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Highly efficient synthesis of spirocyclic (1*R*)-camphor-derived triazolium salts: application in the catalytic asymmetric benzoin condensation

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ABSTRACT

New (1*R*)-camphor-derived triazolium salts, incorporating a spirocyclic system, are described. Benzoin condensation of aromatic aldehydes, mediated by these salts affords α-hydroxyketones in good yields and moderate enantiomeric excesses.

1. Introduction

In the area of rapidly expanding organocatalysis, *N*-heterocyclic carbenes (NHCs) have received considerable attention due to their capability of catalyzing a broad range of synthetic transformations.[1] The attractive ability of NHCs to invert the reactivity of aldehydes (umpolung) has led to intensive research in the area, providing an unconventional access to designed target molecules.[2]

Since the first report by Liebig and Wöhler[3] on the dimerization of benzaldehyde to benzoin in the presence of cyanide, a lot of effort has been devoted towards further development of this reaction. More than 100 years later, Ukai and co-workers showed that a catalytic amount of thiazolium salts could achieve the same transformation.[4] The mechanism of the thiazolium catalyzed benzoin condensation was elucidated by Breslow in 1958.[5] Initial attempts to develop an asymmetric variant of the reaction using chiral thiazolium precatalysts, designed by Sheehan resulted in a low to moderate enantiomeric excess (Fig. 1).[6] The real breakthrough, achieved by Enders[7] and then Leeper and Knight,[8] demonstrated the clear superiority of chiral triazolium-derived NHCs in terms of thiazolium analogues. Further catalyst optimization by Enders allowed the condensation of benzaldehyde to benzoin in greater than 90% ee.[9]

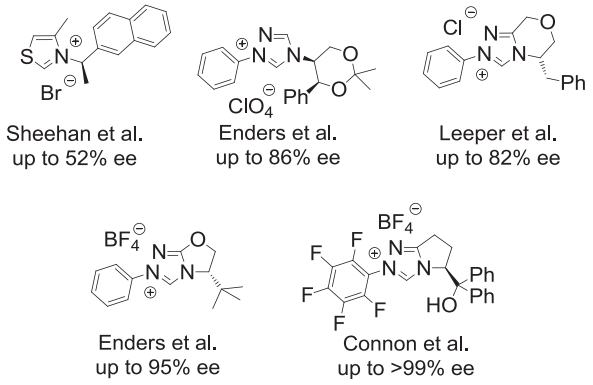

Fig. 1. Chiral *N*-heterocyclic carbene precursors.

More recently, Connon reported the first example of bifunctional catalysts, employing hydrogen bond donation as a control element, providing stabilizing interactions in the transition state, leading to >99% ee.[10]

Chiral carbene catalysts (NHCs) were shown to be powerful organocatalysts in various kinds of asymmetric reactions. However, only a limited number of NHCs backbone scaffolds are effective in highly enantioselective reactions. Many of them suffer from intricate synthetic procedures and relatively high cost of enantiopure starting materials.

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Consequently, the design of new catalysts from readily available chiral sources with improved reactivity profiles having fine-tuning of the steric and electronic environment around the carbene centre is still in great demand. On the basis of our previous success utilizing β-pinene-derived triazolium salts as very efficient and selective carbene precatalysts in Stetter reaction,[11] we report the synthesis of chiral spirocyclic triazolium salts derived from (1*R*)-camphor and their evaluation in the benzoin condensation. To the best of our knowledge, this is the first example of the synthesis of chiral spirocyclic triazolium NHCs.

2. Results and discussion

Camphor as a natural source of chirality has been widely used in asymmetric synthesis.[12] The readily available enantiomers of camphor guarantee access to either enantiomer of the chiral products. We started our investigation by the synthesis of a series triazolium salts as outlined in Scheme 1. The synthesis commences from the highly diastereoselective addition TMSCN to (1*R*)-camphor **1**, according to the reported method.[13] The reduction of cyanohydrin silyl ether **2** by $LiAlH_4$ proceeded smoothly to the corresponding aminoalcohol **3** in quantitative yield. Conversion into the lactam **5** was achieved using an optimized two-step procedure involving the formation of amide **4**, followed by cyclization with potassium *tert*-butoxide in excellent overall yields. Then, the diastereo- and enantiopure lactam **5** was methylated with the Meerwein's reagent to form the corresponding amidate. It was treated in situ with arylhydrazines to yield tetrafluoroborate hydrazonium salts, which were directly cyclized with triethyl orthoformate to give the tetracyclic triazolium salts **A**–**C** in high yield as crystalline solids. The configuration of triazolium salt **B** was confirmed by X-ray crystallographic analysis as shown in Fig. 2.

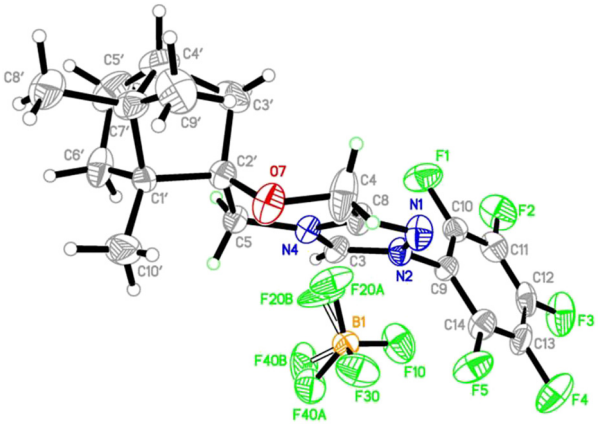
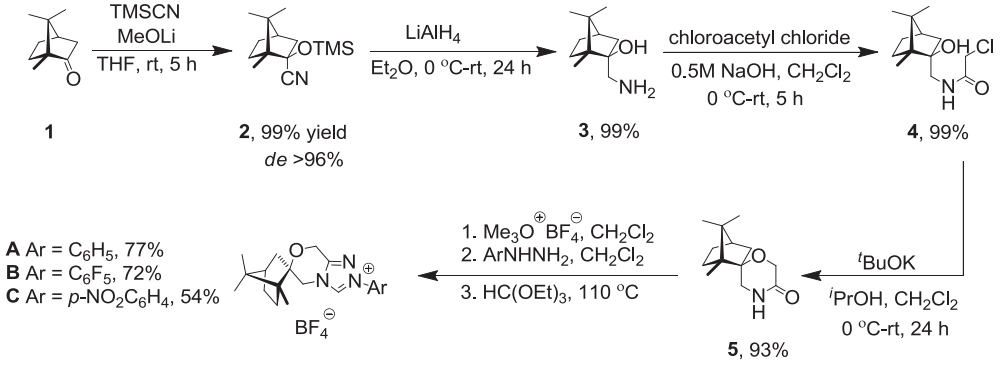


Fig. 2. ORTEP drawing structure of molecular structure of **B**. Thermal ellipsoids are set at the 30% probability level.

group of the spirocyclic triazolium salts **A**, **B**, **D** showed that the enantiomeric excess was constant over time regardless of the catalysts used. In the case of *N*-C_6F_5 triazolium precatalyst, reaction monitoring showed that after 15 min most of benzaldehyde was consumed to afford the racemic acryloin product. We suppose that the differences in the enantioselectivity results from reversibility of the benzoin reaction by using the *N*-C_6F_5 triazolium precatalyst. Insightful studies from Smith described the effect of the aryl substituent of azolium salts on the reactivity and reversibility in benzoin condensation.[15]

The reaction parameters were further examined in the presence of **D**, and the results are summarized in Table 2. Several tested bases (entries 1–5) were found tolerable and DIPEA was optimal in terms

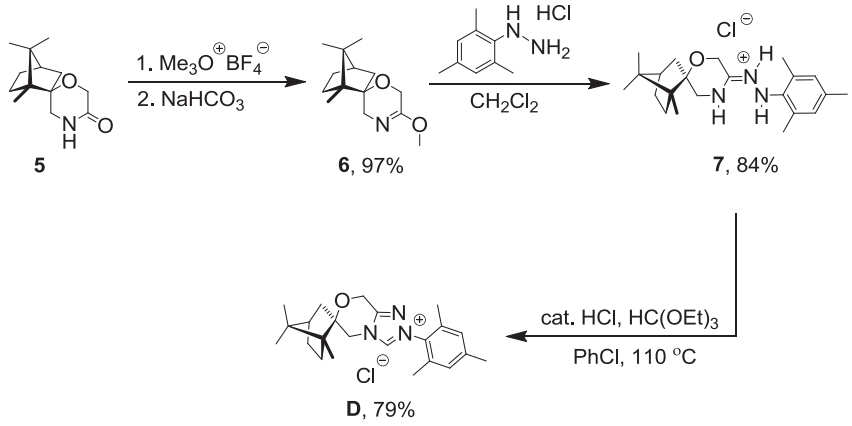


Scheme 1. Synthesis of triazolium salts from (1*R*)-camphor.

The tetracyclic triazolium salt **D** was then obtained as a white solid in 64% overall yield from **5** by a modified three-step procedure developed by Bode (Scheme 2).[14] The structure of triazolium salt **D** was confirmed by X-ray structural analysis (Fig. 3).

With these four novel chiral carbene precursors in hand, the model intermolecular benzoin condensation of benzaldehyde was evaluated. As shown in Table 1, when triazolium salts **A**–**D** (10 mol %) and triethylamine (10 mol %) in THF were used, **D** gave the best results, affording the benzoin product in 98% yield and 71.5:28.5 enantiomeric ratio (entry 4). Under the same condition precatalyst **A** showed slightly lower selectivity (71:29 er) and provided the product with a much lower yield (entry 1). Triazolium salt **B** bearing a pentafluorophenyl moiety gave the desired benzoin in excellent yields but only with 52:48 er. The carbene generated from **C** was found to be ineffective leading to a trace amount of the desired benzoin. Monitoring the enantiomeric excess of benzoins with time and with variation in the aryl of both yield and er of the product (entry 2). Other organic and inorganic bases, such as *t*-BuOK, K_2CO_3, Cs_2CO_3, DBU and phosphazene bases, also gave the desired product with high to excellent yields but as racemates. We suppose that this results from incomplete conversion to carbene, so that free base might racemize the product. To confirm this, the catalytic process was repeated with enantioenriched benzoin **9a** (55% ee) replacing benzaldehyde as the starting material. After stirring 20 min, the acryloin **9a** was recovered as the racemate (Scheme 3).[16]

Subsequently, various solvents were also examined and found to be tolerated, affording the desired product with good to excellent yields and moderate selectivity (entries 1–8, Table 3). However, using solvents, such as dimethoxyethane, dichloromethane and octafluorotoluene, a significant drop in yield was observed but with the same level of selectivity (entries 9–11). Finally, the reaction in THF led to an optimal combination of yield (93%) and enantiomeric ratio, 77.5:22.5 (entry 1, Table 3).



Scheme 2. Preparation of spirocyclic triazolium salt **D**.

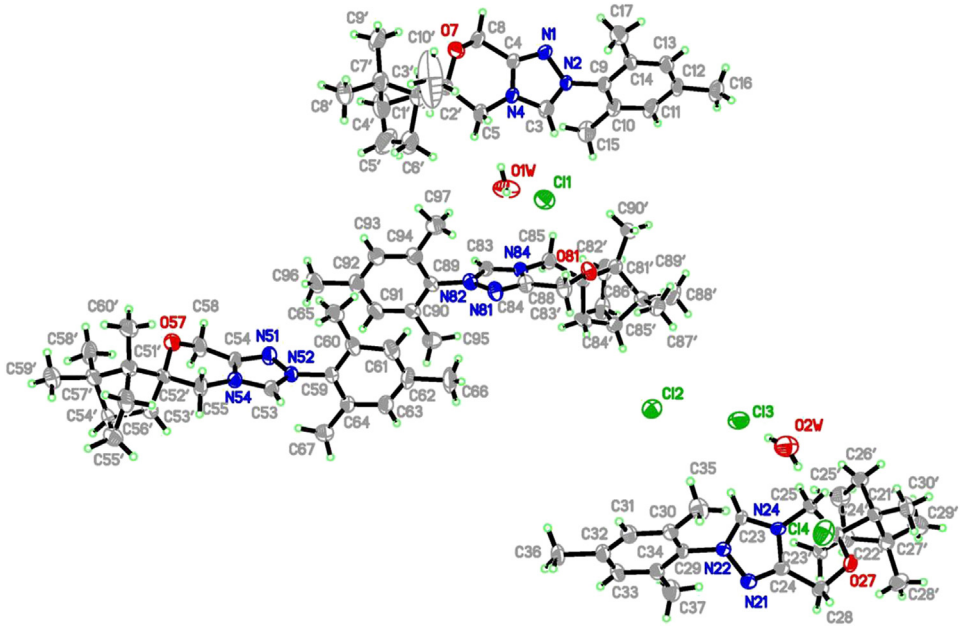
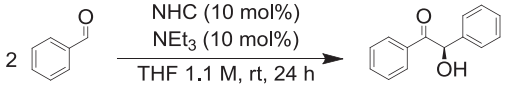


Fig. 3. X-ray crystal structure of triazolium salt **D**. Thermal ellipsoids are set at the 30% probability level.

Table 1
Screening of the chiral NHC catalysts[a]



8a **9a**

Entry	NHC	Yield[b] (%)	er[c]
1	**A**	31	71:29
2	**B**	99	52:48
3	**C**	<5	—
4	**D**	98	71.5:28.5

[a] Reaction conditions: **8a** (1 mmol), catalyst (10 mol %), triethylamine (10 mol %) in THF (1.1 mL).
[b] Yields of isolated benzoin.
[c] Determined by chiral HPLC (Daicel Chiralcel OD-H).

Under optimized conditions using carbene precatalyst **D**, the scope of the intermolecular benzoin reaction was demonstrated with various aromatic aldehydes **8a**–**f** (Table 4). In general, condensation of aldehydes occurred smoothly affording the corresponding acryloins in good yields and acceptable enantioselectivities. Generally, the reaction of aldehydes bearing electron-donating groups led to their desired products with higher selectivities but with relatively low yields. The best result was obtained for the *p*-methoxybenzaldehyde **8f** affording the acryloin in 82:18 er. The absolute configuration of the acryloin product was determined to be *R* by comparison of its optical rotation with that reported in the literature.[9a]

3. Conclusion

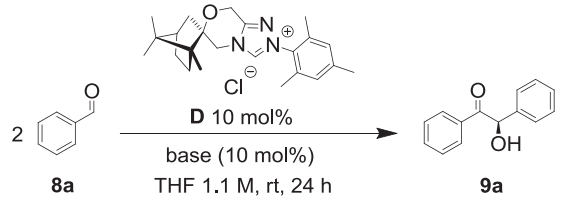
In summary, we have developed a series of novel spirocyclic triazolium salts from readily available and inexpensive (1*R*)-camphor. The catalyst derived from **D** and DIPEA was successfully employed in the asymmetric benzoin condensation. The resulting acryloins were obtained in moderate to excellent yields and acceptable enantioselectivities. Further structural modification of the spirocyclic triazolium salts derived from (1*R*)-camphor and their application in other asymmetric reactions are currently under way.

4. Experimental section

4.1. General methods

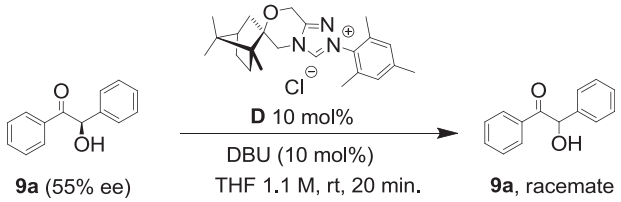
All chemicals used in this study were obtained from commercial sources and used without further purification. Reactions

Table 2
Screening of different bases[a]



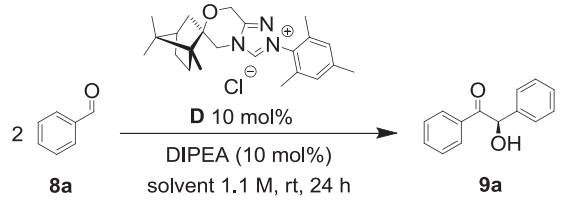
Entry	Base	Yield[b] (%)	er[c]
1	NEt_3	98	71.5:28.5
2	DIPEA	93	77.5:22.5
3	DCyEA	92	74:26
4	DMAP	62	78:22
5	DABCO	69	74:26
6	*t*-BuOK	75	Racemate
7	P_2–Et	73	Racemate
8	P_2–*t*-Bu	72	Racemate
9	K_2CO_3	93	Racemate
10	Cs_2CO_3	80	Racemate
11	DBU	95	Racemate

[a] Reaction conditions: **8a** (1 mmol), catalyst (10 mol %), base (10 mol %) in THF (1.1 mL).
[b] Yields of isolated benzoin.
[c] Determined by chiral HPLC (Daicel Chiralcel OD-H). P_2–Et, P_2–*t*-Bu=phosphazene bases, DCyEA=dicyclohexylethylamine.



Scheme 3. Racemization of **9a** under the reaction conditions.

Table 3
Screening of different solvents[a]

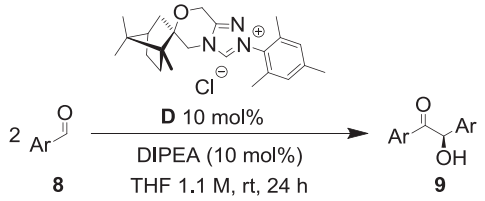


Entry	Aldehyde	Yield[b] (%)	er[c]
1	THF	93	77.5:22.5
2	Toluene	54	76.5:23.5
3	DMF	98	63.5:36.5
4	MeCN	76	62:38
5	EtOH	85	72:28
6[d]	CMPE	51	79:21
7[d]	TAME	49	78:22
8[d]	MTBE	56	79:21
9	CH_2Cl_2	28	72:28
10	DME	28	77:23
11[d]	OFT	26	74:26

[a] Reaction conditions: **8a** (1 mmol), catalyst (10 mol %), DIPEA (10 mol %) in THF (1.1 mL).
[b] Yields of isolated benzoin.
[c] Determined by chiral HPLC (Daicel Chiralcel OD-H).
[d] MTBE=methyl *tert*-butyl ether, CPME=cyclopentyl methyl ether, TAME=*tert*-amyl methyl ether, OFT=octafluorotoluene.

utilizing air- or moisture-sensitive reagents were carried out in flame-dried glassware under a dry Ar atmosphere. All solvents were purified and dried according to standard methods prior to use.

Table 4
Substrate scope for enantioselective intermolecular benzoin condensation[a]



Entry	Ar	Yield[b] (%)	er[c]
1	Ph (**8a**)	93 (**9a**)	77.5:22.5
2	2-Naphthyl (**8b**)	54 (**9b**)	74:26
3	4-MeC_6H_4 (**8c**)	28 (**9c**)	72:28
4	2-$MeOC_6H_4$ (**8d**)	51 (**9d**)	79:21
5	2-ClC_6H_4 (**8e**)	20 (**9e**)	62:38
6	4-$MeOC_6H_4$ (**8f**)	28 (**9f**)	82:18

[a] Reaction conditions: **8a**–**f** (1 mmol), **D** catalyst (10 mol %), DIPEA (10 mol %) in THF (1.1 mL).
[b] Yields of isolated benzoin.
[c] Determined by chiral HPLC (Daicel Chiralcel OD-H).

Reactions were monitored by thin layer chromatography using UV light to visualize the course of reaction. Purification of reaction products was carried out by column chromatography on silica gel. Chemical yields refer to pure isolated substances.

^1H and ^{13}H NMR spectra were obtained using a Bruker DPX-400 or Bruker DPX-700 spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, h=heptet, m=multiplet, br s=broad singlet. The melting points were determined on a Buchi SPM-20 melting point apparatus. Elemental analyses were performed on a Vario MACRO CHN analyzer. Optical rotations ($[\alpha]_D$) were measured on a PolAAr 3000 (Optical Activity LTD) polarimeter. IR spectra were recorded on Perkin–Elmer Spectrum Two spectrometer and are reported in terms of frequency of absorption cm^{-1}. Mass spectra were collected on a Shimadzu High Performance Liquid Chromatograph/Mass Spectrometer LCMS-8030 (ESI, operating both in positive and negative mode). Enantiomeric excesses were determined by HPLC analysis on chiral stationary phase using 4.6 mm×250 mm Daicel Chiralcel OD-H with *n*-hexane, 2-propanol as eluent.

The X-ray data for reported structure were collected at 293(2) K with an Oxford Sapphire CCD diffractometer using Mo Kα radiation λ=0.71073 Å and ω-2θ method. The numerical absorption correction was applied with CrysAlis171 package of programs, Oxford Diffraction, 2000.[17] Structure was solved by direct methods and refined with the full-matrix least-squares method on F^2 with the use of SHELX-97 program package.[18] The hydrogen atoms have been located from the difference electron density maps and constrained during refinement. The absolute configuration was determined by the Flack method.[19] CCDC No. 988374 for X-ray crystal structure **B**, and CCDC No. 988376 for X-ray crystal structure **D**.

4.2. Experimental procedure and characterization data for compounds

*4.2.1. (1R,2R,4R)-2-Cyano-2-trimethylsilanyloxy-1,3,3-trimethyl [2.2.1bicyclo]heptane-2-carbonitrile (**2**).* To a solution of lithium methoxide (158 mg, 4.2 mmol, 0.05 equiv) in 140 mL of anhydrous THF was added a trimethylsilylcyanide (10.4 mL, 83 mmol). The resulting clear yellow solution was stirred at rt for 20 min and 10.7 g (70 mmol) of (1*R*)-(+)-camphor **1** was added. The reaction mixture was stirred at rt until all the starting material was consumed. After completion, the reaction was quenched with 10% Na_2CO_3 (100 mL), and extracted with *tert*-butyl methyl ether

(3×100 mL). The combined organic layers were concentrated in vacuo to afford a crude liquid. The crude product was diluted with 200 mL of hexanes and washed twice with 2×25 mL of acetonitrile. The hexane layer was separated, and concentrated to afford 17.6 g (yield 99%) of the desired product as a colourless liquid **1**. $[\alpha]_D^{22}$ −2.2 (*c* 1.2, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.25 (s, 9H; 3× CH_3), 0.89 (s, 3H; CH_3), 0.97 (s, 3H; CH_3), 1.00 (s, 3H; CH_3), 1.14–1.22 (m, 1H), 1.56–1.67 (m, 1H), 1.71–1.80 (m, 2H), 1.83 (t, *J*=4.0 Hz, 1H), 2.07 (d, *J*=13.6 Hz, 1H), 2.19–2.24 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.1 (3× CH_3), 10.6 (CH_3), 20.4 (CH_3), 21.1 (CH_3), 26.5 (CH_2), 31.7 (CH_2), 45.2 (CH), 47.9 (C), 48.7 (CH_2), 54.1 (C), 78.6 (C), 122.1 (C). IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2947, 2228, 1482, 1457, 1254, 1150, 1104, 990, 922, 881, 844, 751. LRMS (ESI): *m*/*z* calcd for $C_{14}H_{25}NOSi$ $[M+Na]^+$, 274.2; found, 274.2. Anal. Calcd for $C_{14}H_{25}NOSi$ (251.44): C, 66.87; H, 10.02; N, 5.57. Found: C, 66.75; H, 10.14; N, 5.69%.

*4.2.2. (1R,2R,4R)-2-(Aminomethyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (**3**).* To a suspension of $LiAlH_4$ (2.3 g, 59.6 mmol) in 150 mL of anhydrous diethyl ether was added dropwise a solution of **2** (7.5 g, 29.8 mmol) in 150 mL of anhydrous diethyl ether at −10 °C over 45 min. The mixture was stirred for 3 h at this temperature, then allowed to warm to rt and stirred additionally for 20 h The reaction mixture was then carefully hydrolyzed with 4 N NaOH solution (10 mL) and water (20 mL). The precipitate was filtered off and washed with ether (3×75 mL). The combined organic layers were concentrated under vacuum to give aminoalcohol in very good purity as a white solid and was carried on without further purification (5.35 g, yield 99%). Mp=100–102 °C. $[\alpha]_D^{22}$ −18.2 (*c* 1.1, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$), 0.85 (s, 3H; CH_3), 0.88 (s, 3H; CH_3), 0.96–1.01 (m, 1H), 1.13 (s, 3H; CH_3), 1.25 (d, *J*=12.6 Hz, 1H), 1.29–1.34 (m, 1H), 1.38–1.44 (m, 1H), 1.66–1.74 (m, 2H), 1.95 (dt, *J*=3.5, 12.6 Hz, 1H), 2.69 (d, *J*=12.6 Hz, 1H), 2.77 (d, *J*=12.6 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 11.2 (CH_3), 20.4 (CH_3), 21.2 (CH_3), 27.2 (CH_2), 29.9 (CH_2), 45.0 (CH), 45.1 (CH_2), 49.1 (CH_2), 49.6 (C), 51.1 (C), 78.7 (C). IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3338, 2940, 2874, 1700, 1389, 1369, 1149, 1099, 1011, 945, 908, 855. LRMS (ESI): *m*/*z* calcd for $C_{11}H_{21}NO$ $[M+1]^+$, 184.2; found, 184.2. Anal. Calcd for $C_{11}H_{21}NO$ (183.29): C, 72.08; H, 11.55; N, 7.64. Found: C, 72.16; H, 11.67; N, 7.76%.

*4.2.3. 2-Chloro-N-(((1R,2R,4R)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)methyl) acetamide (**4**).* A solution of chloroacetic chloride (3.1 mL, 39.0 mmol) in 78 mL of dichloromethane was added dropwise to a biphasic solution of aminoalcohol **3** (6.5 g, 35.5 mmol) in 39 mL of dichloromethane and NaOH in water (0.5 N, 156 mL) over 45 min at 0 °C. The reaction mixture was warmed to rt and stirred for 4 h at that temperature. The biphasic solution was transferred to a separatory funnel, the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2×75 mL). The combined organics were washed 10% aqueous solution of sodium bicarbonate (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product (10.0 g, yield 99%) was obtained in very good purity and was carried on without further purification. White solid, mp=42–46 °C. $[\alpha]_D^{22}$ −26.7 (*c* 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 3H; CH_3), 0.94 (s, 3H; CH_3), 1.07–1.12 (m, 1H), 1.10 (s, 3H; CH_3), 1.38–1.54 (m, 3H), 1.60–1.90 (br s, 1H; OH), 1.70–1.78 (m, 2H), 1.98 (dt, *J*=4.0, 13.6 Hz, 1H), 3.30 (dd, *J*=4.8, 13.6 Hz, 1H), 3.54 (dd, *J*=6.8, 13.6 Hz, 1H), 4.09 (s, 2H; CH_2), 7.08 (br s, 1H; NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8 (CH_3), 20.6 (CH_3), 21.2 (CH_3), 26.7 (CH_2), 30.2 (CH_2), 42.6 (CH_2), 44.4 (CH_2), 44.7 (CH), 47.9 (CH_2), 49.5 (C), 51.6 (C), 80.6 (C), 166.7 (C=O). IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3317, 2943, 2875, 1655, 1560, 1432, 1255, 1101, 1074, 851, 788, 726, 689, 588. LRMS (ESI): *m*/*z* calcd for $C_{13}H_{22}{}^{35}ClNO_2$ $[M+Na]^+$, 282.1; found, 282.2. Anal. Calcd for $C_{13}H_{22}ClNO_2$ (259.77): C, 60.11; H, 8.54; N, 5.39. Found: C, 60.02; H, 8.50; N, 5.47%.

*4.2.4. (1R,2R,4R)-1,7,7-Trimethylspiro[bicyclo[2.2.1]heptane-2,2′-morpholin]-5′-one (**5**).* To a solution of chloroamide **4** (5.0 g, 19.2) in 94 mL of anhydrous dichloromethane was added dropwise a solution of potassium *tert*-butoxide (8.6 g, 76.8 mmol) in *iso*-propanol over 45 min at 0 °C. The solution was allowed to warm to ambient temperature and stirred for 24 h. After that time all volatile materials were evaporated under reduced pressure. Water (200 mL) was added and mixture was extracted with ethyl acetate (3×100 mL). The combined organic phases were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by crystallization (petroleum ether/ethyl acetate) provided the title compound as a white solid (4.0 g, yield 93%). Mp=139–141 °C. $[\alpha]_D^{22}$ −105.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (s, 3H; CH_3), 0.88 (s, 3H; CH_3), 0.98 (s, 3H; CH_3), 1.05 (ddd, *J*=5.2, 9.2, 12.4 Hz, 1H), 1.30 (ddd, *J*=3.2, 9.2, 12.4 Hz, 1H), 1.29 (d, *J*=13.2 Hz, 1H), 1.44 (ddd, *J*=5.6, 12.0, 13.6 Hz, 1H), 1.70–1.80 (m, 1H), 1.83 (t, *J*=4.8 Hz, 1H), 2.22–2.30 (m, 1H), 2.99 (dd, *J*=4.8, 11.6 Hz, 1H), 3.52 (d, *J*=11.6 Hz, 1H), 4.05 (d, *J*=17.6 Hz, 1H), 4.15 (d, *J*=17.6 Hz, 1H), 7.66 (br s, 1H; NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.2 (CH_3), 20.2 (CH_3), 20.8 (CH_3), 26.7 (CH_2), 29.9 (CH_2), 37.7 (CH_2), 45.1 (CH), 48.2 (CH_2), 49.0 (C), 51.7 (C), 60.7 (CH_2), 80.1 (C), 170.0 (C=O). IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3062, 2918, 1681, 1427, 1334, 1120, 1088, 1062, 905, 836, 767. LRMS (ESI): *m*/*z* calcd for $C_{13}H_{21}NO_2$ $[M+Na]^+$, 246.2; found, 246.2. Anal. Calcd for $C_{13}H_{21}NO_2$ (223.31): C, 69.92; H, 9.48; N, 6.27. Found: C, 70.01; H, 9.39; N, 6.35%.

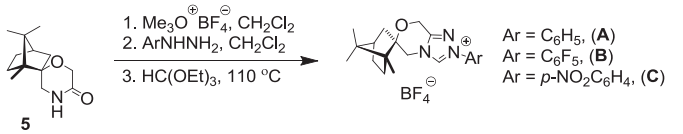
*4.2.5. (1R,2R,4R)-5′-Methoxy-1,7,7-trimethyl-3′,6′-dihydrospiro[bicyclo[2.2.1]-heptane-2,2′-[1,4]oxazine] (**6**).* A flame-dried 50 mL round-bottomed flask was charged with morpholinone **5** (1.0 g, 4.5 mmol), anhydrous dichloromethane (22 mL) and trimethyloxonium tetrafluoroborate (0.67 g, 4.5 mmol, 1.0 equiv). The white suspension was stirred at ambient temperature under an atmosphere of Ar for 6 h. The solution was cooled to 0 °C and quenched by slow, portion-wise addition of saturated aqueous $NaHCO_3$ (15 mL) over 15 min. Stirring was maintained for an additional 1 h. The biphasic solution was transferred to a separatory funnel, the organic phase separated and the aqueous phase extracted with CH_2Cl_2 (3×50 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated to afford the crude iminoether **6** as a yellowish liquid. Purification by column chromatography on silica gel (petroleum ether/ethyl acetate, 95:5) afforded the title compound as a colourless liquid (1.0 g, yield 97%). $[\alpha]_D^{22}$ −86.8 (*c* 1.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 3H; CH_3), 0.88 (s, 3H; CH_3), 1.01 (s, 3H; CH_3), 1.06–1.14 (m, 1H), 1.17 (d, *J*=13.2 Hz, 1H), 1.41 (d, *J*=7.6 Hz, 1H), 1.43 (d, *J*=7.6 Hz, 1H), 1.71–1.78 (m, 1H), 1.80 (t, *J*=4.8 Hz, 1H), 2.24 (dt, *J*=3.2, 13.2 Hz, 1H), 3.35 (dd, *J*=2.0, 15.2 Hz, 1H), 3.58 (d, *J*=15.2 Hz, 1H), 3.70 (s, 3H; OCH_3), 3.97 (d, *J*=16.8 Hz, 1H), 4.12 (dt, *J*=2.0, 16.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.3 (CH_3), 20.2 (CH_3), 21.0 (CH_3), 27.0 (CH_2), 29.8 (CH_2), 38.4 (CH_2), 45.3 (CH), 48.9 (C), 51.7 (C), 52.0 (OCH_3), 52.5 (CH_2), 56.9 (CH_2), 79.2 (C), 161.4 (C). IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2946, 1682, 1448, 1427, 1335, 1088, 1048, 1063, 838, 465. LRMS (ESI): *m*/*z* calcd for $C_{14}H_{23}NO_2$ $[M+Na]^+$, 260.2; found, 260.2. Anal. Calcd for $C_{14}H_{23}NO_2$ (237.34): C, 70.85; H, 9.77; N, 5.90. Found: C, 70.96; H, 9.68; N, 5.97%.

*4.2.6. (Z)-2-Mesityl-1-((1R,2R,4R)-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,2′-morpholin]-5′-ylidene)hydrazin-1-ium chloride (**7**).* A flame-dried 50 mL round-bottomed flask was charged with a magnetic stir bar, 2-mesitylhydrazinium chloride (0.79 g, 4.2 mmol, 1.0 equiv) and MeOH (17 mL) resulting in a light red/orange solution. To this solution was added **6** (1.0 g, 4.2 mmol, 1.00 equiv) and the stirred at ambient temperature for 5 min. A catalytic amount of anhydrous HCl (4 M in 1,4-dioxane, 0.1 mL) was added, the reaction flask equipped with a water-jacketed condenser and the solution stirred at 60 °C under an inert atmosphere for 4 h. The reaction was allowed to cool to ambient temperature and concentrated under reduced pressure to afford a crude orange

solid. The crude material was suspended in ethyl acetate (22 mL) and stirred vigorously at reflux for 30 min causing a light yellow precipitate to form. The suspension was allowed to cool to ambient temperature with vigorous stirring and immersed in an ice/water bath at 0 °C. The precipitate was collected by suction filtration and washed with EtOAc (3×5 mL) affording the title compound (1.4 g, yield 84%) as a white powder. Mp=206–208 °C, yield 84%. $[\alpha]_D^{22}$ −8.3 (*c* 1.1, CH_3OH). ^1H NMR (400 MHz, DMSO-d_6) δ 0.86 (s, 3H; CH_3), 0.88 (s, 3H; CH_3), 0.96 (s, 3H; CH_3), 1.08–115 (m, 1H), 1.24–1.30 (m, 1H), 1.48–1.61 (m, 2H), 1.43 (dt, *J*=5.6, 13.2 Hz, 1H), 1.70–1.76 (m, 1H), 1.83 (t, *J*=4.0 Hz, 1H), 2.19 (s, 6H; 2× CH_3), 2.34 (s, 3H; CH_3), 3.17 (dd, *J*=5.6, 13.2 Hz, 1H), 3.50 (d, *J*=13.2 Hz, 1H), 6.86 (s, 2H; 2× CH_{Ar}), 6.89 (s, 1H), 6.98 (s, 1H), 9.6 (br s, 1H, NH), 10.24 (d, *J*=4.4 Hz, 1H; NH), 11.11 (br s, 1H; NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.6 (CH_3), 18.3 (2× CH_3), 20.6 (CH_3), 20.7 (CH_3) 21.3 (CH_3), 26.7 (CH_2), 29.5 (CH_2), 38.6 (CH_2), 45.1 (CH), 46.6 (CH_2), 49.2 (C), 52.3 (C), 55.8 (CH_2), 81.7 (C), 129.9 (2× CH_{Ar}), 131.3 (2× C), 134.1 (C), 138.9 (C), 160.1 (C). IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3205, 2959, 1726, 1684, 1483, 1339, 1120, 1089, 1045, 850, 762. LRMS (ESI): *m*/*z* calcd for $C_{22}H_{34}N_3O$ $[M-Cl]^+$, 356.3; found, 356.3. Anal. Calcd for $C_{22}H_{34}ClN_3O$ (391.98): C, 67.41; H, 8.74; N, 10.72. Found: C, 68.79; H, 8.11; N, 10.37%.

*4.2.7. (1′R,2′R,4′R)-2-Mesityl-1′,7′,7′-trimethyl-5,8-dihydrospiro [[1,2,4]-triazolo[3,4-c][1,4] oxazine-6,2′-bicyclo[2.2.1]heptan]-2-ium chloride (**D**).* An oven-dried 50 mL round-bottomed flask was charged with a magnetic stir bar, **7** (1.2 g, 3.14 mmol), triethyl orthoformate (5.2 mL, 31.4 mmol, 10 equiv), chlorobenzene (15 mL) and anhydrous HCl (4 M in 1,4-dioxane, 0.78 mL, 3.14 mmol). The suspension was stirred at 120 °C for 2 h. The tan-coloured solution was allowed to cool to ambient temperature, and concentrated under reduced pressure to afford a crude brown foam. Recrystallization from diethyl ether afforded the title compound (1.0 g, 79%) as a white solid. Mp=260–262 °C, yield 79%. $[\alpha]_D^{22}$ −45.5 (*c* 1.0, $CHCl_3$). ^1H NMR (700 MHz, $CDCl_3$) δ 0.92 (s, 3H; CH_3), 0.97 (s, 3H; CH_3), 1.04 (s, 3H; CH_3), 1.33 (d, *J*=12.6 Hz, 1H), 1.40–1.45 (m, 1H), 1.48–1.61 (m, 3H), 1.91 (t, *J*=4.2 Hz, 1H), 2.08 (s, 6H; 2× CH_3), 2.20–2.25 (m, 1H), 2.34 (s, 3H; CH_3), 4.33 (d, *J*=12.6 Hz, 1H), 5.00 (d, *J*=17.5 Hz, 1H), 5.06 (d, *J*=17.5 Hz, 1H), 5.33 (d, *J*=12.6 Hz, 1H), 6.99 (s, 2H; 2× CH_{Ar}), 11.97 (s, 1H; CH). ^{13}C NMR (176 MHz, $CDCl_3$) δ 10.2 (CH_3), 17.7 (2× CH_3), 20.2 (CH_3), 20.7 (CH_3), 21.2 (CH_3), 26.2 (CH_2), 29.8 (CH_2), 35.9 (CH_2), 45.3 (CH), 49.4 (C), 52.5 (CH_2), 52.8 (C), 54.5 (CH_2), 82.2 (C), 129.8 (2× CH_{Ar}), 131.2 (C) 134.7 (C), 142.1 (C), 145.5 (CH), 145.8 (d, *J*=26.4 Hz, CH), 149.3 (C). IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3333, 2941, 1585, 1448, 1390, 1122, 1082, 976, 846, 580. LRMS (ESI): *m*/*z* calcd for $C_{23}H_{32}N_3O$ $[M-Cl]^+$, 366.3; found, 366.3. Anal. Calcd for $C_{23}H_{32}ClN_3O$ (401.97): C, 68.72; H, 8.02; N, 10.45. Found: C, 68.79; H, 8.11; N, 10.37%. X-ray crystal structure: $C_{23}H_{33}ClN_3O_{1.5}$, M_r=410.97. Colourless 0.47×0.32×0.26 mm crystal obtained from the methanol, triclinic space group *P*1. Cell parameters: *a*=12.7769(4), *b*=13.5683(4), *c*=13.8845(5) Å, α=97.978(3), β=93.633(3), γ=106.138(3)°, *V*=2276.62(13) A^3, D_{calcd}=1.199 mg/m^3, *Z*=4, *F*(000)=884, μ=0.188 mm^{-1}. The maximum and minimum transmissions of 0.9534 and 0.9161. *R*1=0.0754, *wR*2=0.2097 for reflections $I>2\sigma(I)$. The absolute structure Flack parameter *x*=0.00(9). The structural data have been deposited at the Cambridge Crystallographic Data Centre: (CCDC No. 988376).

4.3. Preparation of (1*R*)-camphor-derived triazolium salts A–C



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A flame-dried 50 mL round-bottomed flask was charged with morpholinone (1.0 g, 4.5 mmol) and dichloromethane (22 mL). Trimethyloxonium tetrafluoroborate (0.67 g, 4.5 mmol, 1.0 equiv) was added and stirred under atmosphere of Ar for 6 h. The corresponding aryl hydrazine was added (4.5 mmol, 1 equiv) and stirred at ambient temperature until the starting material was consumed as visualized by TLC (ca. 6 h). The solvent was evaporated and the triethyl orthoformate (40 equiv) was added. The mixture was then heated to 110 °C and stirred at this temperature for 18 h. After completion, the solvent was removed in vacuo. The crude product was washed with AcOEt affording the pure salt as a white or ochre powder.

*4.3.1. (1′R,2′R,4′R)-1′,7′,7′-Trimethyl-2-phenyl-5,8-dihydrospiro [[1,2,4]-triazolo[3,4-c][1,4]-oxazine-6,2′-bicyclo[2.2.1]heptan]-2-ium tetrafluoroborate (**A**).* White solid, mp=255–256 °C, yield 77%. $[\alpha]_D^{22}$ −78.0 (*c* 1.0, $CHCl_3$). ^1H NMR (700 MHz, DMSO-d_6) δ 0.91 (s, 3H; CH_3), 0.97 (s, 3H; CH_3), 1.03 (s, 3H; CH_3), 1.16–1.22 (m, 1H), 1.34–1.39 (m, 2H), 1.53–1.59 (ddd, *J*=5.6, 11.9, 14.0 Hz, 1H), 1.75–1.82 (m, 1H), 1.88 (t, *J*=4.2 Hz, 1H), 2.30–2.36 (m, 1H), 4.33 (s, 2H; CH_2), 5.24 (d, *J*=17.5 Hz, 1H), 5.28 (d, *J*=17.5 Hz, 1H), 7.65–7.75 (m, 3H), 7.90–7.94 (m, 2H), 10.80 (s, 1H; CH). ^{13}C NMR (176 MHz, DMSO-d_6) δ 10.5 (CH_3), 20.6 (CH_3), 21.2 (CH_3), 26.5 (CH_2), 29.7 (CH_2), 36.2 (CH_2), 45.1 (CH), 49.3 (C), 51.4 (CH_2), 52.7 (C), 54.5 (CH_2), 81.4 (CH), 121.1 (2× CH_{Ar}), 130.8 (2× CH_{Ar}), 131.1 (CH_{Ar}), 135.4 (C_{Ar}), 142.5 (CH), 149.6 (C). IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2942, 1589, 1438, 1226, 1084, 1048, 979, 761, 686, 521. LRMS (ESI): *m*/*z* calcd for $C_{20}H_{26}N_3O$ $[M-BF_4]^+$, 324.2; found, 324.2. Anal. Calcd for $C_{20}H_{26}BF_4N_3O$ (411.24): C, 58.41; H, 6.37; N, 10.22. Found: C, 58.46; H, 6.28; N, 10.33%.

*4.3.2. (1′R,2′R,4′R)-1′,7′,7′-Trimethyl-2-(perfluorophenyl)-5,8-dihydrospiro-[[1,2,4]triazolo[3,4-c][1,4]oxazine-6,2′-bicyclo[2.2.1] heptan]-2-ium tetrafluoroborate (**B**).* White solid, mp=250–252 °C, yield 72%. $[\alpha]_D^{22}$ −50.0 (*c* 1.0, acetone). ^1H NMR (400 MHz, acetone-d_6) δ 0.96 (s, 3H; CH_3), 1.02 (s, 3H; CH_3), 1.09 (s, 3H; CH_3), 1.25–1.32 (m, 1H), 1.46–1.53 (m, 1H), 1.56 (d, *J*=13.2 Hz, 1H), 1.60–1.68 (m, 1H), 1.79–1.88 (m, 1H), 1.94 (t, *J*=4.4 Hz, 1H), 2.45–2.52 (m, 1H), 4.63 (d, *J*=13.2 Hz, 1H), 4.86 (d, *J*=13.2 Hz, 1H), 5.33 (d, *J*=17.6 Hz, 1H), 5.40 (d, *J*=17.6 Hz, 1H), 10.45 (s, 1H). ^{13}C NMR (100 MHz, acetone-d_6) δ 9.4 (CH_3), 19.6 (CH_3), 20.3 (CH_3), 25.9 (CH_2), 29.4 (CH_2), 36.1 (CH_2), 45.4 (CH), 46.8 (C), 52.3 (CH_2), 52.7 (C), 54.3 (CH_2), 81.5 (C), 147.2 (CH), 151.1 (C). IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930, 1595, 1522, 1438, 1075, 1051, 1020, 999, 857, 626, 522. LRMS (ESI): *m*/*z* calcd for $C_{20}H_{21}F_5N_3O$ $[M-BF_4]^+$, 414.2; found, 414.2. Anal. Calcd for $C_{20}H_{21}BF_9N_3O$ (501.20): C, 47.93; H, 4.22; N, 8.38. Found: C, 47.81; H, 4.16; N, 8.45%. X-ray crystal structure: $C_{20}H_{21}BF_9N_3O$, M_r=501.20. Colourless 0.27×0.16×0.07 mm crystal obtained from the methanol, monoclinic space group *P*2(1). Cell parameters: *a*=10.001(2), *b*=7.501(2), *c*=14.747(3) Å, β=96.62(3)°, V=1098.9(4) A^3, D_{calcd}=1.515 mg/m^3, *Z*=2, *F*(000)=512, μ=0.146 mm^{-1}. The maximum and minimum transmissions of 0.9893 and 0.9606. *R*1=0.0533, *wR*2=0.1150 for reflections $I>2\sigma(I)$. The absolute structure Flack parameter *x*=0.01(11). The structural data have been deposited at the Cambridge Crystallographic Data Centre: (CCDC No. 988374).

*4.3.3. (1′R,2′R,4′R)-1′,7′,7′-Trimethyl-2-(4-nitrophenyl)-5,8-dihydrospiro-[[1,2,4]triazolo[3,4-c][1,4]oxazine-6,2′-bicyclo[2.2.1] heptan]-2-ium tetrafluoroborate (**C**).* Ochre solid, mp=316–317 °C, yield 54%. $[\alpha]_D^{22}$ −76.6 (*c* 1.0, acetone). ^1H NMR (700 MHz, acetone-d_6) δ 0.92 (s, 3H; CH_3), 0.99 (s, 3H; CH_3), 1.05 (s, 3H; CH_3), 1.24 (ddd, *J*=4.9, 9.1, 12.6 Hz, 1H), 1.46 (m, 1H), 1.47 (d, *J*=13.3 Hz, 1H), 1.60 (ddd, *J*=4.9, 11.2, 14.0 Hz, 1H), 1.78–1.83 (m, 1H), 1.89 (t, *J*=4.9 Hz, 1H), 2.44 (dt, *J*=2.8, 14.0 Hz, 1H), 4.52 (d, *J*=12.6 Hz, 1H), 4.70 (d, *J*=12.6 Hz, 1H), 5.30 (d, *J*=17.5 Hz, 1H), 5.34 (d, *J*=17.5 Hz, 1H), 8.24–8.27 (m, 2H), 8.53–8.56 (m, 2H), 10.67 (s, 1H). ^{13}C NMR (176 MHz, acetone-d_6) δ 9.5 (CH_3), 19.7 (CH_3), 20.3 (CH_3), 25.9 (CH_2),

29.2 (CH_2), 35.9 (CH_2), 45.3 (CH), 49.1 (C), 51.8 (CH_2), 52.6 (C), 54.3 (CH_2), 81.6 (C), 122.6 (2× CH_{Ar}), 125.7 (2× CH_{Ar}), 139.5 (C), 142.8 (CH), 148.8 (C), 150.4 (C). IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2953, 2933, 1595, 1528, 1350, 1227, 1049, 972, 854, 749, 523. LRMS (ESI): *m/z* calcd for $C_{20}H_{25}N_4O_3$ $[M-BF_4]^+$, 369.2; found, 369.2. Anal. Calcd for $C_{20}H_{25}BF_4N_4O_3$ (456.24): C, 52.65; H, 5.52; N, 12.28. Found: C, 52.60; H, 5.44; N, 12.39%.

4.4. Benzoin reaction

To a stirred solution of triazolium salt **D** (0.1 mmol, 10 mol %) in anhydrous THF (1 mL), was added DIPEA (0.1 mmol, 10 mol %) in one portion. After 15 min aromatic aldehyde (1 mmol) was added dropwise at rt under argon. The reaction mixture was stirred for 20 h, then the reaction mixture was directly purified by chromatography (silica gel, petroleum ether/ethyl acetate, 8:2) to give the desired benzoins as white or yellow solids.

*4.4.1. (R)-2-Hydroxy-1,2-diphenylethanone (**9a**).*[10] Purification by silica gel column chromatography (petroleum ether/ethyl acetate, 8:2) gave (*R*)-**9a** (93% yield) as a white solid, mp=130–132 °C. $[\alpha]_D^{21}$ −82.2 (*c* 1.2, MeOH). Lit.:[20] $[\alpha]_D^{25}$ −150.1 (*c* 0.56, MeOH), for *R* enantiomer with 99% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.56 (br s, 1H), 5.94 (s, 1H), 7.27–7.44 (m, 7H), 7.50 (t, *J*=8.0 Hz, 1H), 7.94 (d, *J*=8.0 Hz, 2H); 77.5:22:5 er [Daicel Chiralcel OD-H, hexanes/2-propanol 90:10, *v*=0.7 mL/min^{-1}, λ=254 nm, *t* (minor)=16.6 min, *t* (major)=23.7 min].

*4.4.2. (R)-2-Hydroxy-1,2-di(naphthalen-2-yl)ethanone (**9b**).*[10] Purification by silica gel column chromatography (petroleum ether/ethyl acetate, 8:2) gave (*R*)-**9b** (54% yield) as a white solid, mp=116–118 °C. $[\alpha]_D^{21}$ +26.8 (*c* 0.9, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (br s, 1H), 6.33 (s, 1H), 7.45–7.65 (m, 5H), 7.74–7.83 (m, 5H), 7.87 (d, *J*=8.1 Hz, 1H), 7.94 (s, 1H), 8.05 (d, *J*=8.1 Hz, 1H), 8.51 (s, 1H); 77.5:22:5 er [Daicel Chiralcel OD-H, hexanes/2-propanol 90:10, *v*=0.7 mL/min^{-1}, λ=254 nm, *t* (major)=45.6 min, *t* (minor)=49.2 min].

*4.4.3. (R)-2-Hydroxy-1,2-di(p-tolyl)ethanone (**9c**).*[10] Purification by silica gel column chromatography (petroleum ether/ethyl acetate, 8:2) gave (*R*)-**9c** (28% yield) as a yellow solid, mp=87–89 °C. $[\alpha]_D^{21}$ −55.1 (*c* 1.1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.37 (s, 3H), 4.60 (br s, 1H), 5.94 (s, 1H), 7.09–7.25 (m, 6H), 7.81 (d, *J*=8.0 Hz, 2H); 72:28 er [Daicel Chiralcel OD-H, hexanes/2-propanol 90:10, *v*=0.7 mL/min^{-1}, λ=254 nm, *t* (major)=26.4 min, *t* (minor)=33.7 min].

*4.4.4. (R)-2-Hydroxy-1,2-bis(2-methoxyphenyl)ethanone (**9d**).*[10] Purification by silica gel column chromatography (petroleum ether/ethyl acetate, 7:3) gave (*R*)-**9d** (51% yield) as a white solid, mp=98–100 °C. $[\alpha]_D^{21}$ −59.6 (*c* 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (3H, s), 3.74 (3H, s), 4.50 (br s, 1H), 6.15 (1H, s), 6.73–6.79 (m, 2H), 6.84–6.88 (m, 1H), 6.90–6.95 (m, 1H), 7.19–7.25 (m, 2H), 7.37–7.41 (m, 1H), 7.70 (d, *J*=7.8 Hz, 1H); 79:21 er [Daicel Chiralcel OD-H, hexanes/2-propanol 85:15, *v*=0.5 mL/min^{-1}, λ=254 nm, *t* (minor)=30.6 min, *t* (major)=43.5 min].

*4.4.5. (R)-1,2-Bis(2-chlorophenyl)-2-hydroxyethanone (**9e**).*[10] Purification by silica gel column chromatography (petroleum ether/ethyl acetate, 8:2) gave (*R*)-**9e** (20% yield) as an off-white solid, mp=61–63 °C. $[\alpha]_D^{21}$ −8.8 (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 4.05 (br s, 1H), 6.27 (s, 1H), 7.11–7.39 (m, 8H). 62:38 er [Daicel Chiralcel OD-H, hexanes/2-propanol 90:10, *v*=0.7 mL/min^{-1}, λ=254 nm, *t* (major)=26.6 min, *t* (minor)=31.4 min].

*4.4.6. (R)-2-Hydroxy-1,2-bis(4-methoxyphenyl)ethanone (**9f**).*[10] Purification by silica gel column chromatography (petroleum ether/ethyl acetate, 7:3) gave (*R*)-**9f** (28% yield) as a yellow solid, mp=120–121 °C. $[\alpha]_D^{21}$ −30.2 (*c* 0.45, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 3H), 3.80 (s, 3H), 4.42 (br s, 1H), 5.84 (s, 1H), 6.80–6.89 (m, 4H), 7.24–7.31 (m, 2H), 7.90 (d, *J*=8.8 Hz, 2H). 82:18 er [Daicel Chiralcel OD-H, hexanes/2-propanol 80:20, *v*=0.7 mL/min^{-1}, λ=254 nm, *t* (major)=47.7 min, *t* (minor)=64.2 min].

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Supplementary data

A supplementary data file (^{1}H and ^{13}C NMR) of newly synthesized compounds (**2**–**7**, **A**–**D**) is available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.06.066.

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