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Organocatalyzed, enantioselective synthesis of bicyclo-[2.2.2]-octanes containing benzylic, all-carbon quaternary centers

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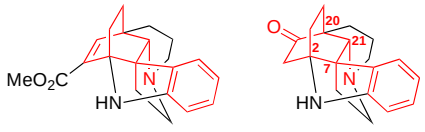
ABSTRACT

Proline aryl sulfonamide-catalyzed, multi-component couplings have been developed for accessing densely functionalized [2.2.2] bicyclic ketones containing up to four contiguous chiral centers including an all-carbon benzylic quaternary center in high enantio- and diastereoselectivity. Application to the bicyclic core of the recently isolated alkaloid kopsonoline is illustrated.

1. Introduction

Bicyclo-[2.2.2]-octane ring systems are found in numerous natural products, which have attracted considerable synthetic attention—from maoecrystal V[1] to vinigrol.[2] An important subclass of this skeleton in which stereogenic, all-carbon quaternary centers are embedded within one of the non-bridgehead carbons are particularly challenging to address—despite their presence in several natural product skeletons. For example, Kam and coworkers have recently reported the isolation and structural determination of kopsijasminine (**1**) and kopsonoline (**2**)—both of which contain this key combination of motifs (Fig. 1).[3]



kopsijasminine (**1**) kopsonoline (**2**)

Figure 1. Select examples of bicyclo-[2.2.2]-octane, quaternary center-containing alkaloids.

Our research group has recently developed a novel proline aryl sulfonamide containing a lipophilic, dodecyl sidearm (catalyst **5**), which has proven effective in a range of reaction pathways.[4,5] The non-polar solubility properties of sulfonamide **5** provides access to reaction protocols that may not be readily accessible through other catalyst systems. For example, we have recently disclosed a organocatalyzed protocol for accessing bicyclo-[2.2.2]-octanes through the use of α,α-disubstituted aldehydes (Scheme 1).[5] This transformation is uniquely facilitated through use of our proline sulfonamide derivative **5**. These reactions proceeded in modest to good chemical yield with good *endo*/*exo* selectivity (>10:1 in each case). These transformations were performed in the absence of solvent and generally proceeded to completion in between 2 and 4 days. The overall scope of these reactions was modest. The chemical yield of the transformation was sensitive to steric effects. For example, use of 3-pentyl compound **4b** instead of isopropyl compound **4a** led to a noticeable drop in chemical efficiency (34% vs 62% yield). Aldehydes not containing α-branching (e.g., R–CH_2CHO) proved poor substrates in these transformations—likely due to slow rate of enamine formation under the reaction conditions. It is important to note in three of the four examples shown in Scheme 1, products **6a**–**6c** do not contain a stereogenic quaternary center. In a single case, we were able to access a stereogenic quaternary center-containing product **4d** in modest chemical yield (27%) and good enantioselectivity (95.5:4.5 er). Prior to this work, we are aware of only a single case, which exploits an α,α-disubstituted aldehyde as the nucleophile in this transformation.[6]

While product **6d** was an encouraging result, a higher yielding transformation with improved substrate scope is necessary to provide access to biologically relevant scaffolds such as alkaloids **1** and **2**. We attribute the challenges in the above reaction to the nature of the imine substituent R and the protecting group on the

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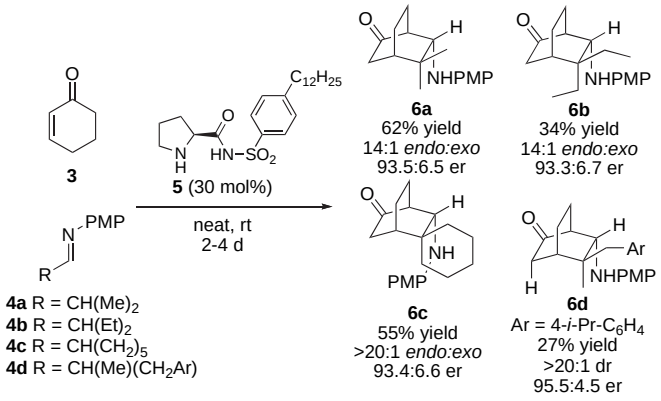
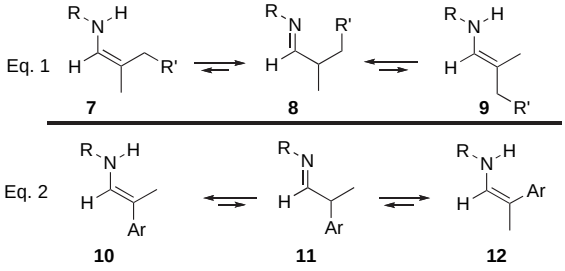
imine nitrogen. In the four cases shown above, we employed a preformed imine derived from *p*-methoxyaniline (PMP) under neat reaction conditions. These PMP-based imines often provide good levels of enantioselectivity, but at the cost of poor overall chemical yield. The high stereoselectivity in these reactions may be attributed to the structural rigidity of the aniline-derived imines, while the lower chemical yields are a function of the poorer stability of PMP-containing imines—likely due to their electron-rich nature. Additionally, a PMP-protecting group is not ideal as its removal can require harsh conditions (e.g., CAN).[7] We hoped that an alternate protecting group could address the poor chemical efficiency of these transformations in several cases while not compromising enantioselectivity and generating a readily removable moiety on the product amine.



Scheme 1. Prior published work toward accessing [2.2.2] bicycles.[5]

The performance of the reaction detailed in Scheme 1 is also a function of the equilibrium between the starting imines **8** and **11** and the necessary enamines **7**/**9** and **10**/**12** (Scheme 2, Eq. 1). In cases where the imine is substituted with two alkyl substituents (e.g., **8**), the rate of this equilibrium is likely slow and favors relatively the imine tautomer. In contrast, if the imine was substituted with at least one aryl ring (e.g., **11**), the rate of enamine/imine tautomerization as well as the equilibrium concentration of the enamines **10** and **12** are likely increased (Eq. 2). This modification of the starting imine would also nicely provide access to the benzylic, all-carbon quaternary center present in both kopsijasminine (**1**) and kopsonoline (**2**). Herein, we provide a full account of the synthesis of the bicyclo-[2.2.2]-octane core of kopsonoline including the stereogenic, all-carbon benzylic stereocenter through the use of a cascading, organocatalyzed transformation.

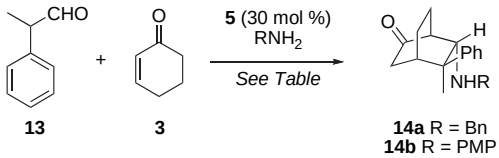


Scheme 2. Comparisons of likely equilibriums between different imine substitution patterns.

2. Results

Based on our prior work,[5] we envisioned that a multi-component coupling between aldehyde **13**, 2-cyclohexenone (**3**), and an amine could be facilitated via proline sulfonamide catalyst **5** (Table 1). Benzyl amines should be particularly useful in these types

Table 1
Optimization of three-component coupling with cyclohexenone



Entry	R	Conditions	Yield (%)	er[a] (dr)[b]
a	Bn	DCE, 1 d, rt	71	92.2:7.8 (>20:1)
b	PMP	DCE, 3 d, rt	53	98.3:1.7 (>20:1)
c	Bn	PhMe, 1 d, rt	76	90.4:9.6 (>20:1)
d	Bn	DCE, 2 d, rt, mol. sieves	31	79.9:20.1 (>20:1)
e	Bn	PhMe, 3 d, rt, mol. sieves	48	96.0:4.0 (>20:1)
f	Bn	PhMe, 3 d, 4 °C	72	93.3:6.7 (>20:1)

[a] Determined by chiral HPLC analysis.
[b] Determined by ^{1}H NMR analysis.

of transformations—likely due to the increased localization of the lone pair on nitrogen as compared to anilines. Our initial conditions utilized DCE as the solvent of choice[5,8] (entry a) to generate the desired [2.2.2] bicycle **14a** in good levels of enantioselectivity and diastereoselectivity. In contrast, use of *p*-methoxyaniline yielded a noticeable drop in chemical yield of **14b** and rate of reaction (entry b). Product **14b** did provide us with the opportunity to establish relative stereochemistry through X-ray crystallographic analysis (Fig. 2).[†] Substitution of DCE for toluene led to comparable levels of stereoselectivity with slightly improved chemical yield. Interestingly, addition of molecular sieves had a dramatic impact of the reaction performance. This transformation generates an equivalent of water during initial enamine formation. In the case of DCE (entry d), a dramatic reduction in chemical yield (31%) and enantioselectivity was observed. Use of molecular sieves with toluene as the solvent (entry e) also led to a significant reduction in the chemical efficiency of the reaction (48%). Ultimately, the use of toluene without molecular sieves with a reaction temperature of 4 °C proved to be the optimum conditions (entry f). It is important to note that this transformation generates four contiguous stereogenic centers including an all-carbon quaternary center. This compound **14** contains the central bicyclic core and benzylic quaternary center of kopsonoline (**2**).

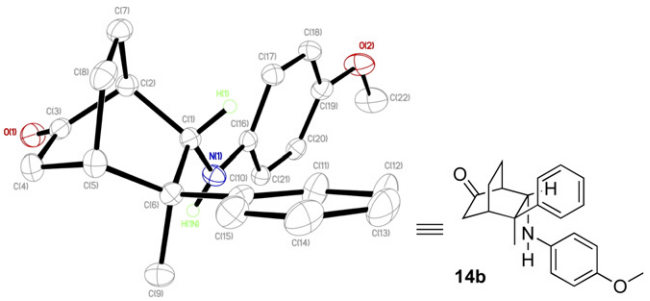


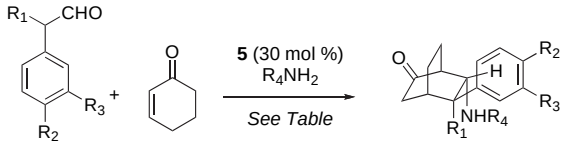
Figure 2. ORTEP representation of bicycle **14b**.

We next sought to probe the scope of the aldehyde component **15** with the optimized conditions (Table 2). These aldehydes **15** can be readily synthesized from the corresponding benzylic nitrile or methyl ketone through a two-step sequence.[9] A range of electron-donating and electron-withdrawing groups was tolerated on the aromatic ring (entries a–e). Increasing in the electron-withdrawing

† CCDC-765,281 (**14b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

nature of the arene appeared to lead to a modest increase in enantioselectivity. Use of alternate groups at R_1 was also feasible—albeit with slightly reduced enantioselectivity (entries f and g). It should be noted that more sterically congested aldehydes [e.g., 2-(*o*,*o*-dichlorophenyl)-propanal] were unreactive under the reaction conditions. We were pleased to see that alternate amines could also be used in this transformation—with propargyl amine giving particularly useful levels of stereoselectivity and chemical yield (entry i).

Table 2
Exploration of scope of multi-component coupling with cyclohexenone

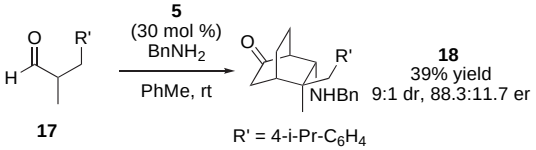


15 3 16

Entry	R_1	R_2	R_3	R_4	Conditions	Yield (%)	er[a] (dr)[b]
a	Me	Me	H	Bn	PhMe, 4 °C, 3 d	65	92.2:7.8 (>20:1)
b	Me	Br	H	Bn	PhMe, 4 °C, 5 d	52	94.6:5.4 (>20:1)
c	Me	Br	H	PMP	DCE, rt, 3 d	53	95.4:4.6 (>20:1)
d	Me	Cl	H	Bn	PhMe, 4 °C, 3 d	69	94.3:5.7 (>20:1)
e	Me	Cl	Cl	Bn	PhMe, 4 °C, 5 d	53	95.8:4.2 (>20:1)
f	Allyl	Br	H	PMP	DCE, rt, 3 d	31	90.6:9.4 (>20:1)
g[c]	Allyl	Br	H	Bn	PhMe, 4 °C, 6 d	46	88.0:12.0 (>20:1)
h[c]	Me	H	H	Allyl	PhMe, 4 °C, 3 d	66	88.8:11.2 (>20:1)
i[c]	Me	H	H	Propargyl	PhMe, 4 °C, 3 d	63	92.8:7.2 (>20:1)

[a] Determined by chiral HPLC analysis.
[b] Determined by ^{1}H NMR analysis.
[c] Reaction was performed at rt.

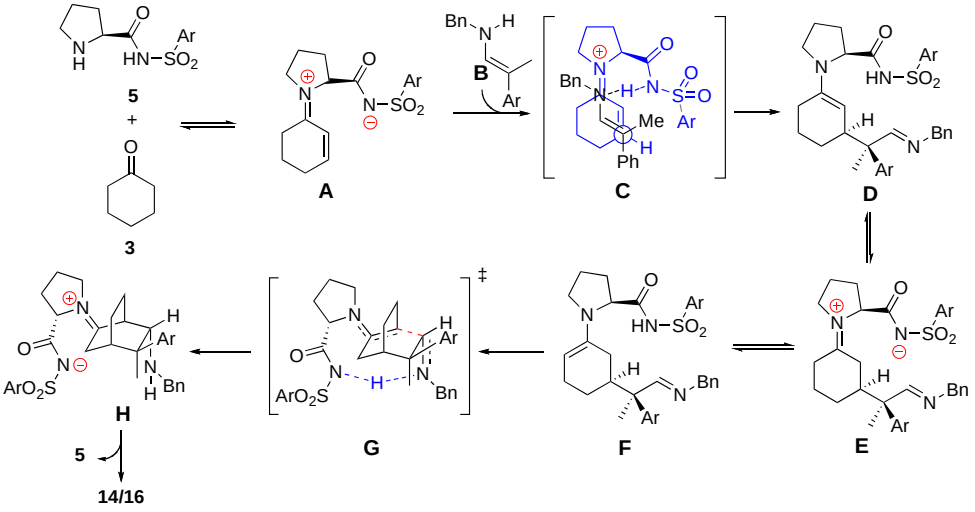
We also explored the possibility of using these new optimized conditions on α,α-dialkylsubstituted aldehydes (Scheme 3). Unfortunately, the benzyl amine derived product was formed in modestly better chemical yield but reduced diastereo- and enantioselectivity as compared to the PMP-derived example (27% yield, >20:1 dr, 95.5:4.5 er, see Scheme 1). We hope that we can address this shortcoming through modification of the catalyst structure. Such findings will be reported in due course.



Scheme 3. Exploration of alkyl,alkyl disubstituted aldehydes.

3. Discussion and conclusion

We are currently working to gain a better understanding of the controlling elements in this transformation; however, a tentative explanation for the observed stereochemical outcome is presented in Scheme 4. After formation of iminium ion **A**, we hypothesize that the enamine **B** hydrogen bonds with the sulfonamide nitrogen to preorganize the nucelophile as drawn in intermediate **C**. Conjugate addition by the enamine would establish the stereogenic quaternary center present in imine **D**. The nature of the stereochemical outcome is dependent on both the enamine geometry and facial approach of the enamine (*re* or *si*) on the β-carbon of the conjugated iminium ion. We have attempted to characterize the enamine **B** by NMR; however, spectroscopic analysis of the compound generated upon mixing benzyl amine and aldehyde **13** revealed a complex mixture—likely indicated a dynamic equilibrium is present. After interconversion between enamine **D** and enamine **F**, intramolecular Mannich cyclization could be facilitated by sulfonamide N–H activation to provide the bicyclic intermediate **H**. Finally, hydrolysis of the pyrrolidine moiety would regenerate **5** and provide the product **14/16**.



Scheme 4. Possible mechanistic explanation for [2.2.2] bicycle formation.

In summary, a rapid, multi-component coupling method has been developed for accessing all-carbon quaternary centers in a highly enantio- and diastereoselective fashion. The importance of substitution on nitrogen and on the aldehyde moiety has been demonstrated. Further applications of this technology will be reported in due course.

4. Experimental section

4.1. General

Infrared spectra were recorded neat unless otherwise indicated and are reported in cm^{-1}. ^{1}H NMR spectra were recorded in deuterated solvents and are reported in parts per million relative to tetramethylsilane and referenced internally to the residually protonated solvent. ^{13}C NMR spectra were recorded in deuterated solvents and are reported in parts per million relative to

tetramethylsilane and referenced internally to the residually protonated solvent. Chiral HPLC was performed with chiral columns [Chirapak AD, OD, OJ, AS-H columns, (Daicel Chemical Ind., Ltd.)].

Routine monitoring of reactions was performed using EM Science DC-Alufolien silica gel, aluminum-backed TLC plates. Flash chromatography was performed with the indicated eluents on EM Science Gedurian 230–400 mesh silica gel.

Air and/or moisture sensitive reactions were performed under usual inert atmosphere conditions. Reactions requiring anhydrous conditions were performed under a blanket of argon, in glassware dried in an oven at 120 °C or by flame, then cooled under argon. Dry THF and CH_2Cl_2 were obtained via a solvent purification system. All other solvents and commercially available reagents were either purified via literature procedures or used without further purification. 2-(4-Bromophenyl)-propanal **15b** and 2-(4-chlorophenyl)-propanal **15d** were prepared according to the reported procedure.[9d]

4.2. General procedure for three-component formal aza-Diels–Alder reaction with cyclohexenone (30 mol % catalyst)

The aldehyde (0.25 mmol) and amines (0.25 mmol) were dissolved in toluene (0.26 mL). After stirring at rt for 30 min, cyclohexenone (0.24 mL, 10 equiv) and sulfonamide **9** (31.7 mg, 0.75 mmol) were added to it at 4 °C or rt. After stirring for the prescribed time, reaction mixture was loaded directly onto silica gel and was purified by chromatography, eluting with 2–15% EtOAc/hexanes, to give the corresponding product.

4.3. 6-(Benzylamino)-5-methyl-5-phenyl-bicyclo[2.2.2]octan-2-one (14a)

Reaction time 3 d, 4 °C. Purified by chromatography over silica gel, eluting with 2–6% EtOAc/hexanes, to give the bicycle **14a** (57.5 mg, 72%, 93.3:6.7 er, >20:1 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 16.6 min (major) and 20.8 min (minor)] to be 93.3:6.7 er: $[\alpha]_D^{23}$ +40.1 (*c* 1.7, $CHCl_3$); IR (neat) 3330, 2949, 2867, 1718, 1495, 1457, 1113, 765, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.42 (m, 4H), 7.37 (t, *J*=7.6 Hz, 2H), 7.26–7.31 (m, 3H), 7.20 (t, *J*=7.2 Hz, 1H), 4.09 (d, *J*=13.2 Hz, 1H), 3.76 (d, *J*=13.2 Hz, 1H), 3.51 (d, *J*=2.0 Hz, 1H), 2.70–2.71 (m, 3H), 2.29 (dd, *J*=19.6, 3.2 Hz, 1H), 1.37–1.86 (m, 5H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.5, 150.3, 140.2, 128.6, 128.4, 128.3, 127.1, 125.9, 125.7, 66.1, 51.5, 46.5, 44.7, 41.2, 37.1, 25.4, 21.7, 21.2; HRMS (CI^+) calcd for $C_{22}H_{25}NO$ (M^+), 319.1936, found 319.1926.

4.4. 6-(p-Methoxyphenylamino)-5-methyl-5-phenyl-bicyclo[2.2.2]octan-2-one (14b)

Reaction time 3 d. Purified by chromatography over silica gel, eluting with 2–10% EtOAc/hexanes, to give the bicycle **14b** (40.6 mg, 53%, 98.3:1.7 er, >20:1 dr, colorless crystal). Enantiomeric excess was determined by chiral HPLC [4.6×250 mm Daicel OD column, 92:8 hexanes/*i*-PrOH, 1.0 mL min^{-1}, retention times 15.9 min (major) and 13.1 min (minor)] to be 98.3:1.7 er: mp: 138–139 °C; $[\alpha]_D^{23}$ +7.7 (*c* 1.0, $CHCl_3$); IR (neat) 3379, 2943, 1718, 1511, 1462, 1228, 1103, 1032, 819, 765, 705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J*=7.6 Hz, 2H), 7.36 (t, *J*=7.2 Hz, 2H), 7.26 (t, *J*=7.2 Hz, 1H), 6.81–6.84 (m, 2H), 6.66–6.68 (m, 2H), 4.24 (d, *J*=8.4 Hz, 1H), 3.79 (s, 3H), 3.66 (br s, 1H), 2.70–2.79 (m, 2H), 2.54 (s, 1H), 2.35 (dd, *J*=18.4, 2.0 Hz, 1H), 1.61–1.88 (m, 4H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.9, 152.7, 149.9, 140.2, 128.6, 126.2, 125.6, 115.7, 115.1, 63.4, 55.8, 47.6, 44.3, 41.2, 36.7, 25.1, 21.7, 21.1; HRMS (CI^+) calcd for $C_{22}H_{25}NO_2$ (M^+), 335.1885, found 335.1874.

4.5. 2-(4-Methylphenyl)-propanal (15a)[9c]

To a stirred solution of **19**[9b] (1.12 g, 7.71 mmol) in CH_2Cl_2 (25 mL) at −78 °C was added DIBAL-H (8.48 mL, 8.48 mmol, 1.0 M in CH_2Cl_2) dropwise. After stirring at −78 °C to rt for 3 h, the reaction was quenched with satd aq NH_4Cl (50 mL) and extracted with Et_2O (3×40 mL). The dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 0.5–1% ether/pentane, to give aldehyde **15a** (0.731 g, 4.93 mmol, 64%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 9.701–9.704 (m, 1H), 7.23 (d, *J*=8.0 Hz, 2H), 7.14 (d, *J*=8.0 Hz, 2H), 3.63 (q, *J*=6.8 Hz, 1H), 2.39 (s, 3H), 1.46 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 137.3, 134.7, 129.8, 128.2, 52.6, 21.0, 14.6.

4.6. 6-(Benzylamino)-5-methyl-5-(4-methylphenyl)-bicyclo[2.2.2]octan-2-one (16a)

Reaction time 3 d, 4 °C. Purified by chromatography over silica gel, eluting with 2–6% EtOAc/hexanes, to give the bicycle **16a** (54.2 mg, 65%, 92.2:7.8 er, >20:1 dr, colorless oil). 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 10.5 min (major) and 12.7 min (minor)] to be 92.2:7.8 er: $[\alpha]_D^{23}$ +34.2 (*c* 2.5, $CHCl_3$); IR (neat) 3341, 2943, 2867, 1718, 1457, 1113, 819, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J*=7.2 Hz, 2H), 7.37 (t, *J*=7.2 Hz, 2H), 7.29–7.32 (m, 3H), 7.10 (d, *J*=8.0 Hz, 2H), 4.09 (d, *J*=13.2 Hz, 1H), 3.76 (d, *J*=13.2 Hz, 1H), 3.50 (d, *J*=2.0 Hz, 1H), 2.64–2.71 (m, 3H), 2.26–2.38 (m, 5H), 1.46–1.86 (m, 4H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.6, 147.3, 140.2, 135.4, 129.0, 128.6, 128.4, 127.1, 125.6, 66.1, 51.5, 46.6, 44.3, 41.1, 37.2, 25.4, 21.7, 21.2, 20.9; HRMS (CI^+) calcd for $C_{23}H_{27}NO$ (M^+), 333.2093, found 333.2086.

4.7. 6-(Benzylamino)-5-(4-bromophenyl)-5-methyl-bicyclo[2.2.2]octan-2-one (16b)

The starting aldehyde **15b** was prepared in accord with literature procedure.[9d] Reaction time 5 d, 4 °C. Purified by chromatography over silica gel, eluting with 2–7% EtOAc/hexanes, to give the bicycle **16b** (51.9 mg, 52%, 94.6:5.4 er, >20:1 dr, colorless oil). 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 14.2 min (major) and 19.3 min (minor)] to be 94.6:5.4 er: $[\alpha]_D^{23}$ +34.4 (*c* 1.2, $CHCl_3$); IR (neat) 3342, 2945, 2875, 1719, 1490, 1451, 1112, 1077, 820, 727, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.42 (m, 9H), 4.08 (d, *J*=12.8 Hz, 1H), 3.74 (d, *J*=13.2 Hz, 1H), 3.40–3.41 (m, 1H), 2.62–2.73 (m, 3H), 2.30 (dd, *J*=18.4, 1.2 Hz, 1H), 1.46–1.88 (m, 5H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.1, 149.4, 139.9, 131.3, 128.6, 128.4, 127.6, 127.3, 119.7, 66.0, 51.3, 46.2, 44.5, 41.1, 37.0, 25.1, 21.6, 21.1; HRMS (CI^+) calcd for $C_{22}H_{24}ONBr$ (M^+), 397.1041, found 397.1028.

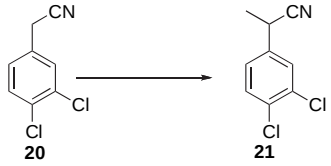
4.8. 5-Methyl-5-(4-bromophenyl)-6-(4-methoxyphenylamino)-bicyclo[2.2.2]octan-2-one (16c)

The starting aldehyde **15b** was prepared in accord with literature procedure.[9d] Reaction time 3 d, rt. Purified by chromatography over silica gel, eluting with 2–10% EtOAc/hexanes, to give the bicycle **16c** (51.9 mg, 51%, 95.4:4.6 er, >20:1 dr, colorless oil). 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 17.2 min (major) and 21.8 min (minor)] to be 95.4:4.6 er: $[\alpha]_D^{23}$ −3.0 (*c* 1.0, $CHCl_3$); IR (neat) 3370, 2949, 1715, 1513, 1233, 1007, 824, 754, 719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J*=8.8 Hz, 2H), 7.40 (d, *J*=8.8 Hz, 2H), 6.82 (d, *J*=8.8 Hz, 2H), 6.64 (d, *J*=8.8 Hz, 2H), 4.13 (d, *J*=10.0 Hz, 1H), 3.77 (s, 3H), 3.60 (d, *J*=11.2 Hz, 1H), 2.29–2.71 (m, 4H), 1.61–1.83 (m, 4H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.4, 152.9, 149.0, 139.9, 131.7, 127.5, 120.1, 115.8, 115.1,

63.5, 55.8, 47.5, 44.1, 41.1, 36.6, 24.9, 21.7, 21.1; HRMS (CI^+) calcd for $C_{22}H_{24}NO_2Br$ (M^+), 413.0990, found 413.0989.

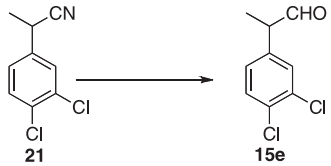
4.9. 6-(Benzylamino)-5-(4-chlorophenyl)-5-methyl-bicyclo[2.2.2]octan-2-one (16d)

The starting aldehyde **15d** was prepared in accord with literature procedure.[9d] Reaction time 3 d, 4 °C. Purified by chromatography over silica gel, eluting with 2–6% EtOAc/hexanes, to give the bicycle **16d** (61.1 mg, 69%, 94.3:5.7 er, >20:1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6×250 mm Daicel OD column, 92:8 hexanes/*i*-PrOH, 1.0 mL min^{-1}, retention times 11.7 min (major) and 15.4 min (minor)] to be 94.3:5.7 er: $[\alpha]_D^{23}$ +44.8 (*c* 1.5, $CHCl_3$); IR (neat) 3324, 2943, 1718, 1484, 1451, 1092, 1010, 825, 732, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.43 (m, 7H), 7.23 (d, *J*=8.8 Hz, 2H), 4.09 (d, *J*=12.8 Hz, 1H), 3.74 (d, *J*=13.2 Hz, 1H), 3.40 (d, *J*=2.0 Hz, 1H), 2.62–2.73 (m, 3H), 2.30 (d, *J*=18.4 Hz, 1H), 1.52–1.89 (m, 5H), 1.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.1, 148.8, 139.9, 131.6, 129.1, 128.6, 128.4, 128.3, 127.2, 66.0, 51.3, 46.3, 44.4, 41.1, 37.0, 25.2, 21.6, 21.1; HRMS (CI^+) calcd for $C_{22}H_{24}NOCl$ (M^+), 353.1546, found 353.1536.



4.10. 2-(3,4-Dichlorophenyl)-propionitrile (21)[10]

To a stirred solution of nitrile **20** (1.86 g, 10 mmol) in THF (50 mL) at −78 °C was added LiHMDS (10 mL, 10 mmol, 1.0 M in THF) dropwise. After 1 h, a solution of iodomethane (1.42 g, 0.63 mL, 10 mmol) was added dropwise to the reaction solution at −78 °C. After stirring at −78 °C for 1 h and then at rt for 2 h, the reaction mixture was removed from the cooling bath, quenched with water (40 mL) and extracted with Et_2O (3×30 mL). The dried (Na_2SO_4) extract was concentrated in vacuo and purified chromatography over silica gel, eluting with 1–4% Ether/hexanes, to give nitrile **21** (1.62 g, 8.10 mmol, 81%) as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) 7.49–7.51 (m, 2H), 7.24 (dd, *J*=8.4, 2.0 Hz, 1H), 3.90 (q, *J*=7.2 Hz, 1H), 1.67 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 133.4, 132.5, 131.2, 128.9, 126.1, 120.5, 30.5, 21.2.

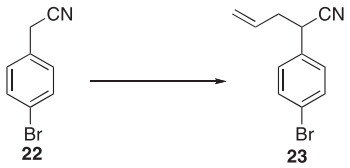


4.11. 2-(3,4-Dichlorophenyl)-propanal (15e)

To a stirred solution of **21** (1.62 g, 8.11 mmol) in CH_2Cl_2 (16 mL) at −78 °C was added DIBAL-H (8.92 mL, 8.92 mmol, 1.0 M in CH_2Cl_2) dropwise. After stirring at −78 °C for 2 h, the reaction mixture was warmed to rt. After 8 h, the reaction was quenched with satd aq NH_4Cl (20 mL) and extracted with Et_2O (3×30 mL). The dried (Na_2SO_4) extract was concentrated in vacuo and purified chromatography over silica gel, eluting with 0.5–2% ether/pentane, to give aldehyde **15e** (1.23 g, 7.04 mmol, 87%) as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) 9.68 (d, *J*=1.2 Hz, 1H), 7.46 (d, *J*=8.4 Hz, 1H), 7.33 (d, *J*=2.0 Hz, 1H), 7.07 (dd, *J*=8.4, 2.0 Hz, 1H), 3.63 (qd, *J*=7.2, 1.2 Hz, 1H), 1.46 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 137.9, 133.1, 131.8, 130.9, 130.3, 127.6, 52.0, 14.0.

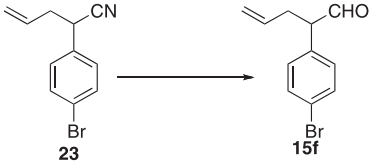
4.12. 6-(Benzylamino)-5-(3,4-dichlorophenyl)-5-methyl-bicyclo[2.2.2]octan-2-one (16e)

Reaction time 5 d, 4 °C. Purified by chromatography over silica gel, eluting with 2–20% EtOAc/hexanes, to give the bicycle **16e** (51.5 mg, 53%, 95.8:4.2 er, >20:1 dr, colorless oil). 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 15.9 min (major) and 23.2 min (minor)] to be 95.8:4.2 er: $[\alpha]_D^{23}$ +26.4 (*c* 0.7, $CHCl_3$); IR (neat) 3341, 2949, 1718, 1473, 1457, 1135, 1026, 819, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.27–7.41 (m, 6H), 7.21 (d, *J*=8.4 Hz, 1H), 4.07 (d, *J*=12.8 Hz, 1H), 3.74 (d, *J*=12.8 Hz, 1H), 3.33 (br s, 1H), 2.59–2.74 (m, 3H), 2.29 (d, *J*=18.4 Hz, 1H), 1.49–1.90 (m, 6H), 1.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.7, 150.7, 139.6, 132.3, 130.1, 129.8, 128.7, 128.5, 128.2, 127.3, 125.2, 65.9, 51.2, 45.9, 44.5, 41.0, 36.9, 25.0, 21.6, 21.1; HRMS (CI^+) calcd for $C_{22}H_{23}NOCl_2$ (M^+), 387.1157, found 387.1152.



4.13. 4-Bromo-α-2-propen-1-yl-benzeneacetonitrile (23)[10]

To a stirred solution of nitrile **22** (1.96 g, 10 mmol) in THF (50 mL) at −78 °C was added LiHMDS (10 mL, 10 mmol, 1.0 M in THF) dropwise. After 1 h, a solution of allyl bromide (1.21 g, 0.866 mL, 10 mmol) was added dropwise to the reaction solution at −78 °C. After stirring at −78 °C for 1 h, the reaction mixture was removed from the cooling bath, quenched with water (50 mL), and extracted with Et_2O (2×50 mL). The dried (Na_2SO_4) extract was concentrated in vacuo and purified chromatography over silica gel, eluting with 1–5% ether/hexanes, to give nitrile **23** (2.12 g, 8.98 mmol, 90%) as a colorless oil; IR (neat) 3085, 2987, 2241, 1489, 1408, 1075, 1010, 923, 814 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.50–7.53 (m, 2H), 7.21–7.24 (m, 2H), 5.73–5.81 (m, 1H), 5.16–5.21 (m, 2H), 3.85 (d, *J*=7.2 Hz, 1H), 2.56–2.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3, 132.22, 132.17, 129.1, 122.2, 119.9, 119.8, 39.6, 37.0.



4.14. 4-Bromo-α-2-propen-1-yl-benzeneacetaldehyde (15f)

To a stirred solution of **23** (1.11 g, 4.70 mmol) in CH_2Cl_2 (14 mL) at −78 °C was added DIBAL-H (5.17 mL, 5.17 mmol, 1.0 M in CH_2Cl_2) dropwise. After stirring at −78 °C to rt for 3 h, the reaction mixture was quenched with satd aq NH_4Cl (20 mL) and extracted with Et_2O (3×30 mL). The dried (Na_2SO_4) extract was concentrated in vacuo and purified chromatography over silica gel, eluting with 1–5% Ether/pentane, to give aldehyde **15e** (0.890 g, 3.72 mmol, 79%) as a light yellow oil; IR (neat) 3248, 2922, 1723, 1680, 1582, 1489, 1075, 1010, 917, 825, 721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 9.68 (d, *J*=2.0 Hz, 1H), 7.49–7.54 (m, 2H), 7.06–7.12 (m, 2H), 5.63–5.75 (m, 1H), 5.00–5.10 (m, 2H), 3.58–3.63 (m, 1H), 2.46–2.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 134.7, 134.4, 132.2, 130.6, 121.8, 117.6, 94.9, 58.1, 33.9; HRMS (EI+) calcd for $C_{11}H_{11}OBr$ (M^+), 237.9993, found 237.9985.

4.15. 5-Allyl-5-(4-bromophenyl)-6-(4-methoxyphenylamino)-bicyclo[2.2.2]octan-2-one (16f)

Reaction time 3 d, rt. Purified by chromatography over silica gel, eluting with 2–15% EtOAc/hexanes, to give the bicycle **16f** (34.6 mg, 31%, 90.6:9.4 er, >20:1 dr, colorless crystal). Enantiomeric excess was determined by chiral HPLC [4.6×250 mm Daicel AD column, 99:1 hexanes/*i*-PrOH, 0.8 mL min^{-1}, retention times 60.9 min (major) and 55.7 min (minor)] to be 90.6:9.4 er: mp: 68–69 °C; $[\alpha]_D^{23}$ +3.4 (*c* 1.0, $CHCl_3$); IR (neat) 3363, 2949, 1718, 1598, 1506, 1446, 1228, 1043, 863, 814, 727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J*=8.7 Hz, 2H), 7.41 (d, *J*=8.7 Hz, 2H), 6.82 (d, *J*=8.7 Hz, 2H), 6.67 (d, *J*=9.0 Hz, 2H), 5.31–5.38 (m, 1H), 4.96–5.00 (m, 2H), 4.07 (d, *J*=12.6 Hz, 1H), 3.84 (s, 3H), 3.62 (d, *J*=12.6 Hz, 1H), 2.28–2.76 (m, 6H), 1.75–1.90 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.4, 153.2, 146.6, 140.0, 133.4, 131.4, 128.5, 120.3, 118.1, 116.3, 115.2, 65.9, 55.8, 47.8, 46.5, 40.5, 40.4, 32.1, 22.0, 20.8; HRMS (CI$^+$) calcd for $C_{24}H_{26}NO_2Br$ (M$^+$), 439.1147, found 439.1139.

4.16. 5-Allyl-6-(benzylamino)-5-(4-bromophenyl)-bicyclo[2.2.2]octan-2-one (16g)

Reaction time 6 d, rt. Purified by chromatography over silica gel, eluting with 2–8% EtOAc/hexanes, to give the bicycle **16g** (48.8 mg, 46%, 88.0:12.0 er, >20:1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6×250 mm Daicel AS-H column, 96:4 hexanes/*i*-PrOH, 1.0 mL min^{-1}, retention times 31.8 min (major) and 15.1 min (minor)] to be 88.0:12.0 er: $[\alpha]_D^{23}$ +48.6 (*c* 1.8, $CHCl_3$); IR (neat) 3327, 2945, 1719, 1486, 1455, 1112, 1007, 910, 863, 735, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.43 (m, 9H), 5.27–5.37 (m, 1H), 4.89–4.93 (m, 2H), 4.09 (d, *J*=12.8 Hz, 1H), 3.71 (d, *J*=12.8 Hz, 1H), 3.32 (d, *J*=2.0 Hz, 1H), 2.53–2.71 (m, 4H), 2.22–2.29 (m, 2H), 1.40–1.92 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.1, 147.0, 139.8, 134.1, 130.9, 128.64, 128.59, 128.46, 127.3, 119.9, 117.6, 68.5, 51.7, 47.0, 46.5, 40.44, 40.35, 32.1, 21.8, 20.9; HRMS (CI$^+$) calcd for $C_{24}H_{26}BrNO$ (M$^+$), 423.1198, found 423.1217.

4.17. 6-(Allylamino)-5-methyl-5-phenyl-bicyclo[2.2.2]octan-2-one (16h)

Reaction time 3 d, rt. Purified by chromatography over silica gel, eluting with 2–7% EtOAc/hexanes, to give the bicycle **16h** (44.6 mg, 66%, 88.8:11.2 er, >20:1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6×250 mm Daicel OD column, 98:2 hexanes/*i*-PrOH, 0.8 mL min^{-1}, retention times 14.5 min (major) and 16.1 min (minor)] to be 88.8:11.2 er: $[\alpha]_D^{23}$ −9.5 (*c* 1.5, $CHCl_3$); IR (neat) 3330, 2949, 1718, 1440, 1233, 1108, 923, 754, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J*=7.6 Hz, 2H), 7.35 (t, *J*=7.6 Hz, 2H), 7.23 (t, *J*=7.2 Hz, 1H), 5.94–6.04 (m, 1H), 5.24 (d, *J*=17.2 Hz, 1H), 5.14 (d, *J*=10.0 Hz, 1H), 3.53 (dd, *J*=13.6, 5.6 Hz, 1H), 3.49 (d, *J*=1.6 Hz, 1H), 3.25 (dd, *J*=13.6, 6.0 Hz, 1H), 2.59–2.69 (m, 3H), 2.27 (dd, *J*=19.6, 2.8 Hz, 1H), 1.40–1.83 (m, 5H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.6, 150.3, 136.9, 128.4, 125.9, 125.7, 116.3, 66.1, 50.1, 46.5, 44.5, 41.2, 37.1, 25.2, 21.6, 21.2; HRMS (CI$^+$) calcd for $C_{18}H_{24}NO$ (M$^+$1), 270.1858, found 270.1849.

4.18. 5-Methyl-5-phenyl-6-(propargylamino)-bicyclo[2.2.2]octan-2-one (16i)

Reaction time 3 d, rt. Purified by chromatography over silica gel, eluting with 2–8% EtOAc/hexanes, to give the bicycle **16i** (42.2 mg, 63%, 92.8:7.2 er, >20:1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6×250 mm Daicel AD column, 98:2 hexanes/*i*-PrOH, 1.0 mL min^{-1}, retention times 16.3 min (major) and 19.6 min (minor)] to be 86% er: $[\alpha]_D^{23}$ −29.2 (*c* 1.4, $CHCl_3$); IR (neat) 2943, 2878, 1718, 1113, 765, 705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J*=7.6 Hz, 2H), 7.36 (t, *J*=7.6 Hz, 2H), 7.23 (t, *J*=7.2 Hz, 1H), 3.81 (d, *J*=2.0 Hz, 1H), 3.60 (qd, *J*=17.2, 2.4 Hz, 2H), 2.67–2.71 (m, 2H), 2.57–2.58 (m, 1H), 2.24–2.31 (m, 2H), 1.54–1.83 (m, 5H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.2, 149.9, 128.4, 126.0, 125.8, 81.7, 72.0, 64.1, 46.0, 44.2, 41.1, 37.6, 35.6, 25.6, 21.28, 21.26; HRMS (CI$^+$) calcd for $C_{18}H_{21}NO$ (M$^+$), 267.1623, found 267.1621.

4.19. 6-(Benzylamino)-5-(4-isopropylbenzyl)-5-methyl-bicyclo[2.2.2]octan-2-one (18)

Reaction time 7 d, 4 °C. Purified by chromatography over silica gel, eluting with 2–10% EtOAc/hexanes, to give the bicycle **18** (36.6 mg, 39%, 88.3:11.7 er, 9:1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6×250 mm Daicel AD column, 99:1 Hexanes/*i*-PrOH, 1.0 mL min^{-1}, retention times 14.0 min (major) and 10.9 min (minor)] to be 88.3:11.7 er: $[\alpha]_D^{23}$ =−20.5° (*c*= 2.5, $CHCl_3$); IR (neat) 3341, 2960, 2927, 1713, 1451, 1112, 825, 738, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.34 (m, 4H), 7.17 (d, *J*=8.0 Hz, 2H), 7.10 (d, *J*=8.0 Hz, 2H), 3.90 (d, *J*=13.2 Hz, 1H), 3.57 (d, *J*=13.2 Hz, 1H), 2.92 (p, *J*=6.8 Hz, 1H) 2.86 (d, *J*=2.0 Hz, 1H), 2.79 (d, *J*=13.2 Hz, 1H), 2.72 (d, *J*=13.2 Hz, 1H), 2.58 (q, *J*=2.4 Hz, 1H), 2.48 (dt, *J*=18.8, 3.2 Hz, 1H), 2.23–2.31 (m, 1H), 2.09 (dd, *J*=18.8, 1.6 Hz, 1H), 1.88–1.93 (m, 3H), 1.64–1.69 (m, 1H), 1.28 (d, *J*=6.8 Hz, 6H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.8, 146.8, 140.3, 135.6, 130.4, 128.27, 128.23, 126.9, 126.0, 66.9, 51.7, 47.1, 46.0, 41.9, 40.6, 36.8, 33.7, 24.1, 21.9, 20.9, 19.4; HRMS (CI$^+$) calcd. for $C_{26}H_{34}NO$ (M+1), 376.2640 found 376.2644.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.01.094.

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