Ligand-Enabled Palladium(II)-Catalyzed γ-C(sp^3)−H Arylation of Primary Aliphatic Amines

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Abstract:

Amines are common scaffolds in bioactive molecules as well as building blocks for chemical synthesis. Despite significant advances in palladium-catalyzed C(sp^3)−H functionalization of amines over the past decades, it remains challenging to perform directed C−H metalation with native amine groups rather than amine-derived or transient directing groups (DGs). Recently, our group developed the Pd(II)/sulfoxide-2-hydroxypyridine (SOHP) catalytic system, in which SOHP ligands play a pivotal role as a crucial functional module, enabling regioselective C(sp^2)−H and enantioselective C(sp^3)−H functionalization reactions. In this work, we demonstrate that this chemistry provides an ideal solution for native primary amine-directed γ-C(sp^3)-H arylation. Primary amines of varying degrees of complexity, encompassing amino acid esters and aminol silyl ethers, were found to be compatible with the established methodology. Additionally, we achieved a preliminary implementation of the asymmetric variant of this γ-C−H arylation reaction by employing a chiral SOHP ligand. Moreover, the range of applicable substrates could be extended to pyridine, oxime ether, and pyridine-*N*-oxide.

Aliphatic amines are fundamental structural motifs in organic and bioorganic chemistry. In particular, γ-arylamines prevalently exist in natural products, pharmaceuticals, and other bioactive entities[1] (Figure 1). Consequently, the development of efficient strategies for the construction and modification of γ-arylamines is of great importance and high demand.

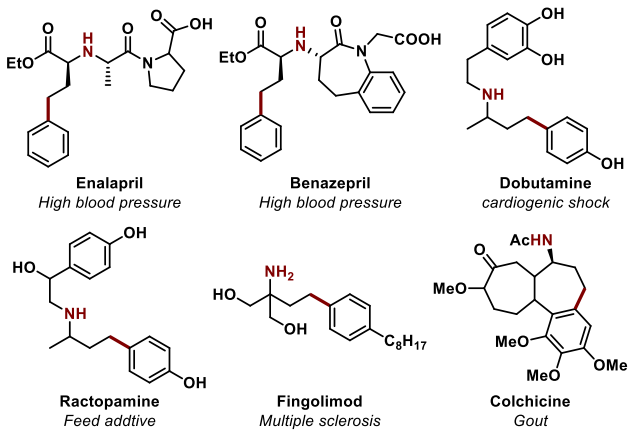


Figure 1. Bioactive γ-arylamine compounds

Direct C−H bond functionalization is an ideal method for the construction of multifunctional molecules and late-stage modification of complex structures.[2] Over the past decades, tremendous progress has been made in terms of palladium-catalyzed C(sp^3)−H functionalization reactions of aliphatic amines.[3] Initially, amine-derived directing groups (DGs) were employed to facilitate Pd-catalyzed C−H functionalization of the amine aliphatic chain (Figure 2a), and a variety of α-,[4] β-,[5] γ-,[6] and δ-C(sp^3)-H[7] functionalization reactions have been accomplished by the groups of Daugulis, Yu, Dong, and numerous others.[8] Although highly effective, these approaches often require additional steps for DG installation and removal. A preferred alternative strategy is to introduce transient directing groups, whereby exogenous DGs are reversibly generated *in situ*, leading to the formation of imine-based or carbamate transient DGs that enable Pd-catalyzed γ-,[9] and δ-C(sp^3)-H[10] functionalization of aliphatic amines as demonstrated by Yu,[9a, 10] Dong,[9b] Ge,[9c] Young,[9d] and many others[9e-g] (Figure 2b).

Even more preferable would be a method using the amine itself as the DG, which is conceptually straightforward but challenging,[3c] since free aliphatic amines have been proved to readily form the inactive bis(amine)-Pd(II) complex,[3a, 11] undergo α-oxidation,[12] and undergo Buchwald-Hartwig coupling with aryl substrates.[13] In this line, Gaunt and coworkers disclosed β- and γ-C(sp^3)-H functionalization of free secondary amines without ligand[14] and γ-C(sp^3)-H functionalization of tertiary aliphatic amines with *N*-monoprotected amino acid (MPAA) ligand.[15] For free primary aliphatic amines, only a handful of methods were established and their applicability remains largely limited to specific substrates (Figure 2c). Under ligand free conditions, Shi and coworkers documented the pioneering case of γ-acetoxylation in 2017,[16] subsequently Bannister and coworker realized the δ-arylation,[17] in which only α-fully substituted amines showed good reactivity; Yao and coworkers developed the γ-C(sp^3)−H functionalization on amino acid esters and oligopeptides preliminarily overcoming the α-fully substitution limit.[18] In 2020, Yu and coworkers reported the first enantioselective case on cyclopropylmethylamine employing the MPAAThio ligand.[19] To further overcome the substrate limitation, Li and coworkers introduced pyridone as ligand and achieved normal primary amine-directed γ-C(sp^3)−H arylation successfully.[20] Despite these achievements, to date, the pursuit of an alternative and efficient catalytic system for challenging normal primary amine-directed C(sp^3)−H functionalization remains a highly coveted goal.[21]

Previously we have developed a series of sulfoxide-2-hydroxypyridine (SOHP) ligands, which exhibited remarkable activity in regioselective C(sp^2)−H alkenylation of indoles[22] and enantioselective β-C(sp^3)−H arylation of aliphatic tertiary amides.[23] Herein, we show that the Pd(II)/SOHP catalytic system is also able to promote the γ-C(sp^3)−H arylation reaction of free primary aliphatic amines, including amino acid esters and aminol silyl ethers. Notably, an asymmetric variant of this reaction has also been accomplished with chiral SOHP ligand for specific substrates. In addition to primary aliphatic amines, the scope could be broadened to pyridine, oxime ether, and pyridine-*N*-oxide. The present work provides a valuable approach to the synthesis of γ-arylamines and demonstrates chiral SOHP as a potential ligand type competent for enantioselective C(sp^3)−H activation of diverse substrates.

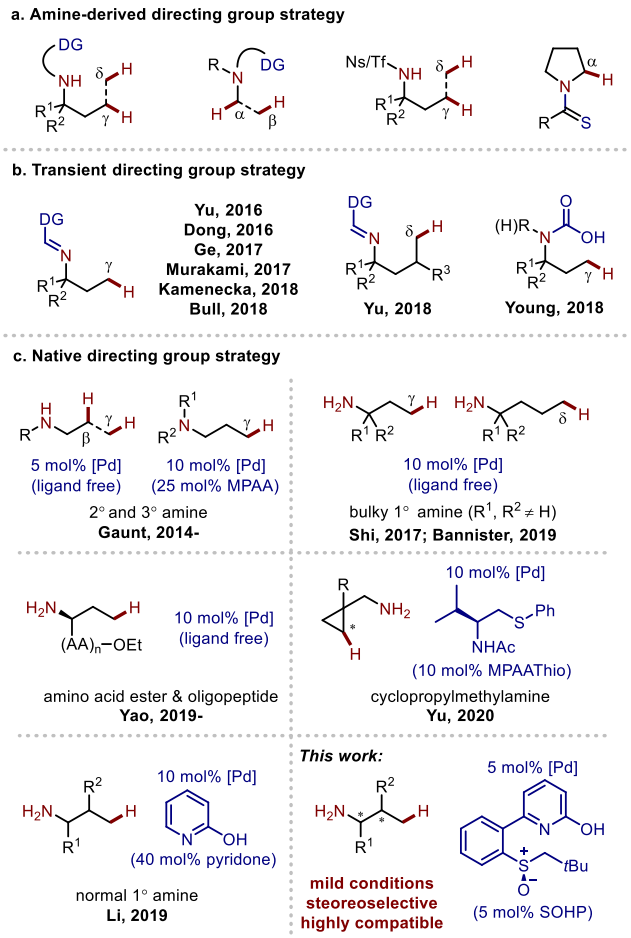
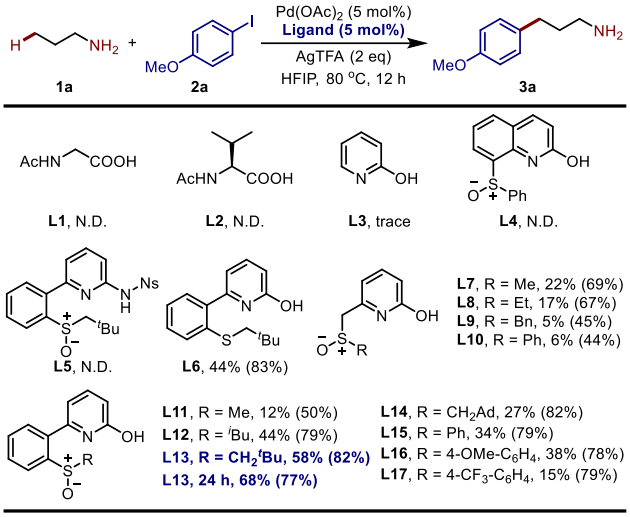


Figure 2. Pd(II)-catalyzed C(sp^3)−H functionalization of amines.

Inspired by our previous discovery that SOHP ligands facilitated the β-C(sp^3)−H activation/arylation of aliphatic tertiary amides with aryl iodides,[23] we commenced our study with the Pd-catalyzed γ-C−H arylation of propylamine (**1a**) with 1-iodo-4-methoxybenzene (**2a**) as a model reaction (Table 1). It is noteworthy that aliphatic amines without α-substituents such as propylamine (**1a**) are considered to be a quite challenging substrate in C−H activation of amines, which is usually unreactive in previous reports.[3a, 16, 24] It was found that, under ligand free conditions, no desired product could be observed with $Pd(OAc)_2$ (5 mol%) and AgTFA in HFIP at 80 °C. Two MPAA ligands Ac−Gly−OH (**L1**) and Ac−Val−OH (**L2**), which have been recognized as efficient ligands for Pd-catalyzed C−H functionalization,[25] also exhibited no reactivity (Table 1). In addition to MPAA ligands, pyridones were also be introduced as effective ligands in this chemistry,[20, 26] thus the representative pyridine-2-ol (**L3**) was selected to be tested under aforementioned conditions, resulting in the detection of only trace amount of the arylation product. Subsequently, we extensively screened ligands developed in our group.[22-23] The sulfoxide-2-hydroxyquinoline ligand **L4** and sulfoxide-2-(*N*-sulfonylamino)pyridine ligand **L5** were initially investigated but found to be inactive. To our delight, the sulfide-2-hydroxypyridine ligand **L6**, along with most of the SOHP ligands (**L7**-**L17**), exhibited significant reactivity in the model reaction, giving moderate to good yields of the desired product, and the benzene-tethered SOHP ligands (**L11**-**L17**) performed better than the methylene-tethered ones (**L7**-**L10**) in general. Among the benzene-tethered SOHP ligands **L11**-**L17**, the bulky alkyl-substituted ligand **L13** exhibited superior reactivity, affording the arylation product with 58% yield (82% brsm). With the effective ligand **L13** in hand, we prolonged the reaction time to 24 h and got a satisfactory NMR yield of 68% (77% brsm), which was identified it as the optimal condition for subsequent substrate scope studies.

Table 1. Ligand screen for C(sp^3)–H arylation of amine **1a**.[a]



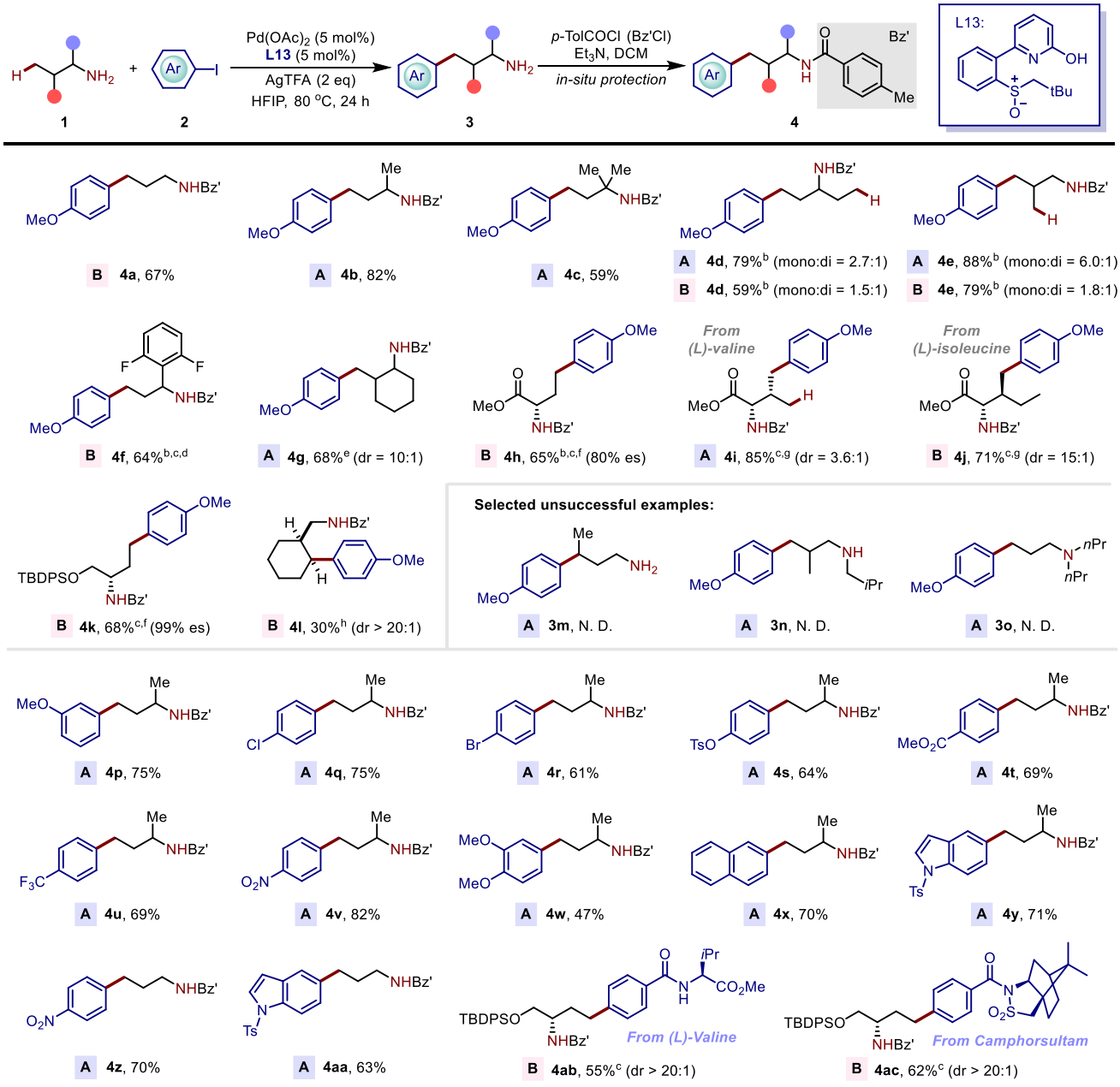
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.1mmol), $Pd(OAc)_2$ (0.005 mmol), ligand (0.005 mmol), AgTFA (0.2 mmol), HFIP (1 mL), 80 °C, 12 h. All sulfoxide ligands used were racemic. Yields were determined by ^1H NMR analysis and yields based on recovered starting materials (brsm) were in the parentheses. Abbreviations: AgTFA = silver trifluoroacetate; HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

The substrate scope of this amine C–H arylation reaction was explored under the optimal conditions (Table 2). For ease of purification, the products were isolated as the corresponding 4-methylbenzamides (Bz'NHR). The scope of primary aliphatic amines was first investigated for methyl C(sp^3)–H arylation and we were delighted to find that the reaction proceeded well regardless of the α-substitution pattern of the amine substrate (**4a-4c**). Both mono- and di-arylation products were obtained for aliphatic amines with two equivalent reactive methyl groups and the mono-arylation product predominated whether amine or iodoarene was used as the limiting reagent (**4d, 4e**). For α-aryl substituents, the presence of 2,6-diflurophenyl group was well tolerated (**4f**), while the phenyl group was not compatible. Moreover, cycloalkylamine such as 2-methylcyclohexan-1-amine was also compatible with good diastereoselectivity (**4g**). The amino acid esters were then tested to be compatible with satisfactory yields (65%-85%) and good chiral retention (**4h-4j**), and for (*L*)-valine esters only mono-arylation product was obtained (**4i**), which distinguishes this catalytic system from previous systems that showed poor chiral retention (5% es and 1.4:1 dr for the arylation of ethyl (*S*)-2-aminobutanoate and ethyl *L*-isoleucinate, respectively) and mono-/di-selectivity (di-arylation products were obviously observed).[18, 20] Besides, aminol silyl ether yielded the corresponding arylation product with good yields (68%) and excellent chiral retention (99% es) (**4k**). Moving on to methylene C(sp^3)–H arylation, the acyclic primary aliphatic amine showed no reactivity, paralleling the results of previously reported native amine-directed C(sp^3)–H functionalization reactions (**3m**).[16-18, 20] However, to our surprise, the cyclohexanemethanamine gave the desired cyclic methylene C–H arylation product with perfect diastereoselectivity (>20:1 dr), albeit with a diminished yield (**4l**). We have also attempted to extend the scope to secondary and tertiary amines, but no desired product was observed as the previous primary amine-directed catalytic systems presented (**3n, 3o**).[16-19]

The scope of aryl iodides was next investigated for this transformation. A variety of functionalities such as halogen atoms (**4q, 4r**), sulfonate (**4s**), ester (**4t**), trifluoromethyl (**4u**), and nitro (**4v, 4z**) were compatible with the reaction conditions, and the electronic feature of the substituent on the benzene ring did not exert considerable influence on the reaction performance as shown in the cases (**4b, 4q-4v**), though 3,4-dimethoxyiodobenzene led to the product with a slightly diminished yield (**4w**). In addition to substituted phenyl iodides, heteroaryl iodide was also tolerated by this reaction with satisfactory yields (**4y, 4aa**). Aryl iodides derived from (*L*)-valine (**4ab**) and camphorsultam (**4ac**) could

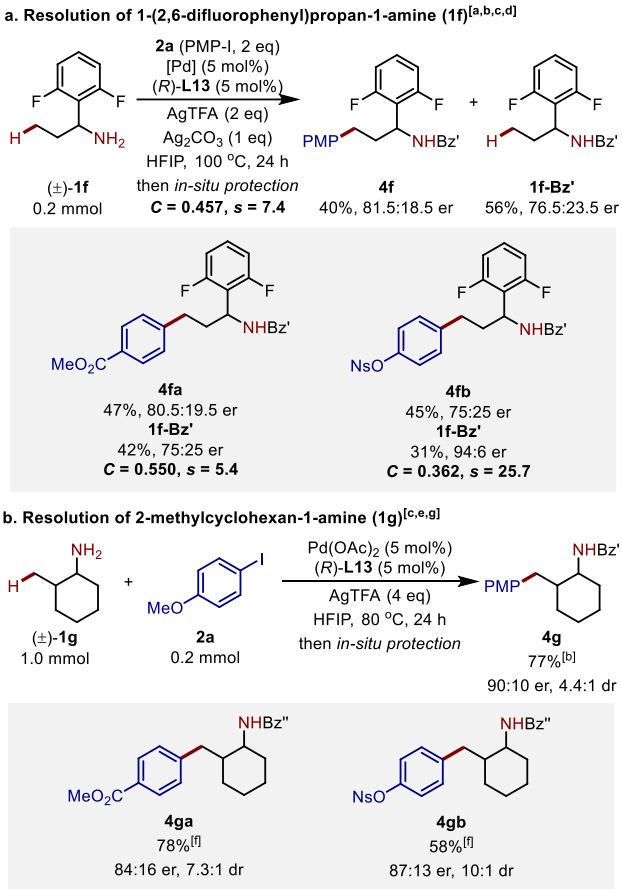
also be employed as substrates to deliver the corresponding products in good yields (55−62%) and diastereomeric ratios (>20:1 dr), which highlighted the general applicability and mild nature of this method.

Table 2. Substrate scope.[a]



[a] **Conditions A**: amine **1** (0.2 mmol), iodoarene **2** (0.1 mmol), $Pd(OAc)_2$ (0.005 mmol), **L13** (0.005 mmol), AgTFA (0.2 mmol), HFIP (1 mL), 80 °C, 24 h, 0.1 mmol scale; **Conditions B**: amine **1** (0.1 mmol), iodoarene **2** (0.2 mmol), $Pd(OAc)_2$ (0.005 mmol), **L13** (0.005 mmol), AgTFA (0.2 mmol), HFIP (1 mL), 80 °C, 24 h, 0.1 mmol scale; Diastereomeric ratios (dr) were determined by ^1H NMR analysis; Isolated yields of the corresponding 4-methylbenzamides (Bz'NHR) were shown. [b] Reaction performed at 0.2 mmol scale. [c] Extra Ag_2CO_3 (1 eq) added. [d] Reaction performed at 100 °C. [e] Amine **1** (3 eq) and AgTFA (3 eq) added; The absolute steoreochemistry was not assigned. [f] Enantiospecificity (es) was determined by HPLC with a chiral stationary phase. [g] Enantiomeric ratio (er) was not determined. [h] Reaction performed at 0.4 mmol scale and reaction time 48 h; The *syn*-configuration was determined by ^1H NMR analysis. N.D. = not detected.

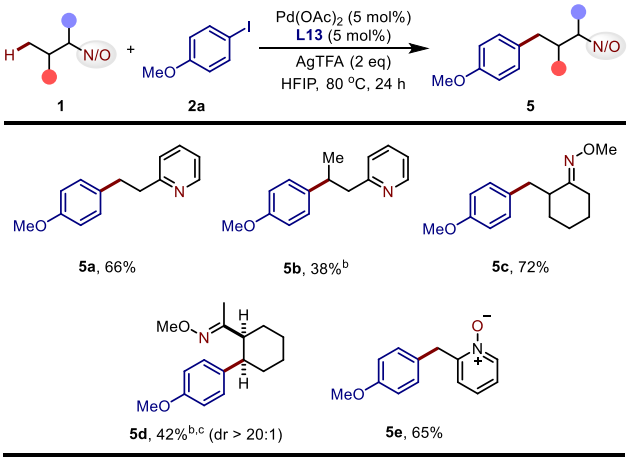
Subsequently, we focused on developing the asymmetrical variant of this γ-C−H arylation reaction utilizing chiral SOHP ligands. After extensive condition optimization, we are pleased to report that the resolution of (±)-**1f** and (±)-**1g** resulted in reasonable yields with good enantioselectivity and diastereoselectivity (Scheme 1), even though most of substrates exhibited insufficient outcomes with moderate enantiomeric ratio (er) (See Supporting Information, Section 6.3). For resolution of (±)-**1f**, the arylation products and recycled **1f**-Bz' were afforded with acceptable enantiomeric ratio (75:25 to 94:6), which gave the calculated *s*-factors ranging from 5.4 to 25.7. As for resolution of (±)-**1g**, one of the four stereoisomers was converted to different arylation products with good yields and selectivity.



Scheme 1. Resolution of racemic amides. [a] Reaction conditions: (±)-**1f** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (0.01 mmol), (*R*)-**L13** (0.01 mmol), AgTFA (0.4 mmol), Ag_2CO_3 (0.2 mmol), HFIP (2 mL), 100 °C, 24 h [b] Isolated yields of the corresponding 4-methylbenzamides (Bz'NHR) were shown. [c] Enantiomeric ratio (er) were determined by HPLC with a chiral stationary phase; The absolute steoreochemistry was not assigned. [d] $C = ee_s/(ee_s+ee_p)$, $s = \ln[(1-C)(1-ee_s)]/\ln[(1-C)(1+ee_s)]$. [e] Reaction conditions: (±)-**1g** (1.0 mmol), **2** (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), (*R*)-**L13** (0.01 mmol), AgTFA (0.8 mmol), HFIP (2 mL), 80 °C, 24 h. [f] Isolated yields of the corresponding 4-chlorobenzamides (Bz''NHR) were shown. [g] Diastereomeric ratios (dr) were determined by ^1H NMR analysis.

Moreover, during substrate scope studies, we serendipitously discovered that this catalytic system not only facilitates the activation of C(sp^3)-H bonds in amines, but also in pyridine (**5a, 5b**), oxime ether (**5c, 5d**), and pyridine-*N*-oxide (**5e**) substrates (Table 3). Worth mentioning, unlike the performance in amine-directed reactions, pyridine and oxime ether could direct acyclic methylene C-H activation/arylation with moderate yields (**5b, 5d**). These results indicated that the Pd(II)/SOHP catalytic system exhibits immense potential in C(sp^3)−H functionalization of various substrates.

Table 3. Extended substrate scope of pyridine, oxime ether, and pyridine-*N*-oxide.[a]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.1 mmol), $Pd(OAc)_2$ (0.005 mmol), **L13** (0.005 mmol), AgTFA (0.2 mmol), HFIP (1 mL), 80 °C, 24 h, isolated yield, 0.1 mmol scale. [b] Reaction performed at 0.2 mmol scale. [c] Diastereomeric ratio (dr) and *syn*-configuration were determined by ^{1}H NMR analysis.

In summary, we have developed a Pd(II)/SOHP-catalyzed γ-C(sp^3)−H arylation reaction targeting primary aliphatic amines. A wide range of amines and aryl iodides were tolerated and various γ-arylamines were constructed, in particular, amino acid ester and aminol silyl ether substrates were compatible with good chiral retention. The asymmetrical variant of this γ-C−H arylation reaction has also been achieved for specific amines. In addition, this catalytic system enabled C(sp^3)−H arylation of pyridine, oxime ether, and pyridine-*N*-oxide. The present work demonstrated the exceptional practicality and enormous potential of SOHP ligands in catalytic C(sp^3)−H bond functionalization over a broad range of substrates.

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Keywords

primary aliphatic amines; amino acid ester; palladium catalysis; C(sp^3)-H functionalization; ligand design

References

[1] For selected reviews, see: a) T. K. Allred, F. Manoni, P. G. Harran, *Chem. Rev.* **2017**, *117*, 11994-12051; b) P. Das, M. D. Delost, M. H. Qureshi, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2019**, *62*, 4265-4311.

[2] For selected reviews, see: a) L. Guillemard, N. Kaplaneris, L. Ackermann, M. J. Johansson, *Nat. Rev. Chem.* **2021**, *5*, 522-545; b) N. Y. S. Lam, K. Wu, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2021**, *60*, 15767-15790; c) G. Prakash, N. Paul, G. A. Oliver, D. B. Werz, D. Maiti, *Chem. Soc. Rev.* **2022**, *51*, 3123-3163.

[3] For selected reviews, see: a) C. He, W. G. Whitehurst, M. J. Gaunt, *Chem* **2019**, *5*, 1031-1058; b) A. Trowbridge, S. M. Walton, M. J. Gaunt, *Chem. Rev.* **2020**, *120*, 2613-2692; c) S. Saha, J. Das, S. A. Al-Thabaiti, S. M. Albukhari, Q. A. Alsulami, D. Maiti, *Catal. Sci. Technol.* **2023**, *13*, 11-27.

[4] For representative examples, see: a) D.-H. Wang, X.-S. Hao, D.-F. Wu, J.-Q. Yu, *Org. Lett.* **2006**, *8*, 3387-3390; b) P. Jain, P. Verma, G. Xia, J.-Q. Yu, *Nat. Chem.* **2017**, *9*, 140-144.

[5] Z. Huang, C. Wang, G. Dong, *Angew. Chem. Int. Ed.* **2016**, *55*, 5299-5303.

[6] For representative examples, see: a) V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154-13155; b) K. S. L. Chan, M. Wasa, L. Chu, B. N. Laforteza, M. Miura, J.-Q. Yu, *Nat. Chem.* **2014**, *6*, 146-150.

[7] For representative examples, see: a) E. T. Nadres, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 7-10; b) J.-W. Xu, Z.-Z. Zhang, W.-H. Rao, B.-F. Shi, *J. Am. Chem. Soc.* **2016**, *138*, 10750-10753.

[8] For other representative examples, see: a) G. He, G. Chen, *Angew. Chem. Int. Ed.* **2011**, *50*, 5192-5196; b) M. Fan, D. Ma, *Angew. Chem. Int. Ed.* **2013**, *52*, 12152-12155; c) N. Rodríguez, J. A. Romero-Revilla, M. Á. Fernández-Ibáñez, J. C. Carretero, *Chem. Sci.* **2013**, *4*, 175-179; d) J. J. Topczewski, P. J. Cabrera, N. I. Saper, M. S. Sanford, *Nature* **2016**, *531*, 220-224.

[9] For representative examples, see: a) Y. Wu, Y.-Q. Chen, T. Liu, M. D. Eastgate, J.-Q. Yu, *J. Am. Chem. Soc.* **2016**, *138*, 14554-14557; b) Y. Xu, M. C. Young, C. Wang, D. M. Magness, G. Dong, *Angew. Chem. Int. Ed.* **2016**, *55*, 9084-9087; c) Y. Liu, H. Ge, *Nat. Chem.* **2017**, *9*, 26-32; d) M. Kapoor, D. Liu, M. C. Young, *J. Am. Chem. Soc.* **2018**, *140*, 6818-6822; e) A. Yada, W. Liao, Y. Sato, M. Murakami, *Angew. Chem. Int. Ed.* **2017**, *56*, 1073-1076; f) H. Lin, C. Wang, T. D. Bannister, T. M. Kamenecka, *Chem. Eur. J.* **2018**, *24*, 9535-9541; g) S. St John-Campbell, A. K. Ou, J. A. Bull, *Chem. Eur. J.* **2018**, *24*, 17838-17843.

[10] Y.-Q. Chen, Z. Wang, Y. Wu, S. R. Wisniewski, J. X. Qiao, W. R. Ewing, M. D. Eastgate, J.-Q. Yu, *J. Am. Chem. Soc.* **2018**, *140*, 17884-17894.

[11] a) A. D. Ryabov, *Chem. Rev.* **1990**, *90*, 403-424; b) J. Vicente, I. Saura-Llamas, M. G. Palin, P. G. Jones, M. C. Ramírez de Arellano, *Organometallics* **1997**, *16*, 826-833; c) H. Font, M. Font-Bardia, K. Gómez, G. González, J. Granell, I. Macho, M. Martínez, *Dalton Trans.* **2014**, *43*, 13525-13536.

[12] a) J.-R. Wang, Y. Fu, B.-B. Zhang, X. Cui, L. Liu, Q.-X. Guo, *Tetrahedron Lett.* **2006**, *47*, 8293-8297; b) B. L. Ryland, S. S. Stahl, *Angew. Chem. Int. Ed.* **2014**, *53*, 8824-8838.

[13] a) J. P. Wolfe, S. Wagaw, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 7215-7216; b) M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1996**, *118*, 7217-7218.

[14] a) A. McNally, B. Haffemayer, B. S. L. Collins, M. J. Gaunt, *Nature* **2014**, *510*, 129-133; b) J. Calleja, D. Pla, T. W. Gorman, V. Domingo, B. Haffemayer, M. J. Gaunt, *Nat. Chem.* **2015**, *7*, 1009-1016.

[15] J. Rodrigalvarez, M. Nappi, H. Azuma, N. J. Flodén, M. E. Burns, M. J. Gaunt, *Nat. Chem.* **2020**, *12*, 76-81.

[16] K. Chen, D. Wang, Z.-W. Li, Z. Liu, F. Pan, Y.-F. Zhang, Z.-J. Shi, *Org. Chem. Front.* **2017**, *4*, 2097-2101.

[17] H. Lin, X. Pan, A. L. Barsamian, T. M. Kamenecka, T. D. Bannister, *ACS Catal.* **2019**, *9*, 4887-4891.

[18] F. Yuan, Z.-L. Hou, P. K. Pramanick, B. Yao, *Org. Lett.* **2019**, *21*, 9381-9385.

[19] Z. Zhuang, J.-Q. Yu, *J. Am. Chem. Soc.* **2020**, *142*, 12015-12019.

[20] Y. Ding, S. Fan, X. Chen, Y. Gao, G. Li, *ChemRxiv* **2019**, DOI: 10.26434/chemrxiv.11301017.v1.

[21] For representative native alkyl amino-directed C(sp^2)-H functionalization reactions, see: a) A. Lazareva, O. Daugulis,

Org. Lett. **2006**, *8*, 5211-5213; b) A. Rodríguez, J. Albert, X. Ariza, J. Garcia, J. Granell, J. Farràs, A. La Mela, E. Nicolás, *J. Org. Chem.* **2014**, *79*, 9578-9585; c) Y. Feng, J. Wang, J. Yang, F. Chen, Z. Zhang, C. Ke, J. Lin, H. Lin, *Org. Lett.* **2023**, *25*, 1348-1352.

[22] Y.-J. Wang, C.-H. Yuan, D.-Z. Chu, L. Jiao, *Chem. Sci.* **2020**, *11*, 11042-11054.

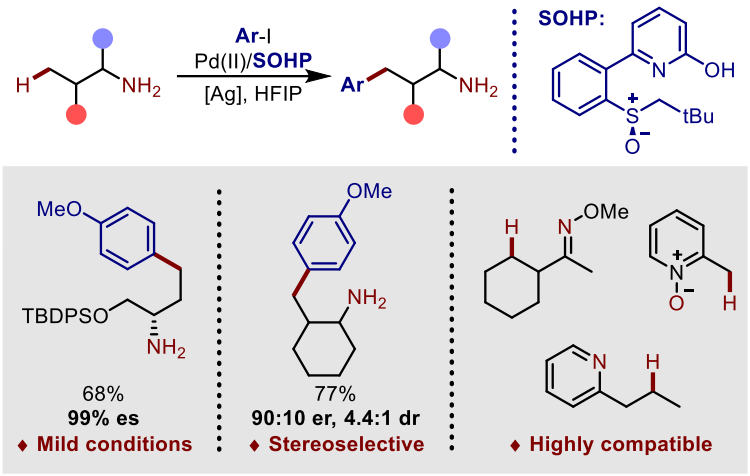
[23] C.-H. Yuan, X.-X. Wang, L. Jiao, *Angew. Chem. Int. Ed.* **2023**, *62*, e202300854.

[24] P. K. Pramanick, Z. Zhou, Z. Hou, Y. Ao, B. Yao, *Chin. Chem. Lett.* **2020**, *31*, 1327-1331.

[25] a) B.-F. Shi, N. Maugel, Y.-H. Zhang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2008**, *47*, 4882-4886; b) Q. Shao, K. Wu, Z. Zhuang, S. Qian, J.-Q. Yu, *Acc. Chem. Res.* **2020**, *53*, 833-851.

[26] a) P. Wang, M. E. Farmer, X. Huo, P. Jain, P.-X. Shen, M. Ishoey, J. E. Bradner, S. R. Wisniewski, M. D. Eastgate, J.-Q. Yu, *J. Am. Chem. Soc.* **2016**, *138*, 9269-9276; b) P. Wang, P. Verma, G. Xia, J. Shi, J. X. Qiao, S. Tao, P. T. W. Cheng, M. A. Poss, M. E. Farmer, K.-S. Yeung, J.-Q. Yu, *Nature* **2017**, *551*, 489-493; c) R.-Y. Zhu, Z.-Q. Li, H. S. Park, C. H. Senanayake, J.-Q. Yu, *J. Am. Chem. Soc.* **2018**, *140*, 3564-3568.

Graphical Abstract



We demonstrated Pd(II)/SOHP catalytic system serve as an ideal solution to native primary amine-directed γ-C(sp^3)-H arylation. (a) Under mild conditions, amino acid ester and aminol silyl ether could afford corresponding products with good chiral retention; (b) Stereoselective version of this γ-C-H functionalization was achieved on specific substrates; (3) Pyridine, oxime ether, and pyridine-N-oxide substrates were compatible.