and V. Zanotti, *RSC Adv.*, 2012, **2**, 6810–6816; (c) A. Mirzaei, S. Biswas and J. S. M. Samec, *Synthesis*, 2012, **44**, 1213–1218; (d) V. Namboodiri and R. S. Varma, *Tetrahedron Lett.*, 2002, **43**, 4593–4595; (e) P. Salehi, N. Iranpoor and F. K Behbahani, *Tetrahedron*, 1998, **54**, 943–948.
- 30 A. Fürstner, *ACS Cent. Sci.*, 2016, **2**, 778–789.
- 31 K. Hovenkotter, H. Braunstein, S. Langevin and T. K. Beng, *Org. Biomol. Chem.*, 2017, **15**, 1217–1221.
- 32 (a) K. Ponsold and H. Kasch, *Tetrahedron Lett.*, 1977, **46**, 4463–4464; (b) G. Pandey, S. Pal and R. Laha, *Angew. Chem., Int. Ed.*, 2013, **52**, 5146–5149; (c) H. Im, D. Kang, S. Choi, S. Shin and S. Hong, *Org. Lett.*, 2018, **20**, 7437–7441; (d) Y. Li and W. Bao, *Adv. Synth. Catal.*, 2009, **351**, 865–868; (e) S. Y. Zhang, H. Gang, Y. Zhao, K. Wright, W. A. Nack and G. Chen, *J. Am. Chem. Soc.*, 2012, **134**, 7313–7316; (f) F.-J. Chen, S. Zhao, F. Hu, K. Chen, Q. Zhang, S.-Q. Zhang and B.-F. Shi, *Chem. Sci.*, 2013, **4**, 4187–4192; (g) G. Shan, X. Y. Yang and Y. Rao, *Angew. Chem., Int. Ed.*, 2013, **52**, 13606–13610.
- 33 T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal and S. W. Krska, *Chem. Soc. Rev.*, 2016, **45**, 546–576.
- 34 H. Hu, S. Chen, M. Mandal, S. M. Pratik, J. A. Buss, S. W. Krska, C. J. Cramer and S. S. Stah, *Nat. Catal.*, 2020, **3**, 358–367.

