

This is the final peer-reviewed accepted manuscript of:

Hartley, W.C., Schiel, F., Ermini, E., Melchiorre, P., 2022. Lewis Base-Catalysed Enantioselective Radical Conjugate Addition for the Synthesis of Enantioenriched Pyrrolidinones. *Angewandte Chemie International Edition* 61, e202204735.

The final published version is available online at:
<https://doi.org/10.1002/anie.202204735>

Rights / License:

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

Lewis Base-Catalysed Enantioselective Radical Conjugate Addition for the Synthesis of Enantioenriched Pyrrolidinones

Will C. Hartley, Florian Schiel, Elena Ermini, and Paolo Melchiorre*

Abstract: We report a catalytic asymmetric protocol for the preparation of chiral pyrrolidinones proceeding via a radical pathway. The chemistry exploits the combination of photoredox catalysis and Lewis base catalysis to realise the first example of asymmetric radical conjugate addition to α,β -unsaturated anhydrides and esters. The reaction is initiated by photoredox activation of *N*-arylglycines to generate, upon decarboxylation, α -amino radicals. These radicals are then intercepted stereoselectively by α,β -unsaturated acyl ammonium intermediates, whose formation is mastered by a chiral isothioureia organocatalyst. Cyclisation leads to catalyst turnover and formation of enantioenriched pyrrolidinones. The utility of the protocol was demonstrated with application to the synthesis of biologically-active γ -amino butyric acids.

Radical conjugate addition (RCA) reactions^[1] are particularly useful to form new carbon-carbon bonds. Developing asymmetric catalytic variants is difficult, since it requires the ability of a chiral catalyst to effectively activate electron-poor olefin substrates while controlling the addition of highly reactive radicals. The majority of successful catalytic strategies reported so far relied on the systematic use of pre-functionalised α,β -unsaturated carbonyl substrates bearing a preinstalled anchoring point (Figure 1a). For example, the seminal studies of Porter^[2] and Sibi^[3] used acyl pyrazoles and acyl imidazoles as templates for bidentate coordination of chiral Lewis acids. The two-point binding activation was essential for stereoselectivity by ensuring optimal geometry control over the substrate. Recently, the combination of photoredox catalysis^[4] with Lewis acid-based catalytic methods have significantly expanded the variety of radicals suitable for asymmetric RCA.^[5] However, these protocols could not alleviate the structural constraints related to the need of a purposely designed binding template within the substrates.

We recently wondered if the synthetic applicability of asymmetric catalytic RCA could be expanded to include unsaturated substrates bearing *native* functional groups. For example, we demonstrated that iminium ion catalysis could effectively activate simple enals^[6] and enones^[7] towards RCA. However, to the best of our knowledge, there are no examples of enantioselective radical conjugate additions to

unsaturated carboxylic acid derivatives. Such higher oxidation-state substrates are abundant and cheap feedstock chemicals, and their direct use in RCA would be synthetically appealing. Here we close this gap in synthetic methodology by developing an organocatalytic strategy for the activation of α,β -unsaturated esters and anhydrides **1** towards enantioselective RCA (Figure 1b).

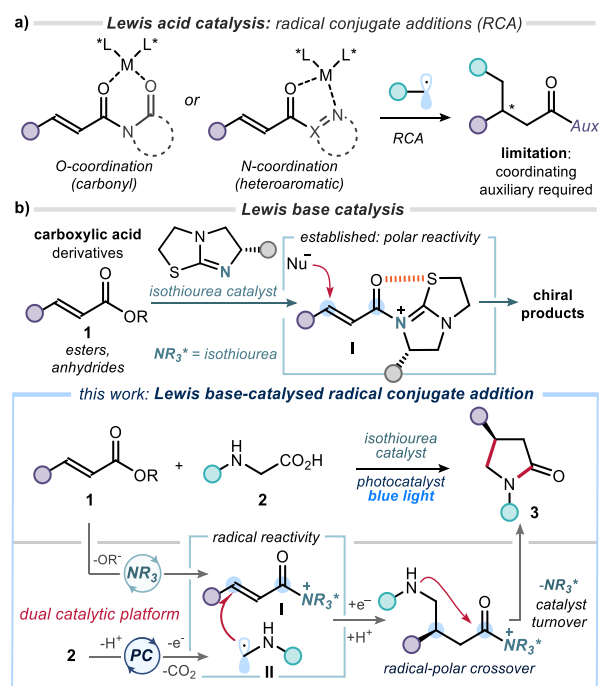


Figure 1. a) Lewis-acid-catalysed asymmetric radical conjugate additions generally require a purposely designed substrate bearing a coordinating auxiliary (*Aux*). b) Design plan for the activation of native substrates at the carboxylic acid oxidation level via Lewis base (isothioureia) catalysis and use in asymmetric radical conjugate additions.

Our design plan was informed by the established ability of isothioureia catalysts (NR_3^* in Figure 1b) to activate carboxylic acid derivatives **1** towards asymmetric ionic processes.^[8] Specifically, acylation of the nucleophilic Lewis base catalyst NR_3^* leads to the chiral α,β -unsaturated acyl ammonium intermediate **I** with an enhanced electrophilic character. While this catalytic platform has found wide application to intercept nucleophiles in polar pathways,^[8,9] it has never been applied in enantioselective radical transformations.^[10] We surmised that *N*-arylglycines **2** could be useful to develop an effective RCA process under isothioureia catalysis. First, the easily-oxidisable **2** is prone to single-electron transfer (SET) oxidation by a photoredox catalyst (PC).^[11] This SET event would generate a nucleophilic α -amino radical **II** upon decarboxylation, potentially suitable for asymmetric RCA with **I**. Second, the nucleophilic amino moiety within **2** may offer a path for effective catalysis, since cyclisation, triggered by radical-polar crossover, could turn over the isothioureia catalyst while affording pyrrolidinones **3**.^[12] These synthetically relevant chiral products are generally accessed via rhodium-catalysed asymmetric manipulation of the parent unsaturated pyrrolidinones,^[13] but these routes are often plagued by alkene isomerisation. A modular enantioselective

[*] Prof. Dr. P. Melchiorre
ICREA – Passeig Lluís Companys 23, 08010 Barcelona, Spain
F. Schiel
University Rovira i Virgili, 43007 Tarragona, Spain

Dr. W. C. Hartley, F. Schiel, E. Ermini and Prof. Dr. P. Melchiorre
ICIQ - Institute of Chemical Research of Catalonia
the Barcelona Institute of Science and Technology,
Avenida Països Catalans 16 – 43007, Tarragona, Spain
E-mail: pmelchiorre@iciq.es
Homepage: http://www.iciq.org/research/research_group/prof-paolo-melchiorre/

[**] Financial support was provided by Agència Estatal de Investigació (PID2019-106278GB-I00 and CEX2019-000925-S). W. C. Hartley thanks the EU for a Horizon 2020 Marie Skłodowska-Curie Fellowship (H2020-MSCA-IF-2020 101031533). We thank Prof. A. D. Smith for gracious donation of a sample of catalyst **C**.

approach that avoids expensive transition metals would therefore offer sustainable access to such scaffolds. It would also constitute a rare application of Lewis base catalysis in asymmetric radical chemistry, which so far has been limited to few examples using NHC carbenes.^[14]

To test the viability of our plan, we chose cinnamic anhydride **1a** and the commercial isothiourea catalyst **A** (30 mol%, Figure 2a). The experiments were conducted in acetonitrile using a single blue LED ($\lambda_{\max} = 460$ nm) with an irradiance at 150 mW/cm² (details of the set-up are reported in Figure S2 of the Supporting Information, SI). *N*-phenylglycine **2a** was selected as the radical precursor because of its redox potential ($E^{\text{ox}}(\mathbf{2a}^+/\mathbf{2a}) = +0.42$ V vs. SCE in MeCN),^[11a] which is significantly lower than the oxidation potential of catalyst **A** ($E^{\text{ox}}(\mathbf{A}^+/\mathbf{A}) = +1.10$ V vs Ag/AgCl in MeCN). Crucially, we believed that this difference in redox properties could protect the isothiourea catalyst from SET oxidation and degradation. Rose Bengal (RB, see Figure S5 in SI for other catalysts tested) was selected as the organic photoredox catalyst because, upon visible-light excitation, it possesses the thermodynamic ability ($E^*(\mathbf{RB}^*/\mathbf{RB}^-) = +0.99$ V vs SCE in MeCN)^[15] to activate **2a** via SET oxidation, leading to α -amino radical formation. We soon realised that, despite good reactivity, commercial catalysts **A** and **B** could provide product **3a** with only moderate enantioselectivity (Figure 2a). Recently reported catalyst **C**, in which the endocyclic sulfur atom is replaced with selenium, did not offer any improvement despite its enhanced ability to generate highly electrophilic intermediates.^[16] Catalyst **D** bearing *anti*-stereodirecting substituents performed poorly, while the presence of sterically hindered substituents in catalysts **E** and **F** did not provide any significant benefit. A better stereoinduction was inferred by catalyst **G** (80:20 e.r.). To rationalise the origin of increased stereocontrol, conformational analyses of the resulting acyl ammonium intermediate **I** were performed via computation. The rigid conformation ensured by the pentacyclic framework in catalyst **G** resulted in a better shielding of the double bond prochiral (*Re*) face, as dictated by the C-H bonds within the stereodirecting arene moiety (see Figure 2b and section L of the SI). To maximise the steric shielding ability, we synthesised catalysts **H–J** where the relevant arene C-H bonds had been replaced with larger substituents (R^2 and R^3). Catalyst **H**, bearing a phenyl moiety at R^2 , completely suppressed reactivity, probably because the catalyst was too bulky to undergo acylation. In contrast, a *meta* substitution pattern proved effective, since catalyst **J** ($R^3 = \textit{tert}$ -butyl) enabled a significant boost in stereocontrol (87.5:12.5 e.r.).

Catalysts **G–J** were then used in a second round of optimisation (Figure 2c). After lowering the catalyst loading to 20 mol%, improved results were obtained using 1,2-DCE as solvent and TBACl as additive. Catalyst **G** (entry 1, **3a** formed in 66% yield and 86.5:13.5 e.r.) outperformed other catalysts in reactivity while enantioselectivity was similar (entries 2 and 3). Varying the leaving group within the acid substrate **1** had a significant impact. The electron-deficient aryl ester **1b** (entry 4) and mixed anhydride **1c** (entry 5) offered product **3a** in reduced yield and enantioselectivity. Control experiments indicated that both visible-light irradiation and the isothiourea catalyst were crucial for reactivity (entry 7). Intriguingly, the reaction proceeded in the absence of photocatalyst, albeit in poor yield and lower enantiocontrol (entry 8, see section K in SI for further discussion). The reaction performed well also under green light irradiation (entry 9).

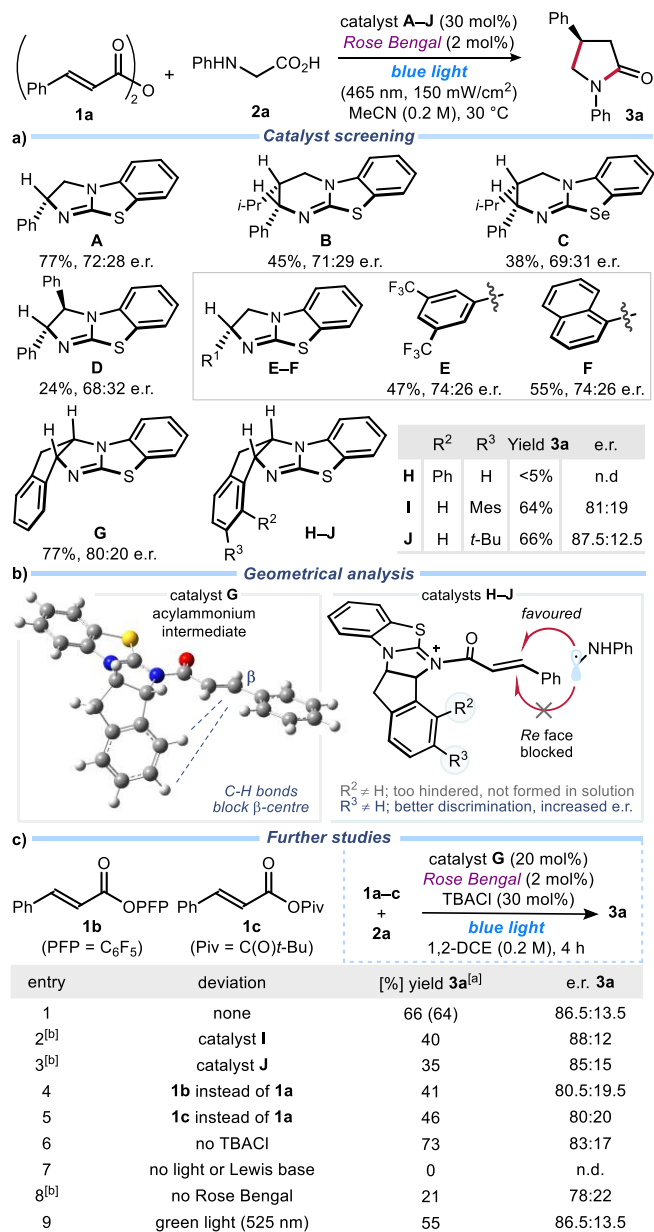


Figure 2. a) Catalyst screening. b) Optimised geometry of acyl ammonium formed from catalyst **G** and **1a**, performed using B3LYP/6-311G* in the gas phase. c) Further optimisation and control experiments. Reactions performed using **1a–c** (0.2 mmol) and **2a** (0.3 mmol). ^[a]Yield of **3a** determined by ¹H NMR analysis of the crude mixture using 1,3,5-trimethoxybenzene. Yield of isolated **3a** in parenthesis. ^[b]Reaction time 16 h.

Applying the optimised conditions (entry 1), the scope of the reaction was investigated using isothiourea **G** and the *tert*-butyl analogue **J** as viable catalysts (Figure 3). Cinnamic acids bearing alkyl substituents on the aryl ring, either in *ortho* (product **3b**) or in *meta* position (**3c**), were well tolerated, as was a range of methoxy-substituted derivatives (**3d–3g**). Incorporation of fluoro-, chloro- or bromo-substituents on the aryl group was successful, since adducts **3h–3o** were obtained in good yields without compromising enantioselectivity. While catalyst **G** was generally required to obtain high yield, catalyst **J** was particularly useful for achieving enhanced enantioselectivity in the formation of halogenated products **3h**, **3i**, **3l–n** (see Figure S4 for a performance comparison between catalysts **G** and **J**). The 2,6-dichloro-substituted cinnamic acid reacted to furnish **3p**. Electron-withdrawing groups were tolerated, including a cyano (product **3q**) and a trifluoromethyl (**3r**) moiety. A heteroaromatic moiety was tolerated, since the thiophene-substituted pyrrolidinone **3s** was obtained in high yield.

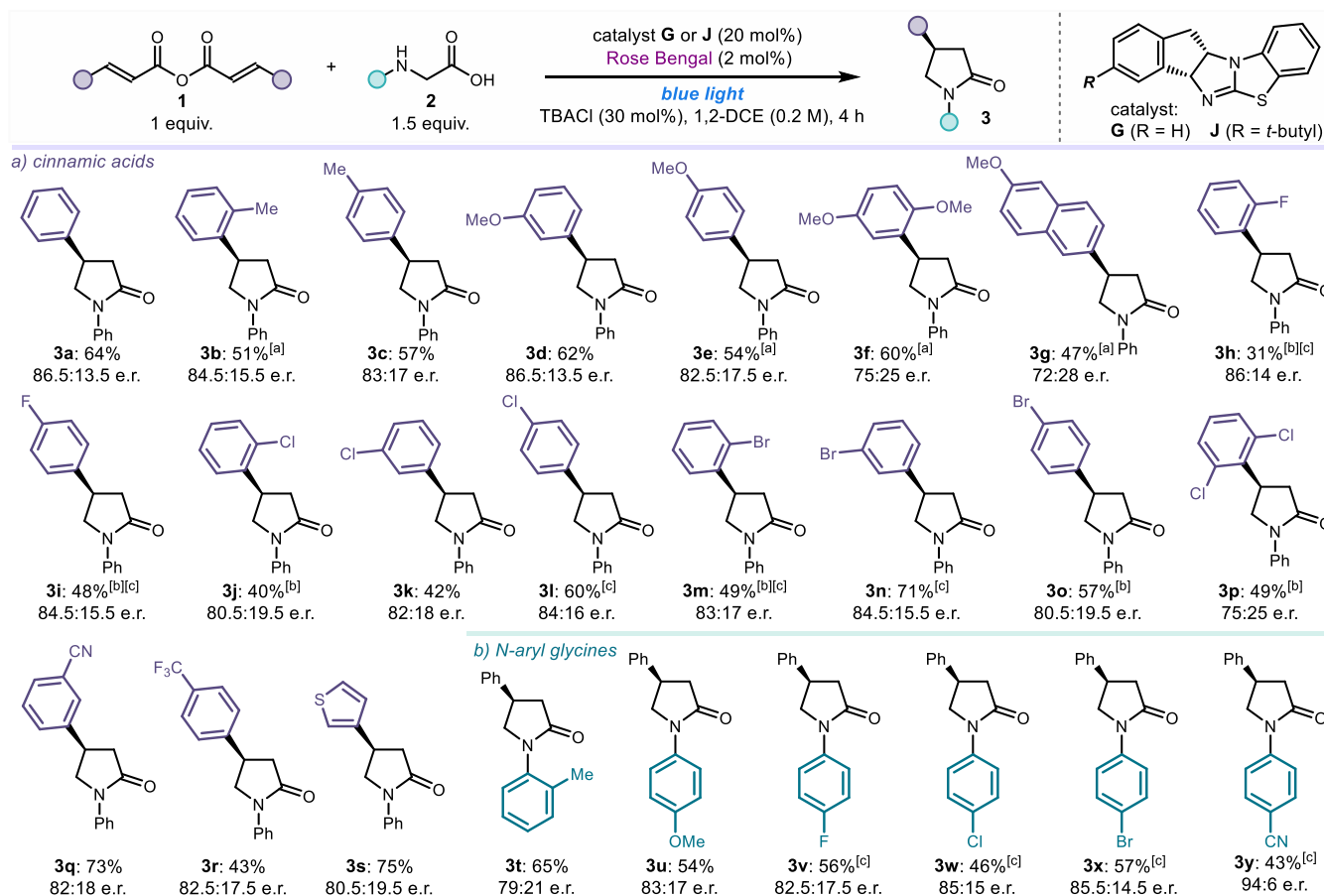


Figure 3: Photochemical radical synthesis of chiral pyrrolidinones **3**. Survey of the (a) cinnamic anhydrides **1** and (b) *N*-aryl glycines **2** that can participate in the process. Reactions performed on a 0.2 mmol scale using catalyst **G**; yields and enantiomeric ratios of the isolated products **3** are reported below each entry. ^[a]Reaction time: 16 h. ^[b] Using the corresponding pivalic anhydride of type **1c**. ^[c] Using catalyst **J**.

The electronic properties of the radical precursor were next investigated by varying the aryl substituents of *N*-aryl glycines **2** (Figure 3b). A sterically demanding 2-methyl substituent afforded product **3t**, while a 4-methoxy substituted amino acid led to the PMP-protected adduct **3u**. This example is relevant since oxidative *N*-PMP deprotection may offer easy access to *N*-unsubstituted pyrrolidinones.^[17] Catalyst **J** was used with halide-substituted *N*-aryl glycines, since it inferred increasing enantioselectivity across fluoro, chloro, and bromo substitution (products **3v-w**, respectively). Pleasingly, the electron-withdrawing 4-cyano group in **2** resulted in a substantial increase of enantioselectivity (**3y** formed in 94:6 e.r.). C2-substituted amino acids (e.g. *N*-phenylalanine) only provided traces of product, while acids bearing non-aryl nitrogen substitution were unsuccessful (see Figure S1 in SI for a list of unsuccessful substrates).

Because of hydrolysis of their corresponding anhydrides, alkyl-substituted carboxylic acids were investigated by preparing their pentafluorophenyl esters (Figure 4). The methyl-substituted pyrrolidinone **3z** was obtained in good yield and enantioselectivity. Variation of the alkyl chain was well accepted, which permitted the synthesis of **3aa** and **3ab**, structural derivatives of *brivaracetam*^[18] and *pregabalin*,^[19] thus highlighting the potential of the protocol to access biologically relevant scaffolds. A thioether moiety was well tolerated (**3ac**), while alicyclic-substituted esters resulted in enhanced enantioselectivity (products **3ad** and **3ae**). A substrate bearing a *N*-Boc protected amine led to the bis-heterocyclic product **3af**.

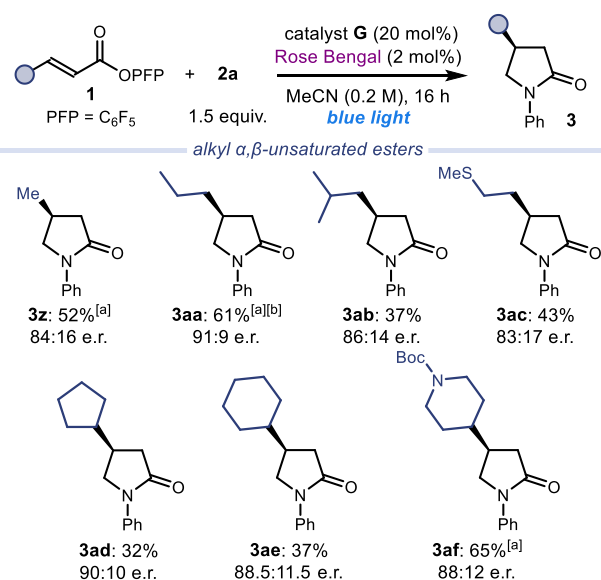


Figure 4: Scope of alkyl-substituted α,β -unsaturated esters. Yields and enantiomeric ratios refer to isolated products **3** after chromatographic purification. ^[a]Using 30 mol% of catalyst. ^[b] Using catalyst **J**. Boc = *tert*-butoxycarbonyl.

Next, the protocol was tested in the synthesis of pharmaceutically relevant compounds (Figure 5a). The pyrrolidinone scaffold offers access to γ -amino butyric acids (GABAs), which comprise important biological compounds. To prepare the active enantiomer of *baclofen*,^[20] a potent anti-spasmodic drug, we subjected anhydride **1d** and *N*-PMP glycine **2b** to our system using catalyst **J** under green-light irradiation (2 mmol scale). Product **4** was obtained in 54% yield

and 81:19 e.r. CAN oxidation followed by acid hydrolysis led to (*R*)-baclofen hydrochloride **5**. Additionally, compound **6**, a precursor to (*R*)-rolipram,^[21] could be accessed in good yield and enantioselectivity.

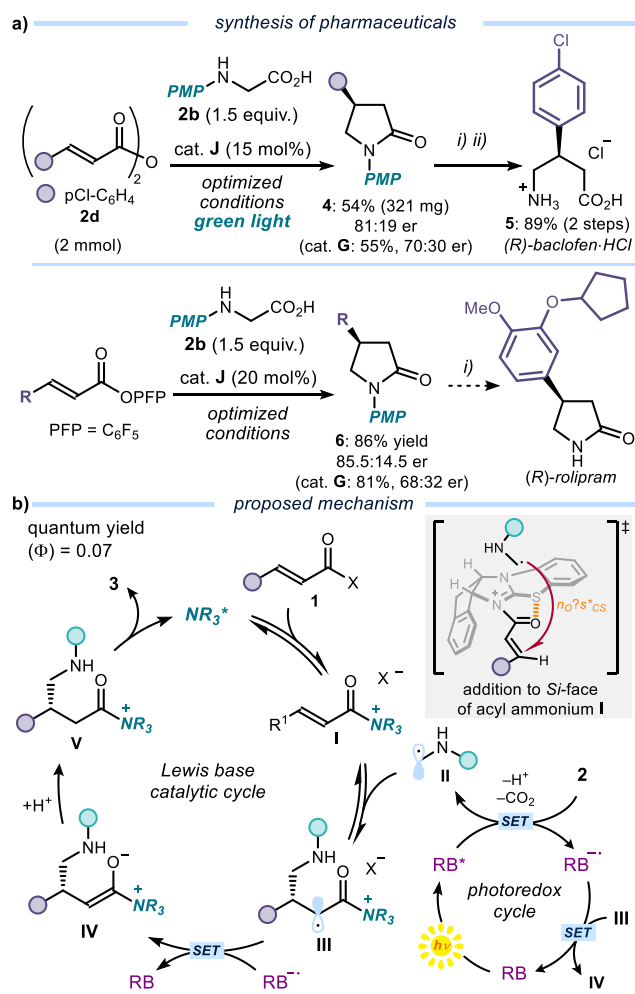


Figure 5: a) Synthesis of (*R*)-baclofen (2 mmol scale) and of (*R*)-rolipram precursor (0.2 mmol scale); i) CAN (3 equiv.), MeCN, 10 min; ii) HCl, reflux, 16 h. b) Proposed mechanism; RB: Rose Bengal.

A plausible mechanism is illustrated in Figure 5b. Visible-light irradiation of Rose Bengal leads to the excited \mathbf{RB}^* , which can trigger an SET oxidation of **2**. Rapid decarboxylation leads to α -amino radical **II** which undergoes stereoselective RCA to the chiral intermediate **I**. Stereocontrol is proposed to arise from an intramolecular 1,5-O \cdots S chalcogen interaction that fixes a syn-coplanar arrangement between the carbonyl oxygen and the catalyst's sulfur atom.^[22] The stereochemical outcome can be rationalised by addition of radical **II** *anti*- to the stereodirecting arene unit of the catalyst. The resulting intermediate **III** is then reduced via SET by \mathbf{RB}^* . This redox step closes the photoredox cycle and drives a radical-polar crossover leading to enolate **IV**. Protonation of **IV** to give the acyl ammonium **V** sets the stage for an intramolecular acylation, which leads to product **3** while turning over the isothiourea catalyst. We measured a quantum yield (Φ) of the reaction between **1a** and **2a** as low as 0.07, which is consonant with the proposed closed catalytic cycle.^[23]

In summary, we have developed a dual organocatalytic system for the enantioselective RCA of α -amino radicals to simple carboxylic acid derivatives, leading to chiral pyrrolidinones. This study offers the first example of radical chemistry in the field of enantioselective isothiourea catalysis.

Keywords: photochemistry • enantioselectivity • organocatalysis • radical reactions • Lewis base catalysis

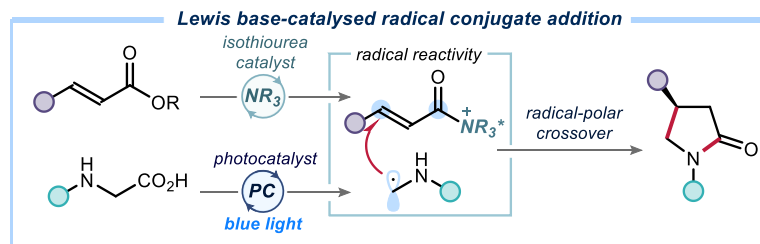
- a) B. Giese, *Angew. Chem. Int. Ed.* **1983**, *22*, 753–764; b) B. Giese, *Angew. Chem. Int. Ed.* **1989**, *28*, 969–980; c) A. L. Gant Kanegusuku, J. L. Roizen, *Angew. Chem. Int. Ed.* **2021**, *60*, 21116–21149; *Angew. Chem.*, **2021**, *133*, 21286–21319.
- H. J. Wu, R. Radinov, N. A. Porter, *J. Am. Chem. Soc.* **1995**, *117*, 11029–11030.
- a) M. P. Sibi, J. Ji, J. H. Wu, S. Gürtler, N. A. Porter, *J. Am. Chem. Soc.* **1996**, *118*, 9200–9201; b) M. P. Sibi, J. Ji, *J. Org. Chem.* **1997**, *62*, 3800–3801; c) M. P. Sibi, J. Ji, J. B. Sausker, C. P. Jasperse, *J. Am. Chem. Soc.* **1999**, *121*, 7517–7526.
- M. Shaw, J. Twilton, D. W. C. MacMillan, *J. Org. Chem.* **2016**, *81*, 6898–6926.
- For selected examples: a) A. Bauer, F. Westkämper, S. Grimme, T. Bach, *Nature* **2005**, *436*, 1139–1140; b) L. Ruiz Espelt, I. S. McPherson, E. M. Wiensch, T. P. Yoon, *J. Am. Chem. Soc.* **2015**, *137*, 2452–2455; c) H. Huo, K. Harms, E. Meggers, *J. Am. Chem. Soc.* **2016**, *138*, 6936–6939; d) S.-X. Lin, G.-J. Sun, Q. Kang, *Chem. Commun.* **2017**, *53*, 7665–7668; e) J. Ma, J. Lin, L. Zhao, K. Harms, M. Marsch, X. Xie, E. Meggers, *Angew. Chem. Int. Ed.* **2018**, *57*, 11193–11197; *Angew. Chem.* **2018**, *130*, 11363–11367; f) C. Wang, K. Harms, E. Meggers, *Angew. Chem. Int. Ed.* **2016**, *55*, 13495–13498; *Angew. Chem.* **2016**, *128*, 13693–13696.
- a) E. Le Saux, D. Ma, P. Bonilla, C. M. Holden, D. Lustosa, P. Melchiorre, *Angew. Chem. Int. Ed.* **2021**, *60*, 5357–5362; *Angew. Chem.* **2021**, *133*, 5417–5422; b) M. Silvi, C. Verrier, Y. P. Rey, L. Buzzetti, P. Melchiorre, *Nat. Chem.* **2017**, *9*, 868–873.
- a) J. J. Murphy, D. Bastida, S. Paria, M. Fagnoni, P. Melchiorre, *Nature* **2016**, *532*, 218–222; b) A. Bahamonde, J. J. Murphy, M. Savarese, É. Brémont, A. Cavalli, P. Melchiorre, *J. Am. Chem. Soc.* **2017**, *139*, 4559–4567; c) Z.-Y. Cao, T. Ghosh, P. Melchiorre, *Nat. Commun.* **2018**, *9*, 3274.
- For recent reviews on α,β -unsaturated acyl ammonium intermediates in ionic pathways, see: a) J. Bitai, M. T. Westwood, A. D. Smith, *Org. Biomol. Chem.* **2021**, *19*, 2366–2384; b) S. Vellalath, D. Romo, *Angew. Chem. Int. Ed.* **2016**, *55*, 13934–13943; *Angew. Chem.* **2016**, *128*, 14138–14148.
- For the first report of chiral isothioureas as catalysts in α,β -unsaturated acyl ammonium chemistry, see: E. R. T. Robinson, C. Fallan, C. Simal, A. M. Z. Slawin, A. D. Smith, *Chem. Sci.* **2013**, *4*, 2193–2200.
- An example of combination of isothiourea and photoredox catalysis was reported recently, but the chemistry relied on the formation of ionic intermediates (iminium ions and ammonium enolates) and did not proceed via radical pathways, see: J. N. Arokianathar, A. B. Frost, A. M. Z. Slawin, D. Stead, A. D. Smith, *ACS Catal.* **2018**, *8*, 1153–1160.
- For selected examples of SET activation of **2**, see: a) H. Peng, S. Bi, M. Ni, X. Xie, Y. Liao, X. Zhou, Z. Xue, J. Zhu, Y. Wei, C. N. Bowman, Y.-W. Mai, *J. Am. Chem. Soc.* **2014**, *136*, 8855–8858; b) A. Millet, Q. Lefebvre, M. Rueping, *Chem. Eur. J.* **2016**, *22*, 13464–13468. For the use of **2** in asymmetric radical catalysis, see: c) Y. Liu, X. Liu, J. Li, X. Zhao, B. Qiao, Z. Jiang, *Chem. Sci.* **2018**, *9*, 8094–8098; d) X. Chai, X. Hu, X. Zhao, Y. Yin, S. Cao, Z. Jiang, *Angew. Chem. Int. Ed.* **2022**, *61*, e202115110.
- For a non-stereocontrolled radical-polar crossover [3+2]-cycloaddition type protocol leading to racemic pyrrolidinones **3**, see: H. Zhao, D. Leonori, *Angew. Chem. Int. Ed.* **2021**, *60*, 7669–7674; *Angew. Chem.* **2021**, *133*, 7747–7752.
- a) C. Shao, H.-J. Yu, N.-Y. Wu, P. Tian, R. Wang, C.-G. Feng, G.-Q. Lin, *Org. Lett.* **2011**, *13*, 788–791; b) Q. Lang, G. Gu, Y. Cheng, Q. Yin, X. Zhang, *ACS Catal.* **2018**, *8*, 4824–4828.
- For a review: a) T. Ishii, K. Nagao, H. Ohmiya, *Chem. Sci.* **2020**, *11*, 5630–5636. For pioneering examples: a) N. A. White, T. Rovis, *J. Am. Chem. Soc.* **2014**, *136*, 14674–14677; c) Y. Zhang, Y. Du, Z. Huang, J. Xu, X. Wu, Y. Wang, M. Wang, S. Yang, R. D. Webster, Y. R. Chi, *J. Am. Chem. Soc.* **2015**, *137*, 2416–2419.
- C. R. Lambert, I. E. Kochevar, *Photochem. Photobiol.* **1997**, *66*, 15–25.
- C. M. Young, A. Elmi, D. J. Pascoe, R. K. Morris, C. McLaughlin, A. M. Woods, A. B. Frost, A. Houpliere, K. B. Ling, T. K. Smith, A. M. Z. Slawin, P. H. Willoughby, S. L. Cockcroft, A. D. Smith, *Angew. Chem. Int. Ed.* **2020**, *59*, 3705–3710; *Angew. Chem.* **2020**, *132*, 3734–3739.

-
- [17] D. R. Kronenthal, C. Y. Han, M. K. Taylor, *J. Org. Chem.* **1982**, *47*, 2765–2768.
- [18] M. Gayke, H. Narode, G. Eppa, R. S. Bhosale, J. S. Yadav, *ACS Omega* **2022**, *7*, 2486–2503.
- [19] A. Carlone, L. Bernardi, P. McCormack, T. Warr, S. Oruganti, C. J. Cobley, *Org. Process Res. Dev.* **2021**, *25*, 2795–2805.
- [20] P. Ramesh, D. Suman, K. S. N. Reddy, *Synthesis*, **2017**, 211–226.
- [21] T. Tsubogo, H. Oyamada, S. Kobayashi, *Nature* **2015**, *520*, 329–332.
- [22] For selected examples of joint experimental/computational assessment of α,β -unsaturated acyl isothiuronium catalysis, see a) M. E. Abbasov, B. M. Hudson, D. J. Tantillo, D. Romo, *J. Am. Chem. Soc.* **2014**, *136*, 4492–4495; b) E. R. T. Robinson, D. M. Walden, C. Fallan, M. D. Greenhalgh, P. H.-Y. Cheong, A. D. Smith, *Chem. Sci.* **2016**, *7*, 6919–6927; c) M. E. Abbasov, B. M. Hudson, D. J. Tantillo, D. Romo, *Chem. Sci.* **2017**, *8*, 1511–1524.
- [23] a) L. Buzzetti, G. E. M. Crisenza, P. Melchiorre, *Angew. Chem. Int. Ed.* **2019**, *58*, 3730–3747; *Angew. Chem.* **2019**, *131*, 3768–3786.

Asymmetric radical catalysis

Will C. Hartley, Florian Schiel, Elena Ermini, and Paolo Melchiorre* _____ Page – Page

Lewis Base-Catalysed Enantioselective Radical Conjugate Addition for the Synthesis of Enantioenriched Pyrrolidinones



The combination of photoredox catalysis and Lewis base catalysis has been developed to realise the first example of asymmetric radical conjugate addition to α,β -unsaturated anhydrides and esters. The chemistry, mastered by a chiral isothioureia organocatalyst, enables the synthesis of enantioenriched pyrrolidinones, with application to the synthesis of biologically-active γ -amino butyric acids.