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Homogeneous Catalysis

Dual Catalytic Decarboxylative Allylations of α-Amino Acids and Their Divergent Mechanisms

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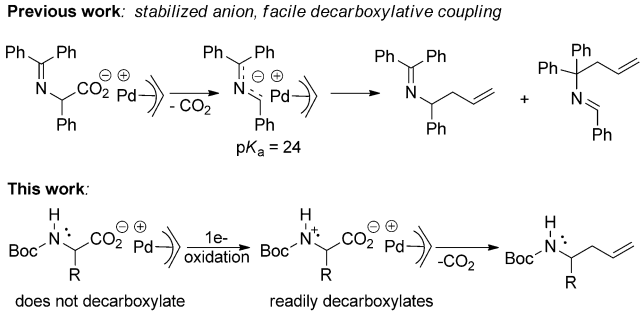
Abstract: The room temperature radical decarboxylative allylation of *N*-protected α-amino acids and esters has been accomplished via a combination of palladium and photoredox catalysis to provide homoallylic amines. Mechanistic investigations revealed that the stability of the α-amino radical, which is formed by decarboxylation, dictates the predominant reaction pathway between competing mechanisms.



Scheme 1. Anionic versus radical decarboxylation pathways.

Homoallylic amines are robust building blocks used to construct a wide variety of natural products and other bioactive molecules.[1] Classically, the addition of stoichiometric organometallic nucleophiles to an electrophilic aldimine has furnished these versatile molecules.[1,2] More recently, catalytic asymmetric methods including metal-free variants have been described in the literature.[1,3]

Alternatively, the palladium-catalyzed decarboxylative coupling of α-imino esters has provided an umpolung approach that couples 2-azaallyl anions with allyl electrophiles (Scheme 1).[4] This method is advantageous because it uses abundant, inexpensive carboxylic acid derivatives to access reactive intermediates under neutral conditions via loss of CO_2.[5] One drawback is that the amine must be activated to stabilize the α-amino anion to facilitate decarboxylation which leads to regio- and chemoselectivity issues that limit the substrate scope (Scheme 1).[6] We endeavored to extend this mode of reactivity towards synthetically useful *N*-protected amino acids that do not undergo anionic decarboxylation due to the formation of highly basic alkyl amino anions by utilizing alternate single electron pathways to facilitate decarboxylation.

The radical decarboxylation of carboxylic acids has historically been accomplished via electrochemical,[7] photochemical,[8] and reagent-based methods.[9,10] Recently, the combination of transition metal and photoredox catalysis has also been used to overcome high-energy two electron processes in catalysis via single-electron-transfer (SET) events.[11,12] For example, MacMillan[12g,h] and Molander[12i,j] have utilized photoredox events to facilitate the generation of alkyl radicals which undergo nickel-catalyzed cross-coupling. In addition, our lab has used palladium and photoredox catalysis to effect the decarboxylative allylation of aminoalkanoic acids and esters.[11] A similar approach for the α-allylation of secondary amines and *N*-aryl tetrahydroisoquinolines has also been employed by Lu and Xiao.[13] Herein we report that a dual catalytic approach allows the decarboxylative allylation of protected amino acids and peptides.

One obstacle encountered in our lab during development of the decarboxylative coupling of *p*-(aminophenyl)acetic acid esters was the products were formed in moderate yields due to the suspected formation of free radicals.[11] DFT calculations on nickel-catalyzed radical cross-coupling by Molander and Kozlowski indicate that free benzylic radicals and the nickel-bound benzyl radical are nearly equienergetic[14] and radical addition to the metal is reversible. Thus, we hypothesized that accessing higher energy radicals should disfavor free radical coupling by favoring formation of metal-bound radical intermediates which can undergo reductive elimination. Readily available amino acid derivatives bearing synthetically useful electron withdrawing nitrogen protecting groups, which generate less stable alkyl radicals upon decarboxylation, were chosen to test this hypothesis.

Optimization studies were initiated by combining Boc-proline-allylester with $[Pd(PPh_3)_4]$ and various visible-light-mediated photoredox catalysts [Eq. (1)]. Low conversion was observed by GC/MS when the strongly reducing $[Ir(dFppy)_3]$[15] (dFppy = 2-(2,4-difluorophenyl)pyridinate) photocatalyst was employed. Substituting more oxidizing cationic heteroleptic iridium complexes led to an increase in conversion, but numerous byproducts were also detected by GC/MS analysis. A solvent screen revealed that the combination of the highly oxidizing photocatalyst $Ir\{dF(CF_3)ppy\}_2(dtbbpy)[PF_6]$ ($dF(CF_3)ppy$ = (2-(2,4-difluorophenyl)-5-(trifluormethyl)pyridine, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) ($E^{red}_{1/2}[Ir^{*III}/Ir^{II}] = +1.21$ V vs. SCE)[16]

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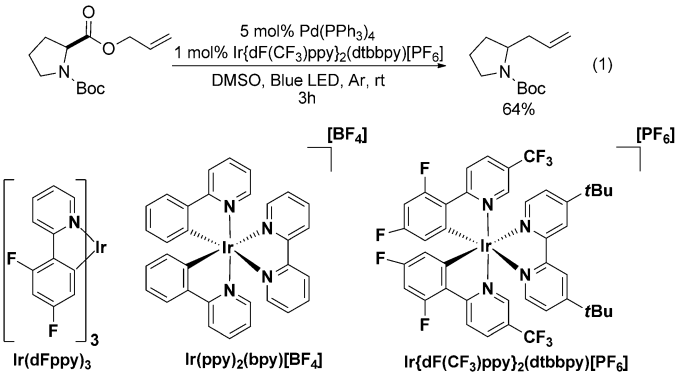


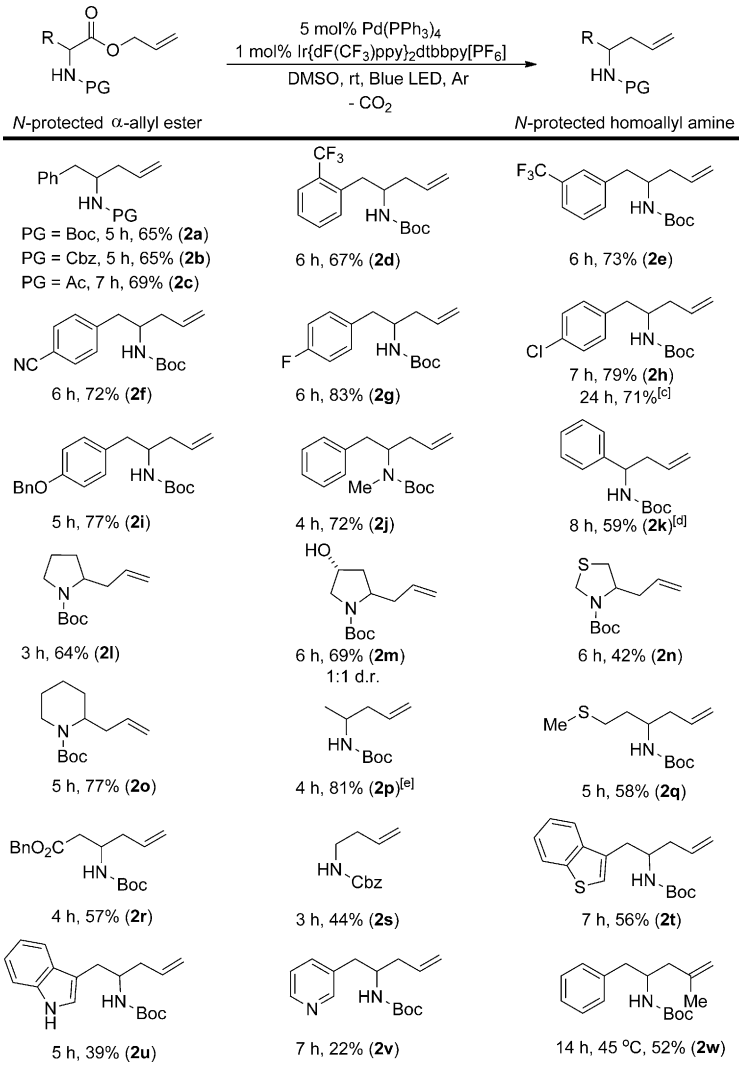
with DMSO led to rapid conversion of the starting material without the previously observed byproduct formation or significant deactivation of the active catalytic species.[17] Control reactions confirmed that no conversion of starting material to product occurred when the reaction was conducted without palladium, photocatalyst, or light.

We next evaluated the scope of α-amino allyl-esters that underwent decarboxylative allylation to furnish homoallyl amines (Scheme 2). A brief survey of nitrogen protecting groups revealed that *tert*-butyl and benzyl carbamates along with acetamides were compatible with the reaction conditions (**2a**–**2c**). A variety of phenylalanine derivatives bearing electron-withdrawing (**2d**–**2f**), halogen (**2g**, **2h**), and electron-donating (**2i**), substituents on the aryl ring were allylated in good yields. The reaction was also performed on gram scale, but it required a longer reaction time when it was performed under more convenient concentrated conditions (**2h**). A phenylalanine allyl ester bearing a tertiary amine and an *N*-Boc phenylglycine allyl ester were also tolerated (**2j**, **2k**).

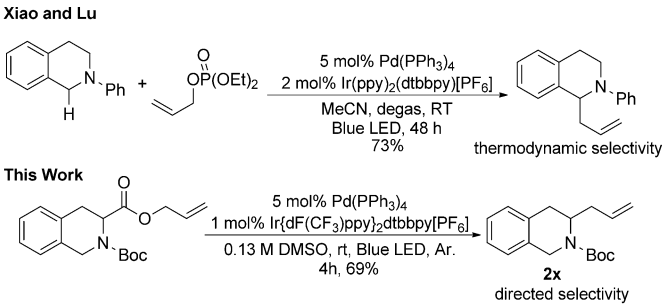
Cyclic amino acid allyl esters derived from proline, 4-hydroxy-, thio-, and homoproline (**2l**–**2o**) were also successfully allylated. Other acyclic tertiary homoallyl amines were constructed from their amino allyl ester precursors including alanine (**2p**), methionine (**2q**), and aspartic acid (**2r**). A protected glycine allyl ester provided a secondary homoallylic amine, albeit in reduced yield (**2s**). Nitrogen- (**2u**, **2v**) and sulfur-containing (**2t**) heterocycles also tolerated the reaction conditions, although lower yields were observed when pyridine (**2v**) or an unprotected indole (**2u**) was present. Lastly, a β-methallyl ester provided the desired homoallylic amine (**2w**), although a slightly higher reaction temperature (45 °C) was required.

One of the hallmarks of anionic decarboxylative couplings is that they are typically site-specific, leading to coupling only at the positon that bears the carboxylate.[5a] With the goal of demonstrating that the typical thermodynamic selectivity of α-amino *radical* formation can be overridden by the structure of the starting material used in decarboxylative coupling, the allyl ester of *N*-Boc tetrahydro-3-isoquinoline carboxylic acid was prepared. Tetrahydroisoquinolines are widely used in photoredox couplings due to the ease of access of the benzylically stabilized α-amino radical; an excellent example involving the allylation of tetrahydroquinoline by Xiao is shown in Scheme 3.[13] When our tetrahydroquinoline carboxylic ester was subjected to the standard reaction conditions, site-specific decarboxylative coupling to form a C–C bond occurred without isomerization to the thermodynamically more stable radical occurred (Scheme 3, >95% selectivity by crude ^{1}H NMR spectroscopy).

We also recognized that, in many cases, it would be beneficial to generate homoallylic amines directly from carboxylic acids via an intermolecular process. It was expected that treatment of the free acid with [Pd(PPh$_3$)$_4$] and allylmethyl carbonate would provide the same ionic intermediates (a carboxylate anion and Pd–π-allyl cation) that were generated from the amino acid allyl esters. Indeed, the Boc-pro-



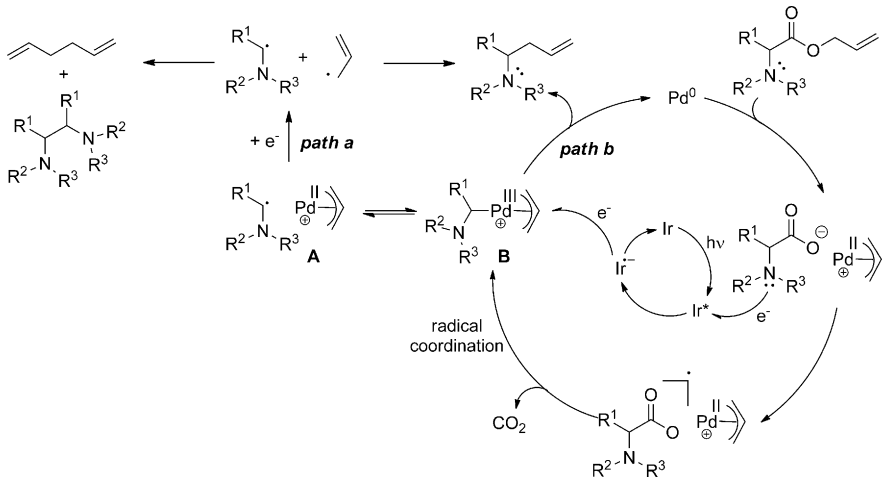
Scheme 2. Decarboxylative allylation of α-amino esters: [a] Reactions performed on a 0.25 mmol scale at 0.13 M. [b] Isolated yields. [c] Gram scale, 0.37 M. [d] 95% pure. [e] Average yield of two runs.



Scheme 3. Site-specific allylation.

tected amino acids phenylalanine and proline provided the corresponding products **2a** and **2l** in higher yields than those generated from their allylic ester counterparts (Scheme 4). Next, several Boc-protected dipeptides, which contained both amide and carbamate moieties that could potentially undergo oxidation by the excited photocatalyst, were examined. The allylated peptides were isolated in moderate to good yields although extended reaction times were required.

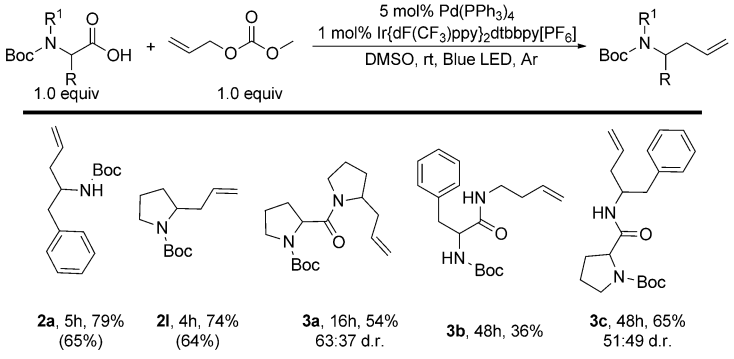
Our initial hypothesis was that higher yields of radical decarboxylative allylation may be achieved by favoring metal-mediated C–C bond formation while avoiding free radical coupling. On the basis of observations by MacMiillan,[12b,g] Molander,[12i,j] and us,[11] two different potential mechanistic pathways were proposed (Scheme 5). In either case, the cycle begins with oxidative addition of the allyl ester to Pd^0 which provides the cationic Pd–π-allyl species and the carboxylate counterion. Since more oxidizing photocatalysts are more effective for the transformation, we propose that the amino carboxylate (for example, Boc-Pro-OCs, $E_{1/2}^{red} = +0.95$ V vs SCE)[18] is then oxidized by the photoexcited iridium complex ($k^{red}_{1/2}[Ir^{*III}/Ir^{II}] = +1.21$ V vs. SCE)[16] which triggers radical decarboxylation to form an α-amino radical. If the radical is suitably stabilized then electron transfer from the reduced iridium catalyst to the the Pd^{II} complex (**A**) can result in homolysis to provide an allyl radical (path a, Scheme 5).[19,20] The ensuing free radical coupling can produce the allylated amine as well as diamine and hexadiene homocoupling products. Alternatively, if the α-amino radical is less stable, it may prefer to coordinate to palladium generating a Pd^{III} intermediate (**B**)[12b,g,i,j] that behaves as a persistent radical.[21] Electron transfer from the reduced iridium complex prior to or after reductive elimination would form the observed product and regenerate Pd(0) (path b, Scheme 5).[12b,g,i,j] A similar possibility was proposed by Molander and Kozlowski on the basis of DFT calculations of the pathways for nickel-catalyzed photoredox coupling of borates and aryl halides.[14]



Scheme 5. Divergent pathways for photoredox decarboxylative coupling.

The allyl esters of *N*,*N*-dibenzyl phenyalanine (**4**), *N*-Boc phenylglycine (**5**), and *N*-Boc phenylalanine (**6**) were prepared to attempt to distinguish if radical stability influenced whether C–C bond formation was occurring within the Pd coordination sphere (path b) or by an undesired free radical (path a) or radical chain process. Initial evaluation of BDEs revealed that the α-amino radical species derived from **6** is ~5–6 kcal mol^{-1} higher in energy than those derived from **4** and **5**.[22] Moreover, the single electron oxidation potential of the radical derived from **6** is expected to be endergonic whereas oxidations of the radicals formed from **4** and **5** are exergonic.[19] In short, substrates **4** and **5** generate relatively stable radicals while substrate **6** generates a less stable radical (Figure 1).

To probe whether C–C bond formation occurs within the coordination sphere of the metal, **4**–**6** were subjected to slightly modified reaction conditions using a chiral non-racemic palladium complex



Scheme 4. Decarboxylative allylation of α-amino acids: [a] Reactions performed on a 0.25 mmol scale at 0.13 M. [b] Isolated Yields. [c] Yields in parentheses refer to entries in Scheme 2.

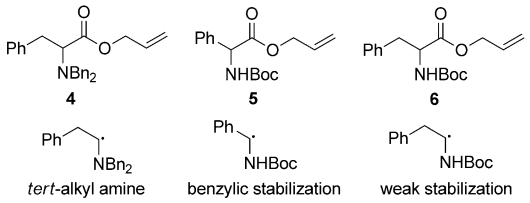
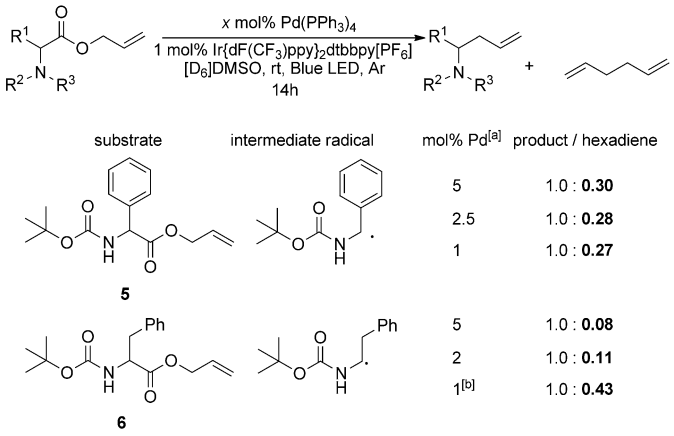
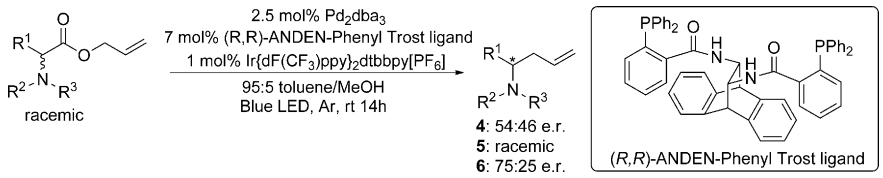


Figure 1. Substrates and radical intermediates.

(Scheme 6). Substrate **6**, which produces a more unstable radical post decarboxylation, provided enantioenriched product which provides evidence that the C–C bond is forming within the coordination sphere of the chiral palladium complex. In contrast, the reactions of **4** and **5**, which generate more stabilized radical intermediates, led to racemic or nearly racemic products.



Scheme 7. Does Pd concentration affect homodimerization? [a] At a constant substrate concentration of 0.0125 M. [b] Reaction did not reach complete conversion



Scheme 6. Stereochemical test for palladium involvement in C–C formation.

The results of reaction with a chiral palladium catalyst suggest that substrate **6** reacts through a Pd-bound intermediate while substrates **4** and **5** react primarily through free radical coupling. One way to potentially test for free radical coupling is to measure products of free-radical homocoupling. Toward this end, ^{1}H NMR spectroscopy was used to monitor the formation of 1,5-hexadiene via allyl-allyl coupling in reactions of **4**–**6**. That free radical coupling is the primary mechanism for the reaction of **4** is supported by the observation of nearly statistical amounts homodimerization was observed in much lower quantity when **6**, which produces a less stable α-amino radical, was utilized (product/hexadiene = 1.0:0.08). Similar NMR spectroscopic studies were used to examine the effect of palladium of homodimerization products, including 1,5-hexadiene (product/hexadiene = 1.0:0.50).[23] In contrast, free radical concentration on the homodimerization of allyl radicals (Scheme 7).

The amount of hexadiene observed did not appreciably change when the concentration of Pd was varied in the reaction of **5**, which indicates a Pd-independent C–C bond formation (path a). Conversely, when **6**, which forms a less stable radical, was subjected to similar inquiry, the quantity of hexadiene was affected by the concentration of palladium. This observation suggests pathways a and b are competitive, but pathway b is favored at higher palladium concentrations. Ultimately, the simplest interpretation of the observations is that, under our standard reaction conditions, less stable α-amino radicals react primarily via metal-mediated C–C bond formation, while more stabilized benzylic and α-*tert*-amino radicals form C–C bonds via radical coupling.

In conclusion, we have developed a direct method for the decarboxylative allylation of α-amino acid derivatives using dual palladium and photoredox catalysis to circumvent traditional limitations in decarboxylative couplings. The coupling is site-specific for the position that bears CO_2, allowing the kinetic formation of contra-thermodynamic radical species. Detailed studies of product and byproduct formation implicate competing mechanisms for the coupling, with more stable radicals preferring to react via radical coupling and less stabilized radicals preferring to react via metal-mediated coupling.

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Keywords: allylation · amino acids · cross-coupling · homogeneous catalysis · photocatalysis

[1] M. Yus, J. C. González-Gómez, F. Foubelo, *Chem. Rev.* **2011**, *111*, 7774–7854.

[2] For allyl addition to imines: a) M. Yus, J. C. González-Gómez, F. Foubelo, *Chem. Rev.* **2013**, *113*, 5595–5698; b) C. O. Puentes, V. Kouznetsov, *J. Heterocycl. Chem.* **2002**, *39*, 595–614; c) H. Ding, G. K. Friestad, *Synthesis* **2005**, 2815–2829; d) T. R. Ramadhar, R. A. Batey, *Synthesis* **2011**, 1321–1346.

[3] a) E. M. Vieira, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2011**, *133*, 3332–3335; b) D. L. Silverio, S. Torker, T. Pilyugina, E. M. Vieira, M. L. Snapper, F. Haeffner, A. H. Hoveyda, *Nature* **2013**, *494*, 216–221; c) S.

Gandhi, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 2573 – 2576; *Angew. Chem.* **2013**, *125*, 2633 – 2636 and references therein.
[4] a) E. C. Burger, J. A. Tunge, *J. Am. Chem. Soc.* **2006**, *128*, 10002 – 10003; b) A. A. Yeagley, J. J. Chruma, *Org. Lett.* **2007**, *9*, 2879 – 2882.
[5] For recent reviews, see: a) J. D. Weaver, A. Recio III, A. J. Grenning, J. A. Tunge, *Chem. Rev.* **2011**, *111*, 1846 – 1913; b) N. Rodriguez, L. J. Goossen, *Chem. Soc. Rev.* **2011**, *40*, 5030 – 5048; c) W. I. Dzik, P. P. Lange, L. J. Goosen, *Chem. Sci.* **2012**, *3*, 2671 – 2678.
[6] F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456 – 463.
[7] a) J. M. Anderson, J. K. Kochi, *J. Am. Chem. Soc.* **1970**, *92*, 2450 – 2460; b) W. S. Trahanovsky, J. Cramer, D. W. Brixius, *J. Am. Chem. Soc.* **1974**, *96*, 1077 – 1081.
[8] a) H. I. Joschek, L. I. Grossweiner, *J. Am. Chem. Soc.* **1966**, *88*, 3261 – 3268; b) R. S. Davidson, P. R. Steiner, *J. Chem. Soc. C* **1971**, 1682 – 1689; c) R. S. Davidson, P. R. Steiner, *J. Chem. Soc. Perkin Trans. 2* **1972**, 1357 – 1362; d) T. O. Meiggs, L. I. Grossweiner, S. I. Miller, *J. Am. Chem. Soc.* **1972**, *94*, 7981 – 7986; e) S. N. Battacharyya, P. K. Das, *J. Chem. Soc. Faraday Trans. 2* **1984**, *80*, 1107 – 1116; f) N. D'Alessandro, A. Albini, P. S. Mariano, *J. Org. Chem.* **1993**, *58*, 937 – 942; g) M. H. Habibi, S. Farhadi, *J. Chem. Res. (S)* **1998**, 776 – 777; h) Z. Su, P. S. Mariano, D. E. Falvey, U. C. Yoon, S. W. Oh, *J. Am. Chem. Soc.* **1998**, *120*, 10676 – 10686; i) M. Xu, P. Wan, *Chem. Commun.* **2000**, 2147 – 2148; j) I. R. Gould, J. R. Lenhard, S. Farid, *J. Phys. Chem. A* **2004**, *108*, 10949 – 10956; k) R. Poupko, I. Rosenthal, D. Elad, *Photochem. Photobiol.* **1973**, *17*, 395 – 402.
[9] a) H. R. D. Barton, Y. Hervé, P. Potier, J. Thierry, *J. Chem. Soc. Chem. Commun.* **1984**, 1298 – 1299; b) H. R. D. Barton, Y. Hervé, P. Potier, J. Thierry, *Tetrahedron* **1987**, *43*, 4297 – 4308; c) A. Vidal-Cros, S. Bory, M. Gaudry, A. Marquet, *Tetrahedron Lett.* **1989**, *30*, 1799 – 1802; d) B. M. Aveline, I. E. Kochevar, R. W. Redmond, *J. Am. Chem. Soc.* **1995**, *117*, 9699 – 9708; e) A. Boto, R. Hernández, E. Suárez, *J. Org. Chem.* **2000**, *65*, 4930 – 4937.
[10] Y. Miyake, K. Nakajima, Y. Nishibayashi, *Chem. Commun.* **2013**, *49*, 7854 – 7856.
[11] S. B. Lang, K. M. O'Nele, J. A. Tunge, *J. Am. Chem. Soc.* **2014**, *136*, 13606 – 13609.
[12] For representative examples of dual catalytic systems employing photoredox catalysts see: a) M. Osawa, H. Nagai, M. Akita, *Dalton Trans.* **2007**, 827 – 829; b) D. Kalyani, K. B. McMurtrey, S. R. Neufeldt, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 18566 – 18569; c) Y. Ye, M. S. Sanford, *J. Am. Chem. Soc.* **2012**, *134*, 9034 – 9037; d) M. Rueping, R. M. Koenigs, K. Poscharny, D. C. Fabry, D. Leonori, C. Vila, *Chem. Eur. J.* **2012**, *18*, 5170 – 5174; e) B. Sahoo, M. N. Hopkinson, F. Glorius, *J. Am. Chem. Soc.* **2013**, *135*, 5505 – 5508; f) X. Shu, M. Zhang, Y. He, H. Frei, F. D. Toste, *J. Am. Chem. Soc.* **2014**, *136*, 5844 – 5847; g) Z. Zuo, D. Ahneman, L. Chu, J. Terrett, A. G. Doyle, D. W. C. MacMillan, *Science* **2014**, *345*, 437 – 440; h) A. Noble, S. J. McCarver, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 624 – 627; i) J. C. Tellis, D. N. Primer, G. A. Molander, *Science* **2014**, *345*, 433 – 436; j) D. N. Primer, I. Karakaya, J. C. Tellis, G. A. Molander, *J. Am. Chem. Soc.* **2015**, *137*, 2195 – 2198.
[13] J. Xuan, T. T. Zeng, Z. J. Feng, Q. H. Deng, J. R. Chen, L. Q. Lu, W. J. Xiao, H. Alper, *Angew. Chem. Int. Ed.* **2015**, *54*, 1625 – 1628; *Angew. Chem.* **2015**, *127*, 1645 – 1648.
[14] O. Gutierrez, J. C. Tellis, D. N. Primer, G. A. Molander, M. C. Kozlowski, *J. Am. Chem. Soc.* **2015**, *137*, 4896 – 4899.
[15] A. B. Tamayo, B. D. Alleyne, P. I. Djurovich, S. Lamansky, I. Tsyba, N. N. Ho, R. Bau, M. E. Thompson, *J. Am. Chem. Soc.* **2003**, *125*, 7377 – 7387.
[16] M. S. Lowry, J. I. Goldsmith, J. D. Slinker, R. Rohl, R. A. Pascal Jr., G. G. Malliaras, S. Bernhard, *Chem. Mater.* **2005**, *17*, 5712 – 5719.
[17] J. J. Devery III, J. J. Douglas, J. D. Nguyen, K. P. Cole, R. A. Flowers II, C. R. Stephenson, *Chem. Sci.* **2015**, *6*, 537 – 541.
[18] Z. Zuo, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 5257 – 5260.
[19] The single electron reduction of cationic Pd^{II} allyl species has been measured (~ −1.4 V versus SCE) a) T. Cantat, E. Génin, C. Giroud, G. Meyer, A. Jutand, *J. Organomet. Chem.* **2003**, *687*, 365 – 376; b) G. Carturan, M. Biasiolo, S. Daniele, G. A. Mazzocchin, P. Ugo, *Inorg. Chim. Acta* **1986**, *119*, 19 – 24. We do not expect Pd^{II} species to be reduced by α-amino radicals given that α-amino radicals of trimethylamine (−0.61 V versus SCE) and *N*-methylacetamide (0.60 V versus SCE) are weaker reductants than the reduced photocatalyst (−1.37 V versus SCE)[15] c) Y. Fu, L. Liu, H. Z. Yu, Y. M. Wang, Q. X. Guo, *J. Am. Chem. Soc.* **2005**, *127*, 7227 – 7234.
[20] H. Kunkely, A. Vogler, *Inorg. Chim. Acta* **2003**, *344*, 262 – 264.
[21] For persistent radicals in transition metal-catalyzed reactions see a) E. Jahn, U. Jahn, *Angew. Chem. Int. Ed.* **2014**, *53*, 13326 – 13328; *Angew. Chem.* **2014**, *126*, 13542 – 13544; b) E. Jahn, *Top. Curr. Chem.* **2012**, *308-319*, 121 – 190 and 323 – 452. For reviews on the persistent radical effect see: c) A. Studer, *Chem. Soc. Rev.* **2004**, *33*, 267 – 273; d) H. Fischer, *Chem. Rev.* **2001**, *101*, 3581 – 3610.
[22] The benzylic stabilization was estimated by comparing the BDE of trimethylamine (91 kcal mol^{-1}) to *N*,*N*-dimethylbenzylamine (84.9 kcal mol^{-1}): Y.-R. Luo, *Handbook of Bond Dissociation Energies in Organic Compound*, CRC Press, Boca Raton (USA), **2003**. The destabilization attributed to a carbamate was estimated by comparing the BDE of triethylamine (91 kcal mol^{-1}): D. D. M. Wayner, K. B. Clark, A. Rauk, D. Yu, D. A. Armstrong, *J. Am. Chem. Soc.* **1997**, *119*, 8925 – 8932. to the BDE of methyl propylcarbamate (96 kcal mol^{-1}): R. J. Berry, A. L. Wilson, M. Schwartz, *J. Mol. Struct. (Theochem).* **2000**, *496*, 121 – 129.
[23] The diamine homocoupling product was also observed (product/diamine/hexadiene = 1.0:0.43:0.50) (see Supporting Information).

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