Proline sulfonamide-catalyzed, domino process for asymmetric synthesis of amine- and alcohol-containing bicyclo[2.2.2]octanes

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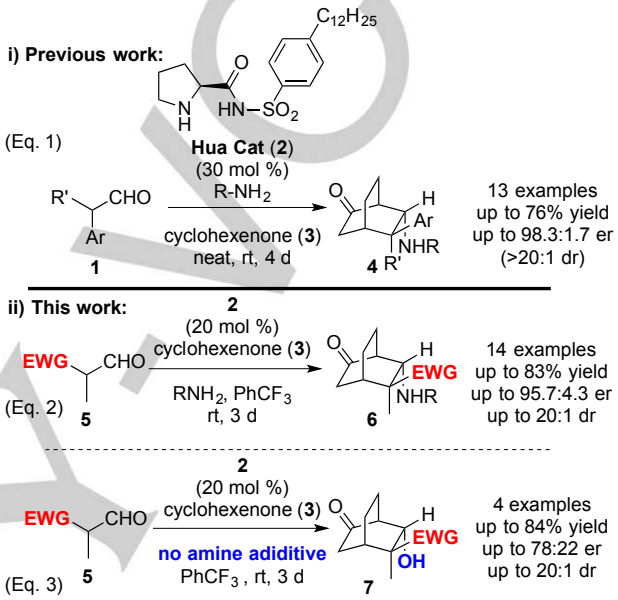
Dedication ((optional))

Abstract: A generalized method for accessing highly functionalized amine-containing bicyclo[2.2.2]octanes via *p*-dodecylphenylsulfonamide catalyst in a good enantio- and diasteroselective fashion has been developed. A discussion of the mechanistic underpinnings of this transformation is presented. Finally, an unexpected discovery enabling the extension of this protocol to the synthesis of alcohol-containing bicyclo[2.2.2]octanes with encouraging levels of stereoselectivity is discussed.

Introduction

Over the past fifteen plus years, a rapid increase in the level of interest in chemical transformations catalyzed by simple organic molecules has transformed the field of asymmetric catalysis.[1] The building blocks from these transformations have proven widely useful in organic synthesis [2] and in the pharmaceutical industry.[3] Our laboratory has been particularly interested in the use of proline sulfonamides in concert with enamines, derived from aldehydes and amine additives, as bi-functional catalysts to facilitate transformations not readily accessible through other reaction pathways.[4] Moreau and co-workers have recently published an detailed review on the reactivity of α,α-disubstituted aldehydes through enamine activation.[5,6] One of our early successes in this area was the development of a proline sulfonamide-catalyzed process for the enantioselective synthesis of [2.2.2] all-carbon bicycles (Scheme 1, Eq. 1).[7] This reaction, while useful, was limited at the time to benzylic aldehydes. We had hoped to extend this transformation to include more readily derivatizable moieties to broaden the utility of these products. The ideal functional handle for this "universal" building block would be a carbonyl moiety – as it can be easily converted into a wide range of different functional groups. In this full paper, we disclose the successful execution of this strategy for accessing [2.2.2] all-carbon bicycles in good levels of stereoselectivity and chemical yield (Scheme 1, Eqs. 2-3).



Scheme 1. i) Prior benzylic aldehyde series in [2.2.2] bicycle-forming reaction. ii) Aldehydes containing a β-electron withdrawing group in the [2.2.2] bicycle-forming reaction.

Results and Discussion

The optimization of this transformation is described in Table 1. The starting 2-methyl-3-oxopropanoate *t*-butyl ester (**5a**) has been previously prepared by hydroformylation.[8] We first screened our previously employed conditions[7] with a slightly lower catalyst loading and were pleased to see encouraging levels of diastereoselectivity and chemical yield (Entry 1). The relative configuration of the transformation was established by 2D NMR (Figure 1). We were somewhat surprised to find that the relationship between the ester and the ethylene bridge was *syn*; however, this stereochemical outcome was consistent with the prior benzylic aldehyde series[7] (Scheme 1, Eq. 1). While this result (Entry a) was encouraging, the enantiomeric ratio was less than ideal. We next screened a series of solvents [dioxane, 1,2-dichloroethane (DCE), toluene and trifluorotoluene]. Dioxane gave good diastereoselectivity and some improvement in the enantiomeric ratio; however, a reduced level of chemical yield was observed (Entry b). While DCE has proven to be an excellent solvent for many of our proline sulfonamide-catalyzed reactions,[4] it did not perform well in this transformation (Entry c). Toluene and trifluorotoluene both proved to be excellent solvents for this process with trifluorotoluene providing slightly better chemical yield (Entries d-e). In accord with what was

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previously observed,[7] addition of molecular sieves to the reaction led to reduced chemical efficiency (Entry f).

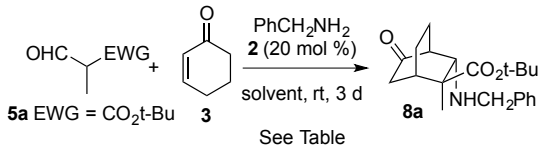


Table 1. Optimization conditions.

Entry	Solvent	dr[a]	er (%)[b]	Yield
a	Neat	11:1	75.5:24.5	71
b	Dioxane	8:1	81.0:19.0	53
c	DCE	6:1	71.0:29.0	82
d	Toluene	10:1	86.5:13.5	72
e	**$PhCF_3$**	**9:1**	**86.7:13.3**	**80**
f[c]	$PhCF_3$	6:1	82.8:17.2	67

[a] Diastereomeric ratio (dr) determined by 1H NMR of crude reaction mixture. [b] Enantiomeric ratio (er) of major diastereomer determined by chiral HPLC analysis. [c] Performed using powdered 4 Å molecular sieves.

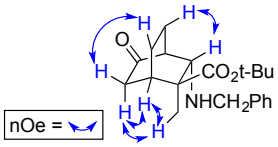
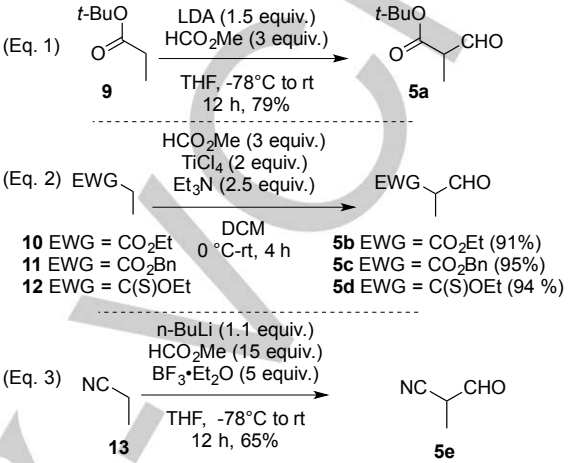


Figure 1. Key nOe Data for Establishment of Stereochemistry in Compound **8a**.

With the optimized conditions in hand, we looked to the chemical literature for the variety of known aldehydes with a β-electron withdrawing group. Surprisingly, only some of the key necessary aldehydes were known compounds.[8,9] Additionally, limited practical experimental procedures were available for known aldehydes. Given the potential utility of these building blocks, we were surprised to find this lack of systematic development in this area. One likely reason might be the potential instability of these types of aldehydes.

Consequently, we next set out to develop a systematic method for preparing the required aldehydes to address this void in the chemical literature (Scheme 2). As discussed earlier, the *t*-butyl ester aldehyde **5a** can be prepared via hydroformylation with syn gas (H_2, CO);[8] however, these conditions are not typically as practical in a laboratory setting. It would appear more convenient to start with the enolate derived from *t*-butyl propionate and quench with a suitable electrophile (e.g., methyl formate). We were pleased to find that this concept works well on a wide range of enolates. We did find that the most effective method for generating the enolate varied somewhat by substrate. For the *t*-butyl ester series, the use of LDA proved ideal (Eq. 1).

In contrast, for the ethyl ester, benzyl ester and ethyl thioester, the use of titanium tetrachloride and triethylamine gave superior results (Eq. 2). Tius and co-workers had reported a closely related example for the ethyl ester series.[10] Finally, for the cyano series, use of butyl lithium proved most effective (Eq. 3).[11]



Scheme 2. General Synthesis of Aldehydes.

With a reliable method to synthesize such aldehydes, we explored the impact of varying the electron-withdrawing group on the aldehyde component (Table 2). Entry a shows our optimized results with the *t*-butyl series. Interestingly, variation in the substituent on the ester from *t*-butyl to ethyl proved problematic as the product **8b** was unstable when analyzed by HPLC (Entry b). This instability inhibited our ability to ascertain the enantioselectivity on this substrate. Only the ethyl ester appeared to suffer from this phenomenon as the benzyl ester was stable to HPLC purification (Entry c). Unfortunately, the benzyl ester resulted in a drop in both chemical yield and stereoselectivity (Entry c). We were pleased to see that a thioester gave high levels of diasteroselectivity and good chemical yield; however, this substitution induced a significant negative impact on the enantioselectivity (Entry d). Finally, cyano aldehyde **5e** produced the desired product in high chemical yield (87%), but in low diastereoselectivity (3:1 dr) (Entry e). We were able to confirm the stereochemistry of the major diastereomer **8e** through X-ray crystallographic analysis (Figure 2).[12]

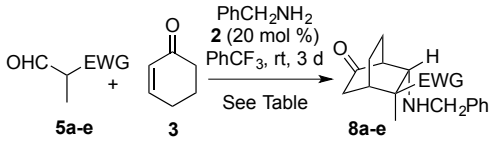


Table 2. Effect of Varying Electron Withdrawing Groups.

Entry	EWG	dr[a]	er (%)[b]	Yield
a	CO_2tBu	9:1	86.7:13.3	80

b	CO_2Et	9:1	nd[c]	79
c	CO_2CH_2Ph	6:1	83.1:16.9	53
d	COSEt	20:1	71.6:28.4	64
e	CN	3:1	88.9:11.1	87[d]

[a] Diastereomeric ratio (dr) determined by 1H NMR of crude reaction mixture. [b] Enantiomeric ratio (er) of major diastereomer determined by chiral HPLC analysis. [c] Compound proved unstable on HPLC purification. [d] Overall yield reported for mixture of diastereomers. Isolated yield for major diastereomer is 68%.

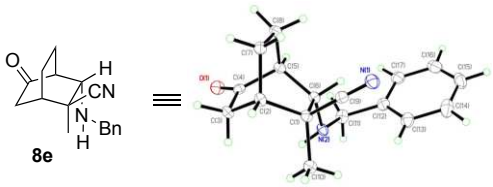


Figure 2. ORTEP Representation of X-ray crystallographic data for compound **8e**.

We next explored the impact of the amine and its interplay with the electron withdrawing group on the aldehydes **5** (Table 3). On the ethyl ester series **5b**, we screened aniline, *p*-methoxy-aniline, 3,5-trifluoromethylbenzylamine and allylamine. Both aniline and *p*-methyoxyaniline provided excellent diastereoselectivity and high levels of enantioselectivity; however, the yields were significantly reduced (Entries a-b). We previously observed a similar phenomenon with other imines/enamines derived from anilines.[7] The stereochemistry of product **6a** was unequivocally established by X-ray crystallographic analysis.[13] Use of a more sterically hindered benzylamine derivative gave similar levels of stereoselectivity to the parent benzylamine series (Entry c); however, the yield was reduced, likely due to the added steric requirements. Allylamine gave reduced diastereoselectivity, but higher chemical yield (Entry d). A similar trend was observed for the *t*-butyl ester series (Entries e-g). We were particularly pleased to see the high stereoselectivity and chemical yield with the *t*-butyl ester and the 3,5-bistrifluoromethylbenzylamine (Entry g).

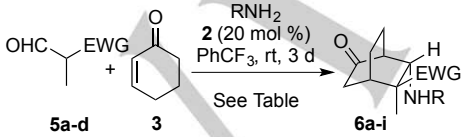


Table 3. Effect of Primary Amine on the [2.2.2] Bicycle Formation.

Entry	EWG	R	dr[a]	er (%)[b]	Yield
a	CO_2Et	Ph-	20:1	73.9:26.1	32
b	CO_2Et	*p*-$MeOC_6H_4$-	20:1	94.3:5.7	50
c	CO_2Et	(3,5-CF_3)$C_6H_3CH_2$-	11:1	88.2:12.8	53
d	CO_2Et	CH_2=$CHCH_2$-	6:1	nd[c]	81
e	CO_2t-Bu	Ph-	20:1	95.7:4.3	30
f	CO_2t-Bu	*p*-$MeOC_6H_4$-	20:1	89.3:10.7	66
g	CO_2t-Bu	(3,5-CF_3)$C_6H_3CH_2$-	12:1	90.3:9.7	83
h	C(O)SEt	*p*-$MeOC_6H_4$-	20:1	83.6:16.4	34
i	CO_2CH_2Ph	CH_2=$CHCH_2$-	6:1	83.2:16.8	57

[a] Diastereomeric ratio (dr) determined by ^{1}H NMR of crude reaction mixture. [b] Enantiomeric ratio (er) determined by chiral HPLC analysis of major diastereomer. [c] Compound proved unstable on HPLC purification

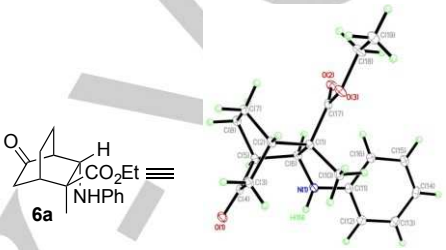
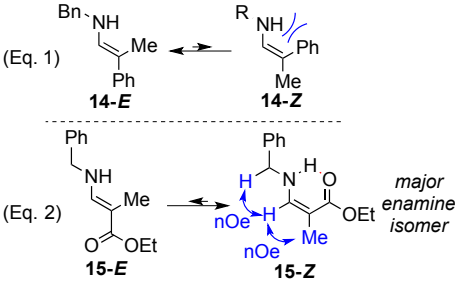


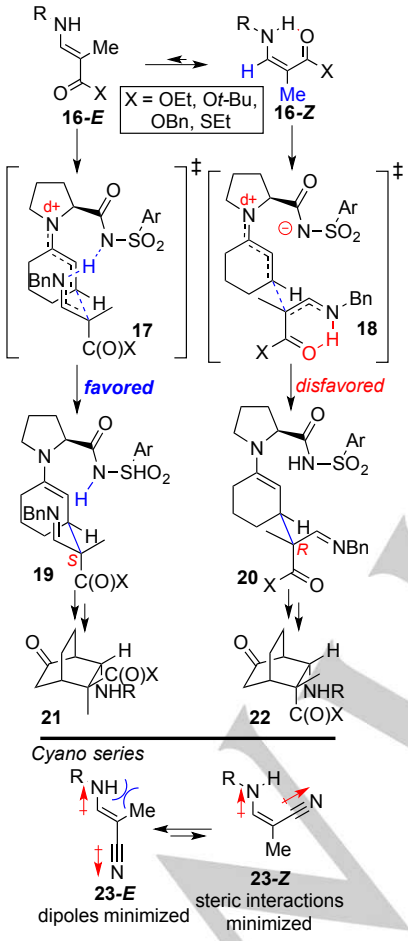
Figure 3. ORTEP Representation of X-ray crystallographic data for compound **6a**.

In order to better understand the stereochemical outcome of this transformation, we explored the nature of the enamine by the premixing of benzylamine with the aldehyde (Scheme 3). Unlike in the benzylic aldehyde series (Scheme 1, Eq. 1) where steric components likely served as the primary controlling elements favoring the enamine **14-*E***, this more elaborate enamine **15** contains a hydrogen bond acceptor, which could disrupt the steric-guided selectivity between the two olefin isomers. ^{1}H NMR analysis of the product from premixing ethyl 2-methyl-3-oxopropanoate (**5b**) with benzylamine showed that the major enamine product was the expected **15-*Z*** enamine. The strong hydrogen bonding interaction between the amine N-H and the electron withdrawing group on **5b** likely guides the formation of **15-*Z*** as the major geometric isomer.



Scheme 3. Impacts of Substituents on the Enamine Geometry.

A possible model for the observed stereochemical outcome from these enamines is shown in Scheme 4. As the *Z* enamine geometry has been shown to be thermodynamically preferred by 2D NMR analysis (Scheme 3), the *E* enamine appears to be more reactive in the Michael addition step – likely due to the availability of the amine N-H to undergo the critical hydrogen bonding interaction **17** with the sulfonamide (Scheme 4). In contrast, the sequestration of the N-H hydrogen bond by the electron withdrawing group in **15-*Z*** disfavors transition state **18**, leading to preferential formation of the Michael product **19**. Imine **19** subsequently undergoes an intramolecular Mannich cyclization to ultimately arrive at the [2.2.2] bicycle **21**. Furthermore, the lower stereoselectivity for nitrile **23** is consistent with the interplay between the reduced steric demands of a nitrile vs. methyl moiety (which would favor the enamine **23-*Z***) and the minimization of the dipoles present in the structure (which would favor the *E* enamine **23-*E***). It is important to note that cyano moiety is incapable of undergoing the intramolecular hydrogen bond interaction with the enamine N-H due to the sp-hybridized nature of the nitrile.



Scheme 4. Possible Explanation for the Stereochemical Outcome.

Through our scope exploration process on the ethyl ester series, we discovered that omission of the amine component still provided a bicyclic product – now containing a 2° alcohol substituent in place of the amine component (Table 4). To our knowledge, these are the first reported examples of this type of reactivity with aldehydes bearing a β-electron withdrawing group.[14] The relative stereochemistry is assigned based on detailed NOESY analysis of **7c**. Interestingly, this transformation does not proceed on parent *t*-butyl ester (Entry b). One plausible explanation could be the more sterically congested *t*-butyl ester moiety inhibits the required transition state for the initial Michael addition. In contrast, the ethyl ester moiety **5a** gave excellent chemical yield (84%) with high diastereoselectivity (12:1 dr), but low levels of enantioselectivity (60.3:39.7 er) (Entry a). The benzyl ester gave excellent chemical yield but low levels of diastereoselectivity (Entry c). The stereochemical assignment of bicycles 7c and 7c' was determined by 2D NMR and key nOe correlations are shown in Figure 4. The enantiomeric ratio for the benzyl ester series was 65.8:34.2. The thioester gave dramatically reduced levels of diastereoselectivity (3:1 dr) which were inseparable and prevented determination of enantioselectivity (Entry d). The most promising substrate for this reaction appeared to be the cyano compound **5e** as it provided >20:1 diastereoselectivity and acceptable overall yield (62%) with encouraging levels of enantioselectivity (78.1:21.9 er) (Entry e). Given the optimum results with the sterically unhindered nitrile **5e** and the lack of reaction for the *t*-butyl ester series, it appears likely that the steric component on the aldehyde combined with the availability of enol OH for hydrogen bonding regulates the stereoselectivity of this process. That said, we are unsure of a working model to fully rationalize these early, empirical results at this juncture.

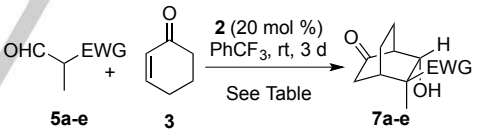


Table 4. Synthesis of Hydroxy-[2.2.2] Bicycles.

Entry	EWG	dr[a]	er (%)	Yield
a	CO_2Et	12:1	60.3:39.7[b]	84
b	CO_2t-Bu	-	-	0
c	CO_2CH_2Ph	3:1	65.8:34.2	88
d[c]	C(O)SEt	3:1	nd	79
e	CN	>20:1	78.1:21.9[b]	62

[a] Diastereomeric ratio (dr) determined by 1H NMR of crude reaction mixture. [b] Enantiomeric ratio (er) determined ^{1}H NMR using Mosher ester derivatization. [c] The diastereomers were inseparable by column chromatography.

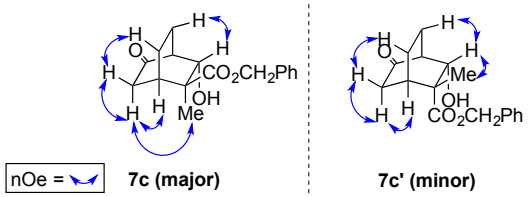


Figure 4. Key nOe Data for Establishment of Stereochemistry in Compounds **7c** and **7c'**.

Conclusions

In conclusion, we have developed a general approach for the enantioselective construction of densely functionalized, [2.2.2] all-carbon bicycles via a proline sulfonamide-catalyzed transformation. Reasonable tolerance for both the nucleophilic (aldehyde) component and amine additive has been demonstrated. The first systematic, non-carbonylative method for preparing the starting aldehydes **5a-e** has been reported which should prove generally useful. Finally, an unexpected, non-amine-mediated pathway has been unearthed that provides encouraging levels of enantioselectivity for accessing bicyclic alcohols **7a-e**. Further exploration of this methodology will be reported in due course.

Experimental Section

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

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 DCM 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.

Aldehyde 5a. To a stirred solution of *tert*-butyl propionate (2.5 g, 2.9 mL, 19.0 mmol) in THF (20 mL) at -78 °C was added solution of LDA[15] (4.1 mL, 1.0 M solution in THF/hexanes). After 30 min, methyl formate (3.4 g, 3.5 mL, 57.0 mmol) was added. After an additional 30 min, the mixture was warmed to room temperature. After 12 h, the reaction was quenched with cold water (20 mL) and extracted with ethyl acetate (3 X 15 mL). The remaining aqueous layer was acidified with aq. HCl (10 %) until pH = 4 and extracted with diethyl ether (3 X 15 mL). The dried ($NaSO_4$) extract was concentrated *in vacuo* purified by chromatography over silica gel, eluting with 10-90% EtOAc in hexanes to give known **5a**[8] (2.35 g, 14.9 mmol, 79 %) as a colorless oil which exists as a mixture of the keto and enol forms. ^1H NMR (700 MHz, $CDCl_3$) δ 11.42 (d, *J* = 11.9 Hz, 1 H), 9.75 (d, *J* = 1.3 Hz, 1 H), 6.95 (dd, *J* = 12.3, 0.9 Hz, 1 H), 3.27 - 3.31 (m, 1 H), 1.61 (d, *J* = 0.9 Hz, 3 H), 1.50 (s, 9 H), 1.48 (s, 9 H), 1.29 (d, *J* = 7.5 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 198.0, 172.5, 169.1, 159.6, 101.6, 82.5, 81.4, 53.7, 28.4, 28.2, 13.0, 10.4.

General procedure for aldehydes 5b-d: To a stirring solution of the propionate derivative **12-14** (5.0 mmol), methyl formate (0.90 g, 0.92 mL, 15.0 mmol) in CH_2Cl_2 (5 mL) under argon at 0 °C was added freshly distilled $TiCl_4$ (1.89 g, 1.09 mL, 10.0 mmol) dropwise. After 30 min, freshly distilled Et_3N (1.26 g, 1.73 mL, 12.5 mmol) was added dropwise. After 1 h, the reaction mixture was allowed to warm to rt over a period of 3 h. Next, the reaction was quenched with water (15 mL) and extracted with CH_2Cl_2 (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* purified by chromatography over silica gel, eluting with 100 % CH_2Cl_2 to give the aldehyde **5b-5d** as a colorless oil which exists as a mixture of the keto and enol forms.

Ethyl ester aldehyde 5b.[10] (591 mg, 4.55 mmol, 91 %,); ^1H NMR (700 MHz, $CDCl_3$) δ 11.32 (d, *J* = 12.3 Hz, 1 H), 9.78 (d, *J* = 1.3 Hz, 1 H), 6.99 (dd, *J* = 12.3, 0.9 Hz, 1 H), 4.24 (q, *J* = 7.0 Hz, 5 H), 3.38 (qd, *J* = 7.2, 1.3 Hz, 1 H), 1.67 (d, *J* = 0.9 Hz, 4 H), 1.28 - 1.36 (m, 14 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 197.4, 172.7, 170.0, 160.2, 100.4, 61.7, 60.5, 52.8, 14.4, 14.3, 12.6, 10.4.

Benzyl ester aldehyde 5c. (907 mg, 4.72 mmol, 95 %); ^1H NMR (700 MHz, CDCl3) δ 11.32 (dd, *J* = 9.7, 2.6 Hz, 3 H), 9.81 (s, 1 H), 7.33 - 7.42 (m, 20 H), 7.04 (d, *J* = 12.8 Hz, 3 H), 5.26 (s, 6 H), 5.24 (s, 2 H), 3.46 (q, *J* =7.2 Hz, 1 H), 1.74 (s, 9 H), 1.39 (d, *J* =7.0 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 197.2, 172.3, 169.7, 160.6, 135.9, 135.3, 128.7, 128.6, 128.5, 128.30,128.25, 127.9, 100.1, 67.2,66.0, 52.6, 12.4, 10.2.

Thioester aldehyde 5d. (683 mg, 4.68 mmol, 94 %); ^1H NMR (700 MHz, CDCl3) δ 12.19 (d, *J* = 11.9 Hz, 1 H), 9.71 (d, *J* = 1.3 Hz, 1 H), 6.88 (dd, *J* = 11.9, 0.9 Hz, 1 H), 3.58 (qd, *J* = 7.0, 1.3 Hz, 1 H), 2.89 - 2.97 (m, 6 H), 1.78 (d, *J* = 0.9 Hz, 4 H), 1.40 (d, *J* = 7.0 Hz, 3 H), 1.24 - 1.31 (m, 9 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 198.0, 196.2, 158.3, 157.3, 108.8, 61.4, 23.8, 22.9, 15.1, 14.7, 12.8, 11.4.

Cyanoaldehyde 5e.[11] To a stirring solution of *n*-BuLi (8.0 mL, 20 mmol, 2.5 M solution in hexane) in THF (10 mL) cooled to -78 ℃, was added a solution of propinonitrile (**15**) (1.00 g, 1.3 ml, 18.2 mmol) in THF (13.7 mL) was added by syringe pump over one hour period. After an additional 30 min, this mixture was transferred dropwise via a cannula to a mixture of methyl formate (16.40 g, 16.7 mL, 273.0 mmol) and BF_3•Et_2O (12.90 g, 11.2 mL, 90.9 mmol) at -78 ℃. This reaction was allowed to warm to room temperature over a period of 4 h. After an additional 8 h at room temperature, the reaction was quenched with water (20 mL) and extracted with CH_2Cl_2 (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* purified by chromatography over silica gel, eluting with 50% ethyl acetate / hexanes to give **5e** (968 mg, 11.66 mmol, 65 %) as a colorless oil which exists as a mixture of the keto and enol forms. ^1H NMR (700 MHz, $CDCl_3$) δ 9.62 (s, 1 H), 7.17 (br. s, 4 H), 3.52 (q, *J* = 7.5 Hz, 1 H), 1.78 (s, 11 H), 1.55 (d, *J* = 7.5 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 155.7, 121.7, 116.7, 38.3, 31.0, 11.95, 10.44.

General procedure for amine series 6 & 8: To a solution of the aldehyde **5** (0.25 mmol) in anhydrous trifluoromethyl benzene (0.25 mL) at room temperature was added the amine (0.25 mmol). After 30 min, the sulfonamide catalyst **2** was added (22.0 mg, 0.05 mmol) followed by cyclohexenone (**3**) (72 mg, 73.0 µL, 0.75 mmol). After 3 d, the crude

reaction mixture was directly on purified by chromatography over silica gel, eluting with 10-30 % of EtOAc / hexanes to give the amine **6** or **8.** The racemic version of **6** & **8** for determination of enantiomeric ratio (er) was prepared by use of (±)-**2** catalyst.

Bicyclic amine 6a. (24 mg, 32 %, 0.08 mmol, 73.9: 26.1 er, 20:1 dr), as a colorless solid Mp 94-96 °C, enatiomeric ratio was determined by chiral HPLC [4.6 X 250 mm Phenomenex Lux 5u Cellulose-2 column, 99: 1 to 90 : 10 Hexanes: iPrOH, 1 mL/min, 254 nm, retention times 18.1 min (major) and 19.3 min (minor)]: $[\alpha]_D^{23}$ = + 90.0 (c = 0.2, $CHCl_3$); IR (neat): 3383, 2963, 1718, 1602, 1498, 1260, 1093, 1020, 799 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.12 - 7.16 (m, 2 H), 6.62 - 6.69 (m, 3 H), 4.79 (br. s., 1 H), 4.23 - 4.30 (m, 2 H), 3.45 (br. s., 1 H), 2.58 (dt, *J* = 19.4, 3.1 Hz, 1 H), 2.45 (q, *J* = 3.1 Hz, 1 H), 2.40 (quin, *J* = 2.9 Hz, 1 H), 2.19 (dd, *J* = 19.4, 2.8 Hz, 1 H), 1.96 - 2.01 (m, 1 H), 1.84 (dddd, *J* = 14.2, 11.8, 4.3, 3.3 Hz, 1 H), 1.68 - 1.75 (m, 1 H), 1.58 - 1.61 (m, 1 H), 1.31 (t, *J* = 7.3 Hz, 3 H), 1.22 - 1.23 (m, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 214.9, 177.1, 147.6, 129.5, 117.7, 113.2, 76.9, 61.5, 55.5, 50.0, 49.38, 40.5, 38.0, 22.4, 20.8, 18.8, 14.4. HRMS (ES+) Calcd for $C_{18}H_{23}NO_3$ (M+), 302.1756 found 302.1744.

Bicyclic amine 6b. (42 mg, 0.13 mmol, 50 %, 94.3:5.7 er, 20:1 dr), as a colorless oil, enatiomeric ratio was determined by chiral HPLC [4.6 X 250 mm Daicel IF column, 98.8: 0.2 Hexanes: iPrOH, 2 mL/min, 254 nm, retention times 18.3 min (major) and 36.8 min (minor)]: $[\alpha]_D^{23}$ = + 23 (C = 1.0, $CHCl_3$); IR (neat): 3375, 2949, 2833, 1721, 1515, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.70 - 6.78 (m, 2 H), 6.59 - 6.64 (m, 2 H),) 4.68 (d, *J* = 2.6 Hz, 1 H), 4.25 (qd, *J* = 7.0, 1.3 Hz, 2 H), 3.72 (s, 3 H), 3.19 (br. s., 1 H), 2.57 (dt, *J* = 19.3, 3.1 Hz, 1 H), 2.43 (q, *J* = 2.8 Hz, 1 H), 2.39 (quin, *J* = 2.6 Hz, 1 H), 2.17 (dd, *J* =19.3, 2.6 Hz, 1 H), 1.90 - 2.00 (m, 1 H), 1.80 - 1.87 (m, 1 H), 1.51 - 1.75 (m, 3 H), 1.30 (t, *J* = 7.0 Hz, 3 H), 1.23 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.0, 177.2, 152.3, 141.8, 115.1, 114.7, 61.4, 56.7, 55.9, 49.8, 49.4, 40.4, 38.0, 22.3, 20.8, 14.4. HRMS (ES+) Calcd for $C_{19}H_{25}NO_4$ (M+), 332.1862 found 332.1852.

Bicyclic amine 6c. (61 mg, 0.14 mmol, 53 %, 88.2: 12.8 er, 11:1 dr) as a colorless oil, enatiomeric ratio was determined by chiral HPLC [4.6 X 250 mm Phenomenex Lux 5u Cellulose-2 column, 99: 1 to 90 : 10 Hexanes: iPrOH, 1 mL/min, 254 nm, retention times 11.4 min (minor) and 12.1 min (major)]: $[\alpha]_D^{23}$ = - 8.1 (C = 1, $CHCl_3$); IR (neat): 3350, 2958, 2879, 1731, 1624 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.78 (s, 2 H), 7.75 (s, 1 H), 4.19 (qd, *J* = 7.1, 0.7 Hz, 2 H), 4.01 (d, *J* = 14.4 Hz, 1 H), 3.85 (d, *J* = 2.7 Hz, 1 H), 3.82 (d, *J* = 14.4 Hz, 1 H), 2.55 (dt, *J* = 19.0, 3.2 Hz, 1 H), 2.49 (q, *J* = 2.8 Hz, 1 H), 2.42 (quin, *J* = 2.9 Hz, 1 H), 2.14 (dd, *J* = 19.1, 2.7 Hz, 1 H), 1.78 - 1.83 (m, 2 H), 1.62 - 1.69 (m, 1 H), 1.55 - 1.61 (m, 1 H), 1.31 (s, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H);^{13}C NMR (176 MHz, $CDCl_3$) δ 214.9, 177.1, 143.1, 131.9, 131.7, 131.5, 131.3, 128.3, 125.9, 124.3, 122.8, 121.23, 121.20, 121.17, 121.15, 121.13, 121.11, 61.4, 60.3, 51.3, 49.1, 48.2, 40.2, 37.6, 22.2, 21.0, 19.0, 14.3. HRMS (ES+) Calcd for $C_{21}H_{23}F_6NO_3$ (M+), 452.1660 found 452.1643.

Bicyclic amine 6d. (57 mg, 22 mmol, 85 %, 6:1 dr), as a colorless oil: $[\alpha]_D^{23}$ = + 9.2 (C = 1, $CHCl_3$); IR (neat): 3429, 2949, 2876, 1734, 1672, 1647, 1465, 1453 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 5.80 - 5.86 (m, 1 H), 5.14 (dd, *J* = 17.2, 1.8 Hz, 1 H), 5.05 (d, *J* = 10.1 Hz, 1 H), 4.18 (q, *J* = 7.0 Hz, 2 H), 3.81 (d, *J* = 3.1 Hz, 1 H), 3.30 (dd, *J* = 14.1, 5.7 Hz, 1 H), 3.14 (dd, *J* = 14.1, 6.2 Hz, 1 H), 2.51 (dt, *J* = 18.9, 3.1 Hz, 1 H), 2.43 (q, *J* = 2.6 Hz, 1 H), 2.36 (quin, *J* = 2.6 Hz, 1 H), 2.08 (dd, *J* = 18.9, 2.6 Hz, 1 H), 1.71 - 1.83 (m, 2 H), 1.60 - 1.69 (m, 1 H), 1.52 (dddd, *J* = 14.0, 11.4, 5.0, 3.1 Hz, 1 H), 1.25 - 1.28 (m, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 215.1, 177.3, 136.8, 116.0, 61.1, 59.7, 50.8, 48.0, 40.2, 37.7, 22.3, 21.0, 18.9, 14.3. HRMS (ES+) Calcd for $C_{15}H_{24}NO_3$ (M+), 266.1756 found 266.1753.

Bicyclic amine 6e. (26 mg, 0.08 mmol, 30 %, 95.7:4.3er, 20:1 dr), as a colorless oil, enatiomeric ratio was determined by chiral HPLC [4.6 X 250 mm Daicel IF column, 98.8: 0.2 Hexanes: iPrOH, 2 mL/min, 254 nm, retention times 5.2 min (major) and 7.8 min (minor)]: $[\alpha]_D^{23}$ = + 7.5 (C = 1.0, $CHCl_3$); IR (neat): 3353, 2957, 1710, 1601, 1255, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.09 - 7.18 (m, 2 H), 6.58 - 6.71 (m, 3 H), 4.74 (dd, *J*=8.33, 3.07 Hz, 1 H), 3.45 (d, *J*=8.33 Hz, 1 H), 2.56 (dt, *J*=19.29, 3.07 Hz, 1 H), 2.43 (q, *J*=3.07 Hz, 1 H), 2.35 (quin, *J*=3.10 Hz, 1 H), 2.17 (dd,*J*=19.29, 2.63 Hz, 1 H), 1.94 - 2.03 (m, 1 H), 1.73 - 1.88 (m, 2 H), 1.54 - 1.63 (m, 2 H), 1.51 (s, 9 H), 1.18 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 215.1, 176.0, 147.7, 129.4, 117.6, 113.2 81.3, 55.32, 50.0, 40.6, 38.1, 28.1, 22.3, 20.9, 18.9. HRMS (ES+) Calcd for $C_{20}H_{27}NO_3$ (M+), 330.2069 found 330.2071.

Bicyclic amine 6f. (59 mg, 0.16 mmol, 66 %, 89.3:10.7 er, 20:1 dr), as a colorless oil, enatiomeric ratio was determined by chiral HPLC [4.6 X 250 mm Daicel IF column, 98.8: 0.2 Hexanes: iPrOH, 2 mL/min, 254 nm, retention times 9.3 min (major) and 32.1 min (minor)]: $[\alpha]_D^{23}$ = + 14.6 (C = 1.0, $CHCl_3$); IR (neat): 3387, 2977, 2949, 1723, 1515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.69 - 6.78 (m, 2 H), 6.56 - 6.65 (m, 2 H), 4.64 (br. s., 1 H), 3.72 (s, 3 H), 3.18 (d, *J* = 4.0 Hz, 1 H), 2.55 (dt, *J* = 19.3, 3.1 Hz, 1 H), 2.42 (q, *J* = 2.8 Hz, 1 H), 2.34 (quin, *J* =2.9 Hz, 1 H), 2.15 (dd, *J* = 19.3, 2.6 Hz, 1 H), 1.90 - 2.00 (m, 1 H), 1.72 - 1.86 (m, 2 H), 1.54 - 1.61 (m, 1 H), 1.50 (s, 9 H), 1.18 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.2, 176.1, 152.3, 141.9, 115.0, 114.7, 81.2, 56.5, 55.9, 49.83, 49.75, 40.5, 38.1, 28.1, 22.2, 20.9, 19.0. HRMS (ES+) Calcd for $C_{21}H_{29}NO_4$ (M+), 360.2175 found 360.2175.

Bicyclic amine 6g. (100 mg, 0.22 mmol, 83 %, 90.3: 9.7 er, 12:1 dr), as a colorless oil, enatiomeric ratio was determined by chiral HPLC [4.6 X 250 mm Phenomenex Lux 5u Cellulose-3 column, 99: 1 to 90: 10 Hexanes: iPrOH, 1 mL/min, 254 nm, retention times 7.1 min (minor) and 9.6 min (major)]: $[\alpha]_D^{23}$ = + 15.1 (C = 1, $CHCl_3$); IR (neat): 3357, 2980, 2954, 2881, 1730, 1625 cm^{-1}; ^1H NMR (700 Mz, $CDCl_3$) δ 7.78 (s, 2 H), 7.74 (s, 1 H), 4.00 (d, *J* = 14.4 Hz, 1 H), 3.83 (d, *J* = 2.7 Hz, 1 H), 3.81 (d, *J* = 14.2 Hz, 1 H), 2.53 (dt, *J* = 19.0, 3.1 Hz, 1 H), 2.48 (q, *J* = 2.9 Hz, 1 H), 2.37 (quin, *J* = 3.0 Hz, 1 H), 2.12 (dd, *J* =19.0, 2.6 Hz, 1 H), 1.77 - 1.85 (m, 2 H), 1.66 - 1.71 (m, 1 H), 1.54 - 1.59 (m, 1 H), 1.46 (s, 9 H), 1.28 (s, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 215.2, 176.1, 143.2, 131.7, 131.5, 128.27, 128.25, 125.9, 124.4, 122.8, 121.3, 121.13, 121.11, 81.2, 60.2, 51.3, 49.6, 48.2, 40.2, 37.7, 28.0, 22.2, 21.0, 19.2. HRMS (ES+) Calcd for $C_{23}H_{27}F_6NO_3$ (M+), 480.1973 found 480.1954.

Bicyclic amine 6h. (30 mg, 0.09 mmol, 34 %, 83.6: 16.4 er, 20:1 dr), as a colorless oil, enatiomeric ratio was determined by chiral HPLC [4.6 X 250 mm Daicel IF column, 98.8: 0.2 Hexanes: iPrOH, 2 mL/min, 254 nm, retention times 16.6 min (major) and 34.5 min (minor)]: $[\alpha]_D^{23}$ = + 27.5 (C = 1.0, $CHCl_3$); IR (neat): 3368, 2932, 2876, 1720, 1670, 1513, 1238, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, *J* = 9.2 Hz, 2 H), 6.53 (d, *J* = 8.8 Hz, 2 H), 4.67 (br. s., 1 H), 3.72 (s, 3 H), 2.90 - 3.02 (m, 3 H), 2.60 (dt, *J* = 19.0, 3.2 Hz, 1 H), 2.38 - 2.47 (m, 2 H), 2.21 (dd, *J* = 19.3, 2.6 Hz, 1 H), 1.92 - 1.98 (m, 1 H), 1.70 - 1.82 (m, 1 H), 1.49 - 1.60 (m, 1 H), 1.29 (t, *J* =7.5 Hz, 3 H), 1.29 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.8, 205.8, 117.2, 115.1, 114.9, 56.6, 56.2, 55.9, 49.8, 40.9, 39.2, 23.7, 21.7, 20.8, 19.6, 14.8. HRMS (ES+) Calcd for $C_{19}H_{25}NO_3S$ (M+), 348.1633 found 348.1624.

Bicyclic amine 6i. (41 mg, 0.13 mmol, 57 %, 83.2: 16.8 er, 6:1 dr), as a colorless oil, enatiomeric ratio was determined by chiral HPLC [4.6 X 250 mm Phenomenex Lux 5u Cellulose-3 column, 99:1 to 90:10 Hexanes: iPrOH, 1 mL/min, 254 nm, retention times 27.8 min (minor) and 29.4 min (major)]: $[\alpha]_D^{23}$ = + 8.0 (C = 1, $CHCl_3$); IR (neat 3346, 2951, 2878, 1724, 1642 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.32 - 7.38 (m, 5 H), 5.79 - 5.85 (m, 1 H), 5.18 (d, *J* = 1.5 Hz, 2 H), 5.11 - 5.16 (m, 1 H), 5.05 (dq, *J* = 10.2,

1.4 Hz, 1 H), 3.85 (d, *J* = 2.7 Hz, 1 H), 3.30 (ddt, *J* =14.1, 5.7, 1.5, 1.5 Hz, 1 H), 3.13 (ddt, *J* = 14.0, 6.2, 1.4, 1.4 Hz, 1 H), 2.52 (dt, *J* = 19.0, 3. 2 Hz, 1 H), 2.44 (q, *J* =2.9 Hz, 1 H), 2.39 (quin, *J* = 3.0 Hz, 1 H), 2.08 (dd, *J* = 19.0, 2.7 Hz, 1 H), 1.76 - 1.82 (m, 1 H), 1.70 - 1.76 (m, 1 H), 1.60 (dddt, *J* = 13.9, 11.2, 5.3, 2.8, 2.8 Hz, 1 H), 1.30 (s, 3 H) 1.47 - 1.53 (m, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 215.1, 177.1, 136.7, 136.0, 128.7, 128.5, 128.2, 116.1, 67.0, 59.8, 50.8, 49.0, 47.9, 40.1, 37.8, 22.3, 20.9, 18.9. HRMS (ES+) Calcd for $C_{20}H_{25}NO_3$ (M+), 328.1913 found 328.1905.

Bicyclic amine 8a. (70 mg, 0.20 mmol, 80 %, 86.7: 13.3 er, 9:1 dr), as a colorless solid, enatiomeric ratio was determined by chiral HPLC [4.6 X 250 mm Daicel IF column, 98.8: 0.2 Hexanes: iPrOH, 2 mL/min, 254 nm, retention times 79.2 min (major) and 83.4 min (minor)]: Mp: 71-73 °C $[\alpha]_D^{23}$ = + 10.2 (C = 1.0, $CHCl_3$); IR (neat): 3430, 3337, 2977, 2951, 2878, 1724, 1454 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.27 - 7.32 (m, 4 H), 7.21 -7.24 (m, 1 H), 3.83 - 3.88 (m, 2 H), 3.66 (d, *J* = 12.9 Hz, 1 H), 2.53 (dt, *J* = 18.9, 2.9 Hz, 1 H), 2.50 (q, *J* = 2.9 Hz, 1 H), 2.33 (t, *J* = 2.9 Hz, 1 H), 2.08 (dd, *J* = 19.0, 2.8 Hz, 1 H), 1.71 - 1.84 (m, 3 H), 1.50 - 1.56 (m, 1 H), 1.45 - 1.48 (m, 9 H), 1.28 (s, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 215.4, 176.4, 140.5, 128.4, 128.3, 127.1, 80.9, 60.0, 52.6, 49.3, 48.2, 40.3, 37.9, 28.1, 22.4, 21.0, 19.3. HRMS (ES+) Calcd for $C_{21}H_{29}NO_3$ (M+), 344.2226 found 344.2210.

Bicyclic amine 8b. (63 mg, 0.20 mmol, 79 %, 8.5:1 dr), colorless oil: $[\alpha]_D^{23}$ = + 14.4 (c = 1.0, $CHCl_3$); IR (neat): 3330, 2949, 2867, 1718, 1495, 1457, 1113, 765, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 - 7.32 (m, 5 H), 4.18 (q, *J* = 7.31 Hz, 2 H), 4.18 (q, *J* = 7.3 Hz, 2 H), 4.18 (q, *J* = 7.31 Hz, 2 H), 3.86 (dd, *J* = 7.7, 5.0 Hz, 2 H), 3.67 (d, *J* = 13.2 Hz, 1 H), 2.55 (dt, *J* = 18.9, 3.1 Hz, 1 H), 2.50 (q, *J* = 3.2 Hz, 1 H), 2.37 (quin, *J* = 3.1 Hz, 1 H), 2.10 (dd, *J* = 18.9, 3.1 Hz, 1 H), 1.73 - 1.83 (m, 2 H), 1.62 - 1.71 (m, 1 H), 1.48 - 1.58 (m, 1 H), 1.31 (s, 3 H), 1.26 (t, *J* = 7.00 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$)□δ 215.1, 177.3, 140.3, 128.5, 128.4, 127.1, 61.1, 60.0, 52.4, 48.8, 48.1, 40.2, 37.7, 22.4, 20.9, 19.1, 14.3. HRMS (CI+) Calcd for $C_{22}H_{25}NO$ (M+), 319.1936 found 319.1926.

Bicyclic amine 8c. (50 mg, 0.13 mmol, 53 %, 83.1: 16.9 er, 6:1 dr), as a colorless oil, enatiomeric ratio was determined by chiral HPLC [4.6 X 250 mm Daicel IF column, 98.8:0.2 Hexanes: iPrOH, 2 mL/min, 254 nm, retention times 11.9 min (major) and 16.4 min (minor)]: $[\alpha]_D^{23}$ = + 17.0 (c = 1.0, $CHCl_3$); IR (neat): 3429, 3342, 2956, 2879, 1730, 1607, 1587, 1455 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 - 7.41 (m, 5 H), 7.22 - 7.30 (m, 5 H), 5.13 - 5.21 (m, 2 H), 3.89 (d, *J* = 2.6 Hz, 1 H), 3.86 (d, *J* = 13.0 Hz, 1 H), 3.7 (d, *J*=13.2 Hz, 1 H), 2.55 (dt, *J* = 18.0, 3.1 Hz, 1 H), 2.51 (q, *J* = 2.6 Hz, 1 H), 2.40 (quin, *J* = 2.6 Hz, 1 H), 2.10 (dd, *J*=18.9, 2.6 Hz, 1 H), 1.73 - 1.80 (m, 2 H), 1.57 - 1.66 (m, 1 H), 1.51 (ddd, *J* = 13.4, 6.6, 3.3 Hz, 1 H), 1.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.0, 177.1, 140.3, 128.8, 128.4, 128.2, 127.1, 67.0, 60.1, 52.5, 49.0, 48.1, 40.2, 37.8, 22.3, 20.9, 19.1. HRMS (ES+) Calcd for $C_{24}H_{27}NO_3$ (M+), 378.2069 found 378.2059.

Bicyclic amine 8d. (54 mg, 16 mmol, 64 %, 71.6: 28.4 er, 20:1 dr), as a colorless oil, enatiomeric ratio was determined by chiral HPLC [4.6 X 250 mm Daicel OD-H column, 98.8:0.2 Hexanes: iPrOH, 2 mL/min, 254 nm, retention times 54.6 min (major) and 76.6 min (minor)]: $[\alpha]_D^{23}$ = + 5.4 (c = 1.0, $CHCl_3$); IR (neat): 3348, 2932, 2875, 1724, 1673, 1645, 1605, 1572 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 - 7.34 (m, 5 H), 3.89 (d, *J* = 2.6 Hz, 1 H), 3.86 (d, *J* =13.2 Hz, 1 H), 3.67 (d, *J* = 12.7 Hz, 1 H), 2.84 - 2.98 (m, 2 H), 2.56 (dt, *J* = 18.9, 3.1 Hz, 1 H), 2.52 (q, *J* = 2.6 Hz, 1 H), 2.45 (quin, *J* = 3.1 Hz, 1 H), 2.15 (dd, *J* = 18.9, 2.6 Hz, 1 H), 1.67 - 1.88 (m, 3 H), 1.47 - 1.58 (m, 1 H), 1.34 (s, 3 H), 1.27 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.9, 205.9, 140.2, 128.5, 128.3, 127.1, 60.2, 56.4, 52.6, 48.3, 40.6, 38.5, 23.6, 21.8, 21.1, 20.2, 14.8. HRMS (ES+) Calcd for $C_{19}H_{25}NO_2S$ (M+), 332.1684 found 332.1669.

Bicyclic amine 8e (major) and 8e' (minor). 8e: (46 mg, 0.17 mmol, 68 %, 88.9:11.1 er, 3:1 dr), as a colorless solid, enatiomeric ratio was determined by chiral HPLC [4.6 X 250 mm Phenomenex Lux 5u Cellulose-4 column, 99:1 to 90:10 Hexanes: iPrOH, 1 mL/min, 254 nm, retention times 15.0 min (major) and 17.8 min (minor)]: Mp: 71-74 °C, $[\alpha]_D^{23}$ = + 3.6 (c = 1.0, $CHCl_3$); IR (neat); 3339, 2949, 2233, 1731 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.31 - 7.34 (m, 2 H), 7.24 - 7.29 (m, 3 H), 3.85 (d, *J* = 13.2 Hz, 1 H), 3.72 (d, *J* = 13.2 Hz, 1 H), 3.45 (d, *J* = 3.1 Hz, 1 H), 2.49 - 2.54 (m, 2 H), 2.24 - 2.29 (m, 2 H), 2.20 (dd, *J* = 18.9, 2.6 Hz, 1 H), 1.97 - 2.03 (m, 1 H), 1.86 - 1.92 (m, 1 H), 1.67 - 1.73 (m, 1 H), 1.51 (s, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 211.9, 139.1, 128.7, 128.2, 127.5, 125.6, 63.1, 52.5, 48.0, 39.7, 38.4, 38.3, 22.8, 20.8, 19.3. HRMS (ES+) Calcd for $C_{17}H_{20}N_2O$ (M+), 269.1654 found 269.1644. **8e':** 16 mg, 0.06 mmol, 19 %, 87.7:12.3 er, 3:1 dr), as a colorless oil, enatiomeric ratio was determined by chiral HPLC [4.6 X 250 mm Phenomenex Lux 5u Cellulose-3 column, 99: 1 to 90 : 10 Hexanes: iPrOH, 1 mL/min, 254 nm, retention times 31.3 min (minor) and 32.3 min (major)]: $[\alpha]_D^{23}$ = + 9.4 (c = 0.5, $CHCl_3$); IR (neat); 3442, 3320, 2942, 2232, 2202, 1727, 1453, 1123, 744, 701 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.31 - 7.36 (m, 4 H), 7.27 - 7.28 (m, 1 H), 3.85 - 3.94 (m, 1 H), 2.85 - 2.91 (m, 1 H), 2.70 (d, *J*=2.64 Hz, 1 H), 2.51 - 2.53 (m, 1 H), 2.29 - 2.34 (m, 2 H), 1.82 - 1.95 (m, 3 H), 1.69 - 1.75 (m, 1 H), 1.59 (s, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 211.8, 139.2, 128.6, 128.4, 127.4, 122.4, 62.8, 51.6, 47.4, 42.7, 42.6, 37.9, 25.7, 20.8, 19.1. HRMS (ES+) Calcd for $C_{17}H_{20}N_2O$ (M+), 269.1654 found 269.1644.

General procedure for alcohol series: To a stirred solution of the aldehyde (0.25 mmol) in anhydrous trifluoromethyl benzene (0.25 mL) at room temperature was added the sulfonamide catalyst **2** (22 mg, 0.05 mmol) followed by cyclohexenone (**3**) (72 mg, 73 µL, 0.75 mmol). After 3 d, the crude reaction mixture was directly on purified by chromatography over silica gel, eluting with 20-50 % of EtOAc / hexanes to give the alcohol **7**. The racemic version of **7** for determination of enantiomeric ratio (er) was prepared by use of (±)-**2** catalyst.

Bicyclic alcohol 7a. (48 mg, 0.21 mmol, 84 %, 60.3:39.7 er, 12:1 dr), as a colorless oil, enatiomeric ratio was determined by ^{1}H NMR Mosher ester derivatization: $[\alpha]_D^{23}$ = - 9.5 (c = 0.5, $CHCl_3$); IR (neat); 3445, 2950, 2881, 1725, 1252, 1112, 678 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.87 (br. s., 1 H), 4.21 (q, *J* = 7.0 Hz, 2 H), 2.55 (dt, *J* = 19.4, 2.9 Hz, 1 H), 2.48 (q, *J* =3.4 Hz, 1 H), 2.39 (quin, *J* = 3.1 Hz, 1 H), 2.12 (dd, *J* = 19.4, 3.1 Hz, 1 H), 1.92 (br. s., 1 H), 1.77 - 1.82 (m, 1 H), 1.71 - 1.77 (m, 1 H), 1.61 - 1.63 (m, 2 H), 1.50 (dddd, *J* = 11.2, 8.4, 5.5, 2.6 Hz, 1 H), 1.31 (s, 3 H), 1.29 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 214, 1, 177.0, 71.9, 61.3, 51.4, 49.4, 40.2, 37.2, 22.5, 19.7, 18.5, 14.3. HRMS (ES+) Calcd for $C_{12}H_{18}O_4$ (M+), 227.1283 found 227.1266.

Bicyclic alcohol 7c (major) and 7c' (minor). 7c: (47 mg, 0.21 mmol, 66 %, 57.8:42.2 er, 3:1 dr), as a colorless solid, enatiomeric ratio was determined by chiral HPLC [4.6 X 250 mm Phenomenex Lux 5u Cellulose-1 column, 99:1 to 90:10 Hexanes: iPrOH, 1 mL/min, 254 nm, retention times 21.9 min (minor) and 24.7 min (major)]: Mp 101-102 °C $[\alpha]_D^{23}$ = - 2.3 (c = 1.0, $CHCl_3$); IR (neat); 3435, 2951, 2882, 1725, 1456, 1252, 1209, 1042, 698 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.30 - 7.40 (m, 5 H), 5.18 (s, 2 H), 4.88 (t, *J* = 3.7 Hz, 1 H), 2.54 (dt, *J* = 19.0, 3.0 Hz, 1 H), 2.47 (q, *J* = 3.4 Hz, 1 H), 2.40 (t, *J* = 2.9 Hz, 1 H), 2.20 (d, *J* = 3.1 Hz, 1 H), 2.10 (dd, *J* = 19.2, 3.3 Hz, 1 H), 1.69 - 1.79 (m, 2 H), 1.51 - 1.57 (m, 1 H), 1.42 - 1.48 (m, 1 H), 1.33 (s, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 214.3, 176.8, 135.8, 128.8, 128.5, 128.3, 71.8, 67.1, 51.3, 49.5, 40.2, 37.3, 22.4, 19.6, 18.5. HRMS (ES+) Calcd for $C_{17}H_{20}O_2$ (M+), 289.1440 found 289.1453. **7c':** (16 mg, 0.07 mmol, 22 %, 65.8:34.2 er, 3:1 dr), as a colorless solid, enatiomeric ratio was determined by chiral HPLC [4.6 X 250 mm Phenomenex Lux 5u Cellulose-1 column, 99:1 to 90:10 Hexanes: iPrOH, 1 mL/min, 254 nm, retention times 21.4 min (major) and

24.5 min (minor)]: Mp 104-106°C $[\alpha]_D^{23}$ = - 1.6 (c = 0.7, $CHCl_3$); IR (neat); 3446, 2947, 2880, 1728, 1229, 1108, 739 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.32 - 7.39 (m, 5 H), 5.19 (br. s, 2 H), 3.94 (t, *J* = 3.5 Hz, 1 H), 3.63 (d, *J* = 3.5 Hz, 1 H), 2.58 - 2.62 (m, 1 H), 2.53 (dt, *J* = 21.6, 2.6 Hz, 2 H), 2.18 (dd, *J* = 18.9, 3.1 Hz, 1 H), 1.86 - 1.92 (m, 1 H), 1.77 - 1.81 (m, 2 H), 1.47 (s, 4 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 213.3, 175.5, 135.4, 128.9, 128.8, 128.46, 67.2, 50.7, 49.9, 42.7, 35.1, 25.3, 20.8, 19.7. HRMS (ES+) Calcd for $C_{17}H_{20}O_2$ (M+), 289.1440 found 289.1422.

Bicyclic alcohols 7d & 7d' (3:1, inseperable). (48 mg, 0.20 mmol, 79 %, 1:3 dr), as a colorless oil; IR (neat); 3441, 2935, 2879, 1725, 1672, 1542, 1410, 960, 938, 772 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 4.87 (t, *J* = 4.0 Hz, 3 H), 4.67 - 4.71 (m, 1 H), 2.85 - 2.96 (m, 8 H), 2.58 (dt, *J* = 18.9, 3.1 Hz, 4 H), 2.48 - 2.50 (m, 1 H), 2.47 (q, *J* =3.1 Hz, 3 H), 2.44 (dq, *J* = 5.9, 3.0 Hz, 4 H), 2.20 - 2.25 (m, 5 H), 2.13 - 2.17 (m, 3 H), 2.09 - 2.13 (m, 1 H), 2.03 - 2.09 (m, 1 H), 1.78 - 1.84 (m, 4 H), 1.65 - 1.74 (m, 7 H), 1.54 - 1.60 (m, 1 H), 1.45 - 1.52 (m, 5 H), 1.42 (s, 3 H), 1.34 (s, 10 H), 1.26 (t, *J* = 7.3 Hz, 10 H), 1.23 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 214.4, 214.1, 206.4, 205.7, 71.4, 676.7, 56.8, 56.2, 51.2, 51.7, 42.6, 40.6, 38.2, 37.3, 23.5, 21.9, 21.1, 19.7, 15.2, 14.4. HRMS (ES+) Calcd for $C_{12}H_{19}O_3S$ (M+), 243.1055 found 243.1057.

Bicyclic alcohol 7e. (28 mg, 0.16 mmol, 62 %, 78.1:21.9 er, 20:1 dr), as a colorless solid, enatiomeric ratio was determined by ^1H NMR Mosher ester derivatization: Mp 211-214°C, $[\alpha]_D^{23}$ = - 1.3 (c = 1.0, $CHCl_3$); IR (neat);3435, 2951, 2884, 2235, 1066, 583 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) 4.43 (br. s., 1 H), 2.71 (br. s., 1 H), 2.55 - 2.57 (m, 1 H), 2.50 (dt, *J* = 19.2, 2.8 Hz, 1 H), 2.23 - 2.28 (m, 2 H), 2.20 (dd, *J* =19.2, 3.3 Hz, 1 H), 1.97 - 2.03 (m, 1 H), 1.85 - 1.91 (m, 1 H), 1.60 - 1.67 (m, 1 H), 1.51 (s, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 211.7, 124.8, 73.8, 50.7, 39.7, 38.8, 37.7, 23.0, 19.3, 18.8. HRMS (FAB+) Calcd for $C_{17}H_{20}N_2O$ (M+), 180.125 found 180.1026.

General procedure for Mosher ester synthesis and analysis: To a solution of the alcohol **7** (0.1 mmol) in THF (1 mL) was added (S)-Mosher acid (0.3 mmol) followed by DCC (0.3 mmol) and DMAP (0.06 mmol) at room temperature. After 2 h, TLC showed that no starting material remained in the reaction. Consequently, the reaction filtered through a short plug of silica gel (50% EtOAc / hexanes rinse) to give the crude Mosher ester, which was used for determination of the stereoselectivity. ^1H NMR of Mosher ester of **7a**: 3.56 ppm (major) & 3.47 ppm (minor). ^1H NMR of Mosher ester of **7e**: 3.61 ppm (major) and 3.44 ppm (minor).

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Keywords: organocatalysis • cascade • Mannich • asymmetric • synthesis

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[12] CCDC 1426335 [for **8e**] contains the supplementary crystallographic data for this paper. This data can be obtained free of chare from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for the crystal structure.

[13] CCDC 1426336 [for **6a**] contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for the crystal structure.

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[15] **Procedure to make LDA**: To a solution of diisopropylamine (607 mg, 0.848 mL, 6.0 mmol) in THF (2.75 mL) at -78 °C was added nBuLi (2.4 mL, 6.0 mmol, 2.5 M solution in Hexanes). After 5 min, the white slurry was warmed to -10 °C. After 15 min, the LDA solution (1.0 M in THF/Hexanes) was used for the reaction.

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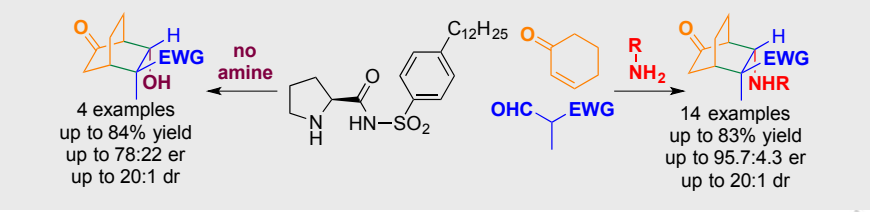

A generalized method for accessing highly functionalized amine- and alcohol-containing bicyclo[2.2.2]octanes via *p*-dodecylphenylsulfonamide catalyst in a good enantio- and diasteroselective fashion has been developed. A discussion of the mechanistic underpinnings of this transformation is presented.

ORganocatalysis*

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Proline sulfonamide-catalyzed, domino process for asymmetric synthesis of amine- and alcohol-containing bicyclo[2.2.2]octanes