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Synthesis of β-Substituted γ-Aminobutyric Acid Derivatives via Enantioselective Photoredox Catalysis

Jiajia Ma, Jiahui Lin, Lifang Zhao, Klaus Harms, Michael Marsch, Xiulan Xie and Eric Meggers*

Abstract: β-Substituted chiral γ-aminobutyric acids feature important biological activities and are valuable intermediates for the synthesis of pharmaceuticals. Herein, an efficient catalytic enantioselective approach for the synthesis of β-substituted γ-aminobutyric acid derivatives through visible-light-induced photocatalyst-free asymmetric radical conjugate additions is reported. Various β-substituted γ-aminobutyric acid analogs, including previously unaccessible derivatives containing fluorinated quaternary stereocenters, were obtained in good yields (42–89%) and with excellent enantioselectivities (90–97% *ee*). Synthetically valuable applications were demonstrated by providing straightforward synthetic access to the pharmaceuticals or related bioactive compounds (*S*)-pregabalin, (*R*)-baclofen, (*R*)-rolipram and (*S*)-nebracetam.

γ-Aminobutyric acid (GABA) is a well-known inhibitory neurotransmitter of the central nervous system (CNS).[1] Structurally diverse chiral GABAs, especially those bearing substituents at the β-position are marketed as pharmaceuticals for the treatment of diseases accompanied with GABA receptors, such as (*S*)-pregabalin[2] and (*R*)-baclofen[3] (Figure 1a). These chiral GABAs are also valuable feedstocks for synthesizing other related drugs like arbaclofen placarbil[4] and (*R*)-rolipram[5]. Due to their diverse and potent bioactivities, considerable efforts have been devoted to the efficient catalytic asymmetric synthesis of a wide spectrum of β-substituted GABAs.[6] Typical strategies rely on Michael additions of C–H acidic carbonyl compounds to nitroalkenes,[7] and nitroalkanes or cyanide to α,β-unsaturated carbonyl compounds (Figure 1b).[8] The asymmetric hydrogenation of unsaturated nitriles has also been demonstrated as an alternative approach.[9] However, these methods require a separate reduction step under relatively harsh conditions. Furthermore, only very few reports accomplish the synthesis of derivatives bearing quaternary stereocenters at the β-position,[10] and fluorinated quaternary stereocenters which might be of biological interest, remain unexplored.[11] Hence, the development of new synthetic protocols to access non-racemic β-substituted GABAs in an economical fashion, including previously unaccessible structural features, is of high interest.

Very recently, the visible-light-induced enantioselective radical conjugate addition of α-aminoalkyl radicals[12] to Michael acceptors, classified as a Giese-type reaction,[13] has been recognized as an interesting alternative avenue to β-substituted GABAs by using a radical as a nucleophilic aminoalkyl equivalent (Figure 1b).[14] However, current methods display severe limitations to aryl substituted amines (Figure 2a). For example, Yoon and coworkers employed aromatic tertiary α-silylalkyl amines as radical precursors under Ru-photoredox conditions and combined it with a Sc-catalyzed enantioselective conjugate addition.[15,16] Melchiorre reported a dual photoredox/organo catalysis system as an approach to β-substituted GABA analogs, but substrates are limited to aromatic tertiary amines and to cyclic enones.[17] Kang and coworkers reported a single Rh-based Lewis acid catalyst to enable a visible-light-induced asymmetric Giese-type reaction but with a severe limitation to *N*-aryl tetrahydroisoquinolines as precursors of the intermediate α-aminoalkyl radicals.[18] Thus, despite this noteworthy progress, the currently narrow substrate scope and limited follow-up functional group interconversions render these methods of low utility. Herein, we introduce a general and practical photoredox-based catalytic asymmetric radical conjugate addition to access a variety of β-substituted GABA analogs including previously unaccessible derivatives with β-fluorinated quaternary stereocenters, and provide applications (Figure 2b).

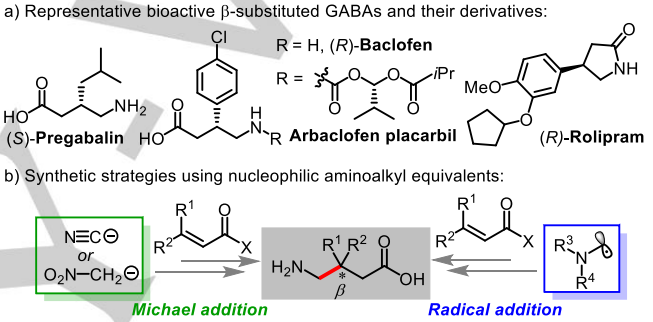

Figure 1. Representative bioactive β-substituted GABAs, related derivatives and their synthetic strategies.

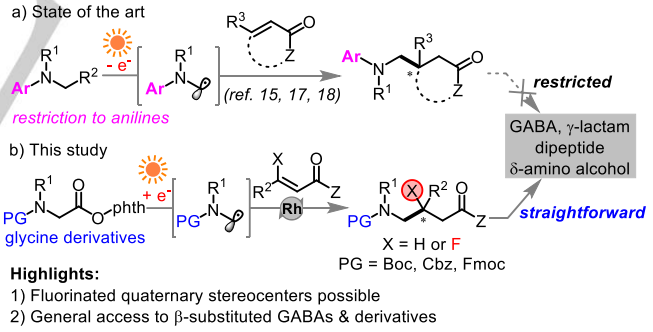

Figure 2. Approaches to non-racemic γ-amino carbonyl derivatives via asymmetric photoredox catalysis. Phth = phthalimide. PG = protecting group.

All previous studies to access GABA derivatives through catalytic enantioselective photoredox catalysis exploit the oxidative generation of α-aminoalkyl radicals from specific tertiary aromatic amines, which can be traced back to the requirement for their single electron oxidation under sufficiently mild conditions. Realizing this limitation to generate α-aminoalkyl radicals under oxidative conditions, we turned our attention to reductive methods and were inspired by studies using *N*-(acyloxy)phthalimides[19,20] as radical precursors under reductive photoredox conditions (Figure 3a). Specifically, we envisioned that glycine derivatives **1**, bearing an easily removable *N*-protected group and an *O*-phthalimide ester group as the redox handle, might constitute easily accessible and very general precursors of a large variety of α-aminoalkyl radicals.[21] These radicals would then be interfaced with established chiral-at-rhodium Lewis acid catalyzed radical conjugate addition to α,β-

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unsaturated *N*-acylpyrazoles **2** (intermediate **Rh-I**) to provide intermediate **Rh-II**, which after reduction and protonation afford the Rh-bound products (**Rh-III**).[22] Replacement of the product by another substrate leads to a new catalytic cycle (Figure 3b).

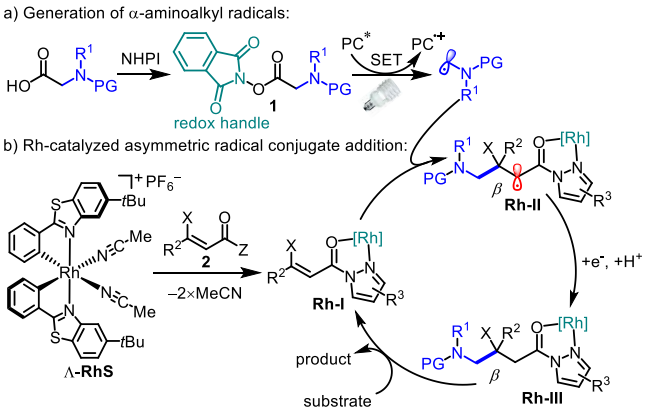
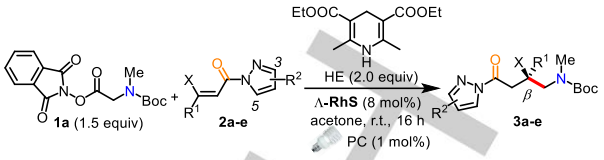


Figure 3. Reaction design. PC = photocatalyst. PG = protecting group.

We commenced our study by investigating the reaction of *N*-(acyloxy)phthalimide **1a** with α,β-unsaturated *N*-acylpyrazole **2a** under photoredox conditions (Table 1). Using the chiral-at-Rh Lewis acid catalyst Λ-**RhS**[23] combined with the photocatalyst *fac*-[Ir(ppy)$_3$] and Hantzsch ester (HE) as the reductant under irradiation with a household CFL, the C–C formation product **3a**, identified as a β-methyl GABA analog, was isolated in 89% yield and 91% *ee* (entry 1). Unexpectedly, in the absence of *fac*-[Ir(ppy)$_3$], **3a** was obtained even with higher enantioselectivity (94% *ee*) (entry 2). This indicates that the HE itself probably serves as the photoexcited reducing agent and directly promotes single electron reduction of the phthalimide.[24,25] Alternatively, a photoexcited Rh complex first oxidizes the HE and then transfers a single electron to a phthalimide substrate, thereby serving as an electron shuttle. Overall, this protocol is very attractive because only a single catalyst is required for this catalytic asymmetric photoredox reaction.

We next investigated the tolerance of a phenyl (**2b**) instead of a methyl group (**2a**) at the β-position of α,β-unsaturated *N*-acylpyrazoles, which showed a more limited scope in our previous reports.[20b,26] As a result, using *N*-acylpyrazole **2b** as substrate, the C–C formation product **3b** was formed with inferior yield (54%) and decreased 90% *ee* (entry 3). However, we found that a 3-Me-substituted pyrazole (**2c**) instead of a 3,5-di-Me-substituted pyrazole moiety (**2b**) not only improved the yield (84%) but also afforded a higher enantioselectivity (95% *ee*) (entry 4).[27] A β-disubstituted β-methyl-β-phenyl alkene (**2d**) did not provide any desired product under these optimized conditions (entry 5). However, a β-fluoro-β-phenyl substituted α,β-unsaturated *N*-acylpyrazole **2e** delivered **3e** in 70% yield and 93% *ee*, containing a fluorinated quaternary stereocenter, which is a formidable challenge in the field of asymmetric photocatalysis (entry 5).[28] Control experiments verified that visible light (entry 7) was essential and air strongly diminished the yield (entry 8).

Table 1. Reaction development and control experiments.[a]



Entry	Substrate **2** X	R^1	R^2	PC	Yield [%][b]	*ee* [%][c]
1	H	Me	3,5-di-Me (**2a**)	*fac*-[Ir(ppy)$_3$]	89 (**3a**)	91
2	H	Me	3,5-di-Me (**2a**)	none	86 (**3a**)	94
3	H	Ph	3,5-di-Me (**2b**)	none	54 (**3b**)	90
4	H	Ph	3-Me (**2c**)	none	84 (**3c**)	95
5	Me	Ph	3-Me (**2d**)	none	0 (**3d**)	n.a.
6[d]	F	Ph	3-Me (**2e**)	none	70 (**3e**)	93
7[e]	H	Ph	3-Me (**2c**)	none	0 (**3c**)	n.a.
8[f]	H	Ph	3-Me (**2c**)	none	14 (**3c**)	93

[a] Conditions: **1a** (0.30 mmol), **2a-e** (0.20 mmol), Λ-**RhS** (0.016 mmol), and HE (0.40 mmol) in acetone (1.0 mL) at r.t. for 16 h under N_2 and irradiated with CFL (23 W) unless noted otherwise. [b] Isolated yield. [c] Determined by HPLC analysis on chiral stationary phase. [d] Δ-**RhS** (0.016 mmol) and 2 mL of acetone were employed. [e] Conducted in the dark. [f] Assembled under air, then sealed. r.t. = room temperature. n.a. = not applicable. PC = photocatalyst.

The scope with respect to the synthesis of β-alkyl and β-aryl substituted GABA analogs is outlined in Figure 4. α,β-Unsaturated *N*-acylpyrazoles display good tolerance with respect to substituents at the β-position, including various alkyl groups (**3g-i**), an ethoxy group (**3j**), electron-rich phenyl moieties (**3k-l**, **3u**), as well as electron-deficient ones (**3m-n**). Heteroaromatic rings, like an indolyl (**3o**) and a thienyl moiety (**3p**) lead to satisfactory results. Furthermore, *N*-(acyloxy)phthalimides with different *N*-protected amino moieties could also enable this transformation smoothly by affording products **3q-t** with 55-87% yields and 91-96% *ee*. It is worth noting that an estrone derived *N*-acylpyrazole (**2q**) provided the corresponding GABA analog **3v** with 85% yield and 92% *de*, thereby demonstrating that our protocol was applicable for the incorporation of bioactive motifs to the side chain of γ-aminobutyric acid.

The scope with respect to the synthesis of β-fluoro-β-aryl GABA analogs is outlined in Figure 5. Accordingly, substituents at different positions of the phenyl moiety show little influence on the reaction outcome by providing **3w-y** in 68-71% yields and with 94-96% *ee*. Electron-donating groups (**3z-3aa**), a *t*Bu group (**3ab**), and a chlorine (**3ac**) were also accommodated. A carbazole moiety was tolerated by affording the C–C formation product **3ad** in 62% yield and 93% *ee*.

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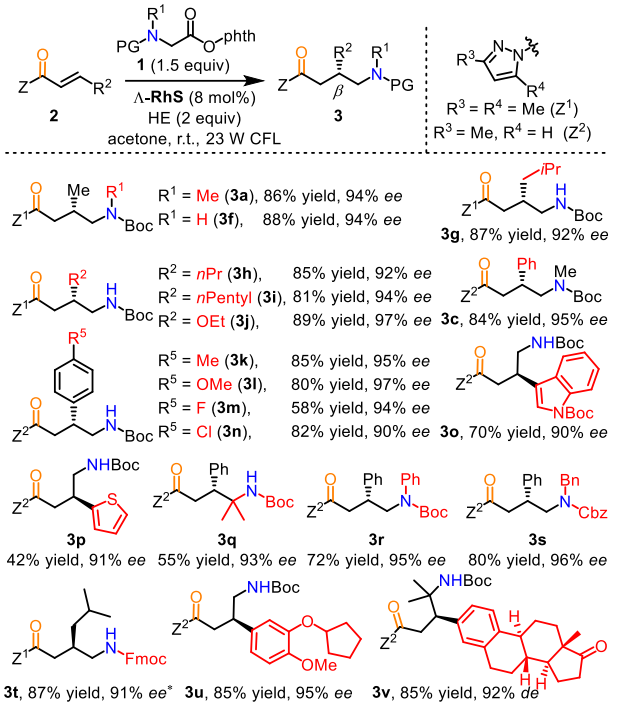

Figure 4. Scope with respect to synthesis of β-alkyl and β-aryl substituted GABA analogs. *Δ-**RhS** was employed.

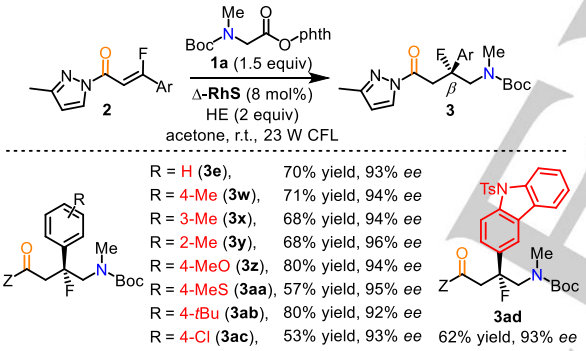

Figure 5. Scope with respect to synthesis of β-fluoro-β-aryl substituted GABA analogs.

With a range of β-substituted GABA analogs in hand, we next evaluated the synthetic application of this protocol (Figure 6). The pyrazole moiety can be transformed into a broad range of functionalities under mild conditions. Treating **3n** with LiOH in THF/H_2O provided the corresponding *N*-protected γ-aminobutyric acid Boc-(*R*)-baclofen (**4**) in 90% yield and complete retention of the *ee*. Boc-(*S*)-pregabalin (**5**) was obtained by the same method. Furthermore, compound **3v** was converted to the dipeptide **6** in 83% yield and as a single diastereomer by reacting with *D*-phenylglycine methyl ester. A δ-amino alcohol (**7**) and a γ-lactam (**8**) bearing fluorinated quaternary stereocenters were obtained smoothly under mild transformation conditions. Additionally, the GABA analog **3u** was converted into the anti-inflammatory drug (*R*)-rolipram (**9**) in 92% yield and with unchanged *ee*. To further demonstrate the practicability of our protocol, the synthetic route to Boc-(*S*)-nebracetam which is an enantioenriched form of a *N*-protected nootropic drug,[29] is shown in Figure 6b. Accordingly, the C–C coupling partners **1e** and **2z** were synthesized over two steps from commercially available materials **10** and **12**, respectively, and were then subjected to the developed asymmetric radial conjugate addition reaction, followed by a cyclization, thereby delivering Boc-(*S*)-nebracetam (**14**) with 55% yield and 94% *ee* over the two steps. Overall, the herein outlined synthetic applications clearly demonstrate that our approach is very versatile for the synthesis of structurally diverse enantioenriched β-substituted γ-aminobutyric acids and their derivatives.

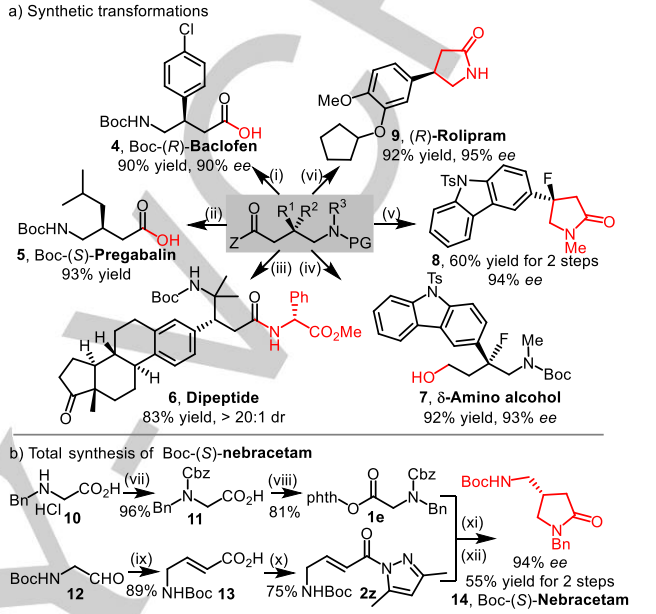

Figure 6. Synthetic applications. Conditions: (i) LiOH, THF/H_2O; (ii) LiOH, THF/H_2O; (iii) *D*-Phenylglycine methyl ester hydrochloride, Et_3N, HOBt; (iv) $NaBH_4$; (v) Pd/C, H_2 (1 atm); (vi) LiCl, MeOH then TFA followed by Et_3N; (vii) *N*-Benzyloxycarbonyloxy succinimide; K_2CO_3; (viii) NHPI, DCC, DMAP; (ix) Diethylphosphonoacetic acid, LHMDS; (x) 3,5-Dimethylpyrazole, T_3P, Et_3N; (xi) Δ-**RhS**, HE, 23 W CFL; (xii) Pd/C, H_2 (1 atm).

In conclusion, we herein introduced a practical and versatile synthetic access to the pharmaceutically important class of β-substituted GABA analogs. The methodology is based on catalytic asymmetric photoredox catalysis using simple glycine derivatives as the precursors for nucleophilic α-aminoalkyl radicals which are then engaged in highly enantioselective Rh-catalyzed radical conjugate additions. Furthermore, for the first time enantioselective radical conjugate additions to β-fluoro-β-aryl substituted α,β-unsaturated enones are reported which provides a potentially very valuable access to GABA analogs with β-fluorinated quaternary stereocenters.

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Keywords: γ-aminobutyric acid • visible light • radical addition • fluorinated quaternary stereocenter • asymmetric catalysis

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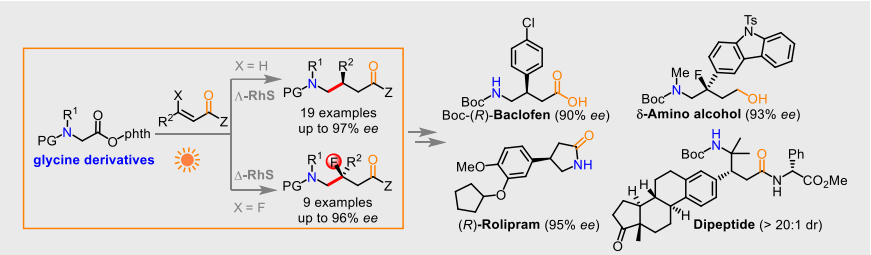

A practical protocol to enantioenriched β-substituted γ-aminobutyric acid analogs, particularly the previously inaccessible ones with fluorinated quaternary stereocenters, was demonstrated via photoinduced catalytic asymmetric Giese-type reaction.

*J. Ma, J. Lin, L. Zhao, K. Harms, M. Marsh, X. Xie, E. Meggers**

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Synthesis of β-Substituted γ-Aminobutyric Acid Derivatives via Enantioselective Photoredox Catalysis