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Decarboxylative hydrazination of unactivated carboxylic acids by cerium photocatalysis†

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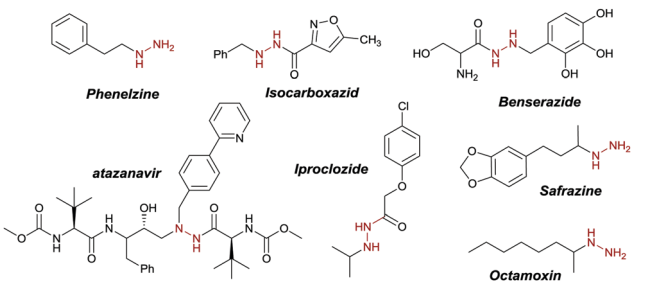
We report the cerium photocatalyzed radical decarboxylative hydrazination of carboxylic acids with di-*tert*-butylazodicarboxylate (DBAD). The operationally simple protocol provides rapid access to synthetically useful hydrazine derivatives and overcomes current scope limitations in the photoredox-catalyzed decarboxylation of carboxylic acids.

Visible-light photocatalysis is a powerful tool to generate various chemical motifs under very mild reaction conditions.[1a–f] Many different classes of photocatalysts have been developed over the past decade, but ruthenium and iridium complexes initiating single electron transfer (SET) from a Metal to Ligand Charge Transfer (MLCT) state still dominate in synthetic procedures.[1a,2a–d] However, these transition-metal complexes are rather expensive, potentially toxic and the metal salts are of limited availability.[3] Recently, visible-light induced Ligand to Metal Charge Transfer (LMCT) emerged as a robust alternative to generate radical species by the homolysis of the metal–ligand bond.[4a–c,5a–c] This strategy replaces transition metal complexes with inexpensive metal salts, thus overcoming some of the aforementioned drawbacks. Moreover, as the coordination of the substrate is required for the electron transfer to occur, this approach allows envisioning new scenarios for the late-stage functionalization of complex molecules.[5a] Decarboxylation reactions convert widely available and inexpensive carboxylic acids into reactive intermediates for the synthesis of valuable chemicals.[6a–c] Radical decarboxylation of carboxylic acids has been widely explored in synthesis,[6c,7a–g] as the liberation of CO_2 as a traceless and volatile by-product provides a strong driving force for the reaction, forming versatile radical intermediates without the need of pre-functionalization or additional activation reagents.[7c] Hydrazine derivatives are widely used in the pharmaceutical, agricultural, photographic and dye stuff industries, as well as precursors for heterocyclic compounds such as pyrazoles, pyrazines, and indoles.[8] Moreover, the reductive cleavage of the N–N bond gives access to amines (Scheme 4).[9a–c] The hydrazine motif is found in many pharmacologically active compounds, such as phenelzine, isocarboxazid, iproclozide, safrazine and octamoxin, which show remarkable monoamine oxidase inhibiting (MAOI) activity.[10,11] Other compounds, such as the anti-retroviral atazanavir (Scheme 1), proved to be effective in HIV-1 infection treatment.[12] Benserazide (Scheme 1), a DOPA decarboxylase inhibitor, is used as therapeutic agent in Parkinson disease treatment.[13a,b] Considering the prevalence of alkyl and benzylic hydrazine derivatives in the clinical practice, more efficient methods for their synthesis are highly desirable. In 2012, Nishibayashi *et al.* developed a visible-light Ir-catalyzed C–H hydrazination, limited to the α-amino position.[14] More recently, the Guan group reported the hydrazination of the protected indoline core *via* α-aminoalkyl radicals, using rose Bengal as the photocatalysts under visible light (Scheme 2, upper).[15] In 2016, Tunge and co-workers were able to perform the radical decarboxylative hydrazination of carboxylic acids with DIAD (di-isopropyl azo dicarboxylate) as a coupling partner, using the highly oxidizing Fukuzumi catalyst.[16] However, no literature method for the deprotection of these DIAD-derived hydrazines into free hydrazine has been reported, thus limiting the broader application of the protocol.[17] Herein, we report the first cerium photocatalyzed decarboxylative hydrazination



Scheme 1 Pharmaceutically relevant hydrazines.

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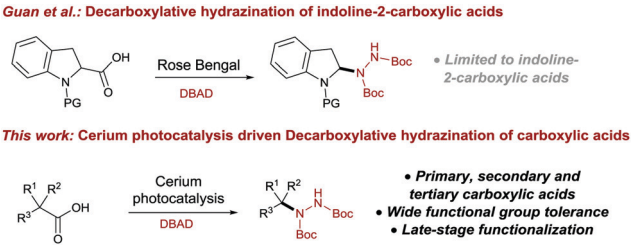


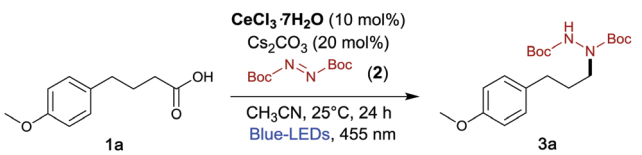
Scheme 2 Visible light driven radical decarboxylative hydrazination of carboxylic acids using DBAD.

reaction of carboxylic acids with DBAD[18] in the presence of visible light at room temperature.

Inspired by the recent work of Zuo *et al.*, who generated 1,5-HAT-hydrazination from alcohols with a cerium-photocatalyst,[5a] we wondered how carboxylic acids would behave under similar reaction conditions. At first, we investigated the reaction of 4-(4-methoxyphenyl)butyric acid (**1a**) with DBAD (**2**) using different reaction conditions (Table 1). To our delight, when a solution of **1a** with 1.5 equiv. of DBAD in the presence of Cs_2CO_3 (20 mol%) and $CeCl_3{\cdot}7H_2O$ (10 mol%) in acetonitrile (MeCN) was illuminated with a blue LED (455 nm) at 25 °C for 24 h, compound **3a** was obtained in 90% yield (Table 1, entry 1). The reaction using anhydrous $CeCl_3$ as a photocatalyst also proceeded smoothly to give **3a** in 80% yield (Table 1, entry 2),[19] while the conversion to **3a** slightly decreased upon use of other cerium salts (Table 1, entry 3 and 4). When Cs_2CO_3 was replaced by K_2CO_3, **3a** was afforded in 66% yield (Table 1, entry 5), while other bases such as Na_2CO_3, Li_2CO_3 and $NaHCO_3$ caused a drastic reduction in the yield (Table 1, entries 6–8).

Solvents such as chloroform ($CHCl_3$) and DMSO had a detrimental effect on the reaction (Table 1, entries 12 and 13).

Table 1 Optimization of the reaction conditions. **1a** (0.1 mmol), DBAD (0.15 mmol), $CeCl_3{\cdot}7H_2O$ (10 mol%), CH_3CN (0.1 M) at 25 °C, 455 nm LED for 24 h



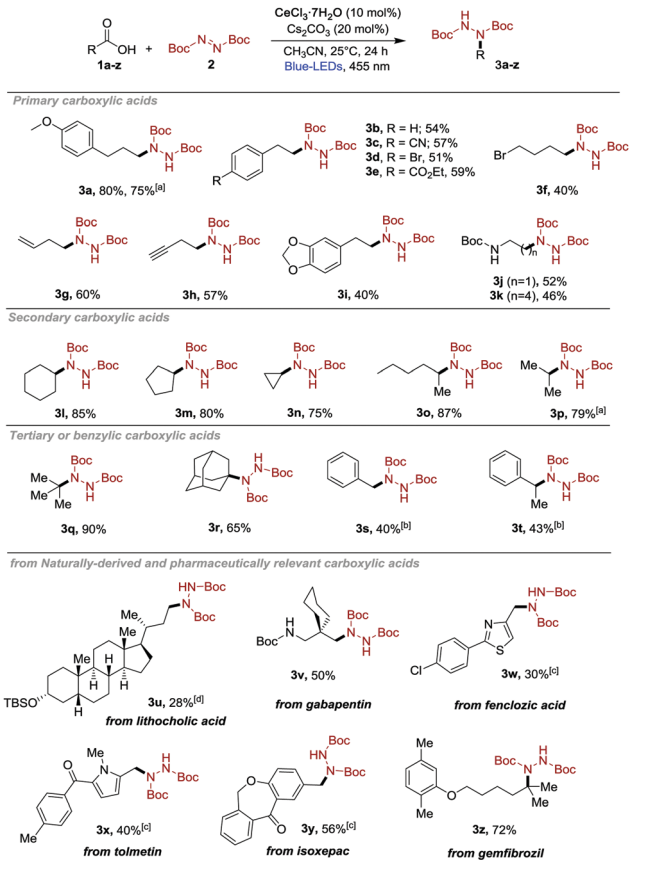
Entry	Deviation from standard conditions	3a[a] (%)
1	*None*	*90 (80)*[b]
2	$CeCl_3$ instead of $CeCl_3{\cdot}7H_2O$	80
3	$Ce(OTf)_3$ instead of $CeCl_3{\cdot}7H_2O$	66
4	$Ce(OTf)_4$ instead of $CeCl_3{\cdot}7H_2O$	63
5	K_2CO_3 instead of Cs_2CO_3	66
6	Na_2CO_3 instead of Cs_2CO_3	55
7	Li_2CO_3 instead of Cs_2CO_3	25
8	$NaHCO_3$ instead of Cs_2CO_3	23
9	Without base	20
10	DCM instead of CH_3CN	85
11	DCE instead of CH_3CN	86
12	$CHCl_3$ instead of CH_3CN	66
13	DMSO instead of CH_3CN	61
14	Without light	0
15	Without $CeCl_3{\cdot}7H_2O$	0

[a] NMR yields using benzoyl benzoate as internal standard. [b] Isolated yield.

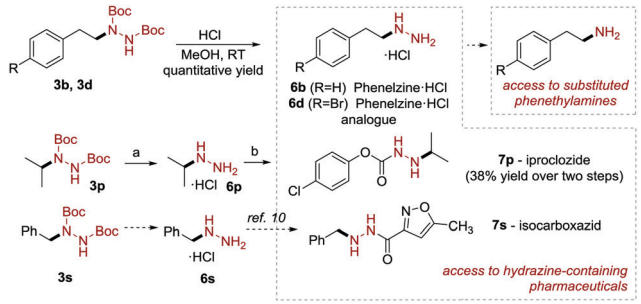
Additionally, control experiments revealed that a catalytic amount of base (Table 1, entry 9), the cerium salt and light irradiation were required for the transformation to occur. Not even traces of **3a** were found in the absence of light or the cerium catalyst (Table 1, entries 14 and 15).

With the optimized conditions in hand, we evaluated the scope of the reaction. As shown in Scheme 3, a broad range of carboxylic acids reacted, providing the corresponding hydrazine derivatives in good to excellent yield. Primary carboxylic acids were found to be generally competent; diverse electron-withdrawing (**3c** and **3e**, 57% and 59% yield), electron-donating (**3a**, 80% yield) or electron-neutral substituents (**3b**, 54% yield) as well as cyclic ketals (**3i**) were tolerated on the aryl ring. Deprotection of **3b** under acidic conditions afforded the HCl salt of phenelzine **6b** (Scheme 4), which is currently used for the treatment of psychiatric disorders, in quantitative yield. Amino acid derivatives (**1j** and **1k**) were also viable substrates and gave the corresponding products **3j** and **3k** in moderate yields (52% and 46%). Terminal alkenes (**3g**) and alkynes (**3h**) were tolerated under the mild reaction conditions.

Next, we turned our attention to secondary and tertiary carboxylic acids (**3l–3r**, **3t**, 65–90% yield). We were pleased to



Scheme 3 Decarboxylative hydrazination of carboxylic acids. Reaction conditions as given in Table 1 (entry 1). Isolated yields, average of at least two independent runs. [a] Reaction performed at 1.0 mmol scale. [b] Degassed CH_3CN was used as a solvent. [c] Degassed DMSO was used as a solvent. [d] Degassed DCM was used.

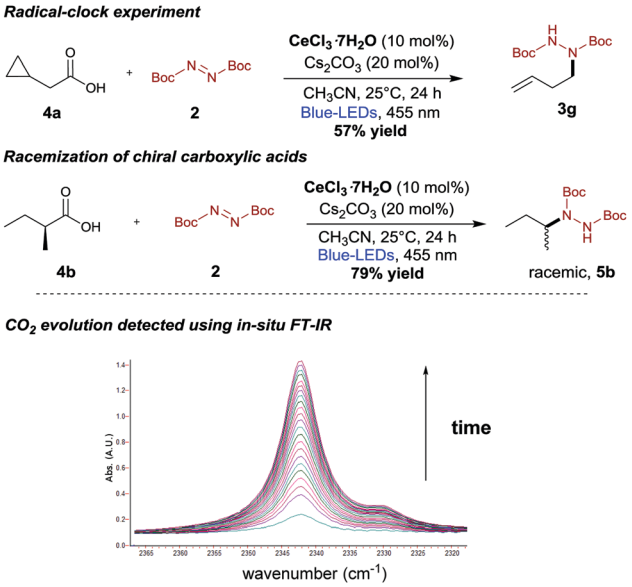


Scheme 4 Access to pharmacologically active scaffolds. Conditions: (a) HCl, MeOH, RT, 3 h, quantitative yield; (b) 4-Cl-phenoxyacetic acid, CDI, THF:DMF, RT, 60 min then **6p**, TEA, DMF, 80 °C, overnight, 38% over two steps.

find that cyclic secondary carboxylic acids, including strained 3-membered rings (**1n**) as well as larger homologues (**1l**, **1m**) participate in this reaction in good to excellent yield (**3n–3m**, 75–85% yield). Moreover, secondary acyclic systems also produced the desired hydrazine derivatives with good efficiency (**3o** and **3p**, 87% and 80% yield, respectively). Compound **3p** was used to prepare iproclozide **7p** (Scheme 4), which is used as antidepressant drug. The acidic deprotection of **3p** yielded the corresponding hydrazium salt (**6p**) in quantitative yield, which was coupled with 4-chlorophenoxyacetic acid. A number of other tertiary alkyl carboxylic acids were also successfully converted to hydrazine derivatives in excellent yields (**3q** and **3r**, 90% and 65% yield). To our surprise, phenyl acetic acids (**1s** and **1t**) afforded the corresponding products (**3s**, **3t**) only in moderate yields (40% and 43%). Nevertheless, the former product (**3s**) can be envisaged as an advanced intermediate for the formal synthesis of isocarboxazid in **7s** in two steps (Scheme 4).[10]

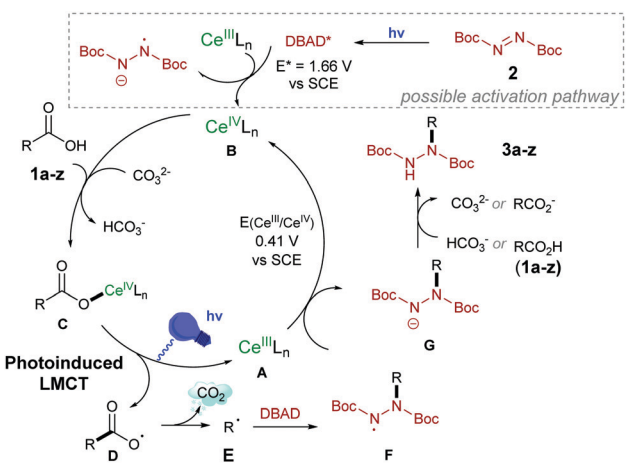
To further demonstrate the utility of this decarboxylative hydrazination approach, we performed a series of late-stage modifications on active pharmaceutical ingredients (API) and compounds derived from natural products (Scheme 3, **1u–z**). To our delight, a large variety of such molecules containing carbonyl groups and heterocycles (**1x–y**) react chemoselectively by introducing the hydrazine moiety (**3u–z**, 28–72% yield). Furthermore, the reaction can be conducted at a one mmol scale without any significant erosion in the yield (**3a** and **3p**).

The efficiency of our decarboxylative hydrazination prompted us to conduct some preliminary mechanistic studies (Scheme 5). As anticipated, intermittent irradiation experiments confirmed that our reaction required a continuous visible light irradiation to proceed (see ESI†). We currently believe that this decarboxylative hydrazination reaction could proceed *via* the generation of alkyl radicals.[20] In a radical clock experiment using 2-cyclopropylacetic acid (**4a**) under our reaction conditions, the ring-opened product **3g** was isolated (Scheme 5, upper). Moreover, enantiopure (*S*)-2-methylbutanoic acid (**4b**) provided the racemic hydrazination product **5b** (Scheme 5, center). The inhibition of any catalytic activity upon TEMPO addition further corroborated the hypothesis that the reaction proceeds *via* radical intermediates. Additionally, we were able to monitor the CO_2 evolution by *in situ* infrared spectroscopy using a custom-made dedicated set-up (Scheme 5, lower).



Scheme 5 Preliminary mechanistic investigations: for full FT-IR spectrum, see ESI.†

Based on these experimental observations and the reports of Zuo *et al.*[5a–c] we propose that the decarboxylative hydrazination proceeds *via* Ligand to Metal Charge Transfer (LMCT), which generates the key carboxy-radical. The simplified mechanistic proposal is shown in Scheme 6. The putative Ce^{III} species **A** could be oxidized to Ce^{IV} ($E_{1/2}(Ce^{III}/Ce^{IV})$ = 0.41 V *vs.* SCE in MeCN) either by the N-centered radical **F** or by the photo-excited DBAD (E^* = 1.66 V *vs.* SCE in MeCN).[5b] The coordination of the substrate forms complex **C**, which undergoes the photo-induced Ce–O(CO) homolytic cleavage[20] to yield the "spring-loaded" carboxy-radical **D** and regenerates the catalytically competent Ce^{III} species **A** (detected by UV spectroscopy, see ESI†). Upon rapid decarboxylation, the carbon-centered radical **E** forms and is trapped by DBAD to provide the more stable N-centered radical (**F**), which upon a SET-protonation cascade yields the product **3a–z**. The proposed mechanism emphasizes



Scheme 6 Proposed mechanism for the decarboxylative hydrazination.

the catalytic role of the base that is consumed in the coordination step from **1a–z** and regenerated upon the proton-transfer to **G.**

In summary, we have developed a general strategy for the catalytic, radical decarboxylative hydrazination of unactivated carboxylic acids using an inexpensive cerium photocatalyst.

This operationally simple protocol allows an efficient synthesis of hydrazine derivatives and was applied to the modification of API related compounds. The method provides a new and simple route to hydrazine derivatives and may be of use for the discovery of new hydrazine-based compounds with biological activity.

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Conflicts of interest

There are no conflicts to declare.

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17 The corresponding ^{i}Pr-carbamates, derived from amines, are usually deprotected under harsh conditions, for instance: (a) HCl, AcOEt, 100 °C; (b) $AlCl_3$, DCM; (c) HBr, H_2O, reflux; (d) HCl, water, 90 °C, 48 h.

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