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Authors: Heng Jiang and Armido Studer

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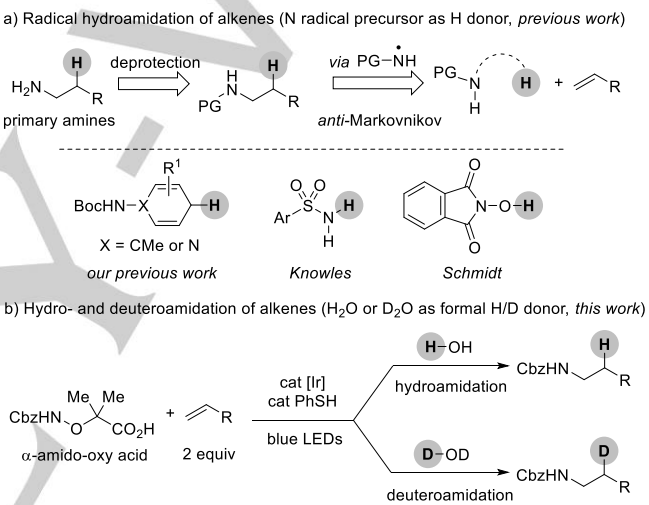
Anti-Markovnikov Radical Hydro- and Deuteroamidation of Unactivated Alkenes

Heng Jiang and Armido Studer*

Abstract: Radical *anti*-Markovnikov hydro- and deuteroamidation of unactivated alkenes is achieved by merging photoredox and thiol catalysis. Reactions proceed by addition of the electrophilic CbzHN-radical, readily generated by SET oxidation of an α-Cbz-amino-oxy acid, to an alkene. The adduct radical is reduced by thiophenol added as an organic polarity reversal cocatalyst which mediates the H-transfer from H_2O to the alkyl radical intermediate. Accordingly, deuteroamidation of alkenes is realized with excellent D-incorporation by using D_2O as the stoichiometric formal radical reducing reagent. The reaction features low redox catalyst loading, excellent *anti*-Markovnikov selectivity, and the use of a large alkene excess is not required. Diverse Cbz-protected primary amines including β-deuterated amines can be obtained by applying this method.

Bioactive natural products, pharmaceuticals and agrochemicals often contain a primary amine functionality. Such amines also serve as precursors for structurally more complex N-containing compounds. Regarding their preparation, the hydroamination of an alkene is an ideal synthetic strategy, since the CC double bond can be readily accessed from various functional groups which themselves are difficult to be transferred to the amino functionality.[1] Considering transition-metal catalysed hydroamination, most methods use secondary amines as N-donors providing the corresponding tertiary amines as products in Markovnikov-type selectivity.[2] Recently, radical hydroamidation has emerged as a promising approach for the preparation of N-protected primary amines from the corresponding alkenes (Scheme 1a).[3] In contrast to transition-metal mediated processes, radical alkene hydroamidation that generally proceeds *via* electrophilic amidyl radicals delivers the *anti*-Markovnikov products.[4] However, the use of a large excess of the alkene component (in general 10 equivalents)[3a],[3c-e] or sulfonyl protecting groups that have to be removed under harsh conditions restricts their synthetic potential,[3b],[3f] especially for late-stage modification of structurally complex alkenes. Consequently, an efficient and practical method for the preparation of protected primary amines by intermolecular radical *anti*-Markovnikov hydroamidation is demanded.[5],[6]

Amides or their derivatives used in established *anti*-Markovnikov radical hydroamidations generally serve as both amidyl radical precursors and as H-donors.[3] Since D-labelled amidyl radical precursors are more difficult to prepare, radical alkene deuteroamidation by using a D-labelled amidyl radical precursor is challenging with existing methodology.[3a] Notably, D-labelling is important for analysis of metabolic pathways of drug candidates and for studying reaction mechanisms by using NMR and mass spectrometry techniques.[7] Moreover, selectively deuterated bioactive molecules are promising pharmaceuticals by enhancing their pharmacokinetic and pharmacodynamic properties.[8] Therefore, the development of practical alkene deuteroamination methods for the synthesis of β-deuterated amines with high D incorporation is of importance.[9]



Scheme 1. *anti*-Markovnikov hydro- and deuteroamidation of alkenes (PG = protecting group).

We report herein cooperative photoredox[10] and thiol catalyzed *anti*-Markovnikov hydroamidation and deuteroamidation of alkenes by using an Ir-complex as a photocatalyst and catalytic thiophenol as the H or D-transfer mediator using an α-amido-oxy acid as N-radical precursor (Scheme 1b).[11] Compared to previous methods for radical hydroamidation, our process uses only two equivalents of the alkene component and a small amount of both photocatalyst and thiophenol polarity reversal catalyst.[12] Notably, the Cbz-group used herein is a common N-protecting group in organic synthesis.[13] Considering the alkene deuteroamidation, satisfactory D-incorporation of diverse alkenes can be achieved, demonstrating the high efficiency of thiophenol acting as a radical deuteration reagent in combination with D_2O.

The proposed catalytic cycle of the *anti*-Markovnikov hydroamidation and deuteroamidation is presented in Scheme 2. The sequence starts by photo-excitation of the Ir(III)-complex upon visible light irradiation to generate the excited Ir(III)*-complex, which is SET-reduced by the α-Cbz-amino-oxy carboxylate, formed by deprotonation with Na_2CO_3, to generate the carboxyl radical along with the reduced Ir(II)-complex. The carboxyl radical sequentially fragments CO_2 and acetone to

[*] Dr. H. Jiang, Prof. Dr. A. Studer
Organisch-Chemisches Institut, Westfälische Wilhelms-Universität
Corrensstraß 40, 48149 Münster (Germany)
E-mail: studer@uni-muenster.de

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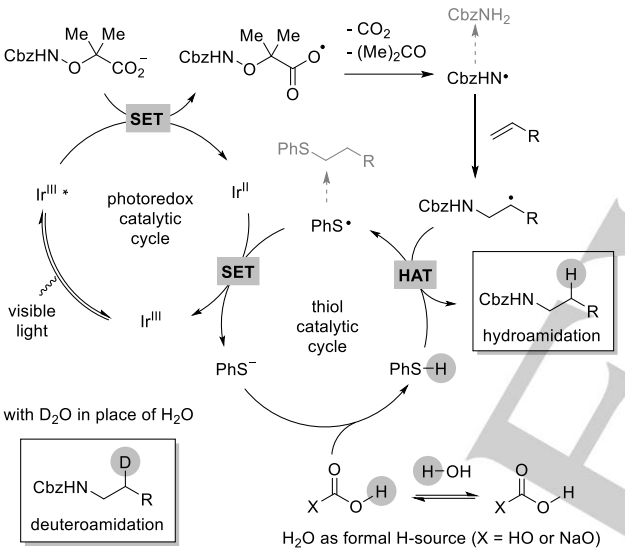
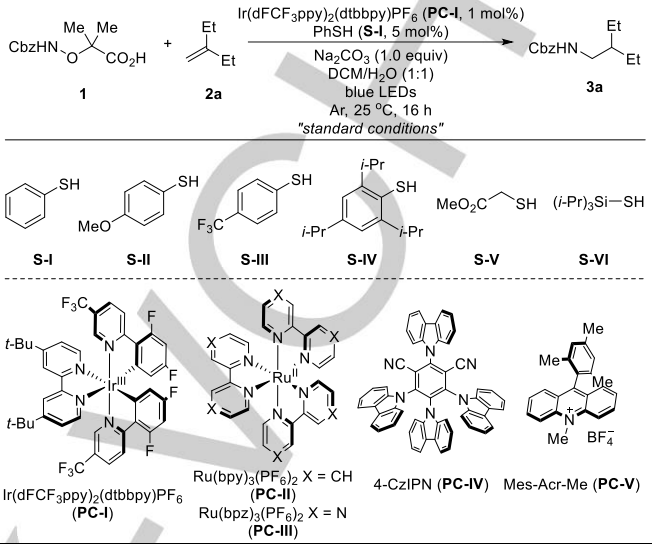
generate the N-centered radical (CbzHN•), which then adds to the terminal position of the alkene to give the corresponding adduct alkyl radical.[11],[14] The high regioselectivity of this addition step explains the *anti*-Markovnikov selectivity.[4] The hydroamidation product is eventually formed by reduction of the alkyl radical with PhSH. This step also delivers the phenylthiyl radical, that undergoes SET-reduction by the Ir(II)-complex to regenerate the ground state Ir(III)-complex along with the thiolate anion.[15] $NaHCO_3$ or H_2CO_3, that readily exchange their protons with H_2O, serve as the proton donor to regenerate thiophenol. Thus, H_2O is the formal H-donor for the reduction step and by simply replacing H_2O with D_2O, the process will deliver the corresponding deuteroamidation product. A pitfall in this dual catalytic cycle is the direct reduction of CbzHN• by PhSH to give $CbzNH_2$. However, considering polar effects, the reduction of the electrophilic amidyl radical by the "electrophilic" H-donor PhSH should be rather slow.[12,16] As an additional problem, radical thiol-ene reaction would consume the thiol cocatalyst.[16]



Scheme 2. Proposed catalytic cycle.

We commenced the study by using the amidyl radical precursor **1** in combination with 2-ethylbutene **2a** to provide **3a** with complete regiocontrol. Extensive experimentation revealed that the hydroamidation is best conducted with $Ir(dFCF_3ppy)_2(dtbbpy)PF_6$ as the photocatalyst (PC-Ⅰ, 1 mol%) in combination with PhSH (5 mol%) as the thiol cocatalyst, Na_2CO_3 as the base in dichloromethane (DCM) and water (1:1) at room temperature for 16 hours under blue light irradiation. Targeted **3a** was isolated in 81% yield. Control experiments revealed the necessity of photocatalyst, thiol, base and light irradiation (entries 2-4 and 6). The yield was diminished in the absence of H_2O due to the lower solubility of the α-amido-oxy acid carboxylate (entry 5). PhSH was demonstrated to be the best thiol cocatalyst, since the use of other thiols including aryl thiols (entries 7-9), an alkyl thiol (entry 10) and a silyl thiol (entry 11) gave lower yields. Other photoredox catalysts such as $Ru(bpy)_3(PF_6)_2$ (**PC-Ⅱ**), $Ru(bpz)_3(PF_6)_2$ (**PC-Ⅲ**) and the organic systems 4-CzIPN (**PC-Ⅳ**) and Mes-Acr-Me (**PC-Ⅴ**) provided worse results (entries 12–15).

Table 1. Reaction optimization.



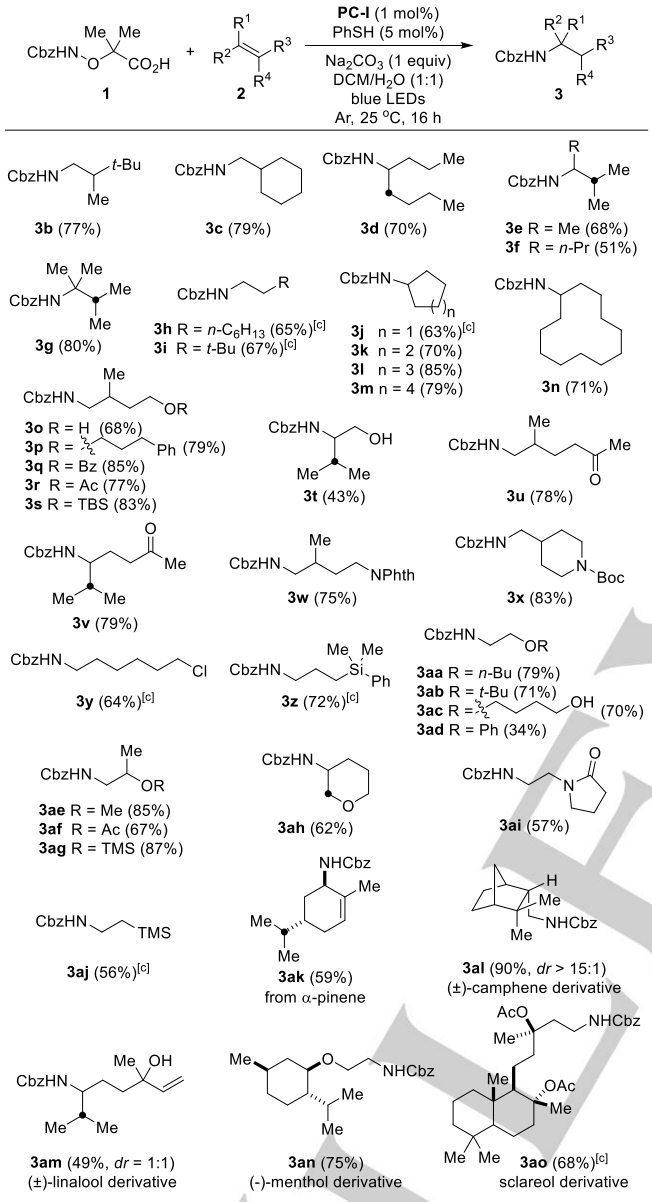
Entry[a]	Deviation from above	Yield%[b]
1	**none**	**83** (81)
2	w/o photocatalyst Ⅰ	n.d.
3	w/o PhSH **S-Ⅰ**	5
4	w/o Na_2CO_3	n.d.
5	w/o H_2O	51
6	conducted in the dark	n.d.
7	**S-Ⅱ** instead of **S-Ⅰ**	73
8	**S-Ⅲ** instead of **S-Ⅰ**	29
9	**S-Ⅳ** instead of **S-Ⅰ**	70
10	**S-Ⅴ** instead of **S-Ⅰ**	22
11	**S-Ⅵ** instead of **S-Ⅰ**	17
12	$Ru(bpy)_3(PF_6)_2$ instead of Ⅰ	n.d.
13	$Ru(bpz)_3(PF_6)_2$ instead of Ⅰ	n.d.
14	4-CzIPN instead of Ⅰ	trace[c]
15	Mes-Acr-Me instead of Ⅰ	6[c]

[a] Reaction conditions: A mixture of **1** (0.2 mmol, 1 equiv), **2a** (0.4 mmol, 2 equiv), photocatalyst (0.002 mmol, 1 mol%), thiol (0.01 mmol, 5 mol%), Na_2CO_3 (0.2 mmol, 1 equiv), H_2O (2 mL) and DCM (2 mL) was irradiated by a 20 W blue LEDs at 25 ℃ for 16 h. [b] The yield was determined by ^1H NMR analysis using CH_2Br_2 as an internal standard. [c] 5 mol% photocatalyst was used.

To explore the reaction scope, various alkenes were examined (Table 2). A series of unactivated radical acceptors including 1,1-disubstituted alkenes (**3b** and **3c**), an internal non-cyclic alkene (**3d**), trisubstituted alkenes (**3e** and **3f**) and terminal alkenes (**3h** and **3i**) engaged in the radical hydroamidation. Amazingly, even a tetrasubstituted alkene could be hydroamidated with the novel method providing **3g** in a very good yield (80%). Moreover, cyclic alkenes were readily converted to the N-protected amines **3j**-**3n** in 63-85% yields. Next, we examined functional group tolerance and found that different functionalities including free alcohols (**3o** and **3t**),

ethers (**3p**), esters (**3q** and **3r**), silyl ethers (**3s**), ketones (**3u** and **3v**), amines (**3w** and **3x**), halides (**3y**) and silanes (**3z**) are all tolerated and the corresponding Cbz-protected primary amines were isolated in moderate to very good yields (43-85%).

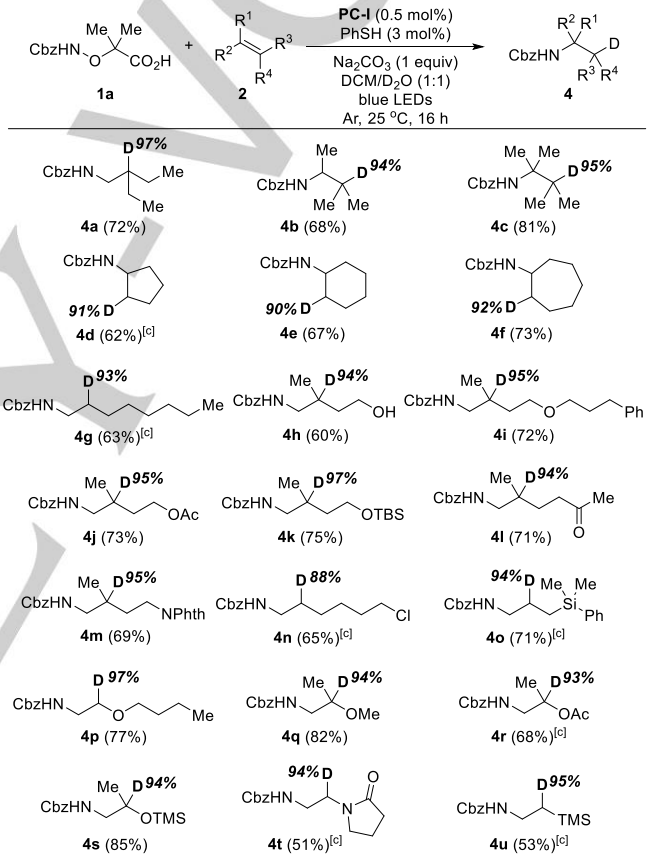
Table 2. Alkene hydroamidation – reaction scope.[a],[b]



[a] Reaction conditions: A mixture of **1** (0.2 mmol, 1 equiv), **2** (0.4 mmol, 2 equiv), **PC-Ⅰ** (0.002 mmol, 1 mol%), PhSH (0.01 mmol, 5 mol%), Na_2CO_3 (0.2 mmol, 1 equiv), H_2O (2 mL) and DCM (2 mL) was irradiated by a 20 W blue LEDs at 25 °C for 16 h. [b] Isolated yields are provided. [c] K_3PO_4 (0.2 mmol, 1 equiv) was used instead of Na_2CO_3.

As expected considering polar effects, electron-rich alkenes such as vinyl ethers, silyl enol ethers, enol esters, enamides and vinyl silanes underwent this hydroamidation reaction smoothly, affording N-protected β-amino alcohols **3aa**-**3ah**, the 1,2-diamine derivative **3ai** and the β-amido alkylsilane **3aj** in moderate to good yields (34-87%), further enlarging the scope of this method. In addition, several alkene containing natural products were employed to evaluate the synthetic potential of this hydroamidation. Reaction of α-pinene provided the ring-opening product **3ak** in 59% yield. This result clearly supported the radical nature of the transformation. Camphene afforded the corresponding amide **3al** with excellent diastereoselectivity and very high yield (90%). The relative configuration was assigned by NOE-experiments (see Supporting Information). It is notable that the hydroamidation of linalool occurred with complete regioselectivity at the more electron rich internal double bond (**3am**). Menthol (**3an**) and sclareol (**3ao**) derivatives also engaged in the hydroamidation reaction to provide structurally more complex Cbz-protected amines in good yields.

Table 3. Radical deuteroamidation of various alkenes.[a],[b]



[a] Reaction conditions: A mixture of **1** (0.2 mmol, 1 equiv), **2** (0.4 mmol, 2 equiv), **PC-Ⅰ** (0.001 mmol, 0.5 mol%), PhSH (0.006 mmol, 3 mol%), Na_2CO_3 (0.2 mmol, 1 equiv), D_2O (1 mL) and DCM (1 mL) was irradiated by a 20 W blue LEDs at 25 °C for 16 h. [b] Isolated yields are provided. [c] **PC-Ⅰ** (0.002 mmol, 1 mol%), PhSH (0.01 mmol, 5 mol%), K_3PO_4 (0.2 mmol, 1 equiv), D_2O (2 mL) and DCM (2 mL) were used.

By simply replacing H_2O with D_2O under otherwise identical conditions, various β-deuterated amides could be prepared *via* photoredox and thiol co-catalyzed deuteroamidation. As shown in Table 3, a 1,1-disubstituted alkene (**4a**), a trisubstituted alkene (**4b**), a tetrasubstituted alkene (**4c**) and cyclic alkenes including cyclopentene (**4d**), cyclohexene (**4e**) and cycloheptene (**4f**) provided the targeted β-deuterated N-Cbz-protected amines in good yields (62-81%) and excellent D incorporation (90-97%). A terminal alkene (**4g**) was also efficiently deuteroamidated in

good yield and 93% D incorporation. Various functionalities such as the alcohol- (**4h**), ether- (**4i**), ester- (**4j**), silyl ether- (**4k**), ketone- (**4l**), imide- (**4m**), halide- (**4n**) and silane-moiety (**4o**) are well tolerated to afford diverse β-deuterated Cbz-protected amines in satisfactory yields (60-75%) and very high D content (88-97%). Electron-rich alkenes including vinyl ethers (**4p** and **4q**), enol esters (**4r**), silyl enol ethers (**4s**), enamides (**4t**) and vinyl silanes (**4u**) worked smoothly, providing β-deuterated N-protected primary amines in good yields and excellent D incorporation (93-97%). Notably, the deuteroamidation of enol ethers and enamides gives access to primary amines containing a deuterium atom adjacent to a heteroatom (O or N), offering a promising approach for the preparation of D-labelled bioactive compounds and drug candidates with increased metabolic stability.[9]

In conclusion, we have established a photoredox and thiol co-catalyzed method for radical hydroamidation and deuteroamidation of various unactivated as well as electron rich alkenes. Diverse Cbz-protected primary amines and the corresponding β-deuterated congeners were obtained in good yields and high D incorporation using practical and mild conditions. Importantly, the Cbz-group used in these transformations is a common N-protecting group in synthetic organic chemistry.

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Conflict of Inerest

The authors declare no conflict of interest.

Keywords: hydroamination • deuteroamination • photoredox catalysis• thiol catalysis • primary amines

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Layout 2:

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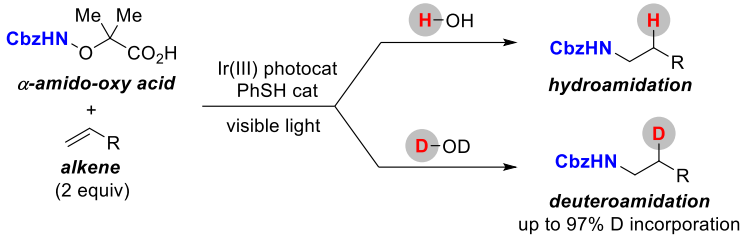

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Anti-Markovnikov Radical Hydro- and Deuteroamidation of Unactivated Alkenes

C–N and C–D bond formation is achieved by mild and highly practical radical deuteroamidation of alkenes. The method uses a readily accessed α-amido-oxy acid as an N-radical precursor and D_2O as a formal radical reducing reagent applying iridium/thiol cocatalysis. Replacing D_2O by H_2O provides the corresponding hydroamidation products.