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Diastereoselective Intramolecular [3 + 2]-Annulation of Donor–Acceptor Cyclopropane with Imine-Assembling Hexahydropyrrolo[3,2-*c*]quinolinone Scaffolds

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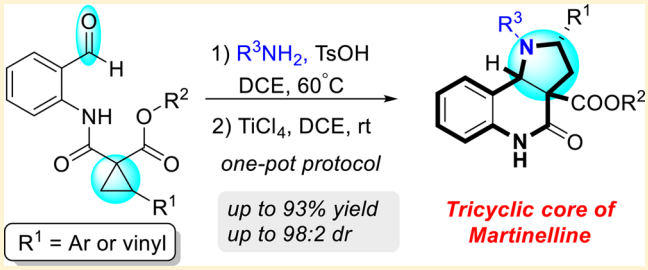
Supporting Information

ABSTRACT: An intramolecular [3 + 2]-annulation of amide-linked donor–acceptor cyclopropane with in situ-generated imine is described. As a result, diverse hexahydropyrrolo[3,2-*c*]quinolinones, as the tricyclic core of martinellines, were efficiently assembled in good to excellent yield (up to 93%) with a good diastereomeric ratio (up to 98:2).



INTRODUCTION

Multicyclic heterocycles are widely present in natural products, and the discovery of efficient pathways for rapidly assembling diversely featured heterocycles is always a fierce battle for synthetic and medicinal chemists.[1] As a payoff, new synthetic strategies have consistently emerged that advanced the studies on bioactive molecules and pharmaceuticals. Among these biologically active molecules, martinelline and martinellic acid (Figure 1), first isolated from *Martinella iquitosensis* roots by

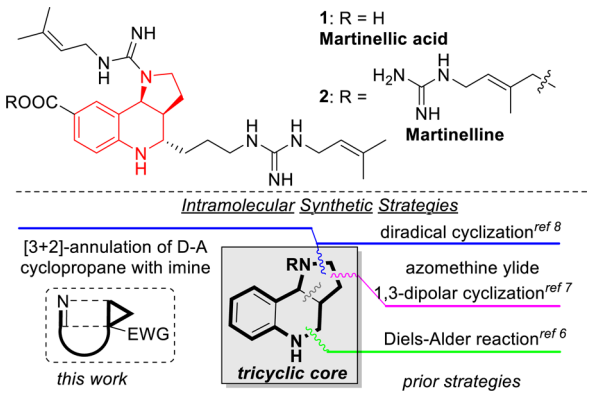


Figure 1. Structures of martinellines and intramolecular synthetic strategies to assemble the tricyclic core.

Merck Laboratories in 1995, are a series of alkaloids possessing antibacterial activity and potent antagonist activity toward bradykinin (BK) B1 and B2 receptors.[2] Not surprisingly, considerable synthetic efforts have been garnered toward their total syntheses,[3] and various methodologies have been developed to construct the tricyclic core of this class of compounds in recent decades.[4,5] Encouragingly, the first total synthesis of martinelline was elegantly accomplished by Ma et al. in 2001.[3a] Considering the efficacy of intramolecular reaction mode in the assembly of multicyclic systems, various intramolecular strategies including Diels–Alder addition,[6] 1,3-dipolar cycloaddition of azomethine ylide,[7] and diradical cyclization[8] were designed to install the tricyclic core in one step. However, novel cyclization pathway is still highly desirable owing to the synthetic and biological importance of these heterocycles. In view of the five-membered pyrrolidine moiety in the tricyclic skeleton, we envisaged that an intramolecular [3 + 2]-annulation of donor–acceptor cyclopropane with imine could serve as an effective solution for the construction of these nitrogen-containing multicyclic skeletons.

In recent years, impressive advances have been achieved through the ring-opening of donor–acceptor cyclopropane (DAC), which can undergo an array of cycloaddition/annulations such as [3 + 2],[9,10] [3 + 3],[11] or [4 + 3] reaction[12] to readily furnish diverse ring systems. Owing to the presence of nitrogen-containing heterocycles especially pyrrolidine in a myriad of natural products and pharmaceuticals, [3 + 2]-annulations of DAC with imines, benzonitrile, or phenyl isocyanate generating five-membered substituted pyrrolidine have attracted substantial synthetic attention.[13] In contrast to the intermolecular annulation of DAC with imines, intramolecular variant seems much underdeveloped.[14] In 2008, Kerr et al. pioneered the intramolecular annulation of DAC with imine by employing oxime ether as a linker, which significantly improved the reactivity and diastereoselectivity (Scheme 1, eq a).[14a] Since then, very limited success has been achieved, and

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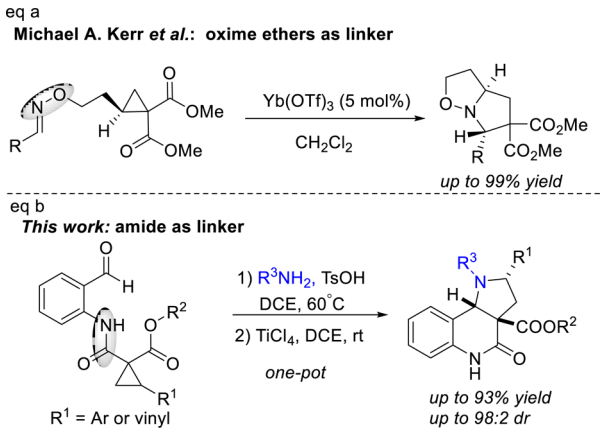
Scheme 1. Strategies for Intramolecular Annulation of D−A Cyclopropane with Imine

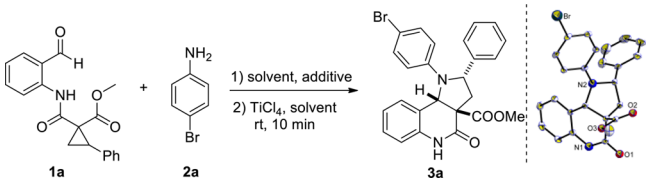


the intramolecular annulation with specifically designed linker is desirable. On the basis of the inherent feature of DAC diester, we recently designed an effective amide linker, which is more accessible and operationable.[15] Our continuing interest in the construction of complex heterocycles motivated us to tackle the amide-linked intramolecular annulation of DAC with imines, which can rapidly install the tricyclic core of martinelline (Scheme 1, eq b). In this paper, we report a diastereoselective approach for the construction of tricyclic hexahydropyrrolo[3,2-*c*]quinolinones via the intramolecular [3 + 2]-annulation of amide-linked cyclopropane with the in situ-generated imine.

RESULTS AND DISCUSSION

To execute our idea, we designed a one-pot process by initially treating aldehyde **1a** with 1.2 equiv of 4-bromoaniline (**2a**) in dry 1,2-dichloroethane at room temperature for 48 h and then adding 1.2 equiv of titanium tetrachloride. It is worth noting that titanium tetrachloride was found to be the most effective promoter for the amide-functionalized cyclopropane, and 1.0 equiv of titanium tetrachloride was requisite for achieving the desired annulation product in high yield.[15] Pleasingly, this title reaction successfully afforded hexahydropyrrolo[3,2-*c*]-quinolinones **3a**, a crystalline solid in 43% yield with 80:20 diastereomeric ratio (Table 1, entry 1). Consequently, the chemical structure and relative configuration of **3a** were unambiguously confirmed through X-ray analysis of a single crystal.[16] Recognizing that the imine formation was relatively slow and the annulation reaction was completed in 10 min, we decided to accelerate the reaction sequence by running the reaction at higher temperature and adding additive. As expected, both high temperature and strong acid such as *p*-toluenesulfonic acid (TsOH), camphorsulfonic acid (CSA), methanesulfonic acid (MsOH), or trifluoroacetic acid (TFA) clearly accelerated the reaction (Table 1, entries 2−6). Moderate yield and good diastereoselectivity were obtained with the addition of TsOH in a shortened reaction time (Table 1, entry 3). At 60 °C, upon addition of acid, the chemical yield was slightly lowered (Table 1, entries 7−9). Subsequently, use of **2a** was enhanced to 1.5 equiv, and both yield and diastereoselectivity were all clearly improved (entry 10). In addition, various solvents, including chloroform, toluene, and acetonitrile, were also tested and inferior results were obtained (entries 11−13). Ultimately, to investigate the influence of temperature on diastereomeric ratio, two other experiments

Table 1. Optimization of Reaction Conditions[a]



entry	solvent[b]	additive (20 mol %)	*T* (°C)	time (h)[c]	yield (%)[d]	dr[e]
1	DCE	–	rt	48	43	80:20
2	DCE	–	60	36	52	73:27
3	DCE	TsOH	rt	36	51	81:19
4	DCE	CSA	rt	36	47	76:24
5	DCE	MsOH	rt	36	41	78:22
6	DCE	TFA	rt	36	32	81:19
7	DCE	TsOH	60	24	48	83:17
8	DCE	CSA	60	24	46	74:26
9	DCE	MsOH	60	24	45	73:27
10[f]	DCE	TsOH	60	24	64	91:9
11[f]	$CHCl_3$	TsOH	60	24	55	59:41
12[f]	toluene	TsOH	60	24	60	83:17
13[f]	MeCN	TsOH	60	24	47	66:34
14[f]	DCE	–	60	36	58	79:21
15[f]	DCE	–	rt	48	55	54:46

[a]Unless otherwise noted, the reaction was performed on 0.2 mmol scale with 0.2 mmol of **1a** and 0.24 mmol of 4-bromoaniline (**2a**) in solvent (2.0 mL) under given conditions. After **1a** was completely consumed, the reaction mixture was cooled to rt and 1.2 equiv of $TiCl_4$ was added. [b]All solvents used in this reaction were dried with 4 Å molecular sieves. [c]The reaction time for step 1. [d]Isolated yield. [e]Determined by ^1H NMR. [f]1.5 equiv of **2a** was used.

were carried out in the absence of additive. The diastereomeric ratio slightly decreased without the assistance of TsOH at 60 °C (entry 14 vs entry 10). Interestingly, at room temperature, the diastereomeric ratio was greatly reduced (entry 15). Accordingly, the optimal reaction conditions were established as **1a**/**2a** (1:1.5) in DCE at 60 °C.

With the optimal reaction conditions in hand, we first extended this reaction to various substituted anilines (Table 2). Satisfyingly, aniline (**2b**) afforded excellent yield (93%) and diastereomeric ratio (95:5 dr) (entry 2). Para-substituted anilines **2c−e** were tested, and good yields were all obtained but with slightly dropped diastereomeric ratios in comparison with **2b** (entries 3−5). Pleasingly, *o*-methoxyaniline also gave good yield with mildly decreased dr in a relatively longer reaction duration (entry 6). Presumably, the steric effect caused by an ortho-substituent might majorly contribute to the difference in reactivity. Not surprisingly, in the case of 2,6-dimethylaniline, the demanding steric hindrance severely slowed down the reaction, leading to the decreased chemical yield without affecting the diastereoselectivity (entry 7). Finally, 2-hydroxyaniline (**2h**) and 2-aminopyridine (**2i**) as well as phenylhydrazine (**2j**) were also probed. Unfortunately, the desired products were unable to be obtained though the corresponding imines could be effectively formed respectively in the first step. We reasoned that the presence of hydroxyl, pyridyl, or other active coordinating sites might severely interfere with the coordination of titanium tetrachloride with carbonyl groups on the cyclopropane moiety and mute the ring-opening reactivity.

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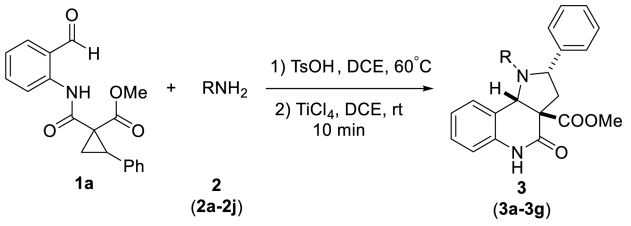
Table 2. Substrate Scope of Aniline 2[a]



entry	$ArNH_2$	time (h)[b]	yield (%)[c]	dr[d]
1	**2a**, 4-$BrC_6H_4NH_2$	24	64 (**3a**)	91:9
2	**2b**, $C_6H_5NH_2$	24	93 (**3b**)	95:5
3	**2c**, 4-$FC_6H_4NH_2$	24	82 (**3c**)	89:11
4	**2d**, 4-$MeC_6H_4NH_2$	24	89 (**3d**)	83:17
5	**2e**, 4-$MeOC_6H_4NH_2$	24	89 (**3e**)	84:16
6	**2f**, 2-$MeOC_6H_4NH_2$	36	82 (**3f**)	85:15
7	**2g**, 2,6-$(Me)_2C_6H_3NH_2$	48	70 (**3g**)	95:5
8	**2h**, 2-$HOC_6H_4NH_2$	12	–	–
9	**2i**, 2-aminopyridine	36	–	–
10	**2j**, phenylhydrazine	12	–	–

[a]Unless otherwise noted, the reaction was performed on 0.2 mmol scale with 0.2 mmol of **1a** and 0.3 mmol of **2** in dry DCE (2 mL) with 20 mol % of TsOH at 60 °C. After **1a** was completely consumed, the reaction mixture was cooled to rt and 1.2 equiv of $TiCl_4$ was added. [b]The reaction time for step 1. [c]Isolated yield. [d]Determined by ^1H NMR.

To further explore the viability and generality of this reaction, a variety of amide-linked cyclopropane derivatives were tested by reacting with **2b**. As shown in Table 3, as para-substituted phenyl cyclopropanes were used, the yields and drs of **3h–l** varied widely depending on the nature of substituents. It seems that both yield and dr were affected by para-substituents and diastereoselectivities were generally decreased. The more sterically demanding substituents usually gave relatively lower yields (**3j**, **3k**, and **3l**). On the other side, electron-withdrawing groups had negative impact on the diastereomeric ratio (**3h**, **3i**, and **3j**). Interestingly, meta-substituents consistently afforded good to excellent yields and good drs (**3m-o**). *o*-Chloro-substituted cyclopropane derivative afforded relatively low yield but a good diastereomeric ratio (**3p**), which might be attributed to the escalated steric effect induced by an ortho-substituent. Other aromatic analogues including 2-thienyl and 2-naphthyl cyclopropanes were well tolerated, and moderate yields and drs were obtained (**3q** and **3r**). In addition, (1*E*)-2-phenylethenyl and vinyl cyclopropane derivatives were also examined. Their diastereoselectivities were markedly reduced though moderate yields were still maintained (**3s** and **3t**). Finally, the ethyl ester analogue afforded tricyclic product **3u** in good yield (76%) and excellent dr (98:2).

To further explore the versatility of this linking strategy, we subsequently studied the possibility of this protocol using glycine methyl ester **2k**, which was frequently employed to react with aldehydes to form reactive dipoles. We were specifically curious about the annulation mode whether [3 + 2] or [3 + 3] annulation would occur under the reaction conditions. Interestingly, it turned out that [3 + 2]-annulation was still observed in moderate yield (47%) with an excellent diastereomeric ratio (92:8 dr) (Scheme 2, eq a). On the other hand, aldehydes **1a** and **1p** were directly subjected to the annulation conditions, which was expected to proceed an intramolecular oxa-[3 + 2]-annulation furnishing tetrahydrofuro[3,2-*c*]quinolinone skeleton. Gratifyingly, treatment of aldehyde **1a** with 1.2 equiv of $TiCl_4$ and 0.1 equiv of MsOH at 60 °C for 12 h successfully delivered tricycle **4a** in good yield (74% yield) and a moderate diastereomeric ratio (74:26 dr) (Scheme 2, eq b). To our surprise, vinyl analogue **1p** failed to afford the desired product under the standard conditions and only severe decomposition was observed. However, the transition metal-assisted ring-opening catalyzed by $Pd(PPh_3)_4$ successfully furnished the corresponding tricycle **4b** in good diastereomeric ratio (80:20 dr) but low yield (Scheme 2, eq c). The structures of tricycle **4a** and **4b** were unambiguously confirmed by X-ray crystal structure analysis.[16] Noticeably, the relative configuration of nitrogen-containing **3a** with phenyl ring trans to the ester group was obviously different from the cis configuration in oxygen-containing **4a.** However, the trans relationship between the vinyl group and ester was also observed in **4b**.

Finally, control experiments were carried out to better mechanistically understand this annulation. We intentionally stopped the reaction sequence, and the intermediate imine **5** was isolated. Then **5** was subjected to Lewis acid, causing annulation to afford tricycle **3a** in 78% yield (Scheme 3, eq a). This result clearly proved that the imine was the key intermediate for this process. To test the necessity of dicarboxylate for cyclopropane, we switched to cyclopropane monocarboxylic acid derivative **6** in this protocol. The reaction turned out to be complex, and the desired product was not isolated (Scheme 3, eq b). On the other hand, cyclopropane 1,1-diester **7**, namely ester as a linker, was unable to give the expected annulation product under the reaction conditions (Scheme 3, eq c). Obviously, dicarboxylate and amide were simultaneously playing vital roles in the annulation process, which is compatible with our previous observation.[15]

On the basis of the above results, we proposed a plausible mechanism as shown in Scheme 4. Presumably, the intramolecular hydrogen-bonding tentatively formed in aldehyde **1a** and imine **int-1**, which was subsequently destroyed upon the addition of $TiCl_4$. It can be postulated that two carbonyl groups in **int-1** simultaneously coordinated with titanium(IV) to generate complex **int-2**, which promoted the ring-opening of the cyclopropane. Subsequently, the intramolecular nucleophilic attack of the resulting zwitterion on the C=N bond effectively formed **TS-1**. Presumably, the orientation of the phenyl group at the terminal alkyl chain would be extremely crucial to the diastereomeric selectivity for the annulation product. As shown in **TS-1b**, the phenyl moiety orienting toward the carboxylate in the process of ring-closure would generate the unpleasant steric repulsion, making the annulation product **3a′** unfavored. However, this steric repulsion could be effectively relieved by positioning the phenyl group far away from ester as illustrated in **TS-1a**, affording **3a** with the phenyl group trans to the ester as the major diastereomer.

■ CONCLUSION

In summary, we have developed an efficient protocol for the diastereoselective construction of a library of hexahydropyrrolo-[3,2-*c*]quinolinones, as the tricyclic core of martinelline, in moderate to good yield with a good diastereomeric ratio. The newly designed intramolecular ring-opening of cyclopropane with imine was successfully realized with the aid of amide as an effective linker, which would broaden the synthetic versatility of ring-opening of cyclopropane. Moreover, this strategy might provide a useful hint for the assembly of other multicyclic systems.

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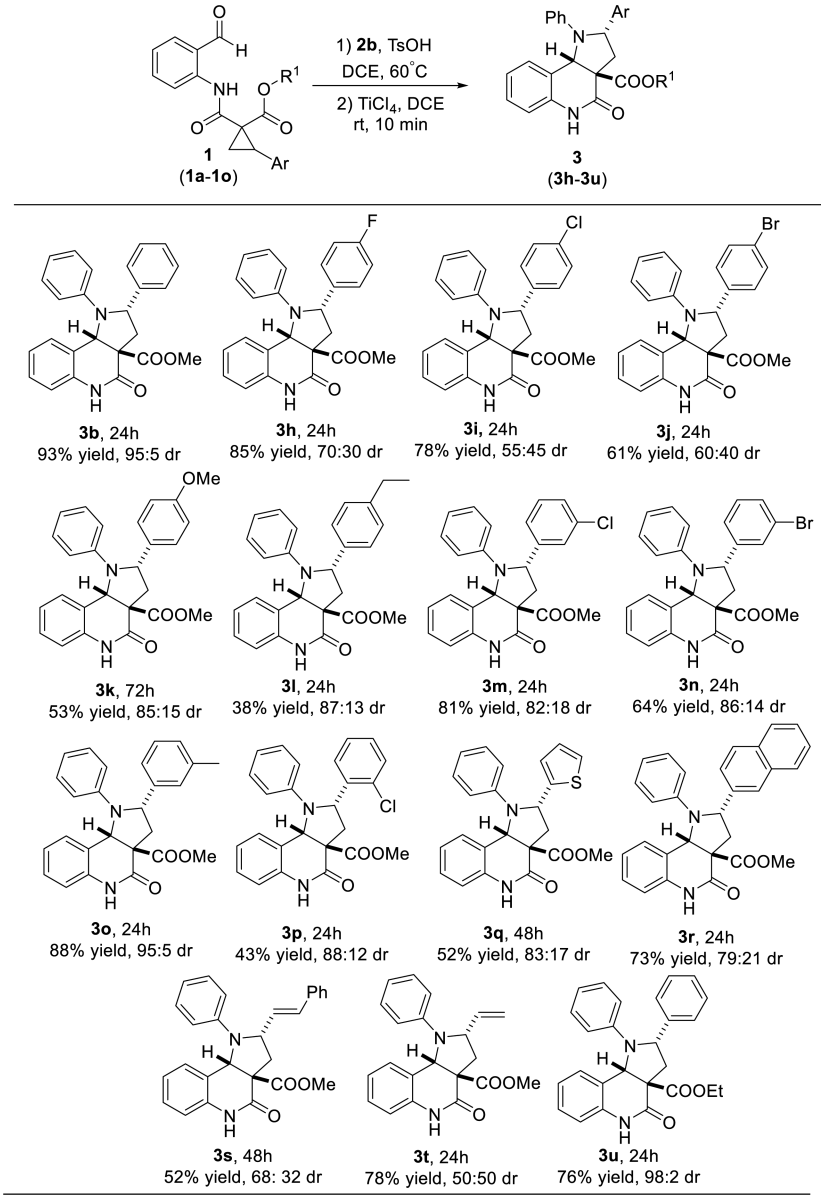
Table 3. Substrate Scope of Cyclopropane 1[a]



[a]Unless otherwise noted, the reaction was performed on 0.2 mmol scale with 0.2 mmol of **1** and 0.3 mmol of **2b** in dry DCE (2 mL) with 20 mol % of TsOH at 60 °C. After **1** was completely consumed, the reaction mixture was cooled to rt and 1.2 equiv of $TiCl_4$ was added.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all the reagents were purchased from commercial suppliers and used without further purification. ^{1}H NMR spectra were recorded at 400 MHz. The chemical shifts were recorded in ppm relative to tetramethylsilane and with the solvent resonance as the internal standard. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (Hz), integration. ^{13}C NMR data were collected at 100 MHz with complete proton decoupling. Chemical shifts were reported in ppm from the tetramethylsilane with the solvent resonance as internal standard. Infrared spectra (IR) were measured by FT-IR spectroscopy. High resolution mass spectroscopy (HRMS) was recorded on a TOF-MS mass spectrometer, and acetonitrile was used to dissolve the sample. Column chromatography was carried out on silica gel (200–300 mesh). All solvents and commercially available reagents were either purified via literature procedures or used without further purification. 2-Phenyl-1,1-cyclopropanedicarboxylic acid ester,[17a] 2-vinyl-1,1-cyclopropanedicarboxylic acid ester,[17b] and 2-phenyl-cyclopropanecarboxylic acid[17c] were prepared according to the reported procedures, respectively.

*General Experimental Procedures for the Synthesis of Aldehyde **1a–o** and **6**.* To a solution of 2-aminobenzyl alcohol (1.0 equiv) in dichloromethane (concn 0.05 M) were added 2-phenyl-1,1-cyclopropanedicarboxylic acid ester, 2-vinyl-1,1-cyclopropanedicarboxylic acid ester, or 2-phenyl-cyclopropanecarboxylic acid (1.0 equiv) and DCC (1.2 equiv), respectively. The reaction was stirred at room temperature for 12 h. Then the white solid was filtered, and the resulting cake was washed with ethyl acetate. Then saturated ammonium chloride solution was added to the filtrate and extracted twice with ethyl acetate. Then the combined organic layer was washed with brine twice, dried over Na_2SO_4, and concentrated in vacuo to afford crude product, which was used in the next step without further purification.

To the crude product in dichloromethane (0.5 M) was added PCC (1.5 equiv). The mixture was stirred at room temperature for 2 h, and the black solid was filtered. Then the filtrate was concentrated and purified via silica gel column chromatography, eluting with ethyl

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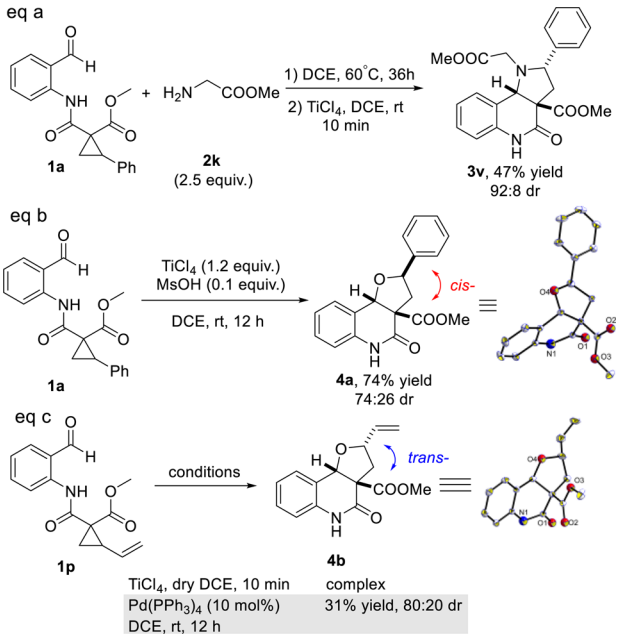
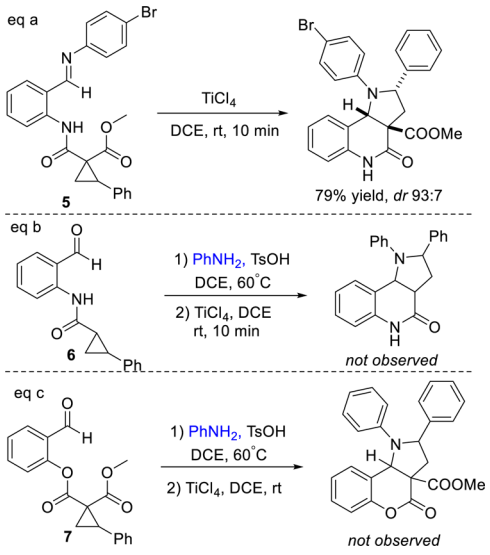
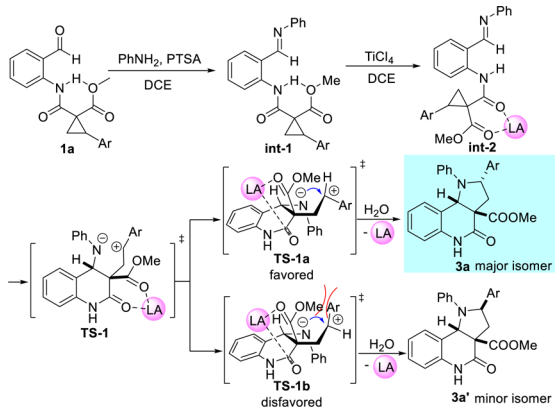
Scheme 2. Divergent [3 + 2]-Annulation Reactions



Scheme 3. Control Experiments of Intramolecular [3 + 2]-Annulation Reactions



Scheme 4. Plausible Pathway for [3 + 2]-Annulation



acetate:petroleum ether = 1:9 to afford cyclopropane-aldehyde derivatives as a single diastereoisomer over two steps.

Alcohol ***8***. White solid (12 g, 38 mmol, 86% yield for step one; in this single case, the intermediate alcohol was isolated to confirm the structure): mp 95−96 °C; IR (KBr) ν 3413, 3284, 2362, 1798, 1530, 1138, 999, 751 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.70 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.23−7.36 (m, 7H), 7.14 (td, J = 7.6, 1.2 Hz, 1H), 4.71 (q, J = 12.0 Hz, 2H), 3.31 (t, J = 8.8 Hz, 1H), 3.22 (s, 3H), 2.38 (dd, J = 8.4, 4.8 Hz, 1H), 2.29 (dd, J = 9.6, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 167.2, 136.6, 135.1, 131.6, 129.5, 129.2, 129.0, 128.1, 127.5, 125.0, 123.3, 63.2, 51.8, 38.4, 36.1, 19.7; HRMS (TOF-ES+) m/z: [M + Na]$^+$ calcd for $C_{19}H_{17}NO_4Na$ 346.1055, found 346.1041.

Aldehyde ***1a***. White solid (11 g, 35 mmol, 93% yield from alcohol **8**): mp 102−103 °C; IR (KBr) ν 3417, 3027, 2728, 1963, 1696, 1335, 1142, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.29 (s, 1H), 9.97 (s, 1H), 8.77 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 7.2 Hz, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.24−7.28 (m, 6H), 3.44 (s, 3H), 3.31 (t, J = 8.8 Hz, 1H), 2.35 (dd, J = 8.0, 4.4 Hz, 1H), 2.15 (dd, J = 9.2, 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.4, 168.5, 167.9, 140.0, 135.9, 135.8, 135.0, 129.1, 128.1, 127.5, 123.3, 123.0, 120.9, 52.2, 38.1, 37.1, 19.8; HRMS (TOF-ES+) m/z: [M + Na]$^+$ calcd for $C_{19}H_{17}NO_4Na$ 346.1055, found 346.1060.

Aldehyde ***1b***. White solid (1.5 g, 4.5 mmol, 60% yield over two steps): mp 85−86 °C; IR (KBr) ν 3421, 2065, 1640, 1511, 1322, 1192, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.26 (s, 1H), 9.95 (d, J = 5.2 Hz, 1H), 8.76 (d, J = 8.4 Hz, 1H), 7.69−7.71 (m, 1H), 7.59−7.63 (m, 1H), 7.23−7.28 (m, 3H), 6.96−7.01 (m, 2H), 3.49 (s, 3H), 3.27 (t, J = 8.4 Hz, 1H), 2.31 (dd, J = 8.0, 4.8 Hz, 1H), 2.14 (dd, J = 9.2, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.5, 168.3, 167.7, 162.1 (d, $^1J_{C-F}$ = 251 Hz), 140.0, 136.0, 135.8, 130.7 (d, $^3J_{C-F}$ = 8 Hz), 130.7, 123.3, 122.9, 120.8, 115.0 (d, $^2J_{C-F}$ = 22 Hz), 52.3, 38.1, 36.1, 19.9; HRMS (TOF-ES+) m/z: [M + Na]$^+$ calcd for $C_{19}H_{16}FNO_4Na$ 364.0961, found 364.0952.

Aldehyde ***1c***. White solid (2.4 g, 6.7 mmol, 72% yield over two steps): mp 77−78 °C; IR (KBr) ν 3267, 2839, 2756, 1723, 1585, 1322, 779, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.26 (s, 1H), 9.96 (s, 1H), 8.75 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.12−7.28 (m, 5H), 3.51 (s, 3H), 3.26 (t, J = 8.8 Hz, 1H), 2.31 (dd, J = 8.4, 4.8 Hz, 1H), 2.14 (dd, J = 9.2, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.5, 168.2, 167.6, 140.0, 136.0, 135.8, 133.5, 133.4, 130.5, 128.3, 123.4, 122.9, 120.9, 52.4, 38.2, 36.0, 19.9; HRMS (TOF-ES+) m/z: [M + Na]$^+$ calcd for $C_{19}H_{16}ClNO_4Na$ 380.0666, found 380.0650.

Aldehyde ***1d***. White solid (3.5 g, 8.7 mmol, 79% yield over two steps): mp 75−76 °C; IR (KBr) ν 3418, 3270, 2756, 1672, 1520, 1319, 1007, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.26 (s, 1H), 9.97 (s, 1H), 8.75 (d, J = 8.4 Hz, 1H), 7.71 (dd, J = 7.6, 1.2 Hz, 1H), 7.63 (td, J = 8.0, 1.6 Hz, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.25−7.29 (m, 1H), 7.15 (d, J = 8.4 Hz, 2H), 3.51 (s, 3H), 3.25 (t, J = 8.8 Hz, 1H), 2.31 (dd, J = 8.0, 4.8 Hz, 1H), 2.14 (dd, J = 9.2, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.5, 168.2, 167.6, 140.0, 136.0, 135.8, 134.1, 131.3, 130.8, 123.4, 122.9, 121.5, 120.9, 52.5, 38.1, 36.0, 19 0.8; HRMS (TOF-ES+) m/z: [M + Na]$^+$ calcd for $C_{19}H_{16}BrNO_4Na$ 424.0160, found 424.0175.

Aldehyde ***1e***. White solid (1.4 g, 3.8 mmol, 45% yield over two steps): mp 69−70 °C; IR (KBr) ν 3415, 2957, 1732, 1671, 1517, 1247, 846, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.29 (s, 1H), 9.98 (s, 1H), 8.78 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 6.8 Hz, 1H), 7.63 (t, J = 7.2 Hz, 1H), 7.21−7.29 (m, 3H), 6.84 (d, J = 7.6 Hz, 1H), 3.80 (s, 3H), 3.50 (s, 3H), 3.27 (t, J = 8.4 Hz, 1H), 2.32−2.35 (m, 1H), 2.14−2.17 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.4, 168.5, 168.0, 159.0, 140.1, 135.9, 135.8, 130.3, 126.8, 123.2, 123.0, 120.9, 113.5, 55.3, 52.3, 38.2, 36.9, 19.9; HRMS (TOF-ES+) m/z: [M + Na]$^+$ calcd for $C_{20}H_{19}NO_5Na$ 376.1161, found 376.1149.

Aldehyde ***1f***. White solid (0.63 g, 1.8 mmol, 32% yield over two steps): mp 68−69 °C; IR (KBr) ν 3251, 2959, 1732, 1670, 1445, 1322, 1195, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.28 (s, 1H), 9.97 (s, 1H), 8.77 (d, J = 7.6 Hz, 1H), 7.69 (dd, J = 7.6, 0.8 Hz, 1H), 7.61 (t, J = 8.4 Hz, 1H), 7.23−7.27 (m, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.11

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(d, J = 8.0 Hz, 2H), 3.45 (s, 3H), 3.27 (t, J = 8.8 Hz, 1H), 2.61 (q, J = 7.6 Hz, 2H), 2.34 (dd, J = 8.4, 4.8 Hz, 1H), 2.14 (dd, J = 9.2, 4.8 Hz, 1H), 1.21 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.4, 168.5, 168.0, 143.5, 140.1, 135.9, 135.8, 132.0, 129.1, 127.6, 123.2, 122.9, 120.9, 52.2, 38.2, 37.1, 28.5, 19.8, 15.6; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{21}H_{21}NO_4Na$ 374.1368, found 374.1380.

Aldehyde ***1g***. White solid (0.56 g, 1.6 mmol, 31% yield over two steps): mp 72−73 °C; IR (KBr) ν 3416, 3011, 2753, 2364, 1730, 1518, 1324, 1198, 761 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.28 (s, 1H), 9.97 (s, 1H), 8.76 (d, J = 8.4 Hz, 1H), 7.71 (dd, J = 7.6, 1.6 Hz, 1H), 7.61−7.65 (m, 1H), 7.16−7.29 (m, 5H), 3.52 (s, 3H), 3.28 (t, J = 8.8 Hz, 1H), 2.32 (dd, J = 8.0, 4.4 Hz, 1H), 2.14 (dd, J = 9.2, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.5, 168.2, 167.5, 139.9, 137.1, 136.0, 135.8, 134.0, 129.4, 129.3, 127.7, 127.4, 123.4, 122.9, 120.9, 52.4, 38.1, 36.1, 19.9; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{19}H_{16}ClNO_4Na$ 380.0666, found 380.0668.

Aldehyde ***1h***. White solid (1.9 g, 4.5 mmol, 49% yield over two steps): mp 75−76 °C; IR (KBr) ν 3416, 3010, 1729, 1585, 1516, 1323, 1198, 762 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.27 (s, 1H), 9.96 (s, 1H), 8.75 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.43 (s, 1H), 7.38 (dd, J = 7.6, 0.4 Hz, 1H), 7.22−7.28 (m, 1H), 7.14−7.20 (m, 2H), 3.52 (s, 3H), 3.27 (t, J = 8.6 Hz, 1H), 2.31 (dd, J = 8.0, 4.4 Hz, 1H), 2.13 (dd, J = 9.2, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.5, 168.2, 167.5, 139.9, 137.4, 136.0, 135.8, 132.2, 130.6, 129.7, 127.9, 123.4, 122.9, 122.1, 120.9, 52.4, 38.1, 36.0, 19.9; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{19}H_{16}BrNO_4Na$ 424.0160, found 424.0179.

Aldehyde ***1i***. White solid (2.0 g, 5.9 mmol, 61% yield over two steps): mp 62−63 °C; IR (KBr) ν 3281, 3031,, 2836, 1732, 1587, 1323, 1200, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.28 (s, 1H), 9.95−9.97 (m, 1H), 8.77 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 6.2 Hz, 1H), 7.58−7.63 (m, 1H), 7.22−7.27 (m, 1H), 7.17 (t, J = 7.6 Hz, 1H), 7.04−7.09 (m, 3H), 3.46 (s, 3H), 3.28 (t, J = 8.8 Hz, 1H), 2.23−2.36 (m, 1H), 2.32 (s, 3H), 2.13 (dd, J = 9.6, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.4, 168.5, 168.0, 140.1, 137.7, 135.9, 135.8, 134.9, 129.9, 128.2, 128.0, 126.0, 123.2, 122.9, 120.9, 52.2, 38.1, 37.1, 21.3, 19.8; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{20}H_{19}NO_4Na$ 360.1212, found 360.1227.

Aldehyde ***1j***. White solid (1.8 g, 5.1 mmol, 48% yield over two steps): mp 103−104 °C; IR (KBr) ν 3247, 3021, 1737, 1587, 1320, 1204, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.43 (s, 1H), 10.00 (s, 1H), 8.80 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.64 (t, J = 7.2 Hz, 1H), 7.36−7.38 (m, 1H), 7.23−7.30 (m, 4H), 3.49 (s, 3H), 3.35 (t, J = 9.0 Hz, 1H), 2.38 (dd, J = 8.4, 4.8 Hz, 1H), 2.29 (dd, J = 9.2, 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.2, 168.5, 167.7, 140.0, 136.3, 135.8, 135.7, 133.4, 130.3, 129.1, 128.8, 126.3, 123.3, 123.2, 121.1, 52.3, 37.2, 36.3, 20.3; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{19}H_{16}ClNO_4Na$ 380.0666, found 380.0678.

Aldehyde ***1k***. White solid (1.3 g, 3.9 mmol, 44% yield over two steps): mp 83−84 °C; IR (KBr) ν 3416, 2846, 1732, 1536, 1201, 761 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.23 (s, 1H), 9.95 (s, 1H), 8.75 (d, J = 8.8 Hz, 1H), 7.69 (dd, J = 7.6, 1.6 Hz, 1H), 7.59−7.63 (m, 1H), 7.23−7.27 (m, 1H), 7.17−7.19 (m, 1H), 6.91−6.93 (m, 2H), 3.61 (s, 3H), 3.33 (t, J = 8.0 Hz, 1H), 2.32 (dd, J = 9.2, 4.8 Hz, 1H), 2.22 (dd, J = 9.2, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.5, 167.9, 167.2, 140.0, 138.3, 136.0, 135.8, 127.1, 126.7, 125.2, 123.3, 122.9, 120.8, 52.6, 39.1, 31.3, 21.5; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{17}H_{15}SNO_4Na$ 352.0619, found 352.0609.

Aldehyde ***1l***. White solid (0.82 g, 2.2 mmol, 56% yield over two steps): mp 100−101 °C; IR (KBr) ν 3259, 3018, 1728, 1589, 1447, 1201, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.31 (s, 1H), 9.96 (s, 1H), 8.80 (d, J = 8.4 Hz, 1H), 7.61−7.79 (m, 6H), 7.39−7.46 (m, 3H), 7.26−7.27 (m, 1H), 3.47 (t, J = 8.4 Hz, 1H), 3.37 (s, 3H), 2.47−2.50 (m, 1H), 2.22−2.25 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.5, 168.5, 167.9, 140.1, 136.0, 135.8, 133.1, 132.7, 132.5, 128.0, 127.82, 127.78, 127.6, 127.1, 126.2, 126.0, 123.3, 123.0, 120.9, 52.3, 38.3, 37.3, 20.1; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{23}H_{19}NO_4Na$ 396.1212, found 396.1225.

Aldehyde ***1m***. White solid (1.1 g, 3.0 mmol, 27% yield over two steps): mp 78−79 °C; IR (KBr) ν 3416, 3249, 2752, 1660, 1442, 1196, 953, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.25 (s, 1H), 9.96 (s, 1H), 8.74 (d, J = 8.8 Hz, 1H), 7.68 (dd, J = 7.6, 1.2 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.20−7.34 (m, 6H), 6.68 (d, J = 15.6 Hz, 1H), 6.04 (dd, J = 16.0, 9.2 Hz, 1H), 3.92 (s, 3H), 2.83 (dd, J = 17.2, 8.4 Hz, 1H), 2.05−2.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.5, 169.1, 167.6, 140.1, 136.8, 136.0, 135.8, 134.7, 128.6, 127.7, 124.7, 123.3, 122.9, 120.9, 52.8, 37.6, 36.7, 22.7; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{21}H_{19}NO_4Na$ 372.1212, found 372.1213.

Aldehyde ***1n***. White solid (2.5 g, 9.1 mmol, 76% yield over two steps): mp 79−80 °C; IR (KBr) ν 3415, 3263, 2851, 1728, 1687, 1519, 1199, 948, 790 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.20 (s, 1H), 9.96 (s, 1H), 8.71 (d, J = 8.4 Hz, 1H), 7.69 (dd, J = 7.6, 1.2 Hz, 1H), 7.59 (td, J = 8.0, 1.6 Hz, 1H), 7.22−7.28 (m, 1H), 5.60−5.69 (m, 1H), 5.36 (dd, J = 17.2, 0.8 Hz, 1H), 5.20 (dd, J = 10.4, 1.2 Hz, 1H), 3.92 (s, 3H), 2.66 (q, J = 8.4 Hz, 1H), 2.01 (dd, J = 8.8, 4.4 Hz, 1H), 1.94 (dd, J = 8.0, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.5, 169.0, 167.6, 140.0, 136.0, 135.8, 133.0, 123.2, 122.8, 120.8, 119.6, 52.7, 37.2, 36 0.3, 22.0; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{15}H_{15}NO_4Na$ 296.0899, found 296.0910.

Aldehyde ***1o***. White solid (1.6 g, 4.6 mmol, 46% yield over two steps): mp 77−78 °C; IR (KBr) ν 3415, 2983, 2774, 1727, 1675, 1447, 1315, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.32 (s, 1H), 9.97 (s, 1H), 8.76 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.61 (td, J = 8.8, 1.2 Hz, 1H), 7.22−7.29 (m, 5H), 3.96−4.04 (m, 1H), 3.82−3.90 (m, 1H), 3.31 (t, J = 8.8 Hz, 1H), 2.35 (dd, J = 8.0, 4.4 Hz, 1H), 2.14 (q, J = 9.2, 4.4 Hz, 1H), 0.79 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.3, 168.3, 168.1, 140.0, 135.9, 135.7, 135.0, 129.3, 128.1, 127.4, 123.3, 123.0, 121.0, 61.6, 37.7, 37.0, 19.6, 13.5 ; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{20}H_{19}NO_4Na$ 360.1212, found 360.1223.

Aldehyde ***6***. White solid (0.43 g, 1.6 mmol, 44% yield over two steps): mp 101−102 °C; IR (KBr) ν 3415, 3252, 1675, 1585, 1289, 1114, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.42 (s, 1H), 9.91 (s, 1H), 8.76 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.61 (dt, J = 7.8, 1.2 Hz, 1H), 7.30 (t, J = 7.2 Hz, 2H), 7.22 (q, J = 7.6 Hz, 2H), 7.14 (d, J = 7.6 Hz, 2H), 2.61−2.66 (m, 1H), 1.90−1.94 (m, 1H), 1.64−1.75 (m, 1H), 1.39−1.43 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.6, 171.6, 141.0, 140.2, 136.3, 136.1, 128.5, 126.5, 126.2, 122.8, 121.4, 119.9, 28.3, 26.5, 17.1; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{17}H_{15}NO_2Na$ 288.1000, found 288.1005.

Experimental Procedure for Aldehyde ***7***. To a solution of salicylic aldehyde (0.83 g, 6.8 mmol, 1.0 equiv) and 2-phenyl-1-methyl ester 1,1-cyclopropanedicarboxylic acid (1.5 g, 6.8 mmol, 1.0 equiv) in dichloromethane (68 mL) was added DCC (1.7 g, 8.2 mmol, 1.2 equiv). The mixture was stirred at room temperature for 12 h, and then the solid was filtered. The residue was concentrated in vacuo and purified through silica gel column chromatography, eluting with ethyl acetate:petroleum ether = 1:9 to afford colorless oil (1.63 g, 5.0 mmol, 73% yield). IR (KBr) ν 3416, 2853, 2756, 1739, 1605, 1267, 1118, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.22 (s, 1H), 7.92 (dd, J = 8.0, 1.6 Hz, 1H), 7.66 (td, J = 8.4, 2.0 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.25−7.34 (m, 6H), 3.45−3.47 (m, 1H), 3.42 (s, 3H), 2.40−2.46 (m, 1H), 2.02 (dd, J = 9.2, 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.7, 168.2, 166.5, 151.7, 135.3, 134.0, 130.5, 128.7, 128.3, 128.2, 127.7, 126.7, 123.3, 52.5, 37.1, 33.6, 20.0 ; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{19}H_{16}O_5Na$ 347.0895, found 347.0894.

General Experimental Procedures for the Synthesis of Tricyclic Product. To a solution of aldehyde (0.2 mmol) and the corresponding amine (0.3 mmol, 1.5 equiv) in dry 1,2-dichloroethane (0.2 mL) was added TsOH (6.9 mg, 0.04 mmol, 0.2 equiv). The mixture was stirred at 60 °C for 12−72 h before the aldehyde was completely consumed. Then the reaction mixture was cooled to room temperature and titanium tetrachloride (46 mg, 0.24 mmol, 1.2 equiv) was added slowly. After being stirred at room temperature for 10 min, the reaction mixture was quenched by water (5 mL). Then the resulting mixture was stirred for 10 min and extracted with ethyl acetate twice (3 mL × 2). The combined organic phase was dried, concentrated, and purified through silica gel column chromatography, eluting with ethyl acetate:petroleum ether = 1:3 to afford tricyclic product as a white solid.

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Tricycle ***3a***. White solid (61 mg, 0.13 mmol, 64% yield): mp 139−140 °C; IR (KBr) ν 3422, 1741, 1639, 1495, 1383, 1239, 754 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.77 (s, 1H), 7.07−7.43 (m, 11H), 6.92−7.00 (m, 1H), 6.65−6.71 (m, 2H), 5.76 (s, 2H), 4.75−4.80 (m, 1H), 3.66 (s, 3H), 3.22 (dd, J = 12.8, 7.2 Hz, 1H), 1.95 (dd, J = 12.8, 10.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.7, 166.7, 147.1, 142.1, 135.2, 132.2, 129.5, 129.2, 128.6, 127.8, 126.4, 123.8, 123.2, 116.2, 115.2, 109.4, 64.7, 62.9, 59.3, 55.4, 53.5; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{25}H_{21}BrN_2O_3$ 499.0633, found 499.0629.

Tricycle ***3b***. White solid (74 mg, 0.19 mmol, 93% yield): mp 232−233 °C; IR (KBr) ν 3416, 3056, 1734, 1676, 1489, 1349, 1240, 1068, 759 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.68 (s, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.12−7.25 (m, 6H), 6.93−6.98 (m, 3H), 6.87 (t, J = 7.6 Hz, 1H), 6.75 (d, J = 8.0 Hz, 2H), 6.55 (t, J = 7.2 Hz, 1H), 5.96 (s, 1H), 5.76 (s, 1H), 4.88 (t, J = 7.2 Hz, 1H), 3.56 (s, 3H), 2.96 (dd, J = 12.4, 8.4 Hz, 1H), 2.54 (t, J = 6.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.0, 167.5, 145.6, 143.0, 136.9, 130.0, 129.4, 128.8, 128.6, 127.2, 122.5, 121.2, 118.8, 118.6, 116.3, 63.6, 60.8, 58.5, 53.1, 41.7 ; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{25}H_{22}N_2O_3Na$ 421.1528, found 421.1534.

Tricycle ***3c***. White solid (68 mg, 0.16 mmol, 82% yield): mp 221−222 °C; IR (KBr) ν 3417, 2081, 1639, 1487, 1387, 1186, 618 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.67 (s, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.14−7.25 (m, 7H), 6.89−6.94 (m, 2H), 6.77 (d, J = 6.4 Hz, 4H), 5.82 (s, 1H), 4.87 (t, J = 7.6 Hz, 1H), 3.57 (s, 3H), 3.02−3.07 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 169.8, 167.4, 155.8 (d, $^1J_{C-F}$ = 235 Hz), 142.9, 141.9, 137.1, 130.6, 129.5, 128.7, 127.5, 122.4, 120.8 (d, $^3J_{C-F}$ = 8 Hz), 120.7, 116.2, 115.1 (d, $^2J_{C-F}$ = 22 Hz), 64.1, 61.7, 58.5, 53.2, 42.0; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{25}H_{21}FN_2O_3Na$ 439.1434, found 439.1450.

Tricycle ***3d***. White solid (73 mg, 0.18 mmol, 89% yield): mp 229−230 °C; IR (KBr) ν 3415, 2956, 1690, 1343, 1188, 1063, 757 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.65 (s, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.11−7.24 (m, 6H), 6.92 (d, J = 8.0 Hz, 1H), 6.87 (t, J = 7.2 Hz, 1H), 6.77 (d, J = 8.0 Hz, 2H), 6.65 (d, J = 8.4 Hz, 2H), 5.88 (s, 1H), 4.83 (t, J = 7.2 Hz, 1H), 3.57 (s, 3H), 2.96 (dd, J = 12.8, 8.4 Hz, 1H), 2.52−2.54 (m, 1H), 2.05 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.0, 167.5, 143.2, 143.1, 136.9, 130.1, 129.4, 129.3, 128.6, 127.3, 127.2, 122.5, 121.3, 119.1, 116.2, 63.8, 61.0, 58.6, 53.1, 41.8, 20.5; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{26}H_{24}N_2O_3Na$ 435.1685, found 435.1685.

Tricycle ***3e***. White solid (76 mg, 0.18 mmol, 89% yield): mp 201−202 °C; IR (KBr) ν 3423, 2997, 2069, 1693, 1510, 1241, 1038, 762 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.63 (s, 1H), 7.34 (d, J = 7.2 Hz, 1H), 7.13−7.22 (m, 7H), 6.84−6.92 (m, 2H), 6.71−6.74 (m, 2H), 6.54−6.56 (m, 2H), 5.77 (s, 1H), 4.81 (t, J = 7.2 Hz, 1H), 3.58 (s, 3H), 3.54 (s, 3H), 3.01 (dd, J = 12.4, 8.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.0, 167.6, 152.7, 143.4, 138.9, 137.1, 130.4, 129.4, 128.6, 127.5, 127.2, 122.4, 121.2, 121.1, 116.2, 114.1, 64.3, 61.7, 58.6, 55.3, 53.2, 42.0; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{26}H_{24}N_2O_4Na$ 451.1634, found 451.1638.

Tricycle ***3f***. White solid (70 mg, 0.16 mmol, 82% yield): mp 125−126 °C; IR (KBr) ν 3424, 2076, 1639, 1429, 1187, 1049, 615 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.62 (s, 1H), 7.06−7.22 (m, 8H), 6.87 (d, J = 7.6 Hz, 1H), 6.80 (t, J = 7.2 Hz, 1H), 6.57−6.63 (m, 3H), 5.76 (s, 1H), 5.64 (s, 1H), 4.90−4.99 (m, 1H), 3.55−3.80 (m, 3H), 3.60 (s, 3H), 3.12−3.22 (m, 1H), 2.44−2.49 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.1, 167.5, 153.3, 143.3, 137.5, 134.1, 129.3, 128.4, 127.7, 127.2, 123.4, 122.8, 122.1, 120.8, 120.2, 115.9, 111.8, 64.4, 62.8, 58.3, 55.4, 53.3, 42.8; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{26}H_{24}N_2O_4Na$ 451.1634, found 451.1632.

Tricycle ***3g***. White solid (60 mg, 0.14 mmol, 70% yield): mp 211−212 °C; IR (KBr) ν 3419, 2076, 1736, 1674, 1496, 1359, 1237, 755 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.86 (s, 1H), 7.26−7.28 (m, 2H), 7.13−7.20 (m, 3H), 7.05−7.09 (m, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 7.2 Hz, 1H), 6.55−6.67 (m, 4H), 5.26 (s, 1H), 4.78 (dd, J = 10.0, 5.2 Hz, 1H), 3.61 (s, 3H), 3.15 (dd, J = 12.0, 5.2 Hz, 1H), 2.91 (t, J = 11.2 Hz, 1H), 2.32 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.2, 167.3, 141.3, 139.4, 138.5, 137.9, 136.9, 129.9, 129.2, 128.5, 128.0, 125.4, 122.2, 120.5, 115.5, 64.3, 63.6, 58.3, 53.4, 42.0, 20.4, 19.4 ; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{27}H_{26}N_2O_3Na$ 449.1841, found 449.1858.

Tricycle ***3h***. White solid (71 mg, 0.17 mmol, 85% yield): mp 230−231 °C; IR (KBr) ν 3416, 3063, 2035, 1742, 1673, 1596, 1233, 759 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz, two diastereomers, dr = 2.5:1) δ 10.76 (s, 0.40H), 10.68 (s, 0.96H), 7.27−7.36 (m, 2.8H), 7.11−7.26 (m, 4.1H), 6.92−7.10 (m, 6.1H), 6.87 (t, J = 7.4 Hz, 1.1H), 6.69−6.76 (m, 3.2H), 6.56 (t, J = 7.2 Hz, 1.0H), 5.96 (s, 1.0H), 4.82−4.91 (m, 1.4H), 3.63 (s, 1.3H), 3.58 (s, 2.9H), 2.95 (dd, J = 12.8, 8.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.7, 170.0, 167.4, 166.8, 161.4 (d, $^1J_{C-F}$ = 241 Hz), 147.7, 145.5, 139.0, 138.8, 136.9, 135.3, 129.9, 129.6, 129.4, 129.2, 129.1, 128.8, 128.7, 128.5, 128.4, 123.7, 123.5, 122.5, 121.2, 119.0, 118.8, 118.5, 116.3, 116.2, 116.0, 115.7, 115.5, 115.3, 113.5, 113.4, 64.7, 63.5, 62.3, 60.1, 59.3, 5 8.5, 53.4, 53.2, 41.7, 41.5; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{25}H_{21}FN_2O_3Na$ 439.1434, found 439.1422.

Tricycle ***3i***. White solid (67 mg, 0.16 mmol, 78% yield): mp 242−243 °C; IR (KBr) ν 3420, 2073, 1740, 1640, 1387, 1238, 1085, 757 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz, two diastereomers, dr = 1.6:1) δ 10.76 (s, 1.0H), 10.68 (s, 0.64H), 7.21−7.36 (m, 8.1H), 7.08−7.19 (m, 5.1H), 6.87−7.01 (m, 3.9H), 6.68−6.75 (m, 4.2H), 6.57 (t, J = 7.4 Hz, 0.70H), 5.97 (s, 0.67H), 5.75 (s, 0.30H), 5.62 (s, 0.92H), 4.80−4.89 (m, 1.7H), 3.63 (s, 3.0H), 3.58 (s, 2.0H), 3.23 (dd, J = 12.8, 7.2 Hz, 1.0H), 2.94 (dd, J = 10.8, 6.4 Hz, 0.72H), 1.97 (dd, J = 12.8, 9.6 Hz, 1.0H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.7, 169.9, 167.4, 167.8, 147.6, 145.4, 142.0, 141.7, 136.8, 135.3, 132.1, 131.7, 129.8, 129.7, 129.4, 129.1, 128.9, 128.7, 128.4, 123.8, 123.4, 122.6, 121.2, 118.9, 118.8, 116.3, 116.2, 113.5, 64.7, 63.4, 62.3, 60.0, 59.3, 58.5, 53.5, 53.4, 53.2, 41.4 ; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{25}H_{21}ClN_2O_3Na$ 455.1138, found 455.1148.

Tricycle ***3j***. White solid (58 mg, 0.12 mmol, 61% yield): mp 233−235 °C; IR (KBr) ν 3416, 2918, 1748, 1675, 1385, 1068, 1011, 756 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz, two diastereomers, dr = 1.5:1) δ 10.75 (s, 1.0H), 10.68 (s, 0.67H), 7.21−7.43 (m, 6.6H), 7.01−7.19 (m, 7.5H), 6.85−7.00 (m, 4.1H), 6.68−6.75 (m, 4.4H), 6.57 (t, J = 7.4 Hz, 0.69H), 5.97 (s, 0.69H), 5.75 (s, 0.22H), 5.69 (s, 0.96H), 4.78−4.89 (m, 1.7H), 3.63 (s, 3.1H), 3.58 (s, 2.2H), 3.23 (dd, J = 12.4, 6.8 Hz, 1.1H), 2.93 (dd, J = 13.6, 8.4 Hz, 0.76H), 1.93−1.99 (m, 1.2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.7, 169.9, 167.3, 166.8, 147.6, 145.4, 142.5, 142.2, 136.8, 135.3, 132.0, 131.5, 129.8, 129.7, 129.5, 129.4, 128.9, 128.8, 128.7, 123.8, 123.4, 122.6, 121.2, 120.6, 120.2, 118.9, 118.8, 116.3, 116.2, 113.5, 64.7, 63.4, 62.3, 60.1, 59.2, 58.5, 53.5, 53.2, 41.3 ; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{25}H_{21}BrN_2O_3Na$ 499.0633, found 499.0627.

Tricycle ***3k***. White solid (45 mg, 0.11 mmol, 53% yield): mp 135−137 °C; IR (KBr) ν 3418, 2068, 1639, 1185, 1151, 1037, 617 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.64 (s, 1H), 7.35 (d, J = 7.2 Hz, 1H), 7.07−7.20 (m, 4H), 6.85−6.98 (m, 4H), 6.73−6.80 (m, 4H), 6.54 (t, J = 6.8 Hz, 1H), 5.92 (s, 1H), 4.81 (t, J = 6.8 Hz, 1H), 3.68 (s, 3H), 3.59 (s, 3H), 2.90−2.95 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.0, 167.5, 158.5, 145.6, 136.9, 134.7, 130.0, 129.4, 128.7, 128.4, 122.5, 121.2, 119.0, 118.6, 116.3, 114.1, 63.5, 60.4, 58.5, 55.4, 53.2, 41.8; HRMS (TOF-ES+) m/z: $[M + H]^+$ calcd for $C_{26}H_{25}N_2O_4$ 429.1814, found 429.1803.

Tricycle ***3l***. White solid (32 mg, 0.076 mmol, 38% yield): mp 204−205 °C; IR (KBr) ν 3421, 2084, 1639, 1421, 1385, 1188, 616 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.63 (s, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.18 (td, J = 7.6, 0.8 Hz, 1H), 7.05−7.07 (m, 4H), 6.92−6.97 (m, 2H), 6.87 (td, J = 7.6, 0.8 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.53 (t, J = 7.4 Hz, 1H), 5.91 (s, 1H), 4.82 (dd, J = 8.0, 6.8 Hz, 1H), 3.56 (s, 3H), 2.92 (dd, J = 12.4, 8.4 Hz, 1H), 1.12 (t, J = 7.6 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 169.9, 167.5, 145.6, 142.5, 140.2, 136.9, 130.1, 129.4, 128.7, 128.0, 127.2, 122.5, 121.2, 118.9, 118.6, 116.3, 63.7, 60.7, 58.5, 53.1, 41.8, 28.2, 15.8; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{27}H_{26}N_2O_3Na$ 449.1841, found 449.1861.

Tricycle ***3m***. White solid (70 mg, 0.16 mmol, 81% yield): mp 249−250 °C; IR (KBr) ν 3419, 2921, 2077, 1733, 1677, 1640, 1389, 1189, 756 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.69 (s, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.25−7.29 (m, 1H), 7.31−7.21 (m, 4H), 7.01 (t, J = 8.0 Hz, 2H), 6.93 (d, J = 7.2 Hz, 1H), 6.87 (td, J = 7.6, 0.8 Hz, 1H), 6.76

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(d, J = 8.0 Hz, 2H), 6.59 (t, J = 7.2 Hz, 1H), 6.00 (s, 1H), 5.76 (s, 1H), 4.91 (dd, J = 8.4, 6.0 Hz, 1H), 3.58 (s, 3H), 2.92−2.97 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 169.9, 167.3, 145.7, 145.4, 136.8, 133.3, 130.5, 129.7, 129.4, 129.0, 127.3, 126.0, 122.6, 121.3, 118.9, 118.7, 116.3, 63.3, 60.0, 58.5, 53.1, 41.3; HRMS (TOF-ES+) m/z: [M + Na]$^+$ calcd for $C_{25}H_{21}ClN_2O_3Na$ 455.1138, found 455.1149.

Tricycle ***3n***. White solid (61 mg, 0.13 mmol, 64% yield): mp 265−265 °C; IR (KBr) ν 3418, 2074, 1752, 1639, 1491, 1190, 756 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.69 (s, 1H), 7.32−7.37 (m, 3H), 7.17−7.23 (m, 3H), 7.01 (t, J = 8.0 Hz, 2H), 6.93 (d, J = 8.0 Hz, 1H), 6.87 (t, J = 7.6 Hz, 1H), 6.76 (d, J = 8.0 Hz, 2H), 6.59 (t, J = 7.2 Hz, 1H), 6.00 (s, 1H), 4.90 (dd, J = 8.4, 6.0 Hz, 1H), 3.58 (s, 3H), 2.94 (dd, J = 12.4, 8.8 Hz, 1H), 2.52−2.54 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 169.9, 167.3, 145.9, 145.4, 136.8, 130.8, 130.2, 129.9, 129.7, 129.4, 129.0, 126.4, 122.6, 122.0, 121.3, 119.0, 118.7, 116.3, 63.4, 60.0, 58.5, 53.1, 41.3; HRMS (TOF-ES+) m/z: [M + Na]$^+$ calcd for $C_{25}H_{21}BrN_2O_3Na$ 499.0633, found 499.0649.

Tricycle ***3o***. White solid (73 mg, 0.18 mmol, 88% yield): mp 253−254 °C; IR (KBr) ν 3419, 2074, 1638, 1489, 1388, 1352, 1187 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.67 (s, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.19 (td, J = 7.6, 1.2 Hz, 1H), 7.10 (t, J = 7.2 Hz, 1H), 6.92−7.00 (m, 6H), 6.87 (td, J = 7.6, 1.2 Hz, 1H), 6.74 (d, J = 8.0 Hz, 2H), 6.54 (t, J = 7.6 Hz, 1H), 5.94 (s, 1H), 5.76 (s, 1H), 4.82 (dd, J = 7.6, 6.4 Hz, 1H), 3.56 (s, 3H), 2.94 (dd, J = 12.4, 8.4 Hz, 1H), 2.22 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.0, 167.5, 145.6, 143.0, 137.6, 136.9, 130.1, 129.4, 128.7, 128.5, 128.0, 127.8, 124.3, 122.5, 121.2, 118.8, 118.6, 116.3, 63.6, 60.9, 58.5, 56.5, 53.1, 41.7, 19.0; HRMS (TOF-ES+) m/z: [M + Na]$^+$ calcd for $C_{26}H_{24}N_2O_3Na$ 435.1685, found 435.1697.

Tricycle ***3p***. White solid (37 mg, 0.086 mmol, 43% yield): mp 166−167 °C; IR (KBr) ν 3448, 2070, 1703, 1640, 1493, 1229, 1059, 754 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.72 (s, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.16−7.28 (m, 5H), 6.94−7.06 (m, 3H), 6.87 (t, J = 7.6 Hz, 1H), 6.64−6.69 (m, 3H), 6.09 (s, 1H), 5.76 (s, 1H), 5.09 (dd, J = 8.8, 5.6 Hz, 1H), 3.54 (s, 3H), 2.91−2.97 (m, 1H), 2.54−2.57 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 169.8, 167.2, 145.3, 139.1, 136.6, 132.2, 130.0, 129.5, 129.2, 129.0, 127.4, 122.8, 121.4, 118.9, 118.0, 116.5, 63.1, 58.6, 57.3, 55.4, 53.2, 40.6; HRMS (TOF-ES+) m/z: [M + Na]$^+$ calcd for $C_{25}H_{21}ClN_2O_3Na$ 455.1138, found 455.1153.

Tricycle ***3q***. White solid (42 mg, 0.10 mmol, 52% yield): mp 196−197 °C; IR (KBr) ν 3418, 2071, 1640, 1493, 1380, 1229, 1059, 753 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.67 (s, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 4.4 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 6.96−7.00 (m, 3H), 6.82−6.92 (m, 5H), 6.60 (t, J = 7.2 Hz, 1H), 5.69 (s, 1H), 5.22 (t, J = 7.2 Hz, 1H), 3.60 (s, 3H), 3.10 (dd, J = 12.8, 8.0 Hz, 1H), 2.65 (dd, J = 12.8, 6.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 169.7, 167.2, 147.0, 145.2, 137.1, 130.7, 129.5, 128.6, 126.7, 126.5, 125.5, 122.4, 120.5, 120.2, 119.8, 116.2, 63.4, 58.4, 57.4, 53.3, 42.1 ; HRMS (TOF-ES+) m/z: [M + Na]$^+$ calcd for $C_{23}H_{20}SN_2O_3Na$ 427.1092, found 427.1074.

Tricycle ***3r***. White solid (65 mg, 0.15 mmol, 73% yield): mp 229−230 °C; IR (KBr) ν 3421, 2077, 1731, 1672, 1494, 1237, 1065, 753 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.71 (s, 1H), 7.74−7.83 (m, 4H), 7.42−7.50 (m, 4H), 7.32 (d, J = 8.8 Hz, 1H), 7.21 (t, J = 7.2 Hz, 1H), 6.88−6.96 (m, 4H), 6.77−6.82 (m, 2H), 6.50 (t, J = 7.2 Hz, 1H), 6.02 (s, 1H), 5.06 (t, J = 7.6 Hz, 1H), 3.57 (s, 3H), 3.02−3.09 (m, 1H), 2.62 (dd, J = 12.8, 6.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.0, 167.4, 145.5, 140.7, 137.0, 133.2, 132.6, 130.3, 129.5, 128.7, 128.4, 128.0, 126.6, 126.2, 125.2, 122.5, 121.1, 116.3, 63.7, 61.2, 58.6, 53.2, 41.6; HRMS (TOF-ES+) m/z: [M + Na]$^+$ calcd for $C_{29}H_{24}N_2O_3Na$ 471.1685, found 471.1693.

Tricycle ***3s***. White solid (44 mg, 0.10 mmol, 52% yield): mp 200−201 °C; IR (KBr) ν 3455, 2074, 1752, 1639, 1429, 1388, 1232, 753 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz, two diastereomers, dr = 3:1) δ 10.74 (s, 0.26H), 10.65 (s, 0.78H), 7.25−7.30 (m, 5.8H), 7.16−7.22 (m, 3.3H), 7.00−7.10 (m, 2.0H), 6.92−6.98 (m, 3.1H), 6.86 (t, J = 7.6 Hz, 1.5H), 6.58−6.66 (m, 2.1H), 5.95−6.04 (m, 1.2H), 5.65−5.76 (m, 1.1H), 4.43−4.49 (m, 1.0H), 3.67 (s, 2.2H), 3.57−3.61 (m, 1.4H), 2.76−2.81 (m, 0.74H), 2.54−2.58 (m, 0.92H); ^{13}C NMR (DMSO-d_6, 100 MHz, two diastereomers, dr = 3:1) δ 170.8, 170.3, 167.4, 167.2, 147.6, 146.0, 136.8, 136.5, 132.4, 131.9, 131.1, 129.7, 129.3, 129.1, 128.9, 128.0, 127.2, 126.6, 123.8, 122.5, 121.4, 121.2, 119.0, 118.9, 116.3, 116.1, 112.9, 63.6, 62.6, 60.9, 60.0, 59.7, 59.0, 58.5, 53.4, 53.3, 39.4, 38.8 ; HRMS (TOF-ES+) m/z: [M + Na]$^+$ calcd for $C_{27}H_{24}N_2O_3Na$ 447.1685, found 447.1664.

Tricycle ***3t***. White solid (54 mg, 0.16 mmol, 78% yield): mp 123−124 °C; IR (KBr) ν 3418, 3066, 1750, 1673, 1496, 1355, 1237, 755 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz, two diastereoisomers, dr =1:1) δ 10.72 (s, 1.0H), 10.62 (s, 1.0H), 7.08−7.21 (m, 8.2H), 6.77−7.02 (m, 8.0H), 6.67−6.72 (m, 2.0H), 5.67 (s, 1.0H), 5.61 (s, 1.0H), 5.50−5.55 (m, 2.0H), 5.24 (t, J = 15.6 Hz, 2.0H), 5.06 (t, J = 9.6 Hz, 2.0H), 4.25−4.29 (m, 2.0H), 3.64 (s, 3.0H), 3.59 (s, 3.0H), 2.97−3.02 (m, 1.0H), 2.69−2.74 (m, 1.0H), 2.44−2.49 (m, 1.0H), 1.84−1.90 (m, 1.0H); ^{13}C NMR (DMSO-d_6, 100 MHz, two diastereoisomers, dr = 1:1) δ 170.7, 170.2, 167.4, 167.2, 147.5, 145.9, 140.6, 139.6, 136.8, 135.4, 129.6, 129.3, 129.2, 128.9, 128.0, 123.9, 122.5, 121.4, 119.0, 118.9, 117.7, 117.4, 116.8, 116.2, 116.0, 112.8, 63.5, 62.58, 62.55, 60.3, 60.1, 59.0, 58.4, 53.3, 53.2, 38.5, 38.1; HRMS (TOF-ES+) m/z: [M + Na]$^+$ calcd for $C_{21}H_{20}N_2O_3Na$ 371.1372, found 371.1366.

Tricycle ***3u***. White solid (63 mg, 0.15 mmol, 76% yield): mp 209−210 °C; IR (KBr) ν 3418, 2084, 1728, 1640, 1388, 1353, 1184, 757 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.65 (s, 1H), 7.35 (d, J = 7.2 Hz, 1H), 7.12−7.24 (m, 6H), 6.92−6.99 (m, 3H), 6.87 (t, J = 7.6 Hz, 1H), 6.74 (d, J = 8.0 Hz, 2H), 6.55 (t, J = 7.6 Hz, 1H), 5.94 (s, 1H), 5.76 (s, 1H), 4.86 (dd, J = 8.0, 6.4 Hz, 1H), 4.07−4.15 (m, 1H), 3.91−3.99 (m, 1H), 3.34 (s, 3H), 2.93 (dd, J = 13.2, 8.4 Hz, 1H), 2.53−2.56 (m, 1H), 0.98 (t, J = 7.0 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 169.3, 167.6, 145.7, 143.0, 137.0, 129.9, 129.4, 128.8, 127.2, 122.5, 121.3, 118.7, 118.6, 116.3, 63.7, 61.8, 60.7, 58.5, 14.1; HRMS (TOF-ES+) m/z: [M + Na]$^+$ calcd for $C_{26}H_{24}N_2O_3Na$ 435.1685, found 435.1706.

Tricycle ***3v***. White solid (37 mg, 0.094 mmol, 47% yield): mp 153−154 °C; IR (KBr) ν 3419, 3213, 1748, 1674, 1498, 1436, 1250, 1172, 897, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.63 (s, 1H), 7.34−7.40 (m, 4H), 7.27−7.31 (m, 2H), 7.21 (d, J = 7.2 Hz, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.79 (d, J = 7.6 Hz, 1H), 4.88 (s, 1 H), 4.52 (t, J = 7.6 Hz, 1H), 3.65 (s, 3H), 3.46−3.55 (m, 2H), 3.34 (s, 3H), 3.14 (d, J = 17.6 Hz, 1H), 2.95 (d, J = 17.6 Hz, 1H), 2.73 (dd, J = 13.2, 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8, 170.0, 168.5, 141.6, 137.0, 130.8, 129.8, 128.6, 128.4, 127.8, 123.0, 119.4, 115.7, 66.1, 64.1, 58.5, 53.1, 51.2, 48.3, 41.4; HRMS (TOF-ES+) m/z: [M + Na]$^+$ calcd for $C_{22}H_{22}N_2O_5Na$ 417.1426, found 417.1407.

Experimental Procedure for the Synthesis of Tricyclic Product ***4a***. To a solution of aldehyde **1a** (65 mg, 0.2 mmol) in dry 1,2-dichloroethane (0.2 mL) were added methanesulfonic acid (1.9 mg, 0.02 mmol, 0.1 equiv) and titanium tetrachloride (46 mg, 0.24 mmol, 1.2 equiv), respectively. The mixture was stirred at room temperature for 12 h. Then water (5 mL) was added to it. The resulting mixture was stirred for 10 min and extracted with ethyl acetate twice (3 mL × 2). The combined organic layer was dried, concentrated, and purified via silica gel column chromatography, eluting with ethyl acetate:petroleum ether = 1:3 to yield tricyclic product **4a** as a white solid (48 mg, 0.15 mmol, 74% yield): mp 161−162 °C; IR (KBr) ν 3453, 3063, 2930, 1736, 1679, 1498, 1251, 1021, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.49 (s, 1H), 7.27−7.49 (m, 8H), 7.20−7.25 (m, 1H), 7.08−7.12 (m, 1H), 6.95 (d, J = 8.0 Hz, 1H), 5.40 (s, 1H), 5.09−5.13 (m, 1H), 3.67 (s, 3H), 3.44 (dd, J = 12.8, 6.8 Hz, 1H), 2.90−2.96 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.0, 167.9, 141.6, 136.2, 130.4, 130.2, 128.6, 127.9, 125.9, 123.8, 119.6, 116.0, 81.0, 80.3, 60.5, 53.3, 43.0; HRMS (TOF-ES+) m/z: [M + Na]$^+$ calcd for $C_{19}H_{17}NO_4Na$ 346.1055, found 346.1069.

Experimental Procedure for the Synthesis of Tricyclic Product ***4b***. To a solution of aldehyde **1p** (55 mg, 0.2 mmol) in dry 1,2-dichloroethane (0.2 mL) was added $Pd(PPh_3)_4$ (23 mg, 0.02 mmol, 0.1 equiv). The resulting mixture was stirred at room temperature for 12 h before it was concentrated and purified via silica gel column chromatography, eluting with ethyl acetate:petroleum ether = 1:3 to yield tricycle **4b** as a white solid (17 mg, 0.062 mmol, 31% yield): mp 179−180 °C; IR (KBr) ν 3426, 1732, 1690, 1242, 1126, 930, 763 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.75 (s, 1H), 7.38 (d, J = 7.2 Hz,

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1H), 7.24 (t, J = 8.0 Hz, 1H), 7.09 (t, J = 7.2 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.00−6.08 (m, 1H), 5.36−5.41 (m, 1H), 5.16−5.30 (m, 2H), 5.05 (s, 1H), 3.48 (s, 3H), 2.72−2.78 (m, 1H), 2.23 (dd, J = 12.8, 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3, 168.6, 137.9, 136.0, 128.3, 124.8, 123.7, 122.9, 116.0, 115.5, 82.5, 80.0, 59.9, 52.7, 36.3; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{15}H_{15}NO_4Na$ 296.0899, found 296.0899.

Experimental Procedure for the Synthesis of Imine ***5***. To a solution of aldehyde **1a** (162 mg, 0.50 mmol) in ethanol (5.0 mL) were added **2a** (94 mg, 0.55 mmol, 1.1 equiv) and sodium acetate trihydrate (62 mg, 0.75 mmol, 1.5 equiv), respectively. The mixture was refluxed for 24 h. Then the solvent was removed, and water (10 mL) was added. The mixture was extracted with ethyl acetate twice (3 mL × 2), and the combined organic layer was dried, concentrated, and purified via silica gel column chromatography, eluting with ethyl acetate:petroleum ether = 1:5 to give imine **6** as a white solid (205 mg, 0.43 mmol, 86% yield): mp 113−114 °C; IR (KBr) ν 3034, 1670, 1616, 1525, 1303, 1182, 832, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.90 (s, 1H), 8.76 (d, J = 8.0 Hz, 1H), 8.51 (s, 1H), 7.47−7.51 (m, 4H), 7.20−7.25 (m, 5H), 7.16 (t, J = 7.6 Hz, 1H), 7.11−7.13 (m, 2H), 3.37 (t, J = 8.4 Hz, 1H), 3.15 (s, 1H), 2.30 (dd, J = 8.0, 4.8 Hz, 1H), 1.98 (dd, J = 9.2, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.4, 167.4, 162.8, 149.4, 139.8, 135.1, 134.3, 132.6, 132.3, 129.0, 128.1, 127.3, 123.2, 122.8, 121.7, 120.9, 120.0, 52.0, 39.2, 34.4, 19. 0; HRMS (TOF-ES+) m/z: $[M + Na]^+$ calcd for $C_{25}H_{21}BrN_2O_3Na$ 499.0633, found 499.0641.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02172.

^{1}H NMR and ^{13}C NMR spectra of all the products (PDF)

X-ray data for **3a**, **4a**, and **4b** (ZIP)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem., Int. Ed.* **2014**, *53*, 5504−5523. (b) Cavitt, M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804−818. (c) Reissig, H.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151−1196. (d) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765−2810. (e) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104−6155. (f) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2015**, *115*, 5366−5412. (g) Masson, G.; Lalli, C.; Benohoud, M.; Dagousset, G. *Chem. Soc. Rev.* **2013**, *42*, 902−23. (h) Properzi, R.; Marcantoni, E. *Chem. Soc. Rev.* **2014**, *43*, 779−91. (i) Guo, X.-X.; Gu, D.-W.; Wu, Z.-X.; Zhang, W.-B. *Chem. Rev.* **2015**, *115*, 1622−1651. (j) Karmakar, R.; Pahari, P.; Mal, D. *Chem. Rev.* **2014**, *114*, 6213−6284. (k) Estevez, V.; Villacampa, M.; Menendez, J. C. *Chem. Soc. Rev.* **2014**, *43*, 4633−57. (l) Rotstein, B. H.; Zaretsky, S.; Rai, V.; Yudin, A. K. *Chem. Rev.* **2014**, *114*, 8323−8359. (m) Yamamoto, Y. *Chem. Soc. Rev.* **2014**, *43*, 1575−600.

(2) Witherup, K. M.; Ransom, R. W.; Graham, A. C.; Bernard, A. M.; Salvatore, M. J.; Lumma, W. C.; Anderson, P. S.; Pitzenberger, S. M.; Varga, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6682−6685.

(3) (a) Ma, D.-W.; Xia, C.-F.; Jiang, J. Q.; Zhang, J.-H. *Org. Lett.* **2001**, *3*, 2189−2191. (b) Davies, S. G.; Fletcher, A. M.; Lee, J. A.; Lorkin, T. J. A.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2013**, *69*, 9779−9803. (c) Davies, S. G.; Fletcher, A. M.; Lee, J. A.; Lorkin, T. J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2013**, *15*, 2050−2053. (d) Snider, B. B.; Ahn, Y.; O'Hare, S. M. *Org. Lett.* **2001**, *3*, 4217−4220. (e) Shirai, A.; Miyata, O.; Tohnai, N.; Miyata, M.; Procter, D. J.; Sucunza, D.; Naito, T. *J. Org. Chem.* **2008**, *73*, 4464−4475. (f) Badarinarayana, V.; Lovely, C. J. *Tetrahedron Lett.* **2007**, *48*, 2607−2610. (g) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913−2916.

(4) (a) Jaroch, S.; Rehwinkel, H.; Hölscher, P.; Sülzle, D.; Burton, G.; Hillmann, M.; McDonald, F. M.; Miklautz, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 743−746. (b) Wang, H.-K.; Wang, C.; Huang, K.-M.; Liu, L.-Y.; Chang, W.-X.; Li, J. *Org. Lett.* **2016**, *18*, 2367−2370. (c) Sun, M.-M.; Zhang, T.-S.; Bao, W.-L. *J. Org. Chem.* **2013**, *78*, 8155−8160. (d) Hu, J.; Hirao, H.; Li, Y.-X.; Zhou, S.J.-R. *Angew. Chem., Int. Ed.* **2013**, *52*, 8676−8680. (e) Palaniappan, S.; Rajender, B.; Umashankar, M. *J. Mol. Catal. A: Chem.* **2012**, *352*, 70−74. (f) Kumar, A.; Srivastava, S.; Gupta, G.; Chaturvedi, V.; Sinha, S.; Srivastava, R. *ACS Comb. Sci.* **2011**, *13*, 65−71. (g) Huang, Y.; Qiu, C.-H.; Li, Z.-J.; Feng, W.-Y.; Gan, H.-F.; Liu, J.-J.; Guo, K. *ACS Sustainable Chem. Eng.* **2016**, *4*, 47−52. (h) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986−90.

(5) (a) Comesse, S.; Sanselme, M.; Daïch, A. *J. Org. Chem.* **2008**, *73*, 5566−5569. (b) Guan, M.-Y.; Pang, Y.-B.; Zhang, J.-Y.; Zhao, Y.-S. *Chem. Commun.* **2016**, *52*, 7043−7046. (c) Lovely, C. J.; Mahmud, H. *Tetrahedron Lett.* **1999**, *40*, 2079−2082. (d) Nyerges, M.; Fejes, I.; Toke, L. *Tetrahedron Lett.* **2000**, *41*, 7951−7954. (e) Ng, P. Y.; Masse, C. E.; Shaw, J. T. *Org. Lett.* **2006**, *8*, 3999−4002. (f) Ueda, M.; Kawai, S.; Hayashi, M.; Naito, T.; Miyata, O. *J. Org. Chem.* **2010**, *75*, 914−921. (g) Zhang, Z.-G.; Zhang, Q.; Yan, Z.-G.; Liu, Q. *J. Org. Chem.* **2007**, *72*, 9808−9810. (h) Ikeda, S.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *Chem. Lett.* **2008**, *37*, 962−963. (i) Batey, R. A.; Powell, D. A. *Chem. Commun.* **2001**, 2362−2363. (j) Chung, P.-Y.; Tang, J.C.-O.; Cheng, C.-H.; Bian, Z.-X.; Wong, W.-Y.; Lam, K.-H.; Chui, C.-H. *SpringerPlus* **2016**, *5*, 271−277. (k) Yang, Y.-J.; Zhang, H.-R.; Zhu, S.-Y.; Zhu, P.; Hui, X.-P. *Org. Lett.* **2014**, *16*, 5048−5051.

(6) Ikeda, S.; Shibuya, M.; Iwabuchi, Y. *Chem. Commun.* **2007**, *5*, 504−506.

(7) (a) Bakthadoss, M.; Kannan, D.; Srinivasan, J.; Vinayagam, V. *Org. Biomol. Chem.* **2015**, *13*, 2870−2874. (b) He, Y.; Mahmud, H.; Moningka, R.; Lovely, C. J.; Dias, H. V. R. *Tetrahedron* **2006**, *62*, 8755−8769.

(8) Takeda, Y.; Nakabayashi, T.; Shirai, A.; Fukumoto, D.; Kiguchi, T.; Naito, T. *Tetrahedron Lett.* **2004**, *45*, 3481−3484.

(9) (a) Fang, J.; Ren, J.; Wang, Z.-W. *Tetrahedron Lett.* **2008**, *49*, 6659−6662. (b) Kitagawa, O.; Fujiwara, H.; Taguchi, T. *Tetrahedron Lett.* **2001**, *42*, 2165−2167. (c) Hu, B.; Xing, S.-Y.; Ren, J.; Wang, Z.-W. *Tetrahedron* **2010**, *66*, 5671−5674. (d) Chagarovskiy, A. O.; Budynina, E. M.; Ivanova, O. A.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Tetrahedron* **2009**, *65*, 5385−5392. (e) Ma, X.-F.; Zhang, J.-C.; Tang, Q.; Ke, J.; Zou, W.; Shao, H.-W. *Chem. Commun.* **2014**, *50*, 3505−3508. (f) Ghorai, M. K.; Talukdar, R.; Tiwari, D. P. *Org. Lett.* **2014**, *16*, 2204−2207. (g) Ghorai, M. K.; Talukdar, R.; Tiwari, D. P. *Chem. Commun.* **2013**, *49*, 8205−8207. (h) Zhu, J.; Liang, Y.; Wang, L.-J.; Zheng, Z.-B.; Houk, K. N.; Tang, Y. *J. Am. Chem. Soc.* **2014**, *136*, 6900−6903. (i) Chagarovskiy, A. O.; Ivanova, O. A.; Rakhmankulov, E. R.; Budynina, E. M.; Trushkov, I. V.; Melnikov, M. Y. *Adv. Synth. Catal.* **2010**, *352*, 3179−3184.

(10) (a) Ivanova, O. A.; Budynina, E. M.; Chagarovskiy, A. O.; Rakhmankulov, E. R.; Trushkov, I. V.; Semeykin, A. V.; Shimanovskii, N. L.; Melnikov, M. Y. *Chem. - Eur. J.* **2011**, *17*, 11738−11742. (b) Chen, H.-Y.; Zhang, J.; Wang, D. Z.-G. *Org. Lett.* **2015**, *17*, 2098−

2101. (c) Rakhmankulov, E. R.; Ivanov, K. L.; Budynina, E. M.; Ivanova, O. A.; Chagarovskiy, A. O.; Skvortsov, D. A.; Latyshev, G. V.; Trushkov, I. V.; Melnikov, M. Y. *Org. Lett.* **2015**, *17*, 770−773. (d) Karadeolian, A.; Kerr, M. A. *J. Org. Chem.* **2010**, *75*, 6830−6841. (e) Wang, Z.-J.; Ren, J.; Wang, Z.-W. *Org. Lett.* **2013**, *15*, 5682−5685. (f) Ivanova, O. A.; Budynina, E. M.; Skvortsov, D. A.; Limoge, M.; Bakin, A. V.; Chagarovskiy, A. O.; Trushkov, I. V.; Melnikov, M. Y. *Chem. Commun.* **2013**, *49*, 11482−11484. (g) Zhu, W.-J.; Fang, J.; Liu, Y.; Ren, J.; Wang, Z.-W. *Angew. Chem., Int. Ed.* **2013**, *52*, 2032−2037. (h) Chakrabarty, S.; Chatterjee, I.; Wibbeling, B.; Daniliuc, C. G.; Studer, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 5964−5968.

(11) (a) Young, I. S.; Williams, J. L.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 953−955. (b) Cheng, Q.-Q.; Qian, Y.; Zavalij, P. Y.; Doyle, M. P. *Org. Lett.* **2015**, *17*, 3568−3571. (c) Ghosh, A.; Pandey, A. K.; Banerjee, P. *J. Org. Chem.* **2015**, *80*, 7235−7242. (d) Liu, Q.-J.; Yan, W.-G.; Wang, L.-J.; Zhang, X. P.; Tang, Y. *Org. Lett.* **2015**, *17*, 4014−4017. (e) Liu, H.-L.; Yuan, C.-H.; Wu, Y.; Xiao, Y.-M.; Guo, H.-C. *Org. Lett.* **2015**, *17*, 4220−4223. (f) Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 1107−1110. (g) Wang, H.-P.; Zhang, H.-H.; Hu, X.-Q.; Xu, P.-F.; Luo, Y.-C. *Eur. J. Org. Chem.* **2015**, *2015*, 3486−3494. (h) Zhu, W.-J.; Ren, J.; Wang, Z.-W. *Eur. J. Org. Chem.* **2014**, *2014*, 3561−3564. (i) Tejero, R.; Ponce, A.; Adrio, J.; Carretero, J. C. *Chem. Commun.* **2013**, *49*, 10406−10408.

(12) Hu, J.-L.; Wang, L.-J.; Xu, H.; Xie, Z.-W.; Tang, Y. *Org. Lett.* **2015**, *17*, 2680−2683.

(13) (a) Cui, B.; Ren, J.; Wang, Z.-W. *J. Org. Chem.* **2014**, *79*, 790−796. (b) Tsunoi, S.; Maruoka, Y.; Suzuki, I.; Shibata, I. *Org. Lett.* **2015**, *17*, 4010−4013. (c) Xing, S.-Y.; Pan, W.-Y.; Liu, C.; Ren, J.; Wang, Z.-W. *Angew. Chem., Int. Ed.* **2010**, *49*, 3215−3218. (d) Wang, H.-N.; Yang, W.; Liu, H.; Wang, W.; Li, H. *Org. Biomol. Chem.* **2012**, *10*, 5032−5035.

(14) (a) Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 4196−4201. (b) Parsons, A. T.; Smith, A. G.; Neel, A. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2010**, *132*, 9688−9692. (c) Carson, C. A.; Kerr, M. A. *J. Org. Chem.* **2005**, *70*, 8242−8244. (d) Lebold, T. P.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 4354−4357. (e) Kang, Y.-B.; Tang, Y.; Sun, X.-L. *Org. Biomol. Chem.* **2006**, *4*, 299−301.

(15) Xiao, J.-A.; Xia, P.-J.; Zhang, X.-Y.; Chen, X.-Q.; Ou, G.-C.; Yang, H. *Chem. Commun.* **2016**, *52*, 2177−2180.

(16) Crystallographic data for **3a**, **4a**, and **4b** have been deposited with the Cambridge Crystallographic Data Centre with deposition nos. CCDC 1497832, 1497833, and 1497834. These data can be obtained free of charge on application to CCDC.

(17) (a) Nishikata, T.; Noda, Y.; Fujimoto, R.; Ishikawa, S. *Chem. Commun.* **2015**, *51*, 12843−12846. (b) Emmett, M. R.; Kerr, M. A. *Org. Lett.* **2011**, *13*, 4180−4183. (c) Binda, C.; Valente, S.; Romanenghi, M.; Pilotto, S.; Cirilli, R.; Karytinos, A.; Ciossani, G.; Botrugno, O. A.; Forneris, F.; Tardugno, M.; Edmondson, D. E.; Minucci, S.; Mattevi, A.; Mai, A. *J. Am. Chem. Soc.* **2010**, *132*, 6827−6833.

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