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Enantioselective Organocatalytic Approach to α-Methylene-δ-lactones and δ-Lactams

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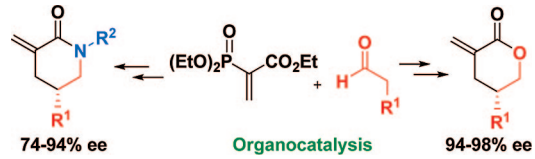

We present the first enantioselective organocatalytic approach for the synthesis of α-methylene-δ-lactones and δ-lactams. Our methodology utilizes the Michael addition of unmodified aldehydes to ethyl 2-(diethoxyphosphoryl)acrylate as the key step affording highly enantiomerically enriched adducts, which can be transformed into the target compounds maintaining the high stereoselectivity achieved in the first step. This methodology has been shown to be general and various optically active γ-substituted α-methylene-δ-lactones and δ-lactams can be easily accessed.

Introduction

Stereoselective synthesis of molecules of biological interest is an important area in organic chemistry. A class of important molecules is the α-methylene-δ-lactone system **1**, which can be found in several naturally occurring compounds such as vernolepin **2**,[1a] vernomenin **3**,[1a] pentalenolactone E **4**,[1b] teucriumlactone **5**,[1c] artemisitene **6**,[1d−f] and crassin **7**[1g,h] (Figure 1), and which have been shown to possess diverse and potentially useful biological properties. The α-methylene-δ-lactones are also very attractive precursors for the preparation of a wide variety of compounds since they readily undergo conjugate additions,[1d−f,2a] reduction of the double bond,[2b] Diels−Alder reaction,[2c] 1,3-Michael−Claisen annulations,[2d,e] or cross methathesis.[2f] On the contrary, the chemistry and biological properties of their isoelectronic analogues—α-methylene-δ-lactams **8**—are scarcely recognized.[3]

In previous years several synthetic routes leading to α-methylene-δ-lactones **1** have been established.[4,5] One approach utilizes Horner−Wadsworth−Emmons olefination of formal-

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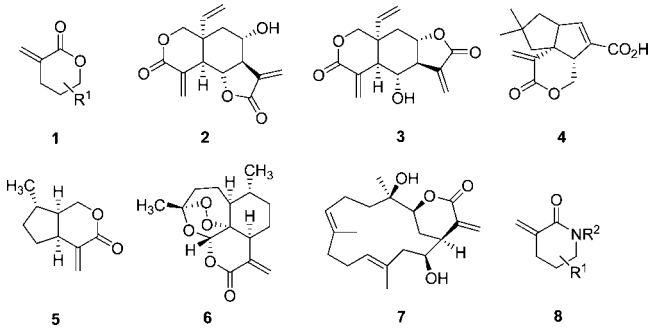


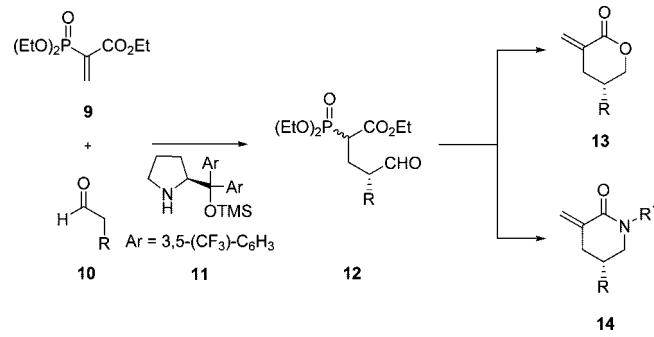
FIGURE 1. Natural Products Containing an α-Methylene-δ-lactone Moiety.

dehyde with diversely functionalized α-diethoxyphosphoryl-δ-lactones for the introduction of the methylene moiety into the lactone ring.[6,7] However, methods for the enantioselective synthesis of this class of compounds are quite limited and rely mainly on chiral auxiliaries[7] or the chiral pool approach.[5] It has, e.g., been demonstrated that the Michael reaction of enamines, derived from enantiomerically pure 1-phenylethylamine and 2-substituted cycloalkanones to dicyclohexylammonium 2-(diethoxyphosphoryl)acrylate, can play a crucial role in the stereoselective synthesis of α-methylene-δ-lactones.[7]

We believed that the methodologies for the enantioselective synthesis of α-methylene-δ-lactones and α-methylene-δ-lactams would significantly benefit from employing catalytic enantioselective reactions for their effective preparation. In this context, enantioselective organocatalysis is especially attractive since it has proven useful as a valuable tool for the stereoselective C−C bond formation.[8] In particular, Michael additions of different carbonyl compounds using simple chiral, secondary amines as catalysts via either iminium or enamine activation constitute an effective and atom economical method for the introduction of stereogenic centers to molecules in an asymmetric fashion. The immense progress in this field has been recently reviewed in a large number of papers.[8−10]

Herein, we report our results on the application of the direct, enantioselective Michael addition of various aldehydes **10** to ethyl 2-(diethoxyphosphoryl)acrylate **9** in the presence of 2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilylanyloxymethyl]pyrrolidine **11**[11] as the catalyst, for preparation of highly enantiomerically enriched γ-substituted α-methylene-δ-lactones **13** and δ-lactams **14** (Scheme 1). We envisioned that reduction of the carbonyl group in the originally formed adducts followed by lactonization and finally a Horner−Wadsworth−Emmons reaction of α-diethoxyphosphoryl-δ-lactones with formaldehyde would result in the formation of γ-substituted α-methylene-δ-lactones **13**. On the other hand, the preparation of α-methylene-δ-lactams **14** would require reductive amination of the Michael adducts obtained in the first step of synthesis. The following disclosed results constitute the first example of an organocatalytic enantioselective synthesis of α-methylene-δ-lactones and δ-lactams (Scheme 1).

SCHEME 1. Organocatalytic, Enantioselective Approach for the Synthesis of α-Methylene-δ-lactones 13 and δ-Lactams 14



Results and Discussion

We began our investigations with the goal of finding appropriate conditions for the Michael addition of isovaleraldehyde **10a** to ethyl 2-(diethoxyphosphoryl)acrylate **9** (Table 1). 2-[Bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine **11** was chosen as the catalyst since it has been recognized as a general catalyst for various α-,[12] β-,[13] and γ-functionalizations[14] of aldehydes. To our delight, the reaction was found to take place efficiently in $CHCl_3$ at room temperature with 20 mol % of the catalyst (*S*)-**11** and 10 equiv of the aldehyde **10a** (Table 1, entry 1). Under these conditions adduct **12a** was formed as a mixture of two epimers in a ratio of 4:1 with the same absolute stereochemistry at the C-4 stereogenic center and with different configuration at the C-2 stereocenter. This was confirmed after the transformation of the adduct **12a** into the corresponding α-methylene-δ-lactone **13a**. Enantiomeric excess determination

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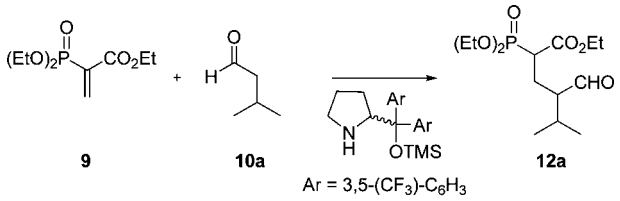
TABLE 1. Screening of Reaction Conditions for the Addition of Isovaleraldehyde 10a to Ethyl 2-(Diethoxyphosphoryl)acrylate 9[a]



entry	solvent	catalyst (loading)	aldehyde (equiv)	conv (%)[b]	dr[b]	ee[c] (%)
1	$CHCl_3$	*S* (20 mol %)	10	100	4:1	96
2	$CHCl_3$	*R* (20 mol %)	10	100	1.7:1	−98
3	$CHCl_3$	*S* (10 mol %)	10	100	4:1	96
4	$CHCl_3$	*S* (10 mol %)	5	100	4:1	96
5	EtOH	*S* (10 mol %)	5	70	4.7:1	95
6	MeOH	*S* (10 mol %)	5	40	4.4:1	Nd

[a] All reactions were performed at 0.25 mmol scale in 2.25 mL of appropriate solvent for 24 h at rt. [b] Estimated by ^{31}P NMR of the crude reaction mixture. [c] Determined by HPLC on a chiral stationary phase after transformation into the corresponding α-methylene-δ-lactone **13a**.

clearly indicated that both diastereoisomers are formed with 96% ee at the C-4 stereogenic center. As expected, the application of the opposite enantiomer of catalyst (*R*)-**11** afforded the enantiomeric product **12a** with 98% ee in 1.7:1 dr (Table 1, entry 2). Further screening of the reaction conditions showed that both catalyst loading and excess of the aldehyde can be reduced to 10 mol % and 5 equiv, respectively, without decrease of enantioselectivity (entries 3 and 4). It is also noteworthy that the addition can be performed in EtOH furnishing the desired product **12a** with slightly lower yield, but maintaining high enantioselectivity (entry 5). Surprisingly, the addition conducted in MeOH was not chemoselective as formation of unidentified organophosphorus side products was observed (entry 6).

The absolute configuration of the C-4 stereogenic center in the product **12a** obtained in the reaction with catalyst (*S*)-**11** is based on the absolute configuration obtained for Michael addition reactions using the (*S*)-**11** as the catalyst.[10a,15] This assignment allows us to propose the transition state of reaction, in which ethyl 2-(diethoxyphosphoryl)acrylate **9** approaches the

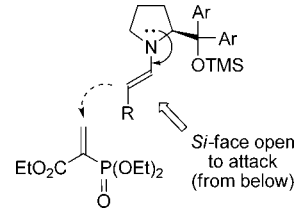


FIGURE 2. Transition state model for the 2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilylanyloxymethyl]pyrrolidine catalyzed Michael addition.

E-enamine, formed in situ from aldehyde and a chiral catalyst, from the less-hindered *Si*-face (Figure 2) to avoid unfavorable steric interactions with the bulky substituent present at C-2 of the catalyst. The formation of two epimeric products with different absolute configuration at the C-2 stereocenter and with the same stereochemistry at the C-4 stereogenic center can be rationalized by similar accessibility of both enantiofaces of the acceptor. Moreover, high acidity of the proton at C-2 makes it very prone to rapid epimerization.

With the optimized reaction conditions in hand (Table 1, entry 4), we turned our attention to effective transformation of the adduct **12a** into α-methylene-δ-lactone **13a** (Scheme 2, Table 2, entries 1 and 2). The obtained product **12a** was not purified, but submitted directly to chemoselective reduction with $NaBH_4$ in MeOH at 0 °C affording δ-hydroxyalkanoate **15a**, which was cyclized to the desired α-diethoxyphosphoryl-δ-lactone **16a** under acidic conditions. The corresponding α-diethoxyphosphoryl-δ-lactone **16a** was formed as a mixture of epimers. Finally, the Horner−Wadsworth−Emmons olefination of lactone **16a** with formaldehyde afforded the target α-methylene-δ-lactone **13a** maintaining the 96% ee achieved in the Michael-addition step.

In the next stage of the studies, the scope of the elaborated synthetic protocol was evaluated by reacting ethyl 2-(diethoxyphosphoryl)acrylate **9** with various aldehydes **10b−f** (Scheme 2, Table 2, entries 3−8). The established reaction sequence involving Michael addition, chemoselective reduction of the carbonyl group, cyclization, and finally a Horner−Wadsworth−Emmons reaction with formaldehyde was proven to be general and different γ-substituted α-methylene-δ-lactones **13b−f** could be efficiently accessed. In all the cases high enantioselectivities (≥94% ee) of the products were obtained. By analogy, we have assigned absolute configuration 5*S* to all α-methylene-δ-lactones **13b−f** obtained in the reaction with catalyst (*S*)-**11**. It was found that the Michael addition of 3,3-dimethylbutyraldehyde **10d** was rather slow and after 7 d at rt we still observed the unreacted phosphonate **9** in the ^{31}P NMR spectrum of the crude reaction mixture. Increasing the reaction temperature to 40 °C improved the reaction rate and application of $PhCO_2H$ (10 mol %) as the cocatalyst allowed us to obtain the desired adduct **12d** within 24 h (entry 5). Interestingly, the elevated temperature had no influence on the stereoselectivity of the addition, which was confirmed after transformation of alkanoate **12d** to the corresponding α-methylene-δ-lactone **13d** according to our synthetic protocol. The final product **13d** was obtained with 96% ee. It should also be emphasized that we were able to perform the Micheal addition of 4-pentenal **10f**, which allowed us to synthesize α-methylene-δ-lactone **13f** bearing an allyl substituent in the γ-position. In this case cyclization of the δ-hydroxyalkanoate **15f** obtained by chemoselective reduction of the carbonyl group in the adduct **12f** had to be performed by using catalytic *p*-TSA in boiling benzene instead of TFA, which was

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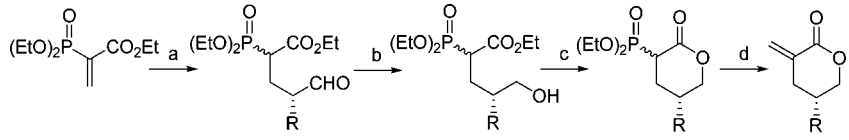
SCHEME 2. Enantioselective Synthesis of α-Methylene-δ-lactones 13[a]



[a] Reagents and conditions: (a) aldehyde **10** (5 equiv), catalyst (*S*)-**11** (0.1 equiv), $CHCl_3$, rt, 24 h; (b) $NaBH_4$ (2.5 equiv), MeOH, 0 °C, 1 h; (c) TFA−CH_2Cl_2 (1:2), rt, overnight; (d) K_2CO_3 (3 equiv), 36% HCHO (6 equiv), THF/H_2O, 0 °C, 1 h.

TABLE 2. Enantioselective Synthesis of γ-Substituted α-Methylene-δ-lactones 13[a]

		yield (%)		dr[c]		
entry	R	**16**[b]	**13**	**12**	**16**	ee[d] (%)
1	*i*-Pr, **10a**	59	62	4:1	43:57	**13a**: 96
2	*i*-Pr, **10a**	65	64	1.7:1	43:57	**13a**: −98[e]
3	Et, **10b**	58	67	3.6:1	55:45	**13b**: 94
4	Bu, **10c**	54	77	3:1	55:45	**13c**: 96
5[f]	*t*-Bu, **10d**	42	71	6.8:1	40:60	**13d**: 96
6	Bn, **10e**	40	34	4:1	55:45	**13e**: 95
7[g]	allyl, **10f**	66	87	3.6:1	53:47	**13f**: 95
8[g]	allyl, **10f**	53	50	3.6:1	53:47	**13f**: −98[e]

[a] Michael additions performed at 0.5 mmol scale with 10 mol % of the catalyst (*S*)-**11** in 4.5 mL of $CHCl_3$ for 24 h at rt. [b] Overall yield for 3 steps. [c] Estimated by ^{31}P NMR. [d] Determined by HPLC on a chiral stationary phase after transformation into the corresponding α-methylene-δ-lactones **13**. [e] Michael additions performed with the enantiomeric catalyst (*R*)-**11**. [f] Michael addition performed at 40 °C with $PhCO_2H$ (10 mol %) as cocatalyst. [g] Cyclization performed with *p*-TSA (cat.) in boiling benzene for 3 h.

generally used for the cyclizations of the other δ-hydroxyalkanoates **15a**−**e** (entry 7). The final α-methylene-δ-lactone **13f** was obtained with high 95% ee. The opposite enantiomer of the product **13f** could also be easily accessed with good enantioselectivity (98% ee) by application of the enantiomeric catalyst (*R*)-**11** in the Michael-addition step (entry 8).

With the general strategy for the synthesis of γ-substituted α-methylene-δ-lactones **13** being established, we decided to turn our attention to the preparation of optically active α-methylene-δ-lactams **14**. Employing reductive amination of the enantiomerically enriched Michael adducts **12** seemed to be attractive in this respect. In the first attempt, benzylamine was chosen as the aminating reagent. Reductive amination of the aldehyde **12a** with benzylamine was performed by using sodium triacetoxyborohydride as the reducing agent in DCE at room temperature for 24 h (Scheme 3). The δ-aminoalkanoate **17** underwent spontaneous lactamization yielding α-diethoxyphosphoryl-δ-lactam **18** as the only product as a mixture of two epimers in a ca. 1:1 ratio. Horner−Wadsworth−Emmons olefination of formaldehyde with α-diethoxyphosphoryl-δ-lactam **18** furnished the target α-methylene-δ-lactam **14a**. Surprisingly, determination of the enantiomeric excess indicated that the established synthetic route proceeded with noticeable decrease of enantioselectivity induced in the Michael addition step. The corresponding α-methylene-δ-lactam **14a** was obtained with 84% ee. This unexpected outcome of the reaction can be rationalized assuming that the imine originally formed in the reaction of aldehyde **12a** with benzylamine can be in equilibrium with the corresponding enamine, which would lead to partial racemization of the product. To overcome these difficulties we decided to use aniline instead of benzylamine in the reductive amination step. We believed that conjugation of the imine C=N double bond with an aromatic system should significantly suppress the corresponding imine−enamine equilibrium and allow us to obtain the corresponding α-methylene-δ-lactam with higher enantiomeric excess.

To confirm our assumptions we performed reductive amination of the aldehyde **12a** with aniline under the previously optimized conditions (Scheme 4, Table 3). Surprisingly, instead of the expected α-diethoxyphosphoryl-δ-lactam, the isolated product was the δ-aminoalkanoate **19a**. All attempts to cyclize this compound under basic conditions were unsuccessful. Therefore, we decided to perform the Horner−Wadsworth−Emmons reaction of formaldehyde with the phosphonate **19a**. We were pleased to find out that the reaction proceeded efficiently. Under the reaction conditions the originally formed α-methylene-δ-aminoalkanoate **20** underwent spontaneous cyclization to the corresponding α-methylene-δ-lactam **14b**. Synthesis of α-methylene-δ-lactams with aniline instead of benzylamine as the aminating reagent proved to be more efficient since the final product was obtained in high 93% ee (Table 3, entry 1). The opposite enantiomer of **14b** also could be easily accessed in high 94% ee (entry 2) by employing the Michael adduct *ent*-**12a** prepared with the enantiomeric catalyst (*R*)-**11**. The generality of this methodology was additionally demonstrated by transformation of the Michael adducts **12b**,**d** to corresponding α-methylene-δ-lactams **14c**,**d** following our established synthetic protocol. We have found that the corresponding imine−enamine equilibrium as well as the stereochemical outcome of the reaction were strongly dependent on the bulkiness of the substituent in the γ-position relative to the ester functionality. More sterically demanding substituents (*i*-Pr, *t*-Bu) suppressed imine−enamine equilibrium favoring the imine form in the reductive amination step and the corresponding α-methylene-δ-lactams **14b** and **14d** could be obtained with good to high enantioselectivity. The formation of the α-methylene-δ-lactam **14c** with the smaller ethyl substituent in the γ-position proceeded with loss of enantioselectivity indicating that the formation of the corresponding enamine in the reductive amination step is more favored than in the other cases.

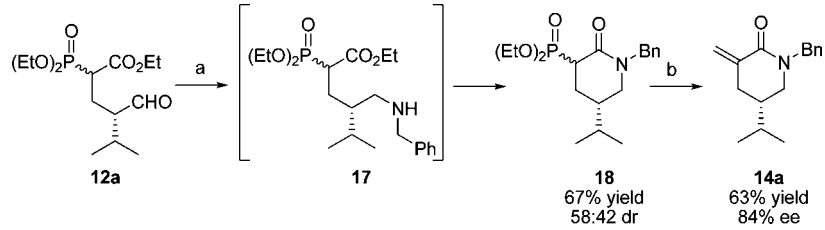
Conclusion

In conclusion, we have developed a novel, enantioselective, organocatalytic approach to α-methylene-δ-lactones and δ-lactams which utilize 2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilylanyloxymethyl]pyrrolidine-catalyzed Michael addition of various aldehydes to 2-(diethoxyphosphoryl)acrylate as the key step. Our methodology proved to be general and the corresponding α-methylene-δ-lactones and δ-lactams were obtained in a highly enantioselective manner.

Experimental Section

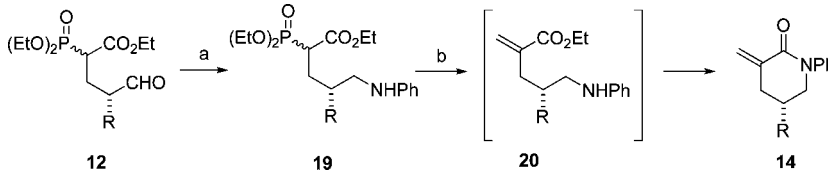
General Procedure for Preparation of α-Diethoxyphosphoryl-δ-lactones 16. In an ordinary vial, the corresponding aldehyde **10** (2.5 mmol) was added to a solution of catalyst **11** (30 mg, 0.05 mmol) in $CHCl_3$ (4.5 mL). After 15 min 2-(diethoxyphosphoryl)-

SCHEME 3. Enantioselective Synthesis of *N*-Benzyl-α-methylene-*δ*-lactam 14a[a]



[a] Reagents and conditions: (a) $NaBH(OAc)_3$ (1.4 equiv), benzylamine (1.05 equiv), DCE, rt, 24 h; (b) *t*-BuOK (1.2 equiv), Et_2O, rt, 0.5 h; then HCHO (5 equiv), Et_2O, rt, 15 min.

SCHEME 4. Enantioselective Synthesis of *N*-Phenyl-α-methylene-*δ*-lactams 14b−d[a]



[a] Reagents and conditions: (a) $NaBH(OAc)_3$ (1.4 equiv), aniline (1.05 equiv), DCE, rt, 24 h; (b) *t*-BuOK (1.2 equiv), Et_2O, rt, 15 min; then HCHO (5 equiv), Et_2O, rt, 30 min.

TABLE 3. Enantioselective Synthesis of *N*-Phenyl-α-methylene-*δ*-lactams 14b−d[a]

		yield (%)			
entry	R	**19**	**14**	dr[b] **19**	ee[c](%)
1	*i*-Pr, **12a**	68	55	40:60	**14b**: 93
2	*i*-Pr, **12a**	66	53	40:60	**14b**: −94[d]
3	Et, **12b**	60	48	52:48	**14c**: 74
4	*t*-Bu, **12d**	41	59	35:65	**14d**: 94

[a] Michael adducts **12a**,**b**,**d** were prepared at 0.5 mmol scale with 10 mol % of the catalyst (*S*)-**11** in 4.5 mL of $CHCl_3$ for 24 h at rt for **12a**,**b** or at 40 °C and with $PhCO_2H$ present for **12d**. [b] Estimated by ^{31}P NMR. [c] Determined by HPLC on a chiral stationary phase after transformation into the corresponding α-methylene-*δ*-lactams **14**. [d] Michael adduct prepared with the enantiomeric catalyst (*R*)-**11** (10 mol %).

acrylate **9** (118 mg, 0.5 mmol) was added and the resulting mixture was stirred overnight at room temperature. After complete consumption of acrylate **9** (monitored by ^{31}P NMR spectroscopy) the solvent was evaporated under reduced pressure. The residue was dissolved in MeOH (7.5 mL) then cooled to 0 °C and $NaBH_4$ (48 mg, 1.25 mmol) was added in portions. The resulting mixture was left at 0 °C for 1 h, quenched with 3 N HCl (10 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (1 mL), TFA (0.5 mL) was added, and the resulting solution was left without stirring at room temperature overnight. The solvent was evaporated under reduced pressure, then the residue was dissolved in CH_2Cl_2 (20 mL), washed with saturated $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/pentane 4:1) to afford α-diethoxyphosphoryl-*δ*-lactone **16**.

Representative Data for α-Diethoxyphosphoryl-*δ*-lactones 16. (5*S*)-3-Diethoxyphosphoryl-5-isopropyltetrahydro-2*H*-pyran-2-one (16a): Colorless oil. Yield: 59% using catalyst (*S*)-**11**. ^1H NMR ($CDCl_3$) δ 0.94 (d, 3H, J = 6.3 Hz, major), 0.95 (d, 3H, J = 6.7 Hz, minor), 0.96 (d, 3H, J = 6.6 Hz, major), 0.96 (d, 3H, J = 6.6 Hz, minor), 1.32−1.37 (m, 6H), 1.52−1.72 (m, 2H), 1.85−1.96 (m, 1H), 2.20−2.36 (m, 1H), 3.07−3.19 (m, 1H), 4.07 (dd, 1H, J = 10.2, 11.1 Hz, major), 4.15−4.26 (m, 5H), 4.34 (ddd, 1H, J = 2.7, 4.1, 11.1 Hz, major), 4.45 (ddd, 1H, J = 0.7, 4.1, 10.2 Hz, minor); ^{13}C NMR ($CDCl_3$) δ 16.20 (d, J = 6.2 Hz, minor), 16.22 (d, J = 4.7 Hz, minor), 16.26 (d, J = 6.4 Hz, major), 16.27 (d, J = 5.8 Hz, major), 19.5 (major), 19.6 (minor), 19.8 (major), 19.8 (minor), 24.6 (d, J = 4.7 Hz, minor), 24.9 (d, J = 4.2 Hz, major), 28.8 (minor), 29.3 (major), 37.0 (d, J = 5.2 Hz, minor), 38.8 (d, J = 138.9 Hz, minor), 39.3 (d, J = 8.3 Hz, major), 39.8 (d, J = 137.8 Hz, major), 62.6 (d, J = 6.8 Hz), 63.4 (d, J = 7.0 Hz, minor), 63.4 (d, J = 6.9 Hz, major), 72.1 (minor), 72.2 (major), 166.6 (d, J = 4.1 Hz, major), 166.9 (d, J = 4.1 Hz, minor); ^{31}P NMR ($CDCl_3$) δ 23.30 (43%), 23.42 (57%); HRMS calcd for $C_{12}H_{23}O_5PNa$ [M + Na] $^+$ 301.1181, found 301.1184.

(5*R*)-3-Diethoxyphosphoryl-5-ethyltetrahydro-2*H*-pyran-2-one (16b): Colorless oil. Yield: 58% with catalyst (*S*)-**11**. ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H, J = 7.5 Hz), 1.26 (t, 3H, J = 7.0 Hz), 1.27 (t, 3H, J = 7.0 Hz), 1.60−1.82 (m, 3H), 1.91−2.08 (m, 1H), 2.18−2.36 (m, 1H), 3.01−3.13 (m, 1H), 3.92 (dd, 1H, J = 8.9, 11.0 Hz, major), 4.00 (t, 1H, J = 11.0 Hz, minor), 4.08−4.20 (m, 4H), 4.22 (ddd, 1H, J = 1.7, 3.6, 11.0 Hz, major), 4.36 (ddd, 1H, J = 1.7, 4.4, 11.0 Hz, minor); ^{13}C NMR ($CDCl_3$) δ 10.97 (major), 11.03 (minor), 16.1 (d, J = 6.2 Hz, minor), 16.2 (d, J = 6.1 Hz, major), 23.8 (minor), 24.2 (major), 26.6 (d, J = 4.6 Hz, minor), 27.3 (d, J = 4.3 Hz, major), 32.1 (d, J = 4.8 Hz, minor), 34.6 (d, J = 8.9 Hz, major), 38.6 (d, J = 137.1 Hz, minor), 39.7 (d, J = 138.3 Hz, major), 62.4 (d, J = 6.4 Hz, major), 62.5 (d, J = 6.1 Hz, minor), 63.2 (d, J = 6.7 Hz, minor), 63.3 (d, J = 6.6 Hz, major), 73.17 (minor), 73.25 (major), 166.3 (d, J = 4.3 Hz, major), 166.5 (d, J = 4.3 Hz, minor); ^{31}P NMR ($CDCl_3$) δ 23.34 (55%), 23.39 (45%); HRMS calcd for $C_{11}H_{21}O_5PNa$ [M + Na]$^+$ 287.1025, found 287.1017.

(5*R*)-5-Benzyl-3-diethoxyphosphoryltetrahydro-2*H*-pyran-2-one (16e): Colorless oil. Yield: 40% with catalyst (*S*)-**11**. ^1H NMR ($CDCl_3$) δ 1.15−1.30 (m, 6H), 1.72−2.35 (m, 3H), 2.44−2.60 (m, 2H), 2.99−3.18 (m, 1H), 3.97 (dd, 1H, J = 2.8, 11.2 Hz, major), 4.00−4.20 (m, 5H), 4.34 (ddd, 1H, J = 1.2, 4.0, 11.2 Hz), 7.07−7.26 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.2 (d, J = 5.3 Hz, minor), 16.3 (d, J = 6.5 Hz, major), 26.8 (d, J = 4.8 Hz, minor), 27.6 (d, J = 4.2 Hz, major), 32.3 (d, J = 4.3 Hz, minor), 35.1 (d, J = 8.9 Hz, major), 37.2 (minor), 37.8 (major), 38.9 (d, J = 135.7 Hz, minor), 39.7 (d, J = 138.3 Hz, major), 62.6 (d, J = 6.8 Hz, major), 62.7 (d, J = 6.9 Hz, minor), 63.5 (d, J = 6.4 Hz, minor), 63.6 (d, J = 6.6 Hz, major), 72.9 (minor), 73.0 (major), 126.6 (minor), 126.7, 128.6 (2×, minor), 128.6 (2×, major), 128.7 (2×, major), 128.8 (2×, minor), 137.8 (major), 137.9 (minor), 166.3 (d, J = 4.4 Hz, major), 166.4 (d, J = 4.2 Hz, minor); ^{31}P NMR ($CDCl_3$) δ 23.15 (55%), 23.17 (45%); HRMS calcd for $C_{16}H_{23}O_5PNa$ [M + Na]$^+$ 349.1181, found 349.1179.

General Procedure for Preparation of α-Methylene-*δ*-lactones 13. To a solution of α-diethoxyphosphoryl-*δ*-lactone **16** (0.2 mmol)

and aq 37% formaldehyde (90 μL, 1.2 mmol) in THF (0.8 mL) at 0 °C was added a solution of K_2CO_3 (83 mg, 0.6 mmol) in H_2O (0.8 mL) and the resulting mixture was stirred at 0 °C for 1 h. The mixture was then quenched with sat. NaCl solution (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/pentane 1:3) to afford α-methylene-δ-lactone **13**.

Representative Data for α-Methylene-δ-lactones 13. (*S*)-5-Isopropyl-3-methylenetetrahydropyran-2-one (13a): Colorless oil. Yield: 62%. The ee was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH 99.5:0.5); flow rate 1.0 mL/min; τ_{minor} = 17.0 min, τ_{major} = 19.6 min (96% ee); $[\alpha]_D$ −41.4 (*c* 0.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.96 (d, 3H, *J* = 6.7 Hz), 0.97 (d, 3H, *J* = 6.7 Hz), 1.55−1.60 (m, 1H), 1.72−1.78 (m, 1H), 2.39 (ddt, 1H, *J* = 2.4, 11.0, 15.8 Hz), 2.74 (ddq, 1H, *J* = 2.4, 3.8, 15.8 Hz), 4.11 (dd, 1H, *J* = 9.8, 11.0 Hz), 4.40 (ddd, 1H, *J* = 2.4, 3.8, 11.0 Hz), 5.56 (dt, 1H, *J* = 1.5, 2.4 Hz), 6.40 (dt, 1H, *J* = 1.5, 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 19.7, 20.1, 28.6, 31.9, 39.8, 72.4, 128.4, 133.7, 165.7; HRMS calcd for $C_9H_{14}O_2Na$ $[M + Na]^+$ 177.0892, found 177.0897.

(*R*)-5-Butyl-3-methylenetetrahydropyran-2-one (13c): Colorless oil. Yield: 77%. The ee was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH 99.5:0.5); flow rate 1.0 mL/min; τ_{minor} = 36.2 min, τ_{major} = 39.3 min (96% ee); $[\alpha]_D$ −24.57 (*c* 1.97, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.83 (t, 3H, *J* = 6.7 Hz), 1.19−1.27 (m, 6H), 1.90−1.96 (m, 1H, *J* = 3.9, 9.3, 10.3 Hz), 2.21 (ddt, 1H, *J* = 2.4, 10.3, 15.8 Hz), 2.68 (ddq, 1H, *J* = 2.4, 3.9, 15.8 Hz), 3.93 (dd, 1H, *J* = 9.2, 10.3 Hz), 4.27 (ddd, 1H, *J* = 2.4, 3.9, 10.3 Hz), 5.34 (dt, 1H, *J* = 1.6, 2.4 Hz), 6.33 (dt, 1H, *J* = 1.6, 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.6, 28.8, 30.6, 33.4, 34.4, 73.7, 128.5, 133.4, 165.6; HRMS calcd for $C_{10}H_{16}O_2Na$ $[M + Na]^+$ 191.1048, found 191.1051.

(*R*)-5-Allyl-3-methylenetetrahydropyran-2-one (13f): Colorless oil. Yield: 87%. The ee was determined by HPLC using a Chiralpak OD column (hexane/*i*PrOH 200:1); flow rate 1.0 mL/min; τ_{minor} = 44.9 min, τ_{major} = 46.9 min (95% ee); $[\alpha]_D$ −4.24 (*c* 1.25, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.99−2.08 (m, 3H), 2.24−2.33 (m, 1H), 2.69 (ddd, 1H, *J* = 2.0, 4.0, 15.6 Hz), 3.99 (ddd, 1H, *J* = 3.2, 8.4, 11.2 Hz), 4.32 (ddd, 1H, *J* = 2.0, 3.2, 11.2 Hz), 5.01 (dd, 1H, *J* = 0.8, 6.8 Hz), 5.04 (d, 1H, *J* = 0.8 Hz), 5.49−5.50 (m, 1H), 5.63−5.73 (m, 1H), 6.34−6.35 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 33.0, 33.8, 35.2, 73.0, 117.6, 128.7, 133.1, 134.4, 165.3; HRMS calcd for $C_9H_{12}O_2Na$ $[M + Na]^+$ 175.0735, found 175.0733.

Procedure for the Preparation of *N*-Benzyl-α-diethoxyphosphoryl-δ-lactam 18. In an ordinary vial, the corresponding aldehyde **10a** (2.5 mmol) was added to a solution of catalyst **11** (30 mg, 0.05 mmol) in $CHCl_3$ (4.5 mL). After 15 min 2-(diethoxyphosphoryl)acrylate **9** (118 mg, 0.5 mmol) was added and the resulting mixture was stirred overnight at room temperature. After complete consumption of acrylate **9** (monitored by ^{31}P NMR spectroscopy) the solvent was evaporated under reduced pressure. The residue was dissolved in dry DCE (1.75 mL). Benzylamine (59 μL, 0.525 mmol) and $NaBH(OAc)_3$ (149 mg, 0.35 mmol) were added, and the heterogeneous mixture was stirred at rt for 20 h. Saturated $NaHCO_3$ (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give the crude α-diethoxyphosphoryl-δ-lactam **18**, which was purified by flash chromatography on Iatrobeads 6RS-8060, eluting with EtOAc:pentane (1:1).

(5*S*)-1-Benzyl-3-diethoxyphosphoryl-5-isopropylpiperidin-2-one (18): Pale-yellow oil. Yield: 67% with catalyst (*S*)-**11**. ^{1}H NMR ($CDCl_3$) δ 0.76 (d, 3H, *J* = 6.7 Hz, major), 0.79 (d, 3H, *J* = 6.5 Hz, minor), 0.83 (d, 3H, *J* = 6.4 Hz, minor), 0.84 (d, 3H, *J* = 6.7 Hz, major), 1.25−1.31 (m, 6H), 1.38−1.48 (m, 1H), 1.63−2.01 (m, 2H), 2.11−2.31 (m, 1H), 2.86−3.21 (m, 3H), 4.08−4.25 (m, 4H), 4.37−4.74 (m, 2H), 7.17−7.27 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.17 (d, *J* = 6.5 Hz, major), 16.23 (d, *J* = 6.6 Hz, minor), 16.3 (d, *J* = 6.1 Hz, minor), 19.3 (minor), 19.4 (major), 19.62 (major), 19.63 (minor), 25.9 (d, *J* = 4.9 Hz, major), 26.5 (d, *J* = 3.8 Hz, minor), 29.7 (major), 30.2 (minor), 36.3 (d, *J* = 2.7 Hz, minor), 39.8 (d, *J* = 12.8 Hz, major), 41.0 (d, *J* = 133.4 Hz, major), 41.7 (d, *J* = 142.4 Hz, minor), 50.4 (major), 50.5 (minor), 50.5 (minor), 50.6 (major), 61.7 (d, *J* = 6.7 Hz, major), 61.9 (d, *J* = 6.8 Hz, minor), 62.7 (d, *J* = 6.7 Hz, minor), 62.8 (d, *J* = 6.8 Hz, major), 127.0 (2×, minor), 127.1 (2×, major), 127.51 (2×, minor), 127.54 (2×, major), 128.33 (minor), 128.35 (major), 136.5, 136.6, 164.9 (d, *J* = 4.8 Hz, major), 165.0 (d, *J* = 4.9 Hz, minor); ^{31}P NMR ($CDCl_3$) δ 26.23 (58%), 26.38 (42%); HRMS calcd for $C_{19}H_{30}NO_4PNa$ $[M + Na]^+$ 390.1810, found 390.1800.

Procedure for the Preparation of *N*-Benzyl-α-methylene-δ-lactam 14a. To a stirred solution of a corresponding lactam **18** (115 mg, 0.315 mmol) in Et_2O (3.2 mL) was added *t*-BuOK (42 mg, 0.378 mmol) and the resulting mixture was stirred at room temperature for 30 min. Then paraformaldehyde (47 mg, 1.575 mmol) was added in one portion. After 15 min the reaction mixture was quenched with brine (10 mL) and the water layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The crude product was purified by flash chromatography (eluent EtOAc/pentane 1:2).

(*S*)-1-Benzyl-5-isopropyl-3-methylenepiperidin-2-one (14a): Colorless oil. Yield: 63%. The ee was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH 96:4); flow rate 1.0 mL/min; τ_{minor} = 15.0 min, τ_{major} = 15.9 min (84% ee); $[\alpha]_D$ +16.29 (*c* 0.62, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.82 (d, 3H, *J* = 6.7 Hz), 0.90 (d, 3H, *J* = 6.7 Hz), 1.46−1.55 (m, 1H), 1.58−1.66 (m, 1H), 2.28 (ddt, 1H, *J* = 2.2, 12.1, 14.6 Hz), 2.65−2.71 (m, 1H), 3.10 (dd, 1H, *J* = 9.8, 12.1 Hz), 3.26 (ddd, 1H, *J* = 2.2, 4.6, 12.1 Hz), 4.66 (s, 2H), 5.32 (dt, 1H, *J* = 1.0, 2.2 Hz), 6.26 (dt, 1H, *J* = 1.0, 2.2 Hz), 7.26−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.6, 20.0, 29.7, 33.5, 40.0, 50.8, 51.2, 122.1, 127.3, 128.0 (2×), 128.6 (2×), 137.1, 137.4, 164.3; HRMS calcd for $C_{16}H_{21}NONa$ $[M + Na]^+$ 266.1521, found 266.1520.

General Procedure for the Preparation of *N*-Phenyl-α-diethoxyphosphoryl-δ-aminoalkanoates 19. In an ordinary vial, the corresponding aldehyde **10** (2.5 mmol) was added to a solution of catalyst **11** (30 mg, 0.05 mmol) in $CHCl_3$ (4.5 mL). After 15 min 2-(diethoxyphosphoryl)acrylate **9** (118 mg, 0.5 mmol) was added and the resulting mixture was stirred overnight at room temperature. After complete consumption of acrylate **9** (monitored by ^{31}P NMR spectroscopy) the solvent was evaporated under reduced pressure. The residue was dissolved in dry DCE (1.75 mL). Aniline (48 μL, 0.525 mmol) and $NaBH(OAc)_3$ (149 mg, 0.7 mmol) were added, and the heterogeneous mixture was stirred at rt for 20 h. Saturated $NaHCO_3$ (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give the crude *N*-phenyl-α-diethoxyphosphoryl-δ-aminoalkanoate **19**, which was purified by flash chromatography, eluting with EtOAc:pentane (1:1).

Representative Data for *N*-Phenyl-α-diethoxyphosphoryl-δ-aminoalkanoates 19. Ethyl (5*S*)-2-diethoxyphosphoryl-5-methyl-4-((phenylamino)methyl)hexanoate (19a): Pale-yellow oil. Yield: 68% with catalyst (*S*)-**11**. ^{1}H NMR ($CDCl_3$) δ 0.83−0.92 (m, 6H), 1.15−1.29 (m, 9H), 1.41−1.64 (m, 2H), 1.69−1.80 (m, 1H), 1.82−2.15 (m, 1H), 2.76−3.17 (m, 3H), 4.02−4.18 (m, 6H), 6.53−6.68 (m, 3H), 7.09−7.13 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9 (major), 14.0 (minor), 16.2 (d, *J* = 5.6 Hz, minor), 16.3 (d, *J* = 4.2 Hz, major), 18.3 (minor), 18.4 (major), 19.6 (major), 19.7 (minor), 26.5 (d, *J* = 4.5 Hz, major), 27.2 (d, *J* = 4.6 Hz, minor), 29.0, 42.1 (d, *J* = 12.7 Hz, minor), 42.6 (d, *J* = 12.3 Hz, major), 43.7 (d, *J* = 129.9 Hz, major), 44.1 (d, *J* = 129.4 Hz, minor), 44.77 (major), 44.83 (minor), 61.3 (minor), 61.4 (major), 62.6 (d, *J* = 5.9 Hz, minor), 62.6 (d, *J* = 6.5 Hz, major), 112.4 (2×, minor), 112.5 (2×, major), 116.7 (minor), 116.9 (major), 129.0 (2×, minor), 129.1 (2×, major), 148.1 (minor), 148.4 (major), 169.2 (d, *J* = 5.1 Hz, major), 169.4 (d, *J* = 5.2 Hz, minor); ^{31}P NMR ($CDCl_3$) δ 23.92 (40%), 24.19 (60%); HRMS calcd for $C_{20}H_{34}NO_5PNa$ $[M + Na]^+$ 422.2072, found 422.2069.

Ethyl (5*S*)-2-diethoxyphosphoryl-5,5-dimethyl-4-((phenylamino)methyl)hexanoate (19c): Pale-yellow oil. Adduct **12d** was prepared according to the procedure for **16d** at 40 °C. Yield: 41% with catalyst (*S*)-**11**. ^{1}H NMR ($CDCl_3$) δ 0.89 (s, 9H, major), 0.91 (s, 9H, minor), 1.13−1.31 (m, 9H), 1.65−2.26 (m, 3H), 2.65 (dd, 1H, J = 1.6, 9.6 Hz, minor), 2.83 (dd, 1H, J = 7.6, 12.0 Hz, major), 3.05−3.25 (m, 2H), 3.98−4.18 (m, 6H), 6.49−6.63 (m, 3H), 7.09 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0 (minor), 14.1 (major), 16.24 (d, J = 6.2 Hz, major), 16.28 (d, J = 5.6 Hz, minor), 16.31 (d, J = 5.8 Hz, major), 16.34 (d, J = 5.0 Hz, minor), 27.1 (d, J = 4.6 Hz, minor), 27.4 (d, J = 4.3 Hz, major), 27.66 (minor), 27.67 (major), 33.3 (major), 33.7 (minor), 44.5 (d, J = 129.0 Hz, major), 45.4 (major), 45.5 (minor), 45.8 (d, J = 127.72 Hz, minor), 46.7 (d, J = 12.1 Hz, major), 47.2 (d, J = 11.6 Hz, minor), 61.3 (major), 61.6 (minor), 62.8 (d, J = 6.9 Hz, major), 62.7 (d, J = 6.7 Hz, minor), 112.4 (2×, minor), 112.5 (2×, major), 116.6 (minor), 116.9 (major), 129.0 (2×, minor), 129.1 (2×, major), 148.2 (minor), 148.6 (major), 169.2 (d, J = 5.1 Hz, major), 170.1 (d, J = 5.0 Hz, minor); ^{31}P NMR ($CDCl_3$) δ 23.65 (35%), 24.52 (65%); HRMS calcd for $C_{21}H_{36}NO_5PNa$ [M + Na]$^+$ 436.2229, found 436.2234.

General Procedure for the Preparation of *N*-Phenyl-α-methylene-*δ*-lactams 14b−d. To a stirred solution of a corresponding *N*-phenyl-α-diethoxyphosphoryl-*δ*-aminoalkanoate **19** (0.2 mmol) in Et_2O (0.4 mL) was added *t*-BuOK (27 mg, 0.24 mmol) and the resulting mixture was stirred at room temperature for 30 min. Then paraformaldehyde (30 mg, 1 mmol) was added in one portion. After 15 min the reaction mixture was quenched with brine (2 mL) and the water layer was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic layers were dried over $MgSO_4$ and evaporated, yielding *N*-phenyl-α-methylene-*δ*-lactams **14b−d**, which were purified by flash chromatography (eluent EtOAc/pentane 1:3).

Representative Data for *N*-Phenyl-α-methylene-*δ*-lactams 14. (*R*)-5-Ethyl-3-methylene-1-phenylpiperidin-2-one (14c): Colorless oil. Yield: 48%. The ee was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH 97:3); flow rate 1.0 mL/min; τ_{major} = 26.4 min, τ_{minor} = 28.9 min (74% ee); $[\alpha]_D$ +12.79 (*c* 1.83, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J = 7.5 Hz), 1.33−1.41 (m, 2H), 1.89−1.97 (m, 1H), 2.31 (ddt, 1H, J = 2.1, 12.1, 15.0 Hz), 2.73−2.77 (m, 1H), 3.41 (dd, 1H, J = 9.3, 12.1 Hz), 3.62 (ddd, 1H, J = 2.1, 4.4, 12.1 Hz), 5.32 (dt, 1H, J = 1.5, 2.1 Hz), 6.24 (dt, 1H, J = 1.5, 2.1 Hz), 7.19−7.22 (m, 3H), 7.31−7.35 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 11.5, 25.8, 35.9, 36.0, 57.1, 123.3, 126.3 (2×), 126.9, 129.3 (2×), 137.4, 143.6, 164.3; HRMS calcd for $C_{14}H_{17}NONa$ [M + Na]$^+$ 238.1208, found 238.1209.

(*S*)-5-*tert*-Butyl-3-methylene-1-phenylpiperidin-2-one (14d): Colorless oil. Yield: 59%. The ee was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH 90:10); flow rate 1.0 mL/min; τ_{major} = 7.6 min, τ_{minor} = 9.1 min (94% ee); $[\alpha]_D$ +11.37 (*c* 1.02, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.89 (s, 9H), 1.78−1.86 (m, 1H), 2.35 (ddt, 1H, J = 2.4, 13.2, 15.6 Hz), 2.69−2.75 (m, 1H), 3.50−3.60 (m, 2H), 5.32 (t, 1H, J = 2.0 Hz), 6.21 (t, 1H, J = 2.4 Hz), 7.17−7.25 (m, 3H), 7.31−7.37 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.5, 31.9, 32.0, 44.4, 53.9, 122.9, 126.4 (2×), 127.0, 129.3 (2×), 138.3, 143.8, 164.4; HRMS calcd for $C_{16}H_{21}NONa$ [M + Na]$^+$ 266.1521, found 266.1516.

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Supporting Information Available: General methods, characterization, and NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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