EurJOC
European Journal of Organic Chemistry

Full Papers
doi.org/10.1002/ejoc.202001428

Chemistry Europe
European Chemical Societies Publishing

Special Collection

Pd-Catalyzed Regio- and Stereoselective sp^3 C–H Arylation of Primary Aliphatic Amines: Mechanistic Studies and Synthetic Applications

Hyeonbin Ha,[a] Ho Jeong Choi[+],[a] Hahyoun Park[+],[b] Yunyeong Gwon[+],[b] Jiin Lee[+],[b] Jaesung Kwak,*[c] Min Kim,*[a] and Byunghyuck Jung*[b]

The Pd-catalyzed γ-position sp^3–C–H arylation of primary amines bearing an aliphatic chain or cycloalkyl substituent and related mechanistic studies are disclosed. 3-Bromo-2-hydroxybenzaldehyde plays a key role in γ-position sp^3–C–H arylation as a transient directing group (TDG) to assist the regio- and stereoselective C–H activation of a Pd catalyst, and the development of a tandem reaction to transform 1°-amines into γ-aryl-substituted ketones demonstrates synthetic utility. Density functional theory (DFT)-based calculations revealed the detailed reaction mechanism and the origins of the high selectivity (γ-position and *cis*-only). The X-ray crystal structure of the isolated endo-palladacycle intermediate supported the DFT results, and a kinetic isotope experiment confirmed the results of DFT calculations indicating that the C–H activation step via simultaneous palladation and deprotonation is rate-determining.

Introduction

C–H functionalizations through transition metal catalysis have been powerful tools in organic synthesis and have played a key role in the synthesis of complex molecules.[1,2] C–H functionalization of substrates often requires a proper functional group (FG) attached to the substrate for reactivity and regioselectivity,[3] but amino groups are challenging as directing groups (DGs) for the C–H activation. Their intrinsic nature as strong Lewis base leads to the formation of a solid link to a transition metal and catalyst deactivation,[4] and the oxidation of the C–N bond to a C=N bond is detrimental to the reaction efficiency.[5]

Gaunt and coworkers overcame these hurdles and were the first to report the free-amine-directed γ–C(sp^3)–H arylation of secondary alkylamines with 2-iodobenzoic acid derivatives acting as a carboxylate ligand.[6] After this report, Gaunt, Yao, Bannister, and Yu's independent works reported methods that did not require the use of transient directing groups (TDG) for the sp^3 C–H arylation of amines.[7–10] Nonetheless, most synthetic examples require an amine-protecting group that also plays the role of a DG.[11] However, the installation and removal of a DG decrease the efficiency and economy of the whole process.[12] Dong and Murakami reported C(sp^3)–H arylation to solve this issue via in situ generation of imines by treatment of free amines with a stoichiometric amount of 8-formylquinoline or an analog of salicylaldehyde.[13] Although the imine-based DG with external chelation functionality showed better catalytic performance than a free-amine DG, more than a stoichiometric amount of aldehyde reagent was necessary for efficient transformation.

In recent years, catalytic TDG-assisted C–H functionalizations have emerged, and γ–C(sp^3)–H arylation of amines via a TDG strategy was developed by Yu, Ge, Bull, Kamenecka, Young, and Liu's research group independently.[14–19] In particular, 2-hydroxynicotinaldehyde or 3-chloro-2-hydroxybenzaldehyde has an outstanding ability as a transient DG to conduct C–O and C–F bond formation as well as C–C bond formation at γ–C(sp^3) in primary amines.[20] From these synthetic protocols utilizing 3-chloro-2-hydroxybenzaldehyde, the roles of –CHO and –OH in the proposed mechanistic pathway were clearly understood as the imine generator and metal-coordination site, respectively. However, a theoretical study has not yet been fully explored with experimental supports. For γ–C(sp^3)–H arylation of aliphatic amine substrates via the TDG strategy, Dang and coworkers reported a density functional theory (DFT)-based computational study with glyoxylic acid as a TDG in 2019,[21] but there is no example of a mechanistic study on γ–C(sp^3)–H arylation of amines with a cycloalkyl substituent, which is expected to be a more complex system than an aliphatic chain. Herein, we report that our efforts towards the mechanistic understanding of the γ–C(sp^3)–H arylation of free cyclic and

[a] H. Ha, H. J. Choi,[+] Prof. Dr. M. Kim
Department of Chemistry, Chungbuk National University
Cheongju 28644, Republic of Korea
E-mail: minkim@chungbuk.ac.kr
https://sites.google.com/site/minkimchem/
[b] H. Park,[+] Y. Gwon,[+] J. Lee,[+] Prof. Dr. B. Jung
Department of Emerging Materials Science
Daegu Gyeongbuk Institute of Science and Technology (DGIST)
Daegu 42988, Republic of Korea
E-mail: byunghyuck.jung@dgist.ac.kr
https://sites.google.com/site/byunghyuckjung/
[c] Dr. J. Kwak
Infectious Diseases Therapeutic Research Center, Korea Research Institute of Chemical Technology (KRICT)
Daejeon 34114, Republic of Korea
E-mail: jkwak@krict.ac.kr
https://english.krict.re.kr/eng/RD03_01

[+] These authors contributed equally to this work.

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202001428

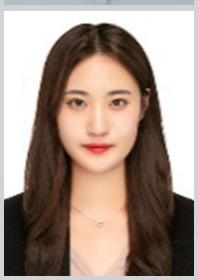
Part of the "YourJOC Talents" Special Collection.

acyclic amines with salicylic aldehyde-type TDGs through DFT-calculations, and their synthetic applications for the β-arylated ketones through tandem catalytic reactions of Pd and Ru. In addition, a kinetic isotope effect (KIE) study and X-ray crystallography with a palladacyclic intermediate support our mechanistic proposal along with DFT calculations, and dopamine derivatives could be prepared through direct arylation of amine. The selective sp^3 C–H arylation of primary aliphatic amines with TDG is reported based on experimental and computational approaches (Scheme 1).

Results and Discussion

Using cyclohexylamine (**1a**) and 4-iodomethylbenzoate (**2d**) as arylation partners, optimization of γ–C(sp^3)–H arylation was investigated. Based on a previous report that salicylaldehyde (**3b**) allowed the formation of the γ-arylated product (**4ad**) in 62% yield, analogs of salicylaldehyde (TDG **3c**-**3f**) were tested (Table 1). The sterically demanding *t*-butyl-substituted TDG (**3c**) could not provide the desired performance. However, 3-halo-2-hydroxybenzaldehydes (**3d**-**3f**) underwent γ–C(sp^3)–H arylation with **1a** to give an 89~91% yield. Although pyridine-functionalized 2-hydroxynicotinaldehyde (**3a**) resulted in the best yield

Hyeonbin Ha received his B.S. degree from the Department of Chemistry in Chungbuk National University in 2015. He obtained his M.S. degree from the same department in 2017 under the supervision of Prof. Min Kim. He is currently a PhD student in the same group and is interested in developing organic transformations with novel catalysis and functionalizing metal-organic frameworks (MOFs).



Ho Jeong Choi received her B.S. degree from the Department of Chemistry in Chungbuk National University in 2020. She is currently a graduate student (Master of Science course) in the research group of Prof. Min Kim, and she is interested in developing new catalytic reactions with various metal catalysis and functionalization of MOFs.

Hahyoun Park received her B.S. degree from Daegu Gyeongbuk Institute of Science & Technology (DGIST) in 2020. She enrolled in Korea Advanced Institute of Science & Technology (KAIST) as an integrated Master & Ph.D. student within the group of Prof. Hyunwoo Kim.

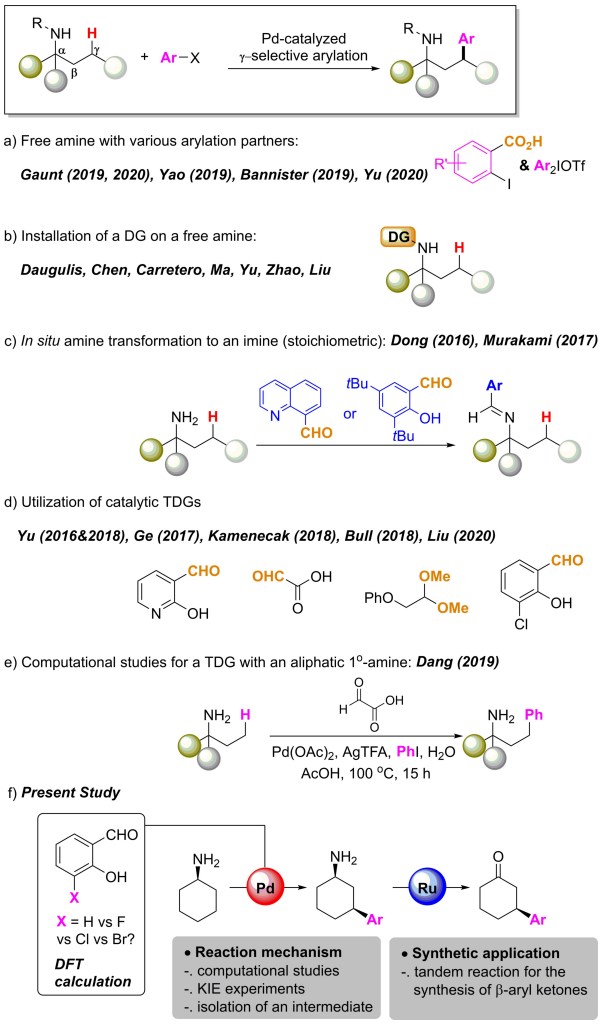
Yunyeong Gwon received her B.S. degree from DGIST in 2020. She joined the group of Prof. Sukbok Chang (at KAIST) with the research topic, transition metal catalysis for the development and application of C–H functionalization reaction.

Jiin Lee received her B.S. degree from DGIST in 2020. She enrolled in DGIST as an integrated Master & Ph.D. student in Prof. Sunggi Lee's group. Her research interest is catalyst development for C–H activation.

Jaesung Kwak obtained his Ph.D. degree in organic chemistry with Prof. Sukbok Chang at KAIST in 2014. After his postdoctoral research with Prof. Theodore A. Betley at Harvard University from 2015 to 2017, he became a senior researcher in Korea Research Institute of Chemical Technology (KRICT) in 2017. His research interests include homogeneous catalyst design, synthesis, and mechanistic studies of catalytic reactions for drug discovery.

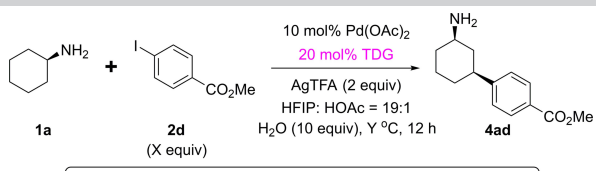
Min Kim received his B.Sc. degree in chemistry from KAIST in 2004. He completed his M.S. and Ph.D. degrees in organic chemistry at KAIST under the guidance of Prof. Sukbok Chang. After his Ph.D., he was a postdoctoral fellow in the laboratory of Prof. Seth M. Cohen at the University of California, San Diego. He began his independent career at Chungbuk National University in 2012, where he is currently a professor in the Department of Chemistry. His research interests are primarily in the area of transition-metal-catalyzed organic reactions (methodology) and the functionalization of MOFs.

Byunghyuck Jung received his Ph.D. degree from KAIST. After postdoctoral studies at Boston College, he joined the school of undergraduate studies at DGIST in 2014. Since 2020, he became an associate professor in the department of emerging materials science at the same institute. His research program currently focuses on transition metal-catalyzed synthetic methodologies.



Scheme 1. Previous studies and developments in the Pd-catalyzed γ–C–H activation of primary amines.

Table 1. Optimizing the reaction conditions with various TDGs.



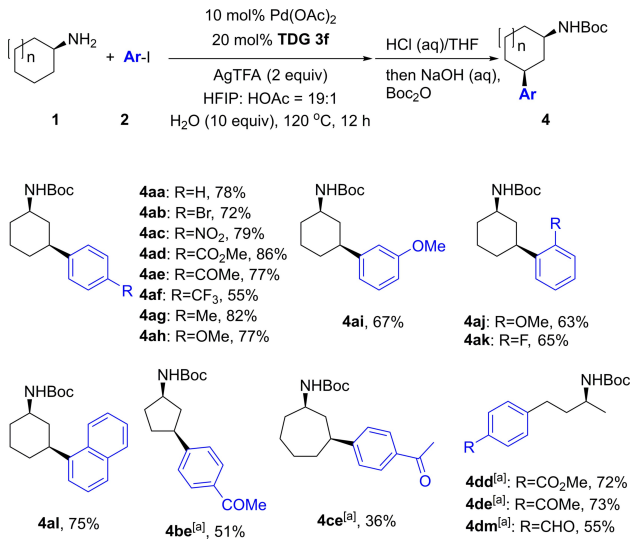
Entry[a]	TDG	X	Y	4ad [%]
1	**3a**	2	120	94
2	**3b**	2	120	62
3	**3c**	2	120	<2
4	**3d**	2	120	89
5	**3e**	2	120	91
6	**3f**	2	120	91
7	**3f**	2	110	63
8	**3f**	2	100	41
9	**3f**	1.5	120	79

[a] cyclohexyllamine (**1a**, 0.2 mmol), aryl iodide (**2d**, 0.4 mmol), $Pd(OAc)_2$ (10 mol%), TDG (20 mol%), and AgTFA (0.4 mmol) were used.

(94% yield) under standard conditions, halogen-functionalized TDGs (**3d**-**3f**) were quite competitive with pyridine-TDG (**3a**) in terms of accessibility. Among the halogens, 3-chloro-TDG (**3e**) was already reported as a reference result for the arylation of an amine substrate by Yu's group, and 3-bromo-TDG (**3f**) was selected as a main TDG in the present study since 3-iodo-TDG was not commercially available and 3-fluoro-TDG (**3d**) had no advantages in terms of price competitiveness and accessibility. Using **3f** as the main TDG, additional optimization of arylation was performed (Table 1). Reducing the reaction temperature caused a decrease in the generation of the desired product, and the use of less than 2 equivalents of aryl iodide (**2d**) decreased the efficiency (entries 4–7 in Table 1).

Under the optimized reaction conditions for selective γ–C-(sp^3)–H arylation, a range of substituted aryl iodides (**2**) were immediately reacted with cyclohexylamine (**1a**, Scheme 2). In general, aryl iodides containing electron-withdrawing groups (EWD, *e.g.*, Br, NO_2, ester, acetyl, and CF_3) reacted with cyclohexylamine in good yields (55-86%), and electron-donating groups (EDGs, *e.g.*, Me and OMe) also showed good yields (82% and 77%) for arylations (**4aa**-**4ah**, in Scheme 2). The electronic effect of substituents affected the reactivity little. Treatment of cyclohexylamine **1** with *para*-, *meta*-, or *ortho*-iodoanisole generated the corresponding arylation products **4ah**, **4ai**, and **4aj** in 77%, 67%, and 63% yield, respectively. The sterically encumbered aryl iodide with *ortho*-F provided desired product **4ak** in 65% yield. Interestingly, the 1-naphthyl group was successfully and selectively installed in the cyclohexylamine moiety without any difficulty (**4al**, 75%, Scheme 2).

Clearly, the amine counterpart was very sensitive to the γ-selective sp^3–C–H arylation efficiency. A small ring, 5-membered cyclopentylamine, showed poor reactivity under the optimized conditions; therefore, the amount of the TDG **3f** was increased to 50 mol% from 20 mol% for efficient arylation (51%, **4be**). In the case of a slightly larger ring, 7-membered cycloheptylamine,

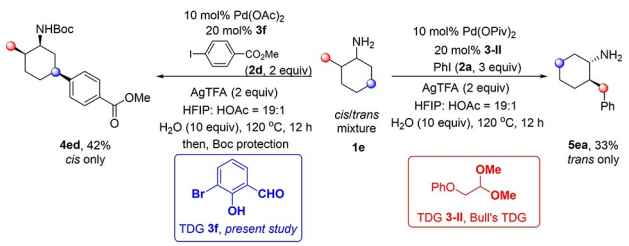


Scheme 2. Substrate scope for γ-selective sp^3–C–H arylation with a TDG. [a] 50 mol% of a TDG ligand was employed.

a poor product yield of **4ce** was obtained under the increased-TDG condition (36%). Notably, the acyclic amine 2-amino-butane also showed good reactivity with various aryl iodides under the increased-TDG condition. Ester (**4dd**, 72%), acetyl (**4de**, 73%), and aldehyde (**4dm**, 55%) groups were successfully incorporated into 1-aryl-3-amino-butane synthesis with Boc protection (**4dd**-**4dm**, Scheme 2).

In line with the selective arylation of aliphatic amines, regioselective γ–C(sp^3)–H arylations were carefully investigated. It was demonstrated that the judicious choice of TDG ligands can enable site-selective γ–C(sp^3)–H arylation under otherwise similar Pd-catalyzed reaction conditions (Scheme 3). When 2-methyl cyclohexylamine (**1e**) was employed under the optimized conditions with aryl iodide (**2d** with ester) and the main TDG in the present system (**3f**), 4-aryl-1-methyl cyclohexylamine (**4ed**) was selectively obtained in 42% product yield. At the same time, when 2-methyl cyclohexylamine (**1e**) was treated with palladium pivalate and Bull's acetal TDG,[17] arylation at the methyl position was achieved (**5ea**, 33%). Two different γ–C-(sp^3)–H sites in a single molecule were selectively activated by Pd–Ag catalysis with different TDGs. Indeed, *cis*-arylation to the methyl group (for **4ed**) and the *trans*-isomer between the arylated methyl and amino groups (for **5ea**) occurred via only two selective pathways. This selectivity clearly indicated that the mechanistic pathway follows very stereospecific and stereoselective steps.

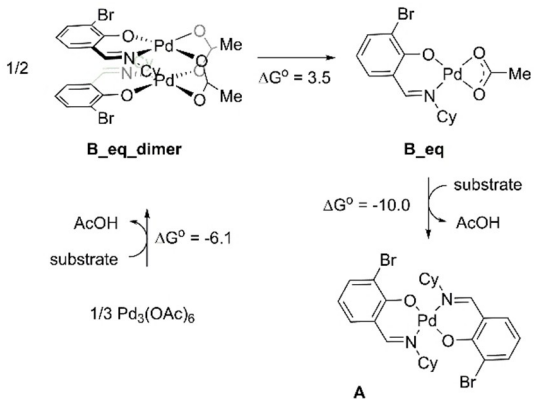
We performed DFT calculations using Gaussian 09[22] to understand the reaction mechanism. All stationary points were optimized in the gas phase with the dispersion-corrected B3LYP–D3[23] level of theory. The LANL2DZ[24] basis set with effective core potential (ECP) was used for Pd, Ag, and I, and the 6–31G** basis set was used for other atoms. Frequency calculations were performed at the same level of theory to verify the nature of ground states and transition states. In addition, intrinsic reaction coordinate (IRC) calculations were carried out to confirm that the optimized transition state structures connected the reactants and products. Single-point energies and solvation calculations were performed with the M06[25] / SDD[26] (Pd, Ag, I)-6-311++G** level of theory by using the SMD solvation model[27] (solvent = generic, eps = 16.7, epsinf = 1.625625) to include the hexafluoro-2-propanol (HFIP) solvation effect.[28] The reported Gibbs free energies included zero-point vibrational energy corrections and thermal corrections at 298 K. All graphical structures were illustrated using CYLview.[29]



Scheme 3. Site-selective sp^3–C–H arylations dependent on the TDG.

Palladium acetate, which has a trimeric structure in non-polar solvents, dissociates into mono- or dipalladium species in the presence of ligands or substrates.[30] To identify the catalyst resting state species, we compared the Gibbs free energies of possible catalytic species (Scheme 4). The homodimeric palladium complex **B_eq_dimer** is 6.1 kcal/mol more stable than trimeric palladium acetate, and the monomeric form **B_eq** is 3.5 kcal/mol less stable than **B_eq_dimer**. When the acetate ligand of **B_eq** is replaced with the substrate, the resulting bis-salicylaldimine palladium species **A** is −10.0 kcal/mol more stable than **B_eq**. Thus, **A** is considered the catalytic resting-state species.

The computed Gibbs free energy profile of the reaction from catalyst resting state species **A** is shown in Figure 1. The reaction is initiated by ligand exchange of the salicylaldimine of **A** with acetic acid, affording Pd(substrate)(OAc) **B**. The cyclohexyl group in **B** has three conformational isomers, which are **B_eq**, **B_ax**, and **B_twist** with respect to the cyclohexyl conformations. Since the Pd(OAc)-bound directing group is extremely large in size, **B_ax** is uphill 7.3 kcal/mol from **B_eq**. Interestingly, **B_ax** is less stable than **B_twist**, presumably due to a high 1,3-axial interaction. For the subsequent concerted metalation-deprotonation (CMD) pathway, alignment between palladium acetate and the target C–H bond is required. While such geometrical requirements are less likely in **B_eq**, **B_ax** satisfies this prerequisite condition. The relative Gibbs free barrier for the CMD transition state (**TS1**) from **B_ax** was computed to be 14.9 kcal/mol (Figure 2a), affording a total CMD barrier of 32.2 kcal/mol. C–H bond is also accessible by the palladium center when the chair conformation of the cyclohexyl ring is distorted to the twisted boat form (Figure 2b). The corresponding CMD barrier is 23.0 kcal/mol, which is energetically infeasible. We further computed the CMD pathway for palladium trifluoroacetate, which is a possible catalytic intermediate in the reaction condition, and the computed overall CMD barrier for **TS1_TFA** from **A** is calculated to be 29.4 kcal/mol. This result indicates that the trifluoroacetate-assisted CMD process is favored over the acetate-assisted CMD process. The resulting cyclometalated species **C** featuring a coordinated carboxylic acid undergoes ligand exchange with iodobenzene



Scheme 4. The relative Gibbs free energies (kcal/mol) of the catalyst formation.

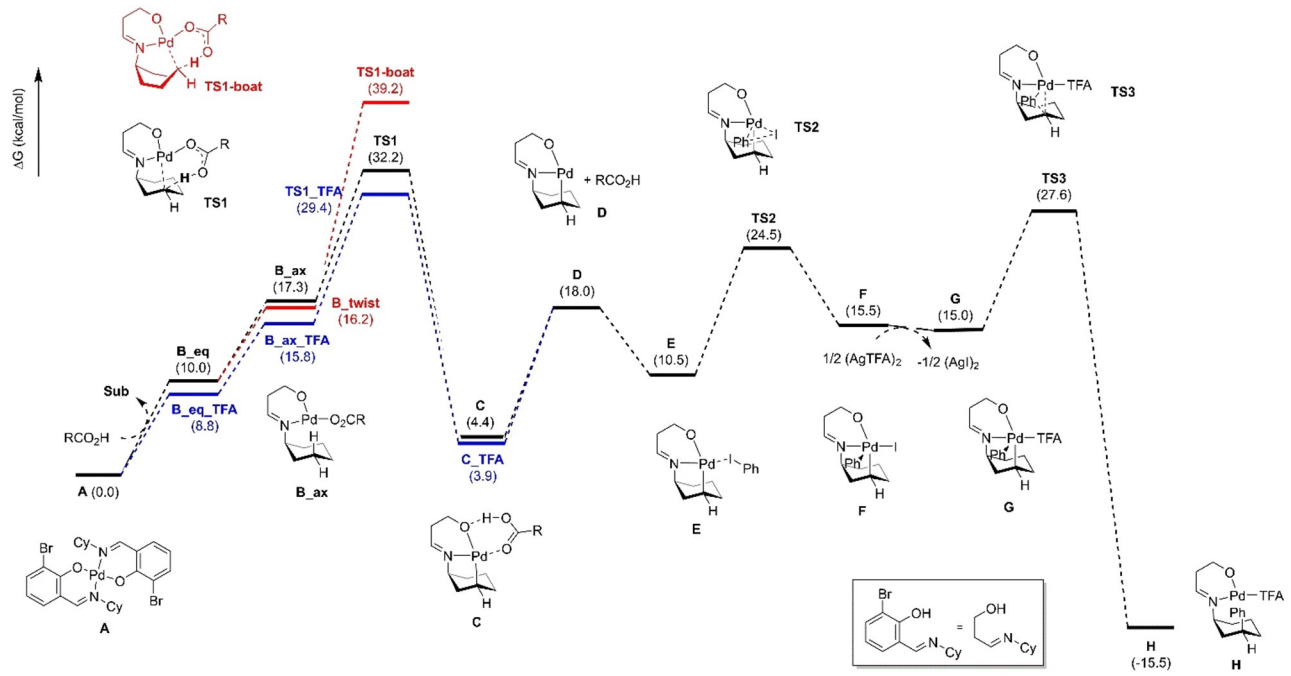


Figure 1. Computed Gibbs free energy profile for Pd-catalyzed C–H arylation using SMD (generic, eps = 16.7, epsinf = 1.625625)/M06/SDD(Pd, Ag, I)/6-311 + + G**//B3LYP–D3/LANL2DZ(Pd, Ag, I)/6-31G**. The relative Gibbs free energies (298.15 K) are given in kcal/mol.

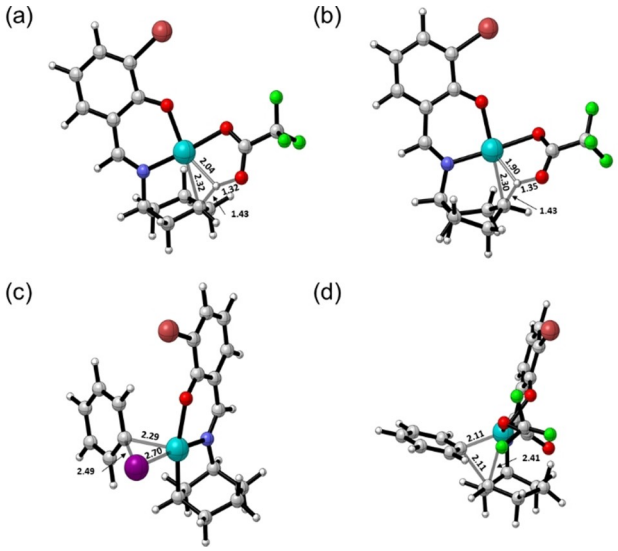


Figure 2. Optimized transition state geometries of (a) **TS1_TFA**, (b) **TS1_boat_TFA**, (c) **TS2**, and (d) **TS3**. The selected bond distances are shown in angstroms.

to give **E** via the coordinatively unsaturated **D**. The oxidative addition of iodobenzene to the Pd center via **TS2** with a barrier of 14.0 kcal/mol affords the high-valence Pd(IV) species (Figure 2c). The iodide abstraction of **F** by AgTFA affords palladium triflate species **G**,[31] and the subsequent reductive elimination via **TS3** (Figure 2d) is uphill 12.6 kcal/mol, giving the arylated product **H**. Based on the free energy profile, the rate-limiting step is determined as the CMD transition state **TS1_TFA**, and this result is consistent with the experimentally determined KIE value (k_H / k_D = 3.54).

Next, we analyzed the experimentally observed site-selectivity for **1e** using DFT calculations. Because each trans/cis isomer of **1e** has two possible reaction sites at 3, 5-positions, we computed four possible pathways to compare the energetics of each pathway (Figure S10, Figure S11).[32] The catalytic resting species **A** can have three species, $\mathbf{A}_{trans,trans}$, $\mathbf{A}_{trans,cis}$, and $\mathbf{A}_{cis,cis}$, with respect to trans/cis isomer of **1e**, and the relative Gibbs free energies for these species are computed to be 0.0, 0.9, and 1.6 kcal/mol, respectively (Figure S9). Therefore, we assumed that $\mathbf{A}_{trans,trans}$ is a catalyst resting species. The CMD barriers for *trans*-**1e** at 3 and 5-position from $\mathbf{A}_{trans,trans}$ are calculated to be 31.4 and 30.9 kcal/mol, respectively (Figure 3). On the other hand, the CMD processes for *cis*-**1e** occurs through $\mathbf{A}_{trans,cis}$, which is uphill by 0.9 kcal/mol from $\mathbf{A}_{trans,trans}$, and the overall CMD barriers are 28.3 and 28.5 kcal/mol at 3- and 5-position, respectively. The lower CMD barriers for *cis*-**1e** than *trans*-**1e** are due to the lack of 1,3-di-axial interaction exerted by an axial methyl group of *trans*-**1e**. The free energy barriers of **TS3** at 3- and 5-position of *cis*-**1e** are computed to be 31.9 and 26.3 kcal/mol, respectively. This selectivity is originated from steric congestion between phenyl and methyl group during the reductive elimination step at 3-position, and these results agree with the experimental results.

The proposed reaction mechanism of the C–H arylation reaction, especially for C–H activation pathway, can be supported by the KIE study (Scheme 5a). Transformation of **1a** and deuterated cyclohexylamine D_{11}-**1a** through Pd catalysis in 20 minutes generated the corresponding arylated products **4ae** and D_{10}-**4ae**. The value of k_H / k_D = 3.54 indicated that the C–H

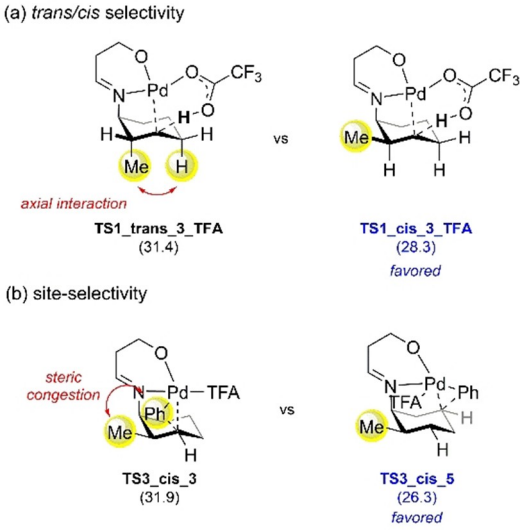
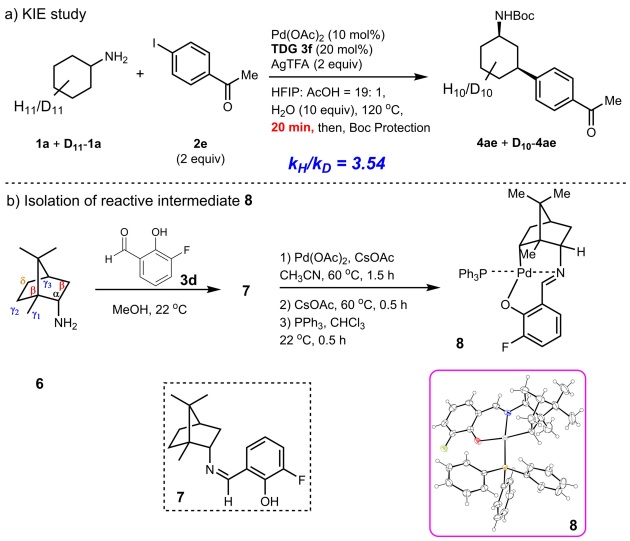


Figure 3. Computed Gibbs free energies (kcal/mol) for the selected transition-states of the site-selective sp^3–C–H arylations of **1 e**.

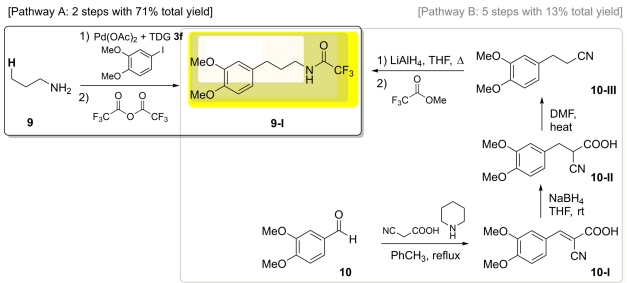


Scheme 5. Experimental studies on the (a) KIE and (b) isolation of a palladacycle **8**.

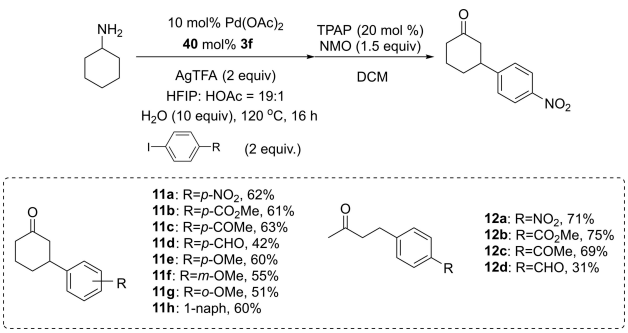
activation step should be rate-determining and supported the computed CMD barrier from **A** to **TS1** in Figure 1. Additionally, we isolated the palladacycle intermediate **8** by the use of (*R*)-bornylamine **6** as an amine substrate (Scheme 5b). Treatment of **6** with a stoichiometric amount of TDG **3 d** led to the formation of imine **7**. A stoichiometric quantity of $Pd(OAc)_2$ was treated with imine **7** in the presence of CsOAc as a base instead of AgTFA, and the subsequent addition of PPh_3 afforded sp^3 C–Pd complex **8**. XRD analysis of intermediate **8** indicated that 1) α- or β-sp^3 C–H activation was not favored (vs. γ-selectivity); 2) the regio- and stereoselectivity (*cis*) were determined at the palladacycle formation step; and 3) TDG **3 d** did not activate γ_1-sp^3 C–H (vs. Bull's TDG 3-II in Scheme 3). However, this palladacycle complex **8** was not fully active in the arylation step due to the attached PPh_3 group. It was also observed that the addition of PPh_3 in the optimized condition for the synthesis of **4 ae** (in Scheme 2) allowed only 48 % product yields.

The usefulness of our method was demonstrated with N-protected 3 C-dopamine **9-I** (Scheme 6). Dopamine and its analogs have shown interesting adhesive and coating properties via their polymerization, and catechol and primary amine moieties are essential.[33] In contrast to dopamine having two methylene units between the benzene ring and amino group, 3 C-dopamine has three methylene units. You and coworkers synthesized a precursor (**9-I**) of 3 C-dopamine in five steps from 3,4-dimethoxybenzaldehyde with 13 % overall yield.[34] Alternatively, Pd-catalyzed γ–C(sp^3)–H arylation of propylamine and successive treatment of trifluoroacetic anhydride under basic conditions provided the target molecule in 71 % overall yield (2 steps) without any regioisomers.

Furthermore, the synthesis of β-aryl-substituted ketones from amines showed the synthetic utility of our method (Scheme 7). The conversion of C–N bonds into C=O bonds is very useful due to its versatility in organic synthesis, and numerous synthetic protocols have been reported.[35] One of the core strategies to generate β-aryl- or alkyl-substituted ketones is the transition metal-catalyzed conjugate addition of proper nucleophiles to α,β-unsaturated ketones.[36] The use of saturated amines as substrates is very rare. We developed a cascade reaction of Pd-catalyzed γ–C(sp^3)–H arylation and Ru-catalyzed oxidation to transform cyclohexanamine into β-aryl-substituted cyclohexanone **11 a**–**11 d** in 42 ~ 63 % yield.[37] The oxidation of amines by the catalytic use of tetrapropylammo-



Scheme 6. Synthetic application to prepare a key intermediate for dopamine derivatives.



Scheme 7. Tandem reaction from aliphatic amines to β-arylated cyclic ketones.

nium perruthenate (TPAP) along with 1.5 equivalents of *N*-methylmorpholine *N*-oxide provided imines easily, and subsequent acidic workup generated the corresponding ketones. We tested 2-iodoxybenzoic acid (IBX)-oxidation[38] and Cu-catalyzed oxidation with H_2O_2 as a co-oxidant,[39] but both conditions generated trace amounts of the desired compounds. The synthesis of 4-aryl-substituted 2-butanone also proceeded smoothly to provide **12a**–**12d** in 31 ~ 75% yield.

Conclusion

In summary, we have investigated the TDG-assisted Pd-catalyzed γ–C(sp^3)–H arylation of amines with high regioselectivities and stereoselectivities. Experimentally and computationally, an easily accessible and useful 3-bromo-TDG (**3f**) was revealed to be an efficient TDG towards Pd-catalyzed γ-selective C(sp^3)–H arylation. These selective γ–C(sp^3)–H arylations were performed with a variety of substrates, including EWGs and EDGs bearing aryl iodides along with various cyclic and acyclic amines. Site-selective γ–C(sp^3)–H arylation based on the choice of TDG ligands and the synthetic utility of the present system are highlighted: i) Pd-catalyzed γ–C(sp^3)–H arylation followed by Ru-catalyzed oxidation provides a novel synthetic pathway to form β-aryl-substituted ketones from amines, and ii) a direct synthetic method for γ-arylation is a key intermediate for several important organic syntheses. Moreover, DFT calculations suggested that these regioselective and stereoselective reactions progressed through a monometallic pathway, and the formation of a 5-membered palladacycle at the 1,3-axial position of cyclohexane determined the superior selectivity. Last, a KIE experiment with deuterium and single-crystal X-ray structural analysis of an intermediate supported our experimental and computational results and findings.

Experimental Section

General Methods. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on Bruker Avance-III 400 MHz or Bruker Avance 500 MHz. Chemical shifts were quoted in parts per million (ppm) referenced to the appropriate solvent peak or 0 ppm for TMS. The following abbreviations were used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Coupling constants, J, were reported in Hertz unit (Hz). X-ray crystallographic analysis was performed using Bruker D8 QUEST diffractometer equipped with molybdenum X-ray tube on a Bruker Photon II diffractometer.

General Procedure for γ–C–H arylation. A screw-caped vial was charged with $Pd(OAc)_2$ (4.5 mg, 10 mol%), 3-bromo-2-hydroxybenzaldehyde (**3f**, 8.0 mg, 20 mol%), aryl halide (0.4 mmol), AgTFA (88.4 mg, 0.4 mmol), solvent (1 mL, HFIP: AcOH = 19:1), and H_2O (36 μL, 0.2 mmol). Alkylamine (0.2 mmol) was added to the reaction vessel. The mixture was stirred at 22 °C of 10 min, placed in a preheated reaction block which temperature was well-controlled at 120 °C, stirred for 12 hr. The crude mixture was cooled using iced water, filtered through celite pad, concentrated under reduced pressure. THF (0.8 mL) and 2 M HCl (0.4 mL) were added to the residue and stirred at 22 °C for 1 hr. The mixture was basified with 10 M NaOH (0.4 mL) and Boc_2O (175 mg, 0.8 mmol) was added. The solution was stirred at 22 °C for 4 hr. After then, EtOAc (3 mL) was added. The mixture was stirred for an additional 10 min. The organic layer was separated and filtered through a silica pad. Three-times repetition of the formal procedure, the organic solution was evaporated using a rotary evaporator. The residue was separated by column chromatography (EtOAc/*n*-hexane) to give the desired product.

***tert*-Butyl (3-phenylcyclohexyl)carbamate (4aa)**: Single diastereomer (*cis*-form), colorless Solid (42.9 mg, 78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (2H, m), 7.19 (3H, m), 4.43 (1H, br), 3.58 (1H, br), 2.62 (1H, m), 2.18 (1H, d, J = 12.24 Hz), 2.04 (1H, d, J = 12.12 Hz), 1.87 (2H, m), 1.44 (12H, m), 1.22 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 146.4, 128.5, 126.9, 126.2, 79.3, 50.2, 43.4, 41.6, 33.7, 33.3, 28.6, 25.3, 25.0.

***tert*-Butyl (3-(4-bromophenyl)cyclohexyl)carbamate (4ab)**: Single diastereomer (*cis*-form), yellowish Solid (51.0 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (2H, d, J = 8.44 Hz), 7.04 (2H, d, J = 8.32 Hz), 4.43 (1H, br), 3.56 (1H, br), 2.58 (1H, m), 2.16 (1H, d, J = 12.16 Hz), 2.04 (1H, d, J = 12.36 Hz), 1.85 (2H, m), 1.43 (10H, m), 1.20 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 145.3, 131.6, 128.7, 119.8, 79.4, 50.0, 42.8, 41.4, 33.2, 28.5, 25.2. EI-MS(+) *m/z* calcd. For $C_{17}H_{24}BrNO_2$ $[M]^+$: 353.0990, found $[M]^+$: 353.0992.

***tert*-Butyl (3-(4-nitrophenyl)cyclohexyl)carbamate (4ac)**: Single diastereomer (*cis*-form), yellowish Solid (50.6 mg, 79%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (2H, d, J = 8.76 Hz), 7.31 (2H, d, J = 8.68 Hz), 4.49, (1H, br), 3.57 (1H, br), 2.73 (1H, m), 2.19 (1H, d, J = 11.8 Hz), 2.04 (1H, m), 1.92 (1H, m), 1.85 (1H, m), 1.51 (1H, m), 1.42 (9H, s), 1.21 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 153.9, 146.5, 127.7, 123.8, 79.4, 49.9, 43.3, 40.9, 33.0, 32.9, 28.5, 25.1

Methyl 4-(3-((*tert*-butoxycarbonyl)amino)cyclohexyl)benzoate (4ad): Single diastereomer (*cis*-form), yellowish Solid (57.3 mg, 86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (2H, d, J = 8.3 Hz), 7.24 (2H, d, J = 8.3 Hz), 4.44, (1H, br), 3.89 (3H, s), 3.59 (1H, br), 2.68 (1H, tt, J_z = 12.3 Hz, J_2 = 3.3 Hz), 2.19 (1H, d, J = 12.05 Hz), 2.04 (1H, d, J = 12.35 Hz), 1.87 (2H, m), 1.51 (1H, m), 1.43 (9H, s), 1.34 (1H, m), 1.24 (1H, m), 1.12 (1H, qd, J_z = 12.55 Hz, J_2 = 3.75 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 155.3, 151.7, 129.9, 128.2, 127.0, 79.4, 52.1, 50.0, 43.5, 33.2, 33.0, 28.6, 25.3.

***tert*-Butyl (3-(4-acetylphenyl)cyclohexyl)carbamate (4ae)**: Single diastereomer (*cis*-form), yellowish Solid (48.8 mg, 77%); ^{1}H NMR (500 MHz, $CDCl_3$) δ7.87 (2H, d, J = 8.25 Hz), 7.26 (2H, d, J = 8.65 Hz), 4.47 (1H, br), 3.58 (1H, br), 3.59 (1H, br), 2.69 (1H, m), 2.19 (1H, d, J = 11.95 Hz), 2.04 (1H, m), 1.88 (2H, m), 1.52 (1H, m), 1.43 (9H, s), 1.36 (1H, qd, J_z = 12.7 Hz, J_2 = 3.35 Hz), 1.25 (2H, m), 1.12 (1H, qd, J_z = 12.5 Hz, J_2 = 3.8 Hz) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 155.3, 152.0, 135.5, 128.8, 127.1, 79.4, 50.1, 43.4, 41.1, 33.2, 33.0, 28.5, 26.7, 25.2.

***tert*-butyl (3-(4-(trifluoromethyl)phenyl)cyclohexyl) carbamate (4af)**: Single diastereomer (*cis*-form), yellowish Solid (37.7 mg, 55%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (2H, d, J = 8.12 Hz), 7.30 (2H, d, J = 8.2 Hz), 4.44 (1H, br), 3.58(1H, br), 2.69 (1H, m), 2.22 (1H, d, J = 12.04 Hz), 2.06 (1H, d, J = 12.4 Hz), 1.91 (2H, m), 1.50 (1H, m), 1.43 (9H, s), 1.24 (3H, m) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 150.3, 128.6 (q, $J_{C\text{-}F}$ = 32.2 Hz), 127.3, 125.5 (q, $J_{C\text{-}F}$ = 3.63 Hz), 124.4 (q, $J_{C\text{-}F}$ = 270 Hz), 79.4, 50.0, 43.3, 41.3, 33.2, 33.1, 28.6, 25.2.

***tert*-Butyl (3-(4-methylphenyl)cyclohexyl)carbamate (4ag)**: Single diastereomer (*cis*-form), yellowish Solid (47.4 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (4H, m), 4.43 (1H, br), 3.57 (1H, br), 3.59 (1H, tt, J_1 = 12.15 Hz, J_2 = 3.15 Hz), 2.32 (3H, s), 2.17 (1H, d, J = 12.4 Hz), 2.05 (1H, d, J = 12.35 Hz), 1.87 (2H, m), 1.50 (1H, m), 1.44 (9H, s), 1.32 (1H, qd, J_1 = 12.45 Hz, J_2 = 3.15 Hz), 1.21 (1H, q, J = 11.95 Hz), 1.09 (1H, qd, J_1 = 12.5 Hz, J_2 = 3.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3,

143.5, 135.7, 129.2, 126.8, 79.3, 50.2, 43.0, 41.7, 33.4,29.8, 28.6, 25.3, 21.1.

***tert*-Butyl (3-(4-methoxyphenyl)cyclohexyl)carbamate (4ah)**: Single diastereomer (*cis*-form), yellowish Solid (47.6 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (2H, d, J=8.56 Hz), 6.82 (2H, d, J=8.72 Hz), 4.44 (1H, br), 3.78 (3H, s), 3.56 (1H, br), 2.57 (1H, m), 2.15 (1H, d, J= 12.12 Hz), 2.06 (1H, m), 1.87 (2H, m), 1.43 (11H, m), 1.20 (4H, m) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 155.3, 138.7, 127.7, 113.9, 79.2, 55.4, 50.2, 42.5, 41.8, 33.5, 33.3, 28.6, 28.5, 25.3.

***tert*-Butyl (3-(3-methoxyphenyl)cyclohexyl)carbamate (4ai)**: Single diastereomer (*cis*-form), yellowish Solid (40.9 mg, 67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (1H, m), 6.78 (1H, d, J=7.65 Hz), 6.73 (1H, m), 4.44 (1H, br), 3.79 (3H, s), 3.57 (1H, br), 2.60 (1H, tt, J_1=12.2 Hz, J_2=3.1 Hz), 2.19 (1H, d, J=12.2 Hz), 2.03 (1H, d, J=12.4 Hz), 1.86 (2H, m), 1.50 (1H, m), 1.44 (9H, s), 1.33 (1H, qd, J_1=12.95 Hz, J_2= 3.6 Hz), 1.21 (1H, q, J=12.1 Hz), 1.09 (1H, qd, J_1=12.55 Hz, J_2= 3.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 155.3, 148.1, 129.5, 119.3, 112.9, 111.4, 79.3, 55.3, 50.2, 43.4, 41.5, 33.3, 33.2, 28.6, 25.3. ; ESI-MS(+) *m/z* calcd. For $C_{18}H_{27}LiNO_3$ $[M+Li]^+$: 312.2145, found $[M+Li]^+$: 312.2147.

***tert*-Butyl (3-(2-methoxyphenyl)cyclohexyl)carbamate (4aj)**: Single diastereomer (*cis*-form), yellowish Solid (38.4 mg, 63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (2H, m), 6.91 (1H, t, J=7.16 Hz), 6.84 (1H, d, J=8.08 Hz), 4.42 (1H, br), 3.81 (3H, s), 3.59 (1H, br), 3.08 (1H, t, J= Hz), 2.11 (2H, m), 1.86 (2H, m), 1.52 (1H, m), 1.44 (9H, s), 1.22 (3H, m) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 134.6, 127.0, 126.6, 120.6, 110.6, 79.2, 55.5, 50.3, 40.1, 35.8, 33.7, 32.0, 28.6, 25.4.

***tert*-butyl (3-(2-fluorophenyl)cyclohexyl)carbamate (4ak)**: Single diastereomer (*cis*-form), yellowish Solid (38.1 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (2H, m), 7.06 (1H, m), 6.99 (1H, m), 4.44, (1H, br), 3.58 (1H, br), 2.95 (1H, tt, J_1=12.24 Hz, J_2=3.28 Hz), 2.15 (2H, m), 1.85 (2H, m), 1.45 (11H, m), 1.1 (1H, m) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7 (d, $J_{C\text{-}F}$=244 Hz), 155.3, 132.9 (d, $J_{C\text{-}F}$=14.4 Hz), 127.9, 127.6 (d, $J_{C\text{-}F}$=8.25 Hz), 124.2 (d, $J_{C\text{-}F}$=3.31 Hz), 115.5 (d, $J_{C\text{-}F}$=22.7 Hz), 79.3, 50.0, 39.7, 36.6, 33.7, 33.4, 32.0, 28.6, 25.3.

***tert*-Butyl (3-(naphthalen-1-yl)cyclohexyl)carbamate (4al)**: Single diastereomer (*cis*-form), yellowish Solid (48.8 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (1H, d, J=8.48 Hz), 7.85 (1H, d, J=8.44 Hz), 7.71 (1H, d, J=8.08 Hz), 7.49 (3H, m), 7.35 (1H, d, J=6.48 Hz), 4.48 (1H, br), 3.76 (1H, br), 3.46 (1H, t, J=11.76 Hz), 2.33 (1H, d, J= 12.44 Hz), 2.15 (1H, d, J=11.52 Hz), 2.00 (2H, m), 1.64 (1H, m), 1.46 (10H, m), 1.36 (1H, m), 1.17 (1H, m) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 142.2, 134.0, 131.3, 129.1, 126.7, 126.0, 125.7, 125.5, 123.2, 122.4, 79.3, 50.4, 41.1, 38.0, 33.7, 33.0, 28.6, 25.6. ESI-MS(+) *m/z* calcd. For $C_{21}H_{27}NNaO_2$ $[M+Na]^+$: 348.1934, found $[M+Na]^+$: 348.1934.

***tert*-Butyl (3-(4-acetylphenyl)cyclopentyl)carbamate (4be)**: Single diastereomer (*cis*-form), yellowish Solid (30.9 mg, 51%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (2H, d, J=8.4 Hz), 7.30 (2H, d, J=8.16 Hz), 4.62 (1H, br), 4.09 (1H, br), 3.12 (1H, m), 2.57 (3H, s), 2.52 (1H, m), 2.12 (2H, m), 1.76 (1H, m), 1.63 (1H, m), 1.44 (9H, s) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 155.6, 151.0, 135.4, 128.7, 127.3, 79.4, 52.1, 44.0, 41.8, 33.0, 32.0, 28.6, 26.7.; ESI-MS(+) *m/z* calcd. For $C_{18}H_{25}LiNO_3$ $[M+Li]^+$: 310.1989, found $[M+Li]^+$: 310.1991.

***tert*-Butyl (3-(4-acetylphenyl)cycloheptyl)carbamate (4ce)**: Single diastereomer (*cis*-form), yellowish Solid (23.9 mg, 36%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, d, J=8.36 Hz), 7.25 (2H, d, J=8.24 Hz), 4.49 (1H, br), 3.74 (1H, br), 2.81 (1H, m), 2.57 (3H, s), 2.05 (2H, m), 1.93 (1H, m), 1.69 (5H, m), 1.54 (1H, m), 1.41 (9H, s) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.0, 155.1, 154.6, 135.2, 128.8, 127.0, 79.4, 51.6, 43.9, 43.6, 36.7, 35.5, 28.6, 26.7, 26.3, 23.7.; ESI-MS(+) *m/z* calcd. For $C_{20}H_{29}LiNO_3$ $[M+Li]^+$: 338.2302, found $[M+Li]^+$: 338.2304.

Methyl 4-(3-((*tert*-butoxycarbonyl)amino)butyl)benzoate (4dd): Yellowish Solid (44.2 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (2H, d, J= Hz), 7.24 (2H, d, J= Hz), 4.36 (1H, br), 3.89 (3H, s), 3.71 (1H, br), 2.71 (1H, dt, J_1= Hz, J_2= Hz), 1.73 (2H, q, J= Hz), 1.44 (9H, s), 1.15 (3H, d, J= Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 155.5, 147.6, 129.9, 128.5, 128.0, 79.3, 52.1, 46.5, 38.9, 32.7, 28.6, 21.5.

***tert*-Butyl (4-(4-acetylphenyl)butan-2-yl)carbamate (4de)**: Yellowish Solid (42.5 mg, 73%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (2H, d, J= 8.24 Hz), 7.26 (2H, d, J=8.16 Hz), 4.38 (1H, br), 3.70 (1H, br), 2.71 (1H, dt, J_1=4.12 Hz, J_2=7.2 Hz), 2.57 (3H, s), 1.69 (2H, m), 1.44 (9H, s), 1.15 (3H, d, J=6.6 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 155.5,147.9, 135.2, 128.7, 128.7, 79.3, 46.4, 38.9, 32.7, 28.6, 26.7, 21.5.; ESI-MS(+) *m/z* calcd. For $C_{17}H_{25}NNaO_3$ $[M+Na]^+$: 314.1727, found $[M+Na]^+$: 314.1726.

***tert*-Butyl (4-(4-formylphenyl)butan-2-yl)carbamate (4dm)**: Yellowish Solid (30.5 mg, 55%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (1H, s), 7.79 (2H, d, J=8.15 Hz), 7.35 (2H, d, J=8.05 Hz), 4.34 (1H, br), 3.72 (1H, br), 2.73 (2H, m), 1.75 (2H, m), 1.44 (9H, s), 1.16 (3H, d, J= 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.1, 155.5, 149.6, 134.7, 130.1, 129.2, 79.4, 46.4, 38.8, 32.9, 28.5, 21.5; ESI-MS(+) *m/z* calcd. For $C_{16}H_{23}NNaO_3$ $[M+Na]^+$: 300.1570, found $[M+Na]^+$: 300.1570.

General Procedure for tandem synthesis of β-Aryl Substituted Ketones. An oven-dried 4 mL vial equipped with a stir bar was charged with 3-bromo-2-hydroxybenzaldehyde (**3f**, 16 mg, 0.08 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), 1-iodo-4-nitrobenzene (199 mg, 0.8 mmol), and AgTFA (177 mg, 0.8 mmol) sequentially. The mixture was dissolved in solvent (hexafluoroisopropanol/acetic acid=19:1, 2 mL) and add cyclohexanamine (46 μL, 0.4 mmol) followed by the addition of water (72 μL, 4 mmol). The vial was sealed with a cap and wrapped with electrical tape. The resulting solution was allowed to stir for ten minutes prior to heating at 120 °C for 12 hours. After allowing the mixture to cool to 22 °C, the reaction was quenched by passing the mixture through a short plug of celite and eluted with tetrahydrofuran (3×2 mL). The filtrate collected in an oven-dried 20 mL vial was concentrated in vacuo and equipped with a stir bar followed by the addition of tetrahydrofuran (2 mL) and HCl (2 M, 2 mL). The mixture was allowed to stir for 30 minutes and CH_2Cl_2 (5 mL) was added. After the removal of the organic layer to exclude the undesired organic compounds, the mixture was basified with NaOH (3 M, pH >10). The basic aqueous solution was transferred into a separatory funnel and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated. An oven-dried 8 mL vial equipped with a stir bar was charged with the crude and CH_2Cl_2 (2 mL). Tetrapropylammonium perruthenate (TPAP, 28.1 mg, 0.08 mmol) and *N*-methylmorpholine *N*-oxide (NMO, 70.3 mg, 0.6 mmol) were added to a mixture. The resulting solution was allowed to stir for 12 hours at ambient temperature and the reaction was quenched by the addition of aqueous HCl (2 M, 3 mL). The mixture was allowed to stir for an additional hour and extracted with diethyl ether (3×4 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated (*CAUTION: due to the volatility of ketones, concentrate the solution in an ice bath) to afford the brown oil, which was purified by silica gel chromatography (gradient 20:1 to 7:1 Petroleum ether/Et_2O) to give the desired ketone **11a** as a colorless oil (54.3 mg, 0.248 mmol, 62% yield).

3-(4-Nitrophenyl)cyclohexan-1-one (11a): Colorless liquid (54.3 mg, 62%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (2H, d, J=8.8 Hz), 7.39 (2H, d, J=8.52 Hz), 3.15 (1H, m), 2.49 (4H, m), 2.14 (2H, m), 1.85 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 151.7, 147.0, 127.7, 124.2, 48.3, 44.6, 41.1, 32.5, 25.4.

Methyl 4-(3-oxocyclohexyl)benzoate (11b): Colorless liquid (56.6 mg, 61%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (2H, d, J=8.4 Hz), 7.29 (2H, d, J=8.2 Hz), 3.90 (3H, s), 3.07 (1H, m), 2.49 (4H, m), 2.14 (2H, m), 1.85 (2H, m) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.4, 167.0, 149.6, 130.2, 128.8, 126.8, 52.2, 48.6, 44.8, 41.2, 32.6, 25.6.

3-(4-Acetylphenyl)cyclohexan-1-one (11c): Colorless liquid (54.5 mg, 63%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (2H, d, J=8.4 Hz), 7.32 (2H, d, J=8.16 Hz), 3.08 (1H, m), 2.50 (7H, m), 2.16 (2H, m), 1.84 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.4, 197.8, 149.8, 136.0, 129.0, 127.0, 48.6, 44.8, 41.3, 32.6, 26.7, 25.6.

3-(4-Formylphenyl)cyclohexan-1-one (11d): Colorless liquid (33.9 mg, 42%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.99 (1H, s), 7.85 (2H, d, J=8.2 Hz), 7.39 (2H, d, J=8.1 Hz), 3.11 (1iH, m), 2.51 (4H, m), 2.14 (2H, m), 1.82 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1, 191.8, 151.3, 135.4, 130.4, 127.5, 48.5, 44.9, 41.2, 32.6, 25.5.

3-(4-Methoxyphenyl)cyclohexan-1-one (11e): Colorless liquid (49.0 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (2H, d, J=8.52 Hz), 6.87 (2H, d, J=8.76 Hz), 3.80 (3H, s), 2.95 (1H, m), 2.45 (4H, m), 2.11 (2H, m), 1.81 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.4, 158.4, 136.7, 127.6, 114.2, 55.4, 49.4, 44.1, 41.3, 33.2, 25.6.

3-(3-Methoxyphenyl)cyclohexan-1-one (11f): Colorless liquid (44.9 mg, 55%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (1H, m), 6.79 (3H, m), 3.81 (3H, s), 2.98 (1H, m), 2.48 (4H, m), 2.11 (2H, m), 1.81 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 160.0, 146.2, 129.8, 119.0, 112.8, 111.8, 55.3, 49.1, 44.9, 43.3, 32.8, 25.7.

3-(2-Methoxyphenyl)cyclohexan-1-one (11g): Colorless liquid (41.6 mg, 51%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (2H, m), 6.94 (1H, td, J_1=7.48 Hz, J_2=1.04 Hz), 6.87 (1H, dd, J_1=8.2 Hz, J_2=0.92 Hz), 3.82 (3H, s), 3.42 (1H, m), 2.50 (4H, m), 2.07 (2H, m), 1.83 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 156.9, 132.7, 127.7, 126.7, 120.8, 110.7, 55.4, 47.7, 41.5, 38.1, 31.2, 25.7.

3-(Naphthalen-1-yl)cyclohexan-1-one (11h): Colorless liquid (53.8 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (1H, d, J=8.32 Hz), 7.87 (1H, m), 7.76 (1H, d, J=8.12 Hz), 7.49 (4H, m), 3.87 (1H, m), 2.60 (4H, m), 2.22 (2H, m), 1.97 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.4, 140.2, 134.1, 131.0, 129.2, 127.4, 126.4, 125.8, 125.7, 122.8, 122.6, 48.7, 41.6, 39.5, 32.4, 25.7.

4-(4-Nitrophenyl)butan-2-one (12a): Colorless liquid (54.8 mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (2H, d, J=8.8 Hz), 7.34 (2H, d, J=8.84 Hz), 2.99 (2H, t, J=7.36 Hz), 2.81 (2H, t, J=7.36 Hz), 2.15 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 149.1, 146.6, 129.4, 123.8, 44.3, 30.2, 29.4.

Methyl 4-(3-oxobutyl)benzoate (12b): Colorless liquid (61.8 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.5 Hz), 3.89 (3H, s), 2.94 (2H, t, J=7.4 Hz), 2.77 (2H, t, J=7.7 Hz), 2.14 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.4, 167.2, 146.7, 130.0, 128.5, 128.3, 52.2, 44.7, 30.2, 29.8.

4-(4-Acetylphenyl)butan-2-one (12c): Colorless liquid (52.5 mg, 69%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (2H, d, J=8.36 Hz), 7.26 (2H, d, J=8.44 Hz), 2.93 (2H, t, J=7.4 Hz), 2.77 (2H, t, J=7.6 Hz), 2.57 (3H, s), 2.14 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3, 197.8, 146.9, 135.4, 128.7, 128.6, 44.5, 30.1, 29.6, 26.6.

4-(3-oxobutyl)benzaldehyde (12d): Colorless liquid (21.8 mg, 31%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (1H, s), 7.80 (2H, d, J=8.1 Hz), 7.35 (2H, d, J=8 Hz), 2.98 (2H, t, J=7.45 Hz), 2.80 (2H, t, J=7.55 Hz), 2.16 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.2, 192.1, 148.6, 134.9, 130.2, 129.2, 44.6, 30.2, 29.9.

Deposition Number 2019569 (for **8**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Acknowledgements

We thank Dr. Dongwook Kim (IBS, Korea) and Dr. Jae-Sun Shin (Dept. of Chemistr, KAIST, Korea) for helpful discussion and experimental support for single X-ray crystallographic analysis and multi-dimensional NMR analysis. This research was supported by the DGIST R&D Program of the Ministry of Science and ICT (20-BRP-05), the Basic Science Research Program (2020R1G1 A1004460 for B. Jung, 2019R1 A2 C4070584 for M. Kim), and the Science Research Center (2016R1 A5 A1009405) through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, and ICT. In addition, J. Kwak was supported by the Korea Research Institute of Chemical Technology (KK2032-00) and H. Ha (Ph.D. student) was supported by Basic Science Research Program (2019R1 A6 A3 A13095922) through the NRF funded by the Ministry of Education.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Aliphatic amines · γ-Arylation · C–H Activation · Homogeneous catalysis · Palladium · Transient directing groups

[1] *C–H Activation; Topics in Current Chemistry* (Eds.: J.-Q. Yu, Z.-J. Shi), Springer, Berlin, **2010**; Vol. 292.
[2] For selected reviews, see: a) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624–655; b) J. Xie, C. Pan, A. Abdukader, C. Zhu, *Chem. Soc. Rev.* **2014**, *43*, 5245–5256; c) J. R. Hummel, J. A. Boerth, J. A. Ellman, *Chem. Rev.* **2017**, *117*, 9163–9227; d) J. He, M. Wasa, K. S. L. Chan, Q. Shao, J.-Q. Yu, *Chem. Rev.* **2017**, *117*, 8754–8786; e) P. Gandeepan, L. Ackermann, *Chem.* **2018**, *4*, 199–222; f) C. Shan, L. Zhu, L.-B. Qu, R. Bai, Y. Lan, *Chem. Soc. Rev.* **2018**, *47*, 7552–7576; g) S. St John-Campbell, J. A. Bull, *Adv. Synth. Catal.* **2019**, *361*, 3662–3682; h) S. Rej, Y. Ano, N. Chatani, *Chem. Rev.* **2020**, *120*, 1788–1887.
[3] N Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 10236–10254; *Angew. Chem.* **2012**, *124*, 10382–10401.
[4] A. D. Ryabov, I. K. Sakodinskaya, A. K. J. Yatsimirsky, *Chem. Soc. Dalton Trans.* **1985**, *12*, 2629–2638.
[5] S.-I. Murahashi, *Angew. Chem. Int. Ed.* **1995**, *34*, 2443–2465; *Angew. Chem.* **1995**, *107*, 2670–2693.
[6] W. G. Whitehurst, J. H. Blackwell, G. N. Hermann, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2019**, *58*, 9054–9059.
[7] J. Rodrigalvarez, M. Nappi, H. Azuma, N. J. Floden, M. E. Burns, M. J. Gaunt, *Nat. Chem.* **2020**, *12*, 76–81.
[8] a) P. K. Pramanick, Z. Zhou, Z.-L. Hou, B. Yao, *J. Org. Chem.* **2019**, *84*, 5684–5694; b) F. Yuan, Z.-L. Hou, P. K. Pramanick, B. Yao, *Org. Lett.* **2019**, *21*, 9381–9385.
[9] H. Lin, X. Pan, A. L. Barsamian, T. M. Kamenecka, T. D. Bannister, *ACS Catal.* **2019**, *9*, 4887–4891.
[10] Z. Zhuang, J.-Q. Yu, *J. Am. Chem. Soc.* **2020**, *142*, 12015–12019.
[11] a) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726–11743; *Angew. Chem.* **2013**, *125*, 11942–11959; b) K. M. Engle, J.-Q. Yu, *J. Org. Chem.* **2013**, *78*, 8927–8955; c) O. Daugulis, J. Roane, L. D. Tan, *Acc. Chem. Res.* **2015**, *48*, 1053–1064; d) Y. Xu, G. Dong, *Chem. Sci.* **2018**, *9*, 1424–1432; e) C. Sambiagio, D. Schönbauer, R. Blieck, T. Dao-Huy, G. Potoschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes, M. Schnürch, *Chem. Soc. Rev.* **2018**, *47*, 6603–6743.

[12] H. Ha, J. Lee, M. H. Park, B. Jung, M. Kim, *Bull. Korean Chem. Soc.* **2020**, *41*, 582–587.
[13] a) Y. Xu, M. C. Young, C. Wang, D. M. Magness, G. Dong, *Angew. Chem. Int. Ed.* **2016**, *55*, 9084–9087; *Angew. Chem.* **2016**, *128*, 9230–9233; b) A. Yada, W. Liao, Y. Sato, M. Murakami, *Angew. Chem. Int. Ed.* **2017**, *56*, 1073–1076; *Angew. Chem.* **2017**, *129*, 1093–1096.
[14] a) Y. Wu, Y.-Q. Chen, T. Lium M. D. Eastgate, J.-Q. Yu, *J. Am. Chem. Soc.* **2016**, *138*, 14554–14557; b) 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.
[15] Y. Liu, H. Ge, *Nat. Chem.* **2017**, *9*, 26–32.
[16] H. Lin, C. Wang, T. D. Bannister, T. M. Kamenecka, *Chem. Eur. J.* **2018**, *24*, 9535–9541.
[17] a) S. St. John-Campbell, A. K. Ou, J. A. Bull, *Chem. Eur. J.* **2018**, 24, 17838–17843; b) J. I. Higham, J. A. Bull, *Org. Biomol. Chem.* **2020**, *18*, 7291–7315.
[18] M. Kapoor, D. Liu, M. C. Young, *J. Am. Chem. Soc.* **2018**, *140*, 6818–6822.
[19] Z. Wang, Y. Fu, Q. Zhang, H. Liu, J. Wang, *J. Org. Chem.* **2020**, *85*, 7683–7693.
[20] a) Y.-Q. Chen, Y. Wu, Z. Wang, J. X. Qiao, J.-Q. Yu, *ACS Catal.* **2020**, *10*, 5657–5662; b) Y.-Q. Chen, S. Singh, Y. Wu, Z. Wang, W. Hao, P. Verma, J. X. Qiao, R. B. Sunoj, J.-Q. Yu, *J. Am. Chem. Soc.* **2020**, *142*, 22, 9966–9974.
[21] W. Feng, T. Wang, D. Liu, X. Wang, Y. Dang, *ACS Catal.* **2019**, *9*, 6672–6680.
[22] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09, Rev. D.01*, Gaussian, Inc., Wallingford, CT, 2010.
[23] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789; c) S. Grimme, J. Antony, S. Ehrlich, H. Krieg, *J. Chem. Phys.* **2010**, *132*, 154104–154122; d) S. Grimme, *J. Comput. Chem.* **2006**, *27*, 1787.
[24] a) P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 299–310; b) L. E. Roy, P. J. Hay, R. L. Martin, *J. Chem. Theory Comput.* **2008**, *4*, 1029–1931.
[25] a) Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215–241; b) Y. Zhao, D. G. Truhlar, *Acc. Chem. Res.* **2008**, *41*, 157–167.
[26] a) M. Dolg, U. Wedig, H. Stoll, H. Preuss, *J. Chem. Phys.* **1987**, *86*, 866–872; b) D. Andrae, U. Häußermann, M. Dolg, H. Stoll, H. Preuß, *Theor. Chem. Acc.* **1990**, *77*, 123–141.
[27] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378–6396.
[28] Z. Fan, K. L. Bay, X. Chen, Z. Zhuang, H. S. Park, K.-S. Yeung, K. N. Houk, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2020**, *59*, 4770–4777.
[29] C. Y. Legault, CYLView, 1.0b; Université de Sherbrooke: Canada, 2009; http://www.cylview.org.
[30] A. C. Skapski, M. L. Smart, *J. Chem. Soc. D* **1970**, *658b–659*.
[31] The byproduct of iodide abstraction was assumed to be a dimeric AgI. For more details, see Reference 16.
[32] For more details, see the supporting information.
[33] a) H. Lee, S. M. Dellatore, W. M. Miller, P. B. Messersmith, *Science* **2007**, *318*, 426–430; b) D. R. Dreyer, D. J. Miller, B. D. Freeman, D. R. Paul, C. W. Bielawski, *Langmuir* **2012**, *28*, 6428–6435; c) S. Hong, Y. S. Na, S. Choi, I. T. Song, W. Y. Kim, H. Lee, *Adv. Funct. Mater.* **2012**, *22*, 4711–4717; d) N. F. Della Vecchia, R. Avolio, M. Alfè, M. E. Errico, A. Napolitano, M. d'Ischia, *Adv. Funct. Mater.* **2013**, *23*, 1331–1340; e) J. Liebscher, R. Mrówczyński, H. A. Scheidt, C. Filip, N. D. Hădade, R. Turcu, A. Bende, S. Beck, *Langmuir* **2013**, *29*, 10539–10548; f) J. Hong, D. G. Jwa, H. Ha, J. Kwak, M. Kim, S. M. Kang, *Langmuir* **2019**, *35*, 6898–6904.
[34] H. Hu, J. C. Dyke, B. A. Bowman, C.-C. Ko, W. You, *Langmuir* **2016**, *32*, 9873–9882.
[35] a) A. H. Haines, in *Methods for the Oxidation of Organic Compounds, Vol. 2*, Academic Press, New York, **1988**, 200–220, 411–415; b) R. C. Larock, in *Comprehensive Organic Transformations, 2nd ed.*, Wiley-VCH, New York, **1999**, 1225–1227; c) M. Hudlicky, in *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, **1990**, p240.
[36] a) A. Alexakis, N. Krause, S. Woodward, in *Copper-Catalyzed Asymmetric Synthesis* (Eds.: A. Alexakis, N. Krause, S. Woodward), VCH-Wiley, **2014**, 33–68; b) B. C. Calvo, J. Buter, A. J. Minaard, in *Copper-Catalyzed Asymmetric Synthesis* (Eds.: A. Alexakis, N. Krause, S. Woodward), VCH-Wiley, **2014**, 373–448.
[37] L. Fan, C. Han, X. Li, J. Yao, Z. Wang, C. Yao, W. Chen, T. Wang, J. Zhao, *Angew. Chem. Int. Ed.* **2018**, *57*, 2115–2119; *Angew. Chem.* **2018**, *130*, 2137–2141.
[38] K. C. Nicolaou, C. J. N. Mathison, T. Montagnon, *Angew. Chem. Int. Ed.* **2003**, *42*, 4077–4082; *Angew. Chem.* **2003**, *115*, 4211–4216.
[39] K. Marui, A. Nomoto, M. Ueshima, A. Ogawa, *Tetrahedron Lett.* **2015**, *56*, 1200–1202.

Manuscript received: October 30, 2020
Revised manuscript received: January 18, 2021
Accepted manuscript online: January 19, 2021