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Three-component dicarbofunctionalization of allylamines *via* nucleopalladation pathway: unlocking vicinal and geminal selectivity†

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A palladium(II)-catalyzed vicinal as well as geminal selective dicarbofunctionalization of allylamine embedded in a removable picolinamide auxiliary is developed by exploiting a nucleopalladation-triggered intermolecular three-component coupling reaction. The vicinal selectivity was accomplished by engaging allylamine, indoles, and aryl or styrenyl halides through a Pd(II)/Pd(IV) reaction manifold, while the two-fold coupling of allylamine and indoles *via* a Pd(II)/Pd(0) reaction modality resulted in geminal selectivity. The protocol is operationally simple, scalable, and offers two distinct types of products bearing functionalized tryptamine and bisindolyl frameworks in very high to excellent yields. The reaction features a wide substrate generality and also remains effective in the presence of various medicinally relevant scaffolds. Notably, this work represents the first example of nucleopalladation-guided intermolecular dicarbofunctionalization of allylamines.

Introduction

Aliphatic amines are ubiquitous substructures found in a wide array of pharmaceutical compounds, natural products, and organic materials.¹ They serve as pivotal building blocks for the production of other important functional groups and value-added molecules.^{1,2} Remarkably, a substantial proportion of top-selling small-molecule drugs are derivatives of aliphatic amines.^{1a,2} Consequently, the pursuit of innovative and efficient methods *en route* to functionally enriched aliphatic amines has become a longstanding focus within the synthetic chemistry community.³ One rewarding route could be the catalytic three-component dicarbofunctionalization of alkenyl amines that potentially allows the installation of two new carbon–carbon bonds across the olefin functionality.⁴ Specifically, the dicarbofunctionalization of a simple allylamine is significant owing to its ready availability while the olefin motif is unactivated and potentially vicinal as well as geminal dicarbofunctionalizations leading to sp^3 -dense products are feasible (Scheme 1a). In 2018, Zhao *et al.* exploited Ni(COD)₂ as a catalyst and showcased difunctionalization of *N*-pyrimidyl allyl amine with aryl boronic acids and diverse organohalides where substrate-dependent vicinal and distal selectivities were observed (Scheme 1b).⁵ In this direction, the Engle group also reported Ni(COD)₂ catalyzed vicinal dicarbofunctionalization of *N*-benzoyl allylamines with

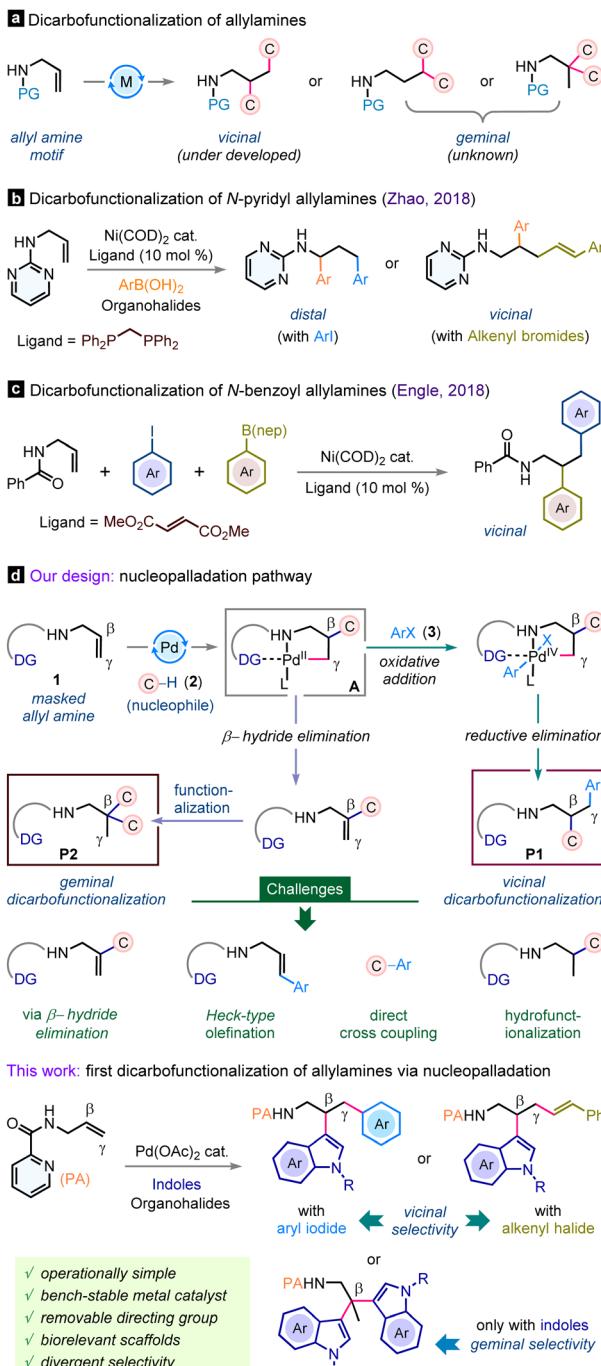
aryl boronates and aryl iodides (Scheme 1c).⁶ However, the operational complexity of these protocols is noteworthy due to the extreme sensitivity of the low valent Ni(COD)₂ catalyst, requiring execution in a glovebox and handling in an utmost inert atmosphere. Meanwhile, the dicarbofunctionalization of allylamines with geminal selectivity still remains elusive. Thus, developing an operationally simple catalytic strategy that is tunable for both vicinal as well as geminal dicarbofunctionalizations of allylamines is highly desirable.

The nucleopalladation methodology is fundamental, capitalizing on the π -activation of alkenes with palladium metal and concomitant nucleophilic addition-triggered functionalization event.⁷ Despite its versatile synthetic portfolio, to our surprise, heretofore, this approach has not been explored for intermolecular three-component dicarbofunctionalization of alkenyl amines. With our continuous interest in allylamine functionalization strategies,⁸ we surmise that the nucleopalladation blueprint may be effective for the rapid dicarbofunctionalization of allylamines (Scheme 1d). Strategically, allylamine (**1**) can be tethered to a suitable directing group, facilitating its binding with the palladium catalyst and expediting olefin π -activation through coordination. This scenario is expected to favor nucleophilic addition to generate the pivotal palladacycle intermediate **A**. We expect a β -regioselective attack of nucleophile **2**, forming a more stable 5,5-palladacycle intermediate. The intermediate **A** can partake in the subsequent cross-coupling reaction with suitable carbon electrophile **3** to produce vicinal dicarbofunctionalized product **P1** (Scheme 1d). Alternatively, by fine-tuning the reaction conditions, the palladacycle intermediate **A** can be pushed forward towards β -hydride elimination to regenerate the allylamine motif, which

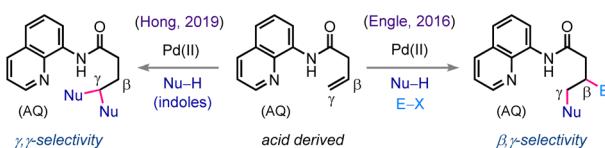
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e β,γ and γ,γ dicarbofunctionalization of 3-butenoic acid



Scheme 1 Regioselective dicarbofunctionalization of allylamines.

can then undergo further functionalization with the carbon nucleophile, enabling access to the geminal dicarbofunctionalized product **P2**. However, at the outset, we foresaw several challenges as the progress of the reaction can be prematurely

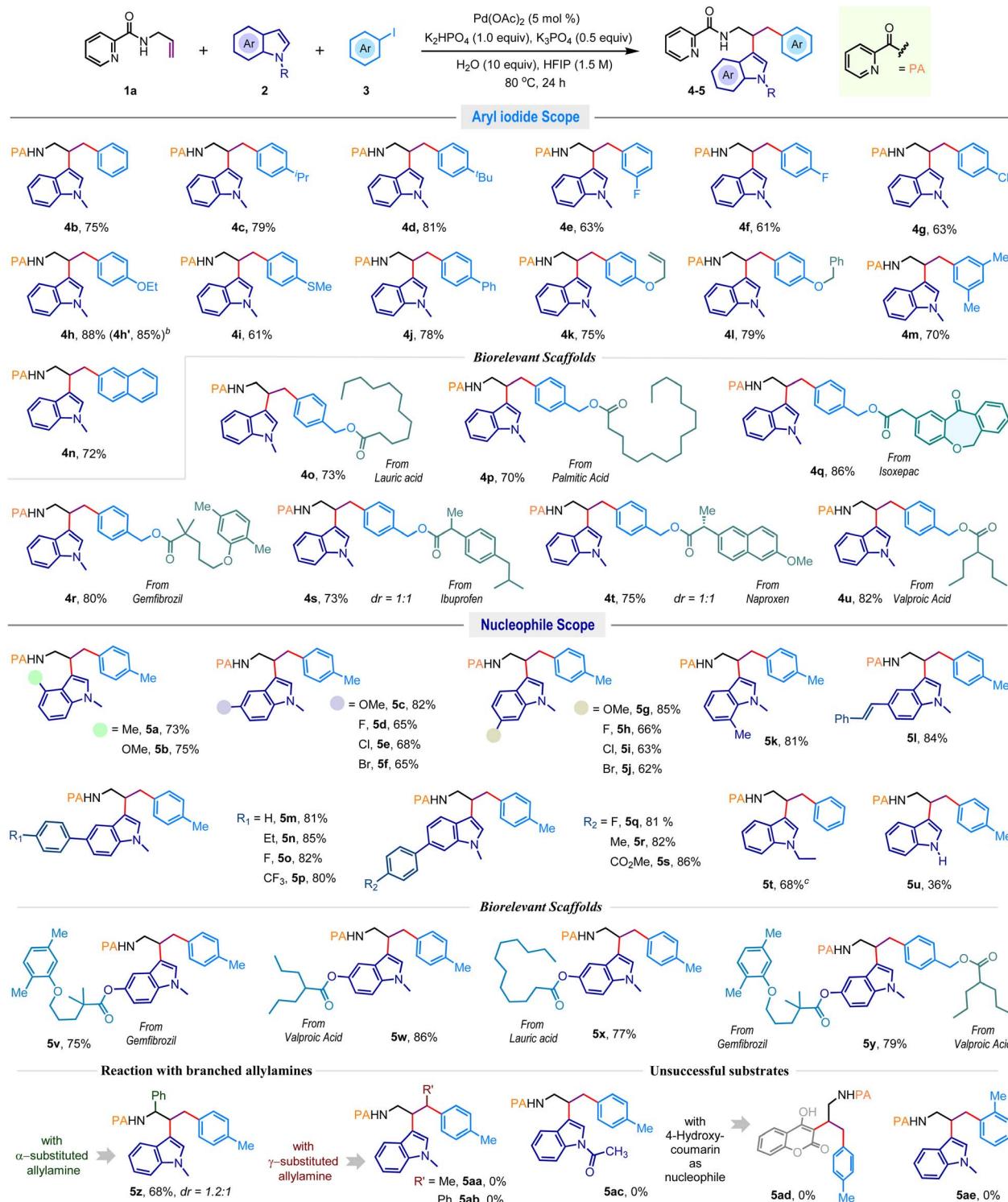
terminated. One potential issue is the susceptibility of the key palladacycle intermediate to facile protodemetalation reactions or a β -hydride elimination event, which may result in undesired mono-functionalization⁹ rather than the intended difunctionalization (Scheme 1d). Also, the direct cross-coupling¹⁰ between nucleophiles and aryl halides or Heck-type functionalization¹¹ of an alkene with aryl iodides in the presence of a palladium catalyst is a renowned protocol and may hamper the reaction outcome.

Herein, we report the first nucleopalladation-guided three-component regioselective dicarbofunctionalization of allylamine bearing a removable picolinamide (PA) auxiliary with inexpensive indole heterocycles and aryl or alkenyl halides. This new protocol is operationally simple, accommodates a wide range of substrates including valuable pharmacophore scaffolds, and has the provision for accessing both vicinal and geminal dicarbofunctionalizations selectively. Notably, our investigations into the dicarbofunctionalization of allylamines complement the prior works of the Engle and Hong groups on dicarbofunctionalization of 3-butenoic amides bearing an 8-aminoquinoline directing group, albeit with different selectivity outcomes (Scheme 1e).¹² In our study, nucleopalladation commences at the β -center of allylamine, in contrast to the nucleophilic attack occurring at the γ -center of the 3-butenoic amide in Engle's study. Similarly, while the Hong group accomplished γ,γ -dicarbofunctionalization, we achieved selective β,β -dicarbofunctionalization. This distinct selectivity can be attributed to the formation of a stable 5,5-palladacycle intermediate, as indicated in the preceding section.

Table 1 Optimization of reaction conditions^a

Entry	Deviation from standard conditions	Yield of 4a (%) ^b
1 ^c	Only with K_3PO_4 (1.0 equiv.)	56
2 ^c	Only with K_2HPO_4 (1.0 equiv.)	52
3 ^c	With K_2CO_3 /KOAc instead of phosphates	38/—
4 ^c	K_3PO_4 (1.0 equiv.) and K_2HPO_4 (1.0 equiv.)	62
5 ^c	K_3PO_4 (0.5 equiv.) and K_2HPO_4 (1.0 equiv.)	69
6 ^c	CH_3CN , TFT, or DCE instead of HFIP	—
7 ^c	TFE, MeOH, or EtOH instead of HFIP	—
8	None	78
9	At 60 °C/100 °C	65/70
10	Without $Pd(OAc)_2$	—
11	With $Co(OAc)_2/Ni(OAc)_2$ instead of $Pd(OAc)_2$	—

^a Reaction conditions: **1a** (0.25 mmol), **2a** (1.1 equiv.), **3a** (4.0 equiv.), $Pd(OAc)_2$ (5 mol%), K_3PO_4 (0.5 equiv.), K_2HPO_4 (1.0 equiv.), H_2O (10.0 equiv.), HFIP (1.5 M), 80 °C for 24 h (open air operation). ^b Isolated yields were provided. ^c Without H_2O additive.

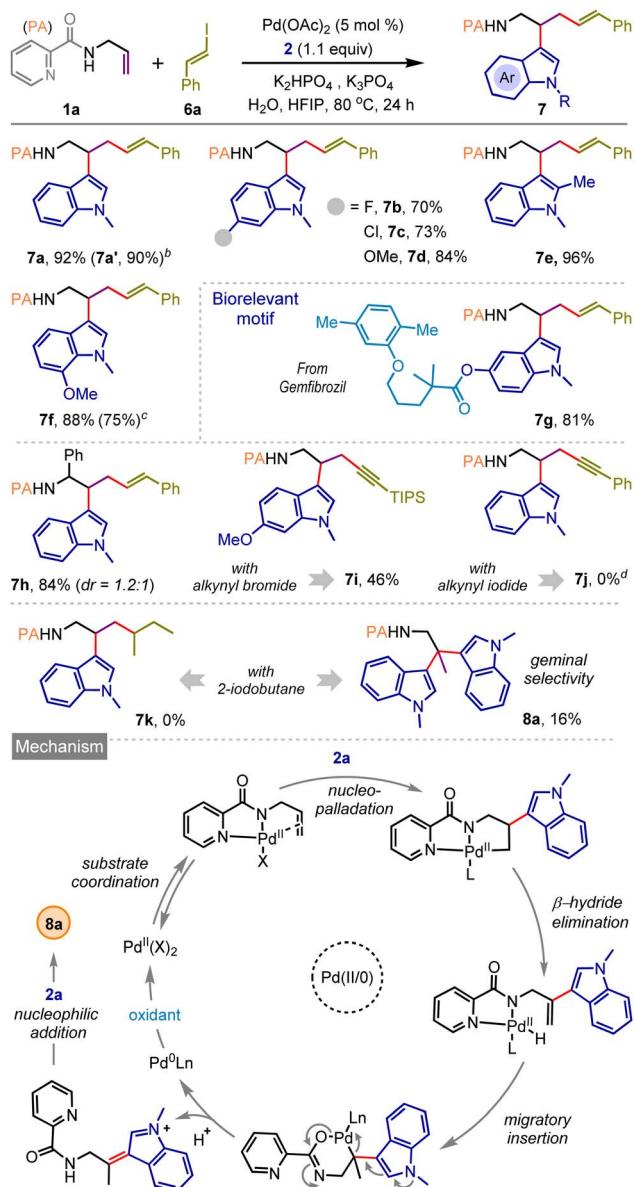


Scheme 2 Substrate scope in the vicinal dicarbofunctionalization reaction^a. ^aReaction conditions: **1a** (0.25 mmol), **2** (1.1 equiv.), **3** (4.0 equiv.) for 24 h. ^bIQA was used as a directing group. ^cIodobenzene (4.0 equiv.) was used. Isolated yields were provided.

Results and discussion

The picolinamide directing group, initially introduced by Daugulis in 2005, has exhibited outstanding directing capabilities in a variety of metal-catalyzed transformations involving both

aromatic and aliphatic amines.¹³ Inspired by these findings, we considered the *N*-allyl amide **1a**, prepared from 2-picolinic acid and allylamine, as a model substrate. Our initial focus was on the three-component coupling of **1a** with indole **2a** and aryl iodide **3a**, potentially yielding a valuable tryptamine derivative



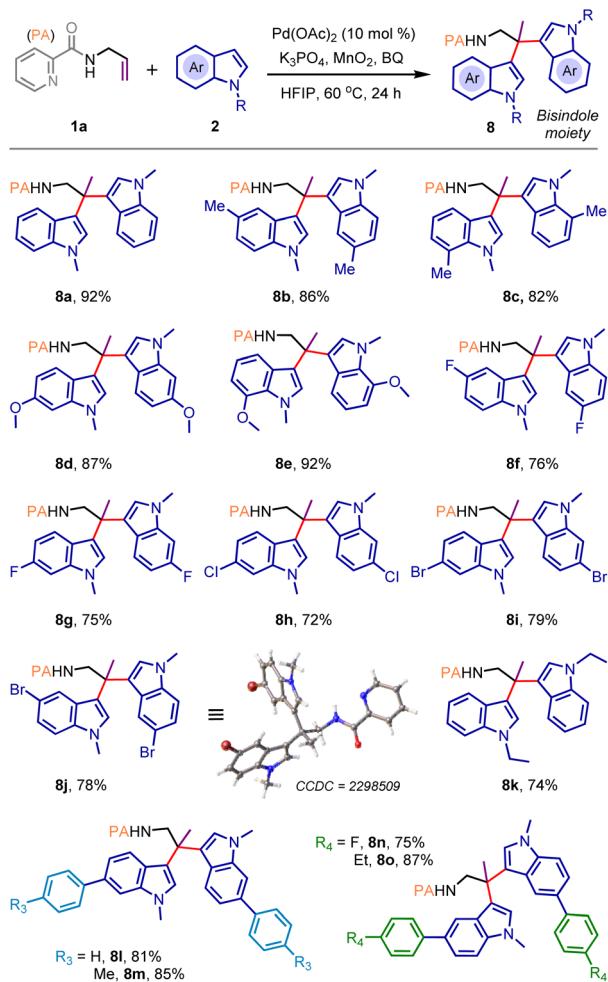
Scheme 3 Exploration of three-component dicarbofunctionalization with styrenyl, alkynyl, and alkyl halides^a. ^aReaction conditions: **1a** (0.25 mmol), **2** (1.1 equiv.), **6a** (4.0 equiv.), $\text{Pd}(\text{OAc})_2$ (5 mol%), K_3PO_4 (0.5 equiv.), K_2HPO_4 (1.0 equiv.), H_2O (10.0 equiv.), HFIP (1.5 M), 80 °C for 24 h. ^bIQA was used as a directing group. ^cStyrenyl bromide (4.0 equiv.) was used. ^dStarting materials decomposed.

(Table 1). Gratifyingly, when a combination of **1a**, **2a**, and **3a** was subjected to a $\text{Pd}(\text{OAc})_2$ catalyst in hexafluoroisopropanol (HFIP) solvent with K_3PO_4 (1.0 equiv.) at 80 °C, we observed the formation of the vicinal dicarbofunctionalization product **4a** in a 56% yield (Table 1, entry 1). A comparable yield of **4a** was achieved with K_2HPO_4 ; however, the reaction yield significantly decreased with K_2CO_3 , and KOAc failed to promote the reaction (entries 2–3). Interestingly, the use of a combination of K_3PO_4 and K_2HPO_4 resulted in an improved yield of 69% for **4a** (entries 4–5). Exploration of other aprotic solvents such as acetonitrile, trifluorotoluene (TFT), and 1,2-dichloroethane (DCE), as well as

polar protic solvents including trifluoroethanol (TFE), methanol, and ethanol, did not yield any difunctionalization product (entries 6–7). Notably, the addition of H_2O (10 equiv.) resulted in a remarkably clean reaction, and the desired vicinal difunctionalization product **4a** was isolated in a 78% yield (entry 8). Performing the reaction at either lower (60 °C) or higher (100 °C) temperatures produced inferior results (entry 9). Control experiments indicated that the reaction was unproductive in the absence of the $\text{Pd}(\text{OAc})_2$ catalyst (entry 10). Additionally, other catalysts such as $\text{Co}(\text{OAc})_2$ and $\text{Ni}(\text{OAc})_2$ were incapable of promoting this dicarbofunctionalization reaction (entry 11). Investigation into other directing groups revealed that the *N*-allyl amide derived from isoquinoline-1-carboxylic acid (**1a'**) also effectively participated in this reaction, yielding **4a'** in a 69% yield. However, such difunctionalization proved unsuccessful with *N*-allyl amides of 2-thiophenecarboxylic acid as well as benzoic acid, indicating that an effective bidentate coordination is critical for this reaction (Table 1, below).

After identifying the optimal reaction conditions (Table 1, entry 8), we aimed to explore the substrate diversity in this three-component vicinal dicarbofunctionalization reaction (Scheme 2). Delightfully, the reaction exhibited uniformity across a broad spectrum of structurally diverse aromatic iodides encompassing both electron-donating and electron-withdrawing groups, and desired dicarbofunctionalized products **4b–j** were obtained in consistently high yields. Disubstituted aromatic iodide (**4m**) and 2-naphthyl iodide (**4n**) were also effective, and commonly used protecting groups, for example, allyl (**4k**) and benzyl (**4l**), were well-tolerated. To advance the synthetic utility further, an array of pharmacophore-coupled aryl iodides were explored where substrates featuring biorelevant motifs like isoxepac (**4q**), gemfibrozil (**4r**), ibuprofen (**4s**), naproxen (**4t**), and valproic acid (**4u**) produced the desired products in good to excellent yields. Furthermore, the protocol proved equally efficacious with aryl iodides linked to saturated fatty acid motifs such as lauric acid and palmitic acid, offering **4o** and **4p** in 73% and 70% yields, respectively.

Next, we evaluated the reaction competence with different indoles (Scheme 2). *N*-methylindoles featuring alkyl, alkoxy, and halogen functionalities at the C4, C5, C6, and C7 positions yielded dicarbofunctionalized products **5a–k** in high yields. Generally, electron-rich indoles exhibited higher reactivity compared to their electron-deficient counterparts. Halogen functionalities such as fluorine (**5d**, **5h**), chlorine (**5e**, **5i**), and bromine (**5f**, **5j**) remained unaffected under the reaction conditions. The presence of a reactive olefin functionality in the indole did not impede the reaction outcome, producing **5l** in 84% yield. Indoles with aryl substitutions at the C5 and C6 positions smoothly produced **5m–p** and **5q–s** in excellent yields. The *N*-ethylindole also delivered the desired product **5t** in 68% yield; however, the difunctionalization was sluggish with *N*-unsubstituted indole, giving **5u** in 36% yield. Of note, indoles encompassing lauric acid, gemfibrozil, and valproic acid frameworks were also suitable substrates for this reaction and produced high-value amines **5v–x** in very high yields. More importantly, the reaction was also fruitful when both indole and aryl iodide were adorned with bioactive motifs. For example, the



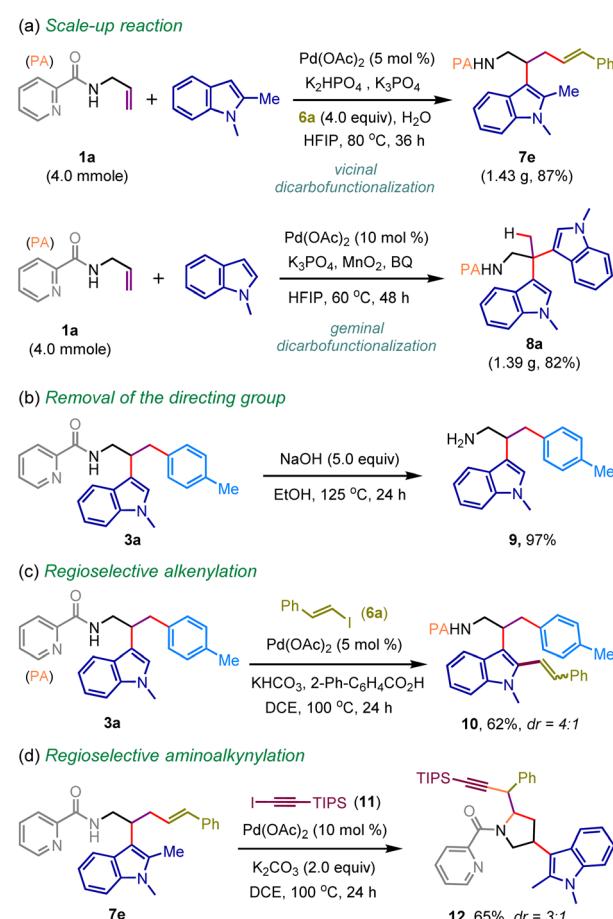
Scheme 4 Substrates scope in the geminal dicarbofunctionalization reaction^a. ^aReaction conditions: **1a** (0.25 mmol), **2** (2.5 equiv.), Pd(OAc)₂ (10 mol%), K₃PO₄ (1.0 equiv.), MnO₂ (3.0 equiv.), 1, 4-benzoquinone (BQ) (0.2 equiv.), HFIP (0.5 M), 60 °C for 24 h (open air operation).

reaction of **1a** with gemfibrozil derived indole and valproic acid derived aryl iodide coupling partners gave densely functionalized amine **5y** in 79% isolated yields (Scheme 2). Examination of branched allylamines showed that α -substitution is tolerable, offering **5z** in 68% yield, while γ -substitution (**5aa**–**5ab**) dramatically hampers the progress of the reaction. Also, the difunctionalization was unsuccessful with less reactive *N*-acylindole (**5ac**) and 4-hydroxycoumarin (**5ad**) nucleophiles, as well as the sterically demanding 2-iodotoluene (**5ae**) electrophile (Scheme 2, below).

Pleasingly, the same catalytic system is also effective for styrenyl iodide **6a**, and vicinal dicarbofunctionalized products bearing a bishomoallylic amine motif (**7a**–**h**) were obtained in very high yields (Scheme 3). The reaction was also amenable with styrenyl bromide and TIPS-protected alkynyl bromide where desired products **7f** and **7i** were isolated in 75% and 46% yields, respectively. However, under the standard reaction conditions, we observed the decomposition of (iodoethynyl)benzene without the formation of the desired product **7j**. When

the reaction was performed with alkyl iodide, for example, 2-iodobutane, the vicinal difunctionalization did not take place; on the contrary, we surprisingly noticed the formation of geminal difunctionalized product **8a**, featuring a valuable bisindole moiety, albeit in poor yield. This finding prompted us to tune the catalytic reaction conditions further to materialize the geminal dicarbofunctionalization of the allylamine motif, which was not heretofore reported. We have realized that such difunctionalization most likely arises through the functionalization of the regenerated olefin as depicted in Scheme 3, below (for an alternative mechanism, see ESI, page S15†).

Accordingly, additional oxidants were introduced under the catalytic conditions. Delightfully, the geminal dicarbofunctionalization proceeded smoothly when a mixture of **1a** and **2a** was treated with the Pd(OAc)₂ catalyst in HFIP (0.5 M) solvent in the presence of K₃PO₄ (1.0 equiv.), 1,4-benzoquinone (BQ, 0.2 equiv.), and MnO₂ (3.0 equiv.) to deliver desired product **8a** in 92% yield (Scheme 4; see ESI page S9 for optimization details†). The protocol is quite general, enabling the construction of a small library of bis-indolyl¹⁴ molecules (**8b**–**8o**) with electronically diverse functional groups and substitution patterns (Scheme 4). Compound **8j** was crystallized, and single-crystal X-ray analysis unequivocally confirmed the product structure and the selectivity of geminal dicarbofunctionalization.



Scheme 5 Scale-up and synthetic application.

To showcase its synthetic utility, we performed gram-scale reactions. The efficacy of the small-scale reaction was comparable to scale-up synthesis, delivering vicinal functionalization product **7e** and geminal functionalization product **8a** in 87% and 82% yields, respectively (Scheme 5a). The picolinamide directing group was also removed to access tryptamine analog **9** in 97% yield (Scheme 5b). The product diversification has also been elaborated through picolinamide-directed regioselective alkenylation of **3a**, providing functionalized indole **10** in 62% yield (Scheme 5c). In addition, the amino alkynylation of the internal olefin was also accomplished to construct pyrrolidine heterocycle **12** from **7e** in synthetically useful yield (Scheme 5d).¹⁵

Conclusions

In summary, we have delineated a palladium(II)-catalyzed dicarbofunctionalization of allylamine, showcasing both vicinal and geminal regioselectivity. This approach utilizes a removable picolinamide auxiliary to facilitate nucleopalladation-triggered intermolecular three-component coupling reactions. The vicinal selectivity is achieved through a Pd(II)/Pd(0) reaction manifold involving allylamine, indoles, and aryl or styrenyl halides. Conversely, geminal selectivity is realized *via* a two-fold coupling of allylamine and indoles employing a Pd(II)/Pd(0) reaction modality. The protocol is characterized by its operational simplicity, scalability, substrate generality including diversification of substrates containing pharmacophore scaffolds, and the generation of two distinct types of products featuring functionalized tryptamine and bisindolyl frameworks, all obtained in very high to excellent yields. Importantly, this work represents a pioneering instance of nucleopalladation-guided dicarbofunctionalization of allylamines.

Data availability

General information, experimental procedures, characterization data for all new compounds, and NMR spectra are in the ESI.† Data for the crystal structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under the deposition number CCDC 2298509.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- (a) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274; (b) A. Ricci, *Amino Group Chemistry: From Synthesis to the Life Sciences*, Wiley-VCH, Weinheim, 2008; (c) S. A. Lawrence, *Amines: Synthesis, Properties and Applications*, Cambridge University Press, 2004.
- (a) A. Hager, N. Vrielink, D. Hager, J. Lefranc and D. Trauner, *Nat. Prod. Rep.*, 2016, **33**, 491–522; (b) N. A. McGrath, M. Brichacek and J. T. Njardarson, *J. Chem. Educ.*, 2010, **87**, 1348–1349.
- (a) A. Das and J. Waser, *Tetrahedron*, 2022, **128**, 133135; (b) L. Zhu, X. Meng, L. Xie, Q. Shen, W. Li, L. Zhang and C. Wang, *Org. Chem. Front.*, 2022, **9**, 3068–3074; (c) L. Xie, S. Wang, L. Zhang, L. Zhao, C. Luo, L. Mu, X. Wang and C. Wang, *Nat. Commun.*, 2021, **12**, 6280; (d) A. Trowbridge, S. M. Walton and M. J. Gaunt, *Chem. Rev.*, 2020, **120**, 2613–2692; (e) D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson and A. Wood, *Nat. Chem.*, 2018, **10**, 383–394; (f) G. Yin, X. Mu and G. Liu, *Acc. Chem. Res.*, 2016, **49**, 2413–2423; (g) C. Lepori and J. Hannoudouche, *Synthesis*, 2016, **48**, 1158–1167; (h) J. W. Xu, Z. Z. Zhang, W. H. Rao and B. F. Shi, *J. Am. Chem. Soc.*, 2016, **138**, 10750–10753; (i) L. Huang, M. Arndt, K. Goofsen, H. Heydt and L. J. Goofsen, *Chem. Rev.*, 2015, **115**, 2596–2697; (j) P. X. Ling, S. L. Fang, X. S. Yin, K. Chen, B. Z. Sun and B. F. Shi, *Chem.-An Euro. J.*, 2015, **21**, 17503–17507; (k) K. S. L. Chan, M. Wasa, L. Chu, B. N. Laforteza, M. Miura and J. Q. Yu, *Nat. Chem.*, 2014, **6**, 146–150; (l) T. E. Müller and M. Beller, *Chem. Rev.*, 1998, **98**, 675–703.
- (a) T. Kang, O. Apolinar and K. M. Engle, *Synthesis*, 2023, **56**, 1–15; (b) J. Han, R. He and C. Wang, *Chem Catal.*, 2023, **3**, 100690; (c) O. Apolinar, T. Kang, T. M. Alturaifi, P. G. Bedekar, C. Z. Rubel, J. Derosa, B. B. Sanchez, Q. N. Wong, E. J. Sturgell, J. S. Chen, S. R. Wisniewski, P. Liu and K. M. Engle, *J. Am. Chem. Soc.*, 2022, **144**, 19337–19343; (d) S. Wang, C. Luo, L. Zhao, J. Zhao, L. Zhang, B. Zhu and C. Wang, *Cell Rep. Phys. Sci.*, 2021, **2**, 100574; (e) V. T. Tran, Z. Q. Li, T. J. Gallagher, J. Derosa, P. Liu and K. M. Engle, *Angew. Chem., Int. Ed.*, 2020, **59**, 7029–7034; (f) O. Apolinar, V. T. Tran, N. Kim, M. A. Schmidt, J. Derosa and K. M. Engle, *ACS Catal.*, 2020, **10**, 14234–14239.
- W. Li, J. K. Boon and Y. Zhao, *Chem. Sci.*, 2018, **9**, 600–607.
- J. Derosa, R. Kleinmans, V. T. Tran, M. K. Karunananda, S. R. Wisniewski, M. D. Eastgate and K. M. Engle, *J. Am. Chem. Soc.*, 2018, **140**, 17878–17883.
- (a) S. Gioffrè, L. Molteni and E. M. Beccalli, *Eur. J. Org. Chem.*, 2023, **26**, e202200976; (b) R. I. McDonald, G. Liu and S. S. Stahl, *Chem. Rev.*, 2011, **111**, 2981–3019.
- (a) C. K. Giri, S. Dana and M. Baidya, *Chem. Commun.*, 2021, **57**, 10536–10539; (b) N. Ballav, S. Dana and M. Baidya, *Org.*



Lett., 2022, **24**, 9228–9232; (c) N. Ballav, S. N. Saha, S. Yadav and M. Baidya, *ChemRxiv*, Preprint, 2024, DOI: [10.26434/chemrxiv-2024-77qnb](https://doi.org/10.26434/chemrxiv-2024-77qnb).

9 (a) Q. Liu, Z. Zhou, Z. Huang and Y. Zhao, *J. Org. Chem.*, 2023, **88**, 15350–15357; (b) K. S. Yang, J. A. Gurak, Z. Liu and K. M. Engle, *J. Am. Chem. Soc.*, 2016, **138**, 14705–14712.

10 (a) P. Kumar, P. J. Nagtilak and M. Kapur, *New J. Chem.*, 2021, **45**, 13692–13746; (b) N. Lebrasseur and I. Larrosa, *Adv. Heterocycl. Chem.*, 2012, **105**, 309–351; (c) L. Joucla, N. Batail and L. Djakovitch, *Adv. Synth. Catal.*, 2010, **352**, 2929–2936.

11 R. Parella and S. A. Babu, *J. Org. Chem.*, 2017, **82**, 6550–6567.

12 (a) Z. Liu, T. Zeng, K. S. Yang and K. M. Engle, *J. Am. Chem. Soc.*, 2016, **138**, 15122–15125; (b) J. Jeon, H. Ryu, C. Lee, D. Cho, M. H. Baik and S. Hong, *J. Am. Chem. Soc.*, 2019, **141**, 10048–10059.

13 (a) O. Daugulis, J. Roane and L. D. Tran, *Acc. Chem. Res.*, 2015, **48**, 1053–1064; (b) V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 13154–13155.

14 (a) M. Xu, R. Peng, Q. Min, S. Hui, X. Chen, G. Yang and S. Qin, *Eur. J. Med. Chem.*, 2022, **243**, 114748; (b) A. Palmieri and M. Petrini, *Synthesis*, 2019, **51**, 829–841; (c) S. Imran, M. Taha and N. Ismail, *Curr. Med. Chem.*, 2015, **22**, 4412–4433; (d) M. Shiri, M. A. Zolfigol, H. G. Kruger and Z. Tanbakouchian, *Chem. Rev.*, 2010, **110**, 2250–2293; (e) S. Safe, S. Papineni and S. Chintharlapalli, *Cancer Lett.*, 2008, **269**, 326–338.

15 N. Müller, B. S. Schreib, S. U. Leutenegger and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2022, **61**, e202204535.

