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Asymmetric Construction of Nitrogen-Containing [2.2.2] Bicyclic Scaffolds Using *N*-(*p*-Dodecylphenylsulfonyl)-2-pyrrolidinecarboxamide

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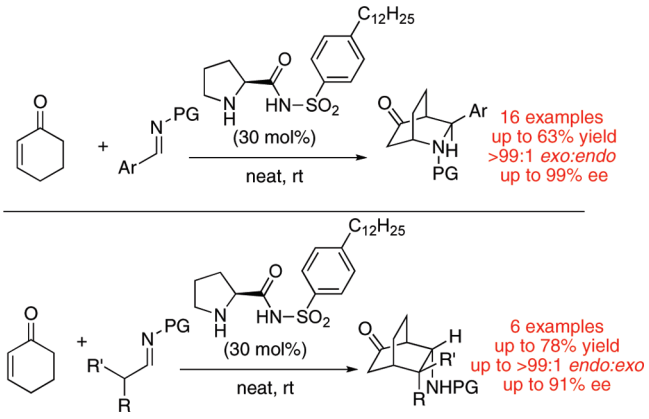

An organocatalyzed approach to enantioenriched isoquinuclidines and bicyclo[2.2.2]octanes via a *p*-dodecylphenylsulfonamide-modified proline catalyst has been developed. A series of aromatic imines have been explored for the formation of isoquinuclidines with high levels of enantioselectivity and diastereoselectivity, strongly favoring the exo product. A series of aliphatic imines has also been explored, which provide access to bicyclo[2.2.2]octanes through a novel mechanistic pathway in high levels of enantioselectivity and diastereoselectivity, favoring the endo product.

Introduction

Over the past decade, a renaissance in the field of enantioselective organocatalysis has emerged.[1] Driven by the potential practicality of the chemistry and the use of nontoxic reagents, a wealth of research has been directed toward the optimization of standard transformations and the development of new mechanistic pathways.[2] Proline and its derivatives have been particularly successful as organocatalysts. Modifications of the amino acid scaffold have principally focused on conversion of the carboxylic acid moiety into an alternate functional group (e.g., tetrazoles and sulfonamides[3−5]) to improve catalyst performance.

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Recently, our laboratory developed *p*-dodecylphenylsulfonamide-based catalysts **1** and *ent*-**1** (Figure 1).[6] These catalysts are readily available from inexpensive starting materials and can be prepared in large quantities.[7] One major advantage to **1** and *ent*-**1** is their greatly improved solubility properties, particularly in nonpolar media.[8] We have previously demonstrated the utility of these catalysts for facilitating enantioselective aldol[6] and Mannich reactions.[9] Herein, we disclose a full account of the highly enantioselective and diastereoselective construction of azabicyclo[2.2.2]octane and bicyclo[2.2.2]octane scaffolds using our proline *p*-dodecylphenylsulfonamide-based catalyst system **1**.

Azabicyclo[2.2.2]octanes (or isoquinuclidines) have generated considerable synthetic attention due to their presence in numerous alkaloid natural products,[10,11] including the iboga alkaloids.[12] Enantioselective syntheses of these azabicycles have been investigated using primarily enantioenriched BINOL-derived phosphoric Brønsted acids.[13] Use of these types of catalysts typically generate modestly endo-selective products (typically 3−4:1 endo/exo selectivity) in reasonable enantioselectivities (typically 76−88% ee). Additionally, Cordova has shown that formaldehyde-based and glycolate-based imines can undergo this type of transformation using proline catalysis in good levels of enantioselectivity (up to 99% ee using DMSO as solvent).[14] Alternatively,

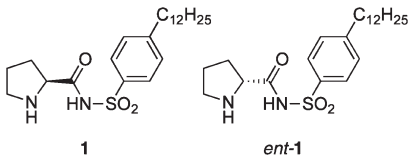

FIGURE 1. *N*-(*p*-Dodecylphenylsulfonyl)-2-pyrrolidinecarboxamide (**1**) and (*ent*-**1**).

Diels−Alder strategies[15] involving dihydropyridines have been employed with good levels of asymmetric induction.[16,17]

Results

We became intrigued by the possibility that our *p*-dodecylphenylsulfonamide-based catalyst **1** might be able to improve the observed levels of diastereoselectivity and enantioselectivity while expanding the reaction scope to include alkyl- and aryl-substituted imines. To this end, we selected 4-chlorophenyl imine **3** as the prototypical substrate (Table 1). Use of our previously reported DCE conditions[6,9] proved modestly effective, generating the desired product in 34% yield with 92% ee (entry a). It should be noted that the endo/exo selectivity for this transformation is completely reversed as compared to the chiral phosphoric acids-catalyst **1** favored exclusively the exo product (> 99:1). Addition of 1 equiv of EtOH led to an improvement in chemical yield (48%) for this transformation (entry b). Use of a purely protic solvent (IPA) proved similarly effective (entry c). Interestingly, omission of the solvent led to an improved chemical yield with now excellent enantioselectivity (entry d). In contrast, use of proline (30 mol %) in place of catalyst **1** under otherwise identical conditions resulted in greatly reduced yield (22%) and lower enantioselectivity (93% ee) (entry e). We attribute this reactivity difference to the greatly improved solubility properties of the catalyst **1** as well as the increased steric component and the modulated pK_a of the sulfonamide moiety (as compared to a carboxylic acid). The substitution on the imine nitrogen also appeared to have a noticeable impact on the reaction (entries f−i). Substitution of the PMP moiety for a 3,4-dimethoxyphenyl led to further improvement in the chemical yield without sacrificing enantioselectivity or the exo/endo ratio (entry f). In contrast, use of the more sterically encumbered 2,4-dimethoxyphenyl group was deleterious to the reaction yield and enantioselectivity (entry g). Both electronically neutral (phenyl) and electron deficient (4-chlorophenyl) moieties were tolerated, albeit with reduced chemical efficiency (entries h and i). Based on these results, it was determined that the 4-methoxyphenyl and the 3,4-dimethoxyphenyl moieties were optimal for substitution on the imine nitrogen.

The scope of this reaction on a series of aromatic imines was also explored (Table 2). We were pleased to observe a good tolerance for a range of aryl substituents. In general, electron-withdrawing groups were well-tolerated; however, *ortho*-substitution did appear to dramatically reduce the reaction rate (entry b). Resonance electron-donating groups also have a negative impact on the reaction yield and

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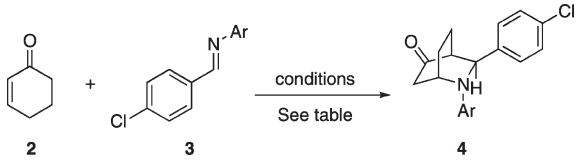
TABLE 1. Optimization of Aniline Substituent in Enantioselective Azabicyclo[2.2.2]octane Formation

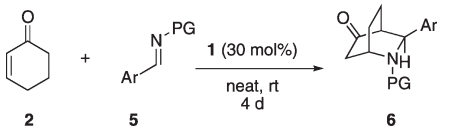


2 + 3 → 4

entry	conditions	Ar	yield (%)	ee[a] (%)	exo/endo[b]
a	**1** (20 mol %), DCE (2 M), rt, 4 d	4-MeO-C_6H_4−	34	92	> 99:1
b	**1** (20 mol %), DCE (2 M), EtOH (1 equiv. rt, 4 d)	4-MeO-C_6H_4−	48	92	> 99:1
c	**1** (20 mol %), IPA (2 M), rt, 4 d	4-MeO-C_6H_4−	5	91	> 99:1
d	**1** (30 mol %), neat, rt, 4 d	4-MeO-C_6H_4−	57	99	> 99:1
e	D-proline (30 mol %), neat, rt, 4 d	4-MeO-C_6H_4−	22	93	> 99:1
f	**1** (30 mol %), neat, rt, 4 d	3,4-$(MeO)_2$-C_6H_3−	63	99	> 99:1
g	**1** (30 mol %), neat, rt, 4 d	2,4-$(MeO)_2$-C_6H_3−	24	84	> 99:1
h	**1** (30 mol %), neat, rt, 4 d	C_6H_5−	36	98	> 99:1
i	**1** (30 mol %), neat, rt, 4 d	4-Cl-C_6H_4−	43	99	> 99:1

[a] ee was determined by chiral HPLC analysis. [b] Exo/endo ratios were determined by ^{1}H NMR analysis.

TABLE 2. Exploration of Scope in Enantioselective Synthesis of Azabicyclo[2.2.2]octanes



2 + 5 → 6

entry	Ar	PG	yield (%)	ee[a] (%)	exo/endo[b]
a	3-Cl-C_6H_4−	PMP[c]	54	99	> 99:1
b	2-Cl-C_6H_4−	PMP	19	96	> 99:1
c	4-pyridyl−	PMP	52	99	> 99:1
d	4-CF_3-C_6H_4−	PMP	54	99	> 99:1
e	C_6H_5−	PMP	51	91	> 99:1
f	4-MeO-C_6H_4−	PMP	25	80	> 99:1
g	3-Cl-C_6H_4−	DMP[d]	58	98	> 99:1
h	4-CF_3-C_6H_4−	DMP	49	99	> 99:1
i	4-Br-C_6H_4−	DMP	53	99	> 99:1
j	C_6H_5−	DMP	61	94	> 99:1
k	4-Me-C_6H_4−	DMP	53	92	> 99:1

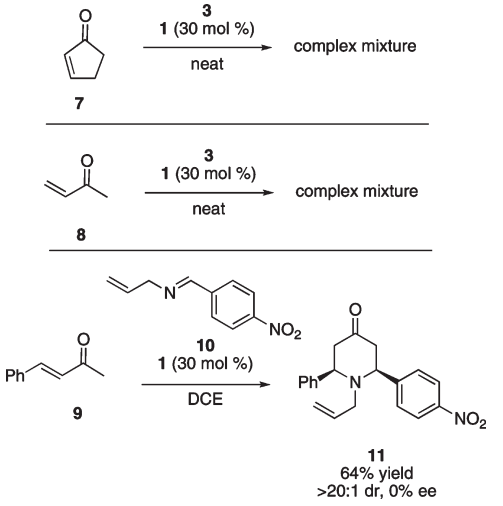
[a] ee was determined by chiral HPLC analysis. [b] Exo/endo ratios were determined by ^{1}H NMR analysis. [c] PMP is defined as 4-MeO-C_6H_4. [d] DMP is defined as 3,4-$(MeO)_2$-C_6H_3.

enantioselectivity (entry f), presumably due to the reduced electrophilicity of the imine. More electron-neutral examples (entries e and i−k) performed well. The absolute configuration of **6a** was established through X-ray crystallographic analysis (see the Supporting Information). While the yields for many of these transformations are modest, the inexpensive starting materials and the highly functionalized products demonstrate the value of this protocol. Furthermore, all of these reactions are performed in the absence of solvent because of the favorable solubility profile of **1**, further adding to the scalability and practicality of this chemistry.

We also explored variation of the enone component in this reaction (Scheme 1). Not surprisingly, use of cyclopentenone (**7**) in place of cyclohexenone (**2**) completely suppressed product formation. The use of the acyclic enone **8** led to a complex mixture of products. Use of 4-phenyl-3-buten-2-one (**9**) with known imine **10**[18] did provide the desired ring system **11** in

(18) Grigg, R.; Stevenson, P. J. *Synthesis* **1983**, 1009–1010.

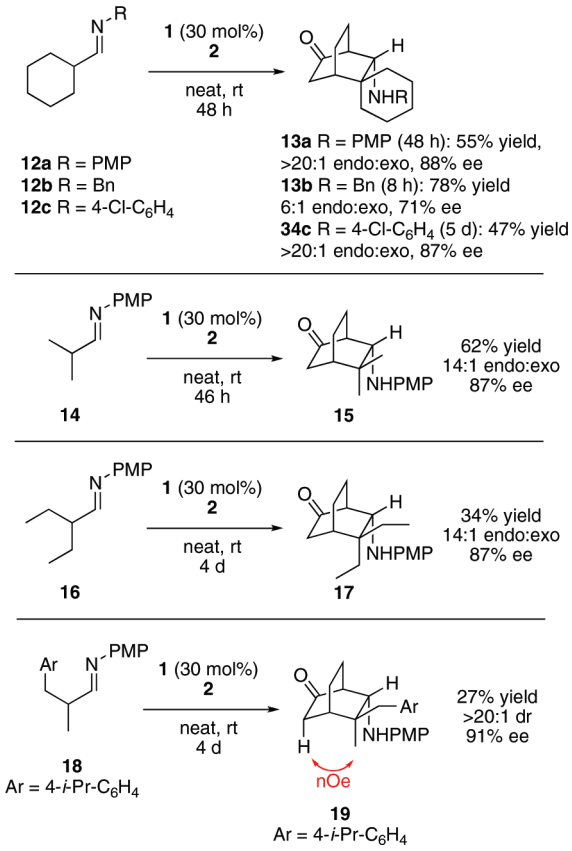
SCHEME 1. Exploration of Alternate Enone Systems in the Bicycle Formation



good chemical yield (64%) and diastereoselectivity (> 20:1 dr), but with essentially no enantioselectivity. We are unsure at this juncture as to the rational for the absence of asymmetric induction in product **11**. Replacement of the enone substrate for an ynone substrate (e.g., 4-TMS-3-butyn-2-one, 4-phenyl-3-butyn-2-one) led to a complex mixture of products.

When our exploration was extended to include aliphatic imine structures, a divergent reaction pathway was observed (Scheme 2). For example, treatment of imine **12a** under the standard conditions did not result in the formation of the corresponding azabicyclo[2.2.2]octane product. Instead, the all-carbon bicyclo[2.2.2]octane variant **13a** was produced. The use of benzyl-protected imine **12** dramatically improved the rate and overall yield of the process; however, reduced levels of diastereoselectivity and enantioselectivity were observed. The 4-chloro product **13c** allowed for the determination of the absolute configuration in this transformation via X-ray crystallographic analysis (see the Supporting Information). Use of the isopropyl imine **14** cleanly provided the *gem*-dimethyl product **15**. The analogous diethyl product **17** could also be prepared. Reaction of imine **18** generated

SCHEME 2. Enantioselective Synthesis of All-Carbon [2.2.2] Bicycles[a]



[a] ee was determined by chiral HPLC analysis. Exo/endo ratios were determined by ^{1}H NMR analysis.

bicycle **19**, which contains four contiguous stereogenic centers, including an all-carbon quaternary center. The relative stereochemistry in compound **19** was assigned via a NOE between the quaternary center methyl group and the *endo* α-keto hydrogen.

Discussion

A possible mechanism for the azabicyclo[2.2.2]octane formation is presented in Scheme 3. The initial Mannich reaction should proceed via the accepted transition state put forth by Houk.[19] The resultant syn stereochemistry illustrated in zwitterions **21**/**22** ultimately governs the subsequent aza-Michael cyclization to produce enamine **24**. This mechanism provides a reasonable explanation for the strong exo preference in these organocatalyzed reactions. In contrast, the chiral phosphoric acid catalyst systems likely generate modest anti selectivity in the initial Mannich reaction leading to modest endo selectivity in those cases.[13] The slow cleavage of the enamine **24** (due increased steric congestion) is likely the cause for the higher catalyst loading (30 mol %) as compared to standard aldol and Mannich reactions.[6,9] A similar catalyst loading was required in Cordova's examples with the formaldehyde-based and glycolate-based imines.[14]

(19) Bahmanyar, S.; Houk, K. N. *Org. Lett.* **2003**, *5*, 1249–1251.

A reasonable mechanistic explanation for the [2.2.2] all-carbon bicycle formation is provided in Scheme 4. Imine **12a** is in equilibrium with its enamine tautomer **25**. Upon suitable activation of cyclohex-2-enone (**2**), conjugate addition of the enamine would provide intermediate **27**. The facial selectivity for conjugate addition may be controlled via a hydrogen bonding interaction between the enamine and the sulfonamide as shown in compound **26**. After enamine isomerization, intramolecular Mannich cyclization would generate zwitterion **29**. Inspection of models indicates that the sulfonamide is well-positioned to direct the facial attack on the imine in intermediate **28**. Subsequent hydrolysis would regenerate the catalyst **1** and reveal the product **13a**. It should be noted that a somewhat related transformation has been reported by Cordova and co-workers involving α,β-unsaturated nitro compounds;[20] however, those examples involve **2** acting as the initial nucleophile in the transformation.

In conclusion, an organocatalyzed method has been developed for accessing nitrogen-containing [2.2.2]-bicyclic scaffolds in a highly enantioselective and diastereoselective manner. The *p*-dodecylphenylsulfonamide catalyst **1** allows for the scope of this formal aza-Diels–Alder process to be expanded to include aryl imines. Additionally, alkyl imines proceed with a divergent and novel reaction pathway, further demonstrating the utility of this technology. Subsequent application of these protocols will be reported in due course.

Experimental Section

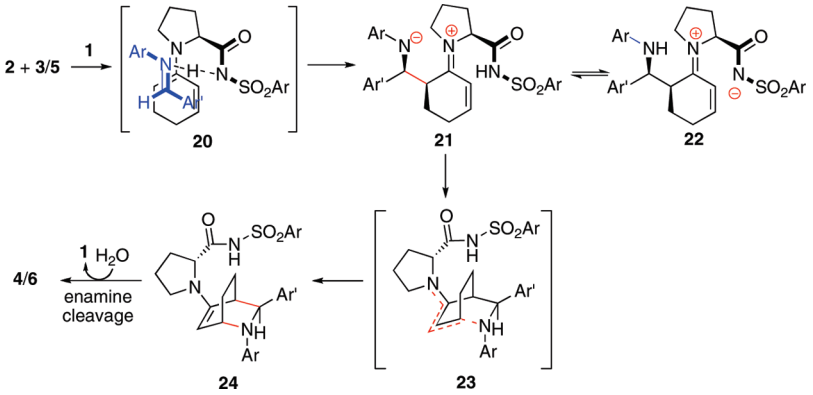
General Procedure for Formal Aza-Diels–Alder Reaction with Cyclohexenone (30 mol % of Catalyst). To a solution of cyclohex-2-enone (**2**) (1.25 mmol, 0.12 mL, 10 equiv) was added the corresponding imine **3**/**5** (0.125 mmol) and sulfonamide **1** (15.8 mg, 0.0375 mmol) at room temperature. After being stirred at the same temperature for the denoted time, the reaction mixture was loaded directly onto silica gel and purified by chromatography, eluting with 2–20% EtOAc/hexanes, to give the corresponding product.

3-(4-Chlorophenyl)-2-(3,4-dimethoxyphenyl)-2-azabicyclo-[2.2.2]octan-5-one (4f). Reaction time 4 d. Purified by chromatography over silica gel, eluting with 2–20% EtOAc/hexanes, to give the bicycle **4f** (29.1 mg, 63%, 99% ee, > 99:1 dr, white solid). Enantiomeric excess was determined by chiral HPLC [4.6×250 mm Daicel OD column, 90:10 hexanes/*i*-PrOH, 1.0 mL min^{-1}, retention times 30.5 min (major) and 38.0 min (minor)] to be 99% ee: mp 42–43 °C; $[\alpha]^{23}_{D} = -86.4$ ($c = 0.8$, $CHCl_3$); IR (neat) 2943, 2867, 1729, 1511, 1244, 1026, 814, 759, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.41 (m, 4H), 6.73 (d, $J = 8.8$ Hz, 1H), 6.20 (d, $J = 2.8$ Hz, 1H), 6.13 (dd, $J = 8.4$, 2.4 Hz, 1H), 4.73 (br s, 1H), 4.45 (br s, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 2.79 (dt, $J = 19.2$, 2.4 Hz, 1H), 2.64–2.66 (m, 1H), 2.42 (dd, $J = 18.4$, 1.6 Hz, 1H), 2.27–2.32 (m, 1H), 1.62–1.97 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.2, 149.9, 143.0, 141.9, 139.0, 133.2, 129.1, 127.7, 113.1, 104.7, 99.4, 62.2, 56.5, 55.7, 50.9, 49.1, 42.1, 26.4, 16.2; HRMS (EI+) calcd for $C_{21}H_{22}NO_3Cl$ (M^+) 371.1288, found 371.1281.

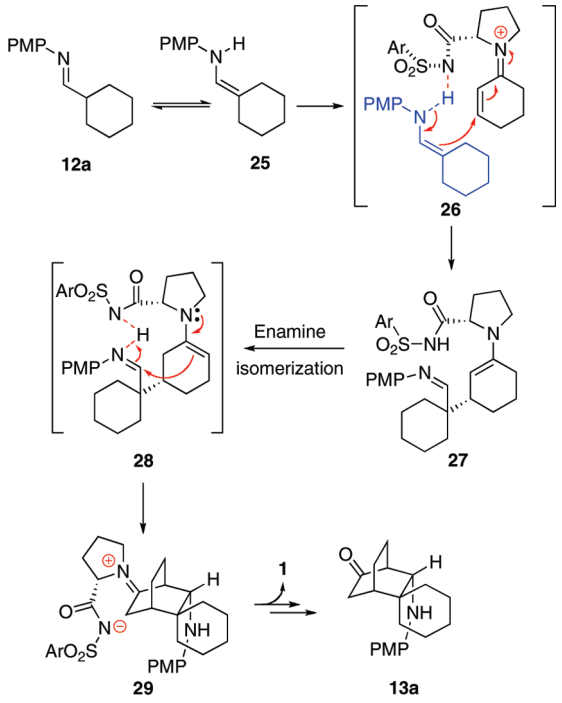
3-(4-Chlorophenyl)-2-(2,4-dimethoxyphenyl)-2-azabicyclo-[2.2.2]octan-5-one (4g).[15a] Reaction time 4 d. Purified by chromatography over silica gel, eluting with 2–20% EtOAc/hexanes, to give the bicycle **4g** (10.2 mg, 24%, 84% ee, > 99:1 dr, colorless crystal). Enantiomeric excess was determined by chiral

(20) (a) Sundén, H.; Rios, R.; Xu, Y.; Eriksson, L.; Córdova, A. *Adv. Synth. Catal.* **2007**, *349*, 2549–2555. For related examples with nitroso electrophiles, see: (b) Momiyama, N.; Yamamoto, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 1190–1195. (c) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962–5963.

SCHEME 3. Possible Mechanistic Hypothesis for Formation of Amines 4 and 6



SCHEME 4. Possible Mechanistic Hypothesis for Formation of Amine 13a



HPLC [4.6×250 mm Daicel OD column, 95: 5 hexanes/*i*-PrOH, 1.0 mL min^{-1}, retention times 14.3 min (major) and 12.9 min (minor)] to be 84% ee: $[\alpha]^{23}_D = +41.2$ ($c = 1.1$, $CHCl_3$); IR (neat) 2943, 1723, 1500, 1206, 836, 803, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, $J = 8.4$ Hz, 2H), 7.26 (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 8.4$ Hz, 1H), 6.49 (d, $J = 2.8$ Hz, 1H), 6.31 (dd, $J = 8.8$, 2.8 Hz, 1H), 5.18 (br s, 1H), 3.90 (s, 3H), 3.79 (br s, 1H), 3.74 (s, 3H), 2.79 (dt, $J = 18.8$, 3.2 Hz, 1H), 2.46−2.55 (m, 2H), 2.24 (dd, $J = 18.8$, 2.0 Hz, 1H), 1.84−1.90 (m, 1H), 1.59−1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.3, 156.2, 154.7, 139.4, 132.7, 131.0, 128.5, 128.4, 121.7, 103.4, 100.2, 58.8, 55.5, 55.4, 55.0, 51.9, 42.4, 27.5, 16.4; HRMS (EI+) calcd for $C_{21}H_{22}NO_3Cl$ (M^+) 371.1288, found 371.1290.

***N*-Allyl-2-(4-nitrophenyl)-6-phenyl-4-piperidinone (11).** Reaction time 72 h in DCE (125 μL). Purified by chromatography over silica gel, eluting with 2−20% EtOAc/hexanes, to give the bicycle **11** (26.7 mg, 64%, 0% ee, > 20:1 dr, light yellow solid): IR (neat) 3077, 3027, 2976, 2933, 2851, 1719, 1603, 1517, 1349, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, $J = 8.4$ Hz, 2H), 7.68 (d, $J = 8.4$ Hz, 2H), 7.25−7.70 (m, 5H), 5.70−5.80 (m, 1H), 5.09 (d, $J = 10.4$ Hz, 1H), 4.65 (d, $J = 16.8$ Hz, 1H), 4.11 (dd, $J = 3.6$, 11.6 Hz, 1H) 4.01 (dd, $J = 3.2$, 11.6 Hz, 1H), 3.08 (dd, $J = 6.4$, 15.2 Hz, 1H), 2.75−3.00 (m, 3H), 2.50−2.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.9, 150.2, 147.5, 141.9, 130.1, 129.0, 128.3, 128.0, 127.3, 124.3, 120.2, 64.4, 63.8, 51.7, 50.6, 50.2; HRMS (EI+) calcd for $C_{20}H_{20}N_2O_3$ ($M + H$) 337.1552, found 337.1549.

3-(4-Methoxyphenylamino)spiro[bicyclo[2.2.2]octane-2,1′-cyclohexan]-5-one (13a). Reaction time 48 h. Purified by chromatography over silica gel, eluting with 2−20% EtOAc/hexanes, to give the bicycle **13a** (21.5 mg, 55%, 88% ee, > 20:1 dr, light yellow oil). Enantiomeric excess was determined by chiral HPLC [4.6×250 mm Daicel OD column, 90:10 hexanes/*i*-PrOH, 1.0 mL min^{-1}, retention times 17.4 min (major) and 23.1 min (minor)] to be 88% ee: mp 117−118 °C; $[\alpha]^{23}_D = +40.9$ ($c = 1.4$, $CHCl_3$); IR (neat) 3374, 2856, 1723, 1511, 1462, 1239, 1184, 1043, 814, 765, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.77−6.79 (m, 2H), 6.56−6.59 (m, 2H), 3.76 (s, 3H), 3.32 (s, 1H), 3.24 (br s, 1H), 2.51 (dt, $J = 18.8$, 2.8 Hz, 1H), 2.38−2.43 (m, 2H), 2.15 (dd, $J = 18.8$, 2.4 Hz, 1H), 1.98−2.03 (m, 1H), 1.82−1.90 (m, 3H), 1.28−1.69 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.6, 152.2, 141.5, 115.2, 115.0, 64.2, 55.8, 49.4, 41.2, 39.1, 37.2, 32.1, 30.0, 25.9, 22.7, 22.1, 21.6, 20.2; HRMS (EI+) calcd for $C_{20}H_{27}NO_2$ (M^+) 313.2042, found 313.2031.

3-(Benzylamino)spiro[bicyclo[2.2.2]octane-2,1′-cyclohexan]-5-one (13b). Reaction time 8 h. Purified by chromatography over silica gel, eluting with 2−10% EtOAc/hexanes, to give the bicycle **13b** (29.1 mg, 78%, 71% ee, 6:1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6 ×250 mm Daicel OD column, 99:1 hexanes/*i*-PrOH, 1.0 mL min^{-1}, retention times 14.3 min (major) and 16.4 min (minor)] to be 71% ee: $[\alpha]^{23}_D = +21.2$ ($c = 1.9$, $CHCl_3$); IR (neat) 3336, 2927, 2851, 1723, 1446, 1097, 738, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24−7.39 (m, 5H), 3.95 (d, $J = 13.2$ Hz, 1H), 3.59 (d, $J = 13.2$ Hz, 1H), 2.50−2.62 (m, 3H), 1.24 (br s, 1H), 2.06 (dd, $J = 18.8$, 2.8 Hz, 1H), 1.76−1.95 (m, 3H), 1.28−1.67 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.9, 140.4, 128.3, 128.2, 126.9, 65.8, 51.5, 47.8, 41.0, 38.4, 37.6, 30.1, 26.1, 22.8, 22.7, 21.1, 20.6; HRMS (EI+) calcd for $C_{20}H_{27}NO$ (M^+) 297.2093, found 297.2098.

3-(4-Chlorophenylamino)spiro[bicyclo[2.2.2]octane-2,1′-cyclohexan]-5-one (13c). Reaction time 5 d. Purified by chromatography over silica gel, eluting with 2−20% EtOAc/hexanes, to give the bicycle **13c** (18.6 mg, 47%, 87% ee, > 20:1 dr, colorless crystal). Enantiomeric excess was determined by chiral HPLC [4.6×250 mm Daicel OD column, 90:10 Hexanes/*i*-PrOH, 1.0 mL min^{-1}, retention times 9.6 min (major) and 10.7 min (minor)] to be 87% ee: Mp: 139−141 °C; $[\alpha]^{23}_D = +56.7°$ ($c = 0.9$, $CHCl_3$); IR (neat) 3374, 2927, 2862, 1718, 1593, 1489, 1315, 1097, 808 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, $J = 8.8$ Hz, 2H), 6.51 (d, $J = 8.8$ Hz, 2H), 3.56 (d, $J = 10.0$ Hz, 1H), 3.37 (dd, $J = 10.0$, 2.4 Hz, 1H), 2.51 (dt, $J = 19.2$, 3.2 Hz, 1H), 2.395−2.402 (m, 2H), 2.17 (dd, $J = 19.2$, 2.8 Hz, 1H), 1.83−2.06 (m, 4H), 1.28−1.67 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.2, 145.9, 129.2, 121.9, 114.4, 62.7, 49.6,

41.2, 39.2, 37.5, 32.1, 30.1, 25.8, 22.6, 22.1, 21.5, 20.2; HRMS (EI+) calcd. for $C_{19}H_{24}NOCl$ (M+), 317.1546 found 317.1556.

5,5-Dimethyl-6-(4-methoxyphenylamino)bicyclo[2.2.2]octan-2-one (15). Reaction time 46 h. Purified by chromatography over silica gel, eluting with 2−20% EtOAc/hexanes, to give the bicycle **15** (21.2 mg, 62%, 87% ee, 14:1 dr, colorless crystal). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel OD column, 95:5 hexanes/*i*-PrOH, 1.0 mL min^{-1}, retention times 16.2 min (major) and 17.9 min (minor)] to be 87% ee (time 46 h, 2−20% EtOAc/hexanes, 21.2 mg, 62%, 87% ee, 14:1 dr, light yellow solid): mp 59−60 °C; $[\alpha]^{23}_D = +47.9$ (c = 0.8, $CHCl_3$); IR (neat) 3385, 2954, 2894, 1713, 1511, 1467, 1233, 1097, 1037, 819 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.76−6.80 (m, 2H), 6.55−6.58 (m, 2H), 3.76 (s, 3H), 3.43 (d, J = 2.0 Hz, 1H), 3.33 (br s, 1H), 2.60 (dt, J = 18.8, 3.2 Hz, 1H), 2.39−2.40 (m, 1H), 2.10−2.18 (m, 2H), 1.81−1.98 (m, 3H), 1.58−1.65 (m, 1H), 1.13 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.3, 152.2, 141.5, 115.1, 114.9, 63.4, 55.8, 49.2, 42.2, 40.3, 36.9, 29.6, 22.7, 21.8, 21.1; HRMS (EI+) calcd for $C_{17}H_{23}NO_2$ (M^+) 273.1729, found 273.1719.

5,5-Diethyl-6-(4-methoxyphenylamino)bicyclo[2.2.2]octan-2-one (17). Reaction time 4 d. Purified by chromatography over silica gel, eluting with 2−20% EtOAc/hexanes, to give the bicycle **17** (12.8 mg, 34%, 87% ee, 14:1 dr, white solid). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel OD column, 90:10 hexanes/*i*-PrOH, 1.0 mL min^{-1}, retention times 11.1 min (major) and 27.5 min (minor)] to be 87% ee: mp 88−90 °C; $[\alpha]^{23}_D = +62.7$ (c = 1.0, $CHCl_3$); IR (neat) 3379, 2960, 1718, 1506, 1239, 1032, 819 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.76−6.79 (m, 2H), 6.55−6.58 (m, 2H), 3.76 (s, 3H), 3.45 (br s, 1H), 3.29 (br s, 1H), 2.52 (dt, J = 18.8, 3.2 Hz, 1H), 2.40−2.41 (m, 1H), 2.13 (dd, J = 19.2, 2.4 Hz, 1H), 2.01−2.05 (m, 2H), 1.54−1.90 (m, 6H), 1.27−1.31 (m, 1H), 0.92 (t, J = 7.2 Hz, 3H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.5, 152.4, 140.8, 115.5, 115.0, 63.7, 55.8, 48.8, 42.0, 40.9, 35.1, 29.8, 21.8, 20.9, 20.4, 8.55, 8.18; HRMS (EI+) calcd for $C_{19}H_{27}NO_2$ (M^+) 301.2042, found 301.2047.

5-(4-Isopropylbenzyl)-5-methyl-6-(4-methoxyphenylamino)bicyclo[2.2.2]octan-2-one (19). Reaction time 4 d. Purified by chromatography over silica gel, eluting with 2−20% EtOAc/hexanes, to give the bicycle **19** (13.2 mg, 27%, 91% ee, > 20:1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6×250 mm Daicel OD column, 90:10 hexanes/*i*-PrOH, 1.0 mL min^{-1}, retention times 11.6 min (major) and 16.2 min (minor)] to be 91% ee: $[\alpha]^{23}_D = -18.6$ (c = 1.2, $CHCl_3$); IR (neat) 3363, 2954, 1713, 1506, 1233, 1108, 1037, 814 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 6.59 (d, J = 8.8 Hz, 2H), 3.77 (s, 3H), 3.52 (br s, 1H), 2.99 (d, J = 13.2 Hz, 1H), 2.87 (d, J = 13.2 Hz, 1H), 2.87−2.94 (m, 1H), 2.37−2.46 (m, 3H), 2.12 (dd, J = 18.4, 2.0 Hz, 1H), 1.71−2.05 (m, 4H), 1.26 (d, J = 7.2 Hz, 6H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.5, 152.6, 146.9, 141.0, 135.1, 130.4, 126.0, 115.9, 115.0, 65.0, 55.8, 48.3, 45.8, 41.9, 40.9, 35.3, 33.7, 24.0, 22.0, 20.8, 19.4; HRMS (EI+) calcd for $C_{26}H_{33}NO_2$ (M^+) 391.2511, found 391.2517.

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Supporting Information Available: Complete experimental procedures for all remaining compounds are provided, including ^1H and ^{13}C spectra, of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.