Ligand-Enabled Pd(II)-Catalyzed Enantioselective *β*-C(sp^3)-H Arylation of Aliphatic Tertiary Amides

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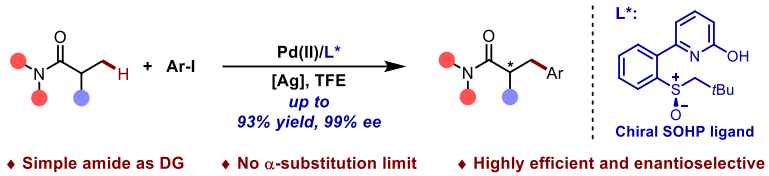
Keywords: Pd catalysis; Ligand design; Aliphatic tertiary amides; Asymmetric C(sp^3)-H activation



Abstract: Amide is one of the most widespread functional groups in organic and bioorganic chemistry, and it would be valuable to achieve stereoselective C(sp^3)-H functionalization in amide molecules. Pd(II) catalysis has been prevalently used in the C-H activation chemistry in the past decades, however, due to the weakly-coordinating feature of simple amides, it is challenging to achieve their direct C(sp^3)-H functionalization with enantiocontrol by Pd(II) catalysis. Our group has developed sulfoxide-2-hydroxypridine (SOHP) ligands, which exhibited remarkable activity in Pd-catalyzed C(sp^2)-H activation. In this work, we demonstrate that chiral SOHP ligands served as an ideal solution to enantioselective C(sp^3)-H activation in simple amides. Herein, we report an efficient asymmetric Pd(II)/SOHP-catalyzed *β*-C(sp^3)-H arylation of aliphatic tertiary amides, in which the SOHP ligand plays a key role in the stereoselective C-H deprotonation-metalation step.

Introduction

Direct C-H bond functionalization is an ideal method for the construction of multifunctional molecules and late-stage modification of complex structures.[1] In particular, C(sp^3)-H bonds exist prevalently in organic compounds, and it has been a long-standing goal of chemists to achieve selective C(sp^3)-H functionalization in various types of molecules.[2]

Amide is a fundamental structural motif in organic chemistry that could serve as an appropriate directing group for C-H functionalization when combined with palladium catalysis.[2c, 3] During the past decades, a series of Pd-catalyzed amide-directed C(sp^3)-H functionalization reactions have been developed. Bidentate amide groups were first employed to facilitate Pd-catalyzed C-H functionalization of the amide aliphatic chain through the formation of a fused palladacycle (Figure 1a), and representative functionalization reactions such as arylation,[4] alkylation,[4b, 5] amination,[6] and alkoxylation[7] have been achieved by the groups of Daugulis, Shi, Chen, and many others.[8]

It is more challenging to utilize monodentate amide directing groups in Pd-catalyzed C-H activation due to the lack of chelation assistance. To this end, monodentate amide directing groups with various structural modifications have been employed (Figure 1b). For instances, Yu and co-workers used *N*-methoxyl amides,[9] *N*-perfluroaryl amides,[9c, 10] and *N*-tosyl amides[11] in the Pd-catalyzed aliphatic C-H functionalization as substrates and achieved the first enantioselective case in this chemistry;[10b] the Yu[12] and Gong[13] groups independently developed enantioselective C-H arylation of thioamides at the *α*-position of the *N*-aliphatic substituent; more recently, Gong and coworkers achieved enantioselective

β-C-H arylation of thioamides.[14] On the other hand, simple amide without special structural motif as the directing group in C-H functionalization would be more demanding. In this line, the groups of Lu and Xu reported amide-directed acyloxylation,[15] mesylation,[16] and arylation[17] employing primary, secondary, and tertiary aliphatic amides as substrates. However, in these reactions enantiocontrol was not achieved, and to date a suitable system for Pd-catalyzed simple amide-directed asymmetric C(sp^3)-H functionalization remains elusive.[18]

In our previous work, we have developed a series of sulfoxide-2-hydroxypyridine (SOHP) ligands for Pd-catalyzed C-H alkenylation of indoles, which exhibited remarkable activity in regioselective C(sp^2)-H activation.[19] In this work, we found that the SOHP ligands were also capable of promoting C(sp^3)-H activation of simple amide substrates with excellent enantiocontrol, and herein we report a Pd(II)/SOHP-catalyzed enantioselective β-C-H arylation of aliphatic tertiary amides (Figure 1c). The present work provides a valuable approach to chiral aliphatic amide products, and showcases the synthetic potential of the SOHP ligands in Pd(II) catalysis.

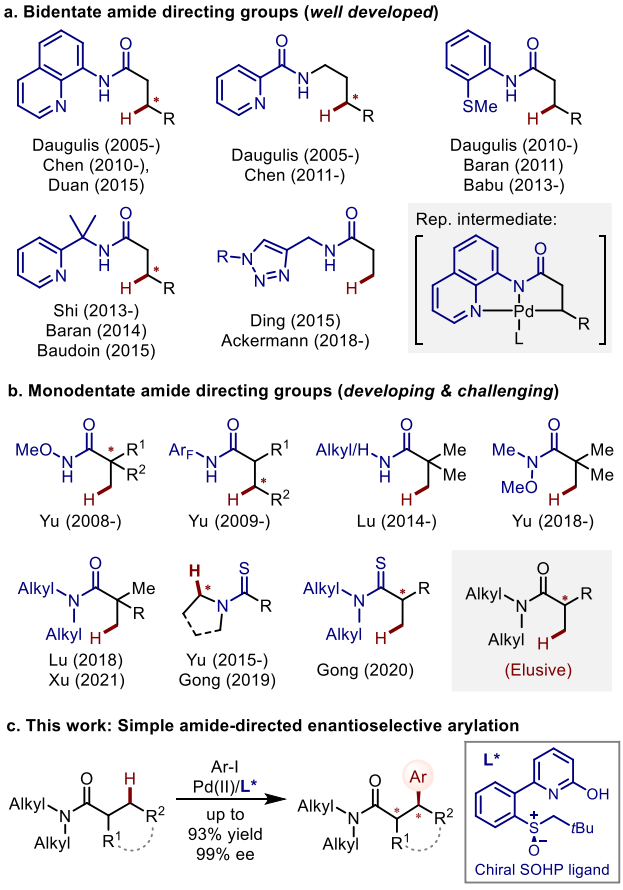


Figure 1. Pd(II)-Catalyzed C(sp^3)–H Functionalization of Amides

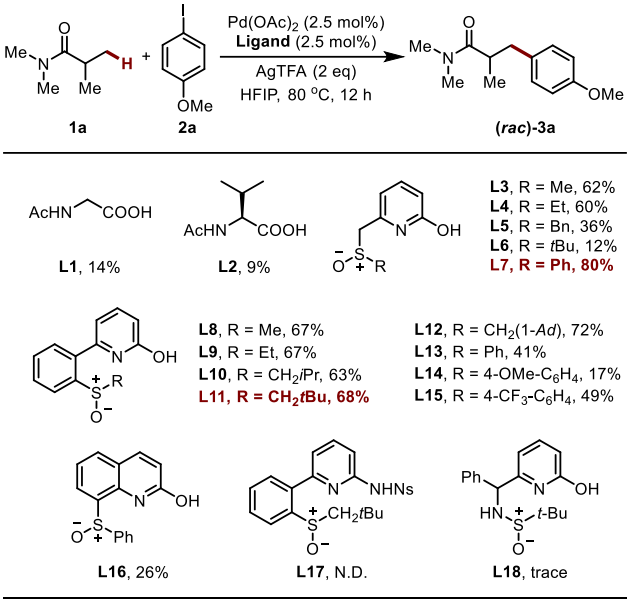
Results and Discussion

We commenced our study with the Pd-catalyzed β-C-H arylation of *N,N*-dimethylisobutyramide (**1a**) with 1-iodo-4-methoxybenzene (**2a**) as a model reaction, in which differentiation of the two methyl groups will lead to desymmetrization and create a chiral center at the α-position of the amide. Similar reactions have been reported to occur at 120 °C free of ligand,[17] and we realized that the key to successful enantiocontrol is to identify appropriate ligands that exhibit significant ligand acceleration.[2d] It was found that, without a ligand, the model reaction afforded 11% yield of product **3a** at 80 °C, and two *N*-monoprotected amino acid (MPAA) ligands Ac-Gly-OH (**L1**) and Ac-Val-OH (**L2**), which were established to be efficient ligands for Pd-catalyzed C–H functionalization,[20] did not show obvious promotive effect

(Table 1). Given that SOHP ligands could significantly accelerate the C(sp^2)-H activation in Pd catalysis, we evaluated the performance of our SOHP ligands in C(sp^3)-H functionalization.

To our delight, most of the SOHP ligands (in racemic form) showed remarkable acceleration effect on the model reaction, providing moderate to good yields of the arylation product. For methylene-tethered ligands **L3-L7**, the aryl-substituted ligand **L7** exhibited superior reactivity to alkyl-substituted ligands **L3-L6**, in which bulkier alkyl groups resulted in lower activity. For benzene-tethered ligands **L8-L15**, alkyl-substituted ligands **L8-L12** performed better than aryl-substituted ligands **L13-L15**, where bulkier alkyl groups and electron-deficient aryl groups in the SOHP ligands led to enhanced activity. The rigid sulfoxide-2-hydroxyquinoline ligand **L16** was found to be less active. Replacing the 2-hydroxypyridine unit with a 2-(*N*-sulfonylamino)pyridine group resulted in the loss of catalytic activity (**L17**), and the sulfinamide-2-hydroxypyridine ligand **L18** also showed no reactivity. This indicated that both sulfoxide and 2-hydroxypyridine units are essential, and an alkyl-aryl sulfoxide is superior to a dialkyl or a diaryl sulfoxide in the SOHP ligand.

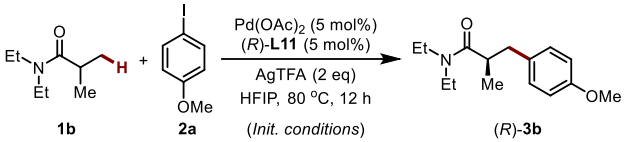
Table 1. Ligand Screen for C(sp^3)−H Arylation of Amide **1a**[a]



[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.2mmol), $Pd(OAc)_2$ (0.005 mmol), ligand (0.005 mmol), AgTFA (0.4 mmol), HFIP (2 mL), 80 °C, 12 h. All sulfoxide ligands used were racemic. Yields were determined by ^1H NMR analysis. Abbreviations: AgTFA = silver trifluoroacetate; HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

With the effective ligands **L7** and **L11** in hand, we sought to achieve enantiocontrol in the model reaction by employing enantioenriched SOHP ligands. The modified Kagan's conditions[21] were utilized to synthesize enantioenriched **L7** (96% ee) and **L11** (>99% ee) from the corresponding thioethers. We found that, for the model reaction between amide **1b** and aryl iodide **2a** (Table 2), **L11** gave a good yield and enantioselectivity (entry 1), while **L7** led to unsatisfactory yield and enantiocontrol (entry 2). Decreased catalyst loading (2.5 mol%) resulted in a similar reactivity and enantioselectivity (entry 3). TFE as the solvent maintained the reactivity and slightly enhanced the enantioselectivity (entry 4). $Pd(MeCN)_2Cl_2$ and $Pd(TFA)_2$ as the palladium source were also compatible with the reaction (entries 5-6). Utilizing amide **1b** as the limiting reagent afforded a similar reaction outcome (entry 7). Therefore, we identified entries 5 and 7 as the optimal reaction conditions, which were used in subsequent substrate scope studies.

Table 2. Condition Optimization for Enantioselective C(sp^3)−H Arylation of Amide **1b**[a]



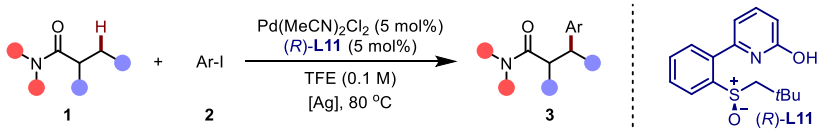
1b **2a** (*R*)-**3b**

Entry	Variation from *init. conditions*	Yield[b]	ee[c]
1	None	87%	91%
2	**L7*** (96% ee)	54%	25%
3	2.5 mol% $Pd(OAc)_2$ & (*R*)-**L11**	83%	89%
4	TFE as the solvent	85%	93%
5	$Pd(MeCN)_2Cl_2$, TFE	86%	94%
6	$Pd(TFA)_2$, TFE	84%	93%
7[d]	**1b**:**2a** = 1:3, $Pd(MeCN)_2Cl_2$, TFE	84%	96%

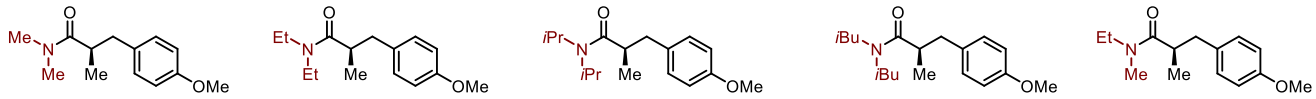
[a] Initial reaction conditions: **1b** (0.2 mmol), **2a** (0.1 mmol), $Pd(OAc)_2$ (0.005 mmol), ligand (0.005 mmol), AgTFA (0.2 mmol), HFIP (1 mL), 80 ℃, 12 h. [b] Yields were determined by ^{1}H NMR analysis. [c] Enantiomeric excesses (ee) were determined by HPLC with a chiral stationary phase. [d] 0.1 mmol of **1b** and 0.3 mmol of **2a** were used. Abbreviation: TFE = 2,2,2-trifluoroethanol.

The substrate scope of this amide C-H arylation reaction was examined under the optimal conditions (Table 3), and the effect of the amine moiety was first explored. Various *N*-alky substituents were found to be compatible, and a bulkier amine moiety afforded slightly better yields and enantioselectivities (**3a-3e**). Amides of cyclic secondary amine also afforded satisfactory reaction outcomes (**3f, 3g**). However, primary (**3ae**) and secondary (**3af**) amide substrates were found incompatible, which resulted in poor reactivity and enantioselectivity. Then the scope of aliphatic moiety was investigated. For methyl C(sp^3)-H arylation, we were delighted to find out that the reaction proceeded well regardless of the *α*-substitution pattern of the amide substrate. Besides isobutyramides, the *β*-arylation products from propionamide (**3h**) and pivalamide (**3i**) were obtained in good yields, albeit enantiodifferentiation of two methyl groups in the α,α-dimethylbutyramide substrate remained difficult (**3j**). This feature is different from some previous catalytic systems in which only *α*- fully substituted amides exhibited good reactivity.[15-17] For methylene C(sp^3)-H arylation, however, the amide substrates bearing either an acyclic (**3ag**) or a 5-/6-membered cyclic (**3ah, 3ai**) aliphatic moiety showed no reactivity, similar to the reported C(sp^3)-H functionalization reactions of simple amides.[15-17] To our delight, cyclopropanecarboxamide and cyclobutanecarboxamide served as suitable substrates, and the methylene C(sp^3)-H arylation proceeded smoothly with good diastereoselectivity and enantioselectivity (**3k-3o**). The *cis*-configuration of these products were confirmed by XRD analysis of products **3k** and **3n**, which is consistent with the directing effect of the amide group. Finally, the scope of aryl iodide substrate was examined. Both electron-rich and electron-deficient aryl iodides gave high enantioselectivities, though slightly lower yields were observed for electron-deficient ones (**3u, 3v, 3x**). An *ortho*-substituted aryl iodide afforded the desired product with a good enantioselectivity but diminished yield (**3aa**).

Table 3. Substrate Scope[a]

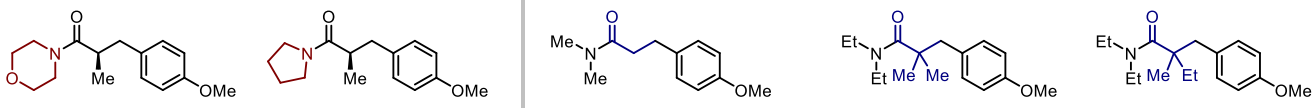


Scope of amine moiety

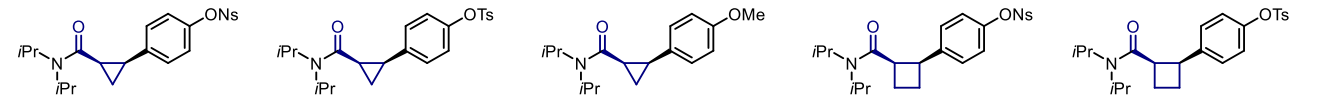


A **3a**, 79%, 92% ee | A **3b**, 86%, 96% ee | A **3c**, 83%, 96% ee | A **3d**, 82%, 95% ee | A **3e**, 80%, 93% ee

Scope of aliphatic moiety

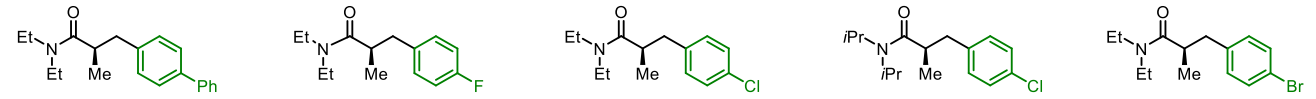


A **3f**, 72%, 90% ee | A **3g**, 68%, 93% ee | A **3h**, 59%[b] | A **3i**, 92%[b] | A **3j**, 96%, 22% ee

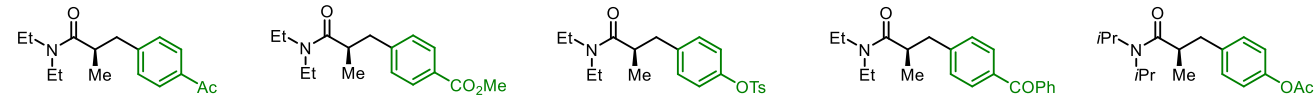


B **3k**, 77%, 96% ee, >19:1 d.r | B **3l**, 64%, 94% ee, >19:1 d.r. | B **3m**, 67%, 95% ee, 12:1 d.r. | A **3n**, 40%, 85% ee, 19:1 d.r.[c] | A **3o**, 61%, 85% ee, >19:1 d.r.[c]

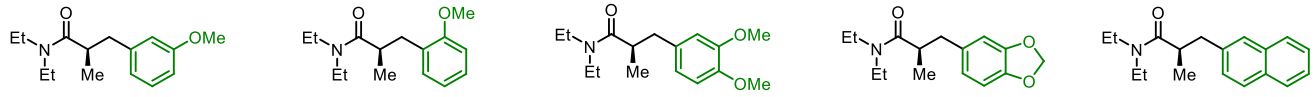
Scope of aryl iodide



A **3p**, 72%, 92% ee | C **3q**, 75%, 94% ee | C **3r**, 70%, 95% ee | C **3s**, 60%, 99% ee | C **3t** 65%, 95% ee

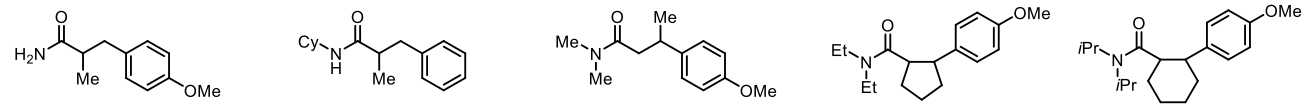


C **3u**, 42%, 93% ee[c] | C **3v**, 65%, 95% ee | C **3w**, 70%, 96% ee | C **3x**, 66%, 96% ee[d] | C **3y**, 93%, 99% ee



C **3z**, 56%, 93% ee | C **3aa**, 32%, 94% ee | A **3ab**, 84%, 95% ee[e] | A **3ac**, 80%, 93% ee | C **3ad**, 60%, 82% ee

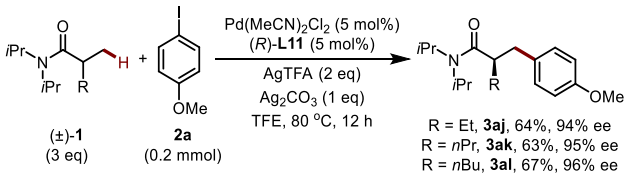
Selected unsuccessful substrates:



A **3ae**, 11%[e,f] | C **3af**, 25%, 46% ee[e,f] | A **3ag**, N.D. | A **3ah**, N.D. | A **3ai**, N.D.

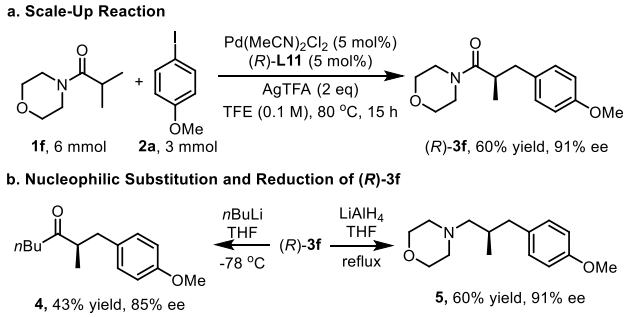
[a] Conditions A: amide **1** (0.4 mmol), iodoarene **2** (0.2 mmol), $Pd(MeCN)_2Cl_2$ (0.01 mmol), (*R*)-**L11** (0.01 mmol), AgTFA (0.4 mmol), TFE (2 mL), 80 °C, 12 h; Conditions B: amide **1** (0.6 mmol), iodoarene **2** (0.2 mmol), $Pd(MeCN)_2Cl_2$ (0.01 mmol), (*R*)-**L11** (0.01 mmol), AgTFA (0.4 mmol), Ag_2CO_3 (0.2 mmol), TFE (2 mL), 80 °C, 12 h; Conditions C: amide **1** (0.2 mmol), iodoarene **2** (0.6 mmol), $Pd(MeCN)_2Cl_2$ (0.01 mmol), (*R*)-**L11** (0.01 mmol), AgTFA (0.6 mmol), TFE (2 mL), 80 °C, 18 h; Yields of isolated products were reported, diastereomeric ratios (dr) were determined by ^1H NMR analysis. [b] Reaction time 18 h. [c] Reaction time 24 h. [d] Reaction time 36 h. [e] Reaction performed at 0.1 mmol scale. [f] Yield was determined by ^1H NMR analysis. N.D. = not detected.

Besides desymmetrization, the kinetic resolution of racemic aliphatic amides bearing an α-methyl substituted stereocenter was carried out. Since we concentrated on obtaining C-H arylation products in good yields and enantioselectivities, excess racemic amide substrates were employed and aryl iodide **2a** was used as the limiting reagent (Scheme 1). It was found that the enantioenriched arylation products were afforded with good yields and high enantioselectivities (**3aj-3al**).



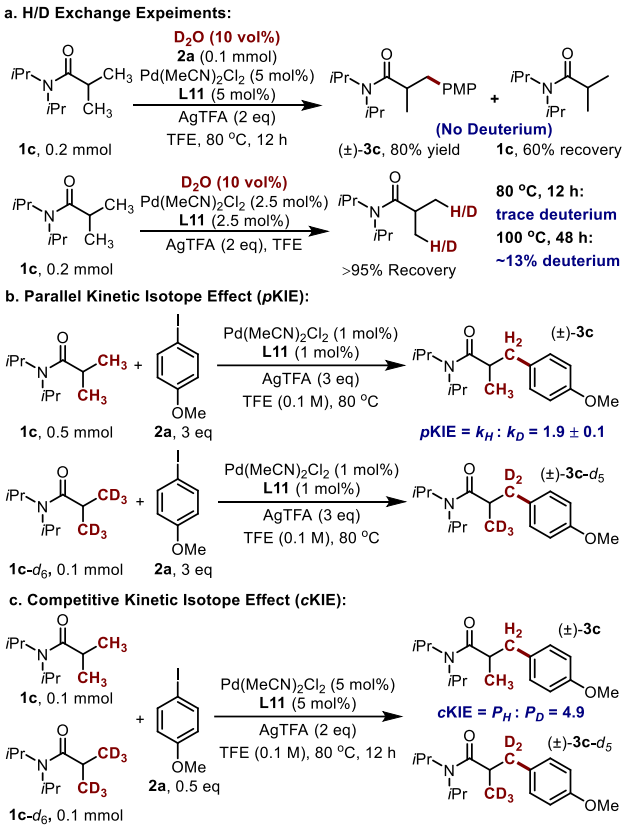
Scheme 1. Kinetic Resolution of Racemic Amides

To demonstrate the synthetic utility of this protocol, the arylation of amide **1f** with **2a** was conducted at 3 mmol scale, and the reaction proceeded smoothly without loss of enantioselectivity (Scheme 2a). Derivatization of the β-arylation product **3f** was achieved to produce enantioenriched molecules bearing other functional groups (Scheme 2b). (*R*)-**3f** (91% ee) was readily converted into amine **5** with by treatment with $LiAlH_4$ without loss of enantiopurity; the nucleophilic substitution of (*R*)-**3f** by *n*-BuLi provided ketone **4** with 85% ee, in which the decreased enantiopurity of ketone **4** may be caused by tautomerization under strongly basic conditions.



Scheme 2. Scale-Up Reaction and Product Derivatization

Preliminary mechanistic study was performed to understand the mechanism of the present arylation reaction. In order to verify the reversibility of C-H activation, H/D exchange experiments were conducted (Scheme 3a). In the reaction between amide **1b** and aryl iodide **2a** in the presence of D_2O (10 vol%), no appreciable deuterium incorporation was observed on either the product **3c** or the recovered amide **1c**, while minor H/D exchange was observed in the absence of aryl iodide **2a** under elevated temperature. This indicated that, the C-H activation step was irreversible in the arylation reaction, but it could become partially reversible when subsequent functionalization pathway is blocked. Next, kinetic isotope effect (KIE) measurements were carried out to identify the rate-limiting step. Initial rate measurements for the parallel reactions using **1c** and **1c**-d_6 gave $k_H/k_D = 1.9 \pm 0.1$ (Scheme 3b), and a competitive reaction employing equal-molar mixture of **1c** and **1c**-d_6 gave $P_H/P_D = 4.9$ (Scheme 3c), suggesting that the C-H activation step might be involved in the rate-limiting step, but it was not clear-cut rate-limiting. Nevertheless, it could be concluded that the irreversible C-H activation step dictates the enantioselectivity of the reaction.



Scheme 3. Mechanistic Studies

To gain some insight into the stereocontrol of the C-H activation step, we performed DFT calculations based on a catalytic model involving monomeric Pd(II)/(*R*)-**L11** complex as the catalyst, which was supported by the non-linear effect (NLE) of the catalytic system (for details, see the Supporting Information, Section 7.3). The diastereomeric C-H activation transition states were modeled using **1a** as the substrate (Figure 2). The calculation showed that **TS1_*R***, which leads to the (*R*)-product, is 3.8 kcal/mol lower in Gibbs free energy than **TS2_*S***, which yields the (*S*)-product. This was in agreement with the experimental results that (*R*)-products were formed predominately. The observed preference could be rationalized by steric interactions in these transition states. It was found that **TS1_*R*** suffered less torsional strain than **TS2_*S***, as witnessed by a staggered conformation through the C(α)-carbonyl bond of **TS1_*R*** ($\alpha1 = 29°$, $\alpha2 = 85°$) and an unfavorable near-eclipsed conformation through the same bond in **TS2_*S*** ($\alpha3 = 4°$, $\alpha4 = 62°$). The non-covalent interaction (NCI) analysis[22] also disclosed key steric interactions involving *N*-alkyl groups crucial for stereocontrol (for details, see the Supporting Information, Section 7.5). Substantial steric repulsion was observed in **TS2_*S*** between the *N*-substituent and α-methyl group of **1a** as well as the *tert*-butyl group of the ligand, while these interactions were much less profound in **TS1_*R***, which accounts for not only the preference for (*R*)-products, but also the observed effect of the *N*-substituents on the stereoselectivity.

Conclusion

In summary, we have developed a palladium-catalyzed highly efficient and enantioselective β-C(sp^3)-H arylation of aliphatic tertiary amides using a chiral SOHP ligand developed by our group. A broad range of amides and aryl iodides were tolerated, and various amides containing a carbonyl α-stereocenter were constructed with high stereoselectivity. Cyclopropanecarboxamides and cyclobutanecarboxamides could also be arylated at the β-position with high diastereoselectivity and enantioselectivity. The mechanistic studies identified ligand-accelerated C-H activation as the key step that determines the stereoselectivity and revealed the role of the SOHP ligand in stereocontrol. The present work

showcased the utility of chiral sulfoxide-2-hydroxylpyridine ligands in catalytic asymmetric C(sp^3)-H bond functionalization.

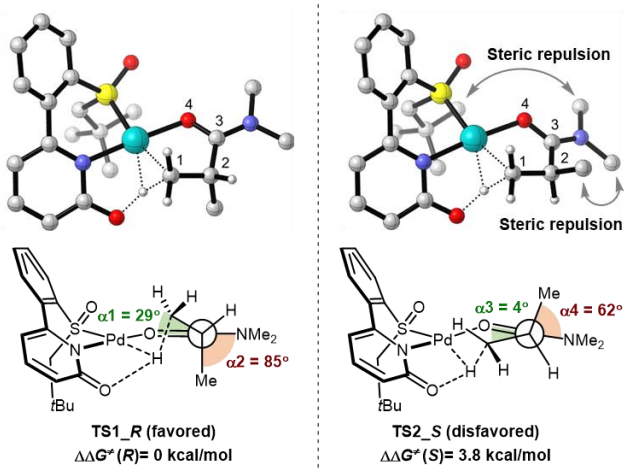


Figure 2. Stereochemical model.

Associated Content

Detailed experimental procedure, characterization data, XRD structures, details for DFT computation, and NMR spectra for the synthesized compound.

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Notes

The authors declare no competing financial interest.

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