Synthetic Methods

International Edition: DOI: 10.1002/anie.201600912 German Edition: DOI: 10.1002/ange.201600912

A Hydrazone-Based *exo*-Directing-Group Strategy for β C–H Oxidation of Aliphatic Amines

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Dedicated to Professor Stephen F. Martin on the occasion of his 70th birthday

Abstract: Described is a new hydrazone-based exo-directing group (DG) strategy developed for the functionalization of unactivated primary β C–H bonds of aliphatic amines. Conveniently synthesized from protected primary amines, the hydrazone DGs are shown to site-selectively promote the β acetoxylation and tosyloxylation via five-membered exo-palladacycles. Amines with a wide scope of skeletons and functional groups are tolerated. Moreover, the hydrazone DG can be readily removed, and a one-pot C–H acetoxylation/DG removal protocol was also discovered.

Control of site selectivity still represents a fundamental and ongoing challenge for C–H functionalization.^[1] In particular, given that aliphatic amines are ubiquitously found in approved drugs and other biologically important compounds,^[2] site-selective C–H functionalization of amines and protected amines, such as amides, sulfonamides, and carbamates, undoubtedly holds significant potential for pharmaceutical and agrochemical applications.^[3–10]

It is known that the α position of aliphatic amines, inherently activated by the adjacent nitrogen atom, can be derivatized by a large collection of pathways (Figure 1a).^[3] Amide- and sulfonamide-type directing group (DG) strategies have been frequently employed to activate the Y C-H bonds of amines via five-membered metallacycle intermediates.^[4,5] To functionalize the remote δ - and ε -positions, either [1,5] or [1,6] H abstraction through generation of highly reactive nitrogen-centered radicals has proved to be a general approach.^[6] Moreover, Sanford and co-workers recently reported a direct approach for hydroxylation and chlorination of terminal positions of amines using platinum catalysis.^[7] Despite all these advances, methods that can site-selectively functionalize unactivated B C-H bonds of amines remain underdeveloped. In 2006, Du Bois and co-workers reported a rhodium-catalyzed intramolecular β C–H amination by nitrene insertion to form masked 1,2-diamines (Figure 1b).^[8] Gaunt and co-workers disclosed a novel free-amine-directed β-functionalization, in which use of sterically hindered secondary amines appears to be important.^[9] In addition, β arylation of Boc-protected dialkylamines has been discovered

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Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201600912.



Figure 1. Amine-directed $C(sp^3)$ -H functionalization. FG = functional group.

to proceed by a deprotonation/migratory pathway.^[10] Herein, an approach for site-selective functionalization of unactivated primary β C–H bonds of aliphatic amines is described to proceed by using a hydrazone-based *exo*-type DG.^[11]

Utilizing an oxime-based exo-DG, $\beta C(sp^3)$ -H functionalization of masked alcohols has been recently achieved by our group.^[12] We envisioned that this *exo*-directing strategy could be extended to the β oxidation of amines through development of a new hydrazone-based DG (Figure 2). It was anticipated that the hydrazone **B**, prepared from the corresponding monoprotected primary amine A, would guide metalation at the primary β -position through forming a fivemembered *exo*-metallacycle (C), which should lead to β functionalized amines. The use of 2,6-dimethoxyphenyl as the hydrazone substituent should prevent endo metalation and stabilize the metallacycle.^[12b,d,e] However, the challenges associated with this strategy are twofold: 1) compared to alcohols, amines are generally more coordinating and susceptible to oxidation. Thus, to enable the desired site selectivity, choosing an appropriate amine protecting group (PG) becomes important. 2) Efficient installation and chemoselective removal of the hydrazone DG through forming and breaking an N-N bond is nontrivial.^[13]

To test the feasibility of the proposed strategy, a practical DG-installation method was first sought. Gratifyingly, when NBzONH₂ was employed as the electrophilic amination reagent,^[14] sec-butylamine was protected and aminated to





Figure 2. β C–H oxidation of protected aliphatic amines.

give a tosyl-protected hydrazine intermediate, which upon condensation with 2,6-dimethoxybenzaldehyde (Ar¹CHO) provided the hydrazone **1a** in 78% yield as a single *E* isomer (Scheme 1a). Both NBzONH₂ and Ar¹CHO are commercially available and can be prepared in bulk.^[15] In addition to this one-pot procedure, **1a** can also be prepared by a convenient chromatography-free protocol from the corresponding sulfonamide (Scheme 1 b). This protocol is also general to other sulfonamide substrates (see Table 2), and can be operated on a multigram scale without need of chromatography or isolation of the hydrazine intermediate.



Scheme 1. Installation of hydrazone DG. Ts = 4-toluenesulfonyl.

The β -acetoxylation reaction was investigated initially using **1a** as the model substrate. After a careful evaluation of various reaction parameters, the desired 1,2-amino alcohol **2a** was isolated in 73 % yield with Pd(OAc)₂ as the catalyst, PhI(OAc)₂ as the oxidant, and LiOAc (1 equiv) and Ar¹CHO Table 1: Optimized reaction conditions and control experiments.^[a]



Entry	Variations from the "standard conditions"	Yield [%] ^[b]	Conv. [%] ^[b]
1	without Pd(OAc) ₂	_	10
2	130 mol% instead of 230 mol% PhI(OAc) ₂	64	85
3	NFSI instead of PhI(OAc) ₂	23	86
4	KPS instead of PhI(OAc) ₂	26	100
5	200 mol% KPS and 20 mol% PhI (OAc) ₂ instead of	24	100
	PhI(OAc) ₂		
6	without LiOAc	42	100
7	LiCl instead of LiOAc	39	84
8	NaOAc instead of LiOAc	69	100
9	KOAc instead of LiOAc	68	100
10	without Ar ¹ CHO ^[c]	64	100
11	without Ac ₂ O	38	93
12	H ₂ O instead of Ac ₂ O	_	100
13	100 mg 4 Å M.S. instead of Ar ¹ CHO and Ac ₂ O ^[d]	< 5	100
14	DCE/AcOH/Ac ₂ O 4:4:1 instead of AcOH/Ac ₂ O	70	90
15	one portion addition of Pd(OAc), and oxidant	66	100

[a] The reactions were run on a 0.1 mmol scale in 1.0 mL solvent. [b] Yields determined by NMR spectroscopy using 1,1,2,2-tetrachloroethane as the internal standard. [c] $Ar^{1}CHO$ was recovered in 11% yield when no extra $Ar^{1}CHO$ was added. [d] DCE/AcOH (1:1) was used as the solvent. KPS = potassium persulfate, M.S. = molecular sieves, NSFI = *N*fluorobenzenesulfonimide.

(20 mol %) as the additives (see equation in Table 1). Air can be well tolerated, and a two-portion addition of the palladium and oxidant was found to be beneficial. To understand the role of each reactant, control experiments were conducted (Table 1). As expected, palladium played a pivotal role in this reaction (entry 1). While 2.3 equivalents of PhI(OAc)₂ proved to be optimal, the yield only dropped marginally with 1.3 equivalents of the oxidant (entry 2). In contrast, other common oxidants, including KPS and NFSI, were less effective (entries 3-5). Acetate additives were found to facilitate the acetoxylation (entries 6-9).^[16] In addition, Ar1CHO and Ar1CN were identified as the major byproducts, presumably from the hydrolysis and elimination of the DG, which was supported by the detrimental effect of added water (entry 12). Thus, additional Ar¹CHO and Ac₂O were intentionally employed to suppress hydrolysis of the hydrazone DG. The extra aldehyde would disfavor the hydrolysis equilibrium and Ac₂O can remove adventitious water. In contrast, the use of molecular sieves instead of Ar¹CHO and Ac₂O was ineffective (entry 13). Finally, DCE can be used as a cosolvent (entry 14), and the one-portion addition procedure slightly decreased the yield (entry 15).

The scope of the β -acetoxylation reaction was then examined under the optimized reaction conditions (Table 2). First, a range of sulfonyl groups other than Ts can be used as the PG for this transformation (**2a**–**e**), including nosyl (**2d**) and SES^[17] (**2e**) groups, which are known to be removable under mild reaction conditions. Nevertheless,



[a] Reactions were run on a 0.15 mmol scale. [b] 400 mol% of PhI(OAc)₂ were used. [c] Drug from which the substrate was directly derived (see the Supporting Information for details). TIPS = triisopropylsilyl, TMS = triimethylsilyl.

Amphetamine)[c]

amide- or carbamate-type PGs remained challenging for this transformation, likely because of their enhanced Lewis basicity which inhibits the cyclopalladation step. Substrates with various alkyl scaffolds afforded the desired acetoxylation products (**2 f-k**) in good yields. The oxidation is selective for the primary β C–H bonds over either secondary/tertiary β -positions or more remote primary positions. The hydrazone substrates can be directly derived from a number of approved drugs, such as Rimantadine (**21**), Forthane (**2k**), Mexiletine (**2n**), and Amphetamine (**2v**), in simple operations without chromatography. Slower reactions were observed for substrates with adjacent coordinating groups, for example, esters (**20**) and ethers (**2m** and **2n**). Nevertheless, moderate to good yields were obtained after an longer reaction time. Several

common and versatile functional groups, including cyclopropane (2t), aryl bromide (2r), electron-deficient olefin (2s), phthalimide (2u), and silyl ether (2p), were also tolerated. It is worth noting that, for the Amphetaminederived substrate, the $C(sp^3)$ -H bond was selectively acetoxylated over the more reactive *ortho*-aryl C-H bond (2v), and represents a feature which is distinct from the amidedirected reactions.^[18] Nevertheless, attempts to activate methylene C-H bonds using this strategy remained unsuccessful (2w and 2x).^[19]

The acetoxylation reaction proved to be scalable, and on a larger scale the palladium loading can be significantly reduced [Eq. (1)]. In addition, the hydrazone DG can be efficiently removed to give the protected 1,2-amino alcohol **3** through cleavage of the N–N bond with zinc powder (Scheme 2 a). Given that this cleavage reaction can also use



Scheme 2. Removal of the DG and PG.

HOAc/Ac₂O as the solvent, a convenient one-pot acetoxylation/DG removal sequence was achieved simply by adding zinc to the reaction mixture after completion of the β acetoxylation step (Scheme 2b). Furthermore, the Ts group in **3** can be efficiently switched to a more labile trifluoroacetyl (TFA) group under mild reaction conditions.^[20]



More recently, a $\beta C(sp^3)$ -H sulfonyloxylation/S_N2 approach was developed for the diverse functionalization of masked alcohols.^[12c] Thus, it was expected that a similar strategy could be adopted for late-stage diversification of aliphatic amines using a hydrazone DG, and in turn should expedite analogue preparation. Indeed, starting with Amphetamine, a chromatography-free three-step sequence afforded the hydrazone **5** in 72 % yield, wherein a quinoline-



Scheme 3. A $\beta\text{-}Tosyloxylation$ strategy to access Amphetamine derivatives. THF = tetrahydrofuran.

based DG (DG^Q) was employed (Scheme 3 a).^[21] After a slight modification of the previously reported sulfonyloxylation conditions,^[12c] the desired β -tosyloxylation product **6** was isolated in 52 % yield. As expected, **6** can be rapidly derivatized by S_N2 reactions to introduce various functional groups, including sulfide, ether, bromide, and azide groups (**7a–d**) at the terminal position (Scheme 3 b). Moreover, the quinoline-based DG can also be smoothly removed with zinc in acetic acid (Scheme 3 c).

In summary, a hydrazone-based DG strategy is described to realize the β C–H functionalization of aliphatic amines. A number of key features can be noted: first, from common primary amines, an efficient chromatography-free or one-pot procedure was made available to install the DG. Second, through forming a hydrazone-directed exo-palladacycle, the β C–H oxidation occurred site- and chemoselectively. Finally, the DGs can be easily removed either in a separate step or through a one-pot acetoxylation/reduction sequence. Considering the critical role of nitrogen-containing aliphatic moieties in pharmaceutical and agrochemical research, this hydrazone-based approach should offer new strategies to synthesize functionalized amines. Efforts to expand substrate and reaction scope, particularly regarding the activation of more challenging methylene C-H bonds, are currently underway.

Acknowledgments

We thank the CPRIT, Frasche Foundation, ACS PRF, and the Welch Foundation (F-1781) for funding. G.D. is a Searle Scholar and Sloan Fellow. Dr. Michael Young is thanked for providing chemicals and X-ray crystallography. We also acknowledge Yan Xu for providing chemicals, and Dr. Vincent Lynch for X-ray crystallography. Johnson Matthey is thanked for a generous donation of palladium salts. **Keywords:** amines \cdot C–H activation \cdot hydrazones \cdot oxidation \cdot palladium

How to cite: Angew. Chem. Int. Ed. 2016, 55, 5299–5303 Angew. Chem. 2016, 128, 5385–5389

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Received: January 26, 2016 Revised: February 24, 2016 Published online: March 22, 2016

