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Photoredox-catalyzed dicarbofunctionalization of styrenes with amines and CO₂: a convenient access to γ -amino acids†

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A visible-light-promoted carbocarboxylation of styrenes using CO₂ and amines is reported. The reaction is catalyzed by a photoredox catalyst and is compatible with a variety of amines and styrenes. This method affords highly functionalized γ -amino acids in good yields with high regioselectivity.

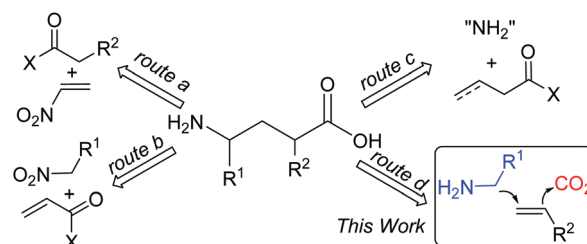
γ -Amino acids are highly valuable compounds that exist widely in pharmaceuticals and exhibit a diverse range of biological activities as agonists and antagonists of receptors for mammalian neurotransmitters in the central nervous system.¹ Thus, considerable efforts have been devoted to the synthesis of γ -amino acids,² such as Michael addition of carbonyl compounds to nitroethylenes (Scheme 1, route a)³ or conjugate addition of nitroalkanes to α,β -unsaturated carbonyl compounds (Scheme 1, route b)⁴ to afford γ -amino acids. Recently, Ye and coworkers reported γ -amination of α,β -unsaturated acyl chlorides with azodicarboxylates followed by reductive ring opening of dihydropyridazinones to afford γ -amino acids (Scheme 1, route c).⁵ Despite all these efforts, these synthetic methods suffer from limited substrate scope, multiple steps, and/or harsh reaction conditions. We envisioned that the simultaneous incorporation of both α -aminoalkyl and carbon dioxide (CO₂) to alkenes *via* dicarbofunctionalization of alkenes would serve as an ideal route to deliver γ -amino acids (Scheme 1, route d).

The evolving visible-light-mediated photoredox catalysis offers an operating strategy to access open shell radical species,⁶ leading to novel methods for difunctionalization of alkenes.⁷ Recently, photoredox-promoted single electron oxidation of amines and subsequent deprotonation to generate α -aminoalkyl radicals **B** have been described (Scheme 2).⁸ The

addition of the α -aminoalkyl radical **B** to alkenes resulted in the formation of the alkyl radical species **C**, which undergoes a single electron reduction to capture an electrophile.⁹ We anticipated that the incorporation of CO₂ as an electrophile in the reaction mixture might enable the formation of γ -amino acids.

CO₂ as a nontoxic, ubiquitous, and recyclable one-carbon source has attracted attention in organic synthesis.¹⁰ The catalytic carboxylation of unsaturated compounds with CO₂ has attracted much attention from chemists.¹¹ Compared with the widely considered hydrocarboxylation of alkene with CO₂,¹² photocatalytic functional carboxylation of alkenes with CO₂ is more challenging and rarely reported. Recently, the Martin, Yu, Wu, and Li groups demonstrated respectively the photoredox-catalyzed difunctionalization of alkenes under visible light to afford β -functionalized alkylcarboxylic acids with CO₂.¹³ Taking into account the potential of these transformations and our ongoing interest in the carboxylation of alkenes with CO₂ for the efficient dicarbofunctionalization reaction, herein, we report the photoredox-catalyzed α -aminomethylcarboxylation of alkenes with amines and CO₂. This strategy is sustainable, general, and practical, representing a rare example of redox-neutral dicarbofunctionalization of alkenes to generate important γ -amino acids with high efficiency and selectivity under mild reaction conditions.

We started the investigation by employing *N,N*-dimethylaniline **1a** and methyl 4-vinylbenzoate **2a** as model substrates



Scheme 1 Typical approaches to γ -amino acid derivatives.

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Scheme 2 Photocatalytic preparation of γ -amino acids from CO_2 .

under the irradiation of 5 W blue light emitting diodes (LEDs) with atmospheric pressure CO_2 . Yields were determined after methyl esterification with TMSCHN_2 (Table 1). After numerous extensions of the reaction parameters, the desired product **3'aa** was obtained in 95% yield when 4 mol% of 1,2,3,5-tetrakis-

Table 1 Optimization of the reaction conditions^a

Entry	Deviation from standard conditions	Yield of 3'aa ^b [%]	Yield of 4aa ^b [%]
1	None	95 (89)	4
2	Ir-1 instead of 4CzIPN	84	4
3	Ir-2 instead of 4CzIPN	76	4
4	Ir-3 instead of 4CzIPN	12	1
5	Ru-1 instead of 4CzIPN	83	2
6	Without 4CzIPN	—	—
7	LiF instead of LiCl	44	3
8	LiBF_4 instead of LiCl	39	5
9	LiOAc instead of LiCl	43	7
10	NaCl instead of LiCl	20	2
11	KCl instead of LiCl	26	3
12	Without LiCl	62	3
13	2 eq. instead of 4 eq. of LiCl	82	5
14	Add 20 mol% Q-1	46	24
15	Add 20 mol% Q-2	48	15
16	DMF instead of DMSO	80	15
17	MeCN instead of DMSO	8	44
18	THF instead of DMSO	8	28
19 ^c	0.025 M instead of 0.1 M	56	19
20	2 eq. instead of 6 eq. of 1a	79	9
21	4 eq. instead of 6 eq. of 1a	73	11
22	7 eq. instead of 6 eq. of 1a	94	3

Ir-1 $\text{R}^1=\text{R}^2=\text{H}$
Ir-2 $\text{R}^1=\text{CF}_3$, $\text{R}^2=\text{F}$

4CzIPN

Q-1 $\text{R}=\text{H}$
Q-2 $\text{R}=\text{OAc}$

^a Reaction conditions: **1a** (0.6 mmol), **2a** (0.1 mmol), 4CzIPN (0.004 mmol), LiCl (0.4 mmol), DMSO (1 mL), 1 atm CO_2 , 5 W blue LED, room temperature, 48 h, quenched with HCl (2 M) solution, after extraction with ethyl acetate, $\text{MeOH}:\text{ether} = 1:1$ (0.5 mL) and TMSCHN_2 (3 equiv.) were added. ^b Yields determined by GC using *n*-dodecane as an internal standard; isolated yield in parentheses. ^c 4 mL of DMSO was used instead of 1 mL.

(carbazole-9-yl)-4,6-dicyanobenzene (4CzIPN) was used as a photoredox catalyst and LiCl as an additive in DMSO (0.1 M) at room temperature after 48 h irradiation (entry 1). The hydro-aminoalkylation product **4aa** was also detected by GC as a by-product. $\text{Ir}(\text{ppy})_2(\text{dtbbpy})(\text{PF}_6)$, $\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})(\text{PF}_6)$, and $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$ were employed as photoredox catalysts which performed less effectively than 4CzIPN (entries 2, 3 and 5). A trace amount of **3'aa** was obtained using $\text{Ir}(\text{ppy})_3$ instead of 4CzIPN (entry 4). The reaction could not proceed without the photoredox catalyst (entry 6). The choice of the additive was pivotal; LiF, LiBF_4 , LiOAc , NaCl, and KCl were used as additives to afford lower yields of **3'aa** (entries 7–11). Notably, the reaction proceeded to give the desired product **3'aa** in 62% yield in the absence of LiCl (entry 12). When two equivalents of LiCl were employed, the desired product **3'aa** was obtained in 82% yield (entry 13). Hydrogen atom transfer (HAT) is frequently involved in photocatalysis, which offers enormous opportunities for C–H activation.¹⁴ The combination of the photoredox catalyst 4CzIPN (4 mol%) with HAT catalysts such as quinuclidin-3-yl acetate and quinuclidine (20 mol%) provided the desired product **3'aa** in 46% and 48% yields, respectively (entries 14 and 15). Among the solvents examined, DMSO resulted in the best reactivity and selectivity (entries 1 and 16–18). Both reactivity and selectivity significantly decreased with the dilution of **1a** as expected (entry 19). The utilization of 6 equivalents of amine was proved to be necessary to obtain the desired product in a good yield (entries 1, 20–22).

With the optimized conditions, a study on the substrate scope was carried out. Firstly, a variety of tertiary amines **1** were used in the reaction with methyl 4-vinylbenzoate **2a** to synthesize γ -amino acids with a range of substituents on anilines. The representative results are shown in Scheme 3. The



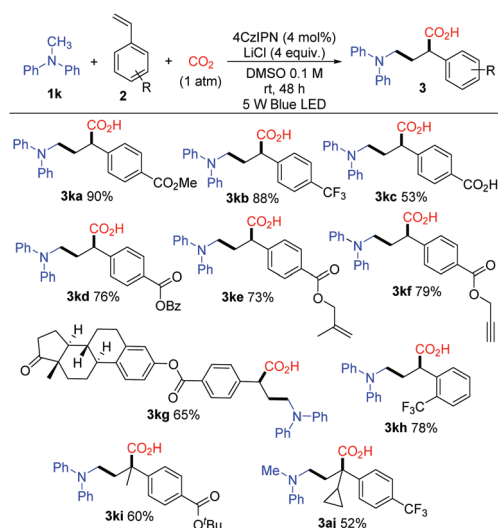
Scheme 3 Photocatalytic reactions of methyl 4-vinylbenzoate **2a** with amines. Reaction conditions: **1** (1.2 mmol), **2a** (0.2 mmol), 4CzIPN (0.008 mmol), LiCl (0.8 mmol), DMSO (2 mL), 1 atm CO_2 , 5 W blue LED, room temperature, 48 h, quenched with HCl (2 M) solution. Yields of isolated carboxylic acid **3** without esterification with TMSCHN_2 .

reaction of **2a** with dimethyldiphenylamine (**1a**) proceeded smoothly to give γ -amino acid **3aa** in 88% isolated yield without esterification with TMSCHN₂. Introduction of a substituent such as methyl, bromo, chloro, or fluoro at the *para*-position of the benzene ring did not affect much the yield of γ -amino acids **3** (**3ba** in 73%, **3ca** in 81%, **3da** in 64%, **3ea** in 75%). The amines bearing highly electron-withdrawing groups such as an ester, keto carbonyl, or cyano group at the *para*-position in the benzene ring yielded the expected products **3** in high yields (**3fa** in 88%, **3ga** in 86%, **3ha** in 80%). The substituents such as methyl or bromo located at the *ortho*-position in the benzene ring also afforded the target products **3** in good yields (**3ia** in 70%, **3ja** in 78%). To our delight, methyl-diphenylamine **1k** was well applicable and delivered the corresponding γ -amino acid **3ka** in 90% yield. γ -Amino acids with a carbazolyl group have potential in materials science; in this reaction, 9-methyl-9H-carbazole **1l** was also applicable and delivered the corresponding γ -amino acid **3la** in 87% yield. The cyclic amine 1-phenylpyrrolidine **1m** was transformed into **3ma** in 60% yield. It is noteworthy that the utilization of primary and secondary amines such as octan-1-amine and *N*-methylaniline as well as other aromatic amines such as 4-methoxy-*N,N*-dimethylaniline and *N*-dimethylnaphthalen-1-amine did not lead to the corresponding products.

Next, we examined the photocatalytic reactions with a variety of alkenes **2**; the typical results are shown in Scheme 4. A series of substituted styrenes with electron-withdrawing substituents at the *para*-position such as trifluoromethyl (**2b**), carboxyl (**2c**) and esters (**2a**, **2d**, **2e**, **2f**, **2g**, and **2i**) could be accommodated and afforded the corresponding products **3** in good yields. Remarkably, γ -amino acid **3kc** was prepared smoothly when 4-vinylbenzoic acid (**2c**) was employed. When

benzyl-, alkenyl-, and alkynyl-derived ester styrenes such as **2d**, **2e**, and **2f** were employed, the corresponding products **3kd**, **3ke**, and **3kf** were formed in good yields, respectively. Moreover, estrone-derived ester styrene **2g** was also tested, and the corresponding α -aminomethylcarboxylation product **3kg** was obtained in 65% yield. It is noteworthy that estrone linked with γ -amino-acid moiety could be well soluble in organic solutions while estrone cannot. Notably, the styrene with a substituent at the *ortho*-position of the benzene ring also gave the corresponding product **3kh** in 78% yield. Vinylpyridine was employed as the styrene in this reaction and a trace amount of the desired product was detected. Furthermore, α -substituted styrenes could be used resulting in the target compounds **3ki** and **3aj** with quaternary carbon centers. Unfortunately, β -substituted styrenes such as methyl (*E*)-4-(prop-1-en-1-yl)benzoate could not undergo the reaction. In addition, we did not detect the desired products when butyl acrylate and acrylonitrile were used in this reaction. In general, an electron-withdrawing group at the benzene ring of the styrene is essential to obtain the corresponding γ -amino acid in this reaction.

Additional experiments were performed to gain insight into the reaction mechanism. Light on-off experiments indicated that continuous light irradiation was essential to perform the reaction, and during the process, hydroaminoalkylation was restrained all the way. The quantum yield of the reaction of **1a** with **2a** under the optimized conditions was 0.0414 (see the ESI†). The isotope labelling experiments with D₂O implied that γ -amino benzylic anionic species could be the intermediates (Scheme 5a). It is noteworthy that the yield of **4aa** increased with increasing amount of D₂O, and LiCl also played

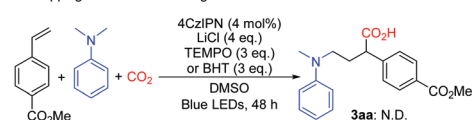


Scheme 4 Photocatalytic reactions of methyl-diphenylamine **1k** and **1a** with alkenes. Reaction conditions: **1k** or **1a** (1.2 mmol), **2** (0.2 mmol), 4CzIPN (0.008 mmol), LiCl (0.8 mmol), DMSO (2 mL), 1 atm CO₂, 5 W blue LED, RT, 48 h, quenched with HCl (2 M) solution. Yields of isolated products.

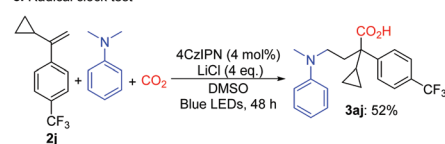
a. Isotope labelling experiments with D₂O



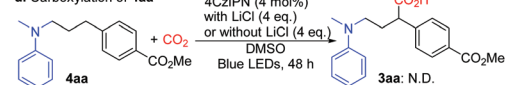
b. Trapping with radical scavengers



c. Radical clock test



d. Carboxylation of 4aa



Scheme 5 Control experiments for elucidation of the mechanism.



Scheme 6 The proposed reaction mechanism.

a vital role in this reaction. When the radical scavengers 2,2,6,6-tetramethyl-piperidinyloxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) were used in the reaction, the desired product **3aa** was not obtained (Scheme 5b) respectively; these results indicated that this transformation might rely on a radical process. Furthermore, the radical clock substrate **2j** was used under the optimal reaction conditions; however, no ring-opening product was detected (Scheme 5c), which suggested that the single electron reduction step from the benzyl radical to the benzyl anion is quite quick. Compound **4aa** was treated with standard conditions, and **3aa** was not observed and **4aa** was retained (Scheme 5d), which rules out the direct C–H carboxylation pathway.¹⁵

Based on the aforementioned results, a plausible mechanism was proposed and is shown in Scheme 6. Photo-excited 4CzIPN is reductively quenched with aniline leading to **I** and the radical cation intermediate **A**, which then deprotonates and gives α -aminoalkyl radical **B** in the presence of a base. The carbon radical **B** undergoes addition to the C=C bond of styrene **2** to selectively generate the γ -amino benzylic radical **C**. A subsequent single-electron transfer (SET) between **C** and the reduced photocatalyst 4CzIPN gives the γ -amino benzylic carbanion **D**, which is proposed as a lithium chelated species to stabilize the carbanion and accelerate the SET process. The nucleophilic addition to CO₂ or activated CO₂ by LiCl and protonation complete this reaction and yield the expected γ -amino acids.

Conclusions

In summary, we have developed a catalytic intermolecular dicarbofunctionalization of styrenes with CO₂ and amines through photoredox catalysis. The carbocarboxylation has the advantages of superior step and atom economy, broad substrate scope, and mild conditions. This study represents a rare example of the catalytic carbocarboxylation of alkenes with CO₂ in a redox-neutral fashion, which could lead to a new general alkene dicarbofunctionalization strategy using abundant and inexpensive chemical feedstock.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- For selected recent reviews, see: (a) P. Conti, L. Tamborini, A. Pinto, A. Blondel, P. Minoprio, A. Mozzarelli and C. De Micheli, *Chem. Rev.*, 2011, **111**, 6919–6946; (b) R. B. Silverman, *Angew. Chem., Int. Ed.*, 2008, **47**, 3500–3504.
- (a) M. Ordóñez and C. Cativiela, *Tetrahedron: Asymmetry*, 2007, **18**, 3–99; (b) K. Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013–3028.
- (a) R. Kastl and H. Wennemers, *Angew. Chem., Int. Ed.*, 2013, **52**, 7228–7232; (b) J. H. Sim and C. E. Song, *Angew. Chem., Int. Ed.*, 2017, **56**, 1835–1839; (c) Y. Chi, L. Guo, N. A. Kopf and S. H. Gellman, *J. Am. Chem. Soc.*, 2008, **130**, 5608–5609; (d) T. Okino, Y. Hoashi, T. Furukawa, X. Xu and Y. Takemoto, *J. Am. Chem. Soc.*, 2005, **127**, 119–125; (e) M. Wiesner, J. D. Revell, S. Tonazzi and H. Wennemers, *J. Am. Chem. Soc.*, 2008, **130**, 5610–5611.
- (a) K. Akagawa and K. Kudo, *Angew. Chem., Int. Ed.*, 2012, **51**, 12786–12789; (b) A. Baschieri, L. Bernardi, A. Ricci, S. Suresh and M. F. Adamo, *Angew. Chem., Int. Ed.*, 2009, **48**, 9342–9345.
- (a) X. Y. Chen, F. Xia, J. T. Cheng and S. Ye, *Angew. Chem., Int. Ed.*, 2013, **52**, 10644–10647; (b) L. T. Shen, L. H. Sun and S. Ye, *J. Am. Chem. Soc.*, 2011, **133**, 15894–15897.
- For selected reviews, see: (a) D. Ravelli, S. Protti and M. Fagnoni, *Chem. Rev.*, 2016, **116**, 9850–9913; (b) D. Stanveness, I. Bosque and C. R. J. Stephenson, *Acc. Chem. Res.*, 2016, **49**, 2295–2306; (c) J.-P. Goddard, C. Ollivier and L. Fensterbank, *J. Am. Chem. Soc.*, 2016, **49**, 1924–1936; (d) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075–10166.
- For selected reviews, see: (a) M. Y. Cao, X. Ren and Z. Lu, *Tetrahedron Lett.*, 2015, **56**, 3732–3742; (b) T. Koike and M. Akita, *Org. Chem. Front.*, 2016, **3**, 1345–1348; (c) T. Koike and M. Akita, *Chem*, 2018, **4**, 1–29.
- (a) A. McNally, C. K. Prier and D. W. MacMillan, *Science*, 2016, **352**, 1304–1308; (b) Y. Cai, Y. Tang, L. Fan, Q. Lefebvre, H. Hou and M. Rueping, *ACS Catal.*, 2018, **8**, 9471–9476; (c) L. Shi and W. Xia, *Chem. Soc. Rev.*, 2012, **41**, 7687–7697; (d) K. Nakajima, Y. Miyake and Y. Nishibayashi, *Acc. Chem. Res.*, 2016, **49**, 1946–1956; (e) S. A. Morris, J. Wang and N. Zheng, *Acc. Chem. Res.*, 2016, **49**, 1957–1968.
- (a) Y. Miyake, K. Nakajima and Y. Nishibayashi, *J. Am. Chem. Soc.*, 2012, **134**, 3338–3341; (b) P. Kohls, D. Jadhav, G. Pandey and O. Reiser, *Org. Lett.*, 2012, **14**, 672–675; (c) Y. Yin, Y. Dai, H. Jia, J. Li, L. Bu, B. Qiao, X. Zhao and Z. Jiang, *J. Am. Chem. Soc.*, 2018, **140**, 6083–6087;

- (d) M. A. Ashley, C. Yamauchi, J. C. K. Chu, S. Otsuka, H. Yorimitsu and T. Rovis, *Angew. Chem., Int. Ed.*, 2019, **58**, 4002–4006.
- 10 For selected reviews, see: (a) D. Yu, S. P. Teong and Y. Zhang, *Coord. Chem. Rev.*, 2015, **293–294**, 279–291; (b) S. Wang, G. Du and C. Xi, *Org. Biomol. Chem.*, 2016, **14**, 3666–3676; (c) S. Wang and C. Xi, *Chem. Soc. Rev.*, 2019, **48**, 382–404; (d) Y. Cao, X. He, N. Wang, H.-R. Li and L.-N. He, *Chin. J. Chem.*, 2018, **36**, 644–659; (e) Q. Liu, L. Wu, R. Jackstell and M. Beller, *Nat. Commun.*, 2015, **6**, 5933; (f) K. Huang, C.-L. Sun and Z.-J. Shi, *Acc. Chem. Res.*, 2011, **40**, 2435–2452; (g) F. Tan and G. Yin, *Chin. J. Chem.*, 2018, **36**, 545–554.
- 11 For selected reviews, see: (a) A. Tortajada, F. Julia-Hernandez, M. Borjesson, T. Moragas and R. Martin, *Angew. Chem., Int. Ed.*, 2018, **57**, 15948–15982; (b) M. Borjesson, T. Moragas, D. Gallego and R. Martin, *ACS Catal.*, 2016, **6**, 6739–6749; (c) F. Julia-Hernandez, M. Gaydou, E. Serrano, M. Gemmeren and R. Martin, *Top. Curr. Chem.*, 2016, **374**, 45; (d) Y. Tsuji and T. Fujihara, *Chem. Commun.*, 2012, **48**, 9956–9964.
- 12 For selected articles, see: (a) B. Yu, Z.-F. Diao, C.-X. Guo and L.-N. He, *J. CO₂ Util.*, 2013, **1**, 60–68; (b) M. Limbach, *Adv. Organomet. Chem.*, 2015, **63**, 175–202; (c) C. M. Williams, J. B. Johnson and T. Rovis, *J. Am. Chem. Soc.*, 2008, **130**, 14936–14937; (d) E. Shirakawa, D. Ikeda, S. Masui, M. Yoshida and T. Hayashi, *J. Am. Chem. Soc.*, 2012, **134**, 272–279; (e) M. D. Greenhalgh and S. P. Thomas, *J. Am. Chem. Soc.*, 2012, **134**, 11900–11903; (f) P. Shao, S. Wang, C. Chen and C. Xi, *Org. Lett.*, 2016, **18**, 2050–2053.
- 13 (a) V. R. Yatham, Y. Shen and R. Martin, *Angew. Chem., Int. Ed.*, 2017, **56**, 10915–10919; (b) J. H. Ye, M. Miao, H. Huang, S. S. Yan, Z. B. Yin, W. J. Zhou and D. G. Yu, *Angew. Chem., Int. Ed.*, 2017, **56**, 15416–15420; (c) Q. Fu, Z.-Y. Bo, J.-H. Ye, T. Ju, H. Huang, L.-L. Liao and D.-G. Yu, *Nat. Commun.*, 2019, **10**, 3592; (d) J. Hou, A. Ee, H. Cao, H.-W. Ong, J. Xu and J. Wu, *Angew. Chem., Int. Ed.*, 2018, **57**, 17220–17224; (e) H. Wang, Y. Gao, C. Zhou and G. Li, *J. Am. Chem. Soc.*, 2020, **142**, 8122–8129.
- 14 For selected reviews, see: (a) J. M. Mayer, *Acc. Chem. Res.*, 2011, **44**, 36–46; (b) L. Capaldo and D. Ravelli, *Eur. J. Org. Chem.*, 2017, 2056–2071.
- 15 Q. Meng, T. E. Schirmer, A. L. Berger, K. Donabauer and B. König, *J. Am. Chem. Soc.*, 2019, **141**(29), 11393–11397.