ChemComm
Chemical Communications

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: X. Li, M. Xiao, L. Zhou , J. Zhang, M. Zhao, S. Wang and S. Tang, *Chem. Commun.*, 2025, DOI: 10.1039/D5CC03029C.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

ChemComm

View Article Online
DOI: 10.1039/D5CC03029C

COMMUNICATION

Nickel-catalyzed sequential 1,2-*N*-migration/BCBs ring-opening to access spirocyclobutyl β-amino acid esters†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Xin-Yu Li‡, Mei-Qiu Xiao‡, Li-Juan Zhou, Jia-Qi Zhang, Meng-Yan Zhao, Shuo-Wen Wang* and Shi Tang*

Hetero-atom migration strategy is a powerful tool to access complex molecules. Herein, we disclosed a cascade radical 1,2-*N*-migration/ring-opening of *N*-aryl bicyclobutyl amides (BCBs) with β-bromo *α*-amino acid esters by cooperative Ni/diboron catalysis, which afforded a wide array of spirocyclobutyl oxindoles tethering β-amino acid motif under room temperature condition. The method suppressed the typical intramolecular C(sp²)-H cyclization of β-bromo amino acid esters after 1,2-*N*-migration, successfully incorporating β-amino acid moieties into the spirocyclobutyl oxindole scaffolds.

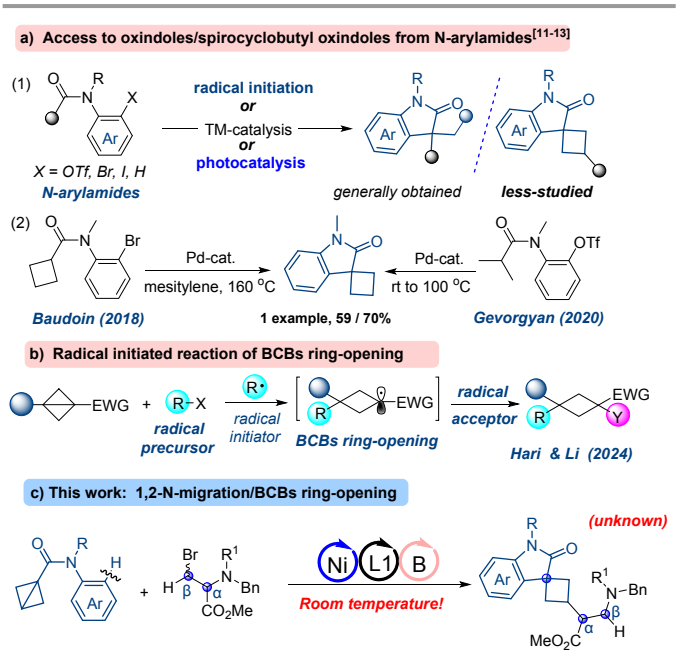
The Spirocyclic scaffolds featuring a three-dimensional architecture exhibit unique physicochemical properties and biological activities due to their rigid and highly strained frameworks.[1] The conformational rigidity of the molecule ensures that its substituents adopt a well-defined and highly predictable spatial arrangement, thereby facilitating efficient and precise interactions with the binding site.[2] Among these motifs, spirocyclobutyl oxindoles has drawn considerable attention of researchers in recent years.[3] The incorporation of cyclobutyl blocks into spirocyclic scaffolds enables more precise control of the spirocyclic three-dimensional structure, and further could improve a wide range of physicochemical and pharmacokinetic properties, including metabolic stability, permeability, lipophilicity, and acidit.[4] Consequently, spirocyclobutyl oxindoles commomly play a crucial role in natural products and exhibit interesting biological properties,[5] such as bromodomain inhibition,[6] antifungal activity,[7] phosphodiesterase inhibitors,[8] p38α-inhibitors,[9] and RSV antiviral activity, among others. Despite the great significance of these molecules in organic and bioorganic chemistry, related reports on the construction of spirocyclobutyl oxindoles are still very rare. Currently, the common strategy involves the use of *N*-arylamides as starting materials, employing radical initiation, transition metal catalysis or photocatalysis. However, most of these approaches focus on the synthesis of oxindoles,[10] with few methods reported for accessing spirocyclobutyl oxindoles (Scheme 1, a1) .[11] In 2018, Baudoin and co-workers developed a Pd-catalyzed C(sp³)–H arylation of 2-bromo-*N*-methylanilides synthesis of benzene heterocycles via a 4π electrocyclic ring-opening and 6π electrocyclization process, with 3-spirocyclobutyl oxindole as one of the substrates (Scheme 1, a2 left).[12] Recently, Gevorgyan group disclosed a visible light-induced Pd-catalyzed intramolecular C–H arylation of 2-trifluoromethanesulfonate-N-methylanilides through C(sp²)-O bond cleavage/1,5-HAT/intramolecular cyclization/rearomatization steps to give oxindole and isoindoline-1-one motifs, and 3-spirocyclobutyl oxindole also is one of the substrates in 70% yield (Scheme 1, a2 right).[13] These methods typically require *ortho*-(halogen or OTf)-substituted *N*-arylamides, precious metal catalysis, and harsh reaction conditions (high temperatures). Therefore, the development of mild methods for direct C(sp²)-H functionalization of *ortho*-*N*-arylamides to access valuable spirocyclobutyl oxindoles remains a significant challenge.

The strained C–C σ-bond of bicyclo[1.1.0]butane (BCB) is an efficient tool for innovating new reactions and increasing molecular complexity, with broad applications in total synthesis and drug discovery.[3c,14b] In particular, radical-initiated ring-opening reactions of BCBs offers significant synthetic potential for accessing challenging scaffolds under mild conditions because of their unique reactivities.[14] In this context, Hari et al.[14b] and the Li1[4a] group independently developed methods to generate 3-spirocyclobutyl oxindoles from N-aryl bicyclo[1.1.0]butane-1-carboxamides using diverse radical species (Scheme 1, b). Despite some reported approaches for these 3-spirocyclobutyl oxindoles, the development of new radical strategies for strain-release-driven ring-opening reactions of BCBs remains highly desirable. In addition, we have

College of Chemistry and Chemical Engineering, Jishou University, Jishou 416000 (China). Email: stang@jsu.edu.cn

‡ *These authors contributed equally this work.*
† *Electronic Supplementary Information (ESI) available: Full experimental details. See DOI: 10.1039/x0xx00000x*

View Article Online DOI: 10.1039/D5CC03020C



Scheme 1. a) Access to oxindoles/spirocyclobutyl oxindoles from N-arylamides; b) Radical initiated reaction of BCBs ring-opening; c) *This work:* 1,2-N-migration/BCBs ring-opening.

demonstrated access to *β*-amino acid motif through 1,2-nitrogen migration of *β*-bromo *α*-amino acid esters to form C(sp^3)-center radical, followed by C(sp^2)–H intramolecular cyclization.[15] To further expand the applications of C(sp^3)-center radical mediated *N*-atom migration strategy in chemical synthesis, we envisioned that Ni-mediated oxidative insertion of the C–Br bond of the *β*-bromo *α*-amino acid esters might generate a transient C(sp^3)-centered radical via radical 1,2-nitrogen migration, followed by further cascade/C(sp^2)-H functionalization with *N*-aryl amides to synthesize challenging 3-spirocyclobutyl oxindoles skeleton. Interestingly, this reaction not only overcome the typical C(sp^2)–H intramolecular cyclization of *β*-bromo *α*-amino acid esters, but also successfully introduces *β*-amino acid ester blocks into 3-spirocyclobutyl oxindole framework. Herein, we want to report a novel cooperative Ni/diboron/ligand-catalyzed 1,2-nitrogen migration/C(sp^2)–H coupling of *N*-aryl bicyclobutyl amides with *β*-bromo *α*-amino acid esters under room temperature conditions. This method operates via 1,2-nitrogen migration leading to electrophilic *α*-carboxyl C(sp^3) radical intermediates, which undergostrained C-C σ-bonds/addition/cyclization/deprotonation steps led to valuable spirocyclobutyl oxindoles bearing *β*-amino acid esters motif with with an all-carbon quaternary center (Scheme 1, c).

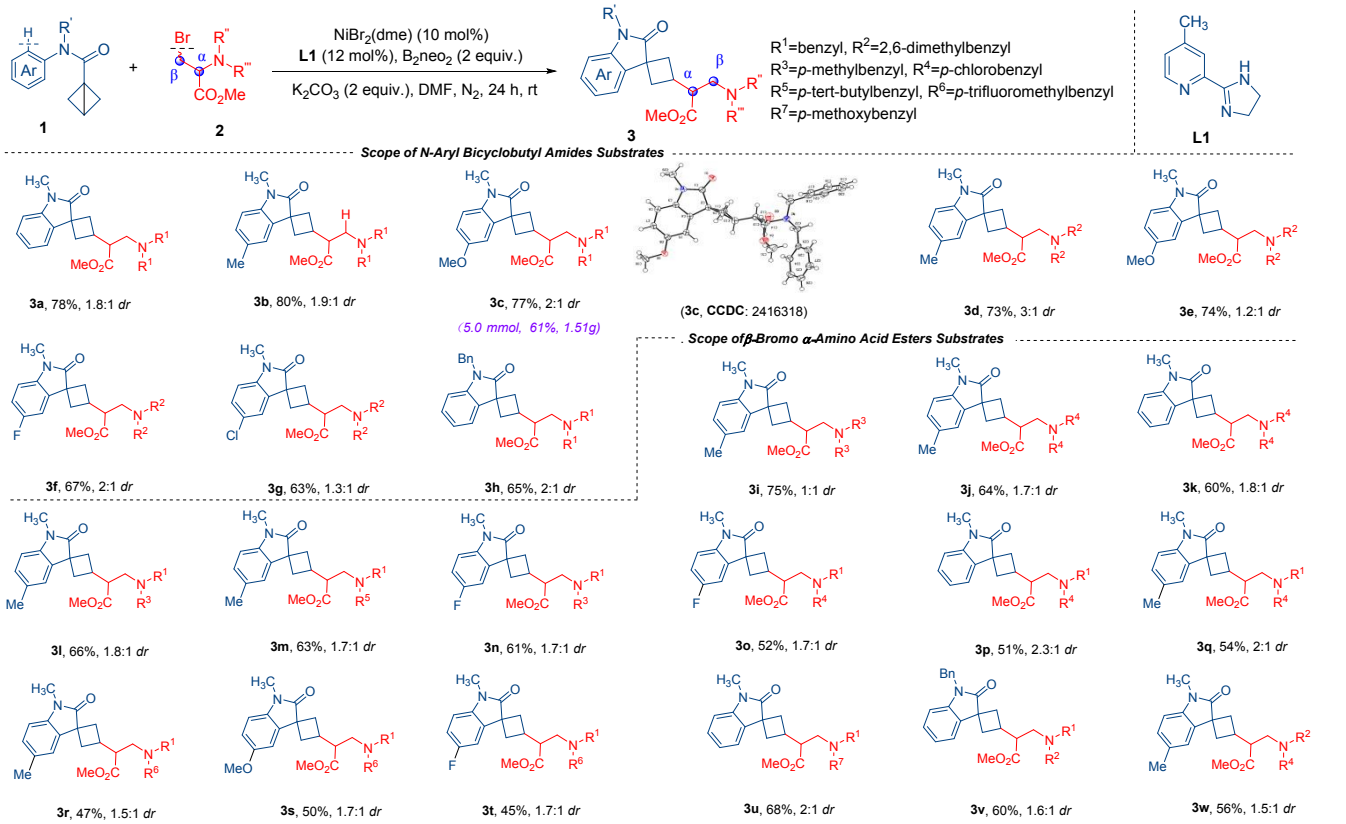
With our optimized reaction conditions (see Table S1 in the SI), we set out to investigate the substrate scope of *N*-aryl bicyclobutyl amides (**1**) with *β*-bromo amino acid esters (**2**). Initially, various *N*-aryl bicyclobutyl amides (**1**) were explored. As shown in Scheme 2, a series of *N*-aryl bicyclobutyl amides bearing various electron- donating or electron-withdrawing groups, such as methyl, methoxy, fluoro and chloro at the 4-position of the aromatic ring were all well tolerated, providing the corresponding products **3a**-**3g** in moderate to good yields (63-80%). Moreover, the nitrogen migration product **3c** could be assembled on a 5.0 mmol scale, maintaining an isolated yield of 61%. The structure the minor diastereomer of **3c** was unambiguously determined by X-ray single crystal analysis and that of other products assigned by analogy.[16] Gratifyingly, substrate with an *N*-benzyl group was also readily accommodated, affording the desired product **3h** in 65% yield. Next, we went on to examine the substrates scope of β-bromo amino acid esters (**2**). The introduction of symmetric benzyl groups (*p*-Me and *p*-$ClC_6H_4CH_2$) on the N atom, underwent cascade 1,2-*N*-shift/C–H coupling reacted smoothly, affording the corresponding spirocyclobutyl oxindoles of *β*-amino acid esters **3i**-**3k** in 60-75% yields. In addition, we further explored the cascade 1,2-*N*-shift capability of different benzyl groups tethered to the N atom. Gratifyingly, the reaction proceeded smoothly, and electron-rich aromatic groups (*p*-Me and *t*-BuC_6H_5) were observed to perform better than electron-deficient ones (*p*-Cl and *p*-$CF_3C_6H_5$) (**3k**-**3t**) while maintaining a benzyl group. Methoxy-substituted benzyl group was proven to be a good candidate as well, affording product **3u** in 68% yield. Furthermore, more complex disubstituted aromatic groups also amenable to this process to obtained product **3v** in 60% yield. It is worth noting that the simultaneous presence of electron-rich and electron-poor benzyl groups on the N atoms was well tolerated and furnished **3w** in 56% yield, which provides a new practical method for the generation of spirocyclobutyl oxindoles of *β*-amino acid esters with diverse electronic properties.

To better understand the reaction mechanism and identify the possible reaction intermediates, a series of control experiments were carried out (Scheme 3). First, we investigated using a radical scavenger and added 2 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) in the reaction. As expected, 1,2-*N*-shift process was obviously inhibited and the 1,2-*N*-shift of **2j** formed to *α*-carboxyl C(sp^3) radical was captured by TEMPO to obtain product 4, suggesting that the reaction likely proceeds via a radical pathway (Scheme 3a). Subsequently, a standard radical clock (cyclopropane) was performed under standard conditions and none of the expected spirocyclobutyl oxindoles of β-amino acid esters (**3x**) was observed. Instead, the formation of ring-opening product **5** was observed by ^{1}H NMR (Scheme 3b). The radical clock experiment further proved the generation of a C(sp^3) radical from the alkyl bromides (**2t**) in the reaction. Notably, the crossover experiment indicated that the above aminyl radical addition onto the acrylate is possible to occur (Scheme 3c). According to the results of the controlled experiments above and related literature reports,[11,17] a plausible reaction mechanism was proposed in Scheme 4.

First, the Ni/B-catalyzed cycle begins with the coordination of B_2neo_2 with a nucleophilic carbonate or bromide anion to form an sp^2-sp^3 diboron adduct, which is further activated by the [Nin]-Br to generate both the [Nin]-Bneo·and (X-Bneo).[18] Then the Bneo-Ni(I)-**L1** species undergoes a single-electron transfer (**SET**) process with **2a**, generating the alkyl radical intermediates **Int-I**, along with oxidized Ni(II) intermediates, which can participate in the next catalytic cycle. Subsequently, the intermediates **Int-I** easily extruded a $(Bn)_2N$ radical, giving the

View Article Online
DOI: 10.1039/D5CC03029C

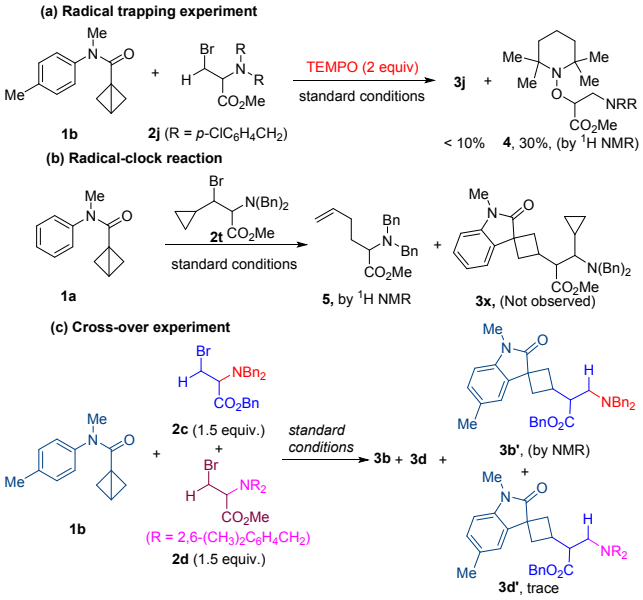
methyl acrylate (**Int-II**). The $(Bn)_2N$ radical was attached to the



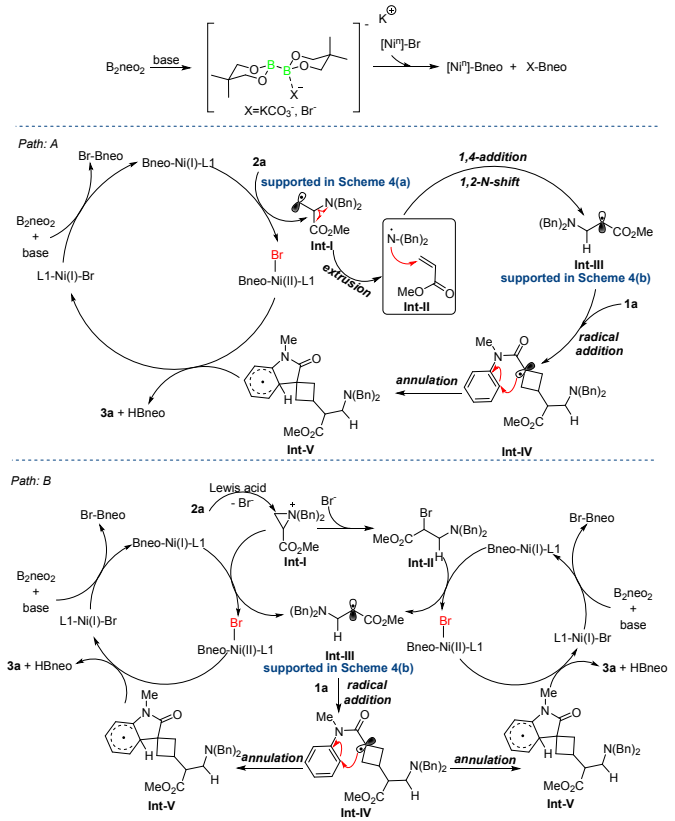
Scheme 2. Scope for the synthesis of spirocyclobutyl oxindoles tailing *β*-amino acid ester motif. Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $NiBr_2$ (dme) (10 mol %), 2-(4,5-dihydro-1H-imidazol-2-yl)-4-methylpyridine (12 mol %), B_2neo_2 (2 equiv.), K_2CO_3 (2 equiv.), add 2 mL DMF as solvent, at room temperature under N_2 atmosphere for 24 h. Yields given refer to isolated yields, and the diastereomeric ratio (dr) was determined by ^1H NMR spectroscopy of the crude reaction mixture.

nascent intermediate methyl acrylate, which undergoes 1,4-addition to form the acetonyl radical intermediate **Int-III**, thereby achieving the formal migration of the 1,2-*N* radical (path A). In addition, we speculate that an alternative pathway may exist for the formation of **Int-III**. In this pathway, Lewis acid-assisted bromine dissociation from the β-bromo α-amino acid ester substrate (**2a**) could generate the aziridinium ion intermediate **Int-I**. Subsequently, **Int-I** might undergo a single-electron transfer (SET) process with Bneo-Ni(I)-**L1** to form the acetonyl radical intermediate **Int-III**. Alternatively, aziridinium ion intermediate **Int-I** could be opened directly via nucleophilic attack by bromide ion to afford the brominated product. This brominated product could then undergo an SET process with Bneo-Ni(I)-**L1** to yield intermediate **Int-III** (path B). The acetonyl radical intermediate **Int-III** addition to the substrate **1a** to generate the intermediate **Int-IV**, followed by further intramolecular cyclization to obtain the intermediate **Int-V**. Finally, the intermediate **Int-V** undergoes oxidative abstraction of an aryl H-atom by the Ni(II) species (**L1**-Ni(Br)-Bneo), affording the product **3a** and HBneo.

In conclusion, we have disclosed a novel cooperative Ni/diboron-catalyzed strategy using the *N*-aryl bicyclobutyl amides and *β*-bromo *α*-amino acid esters as raw materials through a cascade 1,2-*N*-shift/C–H coupling process under room temperature, enabling the formation of spirocyclobutyl oxindoles containing *β*-amino acid ester motif with an all-carbon quaternary center. This work overcomes the challenge of the typical intramolecular C(sp^2)-H cyclization in *β*-bromo esters prior to 1,2-*N*-migration, successfully introducing *β*-amino acid ester motifs into the spirocyclobutyl oxindole framework. In addition, the 1,2-*N*-migration cascade cyclisation



Scheme 3. Control experiments: (a) radical trapping experiment; (b) radical-clock experiments; (c) Cross-over experiment.



Scheme 4. A plausible mechanism.

process involves the tertiary amino migration converts a nucleophilic alkyl radical into an electrophilic acetonyl radical, which facilitates further radical relay reaction. The mechanistic studies demonstrated that the reaction proceeded undergo alkyl radical formation/1,2-*N*-migration/strained C-C σ-bonds/addition/cyclization/ deprotonation sequence. We believe that this strategy has the potential to introduce *β*-amino acid ester motifs in other natural product skeletons via 1,2-*N*-migration of β-amino acid esters. Further development and application of this reaction are currently under investigation in our laboratory.

This work was supported by the National Natural Science Foundation of China (Nos. 22271118 and 22401109), Education Department of Hunan Province of China (24B0494) are gratefully acknowledged.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the ESI.

Notes and references

1 For selected reviews, see: (a) G. S. Singh and Z. Y. Desta, *Chem Rev*, 2012, **112**, 6104; (b) E. M. Carreira and T. C. Fessard, *Chem Rev*, 2014, **114**, 8257; (c) M. J. James, P. O'Brien and R. J. K. Taylor, *Chem-Eur J*, 2016, **22**, 2856; (d) K. Hiesinger, D. Dar'in, E. Proschak and M. Krasavin, *J Med Chem*, 2021, **64**, 150.

2 K. E. Prosser, R. W. Stokes and S. W. Cohen, *ACS Med Chem Lett*, 2020, **11**, 1292.

3 (a) X. Zhong, J. Tan, J. Qiao, Y. Zhou, C. Lv, Z. Su, S. Dong and X. Feng, *Chem Sci*, 2021, **12**, 9991; (b) S.-X. Shi, H.-H. Zhang, Y.-L. Wang, L.-H. Jiang, P.-F. Xu and Y.-C. Luo, *Org Lett*, 2023, **25**, 5426; (c) P.-F. Xia, J. Zhou, J. Yuan, R. Zeng, Y. Liu, K.-W. Tang and J.-H. Fan, *Org Lett*, 2024, **26**, 6486.

4 M. R. van der Kolk, M. A. C. H. Janssen, F. P. J. T. Rutjes and D. Blanco-Ania, *ChemMedChem*, 2022, **17**, e202200020.

5 (a) E. M. Carreira and T. C. Fessard, *Chem Rev*, 2014, **114**, 8257; (b) Y.-Y. Fan, H. Zhang, Y. Zhou, H.-B. Liu, W. Tang, B. Zhou, J.-P. Zuo and J.-M. Yue, *J Am Chem Soc*, 2015, **137**, 138;

6 H. Azizollahi, M. Pérez‐Gómez, M. P. Mehta and J.-A. García‐López, *Adv Synth Catal*, 2020, **362**, 1899.

7 S. E. Reisman, J. M. Ready, A. Hasuoka, C. J. Smith and J. L. Wood, *J Am Chem Soc*, 2006, **128**, 1448.

8 M. Yoshikawa, H. Kamisaki, J. Kunitomo, H. Oki, H. Kokubo, A. Suzuki, T. Ikemoto, K. Nakashima, N. Kamiguchi, A. Harada, H. Kimura, T. Taniguchi, *Biorg Med Chem*, 2015, **23**, 7138.

9 P. Eastwood, J. González, E. Gómez, B. Vidal, F. Caturla, R. Roca, C. Balagué, A. Orellana and M. Domínguez, *Bioorg Med Chem Lett*, 2011, **21**, 4130.

10 For selected examples access to oxindoles from arylamides, see: (a) C. M. Le, T. Sperger, R. Fu, X. Hou, Y. H. Lim, F. Schoenebeck and M. Lautens, *J Am Chem Soc*, 2016, **138**, 14441; (b) S. Xu, K. Wang and W. Kong, *Org Lett*, 2019, **21**, 7498; (c) Z. Liu, S. Zhong, X. Ji, G.-J. Deng and H. Huang, *ACS Catal*, 2021, **11**, 4422; (d) E. M. Larin, J. Masson-Makdissi, Y. Jin. Jang and M. Lautens, *ACS Catal*, 2022, **12**, 12744; (e) N. Xian, J. Yin, X. Ji, G.-J. Deng and H. Huang, *Org Lett*, 2023, **25**, 1161; (f) X. Zhou, J. Wu and Y. Zhao, *Org Chem Front*, 2023, **10**, 3929; (g) Y. Tan and H. Huang, *Chem Commun*, 2023, **59**, 13462.

11 R. Rocaboy, D. Dailler, F. Zellweger, M. Neuburger, C. Salomé, E. Clot and O. Baudoin, *Angew Chem Int Ed*, 2018, **57**, 12131.

12 R. Rocaboy, D. Dailler, F. Zellweger, M. Neuburger, C. Salomé, E. Clot and O. Baudoin, *Angew Chem Int Ed*, 2018, **57**, 12131.

13 M. Ratushnyy, N. Kvasovs, S. Sarkar and V. Gevorgyan, *Angew Chem Int Ed*, 2020, **59**, 10316.

14 (a) J.-H. Fan, J. Yuan, P.-F. Xia, J. Zhou, L.-J. Zhong, P.-F. Huang, Y. Liu, K.-W. Tang and J.-H. Li, *Org Lett*, 2024, **26**, 2073; (b) T. Singha, N. A. Bapat, S. K. Mishra and D. P. Hari, *Org Lett*, 2024, **26**, 6396; (c) J. Yuan, J. Zhou, P.-F. Xia, Y. Liu, K.-W. Tang and J.-H. Fan, *Chin J Chem*, 2024, **42**, 3399; (d) J. Liu, Y. Qian, H. Zhao, Y. Liu, Z. Qin, Z. Zhang and L. Rong, *J Org Chem*, 2024, **89**, 15914; (e) R. Maity, S. Paul, A. Sen, S. Garain and B. Maji, *ChemSusChem*, 2025, **18**, e202401701; (f) J.-H. Fan, J. Yuan, L.-J. Zhong, Y. Liu and K.-W. Tang, *Org Chem Front*, 2024, **11**, 1982; (g) T. Singha, D. P. Hari, *Synlett*, 2025, **36**, 445.

15 Y. Hong, Z.-C. Liao, J.-J. Chen, J. Liu, Y.-L. Liu, J.-H. Li, Q. Sun, S.-L. Chen, S.-W. Wang and S. Tang, *ACS Catal*, 2024, **14**, 5491.

16 CCDC 2416318 (**3c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center.

17 For selected examples on diboron compounds mediated transformations, see: (a) G. Wang, H. Zhang, J. Zhao, W. Li, J. Cao, C. Zhou Proft and S. Li Proft, *Angew Chem Int Ed,* 2016, **55**, 5985; (b) L. Zhang and L. Jiao, *J Am Chem Soc*, 2017, **139**,607;

18 S. Pietsch, E. C. Neeve, D. C. Apperley, R. Bertermann, F. Mo, D. Qiu, M. S. Cheung, L. Dang, J. Wang, U. Radius, Z. Lin, C. Kleeberg and T. B. Marder, *Chem-Eur J*, 2015, **21**, 7082.

View Article Online
DOI: 10.1039/D5CC03029C

Data Availability Statement

The data supporting this article have been included as part of the Supplementary Information.