

Asymmetric Halo-Mannich-Type Reaction Provides Access to Pyrrolidines and β -Proline Derivatives

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A new halo-Mannich-type reaction is reported using cyclopropyl carbonyl-derived enolates and sulfonyl-protected imines. Chiral oxazolidinones auxiliaries were found to be effective for completely controlling the stereochemistry of the products. Variations in the oxazolidinone, protecting group, and imine components show this to be a quite general reaction. The initial iodo-Mannich products were found to be readily cyclized in the presence of triethylamine to afford the resulting protected pyrrolidines, which could be readily deprotected under standard conditions.

Introduction

The asymmetric aldol reaction is among the most powerful methodologies for the construction of C(sp3)– C(sp3) bonds and continues to remain an active topic of study in the organic community.^{1–3} Unfortunately, traditional aldol products lack a high number of sites of functionalization. To increase the synthetic utility of aldol products, we and others have introduced a number of new halo aldol reactions in which the aldol framework is further functionalized by the presence of a halogen that can be a site for coupling, elimination, and displacement reactions.^{4,5} Of particular recent interest in some research groups has been the use of enolates derived from cyclopropyl carbonyl compounds to perform a variety of aldol and related reactions that result in the formation of structurally diverse heterocycles.^{6,7} Recently, we developed an asymmetric halo aldol reaction utilizing enolates derived from chiral cyclopropyl-*N*-acyl oxazolidinones (Scheme 1).⁸ High yields and diastereoselectivities were obtained for a number of aldehyde substrates. Furthermore, the initial products were easily cyclized in the presence of triethylamine to yield the corresponding chiral *cis*-2,3-disubstituted tetrahydrofuran derivatives, thus complementing the existing methods for the syn-

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thesis of heterocycles from cyclopropane ring-opening reactions. $^{\rm 6a,7b,9,10}$

With these initial results in hand, we explored an analogous reaction in which imines replaced aldehydes as electrophilic acceptors. Such a methodology would presumably initially produce asymmetric Mannich products, which could then be cyclized to the corresponding pyrrolidines.^{6e} Such pyrrolidines are of significant synthetic utility for a number of reasons. For example, they have been widely utilized as auxiliaries and ligands for asymmetric synthesis.¹¹ Additionally, the products of this process can, after deprotection, be converted into α-substituted- β -proline derivatives, which are potentially useful for catalysis and peptide studies.¹² Furthermore, a number of natural products, such as indolizidine¹³ and pyrrolizidine¹⁴ alkaloids, contain the five-membered Nheterocyclic moiety. In this paper, we are pleased to report the full details of our study of this new asymmetric halo aldol-type methodology, as well as an extension of this methodology in which a number of new β -proline derivatives have been prepared.

Results and Discussion

During the past few years, several reports have been published in which diethylaluminum iodide (Et₂AlI) was used as Lewis acid/halogen donor.^{4b,5c,6a,8} When excess Et₂-AlI (1.2 equiv) was added to a CH₂Cl₂ solution of cyclopropyl starting material at 0 °C, it was indeed found that within 30 min the enolate was formed, as indicated by a significant change in the appearance of the CH₂ ring protons in the ¹H NMR spectrum. Upon decreasing the reaction temperature to -20 °C, the enolate formation proceeded slowly such that after 20 h, ~40% of the starting material remained.

Initial experiment optimization was carried out using the benzenesulfonyl (Bs) imine derived from *p*-tolualdehyde. When 2 equiv of the imine were added to the enolate (preformed as described above), the reaction went

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R ²¹¹	$ \sum_{i=1}^{N} \sum_{j=1}^{i} \sum_{i=1}^{i} \sum_{j=1}^{i} \sum_{$	H ₂ Cl ₂	R ¹ 9	h	NHPg O	
entry	\mathbb{R}^1	\mathbb{R}^2	Pg	product	yield (%)	% de
1	Ph	Ph	Ts	1	82	>95
2	Ph	<i>i</i> -Pr	\mathbf{Ts}	2	78	>95
3	2-furyl	\mathbf{Ph}	Ts	3	78	>95
4	$4\text{-Me-C}_6\text{H}_4$	\mathbf{Ph}	\mathbf{Bs}	4	81	>95
5	$4-MeO-C_6H_4$	\mathbf{Ph}	Ts	5	76	>95
6	$4-BnO-C_6H_4$	\mathbf{Ph}	Ts	6	79	>95
7	$4-BnO-C_6H_4$	\mathbf{Ph}	\mathbf{Bs}	7	77	>95
8	$3-BnO-C_6H_4$	\mathbf{Ph}	Ts	8	67	>95
9	$4-Cl-C_6H_4$	\mathbf{Ph}	\mathbf{Bs}	9	69	>95
10	$4 - F - C_6 H_4$	Ph	Ts	10	62	>95

TABLE 1.

to completion within 9 h at 0 °C to afford the product in ~80% yield with complete control of diastereoselectivity. When the amount of imine was decreased to 1.5 equiv, the same results were obtained; however, the use of 1.0 equiv or less gave rise to longer reaction times and generally poorer yields. When THF was utilized as solvent, the yield was decreased by ~10% for the same reaction conditions. Of the other solvents tested (toluene, ether, acetonitrile), only toluene worked well, giving results similar to those obtained using CH_2Cl_2 . The use of a slight excess of Et_2AII was found to be necessary for complete conversion.

With these initial results in hand, a series of imines was studied.¹⁵ When the Bs protecting group was replaced by a Ts group, the reaction efficiency was unchanged for a number of examples. Unfortunately, repeated attempts at using the 2-Ns protecting group all led to complex reaction mixtures containing very low yields of the desired product, as evidenced by ¹H NMR analysis of the crude reaction mixture. The initial formation of halo-Mannich products is outlined in Table 1.

As can be seen from Table 1, complete control of diastereoselectivity was achieved in all cases. Both electron-donating and electron-withdrawing substituents on the imine work well. Additionally, the oxazolidinone prepared from valine (entry 2) was found to be as efficient in controlling diastereoselectivity as the oxazolidinone prepared from phenylglycine. Entry 3 is an interesting case in that furyl rings can be considered precursors for carboxylic acids, thus introducing an additional functionality to the molecule.

With these initial products in hand, attention was then turned to focus on cyclization to the corresponding pyrrolidines. It was found that the reaction could be conveniently carried out in CH_2Cl_2 using 5 equiv of Et_3N , without the need for protection in an inert atmosphere. In all cases the reaction proceeded to completion in 2 h or less without any epimerization being observed. The use of an equimolar amount of base resulted in extended reaction times (ca. 4-5 h), while increasing to 10 equiv of Et_3N showed little improvement of reaction rate. In all cases, very high yields were obtained after purification by column chromatography (Table 2). The *cis* stereo-

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chemistry of these 2,3-disubstituted pyrrolidines (vide infra) complements the work of Olsson^{6b} and Lautens,^{7a} who typically obtained *trans* products.

Additionally, it was found that purification of the halo-Mannich intermediate was not necessary for the formation of the cyclized pyrrolidine product. For a number of cases, the initial halo aldol reaction was carried out, quenched with aqueous acid, extracted with CH_2Cl_2 , and concentrated. Treatment of these crude products with Et_3N formed the cyclized products with typically <10% diminishment of yield when compared to the two-step process.

The absolute stereochemistry of this process was determined by X-ray crystallographic analysis. The chirality was found to be the same as that of our previous work in which aldehydes were utilized as electrophiles.⁸ The crystal structure diagram is shown in Figure 1. Two molecules exist in the asymmetric unit, and it is interesting to note that interatomic distances from O2 to C21 of different molecules are quite small (2.77 and 3.00 Å). Full crystallographic data can be found in Supporting Information.

The stereochemistry for this reaction can be explained by the formation of a metal-chelated enolate (Figure 2). With the auxiliary in an orientation fixed by the chelation of the enolate and auxiliary carbonyl oxygens, the imine approaches the less hindered side away from the phenyl group as shown. Such an open chain transition state is



FIGURE 1. Crystal structure for product 11. 7636 J. Org. Chem., Vol. 70, No. 19, 2005



FIGURE 2. Proposed model for asymmetric induction.

SCHEME 2



similar to that proposed by Heathcock and co-workers, who reported similar diastereoselectivity in the standard oxazolidinone aldol reaction.¹⁶

In an effort to demonstrate the utility of these pyrrolidine products, a few were deprotected to the corresponding monoprotected β -proline derivatives (Scheme 2). Under standard conditions reported by Evans and coworkers,¹⁷ the chiral auxiliary was cleaved to produce, after acidic workup, the *N*-protected α -substituted β -prolines. In all cases, the auxiliary cleavage proceeded in high yields with minimal purification and no epimerization.

Additionally, under conditions reported by Rapoport and co-workers,¹⁸ the Ts group of product **11** was cleaved to afford the free amine with the auxiliary intact. Treatment of the *N*-protected pyrrolidine with 33% HBr/ HOAc in the presence of phenol produced the desired product without destruction of the chirality. The product was easily isolated in high yield by simple recrystallization (Scheme 3).

In summary, a new approach has been developed for the formation of chiral halo-Mannich products. These compounds can be easily cyclized to the corresponding *cis*-2,3-disubstituted pyrrolidines in excellent yields. Further manipulation of these pyrrolidine products gives rise to β -proline derivatives, which are important in asymmetric synthesis and pharmaceutical research.

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Experimental Section

Typical Procedure for the Preparation of Asymmetric Halo-Mannich Products. To an oven-dried test tube was added cyclopropyl starting material (80.0 mg, 0.346 mmol). The vessel was capped, vacuumed, and flushed with nitrogen. To this was added 3 mL of CH_2Cl_2 , and the resulting solution was cooled to 0 °C. To this solution was added Et_2AII (1 M in toluene, 0.42 mmol, 0.42 mL) dropwise over 5 min. After 30 min, imine was added (0.70 mmol in 2 mL of CH_2Cl_2) dropwise. The resulting solution was stirred for 9 h at 0 °C, at which time the reaction was quenched with 5 mL of 1 N HCl. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), washed with brine, and dried over anhydrous Na_2SO_4 . The dried solution was concentrated under reduced pressure and subjected to flash chromatography (EtOAc/hexane 1:4) to afford the pure products.

Analytical Data for 1. Isolated as 176.1 mg of a white solid (82%): mp = 128–130 °C. $[\alpha]^{23}_{D} = +57.5^{\circ}$. FTIR: 3300.6 (N–H), 1776.7 (C=O), 1700.4 (C=O) cm⁻¹. ¹H NMR (500 MHz, CDCl₃): 7.36–7.33 (m, 2H), 7.31–7.28 (m, 3H), 7.10–7.06 (m, 1H), 7.00–6.94 (m, 6H), 6.87–6.85 (m, 2H), 6.19 (d, J = 9.5 Hz, 1H), 5.35 (dd, J = 3.5 Hz, 8.5 Hz, 1H), 4.66–4.58 (m, 3H), 4.16 (dd, J = 3.5 Hz, 9.0 Hz, 1H), 3.22–3.12 (m, 2H), 2.27 (s, 3H), 2.23–2.16 (m, 1H), 1.95–1.88 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): 173.3, 153.9, 142.8, 137.9, 137.7, 137.6, 129.3, 129.1, 128.5, 128.4, 127.3, 126.8, 126.5, 125.4, 70.1, 58.5, 58.0, 48.9, 33.3, 21.3, 2.1. HRMS MH⁺: expected 619.0758, found 619.0755.

Analytical Data for 2. Isolated as 158.3 mg of a colorless oil (78%). [α]²³_D = +17.6°. FTIR: 3304.5 (N–H), 1773.7 (C= O), 1697.1 (C=O) cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.39 (d, J = 8.0 Hz, 2H), 7.09–7.04 (m, 3H), 7.01–6.97 (m, 4H), 6.19 (d, J = 10 Hz, 1H), 4.63–4.59 (m, 1H), 4.53–4.48 (m, 1H), 4.40–4.37 (m, 1H), 4.26 (t, J = 9.0 Hz, 1H), 4.19 (dd, J = 2.5 Hz, 9.0 Hz, 1H), 3.13–3.04 (m, 2H), 2.84 (s, 3H), 2.25–2.15 (m, 2H), 1.82–1.75 (m, 1H), 0.86 (d, J = 7.5 Hz, 3H), 0.62 (d, J = 7.0 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): 173.3, 154.5, 142.8, 137.9, 137.6, 129.1, 128.4, 127.5, 126.8, 126.6, 63.4, 59.2, 59.2, 48.9, 33.1, 28.4, 21.3, 18.0, 14.3, 2.2. HRMS MH⁺: expected 585.0915, found 585.0915.

Analytical Data for 3. Isolated as 160.0 mg of a white solid (78%): mp = 140–142 °C (dec). $[\alpha]^{23}_{D} = +44.8^{\circ}$. FTIR: 3304.5 (N–H), 1775.4 (C=O), 1699.4 (C=O) cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.48 (d, J = 8 Hz, 2H), 7.38–7.30 (m, 3H), 7.19–7.17 (m, 2H), 7.10 (d, J = 8.0 Hz, 2H), 6.99 (m, 1H), 5.99 (d, J = 10.0 Hz, 1H), 5.96–5.95 (m, 1H), 5.63 (d, J = 3.5 Hz, 1H), 5.40 (dd, J = 3.5 Hz, 8.5 Hz, 1H), 4.70 (t, J = 9.0 Hz, 1H), 4.64–4.55 (m, 2H), 4.24 (dd, J = 3.5 Hz, 9.0 Hz, 1H), 3.16–3.12 (m, 2H), 2.33 (s, 3H), 2.24–2.17 (m, 1H), 1.99–1.92 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): 172.8, 153.7, 150.4, 143.0, 141.9, 138.0, 137.5, 129.3, 129.2, 128.6, 126.8, 125.7, 110.1, 108.2, 70.1, 58.0, 52.5, 46.9, 33.2, 21.4, 1.2. HRMS MNa⁺: expected 631.0370, found 631.0370.

Analytical Data for 4. Isolated as 173.1 mg of a white solid (81%): mp = 147–149 °C. $[\alpha]^{23}{}_{\rm D}$ = +47.0°. FTIR: 3306.1 (N–H), 1769.7 (C=O), 1693.9 (C=O) cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.47–7.45 (m, 2H), 7.31–7.29 (m, 4H), 7.17–7.14 (m, 2H), 7.03–7.01 (m, 2H), 6.77–6.72 (m, 4H), 6.20 (d, J = 9.5 Hz, 1H), 5.37 (dd, J = 3.5, J = 8.0 Hz, 1H), 4.66 (t, J = 8.5 Hz, 1H), 4.60–4.56 (m, 2H), 4.17 (dd, J = 3.5, J = 9.0 Hz, 1H), 3.20–3.14 (m, 2H), 2.24–2.15 (m, 4H), 1.94–1.88 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): 173.3, 154.0, 140.6, 138.0, 137.1, 134.5, 131.8, 129.2, 129.1, 128.4, 128.4, 126.7, 126.4, 125.4, 70.2, 58.5, 58.1, 48.9, 33.2, 21.0, 2.2. HRMS MH⁺: expected 619.0758, found 619.0742.

Analytical Data for 5. Isolated as 170.5 mg of a colorless oil (76%). $[\alpha]^{23}_{D} = +30.3^{\circ}$. FTIR: 3286.4 (N–H), 1775.6 (C= O), 1701.2 (C=O) cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.36–7.34 (m, 2H), 7.32–7.29 (m, 3H), 7.04–7.02 (m, 2H), 6.98–6.96 (m, 2H), 6.51–6.48 (m, 2H), 6.12 (d, J = 9.5 Hz, 1H), 5.37 (dd, J = 3.0 Hz, 8.5 Hz, 1H), 4.65 (t, J = 8.5 Hz, 1H), 4.55–4.52 (m, 2H), 4.17 (dd, J = 3.5 Hz, 8.5 Hz, 1H), 3.73 (s, 3H), 3.19–3.10

(m, 2H), 2.81 (s, 3H), 2.22–2.14 (m, 1H), 1.93–1.86 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): 173.3, 158.8, 154.0, 142.6, 138.0, 137.7, 129.8, 129.2, 129.1, 128.5, 127.6, 126.8, 125.4, 113.7, 70.2, 58.2, 58.0, 55.2, 49.0, 33.3, 21.3, 2.2. HRMS MNa⁺: expected 671.0683, found 671.0689.

Analytical Data for 6. Isolated as 197.1 mg of a white solid (79%): mp = 168–170 °C. $[\alpha]^{23}{}_{\rm D}$ = +24.4°. FTIR: 3286.4 (N–H), 1774.2 (C=O), 1701.4 (C=O) cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.44–7.40 (m, 4H), 7.37–7.33 (m, 3H), 7.30–7.28 (m, 3H), 7.04–7.01 (m, 2H), 6.96 (d, J = 8.0 Hz, 2H), 6.80–6.77 (m, 2H), 6.60–6.57 (m, 2H), 6.11 (d, J = 9.5 Hz, 1H), 5.37 (dd, J = 3.5 Hz, 8.5 Hz, 1H), 4.97 (s, 2H), 4.66 (t, J = 8.5 Hz, 1H), 4.56–4.52 (m, 2H), 4.18 (dd, J = 3.5 Hz, 9.0 Hz, 1H), 3.19–3.10 (m, 2H), 2.82 (s, 3H), 2.22–2.10 (m, 1H), 1.92–1.82 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): 173.3, 158.1, 154.0, 142.7, 138.0, 137.7, 136.8, 130.1, 129.2, 129.1, 128.7, 128.5, 128.1, 127.2, 127.4, 126.8, 125.5, 114.7, 70.2, 70.0, 58.2, 58.1, 49.0, 33.3, 21.4, 2.2. HRMS MNa⁺: expected 747.0996, found 747.0996.

Analytical Data for 7. Isolated as 190.0 mg of a colorless oil (77%). $[\alpha]^{23}_{D} = +32.3^{\circ}$. FTIR: 3286.7 (N–H), 1774.4 (C=O), 1701.4 (C=O) cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.46–7.40 (m, 6H), 7.38–7.34 (m, 1H), 7.30–7.24 (m, 4H), 7.14–7.11 (m, 2H), 7.05–7.03 (m, 2H), 6.77–6.73 (m, 2H), 6.57–6.54 (m, 2H), 6.16 (d, J = 8.5 Hz, 1H), 5.37 (dd, J = 3.0 Hz, 8.5 Hz, 1H), 4.98 (s, 2H), 4.67 (t, J = 8.5 Hz, 1H), 4.58–4.52 (m, 2H), 4.19 (dd, J = 3.5 Hz, 8.5 Hz, 1H), ¹³C NMR (125 MHz, CDCl₃): 173.3, 158.0, 154.0, 140.6, 138.0, 136.8, 131.9, 129.9, 129.3, 128.6, 128.5, 128.1, 127.7, 127.4, 126.7, 125.4, 114.8, 70.2, 69.8, 58.3, 58.1, 49.0, 33.2, 2.2. HRMS MNa⁺: expected 733.0840, found 733.0835.

Analytical Data for 8. Isolated as 167.5 mg of a colorless oil (67%). $[\alpha]^{23}_{D} = +44.1^{\circ}$. FTIR: 3300.8 (N–H), 1777.8 (C=O), 1689.9 (C=O) cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.42–7.32 (m, 8H), 7.28–7.20 (m, 3H), 6.97–6.92 (m, 5H), 6.72–6.69 (m, 1H), 5.54 (d, J = 8.0 Hz, 1H), 6.42–6.41 (m, 1H), 6.17 (d, J = 8.5 Hz, 1H), 5.35 (dd, J = 3.5 Hz, 8.5 Hz, 1H), 4.70–4.59 (m, 5H), 4.14 (dd, J = 3.5 Hz, 8.5 Hz, 1H), 3.21–3.15 (m, 2H), 2.22–2.17 (m, 4H), 1.95–1.90 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): 173.3, 158.5, 153.9, 142.8, 139.2, 137.9, 137.7, 136.7, 129.3, 129.1, 128.6, 128.4, 128.0, 127.4, 126.8, 125.2, 119.2, 114.5, 112.3, 70.2, 69.5, 58.5, 58.1, 48.8, 33.1, 21.3, 2.2. HRMS MNa⁺: expected 747.0996, found 747.0996.

Analytical Data for 9. Isolated as 152.6 mg of a colorless oil (69%). [α]²³_D = +30.0°. FTIR: 3299.5 (N–H), 1777.9 (C= O), 1696.3 (C=O) cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.51–7.49 (m, 2H), 7.39–7.35 (m, 1H), 7.32–7.27 (m, 3H), 7.23–7.20 (m, 2H), 6.93–6.91 (m, 2H), 6.90–6.87 (m, 2H), 6.30 (d, J = 10 Hz, 1H), 5.32 (dd, J = 3.5 Hz, 8.5 Hz), 4.66–4.56 (m, 3H), 4.16 (dd, J = 3.0 Hz, J = 9.0 Hz, 1H), 3.24–3.21 (m, 2H), 2.26–2.18 (m, 1H), 2.04–1.96 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): 173.3, 153.6, 140.5, 137.9, 136.1, 133.2, 132.3, 129.2, 128.7, 128.6, 128.5, 127.7, 126.7, 125.4, 70.1, 57.8, 57.3, 48.6, 33.0, 1.7. HRMS MNa⁺: expected 661.0031, found 661.0029.

Analytical Data for 10. Isolated as a white solid (%): mp = 135-137 °C (dec). $[\alpha]^{23}{}_{D} = +58.3^{\circ}$. FTIR: 3287.2 (N–H), 1776.9 (C=O), 1698.9 (C=O) cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.38-7.36 (m, 2H), 7.32-7.29 (m, 3H), 7.01-6.96 (m, 4H), 6.82-6.79 (m, 2H), 6.65-6.61 (m, 2H), 6.20 (d, J = 10 Hz, 1H), 5.34 (dd, J = 3.5 Hz, 8.5 Hz, 1H), 4.67-4.53 (m, 3H), 4.18 (dd, J = 3.5 Hz, 8.5 Hz, 1H), 3.24-3.15 (m, 2H), 2.30 (s, 3H), 2.23-2.16 (m, 1H), 1.98-1.91 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): 173.3, 162.8, 160.9, 153.7, 143.1, 138.0, 137.6, 133.6, 133.5, 129.2, 129.2, 128.6, 128.2, 128.1, 126.8, 125.5, 115.3, 115.1, 70.1, 57.9, 57.5, 48.8, 33.1, 21.3, 1.8. HRMS MH⁺: expected 637.0664, found 637.0674.

General Procedure for Cyclization To Afford cis-2,3-Disubstituted Pyrrolidines. To an oven-dried vial was added halo-Mannich product (0.20 mmol), CH_2Cl_2 (3 mL), and Et_3N (ca. 5 equiv, 0.15 mL). This solution was stirred without inert gas protection for 2 h at room temperature, at which time it was concentrated and directly subjected to flash chromatography (EtOAc/hexane 1:2) to afford the pure products.

Analytical Data for 11. Isolated as 88.3 mg of a white solid (90%). Recrystallized by slow evaporation (10 days) of a solution in CH₂Cl₂/EtOAc/hexane (ca. 1:1:1) for X-ray analysis: mp = 91-93 °C. $[\alpha]^{23}_{D} = -61.6^{\circ}$. FTIR: 1778.3 (C=O), 1704.4 (C=O) cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.68-7.66 (m, 2H), 7.29-7.27 (m, 2H), 7.25-7.21 (m, 1H), 7.19-7.15 (m, 2H), 7.09-7.03 (m, 3H), 6.98-6.95 (m, 2H), 6.76-6.74 (m, 2H), 5.49 (d, J = 9.0 Hz, 1H), 5.13 (dd, J = 3.5 Hz, 8.5 Hz, 1H), 4.54 (t, J = 8.5 Hz, 1H), 4.17 (dd, J = 4.0 Hz, 9.0 Hz, 1H), 3.91-3.86 (m, 1H), 3.78-3.74 (m, 1H), 3.21-3.15 (m, 1H), 2.65-2.55 (m, 1H), 2.41 (s, 3H), 1.92-1.86 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): 168.4, 153.3, 143.4, 138.7, 137.6, 134.2, 129.5, 128.9, 128.3, 128.2, 127.7, 127.7, 127.3, 126.0, 70.2, 63.4, 57.9, 49.5, 47.2, 26.2, 21.5. Elemental analysis (C, H, N) expected: 66.11 C, 5.34 H, 5.71 N. Found: 65.88 C, 5.12 H, 5.62 N.

Analytical Data for 12. Isolated as 81.3 mg of a white solid (89%): mp = 144–146 °C. $[\alpha]^{23}_{D} = -59.3^{\circ}$. FTIR: 1776.8 (C= O), 1700.8 (C=O) cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.69 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.25–7.20 (m, 5H), 5.48 (d, J = 9.0 Hz, 1H), 4.14–4.10 (m, 3H), 3.93–3.87 (m, 1H), 3.86–3.82 (m, 1H), 3.25–3.20 (m, 1H), 2.76–2.67 (m, 1H), 2.42 (s, 3H), 1.92–1.86 (m, 1H), 1.57–1.51 (m, 1H), 0.66 (d, J = 7.0 Hz, 3H), 0.49 (m, J = 7.0 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): 168.7, 153.7, 143.4, 139.1, 134.2, 129.6, 128.2, 128.0, 127.7, 127.7, 63.8, 63.7, 58.8, 49.3, 47.5, 28.4, 26.5, 21.5, 18.1, 14.7. HRMS MH⁺: expected 457.1792, found 457.1791.

Analytical Datat for 13. Isolated as 89.0 mg of a white solid (95%): mp = 86–88 °C. $[\alpha]^{23}{}_{D} = -13.8^{\circ}$. FTIR: 1778.2 (C=O), 1706.4 (C=O) cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.70 (d, J = 8.0 Hz, 2H), 7.32–7.29 (m, 5H), 7.16–7.14 (m, 2H), 6.55–6.54 (m, 1H), 6.15 (d, J = 3.0 Hz, 1H), 5.98–5.96 (m, 1H), 5.70 (d, J = 8.0 Hz, 1H), 5.27 (dd, J = 4.0 Hz, 8.5 Hz, 1H), 4.63 (t, J = 9.0 Hz, 1H), 4.32 (dd, J = 3.5 Hz, 9.0 Hz, 1H), 2.66–2.56 (m, 1H), 2.41 (s, 3H), 1.93–1.88 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): 167.7, 153.2, 151.4, 143.4, 142.1, 138.0, 134.4, 129.6, 128.9, 128.5, 127.6, 126.7, 109.8, 108.9, 70.3, 57.8, 57.5, 48.2, 46.3, 25.8, 21.5. HRMS MH⁺: expected 481.1428, found 481.1417.

Analytical Data for 14. Isolated as 97.9 mg of a white solid (96%): mp = 221–223 °C. $[\alpha]^{23}_{D} = -21.7^{\circ}$. FTIR: 1777.0 (C= O), 1704.0 (C=O) cm^{-1.} ¹H NMR (500 MHz CDCl₃): 7.79–7.77 (m, 2H), 7.58–7.54 (m, 1H), 7.50–7.47 (m, 2H), 7.27–7.23 (m, 1H), 7.19–7.15 (m, 2H), 6.92 (d, J = 8.0 Hz, 2H), 6.80–6.75 (m, 4H), 5.48 (d, J = 9.0 Hz, 1H), 5.15 (dd, J = 4.0, J = 8.5 Hz, 1H), 4.57 (t, J = 9.0 Hz, 1H), 4.22 (dd, J = 4.0, J = 8.5 Hz, 1H), 3.91–3.85 (m, 1H), 3.80–3.76 (m, 1H), 3.24–3.18 (m, 1H), 2.68–2.59 (m, 1H), 2.22 (s, 3H), 1.94–1.88 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): 168.4, 153.2, 137.6, 137.3, 137.2, 135.6, 132.6, 129.0, 128.9, 128.8, 128.2, 127.6, 127.3, 126.2, 70.2, 63.2, 57.9, 49.5, 47.2, 26.2, 21.2. HRMS MH⁺: expected 491.1635, found 491.1629.

Analytical Data for 15. Isolated as 100.3 mg of a white solid (93%): mp = 186–188 °C. $[\alpha]^{23}_{D} = -34.3^{\circ}$. FTIR: 1778.1 (C=O), 1704.0 (C=O) cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.67–7.64 (m, 2H), 7.29–7.21 (m, 3H), 7.19–7.15 (m, 2H), 6.74–6.97 (m, 2H), 6.52–6.50 (m, 2H), 5.42 (d, J = 9.0 Hz, 1H), 5.15 (dd, J = 4.0 Hz, 9.0 Hz, 1H), 4.55 (t, J = 9.0 Hz, 1H), 4.17 (dd, J = 4.5 Hz, 9.0 Hz, 1H), 3.92–3.86 (m, 1H), 3.77–3.73 (m, 1H), 3.72 (s, 3H), 3.19–3.13 (m, 1H), 2.66–2.57 (m, 1H), 2.41 (s, 3H), 1.93–1.87 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): 168.6, 159.0, 153.2, 143.3, 137.7, 134.2, 130.9, 129.5, 128.8, 128.7, 128.2, 127.7, 126.0, 113.6, 70.2, 62.9, 57.9, 54.9, 49.6, 47.2, 26.3, 21.5. HRMS MH⁺: expected 521.1741, found 521.1743.

Analytical Data for 16. Isolated as 112.3 mg of a white solid (94%): mp = 77–79 °C. $[\alpha]^{23}_{D} = -58.8^{\circ}$. FTIR: 1777.6 (C=O), 1703.1 (C=O) cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.67–7.65 (m, 2H), 7.46–7.41 (m, 4H), 7.38–7.35 (m, 1H), 7.28–7.26 (m, 2H), 7.21–7.16 (m, 3H), 7.01–6.97 (m, 2H), 6.78–6.75 (m, 2H), 6.62–6.59 (m, 2H), 5.44 (d, J = 9.0 Hz, 1H), 5.16

(dd, J = 4.0 Hz, 8.5 Hz, 1H), 4.93 (s, 2H), 4.57 (t, J = 4.0 Hz, 1H), 4.19 (dd, J = 4.0 Hz, 9.0 Hz, 1H), 3.93–3.87 (m, 1H), 3.77–3.73 (m, 1H), 3.20–3.14 (m, 1H), 2.67–2.58 (m, 1H), 2.41 (s, 3H), 1.94–1.88 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): 168.7, 158.3, 153.2, 143.4, 137.7, 137.0, 134.3, 131.2, 129.5, 128.8, 128.6, 128.3, 128.0, 127.7, 127.5, 126.1, 114.4, 70.2, 69.7, 63.0, 57.9, 49.6, 47.2, 26.4, 21.5. Elemental analysis (C, H, N) expected: 68.44 C, 5.41 H, 4.69 N. Found: 68.18 C, 5.13 H, 4.58 N.

Analytical Data for 17. Isolated as 108.4 mg of a white solid (93%): mp = 79–81 °C. $[\alpha]^{23}{}_{D} = -46.1^{\circ}$. FTIR: 1778.0 (C=O), 1703.7 (C=O) cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.75–7.73 (m, 2H), 7.55–7.34 (m, 8H), 7.21–7.18 (m, 3H), 6.79–6.95 (m, 2H), 6.77–6.75 (m, 2H), 6.60–6.57 (m, 2H), 5.47 (d, J = 9.0 Hz, 1H), 5.15 (dd, J = 4.0 Hz, 9.0 Hz, 1H), 4.93 (s, 2H), 4.56 (t, J = 9.0 Hz, 1H), 4.18 (dd, J = 4.0 Hz, 9.0 Hz, 1H), 2.67–2.58 (m, 1H), 1.95–1.89 (m, 1H). ³²C NMR (125 MHz, CDCl₃): 168.5, 158.3, 153.2, 137.7, 136.9, 132.6, 130.9, 128.9, 128.8, 128.8, 128.6, 128.3, 128.0, 127.6, 127.5, 126.0, 114.4, 70.2, 69.7, 62.7, 57.9, 49.6, 47.2, 26.3. Elemental analysis (C, H, N) expected: 68.03 C, 5.19 H, 4.81 N. Found: 68.08 C, 4.89 H, 4.70 N.

Analytical Data for 18. Isolated as 106.2 mg of a colorless oil (89%). $[\alpha]^{23}_{D} = -31.8^{\circ}$. FTIR: 1778.5 (C=O), 1704.7 (C=O) cm^{-1.} ¹H NMR (500 MHz CDCl₃): 7.64–7.62 (m, 2H), 7.39–7.12 (m, 10H), 6.84 (t, J = 8.0 Hz, 1H), 6.72–6.68 (m, 4H), 6.63–6.61 (m, 1H), 5.47 (d, J = 9.5 Hz, 1H), 5.12 (dd, J = 4.5 Hz, 9.0 Hz, 1H), 4.82 (dd, J = 11.5 Hz, 13.5 Hz, 2H), 4.52 (t, J = 9.0 Hz, 1H), 4.11 (dd, J = 4.5 Hz, 9.0 Hz, 1H), 3.74–3.69 (m, 1H), 3.23–3.18 (m, 1H), 2.62–2.53 (m, 1H), 2.38 (s, 3H), 1.91–1.86 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): 168.4, 158.2, 153.3, 143.3, 140.1, 137.0.6, 136.9, 134.3, 129.5, 129.1, 128.8, 128.5, 128.2, 127.8, 127.6, 127.5, 125.8, 120.2, 114.5, 113.9, 70.1, 69.6, 63.4, 58.0, 49.5, 47.2, 26.4, 21.4. Elemental analysis (C, H, N) expected: 68.44 C, 5.41 H, 4.69 N. Found: 68.54 C, 5.23 H, 4.54 N.

Analytical Data for 19. Isolated as 99.1 mg of a white solid (97%): mp = 194–196 °C. $[\alpha]^{23}_{D} = -57.8^{\circ}$. FTIR: 1777.2 (C= O), 1703.4 (C=O) cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.76–7.74 (m, 2H), 7.60–7.56 (m, 1H), 7.51–7.47 (m, 2H), 7.34–7.30 (m, 1H), 7.27–7.23 (m, 2H), 6.96–6.93 (m, 2H), 6.90–6.87 (m, 2H), 6.83–6.81 (m, 2H), 5.41 (d, J = 9.5 Hz, 1H), 5.16 (dd, J = 4.0 Hz, 9.0 Hz, 1H), 4.58 (t, J = 9.0 Hz, 1H), 4.27 (dd, J = 4.0 Hz, 9.0 Hz, 1H), 3.98–3.92 (m, 1H), 3.81–3.77 (m, 1H), 3.26–3.20 (m, 1H), 2.63–2.54 (m, 1H), 1.95–1.90, (m, 1H). ¹³C NMR (125 MHz, CDCl₃): 168.3, 153.2, 137.4, 137.1, 133.6, 132.8, 129.0, 129.0, 128.8, 128.7, 128.4, 127.6, 126.2, 70.1, 62.9, 57.8, 49.3, 47.5, 26.4. HRMS MH⁺: expected 511.1089, found 511.1079.

Analytical Data for 20. Isolated as 94.9 mg of a white solid (90%): mp = 160-162 °C. $[\alpha]^{23}_{D} = -42.6^{\circ}$. FTIR: 1778.1 (C= O), 1704.2 (C=O) cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.66-7.64 (m, 2H), 7.30-7.27 (m, 3H), 7.24-7.20 (m, 2H), 7.01-6.98 (m, 2H), 6.83-6.81 (m, 2H), 6.62-6.58 (m, 2H), 5.40 (d, J = 9.5 Hz, 1H), 5.15 (dd, J = 4.0 Hz, 9.0 Hz, 1H), 4.57 (t, J = 9.0 Hz, 1H), 4.25 (dd, J = 4.0 Hz, 9.0 Hz, 1H), 3.95-3.90 (m, 1H), 3.79-3.75 (m, 1H), 3.20-3.15 (m, 1H), 2.63-2.54 (m, 1H), 2.42 (s, 3H), 1.92-1.87 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): 168.4, 163.1, 161.1, 153.2, 143.6, 137.5, 134.5, 134.5, 134.0, 129.6, 129.2, 129.1, 128.9, 128.6, 127.7, 126.2, 115.1, 114.9, 70.1, 62.8, 57.8, 49.3, 47.4, 26.3, 21.5. HRMS MH⁺: expected 509.1541, found 509.1544.

General Procedure for Auxiliary Cleavage. To a vial were added pyrrolidine (0.15 mmol), THF (6 mL), and H_2O (2 mL). This mixture was cooled to 0 °C, at which time LiOH (0.3 mmol) and H_2O_2 (30% in H_2O , 0.75 mmol) were added. The mixture was warmed to room temperature and stirred for 16 h. The crude product mixture was quenched with Na₂SO₃, concentrated under reduced pressure, and extracted with CH₂-Cl₂. The aqueous layer was acidified to pH 1, extracted with EtOAc (3 × 15 mL), and dried over anhydrous Na₂SO₄. When

necessary, recrystallization (benzene/hexane ca. 1:1) afforded the analytically pure products.

Analytical Data for 21a. Isolated as 51.8 mg of a white solid (quant): mp = 148-150 °C. $[\alpha]^{23}_{D} = -108.0^{\circ}$. FTIR: 3199.5, 1736.0, 1716.9 cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.59 (d, J = 8.5 Hz, 2H), 7.26–7.16 (m, 5H), 7.13–7.10 (m, 2H), 5.09 (d, J = 8.5 Hz, 1H), 3.78–3.74 (m, 1H), 3.43–3.37 (m, 1H), 3.07–3.02 (m, 1H), 2.41 (s, 3H), 2.37–2.28 (m, 1H), 2.00–1.94. (m, 1H). ¹³C NMR (125 MHz, CDCl₃): 174.2, 143.6, 138.1, 134.9, 129.6, 128.1, 127.9, 127.4, 127.2, 63.9, 49.5, 47.5, 25.3, 21.5. HRMS MH⁺: expected 346.1107, found 346.1100.

Analytical Data for 21b. Isolated as 51.8 mg of a white solid (quant): mp = 52-54 °C. $[\alpha]^{23}_{D} = -97.2^{\circ}$. FTIR: 3246.2, 1735.9, 1717.6 cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.71–7.68 (m, 2H), 7.57–7.53 (m, 1H), 7.46–7.42 (m, 2H), 7.02–6.98 (m, 4H), 5.12 (d, J-8.5 Hz, 1H), 3.80–3.76 (m, 1H), 3.64–3.41 (m, 1H), 3.11–3.06 (m, 1H), 2.40–2.29 (m, 4H), 2.04–1.98 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): 173.3, 138.0, 137.6, 135.0, 132.6, 128.9, 128.8, 127.3, 127.2, 63.8, 49.4, 47.5, 25.4, 21.1. HRMS MH⁺: expected 346.1107, found 346.1097.

Analytical Data for 21c. Isolated as 52.3 mg of a white solid (96%): mp = 188–190 °C. $[\alpha]^{23}_{D} = -118.1^{\circ}$. FTIR: 3187.5, 1735.8, 1718.2 cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.60–7.58 (m, 2H), 7.27–7.25 (m, 3H), 7.13–7.10 (m, 2H), 6.91–6.87 (m, 2H), 5.07 (d, J = 8.5 Hz, 1H), 3.79–3.75 (m, 1H), 3.42–3.36 (m, 1H), 3.10–3.04 (m, 1H), 2.42 (s, 3H), 2.36–2.27 (m, 1H), 2.02–1.97 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): 173.8, 163.3, 161.4, 143.8, 135.0, 134.1, 134.1, 129.7, 129.0, 128.9, 127.4, 115.1, 114.9, 63.2, 49.5, 47.6, 25.3, 21.5. HRMS MH⁺: expected 364.1013, found 364.1006.

Analytical Data for 21d. Isolated as 56.4 mg of a white solid (86%): mp = 193–195 °C. $[\alpha]^{23}_{D} = -94.4^{\circ}$. FTIR: 3256.5, 1736.6, 1711.3 cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.67–7.65 (m, 2H), 7.53–7.49 (m, 1H), 7.42–7.32 (m, 7H), 7.03–7.01 (m, 2H), 6.80–6.77 (m, 2H), 5.10 (s, J = 9.0 Hz, 1H), 4.99 (s, 2H), 3.77–3.73 (m, 1H), 3.45–3.39 (m, 1H), 3.09–3.04 (m, 1H), 2.40–2.29 (m, 1H), 2.03–1.97 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): 173.8, 158.4, 138.0, 136.8, 132.6, 130.3, 128.9, 128.6, 128.5, 128.0, 127.5, 127.3, 114.4, 69.9, 63.5, 49.5, 47.4, 25.3. HRMS MH⁺: expected 438.1370, found 438.1355.

Analytical Data for 21e. Isolated as 42.3 mg of a white solid (84%): mp = 130-131 °C. $[\alpha]^{23}_{D} = -97.9^{\circ}$. FTIR: 3234.4, 1735.9, 1718.1 cm⁻¹. ¹H NMR (500 MHz CDCl₃): 7.51-7.49

(m, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.12–7.10 (m, 1H), 6.26– 6.21 (m, 2H), 5.24 (d, J = 8.0 Hz, 1H), 3.61–3.57 (m, 1H), 3.48–3.43 (m, 1H), 3.16–3.10 (m, 1H), 2.58–2.49 (m, 1H), 2.40 (s, 3H), 2.17–2.11 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): 172.6, 151.0, 143.3, 142.4, 135.1, 129.5, 127.2, 110.1, 109.3, 57.4, 47.7, 46.5, 25.8, 21.5. HRMS MNa⁺: expected 358.0720, found 358.0714.

General Procedure for Cleavage of Ts Group. To a 25mL round-bottom flask were added pyrrolidine (0.15 mmol), phenol (50 mg), and 33% HBr in HOAc (15 mL). The flask was fitted with a reflux condenser and the solution was stirred at reflux for 8 h. The reaction mixture was cooled to room temperature, and to this solution was added ice water (\sim 7 mL). The resulting mixture was extracted with EtOAc (3 × 15 mL). The remaining aqueous layer was neutralized by careful addition of Na₂CO₃ to pH 8. The resulting mixture was extracted with EtOAc (3 × 15 mL), and the organic phase was dried with anhydrous Na₂SO₄. Recrystallization (CH₂Cl₂/ hexane ca. 3:1) afforded the pure product.

Analytical Data for 22. Isolated as 44.4 mg of a white solid (88%): mp = 218–220 °C. $[\alpha]^{23}_{D} = +310.2^{\circ}$. FTIR: 3394.7, 1764.3, 1699.5 cm⁻¹. ¹H NMR (500 MHz CD₃CN): 7.35–7.32 (m, 1H), 7.26–7.22 (m, 4H), 7.21–7.15 (m, 3H), 6.73–6.71 (m, 2H), 5.24 (dd, J = 4.0 Hz, 9.0 Hz, 1H), 5.05 (d, J = 7.5 Hz, 1H), 4.92–4.88 (m, 1H), 4.63 (t, J = 9.0 Hz, 1H), 4.01 (dd, J = 4.0 Hz, 9.0 Hz, 1H), 3.49–3.43 (m, 1H), 2.55–2.48 (m, 1H), 2.44–2.36 (m, 1H). ¹³C NMR (125 MHz, CD₃CN): 172.2, 154.8, 139.7, 133.9, 129.9, 129.9, 129.8, 128.9, 128.3, 126.4, 71.4, 64.9, 58.6, 46.5, 44.9, 28.5. HRMS MH⁺: expected 337.1547, found 337.1542.

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Supporting Information Available: ¹H and ¹³C NMR for all new compounds, and crystallographic data in CIF format for product **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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