Synthesis R. Shimazumi et al. Special Topic

Late-Stage Derivatization of Buflavine by Nickel-Catalyzed Direct Substitution of a Methoxy Group via C–O Bond Activation

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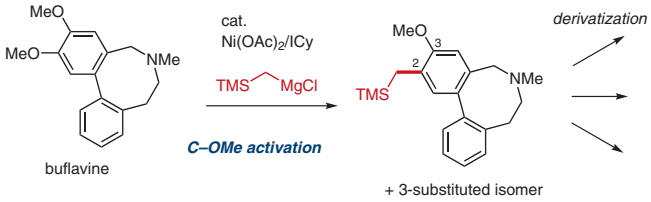


Dedicated to Professor Shinji Murai for his contribution to bond activation.

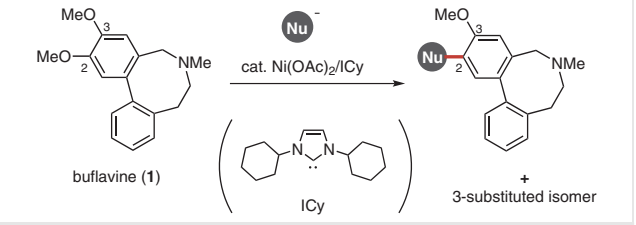
Published as part of the Special Topic *Bond Activation – in Honor of Prof. Shinji Murai*

Received: 10.03.2021
Accepted after revision: 25.03.2021
Published online: 25.03.2021
DOI: 10.1055/a-1467-2494; Art ID: ss-2021-f0122-st

Abstract The nickel-catalyzed cross-coupling of methoxyarenes was applied to buflavine, which allows for the selective monosubstitution of one of the two methoxy groups in the molecule, leading to the formation of 2- and 3-substituted isomers. Trimethylsilylmethyl ($TMSCH_2$), phenyl, and alkynyl groups can be introduced into buflavine using this method. The resulting $TMSCH_2$ analogue of buflavine can also be converted into several other derivatives.

Key words C–O bond activation, cross-coupling, nickel, natural product, late-stage functionalization

The derivatization of natural products allows for libraries of such derivatives to be created, which often leads to the discovery of drugs with improved potency, selectivity, and/or pharmacokinetic profiles. In addition, natural product derivatives can be used to accelerate the discovery and the pharmacological study of new biological targets.[1] However, the limited scope of the methods that are currently available for derivatizing natural products confines the chemical space to be explored, and therefore, new reliable methods applicable for this purpose are required. In this context, modern C–H functionalization chemistry has emerged as a powerful tool for the late-stage derivatization of natural products.[2] We envisioned that our previously reported nickel-catalyzed cross-coupling of methoxy-substituted arenes[3] has some potential for use in rapidly increasing the diversity of natural products, given that a methoxyarene is a common motif found in natural products. In fact, we[4] and others[5] demonstrated that nickel-catalyzed cross-coupling can be used to functionalize monomethoxy-substituted natural products. However, naturally occurring compounds often contain multiple methoxy groups, and their selective monoderivatization is a challenge, especially when the methoxy groups are located in a similar electronic and steric environment. Buflavine (**1**)[6,7] represents a relatively simple natural product that contains two methoxy groups with no steric and electronic bias. Herein, we report on the nickel-catalyzed alkylation of buflavine (**1**), in which one of the two methoxy groups is substituted by an incoming nucleophile to provide an array of buflavine derivatives in a divergent fashion (Scheme 1).



Scheme 1 Nickel-catalyzed functionalization of buflavine (**1**)

We initiated our study by examining the nickel-catalyzed cross-coupling of 1,2-dimethoxyarene derivative **2**, as a model compound of **1**, with the alkyl Grignard reagent **3**, based on our previous success in the monoselective alkylation of 1,2-dimethoxybenzene with this nucleophile.[4a,b] The use of an *N*-cyclohexyl-substituted N-heterocyclic carbene (NHC) ligand (i.e., ICy) led to the formation of the mono-

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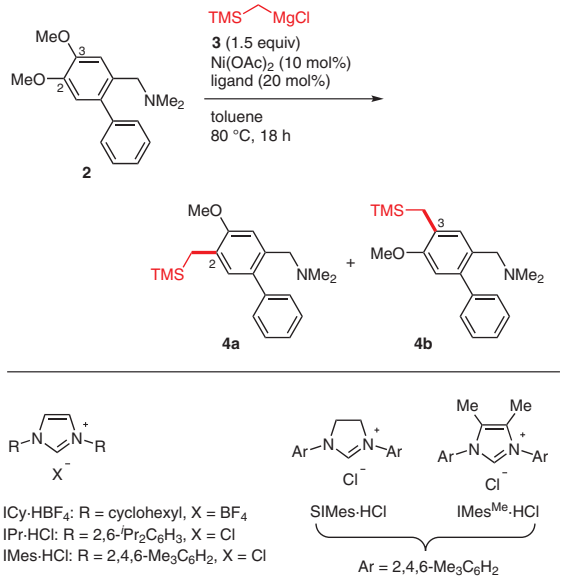
alkylated product **4** in 83% isolated yield with two regioisomers being obtained in a ratio of 1.4:1 (Table 1, entry 1). Other NHC ligands, including IPr (entry 2), IMes (entry 3), and SIMes (entry 4), as well as PCy_3 (entry 6), also promoted this alkylation reaction, although the yields were lower than that obtained with ICy. Notably, the use of $IMes^{Me}$, the 4,5-dimethyl-substituted analogue of IMes,[8] afforded **4** in an excellent yield (entry 5). Based on these results, we used the commercially available ICy as the ligand in the subsequent studies.

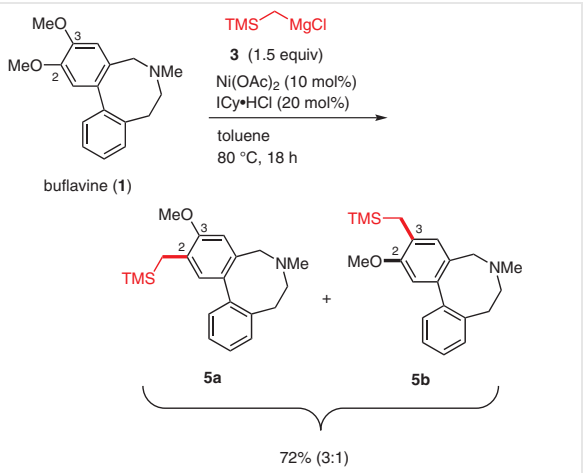
Table 1 Optimization of Nickel-Catalyzed Cross-Coupling Using the Model Substrate **2**[a]



Entry	Ligand	Conv. (%) of **2**	Yield (%) of **4** (**4a**/**4b**)[b]
1[c]	ICy·HBF_4	>99	83 (1.4:1)[d]
2	IPr·HCl	66	39 (1.3:1)
3	IMes·HCl	67	51 (1:1.5)
4	SIMes·HCl	58	32 (1:2.3)
5	$IMes^{Me}$·HCl	92	99 (1:1.7)
6	PCy_3	78	68 (1:1.6)

[a] Reaction conditions: **2** (0.30 mmol), **3** (0.45 mmol), $Ni(OAc)_2$ (0.030 mmol), ligand (0.060 mmol), toluene (1.0 mL), 18 h, 80 °C.
[b] Determined by GC using pentadecane as an internal standard.
[c] Run on a 1.0 mmol scale.
[d] Isolated yield.

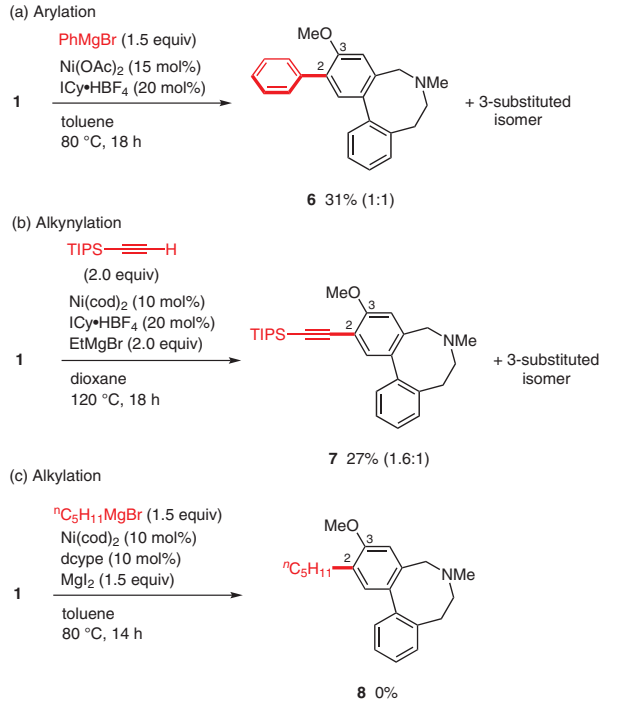
With the optimized reaction conditions in hand, we next investigated the alkylative cross-coupling of buflavine (**1**) with **3** (Scheme 2). The reaction of **1** with **3** in the presence of $Ni(OAc)_2$ (10 mol%) and ICy·HCl (20 mol%) in toluene at 80 °C for 18 hours afforded the monoalkylated products **5** in 72% isolated yield, and no dialkylated product was observed, as was the case when the model substrate **2** was used. The product consisted of two regioisomers **5a** and **5b** in a ratio of 3:1, and the structure of the major isomer **5a** was unambiguously determined by HSQC and HMBC measurements (see the Supporting Information for details). Although a high regioselectivity is desired in target-oriented synthesis, the formation of isomeric mixtures can also be advantageous in diversity-oriented synthesis. For example, in the late-stage derivatization of drug candidates, each product isomer serves as an additional derivative that can be obtained without the need for costly and laborious *de novo* synthesis.



Scheme 2 Nickel-catalyzed cross-coupling of buflavine (**1**) with **3**. *Reagents and conditions*: **1** (0.20 mmol), **3** (0.30 mmol), $Ni(OAc)_2$ (0.020 mmol), ICy·HCl (0.040 mmol), toluene (1.0 mL), 80 °C, 18 h.

The successful cross-coupling of a methoxy group of **1** with $TMSCH_2MgCl$ prompted us to examine the issue of whether **1** could also be functionalized with other nucleophiles (Scheme 3). Although Suzuki–Miyaura-type cross-coupling with $PhB(nep)_2$ (nep = neopentylglycolate) using a Ni/ICy catalyst[4c] failed, it was possible to synthesize the phenylated buflavine **6** using PhMgBr as a nucleophile, affording a mixture of two regioisomers (isomeric ratio = 1:1) in 31% yield (Scheme 3a). Moreover, the alkynylated buflavine **7** can be synthesized by Ni/ICy-catalyzed cross-coupling using a triisopropylsilyl-protected alkynyl Grignard reagent (Scheme 3b).[4b] We also examined cross-coupling of **1** with a β-hydrogen-containing alkyl group using our previously reported Ni/dcype system,[4e] but the desired product **8** was not formed (Scheme 3c).

The $TMSCH_2$ group in **5** serves as a versatile handle for the further derivatization of buflavine (Scheme 4). For example, the benzylsilane moiety in **5** can function as a benzyl anion equivalent in the presence of a suitable fluoride activator, thus allowing for the reaction with electrophiles.[9] In fact, treatment of **5** with tetrabutylammonium difluorotriphenylsilicate (TBAT) in the presence of an aldehyde or an imine afforded buflavine derivatives bearing a pendant alcohol (i.e., **9**) or an amine (i.e., **10**) group. The *in situ* generated benzyl anion can be protonated when **5** is treated with

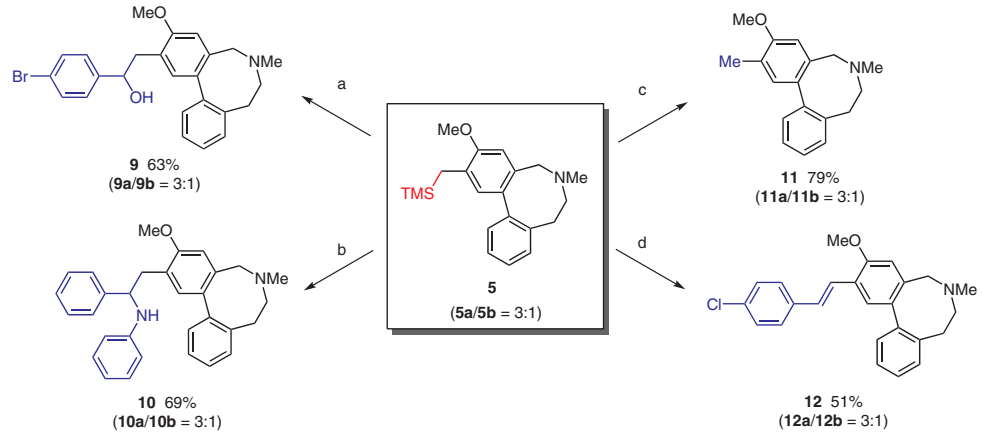


Scheme 3 Scope of nucleophiles [TIPS: triisopropylsilyl; dcype: 1,2-bis(dicyclohexylphosphino)ethane]

TBAF in the absence of added electrophiles to form the methylated analogue **11** of buflavine which could not be accessed directly by cross-coupling with MeMgX under the nickel-catalyzed conditions. Given the fact that a methyl group can have a profound impact on the various aspects of biological activity of a molecule,[10] the late-stage introduction of a methyl group via nickel-catalyzed methoxy-substitution reactions would be useful in this context. The π-extended analogue **12** of buflavine could be synthesized by the addition to an aldehyde, followed by acid-mediated dehydration.

In summary, we have demonstrated that nickel-catalyzed cross-coupling of methoxyarenes can be used to elaborate the methoxy-substituted natural product buflavine. $TMSCH_2$, aryl, and alkynyl groups can be introduced into **1** by using the corresponding Grignard reagents. The $TMSCH_2$ group on the buflavine skeleton is also amenable to further transformations, thus allowing a variety of derivatives of **1** to be generated. The findings reported in this study indicate that such methoxy cross-coupling reactions are potential and powerful tools for rapidly increasing the diversity of natural products.

^1H (400 or 600 MHz) and ^{13}C (101 or 150 MHz) NMR spectra were recorded on a JEOL ECS-400 spectrometer or Bruker Avance III spectrometer, in $CDCl_3$ with tetramethylsilane as the internal standard. The chemical shifts in ^1H NMR spectra were recorded relative to either $CHCl_3$ (δ 7.26) or tetramethylsilane (δ 0.00). The chemical shifts in ^{13}C NMR spectra were recorded relative to $CDCl_3$ (δ 77.00). The data are reported as follows: chemical shift (δ) in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), and integration. IR spectra were obtained using a JASCO FT/IR-4200 spectrophotometer. Absorption is reported in reciprocal centimeters (cm^{-1}) with the following relative intensities: s (strong), m (medium), or w (weak). High-resolution mass spectra (HRMS) were obtained using a JEOL JMS-700 spectrometer. Analytical GC was carried out on a Shimadzu GC-2014 gas chromatograph, equipped with a flame ionization detector. Column chromatography was performed with silica gel (SiliCycle SiliaFlash F60, 230–400 mesh) or NH_2 silica gel (Kanto Chemical Co., Inc., NH_2 Silica Gel 60, spherical, particle size 40–50 μm).



Scheme 4 Derivatization of **5**. The corresponding 3-substituted isomers were also formed in each reaction. *Reagents and conditions*: (a) **5** (0.19 mmol), 4-bromobenzaldehyde (0.4 mmol), TBAT (0.10 mmol), 4 Å MS (200 mg), THF (2.0 mL), 12 h, 70 °C; (b) **5** (0.20 mmol), benzylideneaniline (0.4 mmol), TBAT (0.10 mmol), 4 Å MS (200 mg), THF (2.0 mL), 12 h, 70 °C; (c) **5** (0.15 mmol), 1 M TBAF in THF (0.3 mL), THF (2.0 mL), 12 h, rt; (d) **5** (0.20 mmol), 4-chlorobenzaldehyde (0.4 mmol), TBAT (0.10 mmol), 4 Å MS (200 mg), THF (2.0 mL), 1 h, 75 °C; *p*-TsOH·H_2O (0.80 mmol), toluene (2.0 mL), 1 h, 120 °C (TBAT: tetrabutylammonium difluorotriphenylsilicate).

Toluene, 1,4-dioxane, and THF (dehydrated) were purchased from Wako Chemicals and used as received. $Ni(cod)_2$ (Strem), ICy·HCl (TCI), ICy·HBF_4 (TCI), IMes·HCl (TCI), IPr·HCl (TCI), SIMes·HCl (TCI), and PCy_3 (Aldrich) were purchased from commercial suppliers and used as received. $IMes^{Me}$·HCl[11] [1118916-80-5] and buflavine (**1**)[12] [65762-70-1] were prepared according to literature procedures. (Trimethylsilyl)methylmagnesium chloride (1.0 M in THF, Aldrich), ethynyltriisopropylsilane (TCI), and ethylmagnesium bromide (1.0 M in THF, Aldrich) were purchased from commercial suppliers and used as received. Anhydrous $Ni(OAc)_2$ was prepared by heating $Ni(OAc)_2$·4 H_2O (Wako) at 100 °C under vacuum until the color changed from greenish blue (hydrate) to greenish yellow (anhydride). Tetrabutylammonium fluoride (1.0 M in THF, TCI), tetrabutylammonium difluorotriphenylsilicate (TCI), *p*-toluenesulfonic acid monohydrate (TCI), 4-bromobenzaldehyde (TCI), 4-chlorobenzaldehyde (TCI), and benzylideneaniline (TCI) were purchased from commercial suppliers and used as received.

1-(4,5-Dimethoxy-[1,1′-biphenyl]-2-yl)-*N*,*N*-dimethylmethanamine (2)

This compound was prepared based on a reductive amination reaction procedure reported in the literature.[13] In a round-bottom two-necked flask, 4,5-dimethoxy-[1,1′-biphenyl]-2-carbaldehyde[14] (1.45 g, 6.0 mmol) was dissolved in THF (50 mL). $HNMe_2$·HCl (978 mg, 12 mmol), NaOAc (788 mg, 9.6 mmol), and AcOH (0.2 mL) were then added. The mixture was cooled to 0 °C, and $NaBH(OAc)_3$ (2.8 g, 13.2 mmol) was added portionwise. After stirring the mixture at rt for 12 h, solvent was removed in vacuo. The residue was then dissolved in Et_2O and extracted with 10% citric acid solution (3 × 30 mL). The aqueous layer was neutralized with KOH at 0 °C and extracted with Et_2O (3 × 30 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo to give the desired product **2**.

Yield: 1.52 g (93%); colorless solid; mp 92.1 °C.

IR (ATR): 1219 (w), 772 (s), 599 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.31 (m, 5 H), 7.11 (s, 1 H), 6.74 (s, 1 H), 3.94 (s, 3 H), 3.87 (s, 3 H), 3.31 (s, 2 H), 2.13 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.18, 147.25, 141.36, 134.62, 129.75, 128.74, 127.91, 126.65, 112.79, 112.23, 60.51, 56.03, 55.87, 45.29.

MS: *m*/*z* (%) = 271 (M^+, 33), 270 (19), 257 (14), 256 (79), 240 (10), 228 (24), 227 (73), 226 (15), 212 (22), 197 (22), 196 (100), 195 (12), 181 (21), 165 (13), 153 (13), 152 (11), 141 (10), 115 (14), 58 (67), 42 (11).

HRMS (DART): *m*/*z* calcd for $C_{17}H_{22}NO_2$ [M + H^+]: 272.1645; found: 272.1647.

Nickel-Catalyzed Cross-Coupling of 2 with 3

A 10 mL sample vial with a Teflon-sealed screw cap was placed in a nitrogen-filled glovebox. $Ni(OAc)_2$ (17.6 mg, 0.10 mmol), ICy·HBF_4 (64.0 mg, 0.20 mmol), **2** (272 mg, 1.0 mmol), and **3** (1.0 M in THF; 1.50 mL, 1.5 mmol) were then added sequentially to the vial, and the resulting mixture was stirred at rt for 3 min. The THF was then removed in vacuo to give a residue, which was dissolved in toluene (3.0 mL). The vial was then sealed and the contents were stirred at 80 °C for 18 h. The reaction mixture was then treated with saturated aqueous NH_4Cl (5.0 mL) to give a biphasic mixture. The resulting aqueous layer was collected and extracted with EtOAc (3 × 15 mL). The combined organic extracts were then washed with brine and dried (Na_2SO_4) before being evaporated to dryness to give a residue, which was purified by flash column chromatography over silica gel (hexane/EtOAc 4:1 to EtOAc 100%) to give **4a** and **4b**.

1-(4-Methoxy-5-((trimethylsilyl)methyl)-[1,1′-biphenyl]-2-yl)-*N*,*N*-dimethylmethanamine (4a)

Yield: 161 mg (49%); colorless oil; R_f = 0.16 (EtOAc, on silica gel).

IR (ATR): 2947 (w), 2813 (w), 1486 (m), 1245 (m), 849 (s), 700 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.30 (m, 5 H), 7.02 (s, 1 H), 6.87 (s, 1 H), 3.85 (s, 3 H), 3.35 (s, 2 H), 2.15 (s, 6 H), 2.10 (s, 2 H), –0.01 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.81, 141.69, 134.22, 132.87, 130.92, 129.83, 127.75, 127.49, 126.25, 110.72, 60.92, 55.15, 45.35, 20.12, –1.57.

MS: *m*/*z* (%) = 327 (M^+, 31), 326 (19), 313 (28), 312 (100), 296 (10), 284 (23), 283 (19), 282 (13), 268 (13), 267 (15), 254 (10), 253 (12), 252 (36), 179 (23), 73 (61), 58 (37).

HRMS (DART): *m*/*z* calcd for $C_{20}H_{30}NOSi$ [M + H^+]: 328.2091; found: 328.2089.

1-(5-Methoxy-4-((trimethylsilyl)methyl)-[1,1′-biphenyl]-2-yl)-*N*,*N*-dimethylmethanamine (4b)

Yield: 110 mg (34%); colorless oil; R_f = 0.28 (EtOAc, on silica gel).

IR (ATR): 2922 (m), 2853 (w), 1222 (w), 850 (w), 772 (s), 700 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.33 (m, 5 H), 7.11 (s, 1 H), 6.67 (s, 1 H), 3.77 (s, 3 H), 3.26 (s, 2 H), 2.13 (s, 6 H), 2.13 (s, 2 H), 0.01 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.97, 141.97, 139.03, 130.93, 129.73, 128.11, 127.79, 127.58, 126.51, 111.39, 60.45, 54.97, 45.16, 20.20, –1.46.

MS: *m*/*z* (%) = 327 (M^+, 25), 326 (16), 313 (17), 312 (62), 284 (14), 283 (39), 269 (12), 268 (10), 267 (22), 253 (19), 252 (53), 251 (11), 179 (27), 178 (14), 73 (100), 59 (16), 58 (40), 45 (12).

HRMS (DART): *m*/*z* calcd for $C_{20}H_{30}NOSi$ [M + H^+]: 328.2091; found: 328.2094.

Nickel-Catalyzed Alkylation of 1[4a]

A 10 mL sample vial with a Teflon-sealed screw cap was placed in a nitrogen-filled glovebox. $Ni(OAc)_2$ (3.5 mg, 0.020 mmol), ICy·HCl (11 mg, 0.040 mmol), **1** (55 mg, 0.20 mmol), and **3** (1.0 M in THF; 0.30 mL, 0.30 mmol) were then added sequentially to the vial, and the resulting mixture was stirred at rt for 3 min. The THF was then removed in vacuo to give a residue, which was dissolved in toluene (1.0 mL). The vial was then sealed and the contents were stirred at 80 °C for 18 h. The reaction mixture was then treated with saturated aqueous NH_4Cl (5.0 mL) to give a biphasic mixture. The resulting aqueous layer was collected and extracted with EtOAc (3 × 15 mL). The combined organic extracts were then washed with brine and dried (Na_2SO_4) before being evaporated to dryness to give a residue, which was purified by flash column chromatography over NH silica gel (hexane 100% to hexane/EtOAc 3:1) to give a mixture of **5a** and **5b** (**5a**/**5b** = 3:1, determined by ^1H NMR). A part of **5a** was obtained in a pure form.

3-Methoxy-6-methyl-2-((trimethylsilyl)methyl)-5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocine (5a)

Yield: 48.6 mg (72%) as a mixture with **5b**; yellow oil; R_f = 0.44 (hexane/EtOAc 1:1, on NH silica gel).

IR (ATR, **5a** + **5b**): 1604 (w), 1590 (w), 1560 (w), 1232 (w), 1209 (w), 781 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.22 (m, 4 H), 6.90 (s, 1 H), 6.81 (s, 1 H), 3.85 (s, 3 H), 3.52 (d, *J* = 13.6 Hz, 1 H), 3.30–3.25 (m, 1 H), 3.06 (d, *J* = 13.6 Hz, 1 H), 2.75–2.70 (m, 1 H), 2.56–2.51 (m, 5 H), 2.11 (s, 2 H), –0.03 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.02, 141.20, 140.29, 134.14, 132.45, 130.26, 129.28, 129.15, 128.37, 127.51, 125.97, 111.95, 58.94, 58.83, 54.96, 46.18, 32.69, 20.31, –1.55.

MS: *m*/*z* (%) = 339 (M^+, 18), 324 (19), 281 (37), 266 (14), 191 (12), 179 (10), 178 (21), 165 (12), 73 (100), 59 (11), 45 (28), 44 (11), 42 (10).

HRMS (DART): *m*/*z* calcd for $C_{21}H_{30}NOSi$ [M + H^+]: 340.2091; found: 340.2091.

2-Methoxy-6-methyl-3-((trimethylsilyl)methyl)-5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocine (5b)

Yield: 48.6 mg (72%) as a mixture with **5a**; yellow oil; R_f = 0.60 (hexane/EtOAc 1:1, on NH silica gel).

Spectroscopic data were collected with a 3:1 (**5a**/**5b**) mixture.

^{1}H NMR (400 MHz, $CDCl_3$): δ (selected peaks assigned to **5b**) = 6.96 (s, 1 H), 6.70 (s, 1 H), 3.79 (s, 3 H), 3.56 (d, *J* = 13.6 Hz, 1 H), 3.13 (d, *J* = 13.6 Hz, 1 H), 2.69 (m, 5 H), 0.06 (s, 9 H); other peaks of **5b** are overlapped with those of **5a**.

^{13}C NMR (101 MHz, $CDCl_3$): δ (peaks assigned to **5b**) = 155.39, 141.55, 140.69, 134.20, 132.30, 130.26, 129.35, 129.22, 128.39, 127.75, 125.84, 110.75, 58.38, 57.32, 55.02, 44.10, 31.63, 20.15, –1.46.

MS: *m*/*z* (%) (**5a** + **5b**) = 340 (18), 339 (M^+, 63), 338 (15), 325 (16), 324 (60), 282 (25), 281 (100), 266 (33), 265 (19), 207 (11), 191 (13), 178 (14), 73 (72), 45 (12).

HRMS (DART): *m*/*z* (**5a** + **5b**) calcd for $C_{21}H_{30}NOSi$ [M + H^+]: 340.2091; found: 340.2093.

Nickel-Catalyzed Phenylation of 1[4a]

In a nitrogen-filled glovebox, $Ni(OAc)_2$ (5.5 mg, 0.030 mmol, 0.15 equiv), ICy·HBF_4 (12.8 mg, 0.040 mmol, 0.20 equiv), and 1.0 M PhMgBr in THF (0.30 mL, 0.30 mmol, 1.5 equiv) were added to a 10 mL screw-capped vial. After removing all volatiles, **1** (56.7 mg, 0.20 mmol, 1.0 equiv) and toluene (1.0 mL) were added and the vial was sealed with the cap. The vial was then removed from the glovebox. The resulting mixture was stirred at 80 °C for 18 h. After allowing the reaction mixture to cool to rt, the solvent was removed and the residue was purified by flash column chromatography over silica gel ($CHCl_3$/MeOH) to give phenylated buflavine **6** as a 1:1 mixture of regioisomers (determined by ^{1}H NMR).

3-Methoxy-6-methyl-2-phenyl-5,6,7,8-tetrahydrodibenzo[*c*,*e*]-azocine and Its Regioisomer (6)

Yield: 20.2 mg (31%); colorless oil; R_f = 0.52 and 0.44 ($CHCl_3$/MeOH 4:1, on silica gel).

Spectroscopic data were collected with a 1:1 mixture of regioisomers.

IR (ATR): 1219 (w), 771 (s), 719 (w), 699 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.56 (m, 5 H), 7.45–7.24 (m, 15 H), 7.01 (s, 1 H), 6.91 (s, 1 H), 3.90 (s, 3 H), 3.83 (s, 3 H), 3.62 (t, *J* = 12.6 Hz, 2 H), 3.32–3.25 (m, 2 H), 3.16 (dd, *J* = 13.5, 1.2 Hz, 2 H), 2.65–2.50 (m, 9 H), 2.47 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.9, 155.3, 141.4, 141.2, 140.9, 140.1, 139.7, 138.1, 137.9, 133.7, 133.2, 131.8, 129.8, 129.7, 129.54, 129.51, 129.4, 129.2, 129.1, 128.2, 127.98, 127.96, 127.8, 127.0, 126.1, 113.3, 112.0, 58.9, 58.8, 58.4, 57.5, 55.7, 55.6, 46.2, 44.9, 32.8, 32.1.

MS: *m*/*z* (%) = 330 (11), 329 (M^+, 43), 328 (21), 314 (23), 287 (25), 286 (100), 285 (31), 271 (20), 270 (17), 256 (14), 255 (37), 254 (12), 253 (21), 252 (31), 241 (14), 240 (11), 239 (18), 209 (10), 165 (15), 119 (11), 115 (16), 91 (16), 42 (14).

HRMS (DART): *m*/*z* calcd for $C_{23}H_{24}NO$ [M + H^+]: 330.1852; found: 330.1850.

Nickel-Catalyzed Alkynylation of 1[4b]

A 10 mL sample vial with a Teflon-sealed screw cap was placed in a nitrogen-filled glovebox and charged with ethynyltriisopropylsilane (72 mg, 0.40 mmol). EtMgBr (1.0 M in THF, 0.40 mL, 0.40 mmol) was then added to the magnetically stirred material in a dropwise manner at rt. The resulting mixture was stirred at rt for 5 min. $Ni(cod)_2$ (11 mg, 0.040 mmol), ICy·HBF_4 (22 mg, 0.080 mmol), and **1** (57 mg, 0.20 mmol) were then added sequentially to the vial, and the resulting mixture was stirred at rt for 3 min. The THF was then removed in vacuo, and the resulting residue was dissolved in dioxane (1.0 mL). The vial was then sealed and the contents were heated with stirring at 120 °C for 18 h. After allowing the reaction mixture to cool to rt, the solvent was removed in vacuo to give a residue, which was purified by flash column chromatography over silica gel ($CHCl_3$ 100% to $CHCl_3$/MeOH 20:1) to give **7a** and **7b**.

3-Methoxy-6-methyl-2-((triisopropylsilyl)ethynyl)-5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocine (7a)

Yield: 14.5 mg (17%); colorless oil; R_f = 0.65 (hexane/EtOAc 1:1, on NH silica gel).

IR (ATR, **7a** + **7b**): 2939 (m), 2862 (m), 1461 (w), 882 (w), 760 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (s, 1 H), 7.34–7.26 (m, 3 H), 7.21 (d, *J* = 7.2 Hz, 1 H), 6.87 (s, 1 H), 3.92 (s, 3 H), 3.55 (d, *J* = 13.2 Hz, 1 H), 3.25 (dd, *J* = 7.6, 6.8 Hz, 1 H), 3.14 (d, *J* = 13.2 Hz, 1 H), 2.68 (dd, *J* = 7.6, 6.8 Hz, 1 H), 2.56 (t, *J* = 10.4 Hz, 1 H), 2.48–2.43 (m, 4 H), 1.13 (m, 21 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 160.07, 141.28, 139.13, 134.68, 133.05, 129.41, 129.25, 128.03, 126.13, 113.40, 112.10, 102.97, 94.94, 58.72, 58.60, 56.06, 45.49, 32.33, 29.71, 18.69, 11.40.

MS: *m*/*z* (%) = 434 (37), 433 (M^+, 100), 432 (29), 419 (25), 418 (81), 405 (13), 403 (11), 402 (33), 391 (23), 390 (67), 375 (11), 374 (13), 362 (15), 360 (11), 349 (10), 348 (38), 347 (29), 334 (13), 333 (24), 332 (54), 320 (21), 319 (10), 305 (21), 304 (21), 291 (20), 290 (52), 289 (39), 287 (10), 277 (18), 276 (14), 275 (19), 263 (23), 262 (21), 261 (20), 249 (13), 248 (10), 247 (18), 229 (12), 215 (15), 207 (15), 203 (10), 202 (20), 166 (13), 159 (22), 152 (20), 145 (29), 144 (11), 138 (28), 137 (10), 130 (23), 129 (12), 124 (16), 123 (20), 115 (12), 73 (17), 59 (22), 57 (11), 44 (31).

HRMS (DART): *m*/*z* calcd for $C_{28}H_{40}NOSi$ [M + H^+]: 434.2874; found: 434.2877.

2-Methoxy-6-methyl-3-((triisopropylsilyl)ethynyl)-5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocine (7b)

Yield: 8.9 mg (10%); colorless oil; R_f = 0.52 (hexane/EtOAc 1:1, on NH silica gel).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (s, 1 H), 7.37–7.35 (m, 1 H), 7.29–7.23 (m, 3 H), 6.77 (s, 1 H), 3.87 (s, 3 H), 3.53 (d, *J* = 13.6 Hz, 1 H), 3.24 (dd, *J* = 8.4, 6.8 Hz, 1 H), 3.03 (d, *J* = 13.6 Hz, 1 H), 2.69 (dd, *J* = 8.4, 6.8 Hz, 1 H), 2.54–2.45 (m, 5 H), 1.15 (m, 21 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.56, 142.07, 141.29, 139.94, 136.39, 129.57, 128.88, 128.45, 127.17, 112.42, 111.75, 102.90, 95.29, 58.48, 57.26, 56.02, 45.34, 32.25, 18.71, 18.68, 11.41.

MS: *m*/*z* (%) = 434 (32), 433 (M^+, 100), 432 (58), 419 (11), 418 (33), 391 (13), 390 (23), 348 (17), 347 (27), 333 (11), 332 (31), 319 (10), 305 (22), 304 (13), 291 (19), 290 (46), 289 (25), 277 (17), 275 (12), 263 (12), 261 (10), 207 (14), 159 (13), 145 (10), 138 (12), 73 (10), 44 (18).

HRMS (DART): *m*/*z* calcd for $C_{28}H_{40}NOSi$ [M + H^+]: 434.2874; found: 434.2876.

Addition of 5 to Aldehyde[9a]

To a nitrogen-filled 10 mL screw-capped vial, **5** (**5a**/**5b** = 3:1; 64.5 mg, 0.19 mmol) and 4-bromobenzaldehyde (74.0 mg, 0.40 mmol, 2.0 equiv) were added. THF (2.0 mL) was added. To the resulting mixture, 4 Å MS (200 mg) were added and the reaction was then stirred at rt for several minutes. TBAT (54.9 mg, 0.10 mmol, 0.50 equiv) was added and the vial was sealed with a cap. The mixture was stirred at 70 °C overnight. After cooling to rt, the solvent was removed in vacuo. The residue was purified by flash column chromatography over silica gel ($CHCl_3$/MeOH 19:1 to 4:1) and over NH silica gel (hexane/EtOAc 1:1 to EtOAc 100%) to give alcohol **9** as a mixture of regioisomers (**9a**/**9b** = 3:1).

1-(4-Bromophenyl)-2-(3-methoxy-6-methyl-5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocin-2-yl)ethan-1-ol and Its Regioisomer (9)

Yield: 54.3 mg (63%); colorless solid; mp 98.0–107.2 °C; R_f = 0.44 ($CHCl_3$/MeOH 4:1, on silica gel).

Spectroscopic data were collected with a 3:1 mixture of regioisomers. Each regioisomer of **9** exists as a mixture of two diastereomers, probably based on the axial chirality of the restricted biaryl moiety.[15]

IR (ATR): 1219 (w), 771 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.40 (m, 2 H, **9a** and **9b**), 7.38–7.17 (m, 5 H, **9a** and 6 H, **9b**), 7.13–7.01 (m, 1 H, **9a** and **9b**), 6.88–6.84 (m, 2 H, **9a**), 6.78 (d, *J* = 4.8 Hz, 1 H, **9b**), 4.98–4.86 (m, 1 H, **9a** and **9b**), 3.90 and 3.89 (s, 3 H, **9a**), 3.84 and 3.81 (s, 3 H, **9b**), 3.52–3.49 (m, 1 H, **9a** and **9b**), 3.23–2.91 (m, 5 H, **9a** and **9b**), 2.70–2.61 (m, 1 H, **9a** and **9b**), 2.51–2.37 (m, 2 H, **9a** and **9b**), 2.47 (s, 3 H, **9a**), 2.33 (s, 3 H, **9b**).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.0, 156.4, 143.8, 143.7, 143.5, 143.4, 141.3, 141.1, 141.0, 140.3, 140.2, 140.0, 139.5, 137.3, 134.3, 133.0, 132.6, 132.4, 131.2, 131.11, 131.07, 129.4, 129.3, 129.1, 128.9, 128.8, 128.1, 127.8, 127.7, 127.5, 127.5, 126.0, 125.7, 125.4, 125.1, 125.0, 120.9, 120.80, 120.75, 120.7, 112.6, 111.2, 111.1, 73.54, 73.45, 73.2, 58.72, 58.66, 58.6, 58.4, 58.3, 57.5, 57.3, 55.50, 55.47, 46.0, 45.3, 44.8, 40.9, 40.8, 32.6, 32.5, 32.1, 32.0.

MS: *m*/*z* (%) = 453 (M^++2, 19), 452 (16), 451 (M^+, 21), 438 (19), 436 (19), 267 (27), 266 (44), 252 (26), 236 (11), 225 (12), 224 (58), 223 (100), 222 (11), 209 (20), 194 (10), 193 (45), 191 (14), 179 (27), 178 (75), 166 (10), 165 (37), 115 (11), 78 (23), 77 (44), 57 (14), 44 (40), 42 (19).

HRMS (DART): *m*/*z* calcd for $C_{25}H_{27}NO_2{}^{79}Br$ [M + H^+]: 452.1219; found: 452.1216.

Addition of 5 to Imine[9b]

To a nitrogen-filled 10 mL screw-capped vial, **5** (**5a**/**5b** = 3:1; 67.8 mg, 0.20 mmol) and benzylideneaniline (72.5 mg, 0.40 mmol, 2.0 equiv) were added, followed by THF (2.0 mL). To the resulting mixture, 4 Å MS (200 mg) were added and the solution was stirred at rt for several minutes. After adding TBAT (54.9 mg, 0.10 mmol, 0.50 equiv), the vial was sealed with a cap and stirred at 70 °C overnight. After cooling to rt, the solvent was removed in vacuo. The residue was purified by flash column chromatography over NH silica gel (hexane/EtOAc 1:1) to give amine **10** as a mixture of regioisomers (**10a**/**10b** = 3:1).

N-(2-(3-Methoxy-6-methyl-5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocin-2-yl)-1-phenylethyl)aniline and Its Regioisomer (10)

Yield: 61.4 mg (69%); pale yellow oil; R_f = 0.29 (hexane/EtOAc 1:1, on NH silica gel).

Spectroscopic data were collected with a 3:1 mixture of regioisomers. Each regioisomer of **10** exists as a mixture of two diastereomers, probably based on the axial chirality of the restricted biaryl moiety.[15]

IR (ATR): 1219 (w), 772 (s), 719 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.22 (m, 8 H, **10a** and 9 H, **10b**), 7.12–7.01 (m, 3 H, **10a** and **10b**), 6.91–6.86 (m, 2 H, **10a**), 6.77 (d, *J* = 4.8 Hz, 1 H, **10b**), 6.60–6.57 (m, 1 H, **10a** and **10b**), 6.45–6.39 (m, 2 H, **10a** and **10b**), 4.94–4.65 (m, 1 H, **10a** and **10b**), 4.56–4.55 (m, 1 H, **10a** and **10b**), 4.00 and 3.98 (s, 3 H, **10a**), 3.92 and 3.91 (s, 3 H, **10b**), 3.52 (d, *J* = 13.2 Hz, 1 H, **10a** and **10b**), 3.26–2.95 (m, 4 H, **10a** and **10b**), 2.72–2.32 (m, 6 H, **10a** and **10b**).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.1, 157.0, 156.4, 147.7, 147.63, 147.58, 144.3, 144.1, 144.0, 141.3, 141.2, 140.32, 140.29, 140.11, 140.08, 139.7, 139.6, 137.3, 137.2, 134.1, 133.9, 133.0, 132.9, 132.3, 132.1, 129.44, 129.36, 129.3, 129.1, 129.0, 128.91, 128.88, 128.6, 128.5, 128.4, 128.1, 127.8, 126.84, 126.78, 126.4, 126.33, 126.26, 126.03, 125.98, 125.9, 125.8, 116.8, 116.7, 113.3, 113.2, 113.13, 113.09, 112.6, 111.4, 111.3, 59.8, 59.52, 59.50, 59.0, 58.84, 58.81, 58.75, 58.68, 58.3, 57.2, 55.4, 46.2, 46.1, 44.6, 40.0, 39.7, 39.6, 32.7, 32.6, 31.8.

MS: *m*/*z* (%) (**10a** + **10b**) = 448 (M^+, 0), 267 (43), 183 (14), 182 (100), 104 (28), 77 (28), 44 (22).

HRMS (DART): *m*/*z* calcd for $C_{31}H_{33}N_2O$ [M + H^+]: 449.2587; found: 449.2591.

Desilylation of 5

To a 30 mL flask, **5** (**5a**/**5b** = 3:1; 50.9 mg, 0.15 mmol) and THF (2.0 mL) were added. TBAF (1 M in THF; 0.3 mL, 0.3 mmol, 2.0 equiv) was then added and the solution stirred at rt overnight. After stirring, the volatiles were removed in vacuo. The residue was purified by flash column chromatography over NH silica gel (hexane/EtOAc 3:7 to 1:1) to give desilylated **11** as a mixture of regioisomers (**11a**/**11b** = 3:1).

3-Methoxy-2,6-dimethyl-5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocine and Its Regioisomer (11)

Yield: 31.8 mg (79%); colorless oil; R_f = 0.44 and 0.32 (hexane/EtOAc 1:1, on NH silica gel).

Spectroscopic data were collected with a 3:1 (**11a**/**11b**) mixture of regioisomers.

IR (ATR): 1215 (m), 770 (s), 747 (s), 719 (w), 668 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.21 (m, 4 H, **11a** and 4 H, **11b**), 7.18 (s, 1 H, **11b**), 7.08 (s, 1 H, **11a**), 6.85 (s, 1 H, **11a**), 6.74 (s, 1 H, **11b**), 3.91 (s, 3 H, **11a**), 3.84 (s, 3 H, **11b**), 3.55 (d, *J* = 13.2 Hz, 1 H, **11a**), 3.54 (d, *J* = 13.2 Hz, 1 H, **11b**), 3.29–3.23 (m, 1 H, **11a** and 1 H, **11b**), 3.11 (d, *J* = 13.2 Hz, 1 H, **11a**), 3.06 (d, *J* = 13.2 Hz, 1 H, **11b**), 2.74–2.68 (m, 1 H, **11a** and 1 H, **11b**), 2.57–2.48 (m, 5 H, **11a** and 5 H, **11b**), 2.26 (s, 3 H, **11b**), 2.25 (s, 3 H, **11a**).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.3, 156.7, 141.21, 141.17, 140.0, 139.0, 135.7, 133.4, 132.6, 131.6, 129.4, 129.3, 129.2, 129.0, 128.0, 127.6, 126.1, 126.0, 125.7, 112.1, 110.6, 58.8, 58.6, 58.5, 57.5, 55.4, 55.3, 45.9, 45.5, 32.5, 32.3, 15.9, 15.9.

MS: *m*/*z* (%) (**11a** + **11b**) = 268 (15), 267 (M^+, 82), 266 (29), 253 (13), 252 (74), 236 (13), 225 (17), 224 (58), 223 (19), 210 (20), 209 (100), 208 (12), 194 (13), 193 (12), 190 (10), 181 (13), 179 (10), 178 (17), 166 (25), 165 (41), 44 (11).

HRMS (DART): *m*/*z* (major) calcd for $C_{18}H_{22}NO$ [M + H^+]: 268.1696; found: 268.1698.

Olefination of 5[16]

Compound **5** (**5a**/**5b** = 3:1; 67.8 mg, 0.20 mmol) and 4-chlorobenzaldehyde (56.2 mg, 0.40 mmol) were dissolved in THF (2.0 mL). Then, 4 Å MS (200 mg) were added to the resulting mixture and the reaction was stirred at rt for 30 min, after which, TBAT (54.0 mg, 0.10 mmol) was added. The mixture was stirred at 75 °C for 1 h and then cooled to rt. After, stirring, 4 M HCl (0.10 mL) was added and the mixture was stirred at rt for 20 min. After removing the THF under reduced pressure, the residue was dissolved in toluene (2.0 mL) and *p*-TsOH·H_2O (152 mg, 0.80 mmol) was added. The mixture was stirred at 120 °C for 1 h, then cooled to rt and diluted with Et_2O (5.0 mL). The solution was washed with water (1.0 mL), saturated aqueous $NaHCO_3$ (1.0 mL), and brine (1.0 mL) in that order. The solvent was then removed in vacuo to give a residue, which was purified by flash column chromatography over NH silica gel (hexane 100% to hexane/EtOAc 1:1) to give **12** as a mixture of regioisomers (**12a**/**12b** = 3:1).

(*E*)-2-(4-Chlorostyryl)-3-methoxy-6-methyl-5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocine and Its Regioisomer (12)

Yield: 39.7 mg (51%); yellow oil; R_f = 0.14 and 0.16 (hexane/EtOAc 2:1, on NH silica gel).

Spectroscopic data were collected with a 3:1 (**12a**/**12b**) mixture of regioisomers.

IR (ATR): 2933 (w), 1487 (s), 1236 (w), 812 (w), 754 (s), 731 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (t, *J* = 8.0 Hz, 1 H, **12a**), 7.50–7.24 (m, 8 H, **12a** and 10 H, **12b**), 7.18–7.14 (m, 2 H, **12b**), 7.09 (d, *J* = 16.8 Hz, 1 H, **12a**), 6.93 (s, 1 H, **12a**), 6.83 (s, 1 H, **12b**), 3.97 (s, 3 H, **12a**), 3.91 (s, 3 H, **12b**), 3.88 (d, *J* = 17.2 Hz, 1 H, **12b**), 3.62 (d, *J* = 13.6 Hz, 1 H, **12b**), 3.56 (d, *J* = 13.6 Hz, 1 H, **12a**), 3.29–3.23 (m, 1 H, **12a** and 1 H, **12b**), 3.13 (d, *J* = 13.2 Hz, 1 H, **12a**), 3.12 (d, *J* = 13.2 Hz, 1 H, **12b**), 2.76–2.69 (m, 1 H, **12a** and 1 H, **12b**), 2.58–2.47 (m, 5 H, **12a** and 4 H, **12b**).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.40, 155.82, 141.26, 141.21, 140.04, 139.72, 138.30, 136.50, 135.87, 134.87, 133.24, 132.81, 129.83, 129.76, 129.56, 129.43, 129.27, 129.15, 128.90, 128.70, 128.28, 127.93, 127.77, 127.65, 127.30, 126.13, 125.32, 125.04, 123.58, 113.13, 111.69, 60.38, 58.82, 58.65, 58.49, 57.65, 55.60, 45.91, 45.34, 32.58, 32.23.

MS: *m*/*z* (%) (**12a** + **12b**) = 391 (M^++2, 31), 390 (32), 389 (M^+, 97), 388 (24), 376 (25), 375 (18), 374 (66), 361 (10), 360 (14), 358 (22), 349 (10), 348 (35), 347 (28), 346 (100), 305 (14), 303 (37), 296 (10), 281 (16), 278 (13), 268 (34), 267 (26), 266 (12), 265 (23), 253 (28), 252 (26), 221 (11), 219 (10), 208 (11), 207 (27), 193 (11), 191 (30), 165 (11), 147 (11), 140 (15), 139 (13), 138 (15), 132 (22), 131 (14), 127 (13), 126 (27), 125 (30), 73 (16), 44 (39).

HRMS (DART): *m*/*z* calcd for $C_{25}H_{25}NO^{35}Cl$ [M + H^+]: 390.1619; found: 390.1618.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

This work was supported, in part, by the SEEDS program from Osaka University.

Acknowledgment

We thank the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for their assistance with HRMS.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1467-2494.

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