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Palladium catalyzed tandem Heck/Tsuji-Trost and 6-*endo* cyclization reactions of aryl iodides, vinylacetic acid, and aryl amines

Xiaoya Zhuo, Xiangwen Tan, Yi Wang, Wanqing Wu*, Huanfeng Jiang*

Key Laboratory of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510641, China

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ABSTRACT

Heck/Tsuji-Trost reaction and cyclization reactions have been established as efficient and practical strategies for constructing nitrogen-containing heterocyclic compounds. However, it is challenging to achieve a direct cascade of Heck/Tsuji-Trost and 6-*endo* cyclization reactions in one-pot synthesis, primarily due to the reactivity of intermediates and the regioselectivity control of the reaction. In this work, a palladium-catalyzed, Heck/Tsuji-Trost and 6-*endo* cyclization tandem reaction of aryl iodides, vinylacetic acid, and aryl amines has been developed, providing an effective approach for one-pot synthesis of substituted quinolines in moderate to good yields. The broad functional group tolerance, high regioselectivity, gram-scale experiments, and successful late-stage modification of natural products and pharmaceuticals proved the versatility and practicality of this method. Additionally, mechanistic experiments demonstrate that the branched amination product serves as a key intermediate in this reaction.

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Nitrogen-containing heterocycles are important organic compounds existing in various pharmaceuticals [1–3], agricultural chemicals [4], natural products [5–7], and functional materials [8]. Therefore, the development of methods for the efficient synthesis of nitrogen-containing heterocyclic is of great interest and has been long sought [9–13]. Tandem reactions have emerged as one of the most efficient methods for the delivery of different types of nitrogen containing molecules due to their high synthetic efficiency, avoiding the isolation of intermediates, and reducing the production of waste. Among them, the elegant combination of the classical coupling reaction with other reactions (such as cyclization) represents an efficacious synthetic strategy, facilitating the construction of target nitrogen-containing heterocyclic compounds through the regulation of reaction selectivity.

As a classic example of transition-metal-catalyzed reactions, Heck-type reactions have become a robust and versatile tool in organic synthesis [14–17], especially for constructing structurally diverse and densely functionalized linear molecules through three-component tandem Heck and Tsuji-Trost reactions [18–21]. In these transformations, alkenes are commonly used as substrates, yet its potential for subsequent transformations (especially cyclization-integrated reactions) remains underexplored. Of particular significance, the 6-*endo* cyclization offers a versatile platform for further transformation of alkenes [22–24], which can be effectively integrated with Heck and Tsuji-Trost reactions to access nitrogen-containing heterocyclic compounds.

However, concatenating these two reaction to construct nitrogenous heterocyclic compounds remains challenging because: (1) The Heck/Tsuji-Trost tandem reaction usually results in linear compounds [18], which are relatively simple in structure and lack active sites or functional groups required for further reactions (Fig. 1a). At the same time, the generated intermediates may not be compatible with the conditions required for the subsequent reactions, which makes it difficult for them to directly participate in the subsequent cyclization. (2) Achieving 6-*endo* cyclization has been a difficult process, because it usually requires the formation of larger-sized metallacycles [25,26], which is energetically unfavorable. In contrast, both the 5-*endo* and 6-*exo* cyclization preferentially form thermodynamically stable products, owing to its lower transition-state energy barriers (Fig. 1b) [27–29]. Based on previous work [30–37], we propose that the regulation of reaction regioselectivity is crucial for overcoming these challenges. If the branched-chain compound can be obtained in the Tsuji-Trost reaction, the presence of terminal olefins in branched products not only provides active sites for subsequent reactions but also enables the formation of desired cyclic compounds through 6-*endo* cyclization under suitable reaction conditions. Herein, we report a three-component tandem Heck/Tsuji-Trost and 6-*endo* cyclization reactions (Fig. 1c). The branched allylic aniline is generated

* Corresponding authors.
E-mail addresses: cewuwq@scut.edu.cn (W. Wu), jianghf@scut.edu.cn (H. Jiang).

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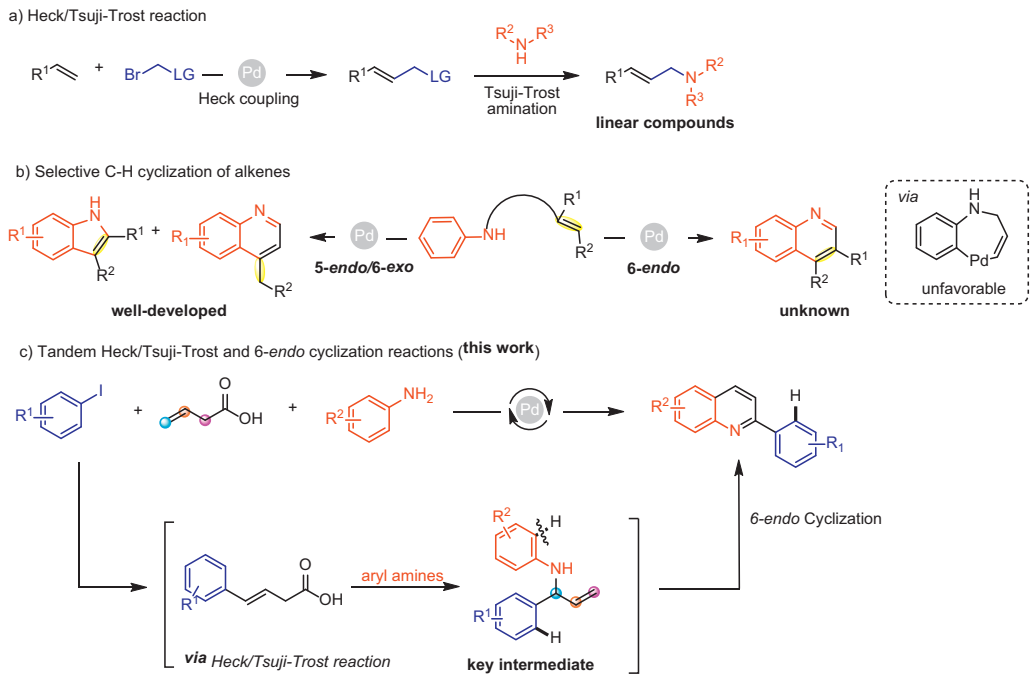
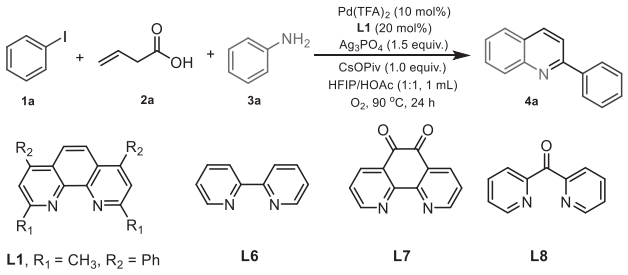


Fig. 1. (a) Heck/Tsuji-Trost reaction. (b) Selective C–H cyclization of alkenes. (c) Desired approach: tandem Heck/Tsuji-Trost and 6-*endo* cyclization reactions.

Table 1
Optimization of reaction conditions.[a]



L2, R_1 = CH_3, R_2 = H; **L3**, R_1 = Ph, R_2 = H; **L4**, R_1 = H, R_2 = CH_3; **L5**, R_1 = H, R_2 = H

Entry	Deviation from the standard conditions	Yields (%)[b]
1	None	52
2	**L2** instead of **L1**	40
3	**L3** instead of **L1**	48
4	**L4** instead of **L1**	21
5	**L5** instead of **L1**	Trace
6	**L6** instead of **L1**	Trace
7	**L7** instead of **L1**	Trace
8	**L8** instead of **L1**	Trace
9	Ag_3PO_4 (4.5 equiv.) instead of Ag_3PO_4 (1.5 equiv.)	67
10	CsOPiv (3.5 equiv.) instead of CsOPiv (1.0 equiv.)	78 (73)
11	Without $Pd(TFA)_2$	n.d.
12	Without Ag_3PO_4	n.d.
13	Without Ligand	38
14	Without CsOPiv	45
15	Conducted under N_2	8

[a] Reaction conditions: **1a** (2.4 equiv.), **2a** (0.25 mmol), **3a** (2.1 equiv.), $Pd(TFA)_2$ (10 mol%), **L1** (20 mol%), Ag_3PO_4 (1.5 equiv.), CsOPiv (1.0 equiv.) in HFIP/HOAc (1:1, 1 mL), at 90 °C under O_2 atmosphere for 24 h.
[b] Yield was determined by LC of the crude product using 9-chloroanthracene as internal standard.

in situ through the Heck/Tsuji-Trost reaction and subsequently undergoes 6-*endo* cyclization to afford quinolines. We initially employed iodobenzene **1a**, vinyl acetate **2a**, and aniline **3a** as model substrates to optimize the reaction conditions (Table 1). To our delight, the desired product could be obtained in 52 % yield with in the presence of $Pd(TFA)_2$ (10 mol%), **L1** (20 mol%), Ag_3PO_4 (1.5 equiv.) and CsOPiv (1.0 equiv.) in HFIP/HOAc (1:1, 1 mL) at 90 °C under O_2 atmosphere for 24 h (entry 1) (see Tables S1–S7 in Supporting information for details). In pursuit of higher yields, we screened various substituted *o*-phenanthroline ligands and found that those with less sterically hindered such as **L2**, **L3**, **L4**, and **L5** exhibited inhibitory effects on the reaction (entries 2–5). Other bidentate nitrogen ligands, for instance, **L6**, **L7** and **L8**, generated merely trace quantities of the desired products (entries 6–8). Increasing the Ag_3PO_4 loading from 1.5 equiv. to 4.5 equiv. resulted in a significant yield improvement from 52 % to 67 %, which we ascribe to the multifunctional nature of silver phosphate serving as: (i) An oxidant, (ii) a decarboxylation facilitator, and (iii) a precipitant for iodide ions from iodobenzene (entry 9). Finally, the target product was obtained in 78 % LC yield and 73 % isolated yield under the following reaction conditions: $Pd(TFA)_2$ (10 mol%), **L1** (20 mol%), Ag_3PO_4 (4.5 equiv.), and CsOPiv (3.5 equiv.) in HFIP/HOAc (1:1, 1 mL) at 90 °C under O_2 atmosphere for 24 h (entry 10). Control experiments confirmed that the reaction failed to proceed in the absence of palladium and Ag_3PO_4 (entries 11 and 12). The absence of Ligand and CsOPiv were found to decrease the yield (entries 13 and 14). Additionally, Oxygen is an essential condition for the reaction (entry 15).

With optimized conditions established, we subsequently investigated the substrate scope (Fig. 2). A range of aryl iodides bearing either electron-withdrawing or electron-donating groups on the aromatic ring at *para*-, *meta*-, and *ortho*-positions were converted to the corresponding products **4b-4j** in moderate to good yields. The disubstituted aryl iodides afforded the corresponding products **4k-4m**. Moreover, the transformation was compatible with strongly electron-donating substrate, affording the corresponding product **4n** in good yields. Products incorporating naphthalene **4o**, thiophene **4p** and pyridine **4q** moieties formed in 46 %, 55 % and 60 % yields, respectively. Significantly, this methodology enables late-stage functionalization modifications of drug molecules, as demonstrated by the efficient conversion of Celecoxib analogue **4r** in 74 % yield. Next, various *para*-substituted anilines were efficiently converted to the corresponding products **4s-4x** under the

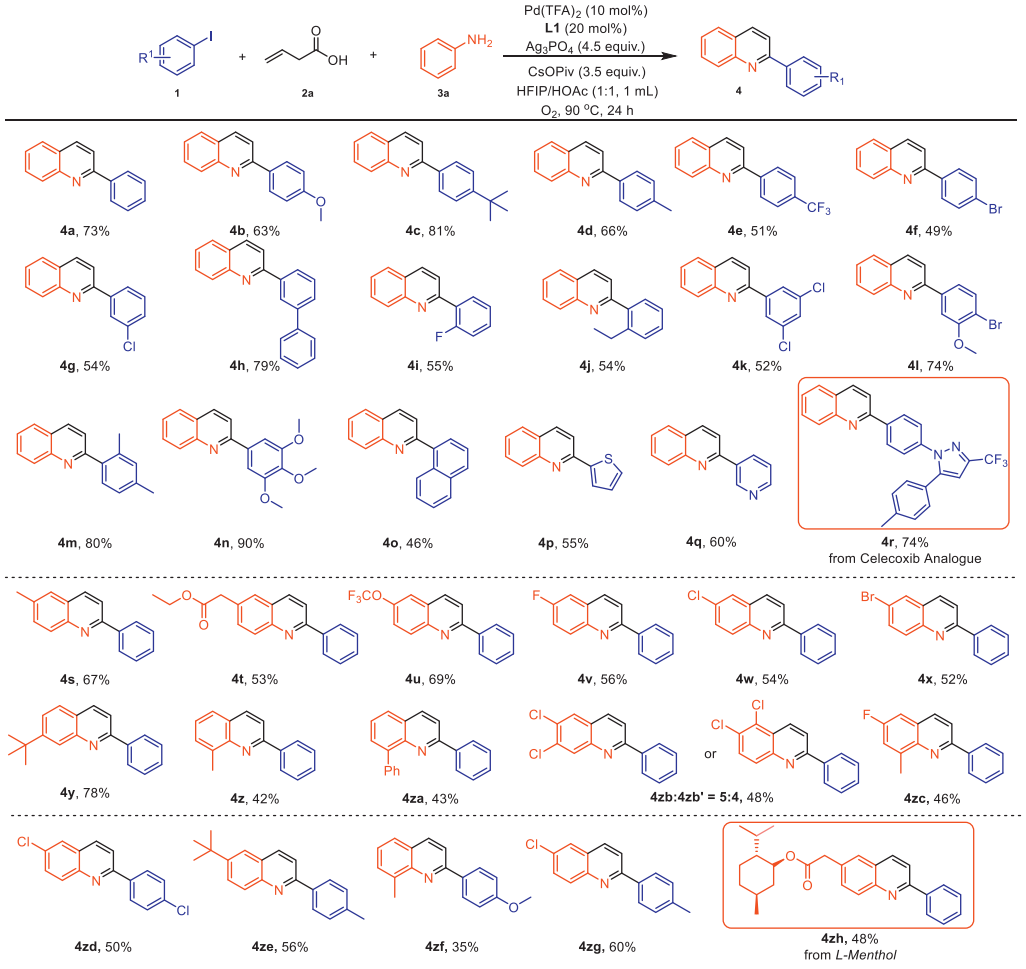


Fig. 2. The substrate scope of substituted aryl iodides and anilines, isolated yields on 0.25 mmol scale.

standard conditions. Electron-deficient aniline substrates **4v-4x** exhibited significantly reduced reactivity. Substrates bearing diverse transformable functional groups, including an ester **4t**, chlorine atom **4w**, and bromine atom **4x**, were readily tolerated, affording the corresponding products. The *meta*–*tert*–butyl–substituted aniline underwent highly regioselective transformation to afford the desired product **4y**. Anilines with *ortho*-substitution produced the target compounds **4z**-**4za** in moderate yields. Disubstituted aromatic amine substrates **4zb-4zc** participated in the reaction but exhibited poor regioselectivity. Finally, both substituted aryl iodides and anilines were efficiently transformed to afford the corresponding target compounds **4zd-4zg**. Notably, the L-menthol-derived aniline underwent efficient late-stage modification to afford the desired product **4zh** in 48 % yield, demonstrating the utility of this methodology for natural product functionalization.

To investigate the reaction mechanism, a series of control experiments were conducted (Fig. 3). In the standard reaction, the introduction of 2-methylbut-3-enoic acid **2b** instead of the vinylacetic acid **2a** led to the formation of the corresponding product **4zi** with a yield of 35 %, which demonstrated that all three carbon atoms of vinylacetic acid **2a** were involved in the reaction and confirmed the positioning of the carbon atoms (Fig. 3a). To probe the reaction initiation pathway and possible intermediates, substrate **5** was subjected to reaction with iodobenzene **1a** under standard conditions. However, the desired product **4a** was not detected by GC–MS, implying that the reaction may be initiated through a Heck-type coupling between iodobenzene **1a** and 3-butenoic acid **2a** (Fig. 3b). Furthermore, when the Heck reaction product **3c** was subjected to subsequent coupling with aniline **3a** under standard

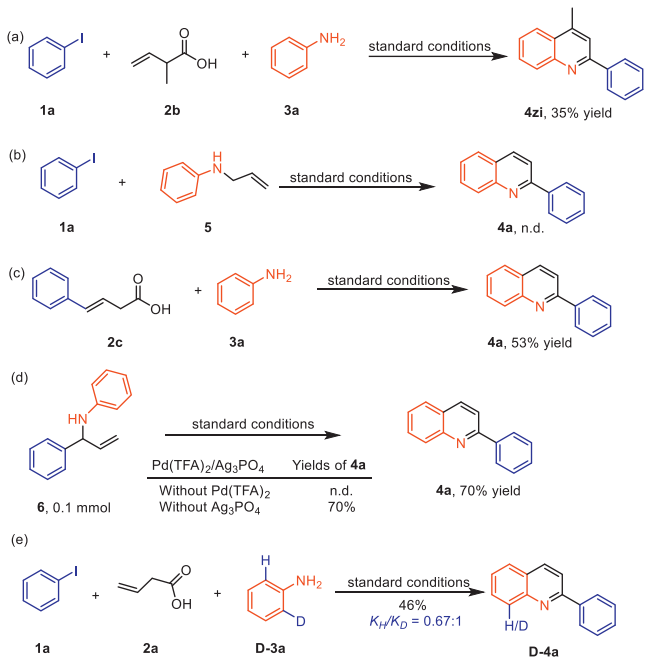


Fig. 3. Mechanistic experiments.

conditions, the target compound **4a** was obtained in 53 % yield, thereby confirming the proposed Heck reaction-driven initiation pathway (Fig. 3c). We propose that the Heck reaction product **2c**

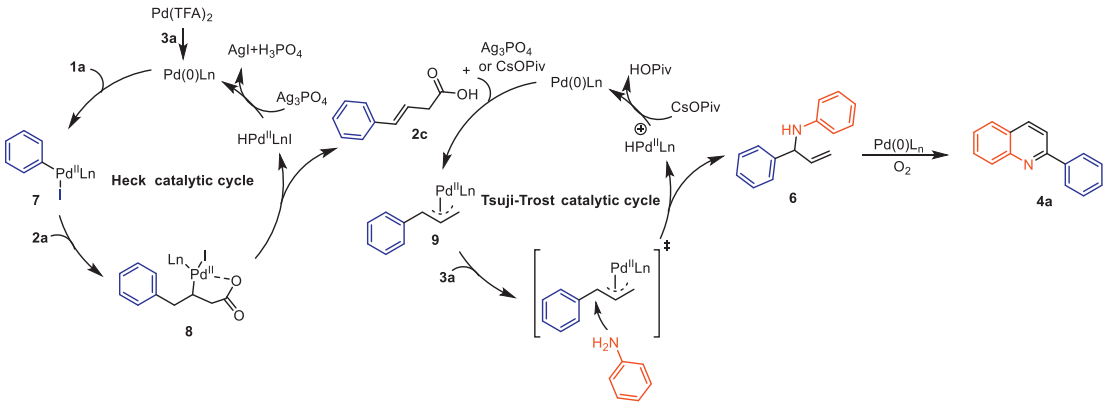


Fig. 4. Proposed mechanism.

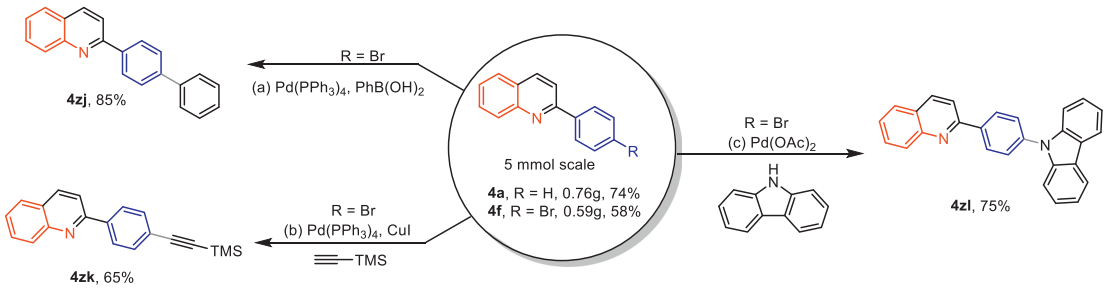


Fig. 5. Synthetic applications of quinolines. (a) $Pd(PPh_3)_4$ (6 mol%), K_3PO_4 (3.2 equiv.), 2-(4-bromophenyl)quinolone (0.1 mmol, 1 equiv.), phenylboronic acid (2.2 equiv.), 1,4-dioxane (1.0 mL), and H_2O (0.1 mL) with N_2 under 110 °C for 12 h; (b) $Pd(PPh_3)_4$ (60 mol%), CuI (120 mol%), 2-(4-bromophenyl)quinolone (0.1 mmol, 1 equiv.), DIPEA (2.0 mL), and ethynyltrimethylsilane (2.2 equiv.) with N_2 under 80 °C for 12 h; (c) $Pd(OAc)_2$ (10 mol%), $PtBu_3$ (20 mol%), Cs_2CO_3 (8.0 equiv.), 2-(4-bromophenyl)quinolone (0.1 mmol, 1 equiv.), 9*H*-carbazole (2 equiv.), and toluene (2.0 mL) with N_2 under 110 °C for 36 h.

undergoes a Tsuji-Trost reaction to generate the key intermediate **6**, which subsequently undergoes cyclization to form the target compound. To validate this hypothesis, the synthetic intermediate **6** was subjected to the reaction under standardized conditions. The reaction proceeded smoothly, yielding the target compound **4a** in 70 % isolated yield and demonstrating the critical role of intermediate **6** in the reaction pathway. In addition, control experiments demonstrate that the palladium catalyst is essential for the reaction to proceed and that the cyclization process is independent of silver phosphate (Fig. 3d). The intramolecular kinetic isotope effect (KIE) study using deuterium-labeled aniline **D-3a** yielded a KIE value of 0.67, indicating that C(sp^2)-H bond cleavage does not dominate the rate-determining step under the current catalytic conditions (Fig. 3e) (see Supporting information for more details).

Building upon our mechanistic investigations and prior literature [38–46], a plausible mechanism has been illustrated in (Fig. 4). The catalytic cycle initiates through aniline-assisted reduction of Pd^{II} to Pd^0, which subsequently undergoes oxidative addition with iodobenzene **1a** to form the Pd^{II}-aryl intermediate **7**. Migratory insertion between the Pd^{II}-aryl intermediate **7** and 3-butenoic acid **2a** is triggered, yielding intermediate **8**, whereupon β-hydrogen elimination occurs to afford intermediate **2c** alongside a Pd^{II}-hydride complex. The Pd^{II}-hydride complex undergoes reductive elimination in the presence of silver phosphate, regenerating the active Pd^0 catalyst and thereby completing the Heck catalytic cycle. Subsequently, mediated by either silver phosphate (Ag_3PO_4) or cesium pivalate (CsOPiv), intermediate **2c** undergoes oxidative addition concerted with decarboxylation, generating a π-allylpalladium(II) complex **9**. Nucleophilic attack of aniline **3a** on the π-allylpalladium intermediate **9** forms intermediate **6** with concomitant release of a palladium hydride species. The Pd-H intermediate undergoes base-assisted reductive elimination, facilitated by cesium pivalate (CsOPiv), regenerating the active Pd^0 catalyst and thereby closing the Tsuji-Trost catalytic cycle. Finally, intermediate **6** undergoes Pd^0-mediated intramolecular C(sp^2)-H activation followed by 6-*endo* cyclization, delivering the target product **4a**.

The obtained products were further employed in diverse synthetic applications (Fig. 5), see Supporting information for more details. Initially, the reaction was scaled up to 5 mmol under standard conditions, successfully affording 0.76 g of product **4a** in 74 % isolated yield and 0.59 g of product **4f** in 58 % isolated yield (Fig. 5a). Subsequently, to further prove the synthetic practicality of this methodology, the brominated product **4f** was successfully employed as a coupling partner for the construction of functionalized quinoline scaffolds. Using phenylboronic acid as the coupling partner, the Suzuki-Miyaura cross-coupling reaction afforded the arylated product **4zj** in 85 % yield (Fig. 5b). Besides, by performing Sonogashira coupling with trimethylsilylacetylene, the alkynylated product **4zk** was delivered in 65 % yield (Fig. 5c). The Ullmann type C–N bond coupling with carbazole also demonstrated good compatibility, furnishing corresponding product **4zl** in 75 % yield (Fig. 5d).

In conclusion, we have reported a palladium-catalyzed tandem Heck/Tsuji-Trost and 6-*endo* cyclization reaction method for synthesizing substituted quinolines from aryl iodides, vinylacetic acid, and aryl amines. The mechanistic experiments demonstrated that the presence of a branched amination product is essential for this tandem reaction, as it provides active sites for subsequent transformations. The practicality of this strategy has been validated through a broad substrate scope and a wide range of functional group compatibility, high regioselectivity, scale-up experiments, and the late-stage modification of natural products and drug molecules. These findings offer valuable insight for the future synthesis of complex nitrogen-containing heterocyclic compounds.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Xiaoya Zhuo: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Xiangwen Tan:** Writing – review & editing, Investigation, Data curation. **Yi Wang:** Writing – original draft, Investigation, Data curation. **Wanqing Wu:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Huanfeng Jiang:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2025.111777.

References

[1] B. Baragaña, B. Hallyburton, I. Lee, et al., Nature 537 (2015) 122.
[2] P. Yadav, K. Shah, Bioorgan. Chem. 109 (2021) 104639.
[3] S. Jain, V. Chandra, P.K. Jain, et al., Arab. J. Chem. 12 (2019) 4920–4946.
[4] Q. Cai, H. Song, Y. Zhang, et al., J. Agric. Food Chem. 72 (2024) 12373–12386.
[5] J.P. Michael, Nat. Prod. Rep. 24 (2007) 223–246.
[6] X.F. Shang, S.L. Morris-Natschke, G.Z. Yang, et al., Med. Res. Rev. 38 (2018) 1614–1660.
[7] Y.Q. Zhao, X. Li, H.Y. Guo, et al., Molecules 28 (2023) 6478.
[8] S. Tao, L. Li, J. Yu, et al., Chem. Mater. 21 (2019) 1284–1287.
[9] L.W. Ye, F.L. Hong, Acc. Chem. Res. 53 (2020) 2003–2019.
[10] B. Zhang, A. Studer, Chem. Soc. Rev. 44 (2015) 3505–3521.
[11] C. Teja, F.R.N. Khan, Chem. Asian J. 15 (2020) 4153–4167.
[12] C. Li, Y.B. Shao, X. Gao, et al., Nat. Commun. 14 (2023) 3380.
[13] G.J. Sherborne, P. Kemmitt, C. Prentice, et al., Angew. Chem. Int. Ed. 62 (2023) e202207829.
[14] A.B. Dounay, L.E. Overman, Chem. Rev. 103 (2003) 2945–2963.
[15] Y. Ping, Y. Li, J. Zhu, W. Kong, Angew. Chem. Int. Ed. 58 (2019) 1562–1573.
[16] R.X. Liang, Y.X. Liang, Acc. Chem. Res. 55 (2022) 734–745.
[17] D. Paul, S. Das, S. Saha, H. Sharma, R.K. Goswami, Eur. J. Org. Chem. 15 (2021) 2057–2076.
[18] N. Kvasovs, J. Fang, F. Kliuev, V. Gevorgyan, J. Am. Chem. Soc. 145 (2023) 18497–18505.
[19] X. Wu, H.C. Lin, M.L. Li, et al., J. Am. Chem. Soc. 137 (2015) 13476–13479.
[20] J.H. Liu, W. Wen, Z.L. Wu, et al., Chem. Sci. 15 (2024) 10232–10236.
[21] R.C. Larock, Y. Lu, A.C. Bain, J. Org. Chem. 56 (1991) 4589–4590.
[22] Z.M. Zhang, B. Xu, L. Wu, et al., Angew. Chem. Int. Ed. 58 (2019) 14653–14659.
[23] Q. Pan, Y. Ping, Y. Wang, Y. Guo, W. Kong, J. Am. Chem. Soc. 143 (2021) 10282–10291.
[24] G. Tan, Q. You, J. Lan, J. You, Angew. Chem. Int. Ed. 57 (2018) 6309–6313.
[25] R.S. Thombal, P.Y.M. Rubio, D. Lee, D. Maiti, Y.R. Lee, ACS Catal. 12 (2022) 5217–5230.
[26] M. Gulías, J.L. Mascareñas, Angew. Chem. Int. Ed. 55 (2016) 11000–11019.
[27] J. Zoller, D.C. Fabry, M.A. Ronge, M. Rueping, Angew. Chem. Int. Ed. 53 (2014) 13264–13268.
[28] S. Würtz, S. Rakshit, J.J. Neumann, T. Dröge, F. Glorius, Angew. Chem. Int. Ed. 47 (2008) 7230–7233.
[29] J.J. Neumann, S. Rakshit, T. Dröge, S. Würtz, F. Glorius, Chem. Eur. J. 17 (2011) 7298–7303.
[30] Y. Jin, Y. Jing, C. Li, et al., Nat. Chem. 14 (2022) 1118–1125.
[31] M. Li, Y. Jing, Y. Chen, W. Wu, H. Jiang, J. Am. Chem. Soc. 145 (2023) 9448–9453.
[32] C. Liu, X. Tan, L. Zhan, et al., Angew. Chem. Int. Ed. 61 (2022) e202215020.
[33] C. Liu, J. Wu, X. Tan, et al., ACS Catal. 13 (2023) 11339–11344.
[34] X. Tan, Y. Jing, J. Wu, et al., Nat. Commun. 15 (2024) 9877.
[35] C. Liu, X. Tan, J. Zhang, et al., Org. Lett. 25 (2023) 2701–2706.
[36] J. Zhang, L. Mao, C. Liu, et al., Chem. Commun. 60 (2024) 9404–9407.
[37] J. Zhang, C. Liu, J. Wu, et al., Org. Lett. 26 (2024) 4422–4426.
[38] P. Tosatti, J. Horn, A.J. Campbell, et al., Adv. Synth. Catal. 352 (2020) 3153–3157.
[39] S. Yang, L. Liu, Z. Zhou, Z. Huang, Y. Zhao, Org. Lett. 23 (2021) 296–299.
[40] S. Shu, A. Leitner, J.F. Hartwig, Angew. Chem. Int. Ed. 43 (2004) 4797–4800.
[41] Q.A. Chen, Z. Chen, V.M. Dong, J. Am. Chem. Soc. 137 (2015) 8392–8395.
[42] S. Shekhar, B. Trantow, A. Leitner, J.F. Hartwig, J. Am. Chem. Soc. 128 (2006) 11770–11771.
[43] A. Sharma, J.F. Hartwig, J. Am. Chem. Soc. 135 (2013) 17983–17989.
[44] S. Hansson, P.O. Hansson, M.P.T. Soegren, et al., Organometallics 12 (1993) 4940–4948.
[45] P. Fristrup, T. Jensen, J. Hoppe, P.O. Norrby, Chem. Eur. J. 12 (2006) 5352–5360.
[46] G. Satyanarayana, D. Pflästerer, G. Helmchen, Eur. J. Org. Chem. 2011 (2011) 6877–6886.