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Organocatalytic conjugate addition of 1-bromonitroalkanes to α,β-unsaturated aldehydes: synthesis of nitrocyclopropanes

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ABSTRACT

A variety of secondary amines were studied as the catalyst in the conjugate addition of 1-bromonitromethane to α,β-unsaturated aldehydes. Proline was identified as the best catalyst for this reaction. MeOH/AcONa system was found to provide much better yields than $CHCl_3$/Et_3N system reported before. Good yields of nitrocyclopropane products were obtained with a variety of β-aryl acroleins. Several substituted 1-bromonitromethanes were also examined in the reaction. Both 1-bromonitroethane and 1-phenyl-1-bromonitromethane gave the corresponding nitrocyclopropanes in good yields. The diastereoselectivity of the reaction was strongly affected by the steric hindrance of 1-bromonitroalkanes.

1. Introduction

Cyclopropane structural units have been widely found in a great number of drugs and natural products.[1] These compounds exhibit various useful biological activities, such as enzyme inhibition, insecticidal, antifungal, herbicidal, antimicrobial, antitumor, and antiviral activities.[2] The small and rigid ring structure of cyclopropanes is also appealing for the preparation of complex molecules with a defined orientation of pendant functional groups.[3] In addition the strain associated with the three-membered ring allows cyclopropanes to undergo a variety of synthetically useful ring-opening reactions.[4,5] The synthetic methods of cyclopropanes have been extensively studied,[6,7] including the asymmetric synthetic versions.[8] Nitrocyclopropanes are a class of special cyclopropane compounds. They are presented in some natural products, such as the peptidolactone hormaomycin and the broad-spectrum antibiotic Trovafloxacin.[9,10] Furthermore nitrocyclopropanes can be converted into a wide range of useful compounds.[11] Several synthetic methods of nitrocyclopropanes have been developed, such as the reaction of nitroalkyl carbene with alkenes, conjugate addition of α-halogenated nucleophiles to nitroolefins.[12] In recent years secondary amines, for example, proline and its derivatives, imidazolidinones, are found to be extremely powerful catalysts for activation of α,β-unsaturated aldehydes and ketones via a LUMO lowing mechanism.[13] Ley and co-workers reported the first organocatalytic nitrocyclopropanation of cyclohexenone with bromonitromethane using proline tetrazole catalyst.[14] The corresponding nitrocyclopropanes were obtained in good yields and enantioselectivities, however, application of proline and several other secondary amines in this reaction only provided low yield of products. Encouraged by this work, we explored the conjugate addition of bromonitromethane to α,β-unsaturated aldehydes catalyzed by secondary amines. The expected nitrocyclopropanes were obtained in good yields and these results are reported in this paper. During our initial study, Córdova and coworkers reported the asymmetric nitrocyclopropanation of α,β-unsaturated aldehydes with bromonitromethane using chiral secondary amines as the catalyst.[15]

2. Results and discussion

Initially a number of secondary amines (**I**–**V**) were examined as the catalyst for the reaction of cinnamaldehyde (**1a**) and bromonitromethane (**2a**). The nitrocyclopropanes **3a** and **3a**′ were obtained in methanol with AcONa as the base additive. The experiment results of the catalyst screen are summarized in Table 1. The relative configurations of **3a** and **3a**′ were assigned via NOESY spectra and were consistent with the data reported by Córdova and co-workers.[15]

The reaction did not occur in the absence of secondary amine catalysts. Piperidine (**I**), morpholine (**II**), and pyrrolidine (**III**)

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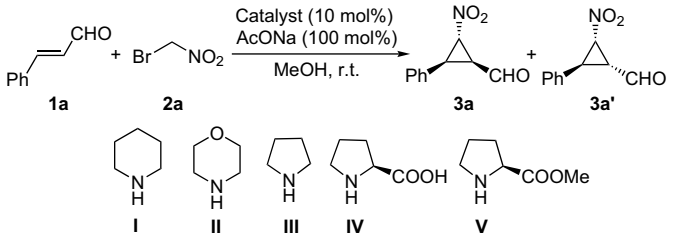
Table 1
The reaction of **1a** and **2a** catalyzed by secondary amines[a]

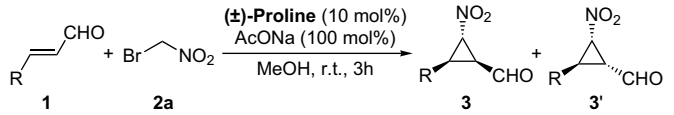


Entry	Catalyst	Time/h	Yield[b]/%	**3a**/**3a**′[c]
1	**I**	5	31	49/51
2	**II**	5	37	50/50
3	**III**	5	40	51/49
4	**IV**	1	64	45/55
5	**IV**	3	67	61/39[d]
6	**IV**	48	71	66/34
7	**IV**	8	39[e]	53/47
8	**V**	5	29	52/48[f]

[a] Cinnamaldehyde **1a** (0.25 mmol), bromonitromethane **2a** (0.26 mmol), catalyst (0.025 mmol), AcONa (0.26 mmol), and 1.0 mL methanol were used.
[b] GC yield of combined **3a** and **3a**′.
[c] The ratios of **3a**/**3a**′ were determined by GC analysis.
[d] The ee values of **3a** and **3a**′ were 5.2% and 10.5%, respectively, as determined by chiral GC.
[e] Cinnamaldehyde **1a** (0.25 mmol), bromonitromethane **2a** (0.26 mmol), proline (0.025 mmol), Et_3N (0.26 mmol), and 1.0 mL $CHCl_3$ were used in this case.
[f] The ee values of **3a** and **3a**′ were 5.6% and 7.5%, respectively.

provided a mixture of **3a** and **3a**′ in low yields. (*S*)-Proline (**IV**) was found to be better catalyst for the reaction. Compounds **3a** and **3a**′ were obtained in 64% yield after 1 h (Table 1, entry 4). The yield could be improved slightly with extension of reaction time (Table 1, entries 5 and 6). It is noted that the ratio of **3a**/**3a**′ increased with the reaction process (Table 1, entries 4–6). Compound **3a** seemed to be the thermodynamically favorable product and **3a**′ seemed to be the kinetically favorable product. The epimerization of **3a**′ to **3a** was supposed through the base-catalyzed enolization of aldehyde or proline-catalyzed formation of the enamine intermediate. The enantioselectivity of the reaction was very low (5.2% ee and 10.5% ee for **3a** and **3a**′, respectively) as determined by chiral GC analysis. In the study of Córdova and co-workers, the same reaction was carried out in $CHCl_3/Et_3N$ system with (*S*)-proline as the catalyst.[15]

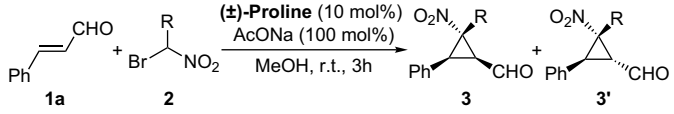
Table 2
Reaction of α,β-unsaturated aldehydes (**1**) with bromonitromethane (**2a**) catalyzed by proline[a]



Entry	Aldehyde (**1**)	Product (**3**/**3**′)[b]	Yield[c]/%
1	R=Ph (**1a**)	**3a**/**3a**′ (61/39)	62
2	R=4-$NO_2C_6H_4$ (**1b**)	**3b**/**3b**′ (62/38)	61
3	R=4-$CH_3C_6H_4$ (**1c**)	**3c**/**3c**′ (53/47)	65
4	R=4-$OMeC_6H_4$ (**1d**)	**3d**/**3d**′ (58/42)	58
5	R=2-$OMeC_6H_4$ (**1e**)	**3e**/**3e**′ (53/47)	60
6	R=4-ClC_6H_4 (**1f**)	**3f**/**3f**′ (58/42)	61
7	R=3-ClC_6H_4 (**1g**)	**3g**/**3g**′ (55/45)	68
8	R=2-ClC_6H_4 (**1h**)	**3h**/**3h**′ (60/40)	67

[a] α,β-Unsaturated aldehyde **1** (1 mmol), bromonitromethane **2a** (1.1 mmol), AcONa (1.1 mmol), (±)-proline (0.1 mmol), and 4.0 mL methanol were used in the reaction.
[b] The ratios of **3**/**3**′ were determined by GC analysis.
[c] Isolated yield of combined **3** and **3**′.

Table 3
Reaction of 1-bromonitroalkanes (**2**) with cinnamaldehyde (**1a**) catalyzed by proline[a]



Entry	1-Bromonitroalkane (**2**)	Product (**3**/**3**′)[b]	Yield[c]/%
1	R=H (**2a**)	**3a**/**3a**′ (61/39)	62
2	R=CH_3 (**2b**)	**3i**/**3i**′ (16/84)	63
3	R=Ph (**2c**)	**3j**/**3j**′ (<1/99)	60
4	R=Et (**2d**)	**3k**/**3k**′ (6/94)	29[d]
5	R=COOEt (**2e**)	—	—[e]

[a] Cinnamaldehyde **1a** (1 mmol), 1-bromonitroalkane **2** (1.1 mmol), AcONa (1.1 mmol), (±)-proline (0.1 mmol), and 4.0 mL methanol were used in the reaction.
[b] The ratios of **3**/**3**′ were determined by GC analysis.
[c] Isolated yield of combined **3** and **3**′.
[d] The yield was determined by ^1H NMR.
[e] No nitrocyclopropane product could be isolated.

For a comparison, we carried out the reaction under this condition. The reaction was found to be rather slow and only low yield of **3a** and **3a**′ was obtained after 8 h (Table 1, entry 7). The result suggests that MeOH/AcONa is the better reaction system than $CHCl_3/Et_3N$. The carboxylic acid group of proline seemed having important effect on its catalytic activity, since proline methyl ester (**V**) showed significantly lower catalytic activity (Table 1, entry 8).

A variety of α,β-unsaturated aldehydes were investigated in the reaction with bromonitromethane and the results are listed in Table 2. Cinnamaldehyde and other β-aryl acroleins are suitable substrates for the reaction and good yields of nitrocyclopropanes (**3** and **3**′) were obtained. The electron-withdrawing and electron-donating substituents on phenyl ring were tolerated very well (Table 2, entries 2–8). Diastereoselectivities of the reaction were low and generally **3** were obtained in excess. Acrolein and crotonaldehyde were also examined in the reaction, however, no nitrocyclopropane products could be isolated.

A couple of substituted bromonitromethanes were explored in the reaction and the results are summarized in Table 3. 1-Bromonitroethane (**2b**) and 1-bromo-1-phenylnitromethane (**2c**) also provided good yield of nitrocyclopropanes.

Interestingly, diastereoselectivities of the reaction were inversed with the introduction of substituents and **3**′ was obtained as the major isomer. In the case of 1-bromo-1-phenylnitromethane (**2c**), **3j**′ was afforded as the only isomer. The relative configurations of these compounds were assigned by NOSEY spectra (Fig. 1) and H–H coupling constants.

While 1-bromonitropropane (**2d**) was used, the corresponding nitrocyclopropanes **3k**/**3k**′ were obtained in low yield. An inseparable by-product **4** was observed by ^1H NMR and GC–MS analyses (34% yield as estimated by ^1H NMR), which was proposed to be the original addition product without elimination of the

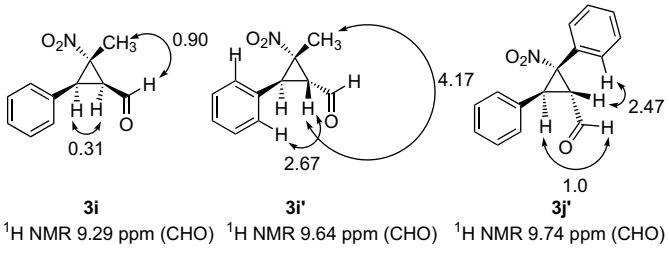
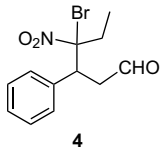


Figure 1. The NOESY spectral analysis of compounds **3i**, **3i**′, and **3j**′ (the value beside the bended arrow indicates the intensity of NOE signal).

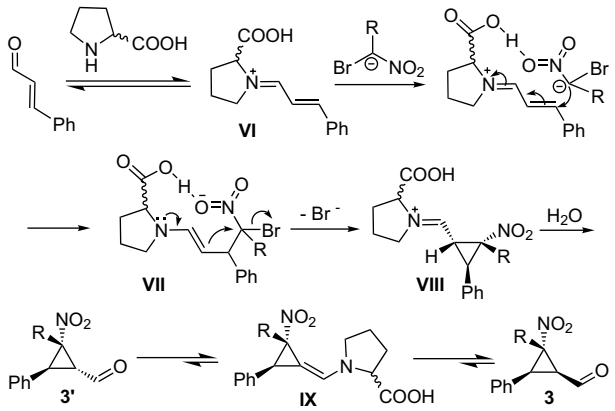


4

Figure 2.

bromide (Fig. 2).[16] The big steric hindrance of **4** hampered the consequent intramolecular cyclopropanation reaction. The similar compound was also reported in the reaction of bromonitromethane with enones.[14a] The reaction with ethyl 2-bromo-nitroacetate (**2e**) was unsuccessful and very complicated products were formed, which did not allow for further separation and qualitative determination.

Base on the present experimental results and the comparison with the results of Córdova and co-workers,[15] a reaction mechanism of proline-catalyzed nitrocyclopropanation is proposed (Scheme 1). Cinnamaldehyde is activated via formation of iminium cation (**VI**) with proline, which is attacked by 1-bromonitroalkane anion. Hydrogen bonding between the carboxyl group of proline with the nitro group is suggested to provide a pre-organized



Scheme 1. Proposed reaction mechanism of proline-catalyzed nitrocyclopropanation.

transition state and to accelerate the reaction. The resulted enamine intermediate (**VII**) undergoes the intramolecular nucleophilic attack to afford the intermediate (**VIII**). The consequent hydrolysis of **VIII** gives **3′** and regenerates the catalyst. Compound **3′** can be epimerized through the enamine intermediate (**IX**) to provide **3**. Due to the electrostatic repulsion between the nitro group and the carbonyl group, **3′** is less stable and the balance favors the formation of **3**. The experiment fact that the ratio of **3a**/**3a′** (R=H) increases with the extension of reaction time (Table 1), supports this hypothesis. However, the epimerization can be hampered by increasing the volume of R group. The ratio of **3**/**3′** changes from 61/39 to 16/84, to 4/96, and to 1/99, while the R group is H, Me, Et, and Ph, respectively. The steric repulsion of the R group with the pyrrolidine ring is probable to inhibit the formation of intermediate **IX**.

3. Conclusion

In conclusion, the conjugate addition of 1-bromonitroalkanes to α,β-unsaturated aldehydes was achieved with proline as the catalyst. MeOH/AcONa system was found to provide much better yields than $CHCl_3$/Et_3N system reported before. Good yields of nitrocyclopropanes were obtained with a number of β-aryl acroleins. Several substituted 1-bromonitromethanes, such as 1-bromonitroethane and 1-phenyl-1-bromonitromethane, are also suitable substrates for this transformation. The diastereoselectivity of the reaction is strongly affected by the steric hindrance of 1-bromonitroalkanes. Further studies are underway to develop efficient asymmetric catalytic nitrocyclopropanation reactions and to explore other catalytic reactions with 1-bromonitroalkanes.

4. Experimental section

4.1. General details

All solvents were used as commercial anhydrous grade without further purification. The flash column chromatography was carried out over silica gel (230–400 mesh), purchased from Qingdao Haiyang Chemical Co., Ltd. Melting points were recorded on an electrothermal digital melting point apparatus. ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer as solutions in $CDCl_3$. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm, δ) downfield from the internal standard Me_4Si (TMS, δ=0 ppm). Chemical shifts in ^{13}C NMR spectra are reported relative to the central line of the chloroform signal (δ=77.0 ppm). High-resolution mass spectra were obtained with the Thermo MAT 95XP mass spectrometer. The low resolution mass spectra were obtained at the Thermo Trace GC Ultra-DSQII and Agilent 6120 (Quadrupole LC-MS) mass spectrometer. Infrared (IR) spectra were recorded on a Bruker Tensor 37 spectrophotometer. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (vs=very strong, s=strong, m=medium, w=weak). GC yield of nitrocyclopropanes and enantiomeric excesses were determined by GC (Agilent 6890N) using a Varian capillary column CP-Chirasil-DexCB (25 m×0.25 mm, 0.25 μm, # CP7502).

4.2. Typical experimental procedure for proline-catalyzed addition of 1-bromonitroalkanes to α,β-unsaturated aldehydes

The mixture of (±)-proline (0.1 mmol) and cinnamaldehyde **1** (1 mmol) in 4.0 mL methanol was stirred for 5 min at room temperature. 1-Bromonitroalkane **2** (1.1 mmol) and AcONa (1.1 mmol) were added. The reaction mixture was stirred for 3 h at room temperature. The solvent was evaporated under vacuum and the residue was purified by flash column chromatography over silica gel (EtOAc/petroleum ether) to provide nitrocyclopropane **3**.

4.3. Spectral data of nitrocyclopropanes (3)[17]

*4.3.1. Compound **3a***

Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ=9.28 (d, J=3.2 Hz, 1H), 7.35–7.26 (m, 5H), 5.33 (dd, J=4.8, 3.6 Hz, 1H), 3.85 (dd, J=11.2, 4.8 Hz, 1H), 3.42 (dt, J=11.2, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=193.0, 130.2, 128.9, 128.7, 126.8, 62.4, 38.5, 36.1; IR (thin film) ν/cm^{-1}: 2855 (w), 1714 (s), 1634 (m), 1548 (s), 1499 (w), 1364 (s), 698 (m); HRMS (EI) calcd for $C_{10}H_9NO_3$ (M^+): 191.0582, found: 191.0585.

*4.3.2. Compound **3a′***

Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ=9.69 (d, J=4.8 Hz, 1H), 7.42–7.17 (m, 5H), 4.82 (dd, J=8.4, 4.8 Hz, 1H), 4.00 (dd, J=8.0, 4.8 Hz, 1H), 2.71 (ddd, J=8.0, 8.0, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=193.2, 133.2, 129.1, 128.53, 128.45, 66.5, 39.2, 32.5.

*4.3.3. Compound **3b***

Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.51 (d, J=2.0 Hz, 1H), 8.20 (d, J=8.8 Hz, 2H), 7.44 (d, J=8.4 Hz, 2H), 5.35 (dd, J=4.8, 4.0 Hz, 1H), 3.90 (dd, J=11.2, 4.8 Hz, 1H), 3.62 (ddd, J=11.2, 3.6, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=192.0, 147.8, 140.4, 127.9, 124.4, 62.4, 38.0, 35.7; IR (thin film) ν/cm^{-1}: 2855 (w), 1713 (s), 1604 (m), 1552 (s), 1519 (s), 1348 (s), 856 (m); HRMS (EI) calcd for $C_{10}H_8N_2O_5$ (M^+): 236.0433, found: 236.0435.

*4.3.4. Compound **3b′***

Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.70 (d, J=4.4 Hz, 1H), 8.24 (d, J=8.8 Hz, 2H), 7.37 (d, J=8.8 Hz, 2H), 4.88 (dd, J=8.4, 4.8 Hz, 1H), 4.08 (dd, J=7.8, 4.4 Hz, 1H), 2.79 (ddd, J=8.0, 8.0, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=192.2, 147.9, 137.4, 129.9, 124.0, 66.0, 38.9, 31.4.

*4.3.5. Compound **3c***

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.26 (d, J=2.8 Hz, 1H), 7.17–7.09 (m, 4H), 5.27 (dd, J=3.8, 3.2 Hz, 1H), 3.80 (dd, J=8.8, 4.0 Hz, 1H), 3.37 (dt, J=9.2, 2.8 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=193.1, 138.5, 129.6, 128.6, 126.7, 62.5, 38.6, 36.0, 21.1; IR (thin film) ν/cm^{-1}: 2925 (w), 1715 (s), 1549 (s), 1456 (w), 1363 (s), 1122 (m), 807 (w); HRMS (EI) calcd for $C_{11}H_{11}NO_3$ (M^+): 205.0739, found: 205.0737.

*4.3.6. Compound **3c′***

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.66 (d, J=4.0 Hz, 1H), 7.21–7.00 (m, 4H), 4.76 (dd, J=6.4, 3.6 Hz, 1H), 3.95 (dd, J=6.2, 3.6 Hz, 1H), 2.66 (ddd, J=6.4, 6.4, 4.0 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=193.3, 138.6, 129.8, 128.5, 127.2, 62.7, 39.3, 32.4, 29.7.

*4.3.7. Compound **3d***

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.27 (d, J=3.2 Hz, 1H), 7.16 (d, J=8.4 Hz, 2H), 6.85 (d, J=8.8 Hz, 2H), 5.25 (dd, J=4.8, 3.6 Hz, 1H), 3.78 (dd, J=11.2, 4.8 Hz, 1H), 3.78 (s, 3H), 3.36 (dt, J=11.2, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=193.1, 159.6, 129.9, 122.1, 114.4, 62.7, 55.26, 38.7, 35.8; IR (thin film) ν/cm^{-1}: 2926 (m), 2852 (m), 1714 (s), 1613 (m), 1549 (s), 1517 (s), 1366 (m), 1251 (m), 1180 (m), 834 (m); HRMS (EI) calcd for $C_{11}H_{11}NO_4$ (M^+): 221.0688, found: 221.0685.

*4.3.8. Compound **3d′***

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.65 (d, J=4.8 Hz, 1H), 7.08 (d, J=8.4 Hz, 2H), 6.88 (d, J=8.8 Hz, 2H), 4.74 (dd, J=8.0, 4.8 Hz, 1H), 3.94 (dd, J=8.0, 4.8 Hz, 1H), 3.80 (s, 3H), 2.64 (ddd, J=8.0, 8.0, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=193.3, 159.8, 128.0, 125.1, 114.6, 66.6, 55.35, 39.3, 32.2.

*4.3.9. Compound **3e***

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.21 (d, J=3.2 Hz, 1H), 7.33–6.84 (m, 4H), 5.15 (dd, J=4.8, 3.6 Hz, 1H), 3.82 (s, 3H), 3.62 (dd, J=10.8, 4.8 Hz, 1H), 3.38 (dt, J=10.8, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=192.9, 157.5, 129.9, 129.7, 120.5, 118.7, 110.5, 62.6, 55.3, 37.8, 31.9; IR (thin film) ν/cm^{-1}: 2841 (w), 1714 (s), 1604 (m), 1547 (s), 1498 (m), 1364 (s), 1252 (s), 1025 (m), 755 (m); HRMS (EI) calcd for $C_{11}H_{11}NO_4$ (M^+): 221.0688, found: 221.0683.

*4.3.10. Compound **3e′***

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.67 (d, J=5.2 Hz, 1H), 7.33–6.84 (m, 4H), 4.86 (dd, J=8.0, 5.2 Hz, 1H), 4.02 (dd, J=8.0, 4.8 Hz, 1H), 3.84 (s, 3H), 2.73 (ddd, J=8.0, 8.0, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=194.3, 157.9, 129.9, 127.6, 121.3, 120.6, 110.7, 65.9, 55.4, 38.2, 29.5.

*4.3.11. Compound **3f***

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.34 (d, J=2.0 Hz, 1H), 7.30 (d, J=6.8 Hz, 2H), 7.18 (d, J=6.4 Hz, 2H), 5.26 (dd, J=3.8, 2.8 Hz, 1H), 3.78 (dd, J=8.8, 3.6 Hz, 1H), 3.44 (dt, J=8.8, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=192.7, 134.4, 130.1, 129.0, 128.7, 62.4, 38.3, 35.6; IR (thin film) ν/cm^{-1}: 2924 (m), 2854 (m), 1714 (s), 1551 (s), 1495 (m), 1364 (m), 1094 (m), 1015 (m), 827 (m); HRMS (EI) calcd for $C_{10}H_8ClNO_3$ (M^+): 225.0193, found: 225.0192.

*4.3.12. Compound **3f′***

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.64 (d, J=4.0 Hz, 1H), 7.34 (d, J=6.8 Hz, 2H), 7.12 (d, J=6.8 Hz, 2H), 4.77 (dd, J=6.6, 4.0 Hz, 1H), 3.95 (dd, J=6.0, 4.0 Hz, 1H), 2.66 (ddd, J=6.4, 6.4, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=192.8, 134.5, 131.8, 129.3, 128.2, 66.3, 38.9, 31.7.

*4.3.13. Compound **3g***

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.36 (d, J=2.8 Hz, 1H), 7.29–7.12 (m, 4H), 5.28 (dd, J=4.8, 3.6 Hz, 1H), 3.80 (dd, J=11.2, 4.8 Hz, 1H), 3.46 (dt, J=11.2, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=192.5, 135.18, 132.2, 130.2, 129.1, 128.85, 127.0, 62.2, 38.2, 35.6; IR (thin film) ν/cm^{-1}: 2925 (w), 2852 (w), 1714 (m), 1636 (s), 1549 (m), 1364 (m), 1082 (w), 784 (w); HRMS (EI) calcd for $C_{10}H_8ClNO_3$ (M^+): 225.0193, found: 225.0195.

*4.3.14. Compound **3g′***

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.67 (d, J=4.4 Hz, 1H), 7.33–7.06 (m, 4H), 4.79 (dd, J=8.4, 4.8 Hz, 1H), 3.96 (dd, J=7.8, 4.8 Hz, 1H), 2.69 (ddd, J=8.0, 8.0, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=192.6, 135.22, 134.9, 130.5, 128.89, 127.1, 125.1, 66.1, 38.8, 31.7.

*4.3.15. Compound **3h***

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.43 (d, J=2.0 Hz, 1H), 7.38–7.25 (m, 4H), 5.22 (dd, J=4.0, 3.2 Hz, 1H), 3.73 (dd, J=8.6, 3.6 Hz, 1H), 3.56 (ddd, J=8.8, 2.8, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=192.1, 134.7, 130.5, 129.9, 127.9, 127.3, 127.0, 62.8, 37.6, 34.7; IR (thin film) ν/cm^{-1}: 2925 (m), 2853 (m), 1715 (s), 1550 (s), 1479 (m), 1441 (m), 1364 (s), 1131 (w), 755 (m); HRMS (EI) calcd for $C_{10}H_8ClNO_3$ (M^+): 225.0193, found: 225.0190.

*4.3.16. Compound **3h′***

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.70 (d, J=3.6 Hz, 1H), 7.45–7.08 (m, 4H), 4.75 (dd, J=6.4, 4.0 Hz, 1H), 4.13 (dd, J=6.4, 4.0 Hz, 1H), 2.65 (ddd, J=6.6, 6.6, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=193.2, 135.4, 131.0, 129.7, 128.6, 128.2, 127.2, 65.8, 38.1, 31.0.

*4.3.17. Compound **3i***

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.29 (d, J=6.0 Hz, 1H), 7.41–7.18 (m, 5H), 3.89 (d, J=11.2 Hz, 1H), 3.27 (dd, J=11.2, 5.6 Hz, 1H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=195.2, 130.2, 129.4, 128.9, 128.4, 69.0, 39.7, 38.9, 12.8; IR (thin film) ν/cm^{-1}: 2921 (s), 2851 (s), 1713 (s), 1539 (s), 1450 (m), 1390 (w), 1351 (m), 1113 (m), 699 (m); HRMS (EI) calcd for $C_{11}H_{11}NO_3$ (M^+): 205.0739, found: 205.0736.

*4.3.18. Compound **3i′***

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.64 (d, J=4.4 Hz, 1H), 7.39–7.20 (m, 5H), 4.19 (d, J=8.0 Hz, 1H), 2.61 (dd, J=8.0, 4.4 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=194.7, 131.8, 129.8, 128.9, 128.4, 72.5, 41.4, 37.2, 16.6.

*4.3.19. Compound **3j′***

White solid. Mp 131–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.74 (d, J=4.0 Hz, 1H), 7.37–7.15 (m, 8H), 6.89–6.86 (m, 2H), 4.31 (d,

J=8.0 Hz, 1H), 3.23 (dd, J=8.0, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=194.0, 131.6, 131.3, 130.3, 129.0, 128.7, 128.5, 128.1, 127.9, 80.1, 40.2, 37.0; IR (thin film) ν/cm^{-1}: 2924 (w), 1703 (s), 1549 (s), 1448 (m), 1338 (m), 1127 (m), 1043 (m), 712 (m); HRMS (EI) calcd for $C_{16}H_{13}NO_3$ (M^+): 267.0895, found: 267.0890.

4.3.20. Compound **3k′**

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.60 (d, J=4.4 Hz, 1H), 7.38–7.23 (m, 5H), 4.13 (d, J=8.0 Hz, 1H), 2.65 (dd, J=8.0, 4.0 Hz, 1H), 1.68 (q, J=7.6 Hz, 2H), 0.94 (t, J=8.0 Hz, 3H); MS (EI) m/e=219.1 (M^+), 190.1, 173.0, 145.0, 131.0, 128.0, 115.0, 105.0, 91.0, 76.9, 65.0, 51.0, 39.0, 29.0.

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17. The diastereoisomers **3** and **3′** are inseparable by column chromatography. Their ^{1}H NMR and ^{13}C NMR data were obtained by analyzing the NMR spectra of **3**/**3′** mixtures. However, IR and MS spectroscopic data could not be assigned individually for **3** and **3′**.