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PAPER

Silver-promoted Friedel–Crafts reaction: concise total synthesis of (−)-ardeemin, (−)-acetylardeemin and (−)-formylardeemin

Y. Wang,[a] C. Kong,[a] Y. Du,[a] H. Song,*[a] D. Zhang[b] and Y. Qin*[a,b]

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Total syntheses of multidrug resistant inhibitors (−)-acetylardeemin **2a**, (−)-ardeemin **2b**, and (−)-formylardeemin **3** have been achieved within 10 steps starting from bromopyrroloinoline **13**. The key step involves direct alkylation of **13** with prenyl tributylstannane **11** to yield **12** *via* a silver-promoted asymmetric Friedel–Crafts reaction. Highly efficient installation of the isoprenyl group allowed excellent overall yield. Moreover, the substrate scope of the asymmetric Friedel–Crafts reaction of **13** was expanded to include a variety of arenes **14** to afford natural product-like library analogues **15**.

Introduction

Alkaloids bearing a pyrroloindoline (**1**) skeleton substituted on C3α with a heteroatomic, alkyl or aromatic moiety form a major class of indoline alkaloids with a broad range of potent biological activities (Fig. 1).[1] Although several methods for constructing C3α-substituted pyrroloindoline **1** have been developed in recent years,[2,3] they involve multi-step procedures. A more concise methodology for assembling C3α-substituted pyrroloindoline **1** is highly desirable (Fig. 1).

(−)-Acetylardeemin **2a** and (−)-ardeemin **2b** were isolated from the extracts of the fungus *Aspergillus fischerii* in 1993.[4] (−)-Acetylardeemin **2a** is one of the most potent inhibitors of multidrug resistance (MDR, Fig. 1).[5] The high anti-MDR activity of **2a** has drawn the attention of synthetic chemists, which led to the development of three total syntheses by Danishefsky,[6] Kawasaki,[7] and our group.[8] SAR studies based on our total synthesis of **2** found that the synthesized (−)-formylardeemin **3** (Fig. 1) inhibited MDR cancer cell lines to a similar extent as the natural **2a**.[9] Indeed, *in vitro* experiments show that **3** at low μM doses significantly sensitizes the multi-drug resistant breast cancer cell lines MCF-7-R and cervical cancer cell lines Siha to vincristine- or adriamycin-induced cell death. In our previous synthesis of **2** and **3** in 20 steps with about 2% overall yield,[8] the stereoselective installation of the isoprenyl group to give intermediate **7** from L-tryptophan took 9 steps (eqn (1),

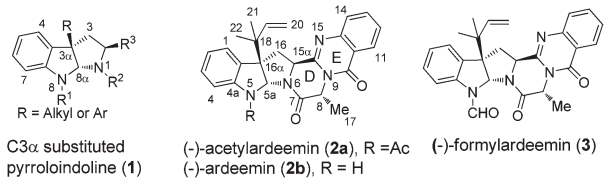


Fig. 1 Structures of ardeemins.

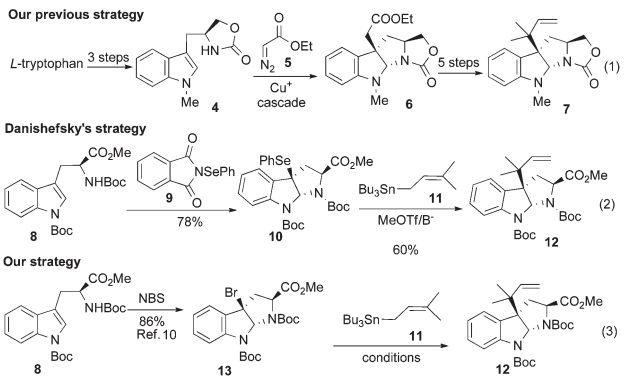


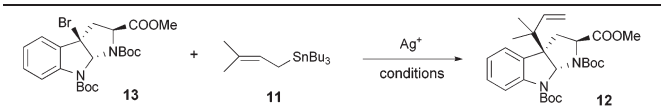
Fig. 2 Strategies for alkylation or arylation of pyrroloindoline at C3α.

Fig. 2). Such tedious preparation of **7** hampered efforts to obtain a large quantity of **2** and **3** for further preclinical studies.

Inspired by Danishefsky's pioneering work on direct C3α alkylation of the phenylselenopyrroloindoline **10** with prenyl tributylstannane **11** to provide **12** *via* Lewis acid-catalyzed nucleophilic substitution (eqn (2), Fig. 2),[6] we envisioned a similar strategy of direct isoprenylation of bromopyrroloindoline **13** with **11** to afford **12** *via* a Friedel–Crafts reaction. This would significantly improve the synthesis of **2** and **3**, since **13** is readily prepared in high yield from the inexpensive L-tryptophan derivative

[a]*Key Laboratory of Drug Targeting of Ministry of Education, West China School of Pharmacy, and State Key Laboratory of Biotherapy, Sichuan University, Chengdu 610041, P. R. China. E-mail: yongqin@scu.edu.cn; Fax: (+86) 28 85503842; Tel: (+86) 28 85503842*
[b]*Innovative Drug Research Center and College of Chemistry and Chemical Engineering, Faculty of Arts and Sciences, Chongqing University, Chongqing 401331, P. R. China. E-mail: qinyong@cqu.edu.cn; Fax: (+86) 23 65678750; Tel: (+86) 23 65678750*

Table 1 Silver-promoted C3α isoprenylation of **13**[a]



Entry	Salts	Additive	Temp. (°C)	Yield[b] (%)
1	Ag_2CO_3	—	−40	4
2	AgF	—	−40	9
3	$AgCO_2CF_3$	—	−40	7
4	$AgSO_2Tol$	—	−40	5
5	$AgSO_2CF_3$	—	−40	18
6	$AgCO_2(CF_2)CF_3$	—	−40	33
7	$AgSbF_6$	—	−40	40
8	$AgBF_4$	—	−40	45
9	$AgClO_4$	—	−40	47
10	$AgClO_4$	$LiClO_4$	−40	70
11	$AgClO_4$	KF	−40	69
12	$AgClO_4$	CsF	−40	77
13	$AgClO_4$	K_2CO_3	−40	66
14	$AgClO_4$	Cs_2CO_3	−40	81
15	$AgClO_4$	Cs_2CO_3	−78	93
16[c]	$AgClO_4$	Cs_2CO_3	−78	91
17[d]	$AgClO_4$	Cs_2CO_3	−78	82
18[ce]	$AgClO_4$	Cs_2CO_3	−78	60
19[cf]	$AgClO_4$	Cs_2CO_3	−78	<20
20[cg]	$AgClO_4$	Cs_2CO_3	−78	90[h]
21[ci]	$AgClO_4$	Cs_2CO_3	−78	87[h]
22[ci]	$AgBF_4$	Cs_2CO_3	−78	92[h]

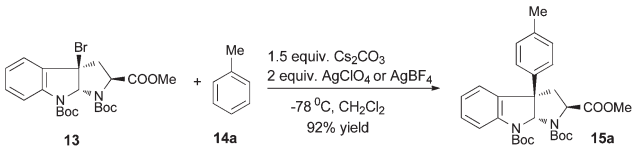
[a] Unless otherwise noted, reactions were performed with 1 equiv. of **13**, 1.5 equiv. of **11**, 3 equiv. of silver salts, 1.5 equiv. of additive in CH_2Cl_2. [b] Isolated yield. [c] 2 equiv. of $AgClO_4$ and 1.5 equiv. of Cs_2CO_3 were used. [d] 1.2 equiv. of $AgClO_4$ and 1.5 equiv. of Cs_2CO_3 were used. [e] Et_2O was used as a solvent. [f] 1,2-Dimethoxythane or THF was used as solvent. [g] Toluene was used as solvent and a reactant. [h] Compound **15a** was isolated as sole product. [i] 3 equiv. of toluene were used as a reactant, and CH_2Cl_2 was used as solvent.

8 and NBS in a single step (eqn (3), Fig. 2).[10] In the meantime, Movassaghi[11] and Stephenson[12] recently made great progress on direct arylation of bromopyrroloindolines on C3α *via*, respectively, a silver-catalyzed Friedel–Crafts reaction with potassium aryltrifluoroborates and rhodium-catalyzed radical coupling with unfunctionalized arenes mediated by visible light. These promising results further encouraged us to complete the planned project.

In this paper, we describe a concise total synthesis of (−)-acetylardeemin **2a**, (−)-ardeemin **2b** and (−)-formylardeemin **3**, which involves highly efficient, single-step asymmetric attachment of an isoprenyl group on C3α of the easily accessible **13** *via* a silver-promoted Friedel–Crafts reaction. We also report the direct asymmetric arylation of **13** with a variety of arenes **14** to give natural product-like library analogues.

Results and discussion

To study the direct asymmetric isoprenylation of **13** with **11**, a variety of silver salts were screened, including Ag_2CO_3, AgF, $AgCO_2CF_3$, $AgSO_3Tol$, $AgSO_3CF_3$, $AgCO_2(CF_2)_2CF_3$, $AgSbF_6$, $AgBF_4$ and $AgClO_4$. Among the salts tested, $AgClO_4$ afforded the desired **12** as sole product with the highest yield of 47% within 10 h under conditions of 3 equiv. of salts, 1.5 equiv. of **11**



Scheme 1 Silver-promoted C3α arylation of **13**.

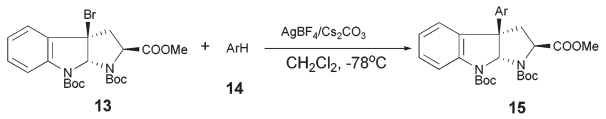
in CH_2Cl_2 at −40 °C (entries 1–9, Table 1). In order to improve the yield, several bases such as $LiClO_4$, KF, CsF, K_2CO_3 and Cs_2CO_3 were individually tested as additives under identical conditions (entries 10–14, Table 1). To our delight, the reaction was significantly promoted by addition of 1.5 equiv of base. Cs_2CO_3 gave the best result with 81% yield. Lowering the temperature from −40 °C to −78 °C improved the yield to 93% (entries 14–15, Table 1). Further optimization of the amount of $AgClO_4$ (entries 15–17, Table 1) gave the best conditions as 2 equiv. of $AgClO_4$, 1.5 equiv. of **11**, and 1.5 equiv. of Cs_2CO_3 at −78 °C. Under optimal conditions, we easily prepared the key intermediate **12** from **13** in 91% yield in a single step, allowing the total synthesis of **2** and **3**.

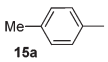
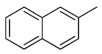
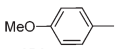
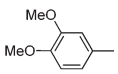
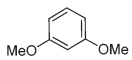
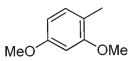
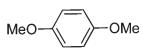
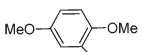
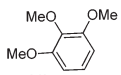
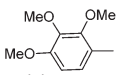
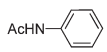
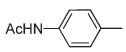
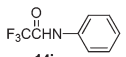
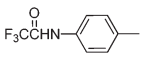
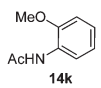
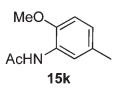
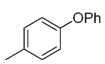
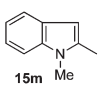
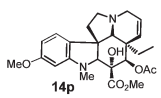
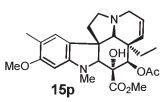
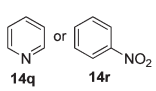
Changing the solvent from CH_2Cl_2 to ethereal solvents such as Et_2O, DME and THF caused significant loss of yield (entries 16, 18–19, Table 1). Surprisingly, when toluene **14a** was used as the solvent, an unexpected arylated product **15a** was isolated as sole product in excellent yield (entry 20, Table 1 and Scheme 1). Interestingly, arylation of **13** with only 3 equiv. of toluene **14a** and 2 equiv. of $AgClO_4$ in CH_2Cl_2 at −78 °C still provided **15a** in 87% yield. Reevaluation of $AgBF_4$ (2 equiv.) under the above arylation conditions showed that $AgBF_4$ promoted the reaction with better yield (92%) than did $AgClO_4$ (87%, entries 21 and 22, Table 1) in the presence of 3 equiv. of toluene **14a** in CH_2Cl_2.

Since pyrroloindoline **1** arylated on C3α belongs to a subclass of indoline alkaloids,[13] the discovery of efficient arylation of **13** with toluene encouraged us to investigate the general reactivity of **13** with a variety of arenes under the same conditions (1.0 equiv of **13**, 3 equiv. of arene **14**, 2 equiv. of $AgBF_4$, 1.5 equiv. of Cs_2CO_3 at −78 °C). As shown in Table 2, we were pleased to find that the reaction of **13** with electron-neutral and electron-rich arenes **14** proceeded smoothly to give **15** in moderate to excellent yields (entries 1–16, Table 2), whereas the reaction with electron-deficient arenes such as pyridine **14q** and nitrobenzene **14r** failed (entry 17, Table 2). All the tested arenes **14** reacted with **13**, providing the corresponding products **15** with excellent regioselectivities, except naphthalene **14c** and *N*-methylindole **14m**. These results are consistent with the *ortho*/*para* directing effect that governs the regioselectivity of the Friedel–Crafts reaction at lower temperature.

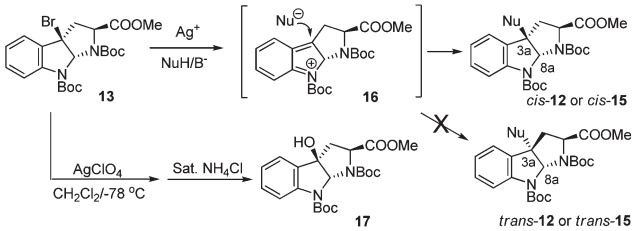
A reasonable mechanism for the C3α Friedel–Crafts reaction is suggested in Scheme 2. Treatment of **13** with silver salts generates a conjugated carbocation **16** at low temperature, which then reacts with the nucleophilic prenyl tributylstannane **11** and arenes **14** to provide *cis*-**12** or *cis*-**15**. Isolation of the hydroxyl product **17** proves that the reaction proceeds through the carbocation **16** when **13** reacts with $AgClO_4$ alone at −78 °C in CH_2Cl_2 for 2 h, after which the reaction was quenched with saturated NH_4Cl solution. The observed excellent stereoselectivity of the Friedel–Crafts reaction at the C3α linkage is mainly due to

Table 2 $AgBF_4$-promoted C3α arylation of **13**[a]



Entry	ArH	Ar	Yield[b] (%)
1	 **14a**	 **15a**	92
2	 **14b**	 **15b**	89
3	 **14c**	 **15c**	80[c]
4	 **14d**	 **15d**	72
5	 **14e**	 **15e**	68
6	 **14f**	 **15f**	62
7	 **14g**	 **15g**	80
8	 **14h**	 **15h**	91
9	 **14i**	 **15i**	90
10	 **14j**	 **15j**	67
11	 **14k**	 **15k**	53
12	 **14l**	 **15l**	44
13	 **14m**	 **15m**	46[d]
14	 **14n**	 **15n**	31[e]
15	 **14o**	 **15o**	94[e]
16	 **14p**	 **15p**	49
17	 **14q** or **14r**	—	0

[a] Reactions were performed with 3.0 equiv. of ArH (**14**), 2.0 equiv of $AgBF_4$, 1.5 equiv. of Cs_2CO_3 at −78 °C in CH_2Cl_2 for 10 h. [b] Isolated yield. [c] The ratio of α-substituted product : β-substituted product was 1 : 3. [d] The C2 linked product **15m** was isolated in 46% yield. Other products linked at different positions of the indoline core were isolated in 38% total yield, but they could not be separated from each other by chromatography and so could not be individually identified. [e] Sole product isolated.

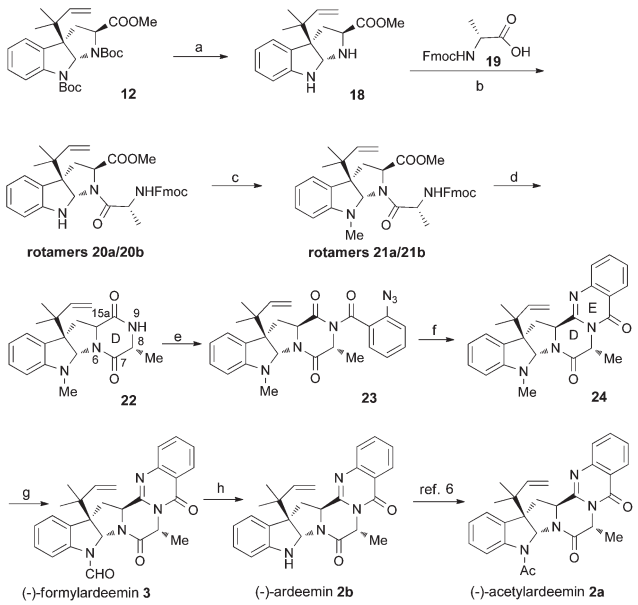


Scheme 2 Proposed mechanism for direct C3α substitution of **13**.

the existing tricyclic ring system in **16**, which excludes a nucleophilic attack occurring from the lower face of the indoline ring to produce the high energy-barrier *trans*-**12** or *trans*-**15** with two *trans*-fused five-membered rings. Therefore, the nucleophile attacks exclusively on the upper face of the indoline ring, yielding *cis*-**12** or *cis*-**15** with excellent stereoselectivities at C3α.

Having developed an efficient method to stereoselectively assemble the isoprenyl group on the pyrroloindoline skeleton, we progressed toward the total synthesis of (−)-formylardeemin **3**, (−)-ardeemin **2b** and (−)-acetylardeemin **2a** from **12**. As shown in Scheme 3, removal of both Boc groups from **12** with TMSI provided **18** in 90% yield. In our previous total synthesis,[8] the D-ring was constructed from a pyrroloindoline intermediate and an D-alanine fragment in consecutive steps, in which the C15α–N9 amide bond was first linked, and then the C7–N6 amide bond was formed. In the second step of C7–N6 amide bond formation, activation of an acid group on C7 with $ClCO_2{}^iBu$–Et_3N inevitably caused epimerization at C8 (1 : 1) due to formation of an active ketene functional group. In the current synthesis, epimerization at C8 during D-ring formation was avoided by first linking the C7–N6 amide bond, then forming the C15α–N9 amide bond. Thus, condensation of **18** with *N*-Fmoc-protected D-alanine **19** in the presence of HATU and Et_3N in DMF afforded a mixture of the rotamers **20a** and **20b** in a 1 : 1 ratio and 80% yield. Without separation of **20a** and **20b** from each other, the mixture was methylated with 37% aqueous HCHO and $NaBH_3CN$ in MeCN and AcOH (10 : 1) to give a mixture of rotamers **21a** and **21b** in a 1 : 4 ratio and 90% yield. The rotameric effects ascribed to the amide bonds in **20** and **21** were eliminated when the D-ring was formed by removal of the Fmoc group in **21** in the presence of Et_2NH in THF. Compound **22** was isolated as a single stereoisomer in 93% yield. As expected, epimerization at C8 was effectively avoided by reversing the order of amide bond formation and varying reaction conditions for D-ring formation.

To form the E-ring, we adopted a strategy similar to our previous synthesis.[8] Condensation of **22** with *o*-azidobenzoic anhydride in the presence of n-BuLi in THF at −78 °C provided azido **23** in 92% yield. Treatment of **23** with n-Bu_3P in toluene afforded **23** in 86% yield. The final step of oxidizing the methyl group in **24** with PDC completed the total synthesis of (−)-formylardeemin **3**. Deformylation of **3** with aqueous NaOH in MeOH at 60 °C provided (−)-ardeemin **2b** in 85% yield. (−)-Acetylardeemin **2a** was obtained from **2b** using a published procedure.[6]



Scheme 3 *Reagents and conditions*: (a) TMSI, MeCN, 0 °C, 90%; (b) **19**, HATU, Et_3N, DMF, −20 °C, **20a** : **20b** 1 : 1, 80%; (c) 37% aqueous HCHO, $NaBH_3CN$, MeCN–AcOH (10 : 1), 25 °C, **21a** : **21b** 1 : 4, 90%; (d) Et_2NH, THF, 0 °C to rt, 93%; (e) n-BuLi (2.5 M in THF), *o*-azidobenzoic anhydride, THF, −78 °C, 92%; (f) n-Bu_3P, toluene, 1 h, 86%; (g) PDC, silica gel, CH_2Cl_2 at rt, 80%; (h) 8% aqueous NaOH in MeOH, reflux 8 h, 85%. TMSI = trimethylsilyl iodide; HATU = 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium; PDC = pyridinium dichromate.

Conclusions

In summary, a concise total synthesis of (−)-formylardeemin **3** has been accomplished from bromopyrroloindoline **13** with 36% overall yield in 8 steps. (−)-Ardeemin **2b** was readily prepared from **3** by simple deformylation. (−)-Acetylardeemin **2a** was prepared from **2b** by a single step of acetylation. The key step in the total synthesis was a silver-promoted asymmetric Friedel–Crafts reaction of **13** with prenyl tributylstannane **11** to give **12**. Highly efficient installation of the isoprenyl group on the pyrroloinoline skeleton greatly enhanced the synthetic efficiency over the previous synthesis and allowed us to shorten the synthesis of **3** from 20 steps to 8 steps. Moreover, the substrate scope of the asymmetric Friedel–Crafts reaction of **13** was expanded to include a variety of arenes **14** to afford natural product-like library analogues **15a–15p**. The current synthesis provides a practical approach to large-scale synthesis of (−)-acetylardeemin **2a** and (−)-formylardeemin **3** for preclinical studies.

Experimental

General methods

All commercially available reagents were used without further purification. All solvents were dried and distilled before use; toluene was distilled from sodium; THF was distilled from sodium–benzophenone ketyl; dichloromethane, acetonitrile and *N*,*N*-dimethylformamide were distilled from calcium hydride. Chromatography was conducted by using 200–300 mesh silica gel. All new compounds gave satisfactory spectroscopic analyses (IR, ^{1}H NMR, ^{13}C NMR, HRMS). IR spectra were recorded on a FT IR spectrometer. NMR spectra were recorded on a 400 MHz NMR spectrometer. HRMS spectra were obtained by the FAB method.

Procedure for synthesis of 12[6a]

To a solution of the bromopyrroloindoline **13** (10.0 g, 20.1 mmol), Cs_2CO_3 (9.8 g, 30.2 mmol) and prenyl tributylstannane (10.9 g, 30.2 mmol) in 300 mL of anhydrous CH_2Cl_2 at −78 °C under nitrogen was added $AgClO_4$ (8.3 g, 40.2 mmol). After stirring at −78 °C for 16 h, the reaction was quenched with 150 mL of saturated NH_4Cl solution and then extracted with CH_2Cl_2 (3 × 200 mL), the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography (ethyl acetate–petroleum 1 : 15) to afford compound **12** (8.8 g, 91%) as a white solid. Mp: 143–145 °C; $[\alpha]_D^{20}$ = −72.1 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.02 (s, 3H), 1.46 (broad s, 9H), 1.55 (s, 9H), 2.25–2.30 (m, 1H), 2.35–2.40 (m, 1H), 3.70 (s, 3H), 3.80 (dd, J = 10, 6.8 Hz, 1H), 4.98–5.08 (m, 2H), 5.86 (dd, J = 17.2, 10.8 Hz, 1H), 6.16 (s, 1H), 7.05 (t, J = 7.6 Hz, 1H), 7.16 (d, J = 7.2 Hz, 1H), 7.25 (t, J = 8.8 Hz, 1H), 7.38 (broad s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 22.5, 27.9, 34.9, 39.8, 51.5, 58.9, 61.3, 78.0, 80.7, 113.9, 117.0, 118.1, 123.0, 124.2, 128.1, 133.3, 142.7, 151.7, 172.0 ppm; HRMS (M + H^+) calcd for $C_{27}H_{39}N_2O_6$ 487.2808, found 487.2816; IR (KBr) 2980, 2932, 1760, 1710, 1481, 1400, 1260, 1155, 1018 cm^{-1}.

General procedure for preparation of 15

Bromopyrroloindoline **13** (1.007 g, 2.0 mmol), Cs_2CO_3 (0.977 g, 3.0 mmol) and **14** (6.0 mmol) were dissolved in 50 mL of anhydrous CH_2Cl_2 under N_2 at −78 °C, then $AgBF_4$ (0.778 g, 4.0 mmol) was added. After complete consumption of **13**, 50 mL of saturated NH_4Cl solution was added to quench the reaction. The reaction mixture was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were dried over Na_2SO_4, and the solvents were removed under reduced pressure. Purification by silica gel chromatography (ethyl acetate–petroleum) provided **15**. Individual isolated yield of **15a–15p** was shown in Table 2.

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