Synthetic Methods

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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 1 a).[3] Amide- and sulfonamide-type directing group (DG) strategies have been frequently employed to activate the γ 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 β 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 1 b).[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

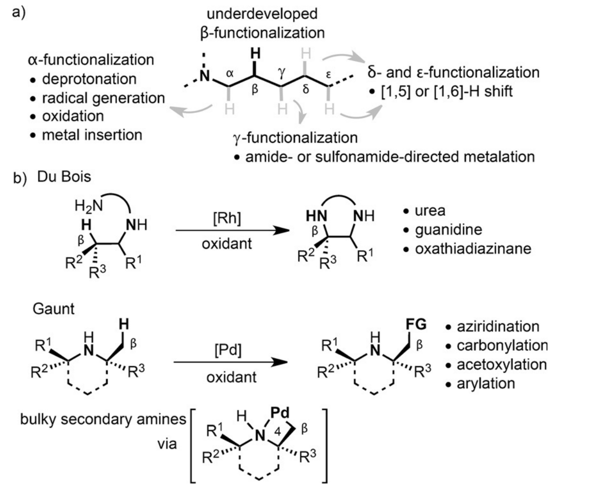

Figure 1. Amine-directed C(sp^3)–H functionalization. FG = functional group.

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, β 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 five-membered *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 NBzONH$_2$ was employed as the electrophilic amination reagent,[14] *sec*-butylamine was protected and aminated to

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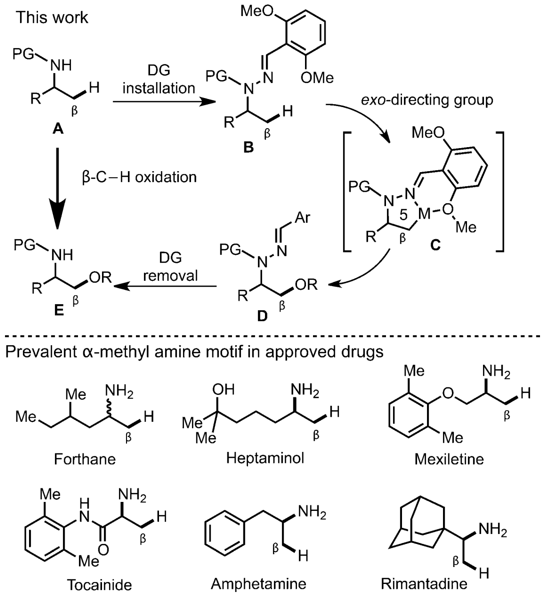
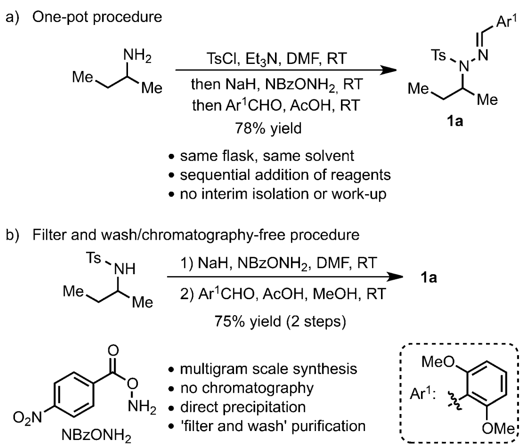


Figure 2. β C−H oxidation of protected aliphatic amines.

give a tosyl-protected hydrazine intermediate, which upon condensation with 2,6-dimethoxybenzaldehyde (Ar^1CHO) provided the hydrazone **1a** in 78% yield as a single *E* isomer (Scheme 1a). Both $NBzONH_2$ and Ar^1CHO 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 1b). 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.

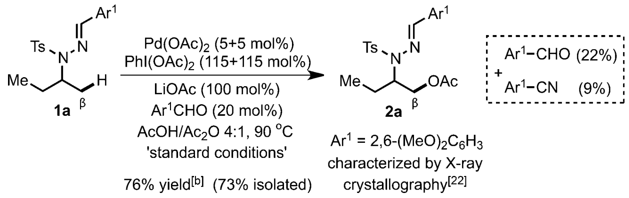


Scheme 1. Installation of hydrazone DG. Ts = 4-toluenesulfonyl.

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 Ar^1CHO (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, Ar^1CHO and Ar^1CN were identified as the major by-products, presumably from the hydrolysis and elimination of the DG, which was supported by the detrimental effect of added water (entry 12). Thus, additional Ar^1CHO and Ac_2O were intentionally employed to suppress hydrolysis of the hydrazone DG. The extra aldehyde would disfavor the hydrolysis equilibrium and Ac_2O can remove adventitious water. In contrast, the use of molecular sieves instead of Ar^1CHO and Ac_2O 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,

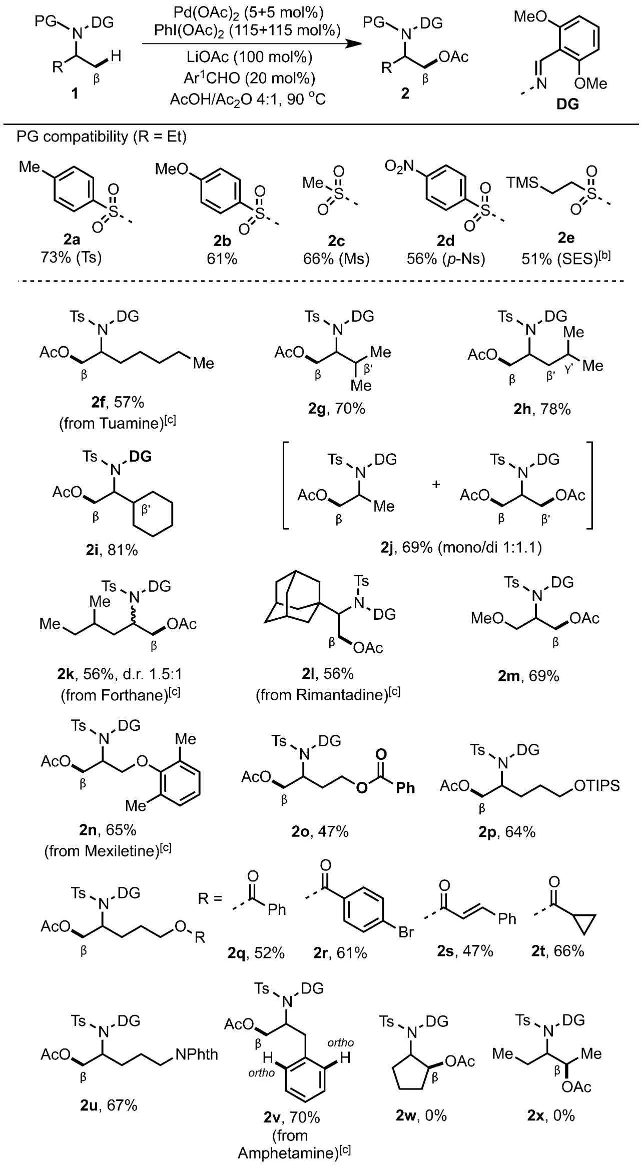
Table 1: Optimized reaction conditions and control experiments.[a]



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 $PhI(OAc)_2$	24	100
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^1CHO[c]	64	100
11	without Ac_2O	38	93
12	H_2O instead of Ac_2O	–	100
13	100 mg 4 Å M.S. instead of Ar^1CHO and Ac_2O[d]	<5	100
14	DCE/AcOH/Ac_2O 4:4:1 instead of AcOH/Ac_2O	70	90
15	one portion addition of $Pd(OAc)_2$ 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^1CHO was recovered in 11% yield when no extra Ar^1CHO was added. [d] DCE/AcOH (1:1) was used as the solvent. KPS = potassium persulfate, M.S. = molecular sieves, NFSI = *N*-fluorobenzenesulfonimide.

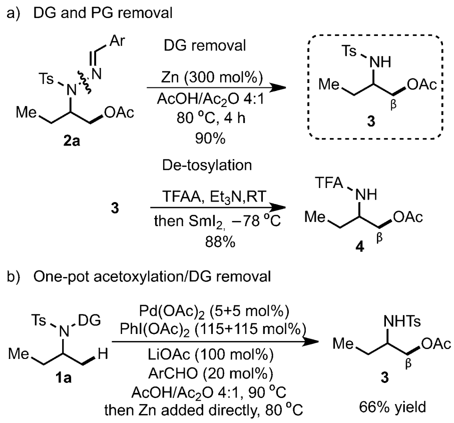
Table 2: Scope of the β-acetoxylation.[a]



[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 = trimethylsilyl.

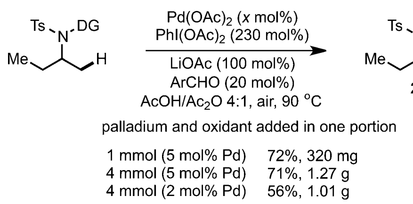
amide- or carbamate-type PGs remained challenging for this transformation, likely because of their enhanced Lewis basicity which inhibits the cyclopalladation step. Substrates with various alkyl scaffolds afforded the desired acetoxylation products (**2f–k**) in good yields. The oxidation is selective 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 (**2l**), 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 (**2o**) 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 Amphetamine-derived 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 amide-directed 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 2a). Given that this cleavage reaction can also use



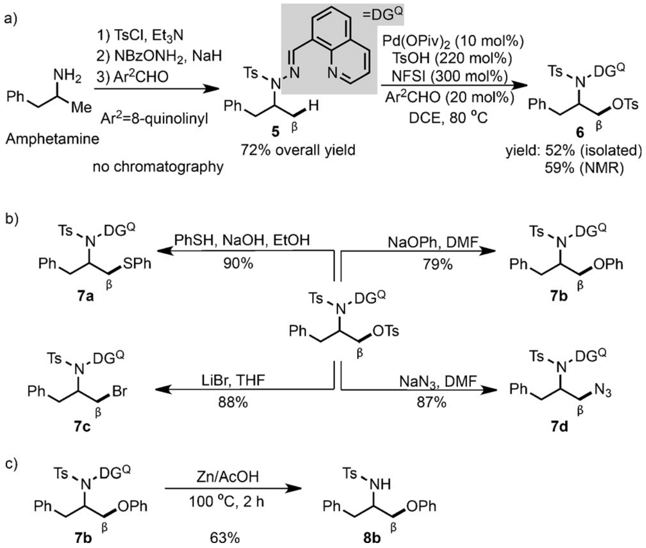
Scheme 2. Removal of the DG and PG.

HOAc/Ac_2O 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]



(1)

More recently, a β $C(sp^3)$–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 β-Tosyloxylation strategy to access Amphetamine derivatives. THF = tetrahydrofuran.

based DG (DG^{Q}) was employed (Scheme 3a).[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 3b). Moreover, the quinoline-based DG can also be smoothly removed with zinc in acetic acid (Scheme 3c).

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.

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Angew. Chem. **2016**, *128*, 5385–5389

[1] For selected reviews, see: a) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.* **2012**, *45*, 936; b) T. Newhouse, P. S. Baran, *Angew. Chem. Int. Ed.* **2011**, *50*, 3362; *Angew. Chem.* **2011**, *123*, 3422; c) H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857; d) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; e) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654; f) O. Daugulis, *Top. Curr. Chem.* **2010**, *292*, 57; g) O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902; h) G. Rousseau, B. Breit, *Angew. Chem. Int. Ed.* **2011**, *50*, 2450; *Angew. Chem.* **2011**, *123*, 2498; i) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726; *Angew. Chem.* **2013**, *125*, 11942; j) Z. Huang, G. Dong, *Tetrahedron Lett.* **2014**, *55*, 5869; k) B. Zhang, H.-X. Guan, B. Liu, B.-F. Shi, *Chin. J. Org. Chem.* **2014**, *34*, 1487; l) G. Qiu, J. Wu, *Org. Chem. Front.* **2015**, *2*, 169; m) Z. Huang, H. N. Lim, F. Mo, M. C. Young, G. Dong, *Chem. Soc. Rev.* **2015**, *44*, 7764.

[2] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257.

[3] For recent reviews, see: a) K. R. Campos, *Chem. Soc. Rev.* **2007**, *36*, 1069; b) E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2012**, *18*, 10092; c) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322.

[4] For seminal and recent examples, see: a) V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154; b) G. He, G. Chen, *Angew. Chem. Int. Ed.* **2011**, *50*, 5192; *Angew. Chem.* **2011**, *123*, 5298; c) G. He, Y. Zhao, S. Zhang, C. Lu, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 3; d) E. T. Nadres, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 7; e) S. Zhang, G. He, Y. Zhao, K. Wright, W. A. Nack, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 7313; f) S.-Y. Zhang, G. He, W. A. Nack, Y. Zhao, Q. Li, G. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 2124; g) N. Rodríguez, J. A. Romero-Revilla, M. A. Fernandez-Ibanez, J. C. Carretero, *Chem. Sci.* **2013**, *4*, 175; h) M. Fan, D. Ma, *Angew. Chem. Int. Ed.* **2013**, *52*, 12152; *Angew. Chem.* **2013**, *125*, 12374; i) X. Ye, Z. He, T. Ahmed, K. Weise, N. G. Akhmedov, J. L. Petersen, X. Shi, *Chem. Sci.* **2013**, *4*, 3712; j) P.-X. Ling, S.-L. Fang, X.-S. Yin, K. Chen, B.-Z. Sun, B.-F. Shi, *Chem. Eur. J.* **2015**, *21*, 17503; k) L.-S. Zhang, G. Chen, X. Wang, Q.-Y. Guo, X.-S. Zhang, F. Pan, K. Chen, Z.-J. Shi, *Angew. Chem. Int. Ed.* **2014**, *53*, 3899; *Angew. Chem.* **2014**, *126*, 3980; l) K. S. L. Chan, M. Wasa, L. Chu, B. N. Laforteza, M. Miura, J.-Q. Yu, *Nat. Chem.* **2014**, *6*, 146.

[5] For a recent γ-C–H functionalization of 1,2-amino alcohols, see: J. Calleja, D. Pla, T. W. Gorman, V. Domingo, B. Haffemayer, M. J. Gaunt, *Nat. Chem.* **2015**, *7*, 1009.

[6] For recent examples, see: a) L. R. Reddy, B. V. S. Reddy, E. J. Corey, *Org. Lett.* **2006**, *8*, 2819; b) C. G. Francisco, A. J. Herrera, A. Martin, I. Perez-Martin, E. Suarez, *Tetrahedron Lett.* **2007**, *48*, 6384; c) R. Fan, D. Pu, F. Wen, J. Wu, *J. Org. Chem.* **2007**, *72*, 8994; d) K. Chen, J. M. Richter, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 7247; e) T. Liu, T.-S. Mei, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 5871.

[7] M. Lee, M. S. Sanford, *J. Am. Chem. Soc.* **2015**, *137*, 12796.

[8] a) M. Kim, J. V. Mulcahy, C. G. Espino, J. Du Bois, *Org. Lett.* **2006**, *8*, 1073; b) D. E. Olson, J. Du Bois, *J. Am. Chem. Soc.* **2008**, *130*, 11248; For a related allylic oxidation, see: I. I. Strambeanu, M. C. White, *J. Am. Chem. Soc.* **2013**, *135*, 12032.

[9] a) A. McNally, B. Haffemayer, B. S. L. Collins, M. J. Gaunt, *Nature* **2014**, *510*, 129; b) A. P. Smalley, M. J. Gaunt, *J. Am. Chem. Soc.* **2015**, *137*, 10632; c) C. He, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2015**, *54*, 15840; *Angew. Chem.* **2015**, *127*, 16066.

[10] a) S. Seel, T. Thaler, K. Takatsu, C. Zhang, H. Zipse, B. F. Straub, P. Mayer, P. Knochel, *J. Am. Chem. Soc.* **2011**, *133*, 4774; b) A. Millet, P. Larini, E. Clot, O. Baudoin, *Chem. Sci.* **2013**, *4*, 2241; c) A. Millet, D. Dailler, P. Larini, O. Baudoin, *Angew. Chem. Int. Ed.* **2014**, *53*, 2678; *Angew. Chem.* **2014**, *126*, 2716.

[11] For seminal examples of *exo*-type DGs in C–H functionalization, with stoichiometric Pd, see: a) B. D. Dangel, K. Godula, S. W. Youn, B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2002**, *124*, 11856; On an aryl C–H bond, see: b) L. V. Desai, K. J. Stowers, M. S. Sanford, *J. Am. Chem. Soc.* **2008**, *130*, 13285.

[12] For a review and examples, see: a) F. Mo, G. Dong, *Chem. Lett.* **2014**, *43*, 264; b) Z. Ren, F. Mo, G. Dong, *J. Am. Chem. Soc.* **2012**, *134*, 16991; c) Y. Xu, G. Yan, Z. Ren, G. Dong, *Nat. Chem.* **2015**, *7*, 829; d) S. J. Thompson, D. Thach, G. Dong, *J. Am. Chem. Soc.* **2015**, *137*, 11586; e) Z. Ren, J. E. Schulz, G. Dong, *Org. Lett.* **2015**, *17*, 2696; f) For an iridium-catalyzed β-amination with an oxime *exo*-DG, see: T. Kang, H. Kim, J. G. Kim, S. Chang, *Chem. Commun.* **2014**, *50*, 12073.

[13] For reviews of electrophilic amination, see: a) Y. Tamura, J. Minamikaw, M. Ikeda, *Synthesis* **1977**, 1; b) E. Erdik, *Tetrahedron* **2004**, *60*, 8747.

[14] a) W. N. Marmer, G. Marerker, *J. Org. Chem.* **1972**, *37*, 3520; b) Y. Shen, G. K. Friestad, *J. Org. Chem.* **2002**, *67*, 6236.

[15] For a kilogram-scale synthesis of $NBzONH_2$, see: Z. Shi, S. Kiau, P. Lobben, J. Hynes, H. Wu, L. Parlanti, R. P. Discordia, W. Doubleday, K. Leftheris, A. J. Dyckman, S. T. Wrobleski, K. Dambalas, S. Tummala, S. S. W. Leung, E. T. Lo, *Org. Process Res. Dev.* **2012**, *16*, 1618.

[16] The acetate anion may facilitate the C–O bond reductive elimination by an S_N2 pathway. For representative studies of S_N2-type reductive elimination on palladium(IV) intermediates, see: a) G. Liu, S. S. Stahl, *J. Am. Chem. Soc.* **2006**, *128*, 7179; b) J. M. Racowski, J. B. Gary, M. S. Sanford, *Angew. Chem. Int. Ed.* **2012**, *51*, 3414; *Angew. Chem.* **2012**, *124*, 3470; c) N. M. Camasso, M. H. Pérez-Temprano, M. S. Sanford, *J. Am. Chem. Soc.* **2014**, *136*, 12771.

[17] The SES protecting group can be readily removed using fluoride salts under mild reaction conditions. See: P. Ribière, V. Declerck, J. Martinez, F. Lamaty, *Chem. Rev.* **2006**, *106*, 2249.

[18] W. A. Nack, G. He, S.-Y. Zhang, C. Lu, G. Chen, *Org. Lett.* **2013**, *15*, 3440.

[19] Preparation of tertiary alkyl substrates was also unsuccessful, likely because of the increased steric hindrance of the hydrazone moiety compared to the corresponding oximes.

[20] Z. Moussa, D. Romo, *Synlett* **2006**, 3294.

[21] The use of 2,6-dimethoxyphenyl-based DG proved much less effective, giving only 14 % yield of the sulfonyloxylation product.

[22] CCDC 1449052 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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