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Entry to Chiral 1,1,2,3-Tetrasubstituted Arylcyclopropanes by Pd(II)-Catalyzed Arylation via Directing Group-Mediated C(sp^3)-H Activation

Naoyuki Hoshiya,*[,†,‡] Moemi Kondo,[†] Hayato Fukuda,[†] Mitsuhiro Arisawa,[†,§] Jun'ichi Uenishi,[‡] and Satoshi Shuto*[,†,∥]

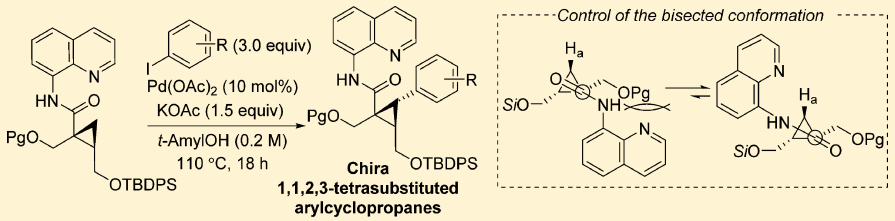
[†]Faculty of Pharmaceutical Sciences, Hokkaido University, Kita 12, Nishi 6, Kita-ku, Sapporo 060-0812, Japan

[‡]Department of Pharmaceutical Chemistry, Kyoto Pharmaceutical University, Shichonocho 1, Misasagi, Yamashina, Kyoto 607-8412, Japan

[§]Graduate School of Pharmaceutical Sciences, Osaka University, Yamada-oka 1-6, Suita, Osaka 565-0862, Japan

[∥]Center for Research and Education on Drug Discovery, Hokkaido University, Kita 12, Nishi 6, Kita-ku, Sapporo 060-0812, Japan

Supporting Information



ABSTRACT: Here we report the construction of highly functionalized chiral 1,1,2,3-tetrasubstituted arylcyclopropanes of medicinal chemical importance using Pd(II)-catalyzed arylation via directing group-mediated C(sp^3)-H activation. The key aspect for the effective arylation was control of the substrate conformation based on the characteristic steric and stereoelectronic features of cyclopropane by manipulating the protecting group at the hydroxyl. The arylation with good functional group tolerance is pivotal as the first entry to chiral 1,1,2,3-tetrasubstituted arylcyclopropanes with wide variety of aryl groups, including heteroaryl groups.

INTRODUCTION

The cyclopropane structure is an attractive motif in organic chemistry because it is often encountered in many artificial and natural biologically active compounds,[1] and key synthetic intermediates for complex molecules.[2] Among these cyclopropane compounds, arylcyclopropanes, in which the cyclopropane ring is directly attached to an aryl or a heteroaryl group, are highlighted as a key structure in biologically active compounds.[3] Arylcyclopropanes are of vital importance in medicinal chemistry, because substituents are effectively restricted on the small rigid cyclopropane ring, thereby creating a unique chemical space,[4] and the aryl and heteroaryl groups function as privileged structures that effectively interact with various proteins.[4d,5] Therefore, many groups, including ours, have extensively studied the preparation of arylcyclopropanes and their biologic activities, examples of which are shown in Figure 1.[4b,6]

As shown in Figure 1, the bioactive arylcyclopropanes known to date have di- or trisubstituted cyclopropane scaffolds. Introduction of an additional substituent to the trisubstituted cyclopropane providing the tetra-substituted cyclopropane scaffold could effectively widen the chemical space, which would be useful for searching novel biologically active compounds. Although considerable efforts have been devoted to the development of effective method for constructing arylcyclopropanes, preparation of chiral tetra-substituted arylcyclopropanes remains a distinct challenge. Only a few methods for constructing chiral tetrasubstituted arylcyclopropanes have been reported.[7] Davies's group reported an excellent asymmetric cyclopropanation of 1,1-diarylethylene with methyl aryldiazoacetate catalyzed by Rh_2(*S*-DOSP)$_4$ to provide 1,1,2,2-tetrasubstituted arylcyclopropanes (Scheme 1, eq 1).[8] Walsh's group developed an enantio- and diastereoselective one-pot halocyclopropanation to provide 1,1,2,3-tetrasubsustituted halocyclopropanes (Scheme 1, eq 2).[9] Charette's groups also developed excellent an enantio- and diastereoselective iodocyclopropanation of allylic alcohols using a substituted zinc carbenoid, in which an example constructing a chiral 1,1,2,3-tetrasubstituted arylcyclopropane appeared (Scheme 1, eq 3).[10] Although these reactions effectively constructed chiral tetrasubstituted arylcyclopropanes, the aryl groups introduced are limited to only nonsubstituted and para-substituted phenyl groups. The structure of the aryl groups, however, is often critical to the biologically activity, and thus the development of methods to prepare chiral tetrasubstituted

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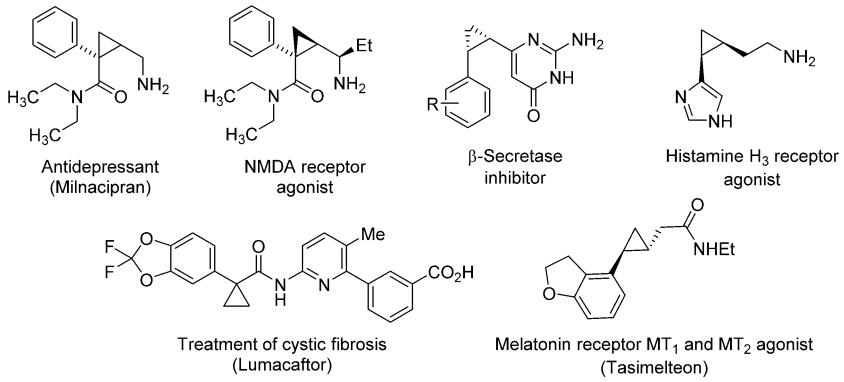
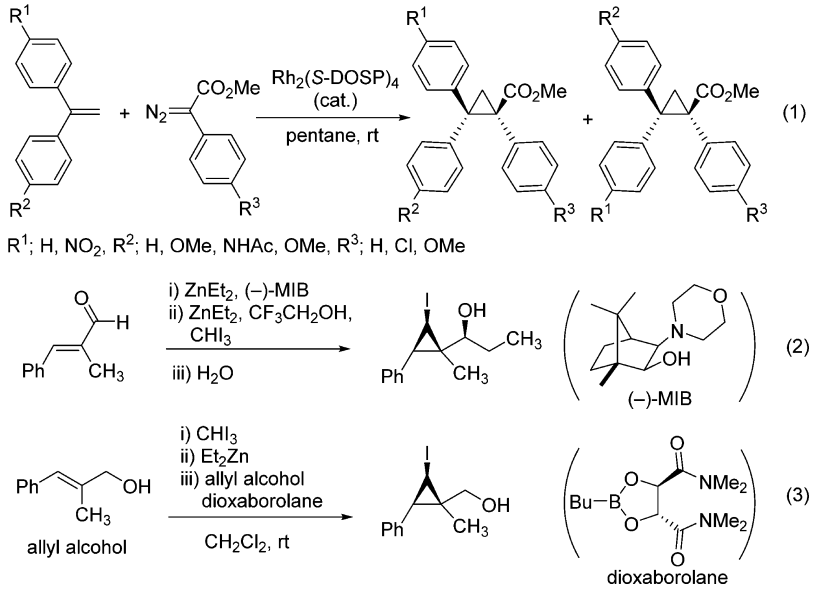


Figure 1. Biologically active arylcyclopropanes.

Scheme 1. Construction of Tetrasubstituted Arylcyclopropanes



arylcyclopropanes with a wide variety of aryl groups, including heteroaryl groups, to search for novel biologically active chiral arylcyclopropanes is needed.

In this context and our continuous studies of the preparation of chiral cyclopropane compounds,[6a−c,11,12] we were interested in developing a versatile synthetic method for chiral tetrasubstituted arylcyclopropanes. In the two regioisomeric tetrasubstituted cyclopropanes shown in Figure 2, the 1,1,2,3-tetrasubstituted regioisomer seems to be more useful scaffold than the 1,1,2,2-regioisomer, because the characteristic conformationally restricting feature of cyclopropane effectively works to arrange the substituents on all three ring carbons in the 1,1,2,3-tetrasubstituted regioisomer to construct a unique chemical space.[4a,e] Thus, we aimed to develop an efficient procedure for preparing 1,1,2,3-type chiral tetrasubstituted arylcyclopropanes with various aryl and heteroaryl groups that would allow us to explore novel biologically active chiral arylcyclopropanes. In this report, we describe the first entry to chiral 1,1,2,3-tetrasubstituted arylcyclopropanes via directing group-mediated Pd(II)-catalyzed C(sp^3)-H arylation.

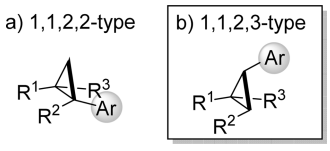


Figure 2. (a) 1,1,2,2-Tetrasubstituted cyclopropanes and (b) 1,1,2,3-tetrasubstituted cyclopropanes.

RESULTS AND DISCUSSION

Planning the Reaction. In previous approaches to chiral tetrasubstituted arylcyclopropanes enantioselective cyclopropanations have been used as described above (Scheme 1, Figure 3a). On the other hand, arylation of cyclopropanes could be a complementary approach to chiral tetrasubstituted arylcyclo-

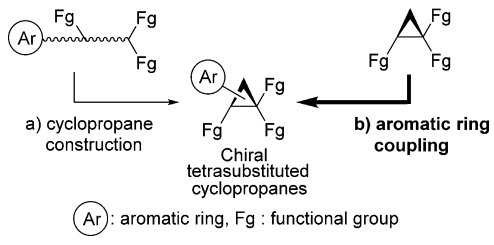


Figure 3. Construction methods for chiral arylcyclopropanes: (a) cyclopropane construction, (b) aromatic ring coupling.

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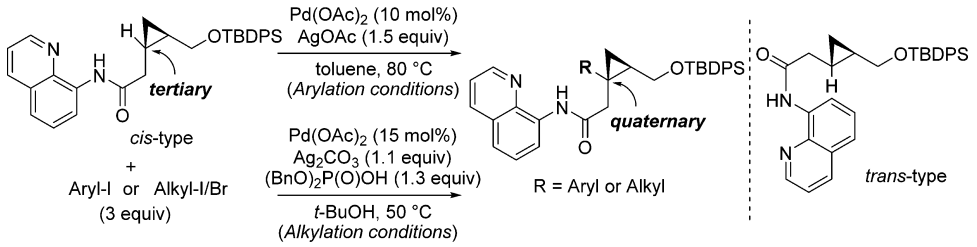
Scheme 2. Our Previous Report on Arylation and Alkylation of Tertiary C(sp^3)-H Bond on Chiral Cyclopropane



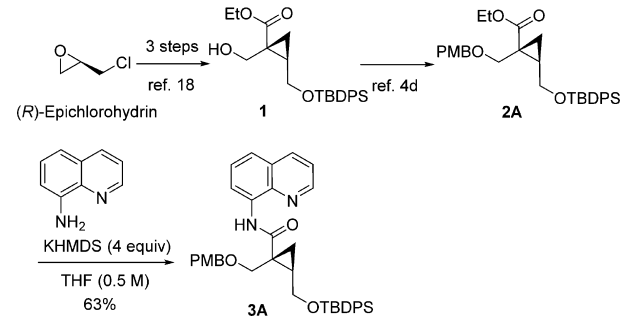
propanes, where an aryl group is introduced at a relatively late stage in the synthesis (Scheme 3b). Such a procedure may allow us to provide arylcyclopropane with a variety of aryl and heteroaryl groups, which would be particularly attractive from the viewpoint of medicinal chemistry. A drawback in the arylation approach, however, is that the preparation of chiral highly substituted cyclopropane substrates for coupling reactions, such as iodocyclopropanes and metalocyclopropanes, is often troublesome, which may be a reason why no arylations for constructing chiral tetrasubstituted arylcyclopropanes have yet been developed.

We have investigated transition metal-catalyzed carbon−carbon bond formation reaction of cyclopropanes,[11b,12] and developed Pd(II)-catalyzed directing group mediated tertiary C(sp^3)-H arylation and alkylation of chiral arylcyclopropanes, which allowed us to introduce various aromatic rings and alkyl groups into the sterically highly hindered chiral tertiary carbon on cyclopropanes (Scheme 2).[12] We expected that the directing group-mediated C−H arylation strategy would provide us a new entry to chiral 1,1,2,3-tetrasubstituted arylcyclopropanes because the transformation possibly introduces various aryl groups via C−H bond activation regio- and stereoselectively without the halogenated or metalated cyclopropane substrates difficult to prepare.[13]

Pioneering studies of Pd(II)-catalyzed direct C−H arylation of cyclopropanes were reported by Yu's group,[14] who achieved the enantioselective C−H arylation of cyclopropanes using chiral mono-*N*-protected amino acids as ligands. Charette's[15] and Babu's group[16] also developed the C−H arylation of cyclopropanes using the directing group-mediated method. Although the directing group-mediated C−H arylation is remarkably effective for synthesizing various compounds, construction of the 1,1,2,3-tetrasubstituted arylcyclopropane structures, which was likely to be troublesome due to the extremely sterically hindered structure having four substituents on the small rigid ring, has not been reported to date. We hypothesized, however, that when chiral cyclopropane substrates, such as **3A**, are used, the C(sp^3) arylation forming the 1,1,2,3-tetrasubstituted arylcyclopropane structure would proceed due to the following characteristic features of cyclopropane: (i) the secondary carbon of cyclopropane rings is less sterically hindered compared with usual secondary carbons due to the small and rigid ring structure, (ii) the ring carbons forming the cyclopropane structure are unusually sp^2-like-hybridized,[17] and (iii) C(sp^3)-H activation might be promoted due to conformational restriction of the directing group on the rigid cyclopropane ring to bring the Pd close to the secondary C−H.

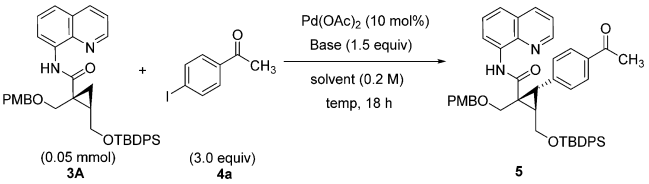
Results. The chiral trisubstituted cyclopropane substrate **3A** bearing an 8-aminoquinoline auxiliary as a directing group was first prepared. The trisubstituted chiral cyclopropane **2A**, which was readily prepared from (*R*)-epichlorohydrin reported previously via a chiral cyclopropane **1** (Scheme 3)[18] was treated with 8-aminoquinoline and KHMDS to give **3A** (Scheme 3).

Scheme 3. Preparation of 3A



Initially, we examined the C−H arylation of **3A** with 4-iodoacetophenone **4a** (3.0 equiv) using various bases (1.5 equiv) and solvents (0.2 M) in the presence of $Pd(OAc)_2$ (10 mol%), and the results are summarized in Table 1. We first tested potassium salts, K_2CO_3, K_3PO_4, and KOAc (entries 1−3). No arylated product was supplied using K_2CO_3 or K_3PO_4 (entries 1 and 2). When the reaction was performed with KOAc in toluene at 110 °C for 18 h, however, the desired 1,1,2,3-tetrasubstituted arylcyclopropane **5** was actually pro-

Table 1. Optimization of Reaction Conditions



entry	base	solvent	temp (°C)	yield (%)[a]
1	K_2CO_3	toluene	110	N.D.
2	K_3PO_4	toluene	110	N.D.
3	KOAc	toluene	110	24
4	LiOAc	toluene	110	3
5	NaOAc	toluene	110	4
6	CsOAc	toluene	110	8
7	KOAc	*p*-xylene	130	27
8	KOAc	THF	75	17
9	KOAc	DMF	110	N.D
10	KOAc	*t*-BuOH	90	32
11	KOAc	cyclohexanol	160	39
12	KOAc	*t*-AmylOH	110	54

[a]Yields were calculated by ^{1}H NMR using anthracene as an internal standard.

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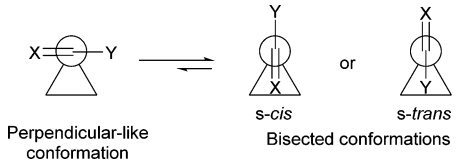
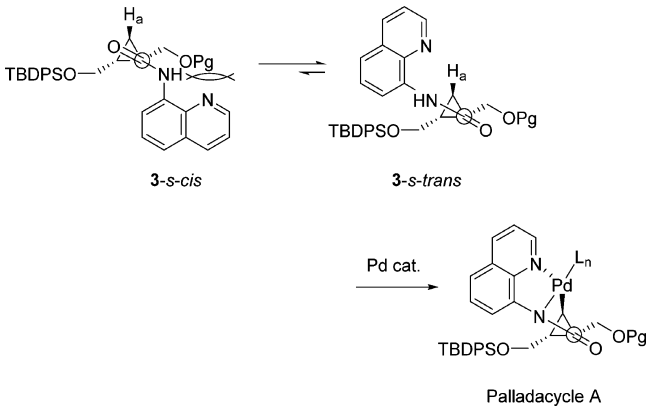
Scheme 4. Bisected Conformation of Cyclopropanes



Scheme 5. Control of Bisected Conformation for Cyclopropane 3



duced, although the yield was low (24%, entry 3). Other metal acetates, LiOAc, NaOAc, and CsOAc, were then tested, and we confirmed that KOAc was a suitable base for the arylation (entries 4–6). We next examined solvents. Performing the reaction with *p*-xylene instead of toluene at higher temperature (130 °C) gave the desired **5** in 27% (entry 7), but the reactions with THF or DMF were unsuccessful (entries 8 and 9). Next, we examined alcohol solvents. When the reaction was performed in *t*-BuOH at 90 °C, the yield slightly increased to 32% (entry 10). Use of cyclohexanol at higher temperature of 160 °C provided **5** in 39% yield (entry 11), and switching the solvent to *t*-AmylOH improved the yield to 54% (entry 12).

Encouraged by these results, we next focused on the conformation of the substrate for improving the yield of the arylation. Cyclopropanes attached to an unsaturated bond, such as vinylcyclopropanes, cyclopropyl ketones, and cyclopropanealdehydes, favor the two bisected conformations, i.e., *s-cis* and *s-trans* conformations, rather than the perpendicular-like conformation (Scheme 4).[17,19] These bisected conformations are stabilized due to the characteristic π-donating stereoelectronic effect of the cyclopropane ring. Thus, in the substrate amide **3A**, the bisected **3**-*s-cis* and **3**-*s-trans* conformers would be stable due to the characteristic stereoelectronic effect as shown in Scheme 5. We hypothesized that a sterically hindered protecting group at the geminal hydroxymethyl substituent makes the **3**-*s-trans* conformer significantly more stable than the **3**-*s-cis* conformer due to the steric repulsion between the bulky protecting group and the 8-aminoquinoline moiety. The **3**-*s-trans* conformer could be favorable for the arylation to proceed, because it seemed to easily form the palladacycle A due to the directing group orientation effectively activating the C–H bond.

Taking these considerations into account, we designed and synthesized substrates **3B**–**3D** bearing various protecting groups at the geminal hydroxymethyl substituent and nonprotected **3E** as illustrated in Scheme 6. Their C–H arylation

Scheme 6. Preparation of 3B–3E

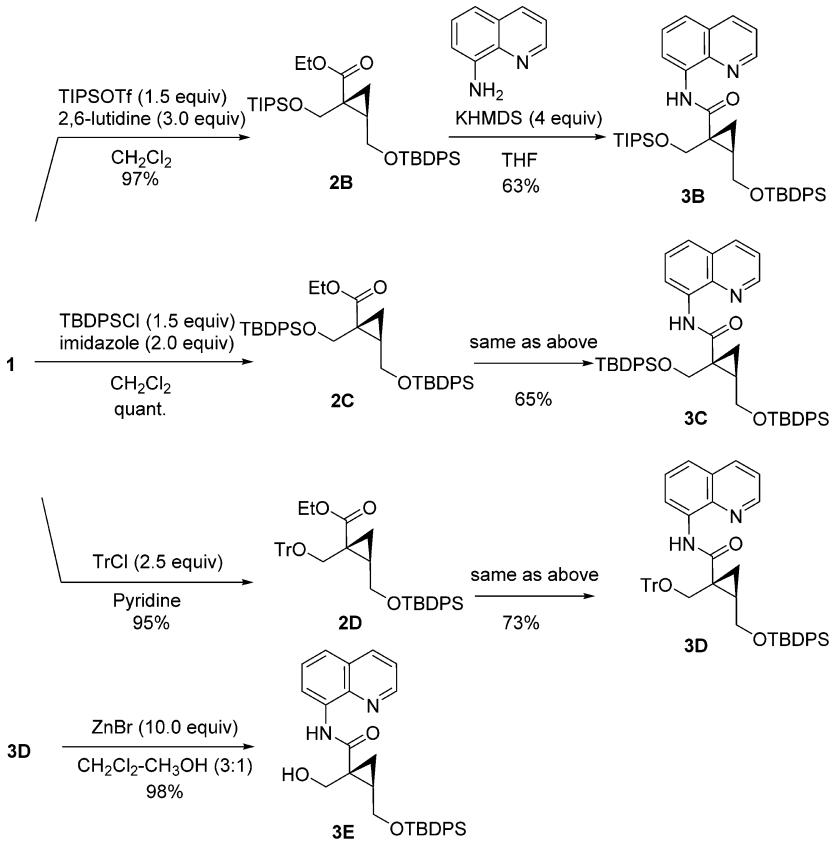


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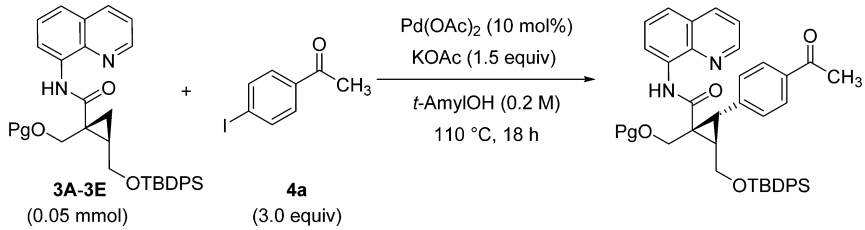
Table 2. Examination of Protecting Groups



entry	substrate	Pg	product	yields (%)
1[a]	**3A**	PMB	**5**	54
2	**3B**	TIPS	**6**	70[b]
3	**3C**	TBDPS	**7**	73[b]
4	**3D**	Tr	**8a**	85[b]
5	**3E**	H	**9**	no reaction

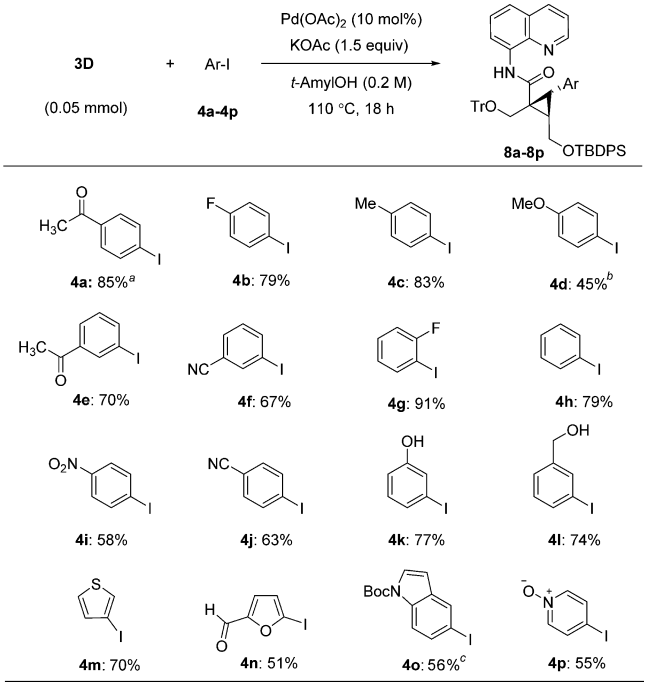
[a]The result is Table 1, entry 12. [b]Isolated yields.

was investigated under the reaction conditions; $Pd(OAc)_2$ (10 mol%), KOAc (1.5 equiv) in *t*-AmylOH (0.2 M) at 110 °C for 18 h, and the results are summarized in Table 2.

The yield of the reaction of substrate **3B** bearing a bulky TIPS group significantly increased to 70% (entry 2) compared with that of **3A**. In the case of **3C** with a TBDPS group, the corresponding arylation product was obtained in 73% yield (entry 3). To our delight, when the reaction was carried out using substrate **3D** with a Tr group, the desired arylated product **8a** was isolated in 85% yield (entry 4). We also examined the reaction of nonprotected substrate **3E**, but its arylation did not proceed (entry 5). Based on these results, we identified **3D** with a Tr protecting group as a suitable substrate for the C−H arylation.

With the optimized reaction conditions and an effective substrate **3D** with a suitable protecting group in hand, we next examined the arylation using various aryl iodides (Scheme 7). The reactions with aryl iodides **4a** and **4b** having an electron-withdrawing group gave the corresponding arylated products in high yields. *p*-Tolyl iodide **4c** with an electron-donating group at *para*-position also provided the corresponding arylated product in 83% yield. Although 4-iodoanisole (**4d**) with a strong electron-donating group at *para*-position was a hard substrate, the use of $Pd(TFA)_2$ instead of $Pd(OAc)_2$ gave the desired arylation product in 45% yield.[20] The reactions with *meta*-substituted (**4e** and **4f**) and *ortho*-substituted (**4g**) aryl iodides proceeded smoothly to afford the corresponding coupling products in good to high yields. Nonsubstituted phenyl iodide (**4h**) was also a good coupling partner to provide the arylated product in 79% yield. In the arylation, nitro (**4i**) and cyano (**4j**) groups were well-tolerated to give the corresponding coupling products in moderate to good yields. Aryl iodides with a phenolic alcohol (**4k**) and an aliphatic alcohol (**4l**) were also good coupling partners in the arylation and the corresponding products were provided in 77 and 74% yields, respectively. We next examined the arylation with heteroaryl idodides, and these reactions proceeded smoothly. The reaction with 3-iodothiphene (**4m**) or 5-iodo-2-furaldehyde (**4n**) afforded the corresponding coupling products in 70 and 51% yields, respectively. In the case of *N*-Boc-5-iodoindole (**4o**), higher catalytic loading (15 mol%) was required to provide the product in 56% yield. Although 4-iodopyridine was not a suitable substrate in the arylation, the reaction with 4-iodopyridine *N*-oxide (**4p**) proceeded smoothly to give the corresponding arylated product in 55% yield.

Scheme 7. Substrate Scope of the C−H Arylation

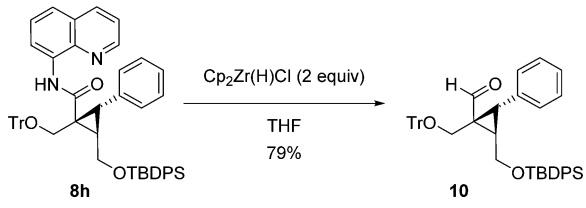


[a]The result is Table 2, entry 4. [b]$Pd(TFA)_2$ (10 mol%) was used. [c]$Pd(OAc)_2$ (15 mol%) was used.

Finally, we examined functionalization of the 8-aminoquinoline moiety. Thus, treatment of **8h** with $Cp_2Zr(H)Cl$ in THF successfully provided the corresponding chiral arylcyclopropanealdehyde **10** in 79% yield as shown in Scheme 8.

In conclusion, we successfully developed an efficient method for synthesizing chiral 1,1,2,3-tetrasubstituted arylcyclopro-

Scheme 8. Transformation of the Resulting Tetrasubstituted Arylcyclopropanes



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panes by the Pd(II)-catalyzed coupling reaction via directing group-mediated C−H activation. The key for the C−H arylation effectively to occur seems to be the conformational restriction of the cyclopropane substrate into the bisected *s-trans* form due to the steric effect of the bulky *O*-Tr protecting group. This kind of conformation restriction strategy using steric effect of protecting groups may be applicable to other cyclopropane substrates in C−H activations due to the characteristic structural feature of cyclopropane ring. The procedure provided chiral 1,1,2,3-tetrasubstituted cyclopropane with various aryl groups including heteroaryl groups. Furthermore, transformation of the resulting chiral tetrasubstituted arylcyclopropane to the corresponding functionalized arylcyclopropane was achieved, demonstrating the synthetic utility of the procedure. This work is of vital importance as the first entry to chiral 1,1,2,3-tetrasubstituted arylcyclopropanes with various aryl and heteroaryl groups constructing a unique chemical space.

EXPERIMENTAL SECTION

General Information. All commercially available materials were used as received unless otherwise noted. Silica gel column was performed using silica gel (63−210 μm). TLC was performed using glass-backed silica gel 60F254. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, and mass spectra. Some compounds were analyzed by elemental analysis. Nuclear magnetic resonance spectra were recorded on a JEOL 400 or 500 MHz instrument. All ^{1}H NMR spectra are reported in δ units, parts per million (ppm), and were measured relative to signals for tetramethylsilane (0.00 ppm) in the deuterated solvent. All ^{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.00 ppm), unless otherwise stated, and all were obtained with ^{1}H decoupling. Low- and high-resolution mass analysis performed on a double-focusing high-resolution magnetic-sector mass-analyzer instrument.

Preparation of 3A. An oven-dried three-necked round-bottom flask, which was equipped with a magnetic stir bar and charged with 8-aminoquinoline (1.05 g, 7.28 mmol, 2.0 equiv), was fitted with rubber septum. The flask was purged with argon and then anhydrous THF (1 mL) were added via syringe. The suspension was cooled to 0 °C. To the suspension was added a solution of KHMDS in toluene (0.5 M, 29 mL, 14.5 mmol, 4.0 equiv) via syringe. After stirring for 1 h, the reaction mixture was cooled to −78 °C. Then, a solution of **2A**[4d] (1.95 g, 3.66 mmol) in anhydrous THF (6 mL) was added to the mixture via cannula. After stirring at −40 °C for 4.5 h, water and then 1 N HCl were added to the reaction mixture. The mixture was extracted with EtOAc. The organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane:EtOAc = 20:1−10:1) to give **3A** in 63% yield (1.46 g, 2.31 mmol).

3A: white form; $[\alpha]_D^{24}$ − 9.9 (*c* 1.43, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.39 (s, 1H), 8.76 (d, *J* = 7.5 Hz, 1H), 8.61 (d, *J* = 1.0 Hz, 1H), 8.12 (dd, *J* = 6.5, 1.5 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 4H), 7.53−7.42 (m, 2H), 7.41−7.33 (m, 9H), 6.81 (d, *J* = 8.5 Hz, 2H), 4.81 (d, *J* = 11.5 Hz, 1H), 4.67 (d, *J* = 11.5 Hz, 1H), 3.95 (d, *J* = 11.0 Hz, 1H), 3.90 (dd, *J* = 11.5, 6.5 Hz, 1H), 3.81 (dd, *J* = 11.5, 6.5 Hz, 1H), 3.79 (s, 3H), 3.75 (d, *J* = 11.0 Hz, 1H), 2.01 (m, 1H), 1.61 (dd, *J* = 9.0, 4.0 Hz, 1H), 1.04 (s, 9H), 0.81 (dd, *J* = 6.5, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 159.1, 148.0, 138.9, 136.1, 135.6, 135.5, 133.6, 129.8, 129.6, 129.3, 127.9, 127.7, 127.6, 127.3, 121.3, 121.1, 116.6, 113.7, 73.0, 69.8, 62.6, 55.2, 29.3, 27.9, 26.8, 19.2, 17.5; LRMS (ESI) *m*/*z* 631 $[M+H]^+$; Anal. Calcd for $C_{39}H_{42}N_2O_4Si{\cdot}0.8H_2O$: C, 72.59; H, 6.81; N, 4.34; found C, 72.22; H, 6.50; N, 4.30.

Typical Procedure of C−H Arylation of 3A (Optimization of Reaction Conditions, Table 1). A flame-dried-test vial was equipped with a magnetic stir bar and charged with **3A** (31.5 mg, 0.05 mmol), **4a** (3.0 equiv), $Pd(OAc)_2$ (1.1 mg, 10 mol%), and base (1.5 equiv). The vial was sealed with a rubber septum, and then evacuated and backfilled with argon (this procedure was repeated a total of three times). Dry solvent (250 μL) was added via syringe. The reaction mixture was stirred at 75−160 °C for 18 h. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2, filtered through Celite. The filtrate was concentrated under vacuum. Anthracene (4.6 mg, 0.026 mmol) was then added as an internal standard and the reaction mixture was analyzed by ^{1}H NMR. Isolation of **5** was performed by silica gel column chromatography to give (hexane:EtOAc = 20:1−10:1).

5: viscous oil, $[\alpha]_D^{24}$ − 66.5 (*c* 0.84, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.39 (s, 1H), 8.55−8.51 (m, 2H), 8.09 (dd, *J* = 10.5, 1.5 Hz, 1H), 7.76 (d, *J* = 10.5 Hz, 2H), 7.69−7.65 (m, 4H), 7.46−7.26 (m, 13H), 6.89 (d, *J* = 10.5 Hz, 2H), 4.95 (d, *J* = 15.0 Hz, 1H), 4.67 (d, *J* = 14.5 Hz, 1H), 4.19 (d, *J* = 13.5 Hz, 1H), 4.04 (dd, *J* = 14.0, 7.0 Hz, 1H), 3.87 (dd, *J* = 14.5, 9.0 Hz, 1H), 3.82 (s, 3H), 3.66 (d, *J* = 13.5 Hz, 1H), 2.98 (dd, *J* = 16.5, 9.5 Hz, 1H), 2.60 (d, *J* = 9.5 Hz, 1H), 2.49 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 168.0, 159.1, 148.0, 142.4, 138.7, 136.0, 135.6, 135.5, 135.3, 133.2, 130.0, 129.78, 129.76, 129.2, 129.0, 128.6, 128.1, 127.8, 127.7, 127.2, 121.3, 121.1, 116.6, 113.9, 113.8, 73.0, 70.1, 62.5, 55.3, 38.8, 35.7, 29.6, 26.8, 26.5, 19.1; LRMS (ESI) *m*/*z* 771 $[M+Na]^+$; HRMS (ESI) *m*/*z* $[M+Na]^+$ Calcd for $C_{47}H_{48}N_2O_5SiNa$ 771.3230, found 771.32247.

Preparation of 3B−3E. *Preparation of 3B.* To a solution of **1**[18] (120 mg, 0.291 mmol) in CH_2Cl_2 (2.9 mL) was added 2,6-lutidine (0.1 mL, 0.863 mmol, 3.0 equiv) and triisopropylsilyl trifluoromethanesulfonate (118 μL, 0.436 mmol) at 0 °C. After stirring at room temperature for 1 h, water (3 mL) was added to the reaction mixture. The mixture was transferred to a separatory funnel and then the aqueous layer was removed. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and then solvent was removed with the aid of a rotary evaporator. The resulting residue was purified by silica gel column chromatography (hexane:EtOAc = 20:1) to give **2B** in 97% yield (161 mg, 0.283 mmol) as colorless oil.

2B: $[\alpha]_D^{24}$ − 10.7 (*c* 1.07, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67−7.65 (m, 4H), 7.42−7.34 (m, 6H), 4.13 (q, *J* = 6.0 Hz, 2H), 3.99 (s, 2H), 3.87 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.72 (dd, *J* = 11.2, 7.2 Hz, 1H), 1.86 (m, 1H), 1.32 (dd, *J* = 9.2, 4.4 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.05−0.96 (m, 30H), 0.83 (dd, *J* = 6.8, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 135.52, 135.49, 133.7, 133.6, 129.6, 127.59, 127.57, 63.6, 61.7, 60.5, 30.1, 28.4, 26.8, 19.1, 18.0, 17.9, 17.7, 14.2, 12.3, 11.9; LRMS (ESI) *m*/*z* 569 $[M+H]^+$; Anal. Calcd for $C_{33}H_{52}O_4Si_2{\cdot}0.1H_2O$: C, 69.45; H, 9.22; found C, 69.12; H, 9.40.

Following the procedure for preparation of **3A**, **2B** (159 mg, 0.279 mmol), 8-aminoquinoline (80.7 mg, 0.560 mmol, 2.0 equiv), KHMDS (0.5 M in toluene, 2.2 mL, 1.10 mmol, 4.0 equiv), and THF (0.56 mL) were used. The crude product was purified by column chromatography (hexane:EtOAc = 20:1−10:1) to provide **3B** in 63% yield (118 mg, 0.177 mmol) as a white foam.

3B: $[\alpha]_D^{24}$ − 15.8 (*c* 0.99, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.04 (s, 1H), 8.83 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.75 (dd, *J* = 4.0, 1.2 Hz, 1H), 8.14 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 4H), 7.55−7.48 (m, 2H), 7.45−7.35 (m, 7H), 4.39 (d, *J* = 12.4 Hz, 1H), 3.93 (d, *J* = 12.4 Hz, 1H), 3.89 (dd, *J* = 12.0, 6.8 Hz, 1H), 3.73 (dd, *J* = 11.6, 8.0 Hz, 1H), 2.15 (m, 1H), 1.51 (dd, *J* = 9.2, 4.0 Hz, 1H), 1.25−1.15 (m, 3H), 1.08−1.04 (m, 27H), 0.78 (dd, *J* = 6.4, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 147.6, 138.9, 135.9, 135.53, 135.50, 135.47, 133.4, 129.6, 127.9, 127.6, 127.2, 121.3, 121.2, 117.1, 63.7, 63.4, 31.5, 27.7, 26.7, 19.1, 18.8, 18.2, 18.0, 17.7, 12.3, 12.2, 12.1, 12.0, 11.7; LRMS (ESI) *m*/*z* 667 $[M+H]^+$; Anal. Calcd for $C_{40}H_{54}N_2O_3Si_2$:C, 72.02; H, 8.16; N, 4.20; found C, 71.63; H, 8.30; N, 4.16.

Preparation of 3C. To a solution of **1**[18] (124 mg, 0.300 mmol) in CH_2Cl_2 (2.4 mL) was added imidazol (40.8 mg, 0.600 mmol, 2.0 equiv) and *tert*-butylchlorodiphenylsilane (117 μL, 0.450 mmol) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was concentrated under vacuum. The resulting residue was purified by silica gel column chromatography (hexane:EtOAc = 20:1) to give **2C** in quantitative yield (195 mg, 0.300 mmol) as colorless oil.

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2C: $[\alpha]_D^{24}$ − 8.6 (*c* 1.15, $CHCl_3$); colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 7.64−7.59 (m, 8H), 7.40−7.38 (m, 4H), 7.33−7.25 (m, 8H), 4.12−4.10 (m, 2H), 3.91 (d, *J* = 11.5 Hz, 1H), 3.87 (d, *J* = 11.5 Hz, 1H), 3.83 (dd, *J* = 11.5, 7.5 Hz, 1H), 3.64 (dd, *J* = 10.5, 7.0 Hz, 1H), 1.88 (m, 1H), 1.33 (dd, *J* = 9.0, 4.0 Hz, 1H), 1.20 (t, *J* = 6.5 Hz, 3H), 1.00 (s, 9H), 0.98 (s, 9H), 0.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 135.62, 135.58, 135.52, 135.47, 133.7, 133.6, 133.5, 129.6, 129.58, 129.49, 127.62, 127.60, 127.52, 127.50, 63.6, 62.6, 60.6, 30.0, 28.5, 26.8, 26.7, 19.2, 19.1, 18.6, 14.2; LRMS (ESI) *m*/*z* 673 $[M+Na]^+$; Anal. Calcd for $C_{40}H_{50}O_4Si_2$:C, 73.80; H, 7.74; found C, 73.65; H, 7.67.

Following the procedure for preparation of **3A**, **2C** (100 mg, 0.154 mmol), 8-aminoquinoline (44.3 mg, 0.307 mmol, 2.0 equiv), KHMDS (0.5 M in toluene, 1.2 mL, 0.600 mmol, 4.0 equiv), and THF (1.0 mL) were used. The crude product was purified by column chromatography (hexane:EtOAc = 10:1) to provide **3C** in 65% yield (75.1 mg, 0.100 mmol) as a white foam.

3C: $[\alpha]_D^{24}$ − 15.4 (*c* 0.97, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 11.30 (s, 1H), 8.88 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.60 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.15 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.79 (d, *J* = 7.2 Hz, 2H), 7.71 (d, *J* = 7.2 Hz, 2H), 7.58−7.50 (m, 6H), 7.43−7.23 (m, 13H), 4.46 (d, *J* = 12.8 Hz, 1H), 3.70 (d, *J* = 12.8 Hz, 1H), 3.53 (dd, *J* = 12.0, 7.2 Hz, 1H), 3.14 (dd, *J* = 11.6, 2.1 Hz, 1H), 2.10 (m, 1H), 1.33 (dd, *J* = 9.2, 4.8 Hz, 1H), 1.10 (s, 9H), 0.92 (s, 9H), 0.24 (dd, *J* = 6.8, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 148.0, 138.9, 136.0, 135.9, 135.8, 135.6, 135.5, 135.4, 135.3, 134.8, 133.5, 133.4, 133.2, 133.0, 129.80, 129.77, 129.5, 128.0, 127.7, 127.62, 127.56, 127.3, 121.4, 121.2, 116.9, 63.9, 63.6, 31.3, 28.1, 27.0, 26.7, 26.5, 19.3, 19.2, 19.0; LRMS (ESI) *m*/*z* 749 $[M+H]^+$; Anal. Calcd for $C_{47}H_{52}N_2O_3Si_2$: C, 74.46; H, 7.05; N, 3.70; found C, 74.85; H, 6.97; N, 3.70.

*Preparation of **3D**.* To a solution of **1** (2.42 g, 5.87 mmol) in pyridine (29 mL) was added trityl chloride (4.09 g, 14.7 mmol, 2.5 equiv) at room temperature. After stirring at 110 °C for 6 h, and then the reaction mixture was cooled to room temperature. Methanol was added to the reaction mixture, and then the mixture was stirred for 10 min. The mixture was concentrated with the aid of a rotary evaporator. The resulting residue was purified by silica gel column chromatography (hexane:EtOAc = 20:1) to give **2D** in 95% yield (3.67 g, 5.60 mmol) as a pale yellow viscous oil.

2D: $[\alpha]_D^{24}$ − 1.3 (*c* 1.31, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.54−7.51 (m, 4H), 7.41−7.37 (m, 8H), 7.31−7.27 (m, 4H), 7.21−7.15 (m, 9H), 4.22−4.15 (m, 2H), 3.53 (dd, *J* = 11.5, 6.5 Hz, 1H), 3.35 (d, *J* = 10.5 Hz, 1H), 3.29 (d, *J* = 10.0 Hz, 1H), 3.26 (dd, *J* = 11.5, 7.5 Hz, 1H), 1.86−1.83 (m, 1H), 1.32 (dd, *J* = 8.5, 2.5 Hz, 1H), 1.29 (t, *J* = 7.0 Hz, 3H), 0.95 (s, 9H), 0.41 (dd, *J* = 4.5, 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 144.0, 135.52, 135.47, 133.7, 133.6, 129.5, 128.7, 127.6, 127.5, 126.8, 86.3, 63.8, 61.9, 60.7, 28.6, 28.1, 26.7, 19.2, 19.0, 14.3; LRMS (ESI) *m*/*z* 678 $[M+Na]^+$; Anal. Calcd for $C_{43}H_{46}O_4Si{\cdot}0.5H_2O$:C, 77.79; H, 7.14; found C, 77.78; H, 6.83.

Following the procedure for preparation of **3A**, **2D** (3.22 g, 4.92 mmol), 8-aminoquinoline (1.42 g, 9.85 mmol, 2.0 equiv), KHMDS (0.5 M in toluene, 39 mL, 19.5 mmol, 4.0 equiv), and THF (9.8 mL) were used. The crude product was purified by column chromatography (hexane:EtOAc = 20:1−10:1) to provide **3D** in 73% yield (2.70 g, 3.59 mmol) as a white foam.

3D: $[\alpha]_D^{24}$ − 16.9 (*c* 1.08, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 11.36 (s, 1H), 8.83 (d, *J* = 7.6 Hz, 1H), 8.11 (m, 2H), 7.65−7.62 (m, 6H), 7.57−7.49 (m, 6H), 7.39−7.28 (m, 7H), 7.18−7.17 (m, 9H), 3.98 (d, *J* = 11.6 Hz, 1H), 3.63 (dd, *J* = 11.6, 6.0 Hz, 1H), 3.34 (d, *J* = 12.0 Hz, 1H), 3.16 (dd, *J* = 12.0, 8.8 Hz, 1H), 2.09 (m, 1H), 1.40 (dd, *J* = 9.2, 4.8 Hz, 1H), 0.90 (s, 9H), 0.28 (dd, *J* = 4.4, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 147.7, 143.8, 138.7, 135.9, 135.7, 135.51, 135.48, 133.44, 133.39, 129.5, 129.0, 127.9, 127.7, 127.6, 127.3, 126.9, 121.4, 121.1, 116.8, 88.1, 63.7, 63.0, 29.9, 28.2, 26.7, 19.0, 18.9; LRMS (ESI) *m*/*z* 753 $[M+H]^+$; Anal. Calcd for $C_{50}H_{48}N_2O_3Si{\cdot}0.3H_2O$:C, 79.18; H, 6.46; N, 3.69; found C, 79.22; H, 6.39; N, 3.68.

*Preparation of **3E**.* To a solution of **3D** (60.2 mg, 0.0799 mmol) in CH_2Cl_2/MeOH (3:1, 0.40 mL) was added zinc bromide (180 mg, 0.799 mmol, 10.0 equiv) at 0 °C. After stirring at room temperature for 18 h, sat. aq. $NaHCO_3$ (0.40 mL) was added to the reaction mixture. The mixture was extracted with EtOAc. The organic layer was washed with sat. brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane:EtOAc = 3:1) to give **3E** in 98% yield (40.0 mg, 0.0783 mmol) as a white foam.

3E: $[\alpha]_D^{24}$ 32.2 (*c* 1.05, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 11.62 (s, 1H), 8.87 (dd, *J* = 4.5, 2.0 Hz, 1H), 8.77 (dd, *J* = 7.5, 2.0 Hz, 1H), 8.14 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.70 (dd, *J* = 8.0, 7.0 Hz, 4H), 7.67−7.46 (m, 7H), 7.29−7.25 (m, 2H), 4.58 (dd, *J* = 12.5, 12.0 Hz, 1H), 4.33 (d, *J* = 11.5 Hz, 1H), 4.22 (dd, *J* = 12.0, 5.0 Hz, 1H), 3.75 (d, *J* = 13.5 Hz, 1H), 3.50 (dd, *J* = 12.0, 11.5 Hz, 1H), 1.83−1.77 (m, 1H), 1.73 (dd, *J* = 9.0, 4.5 Hz, 1H), 1.05 (s, 9H), 0.65 (dd, *J* = 5.5, 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 1485, 139.2, 135.9, 135.53, 135.51, 135.46, 132.5, 132.2, 130.04, 130.01, 128.0, 127.9, 127.8, 127.18, 127.15, 121.4, 117.0, 64.8, 63.1, 32.0, 27.9, 26.8, 19.0, 16.7; LRMS (ESI) *m*/*z* 511 $[M+H]^+$; HRMS (ESI) *m*/*z* $[M+Na]^+$ Calcd for $C_{31}H_{34}N_2O_3SiNa$ 533.2236; found 533.2230.

Typical Procedure for Examination of Protecting Group (Table 2). Following the typical procedure for C−H arylation of **3A**, the arylations of cyclopropane **3B**−**3E** (0.040 mmol) were tested. Purification of **6**, **7**, and **8a** were performed by silica gel column chromatography (hexane:EtOAc = 20:1−10:1).

6: 70% yield (22.1 mg, 0.0281 mmol); white foam; $[\alpha]_D^{24}$ − 37.8(*c* 1.27, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 10.99 (s, 1H), 8.73 (dd, *J* = 4.0, 1.2 Hz, 1H), 8.55 (dd, *J* = 6.8, 1.6 Hz, 1H), 8.10 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.75−7.70 (m, 6H), 7.46−7.34 (m, 11H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.07 (dd, *J* = 11.6, 6.8 Hz, 1H), 3.84 (dd, *J* = 11.2, 7.6 Hz, 1H), 3.77 (d, *J* = 12.0 Hz, 1H), 3.03 (dd, *J* = 15.2, 8.0 Hz, 1H), 2.54 (d, *J* = 7.6 Hz, 1H), 2.47 (s, 3H), 1.34−1.24 (m, 3H), 1.16−1.10 (m, 18H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.8, 168.4, 147.6, 142.6, 138.9, 136.0, 135.60, 135.57, 135.30, 135.27, 133.4, 133.3, 129.7, 129.0, 128.1, 127.9, 127.7, 127.2, 121.34, 121.30, 117.3, 63.8, 63.3, 41.2, 35.7, 30.2, 26.8, 26.5, 19.1, 18.1, 12.0; LRMS (ESI) *m*/*z* 807 $[M+Na]^+$; HRMS(ESI) *m*/*z* $[M+Na]^+$ Calcd for $C_{48}H_{60}N_2O_4Si_2Na$ 807.3989; found 807.3983.

7: 73% yield (25.4 mg, 0.0293 mmol); white foam; $[\alpha]_D^{24}$ − 57.4 (*c* 1.08, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 11.22 (s, 1H), 8.61−8.58 (m, 2H), 8.12 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.81−7.73 (m, 6H), 7.47−7.42 (m, 4H), 7.40−7.20 (m, 17H), 4.63 (d, *J* = 12.4 Hz, 1H), 3.70 (dd, *J* = 11.6, 6.4 Hz, 1H), 3.58 (d, *J* = 12.4 Hz, 1H), 3.15 (dd, *J* = 11.6, 8.8 Hz, 1H), 2.91 (dd, *J* = 15.6, 7.6 Hz, 1H), 2.49 (s, 3H), 1.86 (d, *J* = 8.0 Hz, 1H), 1.23 (s, 9H), 0.96 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 168.4, 148.1, 142.4, 138.8, 136.0, 135.9, 135.52, 135.48, 135.4, 135.2, 133.4, 133.3, 133.0, 132.9, 130.1, 129.9, 129.6, 129.02, 128.99, 128.1, 127.9, 127.8, 127.7, 127.6, 127.4, 127.2, 121.4, 121.3, 117.1, 63.9, 63.4, 40.9, 35.8, 30.8, 27.1, 26.7, 26.5, 19.4, 19.0; LRMS (ESI) *m*/*z* 889 $[M+Na]^+$; Anal. Calcd for $C_{55}H_{58}N_2O_4Si_2$:C, 76.17; H, 6.74; N, 3.23; found C, 75.91; H, 6.64; N, 3.08.

8a: 85% yield (29.6 mg, 0.0340 mmol) ; pale yellow foam; $[\alpha]_D^{24}$ − 104.1 (*c* 1.53, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 11.31 (s, 1H), 8.59 (dd, *J* = 7.0, 1.5 Hz, 1H), 8.21 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.10 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.68 (dd, *J* = 7.5, 4.0 Hz, 6H), 7.57 (dd, *J* = 15.5, 7.0 Hz, 4H), 7.46−7.27 (m, 12H), 7.20−7.19 (m, 8H), 4.13 (d, *J* = 11.5 Hz, 1H), 3.69 (dd, *J* = 11.0, 7.0 Hz, 1H), 3.25 (d, *J* = 11.5 Hz, 1H), 3.21 (dd, *J* = 11.5, 8.0 Hz, 1H), 2.95 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.49 (s, 3H), 1.79 (d, *J* = 7.5 Hz, 1H), 0.94 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.8, 168.1, 147.8, 143.7, 142.3, 138.6, 135.9, 135.6, 135.5, 135.4, 135.3, 133.4, 133.3, 129.7, 129.0, 128.9, 128.1, 127.84, 127.81, 127.7, 127.6, 127.3, 127.1, 121.4, 121.2, 116.7, 88.3, 63.4, 63.0, 39.8, 36.3, 30.8, 26.7, 26.5, 19.0; LRMS (ESI) *m*/*z* 893 $[M+Na]^+$; Anal. Calcd for $C_{58}H_{54}N_2O_4Si{\cdot}0.5H_2O$:C, 79.15; H, 6.30; N, 3.18; found C, 79.08; H, 6.15; N, 3.14.

Typical Procedure of the Arylation (Scheme 7). A flame-dried-test vial was equipped with a magnetic stir bar and charged with **3D** (0.04 mmol), **4a**−**4p** (3.0 equiv), $Pd(OAc)_2$ (10 or 15 mol%), and KOAc (1.5 equiv). The vial was sealed with a rubber septum, and then evacuated and backfilled with argon (this procedure was repeated a total of three times). *t*-AmylOH (250 μL) was added via syringe. The reaction mixture was stirred at 110 °C for 18 h. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2, filtered through

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Celite. The filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane:EtOAc = 20:1−10:1) to give **8a**-**8p**.

8b: 79% yield (26.6 mg, 0.0314 mmol); white foam; $[\alpha]_D^{24}$ − 65.7 (*c* 1.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.30 (s, 1H), 8.60 (dd, *J* = 5.2, 2.0 Hz, 1H), 8.20 (dd, *J* = 3.2, 1.2 Hz, 1H), 8.11 (dd, *J* = 6.8, 1.2 Hz, 1H), 7.72−7.67 (m, 7H), 7.59−7.54 (m, 4H), 7.47−7.27 (m, 10H), 7.21−7.18 (m, 9H), 6.84 (t, *J* = 7.2 Hz, 2H), 4.11 (d, *J* = 9.2 Hz, 1H), 3.67 (dd, *J* = 9.2, 4.8 Hz, 1H), 3.24−3.18 (m, 2H), 2.86 (dd, *J* = 11.6, 6.0 Hz, 1H), 1.78 (d, *J* = 6.0 Hz, 1H), 0.94 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 161.5 (J_{CF} = 242 Hz), 147.8, 143.8, 138.6, 135.9, 135.7, 135.6, 135.5, 134.8, 133.5, 133.4, 132.1 (J_{CF} = 3.6 Hz), 130.3 (J_{CF} = 7.3 Hz), 129.6, 129.5, 129.0, 127.8, 127.7, 127.65, 127.60, 127.3, 127.1, 121.4, 121.1, 116.7, 114.8 (J_{CF} = 21.5 Hz), 88.3, 63.6, 63.1, 39.1, 35.7, 30.7, 26.7, 19.0; LRMS (ESI) *m*/*z* 847 $[M+H]^+$; Anal. Calcd for $C_{56}H_{51}FN_2O_3Si$:C, 79.40; H, 6.07; N, 3.31; found C, 79.00; H, 6.01; N, 3.29.

8c: 83% yield (28.0 mg, 0.0332 mmol); white foam; $[\alpha]_D^{24}$ − 35.3 (*c* 1.59, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.33 (s, 1H), 8.64 (dd, *J* = 5.6, 3.2 Hz, 1H), 8.15 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.10 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.70−7.67 (m, 11H), 7.60−7.55 (m, 9H), 7.19−7.14 (m, 10H), 6.97 (d, *J* = 8.0 Hz, 2H), 4.09 (d, *J* = 11.2 Hz, 1H), 3.70 (dd, *J* = 11.2, 6.4 Hz, 1H), 3.24−3.16 (m, 2H), 2.89 (dd, *J* = 14.4, 7.6 Hz, 1H), 2.21 (s, 3H), 1.85 (d, *J* = 7.6 Hz, 1H), 0.93 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 147.7, 143.9, 138.7, 135.82, 135.78, 135.7, 135.6, 135.5, 134.8, 133.6, 133.4, 133.3, 129.63, 129.57, 129.0, 128.72, 128.67, 127.9, 127.8, 127.71, 127.68, 127.63, 127.59, 127.3, 127.00, 126.96, 121.3, 120.8, 116.7, 88.2, 63.7, 63.4, 39.1, 36.3, 30.6, 26.7, 21.0, 19.0; LRMS (ESI) *m*/*z* 865 $[M+Na]^+$; HRMS(ESI) *m*/*z* $[M+Na]^+$ Calcd for $C_{57}H_{54}N_2O_3SiNa$ 865.3801; found 865.3795.

8d: 45% yield (15.6 mg, 0.0182 mmol); white foam; $[\alpha]_D^{24}$ − 34.2 (*c* 0.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.31 (s, 1H), 8.63 (dd, *J* = 6.0, 3.6 Hz, 1H), 8.17 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.10 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.68 (dd, *J* = 7.6, 4.4 Hz, 6H), 7.60−7.57 (m, 4H), 7.55−7.17 (m, 20H), 6.71 (d, *J* = 9.2 Hz, 2H), 4.08 (d, *J* = 11.6 Hz, 1H), 3.63−3.58 (m, 1H), 3.62 (s, 3H), 3.24−3.17 (m, 2H), 2.87 (dd, *J* = 14.8, 8.0 Hz, 1H), 1.83 (d, *J* = 7.6 Hz, 1H), 0.93 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 158.0, 147.7, 143.9, 138.7, 135.8, 135.7, 135.6, 135.5, 133.6, 133.4, 129.8, 129.59, 129.57, 129.0, 128.5, 127.8, 127.63, 127.59, 127.3, 127.0, 121.3, 120.9, 116.7, 113.4, 88.2, 63.7, 63.3, 55.1, 39.0, 35.9, 30.6, 26.7, 19.0; LRMS (ESI) *m*/*z* 881 $[M+Na]^+$; HRMS(ESI) *m*/*z* $[M+Na]^+$ Calcd for $C_{57}H_{54}N_2O_4SiNa$ 881.3751; found 881.3745.

8e: 70% yield (24.3 mg, 0.0279 mmol); white foam; $[\alpha]_D^{24}$ − 36.8 (*c* 0.89, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.32 (s, 1H), 8.56 (dd, *J* = 7.0, 1.0 Hz, 1H), 8.20 (dd, *J* = 4.0, 2.0 Hz, 1H), 8.11 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.87 (s, 1H), 7.69−7.68 (m, 7H), 7.58 (dd, *J* = 17.5, 6.5 Hz, 4H), 7.45−7.24 (m, 11H), 7.20−7.19 (m, 9H), 4.12 (d, *J* = 11.5 Hz, 1H), 3.71 (dd, *J* = 11.0, 6.5 Hz, 1H), 3.27 (d, *J* = 11.5 Hz, 1H), 3.24 (dd, *J* = 10.5, 8.0 Hz, 1H), 2.95 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.40 (s, 3H), 1.86 (d, *J* = 7.5 Hz, 1H), 0.95 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.1, 168.3, 147.8, 143.7, 138.6, 137.1, 136.8, 135.9, 135.6, 135.5, 135.4, 133.5, 133.4, 133.3, 129.7, 129.6, 129.4, 129.0, 128.3, 127.84, 127.80, 127.7, 127.6, 127.3, 127.1, 126.2, 121.4, 121.1, 116.7, 88.3, 63.5, 63.0, 39.2, 36.0, 30.7, 26.7, 26.5, 19.0; LRMS (ESI) *m*/*z* 871 $[M+H]^+$; Anal. Calcd for $C_{58}H_{54}N_2O_4Si$: C, 79.97; H, 6.25; N, 3.22; found C, 79.53; H, 6.27; N, 3.08.

8f: 67% yield (23.0 mg, 0.0269 mmol); white foam; $[\alpha]_D^{24}$ − 50.6 (*c* 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.31 (s, 1H), 8.56 (dd, *J* = 7.6, 2.0 Hz, 1H), 8.27 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.13 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.68−7.66 (m, 6H), 7.58−7.53 (m, 4H), 7.50−7.28 (m, 12H), 7.24−6.99 (m, 10H), 4.16 (d, *J* = 12.0 Hz, 1H), 3.67 (dd, *J* = 11.6, 6.4 Hz, 1H), 3.22 (d, *J* = 12.0 Hz, 1H), 3.18 (dd, *J* = 12.0, 8.8 Hz, 1H), 2.88 (dd, *J* = 14.8, 8.0 Hz, 1H), 1.65 (d, *J* = 7.6 Hz, 1H), 0.94 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 147.9, 143.7, 138.6, 138.1 136.0, 135.55, 135.50, 135.2, 133.4, 133.2, 133.1, 132.7, 130.1, 129.73, 129.69, 128.9, 128.7, 127.9, 127.7, 127.6, 127.3, 127.2, 121.5, 121.3, 118.9, 116.7, 112.0, 88.4, 63.2, 62.8, 39.5, 35.5, 30.7, 26.7, 19.0; LRMS (ESI) *m*/*z* 876 $[M+Na]^+$; HRMS(ESI) *m*/*z* $[M+Na]^+$ Calcd for $C_{57}H_{51}N_3O_3SiNa$ 876.3597; found 876.3591.

8g: 91% yield (30.7 mg, 0.0362 mmol); white foam; $[\alpha]_D^{24}$ − 25.0 (*c* 1.22, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.37 (s, 1H), 8.59 (dd, *J* = 6.4, 2.8 Hz, 1H), 8.07 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.01 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.72−7.70 (m, 6H), 7.59−7.54 (m, 4H), 7.43−7.26 (m, 9H), 7.23−7.18 (m, 10H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.99 (t, *J* = 8.0 Hz, 1H), 6.90 (t, *J* = 9.6 Hz, 1H), 3.98 (d, *J* = 11.2 Hz, 1H), 3.74 (dd, *J* = 11.2, 6.4 Hz, 1H), 3.37 (d, *J* = 12.0 Hz, 1H), 3.33 (dd, *J* = 11.2, 8.0 Hz, 1H), 2.91 (dd, *J* = 14.8, 8.0 Hz, 1H), 2.12 (d, *J* = 7.2 Hz, 1H), 0.92 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 162.3 (J_{CF} = 246 Hz), 147.7, 143.9, 138.7, 135.71, 135.68, 135.55, 135.47, 133.4 (J_{CF} = 17.9 Hz), 130.5, 130.4, 129.61, 129.59, 129.1, 128.1 (J_{CF} = 8.3 Hz), 127.7 (J_{CF} = 14.3 Hz), 127.6, 127.2, 126.9, 123.7, 123.6, 123.4 (J_{CF} = 3.6 Hz), 121.3, 120.9, 116.7, 115.0, 114.8 (J_{CF} = 21.5 Hz), 88.1, 63.45, 63.42, 38.3, 30.5, 29.7, 26.7, 19.0; LRMS (ESI) *m*/*z* 869 $[M+Na]^+$; HRMS(ESI) *m*/*z* $[M+Na]^+$ Calcd for $C_{56}H_{51}FN_2O_3SiNa$ 896.3551; found 869.3545.

8h: 79% yield (26.1 mg, 0.0315 mmol); white foam; $[\alpha]_D^{24}$ − 63.7 (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.29 (s, 1H), 8.61 (dd, *J* = 6.5, 2.5 Hz, 1H), 8.17 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.10 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.68 (dd, *J* = 8.0, 4.0 Hz, 6H), 7.62−7.55 (m, 4H), 7.45−7.27 (m, 10H), 7.23−7.15 (m,12H), 7.09−7.07 (m, 1H), 4.10 (d, *J* = 11.0 Hz, 1H), 3.70 (dd, *J* = 11.5, 6.5 Hz, 1H), 3.26 (d, *J* = 11.5 Hz, 1H), 3.21 (dd, *J* = 11.0, 8.0 Hz, 1H), 2.92 (dd, *J* = 14.5, 7.5 Hz, 1H), 1.89 (d, *J* = 7.5 Hz, 1H), 0.94 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 147.7, 143.9, 138.7, 136.4, 135.8, 135.7, 135.6, 135.5, 133.6, 129.60, 129.59, 129.1, 128.8, 127.9, 127.8, 127.65, 127.60, 127.3, 127.0, 126.4, 121.3, 120.9, 116.7, 88.2, 63.7, 63.3, 39.2, 36.5, 30.5, 26.7, 19.0; LRMS (ESI) *m*/*z* 829 $[M+H]^+$; Anal. Calcd for $C_{56}H_{52}N_2O_3Si$·:C, 81.12; H, 6.32; N, 3.38; found C, 81.02; H, 6.25; N, 3.38.

8i: 58% yield (20.4 mg, 0.0233 mmol); pale yellow foam; $[\alpha]_D^{24}$ − 130.3 (*c* 0.82, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.34 (s, 1H), 8.57 (d, *J* = 6.5 Hz, 1H), 8.24 (t, *J* = 2.0 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 2H), 7.67 (dd, *J* = 7.5, 4.0 Hz, 6H), 7.58−7.54 (m, 4H), 7.49−7.27 (m, 11H), 7.21−7.19 (m, 9H), 4.18 (d, *J* = 11.5 Hz, 1H), 3.68 (dd, *J* = 11.5, 7.0 Hz, 1H), 3.24 (d, *J* = 11.5 Hz, 1H), 3.19 (dd, *J* = 11.5, 9.0 Hz, 1H), 2.95 (dd, *J* = 14.5, 7.5 Hz, 1H), 1.70 (d, *J* = 7.0 Hz, 1H), 0.94 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 147.9, 146.5, 144.6, 143.6, 138.6, 136.0, 135.54, 135.49, 135.2, 133.3, 133.2, 129.7, 129.5, 128.9, 127.90, 127.87, 127.70, 127.65, 127.3, 127.2, 123.2, 121.5, 121.4, 116.7, 88.5, 63.2, 62.8, 40.1, 36.0, 31.3, 26.7, 19.0; LRMS (ESI) *m*/*z* 896 $[M+Na]^+$; HRMS(ESI) *m*/*z* $[M+Na]^+$ Calcd for $C_{56}H_{51}N_3O_5SiNa$ 896.3496; found 896.34902

8j: 63% yield (21.5 mg, 0.0252 mmol); white foam; $[\alpha]_D^{24}$ − 51.4 (*c* 0.87, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.32 (s, 1H), 8.57 (d, *J* = 8.5, 1H), 8.24 (d, *J* = 3.0 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.68−7.66 (m, 6H), 7.49−7.27 (m, 18H), 7.20−7.19 (m, 8H), 4.16 (d, *J* = 11.5 Hz, 1H), 3.66 (dd, *J* = 11.5, 6.5 Hz, 1H), 3.23 (d, *J* = 12.0 Hz, 1H), 3.18 (dd, *J* = 11.5, 8.5 Hz, 1H), 2.91 (dd, *J* = 14.5, 7.5 Hz, 1H), 1.68 (d, *J* = 7.0 Hz, 1H), 0.94 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 147.9, 143.7, 142.3, 138.6, 136.0, 135.6, 135.54, 135.48, 135.3, 133.4, 133.2, 131.8, 129.7, 129.5, 129.0, 127.9, 127.7, 127.6, 127.3, 127.2, 121.5, 121.4, 119.1, 116.7, 110.1, 88.5, 63.3, 62.8, 39.9, 36.2, 31.0, 26.7, 19.0; LRMS (ESI) *m*/*z* 854 $[M+H^+]$; Anal. Calcd for $C_{57}H_{51}N_3O_3Si$·0.5H_2O:C, 79.32; H, 6.07; N, 4.87; found C, 79.46; H, 6.25; N, 4.75.

8k: 77% yield (25.9 mg, 0.0306 mmol); white foam; $[\alpha]_D^{24}$ − 37.5 (*c* 1.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.31 (s. 1H), 8.64 (dd, *J* = 6.0, 3.2 Hz, 1H), 8.19 (dd, *J* = 4.0, 2.0 Hz, 1H), 8.11 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.67 (dd, *J* = 8.0, 4.4 Hz, 6H), 7.60−7.54 (m, 4H), 7.46−7.22 (m, 9H), 7.20−7.18 (m, 9H), 7.00 (t, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.69 (s, 1H), 6.53 (dd, *J* = 7.6, 2.0 Hz, 1H), 4.77 (s, 1H), 4.08 (d, *J* = 11.6 Hz, 1H), 3.69 (dd, *J* = 11.2, 6.4 Hz, 1H), 3.23 (d, *J* = 11.6 Hz, 1H), 3.17 (dd, *J* = 11.6, 8.8 Hz, 1H), 2.86 (dd, *J* = 14.0, 7.6 Hz, 1H), 1.81 (d, *J* = 7.6 Hz, 1H), 0.93 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 155.4, 147.8, 143.8, 138.7, 138.0, 135.9, 135.6, 135.5, 133.6, 133.3, 129.60, 129.59, 129.1, 129.0, 127.8, 127.7, 127.6, 127.3, 127.0, 121.4, 121.12, 121.09, 116.8, 115.9, 113.6, 88.2, 63.5, 63.3, 39.2, 36.3, 30.7, 26.7, 19.0; LRMS (ESI) *m*/*z* 867 [M

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+Na$^+$]; HRMS(ESI) m/z [M+Na$^+$] Calcd for $C_{56}H_{52}N_2O_4SiNa$ 867.3594; found 867.3588.

8l: 74% yield (25.5 mg, 0.0297 mmol); white foam; $[\alpha]_D^{24}$ − 30.4 (c 0.88, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.26 (s, 1H), 8.57 (dd, J = 6.8, 2.0 Hz, 1H), 8.19 (dd, J = 4.8, 2.0 Hz, 1H), 8.10 (dd, J = 8.0, 1.2 Hz, 1H), 7.69−7.66 (m, 6H), 7.61−7.55 (m, 4H), 7.45−7.25 (m, 10 H), 7.20−7.13 (m, 11H), 7.08 (d, J = 7.2 Hz, 1H), 4.51 (s, 2H), 4.08 (d, J = 11.2 Hz, 1H), 3.73 (dd, J = 11.2, 6.4 Hz, 1H), 3.26 (d, J = 11.6 Hz, 1H), 3.21 (dd, J = 11.6, 8.8 Hz, 1H), 2.91 (dd, J = 14.0, 7.2 Hz, 1H), 1.91 (d, J = 7.2 Hz, 1H), 0.94 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 147.8, 143.8, 140.5, 138.6, 136.9, 135.9, 135.6, 135.5, 133.6, 133.4, 129.62, 129.59, 129.0, 128.2, 128.0, 127.8, 127.7, 127.6, 127.5, 127.3, 127.0, 125.1, 121.4, 121.0, 116.7, 88.2, 65.4, 63.6, 63.2, 39.3, 36.2, 30.5, 26.7, 19.0; LRMS (ESI) m/z 859 [M+H]$^+$; Anal. Calcd for $C_{57}H_{54}N_2O_4Si$·:C, 79.69; H, 6.34; N, 3.26; found C, 79.54; H, 6.38; N, 3.17.

8m: 70% yield (23.3 mg, 0.0279 mmol); white foam; $[\alpha]_D^{24}$ − 22.4 (c 1.64, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.25 (s, 1H), 8.67 (dd, J = 7.5, 4.0 Hz, 1H), 8.17 (dd, J = 6.0, 2.5 Hz, 1H), 8.10 (dd, J = 11.0, 2.0 Hz, 1H), 7.73−7.56 (m, 10H), 7.47−7.26 (m, 8H), 7.21−7.17 (m, 10H), 7.07 (dd, J = 6.0, 4.0 Hz, 1H), 7.02 (s, 1H), 6.96 (d, J = 6.5 Hz, 1H), 4.05 (d, J = 14.0 Hz, 1H), 3.68 (dd, J = 14.5, 9.0 Hz, 1H), 3.25 (d, J = 15.0 Hz, 1H), 3.20 (dd, J = 14.5, 10.5 Hz, 1H), 2.83 (dd, J = 18.5, 9.5 Hz, 1H), 1.77 (d, J = 9.0 Hz, 1H), 0.94 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 147.7, 143.8, 143.7, 140.0, 138.7, 135.8, 135.7, 135.60, 135.58, 135.499, 133.495, 133.3, 129.63, 129.60, 129.5, 129.0, 127.9, 127.8, 127.71, 127.66, 127.6, 127.3, 127.02, 126.95, 126.5, 125.7, 124.1, 121.3, 121.0, 116.7, 88.1, 63.3, 63.0, 40.0, 32.3, 30.6, 26.7, 19.0; LRMS (ESI) m/z 857 [M+Na]$^+$; HRMS(ESI) m/z [M+Na]$^+$ Calcd for $C_{54}H_{50}N_2O_3SSiNa$ 857.3209; found 857.3203.

8n: 51% yield (17.3 mg, 0.0204 mmol); white foam; $[\alpha]_D^{24}$ − 6.9 (c 0.84, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.16 (s, 1H), 9.40 (s, 1H), 8.70−8.67 (m, 1H), 8.22 (d, J = 2.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.60−7.49 (m, 10H), 7.43−7.27 (m, 8H), 7.18−7.16 (m, 9H), 7.03 (d, J = 4.0 Hz, 1H), 6.24 (d, J = 3.6 Hz, 1H), 3.85 (d, J = 12.0 Hz, 1H), 3.69 (dd, J = 11.2, 6.4 Hz, 1H), 3.39 (d, J = 12.0 Hz, 1H), 3.30 (dd, J = 11.6, 8.4 Hz, 1H), 2.83 (dd, J = 14.8, 7.2 Hz, 1H), 1.77 (d, J = 7.2 Hz, 1H), 0.94 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 167.5, 158.7, 152.0, 148.0, 143.5, 138.6, 135.9, 135.545, 135.469, 135.1, 133.3, 133.1, 129.74, 129.71, 128.9, 127.8, 127.69, 127.65, 127.2, 127.1, 121.5, 116.7, 88.1, 62.9, 62.6, 40.1, 31.0, 28.1, 26.7, 19.0; LRMS (ESI) m/z 869 [M+Na]$^+$; HRMS(ESI) m/z [M+Na]$^+$ Calcd for $C_{55}H_{50}N_2O_5SiNa$ 869.3387; found 869.3381.

8o: 56% yield (21.8 mg, 0.0225 mmol); white foam, $[\alpha]_D^{24}$ − 49.5 (c 1.32, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.30 (s, 1H), 8.58 (dd, J = 7.5, 2.5 Hz, 1H), 8.18 (d, J = 2.5 Hz, 1H), 8.08−8.06 (m, 1H), 7.89 (s, 1H), 7.72−7.70 (m, 6H), 7.59 (dd, J = 19.0, 7.0 Hz, 4H), 7.46−7.19 (m, 21H), 6.41 (d, J = 3.5 Hz, 1H), 4.11 (d, J = 11.0 Hz, 1H), 3.74 (dd, J = 11.0, 6.5 Hz, 1H), 3.28−3.22 (m, 2H), 2.98 (dd, J = 14.5, 7.5 Hz, 1H), 1.98 (d, J = 7.5 Hz, 1H), 1.60 (s, 9H), 0.95 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 149.8, 147.7, 143.9, 138.6, 135.8, 135.63, 135.58, 135.5, 133.6, 133.4, 130.7, 130.4, 129.58, 129.56, 129.1, 127.8, 127.63, 127.58, 127.3, 127.0, 125.7, 125.4, 121.3, 121.0, 120.8, 116.7, 114.6, 107.4, 88.2, 83.3, 63.8, 63.4, 39.2, 36.6, 30.7, 28.1, 26.7, 19.0; LRMS (ESI) m/z 990 [M+Na]$^+$; HRMS(ESI) m/z [M+Na]$^+$ Calcd for $C_{63}H_{61}N_3O_5SiNa$ 990.4278; found 990.4272.

8p: 55% yield (18.7 mg, 0.0221 mmol); white foam; $[\alpha]_D^{24}$ − 46.8 (c 0.93, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.33 (s, 1H), 8.60 (dd, J = 6.8, 1.6 Hz, 1H), 8.26 (dd, J = 4.4, 1.6 Hz, 1H), 8.15 (dd, J = 8.0, 1.2 Hz, 1H), 7.97 (d, J = 7.6 Hz, 2H), 7.66−7.64 (m, 6H), 7.57−7.26 (m, 13H), 7.21−7.19 (m, 9H), 7.05 (d, J = 7.2 Hz, 2H), 4.17 (d, J = 11.6 Hz, 1H), 3.63 (dd, J = 12.0, 6.4 Hz, 1H), 3.20 (d, J = 12.0 Hz, 1H), 3.14 (dd, J = 11.2, 8.0 Hz, 1H), 2.86 (dd, J = 14.4, 7.6 Hz, 1H), 1.46 (d, J = 7.6 Hz, 1H), 0.93 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 147.9, 143.5, 138.6, 138.4, 136.4, 136.1, 135.53, 135.47, 135.0, 133.2, 133.1, 129.8, 129.7, 128.9, 127.9, 127.72, 127.66, 127.3, 127.2, 126.1, 121.6, 121.5, 116.8, 88.5, 63.0, 62.5, 40.4, 34.5, 31.1, 26.6, 19.0; LRMS (ESI) m/z 868 [M+Na]$^+$; HRMS(ESI) m/z [M+Na]$^+$ Calcd for $C_{55}H_{51}N_3O_4SiNa$ 868.3547; found 868.3541.

Functionalization of the 8-Aminoquinoline Moiety. To a solution of Schwartz's reagent (33.8 mg, 0.131 mmol) in THF (0.33 mL) was added a solution of **8h** (54.3 mg, 0.655 mmol) in THF (0.33 mL) at room temperature. After stirring at room temperature for 1 h, sat. aq. $NaHCO_3$ (0.40 mL) was added to the reaction mixture. The mixture was extracted with EtOAc. The organic layer was washed with sat. brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (hexane:EtOAc = 20:1) to give **10** in 79% yield (35.4 mg, 0.0515 mmol) a white foam.

10: $[\alpha]_D^{24}$ − 29.4 (c 1.56, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.76 (s, 1H), 7.54 (dd, J = 13.0, 6.5 Hz, 4H), 7.44−7.17 (m, 26H), 3.80 (dd, J = 11.5, 6.0 Hz, 1H), 3.52 (d, J = 10.0 Hz, 1H), 3.47 (dd, J = 11.5, 7.5 Hz, 1H), 3.35 (d, J = 10.0 Hz, 1H), 2.51 (dd, J = 14.0, 7.0 Hz, 1H), 2.30 (d, J = 7.5 Hz, 1H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 143.8, 135.6, 135.50, 135.48, 133.5, 133.4, 129.7, 129.1, 128.7, 128.5, 128.4, 127.8, 127.68, 127.65, 127.0, 126.9, 86.8, 63.0, 60.5, 42.3, 37.2, 31.9, 26.8, 19.0; LRMS (ESI) m/z 709 [M + Na]$^+$; HRMS(ESI) m/z [M+Na]$^+$ Calcd for $C_{47}H_{46}O_3SiNa$ 709.3114; found 709.31084.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02935.

Characterization data for new compounds and chiral HPLC chart (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: hoshiya@mb.kyoto-phu.ac.jp

*E-mail: shu@pharm.hokudai.ac.jp

ORCID

Jun'ichi Uenishi: 0000-0002-7012-3482

Satoshi Shuto: 0000-0001-7850-8064

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Chen, D. Y.-K.; Pouwer, R. H.; Richard, J.-A. *Chem. Soc. Rev.* **2012**, *41*, 4631−4643. (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977−1050. (c) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625−1648. (d) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041−7095.

(2) (a) De Simone, F.; Waser, J. *Synthesis* **2009**, *2009*, 3353−3374. (b) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151−1196.

(3) (a) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117−3179. (b) Gagnon, A.; Duplessis, M.; Fader, L. *Org. Prep. Proced. Int.* **2010**, *42*, 1−69.

(4) (a) Grygorenko, O. O.; Babenko, P.; Volochnyuk, D. M.; Raievskyi, O.; Komarov, I. V. *RSC Adv.* **2016**, *6*, 17595−17605. (b) Talele, T. T. *J. Med. Chem.* **2016**, *59*, 8712−8756. (c) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845−5859. (d) Arisawa, M.; Sato, T.; Hoshiya, N.; Al-Amin, M.; Kogami, Y.; Shuto, S. *ACS Comb. Sci.* **2014**, *16*, 215−220. (e) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752.

(5) (a) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S. *J. Med. Chem.* **1988**, *31*, 2235−2246. (b) Nicolaou, K.

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J. Org. Chem. 2017, 82, 2535−2544

C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939−9953. (c) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893−930. (d) Zhang, M.-Z.; Chen, Q.; Yang, G.-F. *Eur. J. Med. Chem.* **2015**, *89*, 421−441.

(6) (a) Shuto, S.; Ono, S.; Hase, Y.; Kamiyama, N.; Takada, H.; Yamasihita, K.; Matsuda, A. *J. Org. Chem.* **1996**, *61*, 915−923. (b) Kazuta, Y.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2002**, *67*, 1669−1677. (c) Yonezawa, S.; Yamamoto, T.; Yamakawa, H.; Muto, C.; Hosono, M.; Hattori, K.; Higashino, K.; Yutsudo, T.; Iwamoto, H.; Kondo, Y.; Sakagami, M.; Togame, H.; Tanaka, T.; Nakano, T.; Takemoto, H.; Arisawa, M.; Shuto, S. *J. Med. Chem.* **2012**, *55*, 8838−8858. (d) Van Goor, F.; Hadida, S.; Grootenhuis, P. D.; Burton, B.; Stack, J. H.; Straley, K. S.; Decker, C. J.; Miller, M.; McCartney, J.; Olson, E. R.; Wine, J. J.; Frizzell, R. A.; Ashlock, M.; Negulescu, P. A. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 18843−18848. (e) Rajaratnam, S. M. V.; Polymeropoulos, M. M.; Fisher, D. M.; Roth, J.; Scott, C.; Birznieks, G.; Klerman, E. B. *Lancet* **2009**, *373*, 482−491.

(7) Construction of nonchiral tetrasubstituted arylcyclopropanes has also been developed. (a) Yan, N.; Liu, X.; Fox, J. M. *J. Org. Chem.* **2008**, *73*, 563−568. (b) Tarwade, V.; Liu, X.; Yan, N.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 5382−5383. (c) Maurya, R. A.; Kapure, J. S.; Adiyala, P. R.; Srikanth, P. S.; Chandrasekhar, D.; Kamal, A. *RSC Adv.* **2013**, *3*, 15600−15603. (d) Lévesque, É.; Goudreau, S. R.; Charette, A. B. *Org. Lett.* **2014**, *16*, 1490−1493. (e) Pons, A.; Beucher, H.; Ivashkin, P.; Lemonnier, G.; Poisson, T.; Charette, A. B.; Jubault, P.; Pannecoucke, X. *Org. Lett.* **2015**, *17*, 1790−1793. (f) Yavari, I.; Hosseinpour, R.; Skoulika, S. *Synlett* **2015**, *26*, 380−384.

(8) (a) Davies, H. M.; Nagashima, T.; Klino, J. L., III. *Org. Lett.* **2000**, *2*, 823−826. (b) Negretti, S.; Cohen, C. M.; Chang, J. J.; Guptill, D. M.; Davies, H. M. L. *Tetrahedron* **2015**, *71*, 7415−7420.

(9) Kim, H. Y.; Salvi, L.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 954−962.

(10) Beaulieu, L.-P. B.; Zimmer, L. E.; Charette, A. B. *Chem. - Eur. J.* **2009**, *15*, 11829−11832.

(11) (a) Kobayashi, T.; Arisawa, M.; Shuto, S. *Org. Biomol. Chem.* **2011**, *9*, 1219−1224. (b) Tanabe, M.; Watanabe, M.; Hoshiya, N.; Mizuno, A.; Fukuda, H.; Arisawa, M.; Shuto, S. *J. Org. Chem.* **2013**, *78*, 11714−11720. (c) Yotsuji, K.; Hoshiya, N.; Kobayashi, T.; Fukuda, H.; Abe, H.; Arisawa, M.; Shuto, S. *Adv. Synth. Catal.* **2015**, *357*, 1022−1028.

(12) (a) Hoshiya, N.; Kobayashi, T.; Arisawa, M.; Shuto, S. *Org. Lett.* **2013**, *15*, 6202−6205. (b) Hoshiya, N.; Takenaka, K.; Shuto, S.; Uenishi, J. *Org. Lett.* **2016**, *18*, 48−51.

(13) The 8-aminoquinoline group was first used as a directing auxiliary for C-H arylation by Daugulis's group. Other groups have applied the method to various C-H functionalization. (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154−13155. (b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965−3972. (c) Nadres, E. T.; Santos, G. I. F.; Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2013**, *78*, 9689−9714. (d) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726−11743.

(14) (a) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510−3511. (b) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598−19601. (c) Wasa, M.; Chan, K. S. L.; Zhang, X.-G.; He, J.; Miura, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 18570−18572. (d) Chan, K. S. L.; Fu, H.-Y.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 2042−2046.

(15) Roman, D. S.; Charette, A. B. *Org. Lett.* **2013**, *15*, 4394−4397.

(16) Parella, R.; Gopalakrishnan, B.; Babu, S. A. *Org. Lett.* **2013**, *15*, 3238−3241.

(17) Wong, J. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165−198.

(18) (a) Sekiyama, T.; Hatsuya, S.; Tanaka, Y.; Uchiyama, M.; Ono, N.; Iwayama, S.; Oikawa, M.; Suzuki, K.; Okunishi, M.; Tsuji, T. *J. Med. Chem.* **1998**, *41*, 1284−1298. (b) Kato, H.; Ishigame, T.; Oshima, N.; Hoshiya, N.; Shimawaki, K.; Arisawa, M.; Shuto, S. *Adv. Synth. Catal.* **2011**, *353*, 2676−2680.

(19) Kazuta, Y.; Abe, H.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2004**, *69*, 9143−9150.

(20) The reaction of **3D** and **4d** with $Pd(OAc)_2$ gave the desired product **8D** in miserable yield (>10%).

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