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Takahiro Soeta, So Mizuno, Yuichi Hatanaka, Yutaka Ukaji

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Asymmetric cross-benzoin condensation promoted by chiral triazolium precatalyst bearing a pyridine moiety

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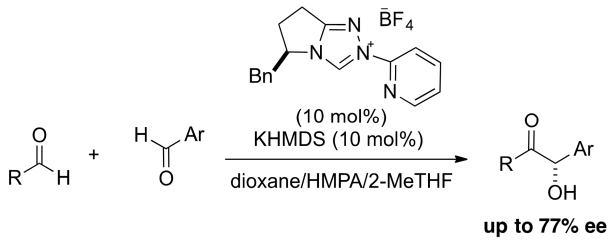
Takahiro Soeta*, So Mizuno, Yuichi Hatanaka, Yutaka Ukaji*
Division of Material Chemistry, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma, Kanazawa 920-1192, Japan



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Takahiro Soeta*, So Mizuno, Yuichi Hatanaka, Yutaka Ukaji*

Division of Material Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma, Kanazawa 920-1192, Japan

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ABSTRACT

Cross-benzoin condensation catalyzed by NHC, prepared from chiral triazolium salts bearing a pyridine ring, afforded α-hydroxy ketones with reasonable chemical yields and enantioselectivities. A wide range of aliphatic and aromatic aldehydes were successfully used in the reaction.

1. Introduction

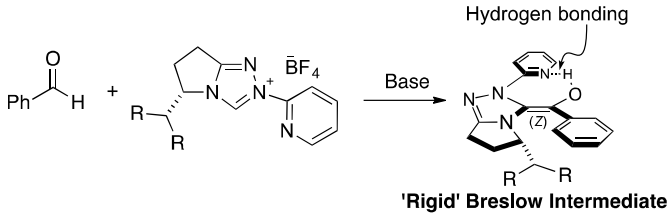
In 1943, Ukai reported that thiamine catalyzed benzoin condensation,[1a] and the mechanism of thiazolium-catalyzed benzoin condensation was elucidated by Breslow in 1958.[2] The introduction of NHCs as an organocatalyst led to a breakthrough in this area. Since the first stable nucleophilic carbene was reported by Bertrand, Arduengo and coworkers in 1990,[1,3] broad application of *N*-heterocyclic carbenes (NHCs) in organic synthesis has been dramatically demonstrated. The first catalytic asymmetric benzoin condensation reaction was developed by Sheehan and Hunnemann in 1966, although the enantioselectivity was low.[4] Recently, several successful catalysts were reported in the reaction of two identical aldehydes,[5] yet cross-benzoin condensation is still a significant challenge. The first example of cross-benzoin condensation catalyzed by a thiazolium salt as an NHC precursor was reported by Stetter in 1977.[6] Imines and iminium salts are also good acceptors for cross-benzoin-type condensation reactions, affording α-aminoketones with high chemoselectivities.[7] In 2005, an asymmetric version of cross-benzoin-type condensation between aldehydes and imine precursors was developed by Miller using a thiazolium-derived catalyst with a peptide backbone.[8] Meanwhile, acylsilanes and acylphosphonates were found to be suitable substrates for aldehyde ketone cross-coupling catalyzed by cyanide ions.[9] Ketones including α-keto esters were also found to be good substrates,[10] thereby largely avoiding chemoselectivity issues. Intramolecular cross-benzoin condensation between different aldehydes and ketones has also been developed, including asymmetric reactions.[11] These are just some of the many examples of benzoin condensation, and particularly promising examples of cross-benzoin condensation have been studied independently by Zeitler, Cannon, Gravel, Glorius and Yang.[12] However, there are still limitations associated with general cross-benzoin condensation between two different aldehydes catalyzed by NHC, especially in terms of enantioselectivity.[12,13]

We recently developed a family of chiral triazolium salts bearing a pyridine moiety, which have been shown to catalyze benzoin condensation and intramolecular Stetter reactions to give products with high enantioselectivity.[14] Herein, we report catalytic asymmetric cross-benzoin condensation between two different aldehydes to afford the corresponding α-hydroxyketones with good enantioselectivity.

2. Results and Discussion

In NHC-catalyzed asymmetric reactions, conformational control of the Breslow intermediate is crucial in order to obtain products with a high degree of enantioselectivity. In the view of these points, we anticipated that a chiral triazolium salt with a Lewis basic moiety would undergo intramolecular hydrogen bonding with the OH group of the Breslow intermediate, giving a more rigid intermediate in the umpolung reaction and giving products with greater stereoselectivity (Scheme 1). We designed and synthesized a variety of chiral triazolium salts bearing a pyridine ring (Figure 1). Our initial reactions attempted cross-benzoin condensation of 1.5 equiv of 3-phenylpropanal (**1a**) and benzaldehyde (**2a**) using 5 mol% of triazolium salt **4**, with 1.0 equiv of diisopropylethylamine (DIPEA) as a base to generate a

carbene catalyst, in THF at 70 °C. The desired α-hydroxyketone **3aa** was obtained in 43% ee with a yield of 24% (eq 1). To determine the importance of the pyridine ring of the precatalyst, we then carried out the reaction using triazolium salt **5**, with no pyridine ring.[15] The reaction proceeded smoothly, but the product **3aa** was obtained in 24% ee with a yield of 14%. This result clearly indicated that the pyridinyl group plays an important role in achieving higher enantioselectivity.



Scheme 1. Working hypothesis

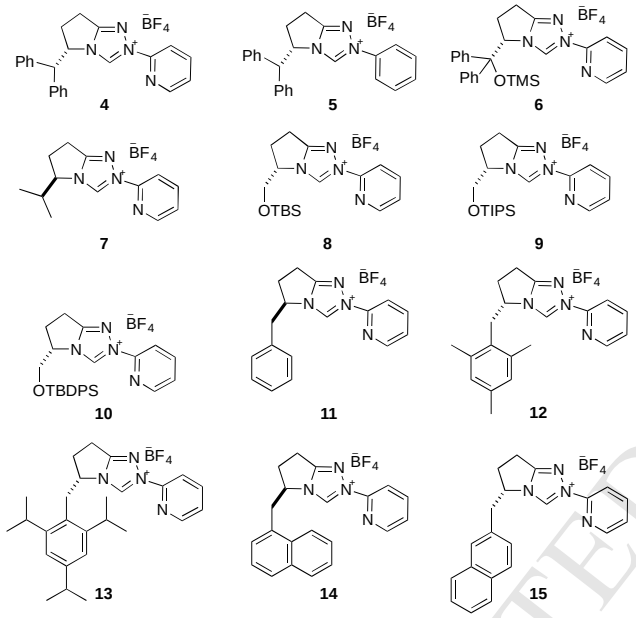
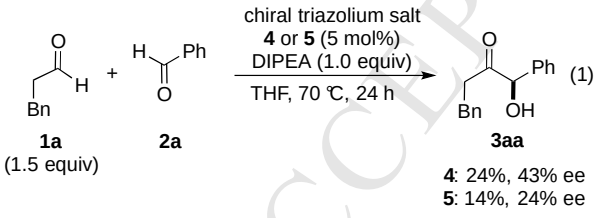
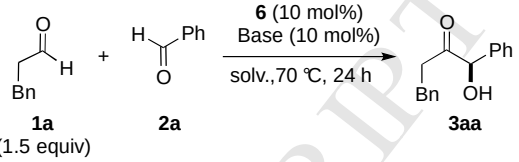


Figure 1. Chiral triazolium salts bearing a pyridine ring



To optimize the reaction conditions, we examined the reaction solvent, base, and reaction temperature using chiral triazolium salt **6**, which has been demonstrated to be useful in benzoin condensation.[14a] The results are shown in Table 1. Cross-benzoin condensation of **1a** and **2a** was carried out using 10 mol% of triazolium salt **6** with 10 mol% of DIPEA as a base in THF at 70 °C, giving α-hydroxyketone **3aa** with 60% ee and a yield of 56% (entry 1). When other solvents such as MeCN, dichloromethane, and toluene were used, the desired product **3aa** was obtained with moderate enantioselectivity but the chemical yields were lower (entries 2–4). A dramatic improvement in enantioselectivity was achieved—up to 80% ee—by using a dioxane/HMPA (1/1) solvent system (entry 5).[14a] To improve the chemical yield, we examined the optimum base and reaction temperature for efficient generation of the carbene catalyst. When KO*t*-Bu was used as a base at 70 °C, the chemical yield of **3aa** increased to 54%, but enantioselectivity was lower (entry 6). When the reaction temperature was decreased to 50 °C and 40 °C, an increase in enantioselectivity, rather than a decrease in chemical yield, was observed (entries 6–8). Finally, we found that the desired product **3aa** was obtained with 60% ee and a yield of 62% when the reaction was carried out at 40 °C using KHMDS as a base and dioxane/HMPA/2-MeTHF (4/1/1) as a solvent (entry 9). 2-MeTHF is a useful solvent for this reaction, as it dissolves solid KHMDS.

Table 1. Optimization of reaction conditions



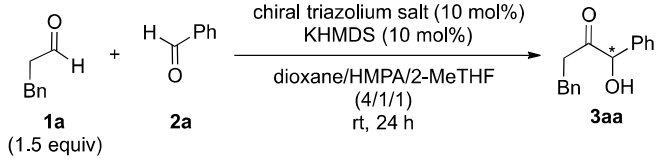
entry	base	solv.	yield/%	ee/%[a]
1	DIPEA	THF	56	60
2	DIPEA	MeCN	13	79
3	DIPEA	CH_2Cl_2	15	46
4	DIPEA	toluene	12	55
5	DIPEA	dioxane/HMPA[b]	19	80
6	KO*t*-Bu	dioxane/HMPA[b]	54	60
7[c]	KO*t*-Bu	dioxane/HMPA[b]	38	80
8[d]	KO*t*-Bu	dioxane/HMPA[b]	13	87
9[d]	KHMDS	dioxane/HMPA/ 2-MeTHF[e]	62	60

[a] The absolute configuration of (*R*)-**3aa** was determined by comparison of the specific rotation with the reported value.[16a] [b] The solvent ratio was 1/1 (volume/volume). [c] Reaction was carried out at 50 °C. [d] Reaction was carried out at 40 °C. [e] The solvent ratio was 4/1/1 (volume/volume).

We then turned our attention to the structure of the chiral triazolium salt (Table 2). The chiral triazolium salt **7**, bearing an isopropyl group at the stereocenter, gave a higher chemical yield of 83% (entry 2). Based on this result, the catalytic efficiency of the chiral triazolium salt is highly dependent on the bulkiness of the substituent on the chiral center. The introduction of a TBS-protected methanol group onto the pyrrolidine ring (**8**) gave the product with high chemical yield, but the enantioselectivity was 47% (entry 3). When the reaction was carried out at room temperature, the reaction still proceeded, affording the product with moderate chemical yield and enantioselectivity (entry 4). Triazolium salts (**9** or **10**) bearing a TIPS group or a TBDMS group on the alcohol moiety gave the product **3aa** with almost same enantioselectivity as **8** (entries 5 and 6). We found that the use of a chiral triazolium salt bearing a benzyl group (**11**) resulted in improved chemical yield and enantioselectivity, giving the product with 65% ee and a yield of 69% at room temperature (entry 7). The use of chiral imidazolium salts bearing more bulky benzyl groups such as mesitylmethyl (**12**), triisopropylphenylmethyl (**13**), 1-naphthylmethyl (**14**), and 2-naphthylmethyl (**15**) resulted in lower enantioselectivities and/or chemical yields (entries 8–11). Enantioselectivities did not

change when the reactions ran for shorter and longer time (entries 7, 12 and 13).

Table 2. Effects of various precatalysts

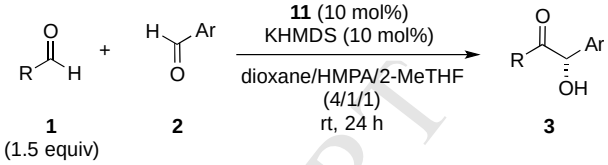


entry[a]	chiral triazolium salt	yield/%	ee/%	absolute configuration[b]
1[c]	**6**	62	60	*R*
2[c]	**7**	83	43	*S*
3[c]	**8**	99	47	*R*
4	**8**	46	63	*R*
5	**9**	48	61	*R*
6	**10**	63	62	*R*
7	**11**	69	65	*S*
8	**12**	42	37	*R*
9	**13**	50	40	*R*
10	**14**	48	69	*S*
11	**15**	38	62	*R*
12[d]	**11**	26	66	*S*
13[e]	**11**	55	64	*S*

[a] 3-Phenylpropanal (**1a**) (1.5 equiv) and benzaldehyde (**2a**) (1.0 equiv) were used as substrates. [b] The absolute configuration of **3aa** was determined by comparison of the specific rotation with the reported value. [16a] [c] The reaction was carried out at 40 °C. [d] Reaction time was 4 h. [e] Reaction time was 48 h.

Under the optimized reaction conditions using the active and selective precatalyst **11**, the scope of the catalytic enantioselective cross-benzoin condensation reaction was demonstrated using various aliphatic and aromatic aldehydes (Table 3). We were delighted to find that our catalytic system was applicable to a wide range of aldehydes using 10 mol% of **11** and 10 mol% of KHMDS in 1,4-dioxane/HMPA/2-MeTHF at room temperature. 3-Phenylpropanal (**1a**) and its derivatives **1b** and **1c** were good substrates for the reaction, affording the products with moderate enantioselectivity (entries 1–3). In the case of linear aliphatic aldehydes such as propionaldehyde (**1d**) and *n*-octanal (**1e**), the products were obtained with reasonable enantioselectivities; however, branched aldehydes were not effective in this reaction system, possibly due to steric hindrance (entries 4–7). Next, we examined the reactions of various types of aromatic aldehyde with 3-phenylpropanal (**1a**), again using chiral triazolium salt **11**. 1-Naphthaldehyde (**2b**) showed lower reactivity, but with moderate enantioselectivity (entry 8). In contrast, 2-naphthaldehyde (**2c**) was a good substrate, affording the product **3ac** with 67% ee and a yield of 76% (entry 9). We also examined substituted benzaldehydes bearing an electron-withdrawing group (entries 10–15). Products **3ad**–**3ai** were obtained with moderate enantioselectivities, except for **3ae** and **3ai** (entries 11 and 15). In the case of 4-bromobenzaldehyde (**2h**), a higher enantioselectivity (77% ee) was achieved (entry 14). Next, we examined substituted benzaldehydes bearing an electron-donating group (entries 16–21). In all cases except one, the reaction proceeded to afford the corresponding α-hydroxyketone with 64–69% enantioselectivity. The exception was 2-methylbenzaldehyde (**2m**), which was possibly due to steric hindrance (entry 19).

Table 3. Reactions with various substrates

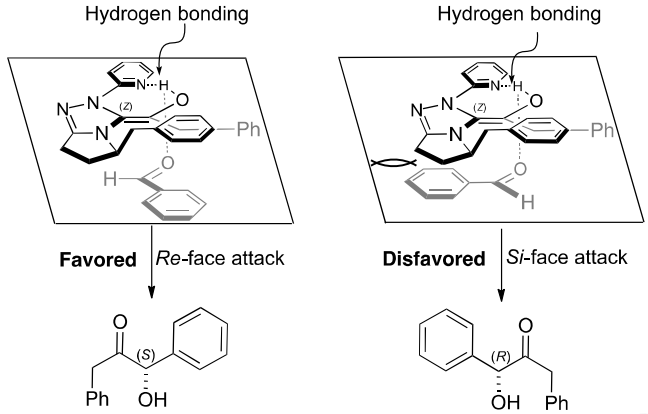


entry[a]	R	Ar	yield/%	ee/%[b]
1	$BnCH_2$ (**1a**)	C_6H_5 (**2a**)	69 (**3aa**)	65
2	4-$MeC_6H_4CH_2$ (**1b**)	C_6H_5 (**2a**)	66 (**3ba**)	56
3	4-$MeOC_6H_4CH_2$ (**1c**)	C_6H_5 (**2a**)	31 (**3ca**)	67
4	Et (**1d**)	C_6H_5 (**2a**)	23 (**3da**)	60[c]
5	*n*-Hept (**1e**)	C_6H_5 (**2a**)	55 (**3ea**)	59
6	*i*-Bu (**1f**)	C_6H_5 (**2a**)	24 (**3fa**)	17
7	*i*-Pr (**1g**)	C_6H_5 (**2a**)	trace	nd
8	$BnCH_2$ (**1a**)	1-naphtyl (**2b**)	28 (**3ab**)	64
9	$BnCH_2$ (**1a**)	2-naphtyl (**2c**)	76 (**3ac**)	67
10	$BnCH_2$ (**1a**)	2-ClC_6H_4 (**2d**)	41 (**3ad**)	69
11	$BnCH_2$ (**1a**)	3-ClC_6H_4 (**2e**)	50 (**3ae**)	39
12	$BnCH_2$ (**1a**)	4-ClC_6H_4 (**2f**)	43 (**3af**)	69
13	$BnCH_2$ (**1a**)	2-BrC_6H_4 (**2g**)	30 (**3ag**)	64
14	$BnCH_2$ (**1a**)	4-BrC_6H_4 (**2h**)	46 (**3ah**)	77
15	$BnCH_2$ (**1a**)	4-$MeO_2CC_6H_4$ (**2i**)	40 (**3ai**)	43
16	$BnCH_2$ (**1a**)	2-$MeOC_6H_4$ (**2j**)	39 (**3aj**)	69
17	$BnCH_2$ (**1a**)	3-$MeOC_6H_4$ (**2k**)	66 (**3ak**)	68
18	$BnCH_2$ (**1a**)	4-$MeOC_6H_4$ (**2l**)	19 (**3al**)	64
19	$BnCH_2$ (**1a**)	2-MeC_6H_4 (**2m**)	nd	nd
20	$BnCH_2$ (**1a**)	3-MeC_6H_4 (**2n**)	46 (**3an**)	70
21	$BnCH_2$ (**1a**)	4-MeC_6H_4 (**2o**)	52 (**3ao**)	64

[a] Aliphatic aldehydes **1** (1.5 equiv) and aromatic aldehydes **2** (1.0 equiv) were used as substrates. [b] The absolute configurations of **3** were assigned based on the analogous reactions in Table 2. [c] The absolute configuration of (*S*)-**3da** was determined by comparison of the specific rotation with the reported value.[16b]

By comparison of its optical rotation with that reported in the literature, the absolute stereochemistry of the major isomer of benzoin **3aa** prepared using the chiral triazolium salt **11** was determined to be *S*.[16a] Based on the determined stereochemistry, a transition state model, as shown in Scheme 2, was proposed. The benzyl group shields the *Si* face of the Breslow intermediate, whose geometry is controlled by hydrogen bonding between the hydroxyl group and the pyridine ring. Therefore, the attack of the incoming aromatic aldehyde molecule occurs from the less hindered *Re* face; that is, the Breslow intermediate predominantly approaches the *Re* face of the aromatic aldehyde, leading to an *S* configuration at the newly formed stereogenic center. *Si* attack by the Breslow intermediate may be disfavored due to steric repulsion between the heterocyclic moiety of the intermediate and the aromatic ring of the aldehyde. The precise mechanism of stereoinduction is now under further investigation in our laboratory.

Scheme 2. Stereochemical model of cross-benzoin condensation



3. Conclusion

In summary, we have developed a cross-benzoin condensation reaction catalyzed by NHC prepared from chiral triazolium salts bearing a pyridine ring, giving α-hydroxy ketones with reasonable chemical yields and enantioselectivities. A wide range of aliphatic and aromatic aldehydes were successfully used in the reaction.

4. Experimental Section

General Method

^{1}H NMR spectra were recorded on a 400 MHz NMR spectrometer. Chemical shifts δ are reported in ppm using TMS as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (*J*) and integration. ^{13}C NMR spectra were recorded on 100 MHz NMR spectrometer. The chemical shifts were determined in the δ-scale relative to $CDCl_3$ (δ = 77.0 ppm). The wave numbers of maximum absorption peaks of IR spectroscopy are presented in cm^{-1}. HRMS (FAB positive, DART) was measured with a quadrupole mass spectrometer and TOF mass spectrometers. All melting points were measured using a micro melting point apparatus. Dehydrated solvents were purchased for the reactions and used without further desiccation.

General procedures for the synthesis of chiral lactams 16–18

Synthesis of chiral lactams 16 and 17[17]

To a solution of corresponding benzyl bromide derivative (6.5 mmol) in THF (20 mL), *t*-BuLi (8.0 mL, 1.63 M in pentane) was added dropwise at –78 °C, and the whole was stirred at 0 °C for 10 min. To the reaction mixture, CuCN (292 mg, 3.26 mmol) was added one portion and the whole was stirred at 0 °C for 20 min. To the reaction mixture, (*S*)-5-(tosylmethyl)pyrrolidin-2-one[18] (584 mg, 2.2 mmol) in THF (2.0 mL) was added dropwise at –78 °C and the whole was stirred at –78 °C for 1 h, and warmed to room temperature. After 24 h, 1 M HCl was added and the organic solvents were removed in *vacuo*. The aqueous layer was extracted with $CHCl_3$ (10 mL x 3). The combined organic layers were washed with water and brine, then, dried over Na_2SO_4. Condensation and the subsequent purification by silica gel flash column chromatography gave the corresponding chiral lactam.

(*S*)-5-(2,4,6-Trimethylbenzyl)pyrrolidin-2-one (16)

Silca gel column chromatography (hexane/ethyl acetate = 20/1~3/1) gave **16** (193 mg, 41%) as a white solid of mp = 144–145 °C and $[\alpha]^{25}_D$ –41.5 (*c* 0.54, EtOH). ^{1}H NMR ($CDCl_3$): 1.78–1.85 (m, 1H), 2.18 (s, 3H), 2.22 (s, 6H), 2.25–2.41 (m, 3H), 2.75–2.81 (m, 2H), 3.78–3.85 (m, 1H), 5.25 (brs, 1H), 6.79 (s, 2H). ^{13}C NMR ($CDCl_3$): 20.4, 20.7, 27.5, 30.0, 35.8, 53.9, 129.4, 131.3, 136.1, 136.4, 177.6. IR (KBr): 2960, 1710, 1460, 1380, 1360, 1250, 1050 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{14}H_{20}NO$ $[M+H]^+$: 218.1545. Found: 218.1551.

(*S*)-5-(2,4,6-Triisopropylbenzyl)pyrrolidin-2-one (17)

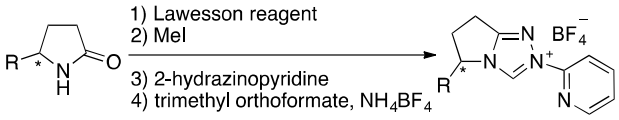
Silca gel column chromatography (hexane/ethyl acetate = 20/1~2/1) gave **17** (271 mg, 41%) as a white solid of mp = 158–159 °C and $[\alpha]^{25}_D$ –38.6 (*c* 0.11, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.14 (d, *J* = 6.8 Hz, 6H), 1.17 (d, *J* = 6.8 Hz, 6H), 1.18 (d, *J* = 6.8 Hz, 6H), 1.82–1.87 (m, 1H), 2.24–2.30 (m, 2H), 2.32–2.42 (m, 1H), 2.73–2.89 (m, 3H), 3.08–3.10 (m, 2H), 3.70–3.77 (m, 1H), 5.23 (brs, 1H), 6.93 (s, 2H). ^{13}C NMR ($CDCl_3$): 23.7, 23.9, 24.1, 26.6, 29.1, 29.9, 32.2, 33.8, 55.3, 120.9, 127.9, 147.7, 146.8, 177.4. IR (KBr): 2970, 1700, 1450, 1390, 1360, 1250, 1060 cm^{-1} HRMS–DART (*m/z*): Calcd for $C_{20}H_{32}NO$ $[M+H]^+$: 302.2484. Found: 302.2470.

(*R*)-5-(Naphthalen-1-ylmethyl)pyrrolidin-2-one (18)

Chiral lactam **18** was synthesized following the reported method[19]

Silca gel column chromatography (hexane/ethyl acetate = 5/1~ethyl acetate) gave **18** as a yellow oil of $[\alpha]^{25}_D$ +18.7 (*c* 0.19, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.66–1.73 (m, 1H), 1.89–1.98 (m, 1H), 2.12–2.19 (m, 1H), 2.23–2.28 (m, 1H), 3.00–3.05 (m, 1H), 3.22 (dd, *J* = 7.2, 14.0 Hz, 1H), 3.89–3.92 (m, 1H), 7.19–7.26 (m, 2H), 7.29–7.33 (m, 1H), 7.38–7.46 (m, 2H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): 26.3, 29.7, 39.0, 54.3, 123.0, 124.9, 125.2, 125.6, 126.7, 127.0, 128.3, 131.3, 133.1, 133.4, 177.7. IR (KBr): 3060, 1700, 1600, 1510, 1400, 1280, cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{15}H_{16}NO$ $[M+H]^+$: 226.1232. Found: 226.1234.

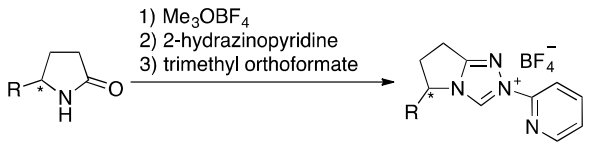
General procedures for the synthesis of chiral triazolium salts



Scheme 3. General synthesis of precatalysts (**Method A**).

Method A[14a]

To a solution of the corresponding lactam in CH_2Cl_2, Lawesson reagent (1.0 equiv) was added in one portion. The reaction mixture was stirred at room temperature for 24 h. The whole was filtered through silica gel on celite and the filtrate was concentrated. The residue was purified by silica gel flash columm chromatography to afford the corresponding thiolactam (Scheme 3, Step 1). To a solution of the thiolactam in benzene, excess mount of iodomethane (15 equiv) was added dropwise at room temperature. The whole was stirred at room temperature. After consumption of the starting thiolactam (monitored by TLC), the solvent and the remaining unreacted iodomethane were removed under reduced pressure. The residue was used without further purification (Scheme 3, Step 2). To a THF solution of the thioimidium iodide obtained above, 2-hydrazinopyridine (1.0 equiv) in THF was added dropwise and the whole was stirred at room temperature. The solvent was removed in vacuo and the residue was purified by silica gel flash column chromatography (Scheme 3, Step 3). A suspension of the resulting iminohydrazine and ammonium tetrafluoroborate (1.05 equiv) in trimethyl orthoformate (40 equiv) was stirred at 90 °C for 12 h. Condensation and the subsequent purification by silica gel flash column chromatography gave the corresponding chiral triazolium salt (Scheme 3, Step 4).



Scheme 4. General synthesis of precatalysts (**Method B**).

Method B[15]

To a solution of the corresponding lactam in CH_2Cl_2 (0.5 M), trimethyloxonium tetrafluoroborate (1.1 equiv) was added in one portion. The reaction mixture was stirred at room temperature for 12 h (Scheme 4, Step 1). To the reaction mixture, 2-hydrazinopyridine (1.1 equiv) in THF (ca. 1 mL) was added at room temperature and stirred for 12 h (Scheme 4, Step 2). After removing the solvent in vacuo, trimethyl orthoformate (20 equiv) was added and the whole was stirred at 120 °C for 12 h (Scheme 4, Step 3). Condensation and the subsequent purification by silica gel flash column chromatography gave the corresponding chiral triazolium salt.

(*R*)-5-Isopropyl-2-(pyridin-2-yl)-6,7-dihydro-5*H*-2λ^4-pyrrolo[2,1-*c*][1,2,4]triazole, tetrafluoroborate salt (7)

Method B (7.23 mmol scale): Silca gel column chromatography ($CHCl_3$/MeOH = 10/1) gave **7** (462 mg, 20%) as a brown solid of mp = 170–172 °C (MeOH) and $[\alpha]^{25}_D$ +30.1 (*c* 0.11, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 0.97 (d, *J* = 6.8 Hz, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 2.35–2.43 (m, 1H), 2.51–2.60 (m, 1H), 2.96–3.06 (m, 1H), 3.16–3.20 (m, 1H), 3.26–3.30 (m, 1H), 5.05–5.10 (m, 1H), 7.49 (t, *J* = 6.0 Hz, 1H), 7.93–8.01 (m, 2H), 8.54 (d, *J* = 3.6 Hz, 1H), 10.1 (s, 1H). ^{13}C NMR ($CDCl_3$): 16.8, 18.4, 21.7, 28.9, 31.5, 66.4, 113.9, 126.0, 136.6, 140.1, 147.4, 149.2, 162.9. IR (KBr): 2970, 1590, 1500, 1460, 1410, 1380, 1200, 1070 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{13}H_{17}N_4$ [$M^+ - {}^-BF_4$]: 229.1453. Found: 229.1457.

(*S*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-(pyridin-2-yl)-6,7-dihydro-5*H*-2λ^4-pyrrolo[2,1-*c*][1,2,4]triazole, tetrafluoroborate salt (8)

Method A (2.49 mmol scale): Silca gel column chromatography ($CHCl_3$/MeOH = 10/1) gave **8** (93 mg, 9%) as a colorless solid of mp = 181–183 °C (ethyl acetate) and $[\alpha]^{25}_D$ –59.5 (*c* 0.12, $CHCl_3$). ^{1}H NMR ($CDCl_3$): –0.06 (s, 3H), 0.00 (s, 3H), 0.75 (s, 9H), 2.54–2.62 (m, 1H), 2.97–3.07 (m, 1H), 3.14–3.22 (m, 2H), 3.80 (dd, *J* = 4.8, 12.0 Hz, 1H), 4.20 (dd, *J* = 2.8, 12.0 Hz, 1H), 5.19–5.22 (m, 1H), 7.43–7.47 (m, 1H), 7.87–7.97 (m, 2H), 8.47 (d, *J* = 3.2 Hz, 1H), 10.1 (s, 1H). ^{13}C NMR ($CDCl_3$): 17.9, 22.2, 25.6, 29.7, 62.5, 64.4, 113.8, 125.8, 136.4, 140.0, 147.4, 149.2, 163.7. IR (KBr): 2950, 1590, 1470, 1420, 1380, 1260, 1200, 1120 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{17}H_{27}N_4OSi$ [$M^+ - {}^-BF_4$]: 331.1954. Found: 331.1961.

(*S*)-2-(Pyridin-2-yl)-5-(((triisopropylsilyl)oxy)methyl)-6,7-dihydro-5*H*-2λ^4-pyrrolo[2,1-*c*][1,2,4]triazole, tetrafluoroborate salt (9)

Method B (11.0 mmol scale): Silca gel column chromatography ($CHCl_3$/MeOH = 10/1) gave **9** (580 mg, 11%) as a white solid of mp = 171–172 °C (ethyl acetate) and $[\alpha]^{25}_D$ –52.1 (*c* 0.15, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 0.96 (d, *J* = 4.8 Hz, 9H), 0.97 (d, *J* = 4.8 Hz, 9H), 1.02–1.11 (m, 3H), 2.64–2.72 (m, 1H), 3.04–3.14 (m, 1H), 3.2–3.29 (m, 2H), 3.95 (dd, *J* = 3.6, 11.5 Hz, 1H), 4.36 (dd, *J* = 2.0, 11.5 Hz, 1H), 5.33–5.37 (m, 1H), 7.47–7.51 (m, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.99 (td, *J* = 2.0, 8.4 Hz, 1H), 8.54 (d, *J* = 4.8 Hz, 1H), 10.2 (s, 1H). ^{13}C NMR ($CDCl_3$): 11.6, 17.7, 17.8, 22.2, 29.6, 62.6, 64.9, 113.8, 125.9, 136.4, 140.0, 147.4, 149.3, 163.7. IR (KBr): 2940, 1600, 1470, 1380, 1190, 1060 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{20}H_{33}N_4OSi$ [$M^+ - {}^-BF_4$]: 373.2424. Found: 373.2410.

(*S*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2-(pyridin-2-yl)-6,7-dihydro-5*H*-2λ^4-pyrrolo[2,1-*c*][1,2,4]triazole, tetrafluoroborate salt (10)

Method B (8.76 mmol scale): Silca gel column chromatography ($CHCl_3$/MeOH = 10/1) gave **10** (210 mg, 42%) as a brown solid of mp = 118–119 °C (ethyl acetate) and $[\alpha]^{25}_D$ –39.6 (*c* 0.15, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.01 (s, 9H), 2.63–2.67 (m, 1H), 3.01–3.07 (m, 1H), 4.24 (t, *J* = 6.8 Hz, 2H), 3.96 (dd, *J* = 4.0, 12.0 Hz, 1H), 4.25 (dd, *J* = 3.6, 12.0 Hz, 1H), 5.31–5.32 (m, 1H), 7.28–7.37 (m, 5H), 7.45–7.53 (m, 6H), 7.91 (d, *J* = 6.0 Hz, 1H), 8.00 (td, *J* = 1.6, 8.0 Hz, 1H), 8.54–8.56 (m, 1H), 9.84 (s, 1H). ^{13}C NMR ($CDCl_3$): 18.9, 21.9, 26.7, 29.1, 62.1, 64.7, 113.6, 125.9, 127.8, 127.9, 130.0, 130.1, 131.2, 131.8, 135.1, 135.2, 135.7, 140.0, 147.0, 148.9, 163.3. IR (KBr): 2930, 1590, 1470, 1430, 1380, 1190, 1060 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{27}H_{31}N_4OSi$ [$M^+ - {}^-BF_4$]: 455.2267. Found: 455.2273.

(*R*)-5-Benzyl-2-(pyridin-2-yl)-6,7-dihydro-5*H*-2λ^4-pyrrolo[2,1-*c*][1,2,4]triazole, tetrafluoroborate salt (11)

Method B (9.06 mmol scale): Silca gel column chromatography ($CHCl_3$/MeOH = 10/1) gave **11** (660 mg, 20%) as a colorless solid of mp = 177–178 °C (MeOH) and $[\alpha]^{25}_D$ +30.5 (*c* 0.20, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 2.53–2.61 (m, 1H), 2.96–3.04 (m, 1H), 3.18–3.22 (m, 2H), 3.29 (dd, J = 7.2, 14.0 Hz, 1H), 3.42 (d, *J* = 4.4 Hz, 1H), 5.23–5.73 (m, 1H), 7.19–7.32 (m, 5H), 7.38–7.42 (m, 1H), 7.84–7.88 (m, 1H), 7.90 (td, *J* = 2.0, 8.4 Hz, 1H), 8.04–8.41 (m, 1H), 9.58 (s, 1H). ^{13}C NMR (MeCN-d_3): 22.5, 33.7, 40.5, 63.5, 115.1, 127.5, 128.9, 130.4, 130.7, 136.8, 137.3, 142.1, 148.8, 150.6, 164.7. IR (KBr): 3030, 1600, 1510, 1470, 1390, 1200, 1060 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{17}H_{17}N_4$ [$M^+ - {}^-BF_4$]: 277.1453. Found: 277.1450.

(*S*)-2-(Pyridin-2-yl)-5-(2,4,6-trimethylbenzyl)-6,7-dihydro-5*H*-2λ^4-pyrrolo[2,1-*c*][1,2,4]triazole, tetrafluoroborate salt (12)

Method A (0.28 mmol scale): Silca gel column chromatography ($CHCl_3$/MeOH = 10/1) gave **12** (30 mg, 27%) as a white solid of mp = 195–196 °C ($CHCl_3$/hexane) and $[\alpha]^{25}_D$ +64.4 (*c* 0.07, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 2.16 (s, 6H), 2.29 (s,

3H), 2.54–2.62 (m, 1H), 3.14 (dd, *J* = 10.0, 14.0 Hz, 1H), 3.23–3.31 (m, 3H), 3.35–3.41 (m, 1H), 5.35–5.37 (m, 1H), 6.91 (s, 2H), 7.43–7.46 (m, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.95 (t, *J* = 8.0 Hz, 1H), 8.44 (d, *J* = 4.8 Hz, 1H), 8.72 (s, 1H). ^{13}C NMR ($CDCl_3$): 19.8, 20.9, 21.4, 33.1, 33.4, 60.2, 113.9, 125.8, 128.4, 129.9, 136.0, 136.8, 137.6, 140.0, 147.3, 149.0, 162.7. IR (KBr): 3410, 2940, 1600, 1470, 1420, 1380, 1200, 1060 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{20}H_{23}N_4$ [M^+ – $^-BF_4$]: 319.1923. Found: 319.1919.

(*S*)-2-(Pyridin-2-yl)-5-(2,4,6-triisopropylbenzyl)-6,7-dihydro-5*H*-2λ^4-pyrrolo[2,1-*c*][1,2,4]triazole, tetrafluoroborate salt (13)

Method A (2.28 mmol scale): Silca gel column chromatography ($CHCl_3$/MeOH = 10/1) gave **13** (56 mg, 5%) as a white solid of mp = 196–197 °C ($CHCl_3$/*n*-hexane) and $[\alpha]^{25}_D$ +63.1 (*c* 0.12, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.04 (d, *J* = 6.4 Hz, 3H), 1.24 (d, *J* = 6.4 Hz, 3H), 1.27 (d, *J* = 5.2 Hz, 6H), 1.29 (d, *J* = 5.2 Hz, 6H), 2.60–2.63 (m, 1H), 2.73–2.81 (m, 1H), 2.87–2.92 (m, 1H), 3.12–3.18 (m, 2H), 3.20–3.46 (m, 4H), 5.21–5.24 (m, 1H), 7.05 (s, 2H), 7.40–7.44 (m, 1H), 7.86–7.96 (m, 2H), 8.23 (s, 1H), 8.37 (d, *J* = 4.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): 21.3, 23.7, 24.2, 24.4, 29.7, 31.2, 33.3, 34.3, 61.8, 113.9, 121.8, 125.8, 135.5, 140.0, 147.1, 147.1, 147.5, 148.8, 149.1, 162.7. IR (KBr): 3420, 2960, 1590, 1470, 1420, 1380, 1190, 1070 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{26}H_{35}N_4$ [M^+ – $^-BF_4$]: 403.2862. Found: 403.2867.

(*R*)-5-(Naphthalen-1-ylmethyl)-2-(pyridin-2-yl)-6,7-dihydro-5*H*-2λ^4-pyrrolo[2,1-*c*][1,2,4]triazole, tetrafluoroborate salt (14)

Method B (2.85 mmol scale): Silca gel column chromatography ($CHCl_3$/MeOH = 10/1) gave **14** (125 mg, 11%) as a white solid of mp = 198–199 °C (MeOH) and $[\alpha]^{25}_D$ +51.5 (*c* 0.30, MeCN). ^{1}H NMR ($CDCl_3$): 2.57–2.66 (m, 1H), 2.98–3.08 (m, 2H), 3.20–3.26 (m, 2H), 3.33 (dd, *J* = 7.2, 10.0 Hz, 1H), 5.34–5.42 (m, 1H), 7.24–7.36 (m, 7H), 7.42–7.50 (m, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.94 (td, *J* = 1.6, 8.0 Hz, 1H), 8.45 (d, *J* = 8.0 Hz, 1H), 9.64 (s, 1H). ^{13}C NMR (MeCN-d_3): 22.4, 34.2, 37.7, 41.3, 62.5, 115.0, 116.1, 120.0, 124.6, 126.9, 127.1, 127.5, 128.0, 129.2, 129.7, 130.3, 132.9, 137.6, 142.1, 148.7, 150.5, 164.6. IR (KBr): 3420, 2960, 1590, 1460, 1420, 1380, 1190 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{21}H_{19}N_4$ [M^+ – $^-BF_4$]: 327.1610. Found: 327.1609.

(*S*)-5-(Naphthalen-2-ylmethyl)-2-(pyridin-2-yl)-6,7-dihydro-5*H*-2λ^4-pyrrolo[2,1-*c*][1,2,4]triazole, tetrafluoroborate salt (15)

Method B (0.66 mmol scale): Silca gel column chromatography ($CHCl_3$/MeOH = 10/1) gave **9** (100 mg, 37%) as a white solid of mp = 217–218 °C ($CHCl_3$/MeOH) and $[\alpha]^{25}_D$ –20.0 (*c* 0.12, $CHCl_3$). ^{1}H NMR (MeCN-d_3): 2.76–2.84 (m, 1H), 3.01–3.08 (m, 1H), 3.29–3.31 (m, 2H), 3.47 (dd, *J* = 8.0, 14.4 Hz, 1H), 3.64 (dd, *J* = 6.8, 14.4 Hz, 1H), 5.23–5.30 (m, 1H), 7.58 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.64–7.67 (m, 2H), 7.69–7.73 (m, 2H), 7.92 (s, 1H), 7.96–7.99 (m, 1H), 8.03–8.08 (m, 2H), 8.21–8.25 (m, 1H), 8.61–8.62 (m, 1H), 9.77 (s, 1H). ^{13}C NMR (MeCN-d_3): 22.5, 33.9, 40.8, 63.3, 115.1, 127.5, 127.6, 127.9, 128.5, 129.0, 129.1, 129.6, 130.2, 134.0, 134.4, 137.5, 142.1, 150.6, 164.7. IR (KBr): 3420, 3140, 1590, 1500, 1470, 1420, 1370, 1190, 1060 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{21}H_{19}N_4$ [M^+ – $^-BF_4$]: 327.1610. Found: 327.1602.

General procedure for the catalytic asymmetric cross-benzoin condensation reactions

To a suspension of chiral triazolium salt (0.05 mmol, 10 mol%), aliphatic aldehyde **1** (0.75 mmol), aromatic aldehyde **2** (0.5 mmol) in 1,4-dioxane-hexamethylphosphoramide (HMPA) (0.5 mL, 4/1), a suspension of KHMDS (0.05 mmol, 10 mol%) in 2-methylTHF (0.1 mL) was added dropwise at room temperature. The reaction mixture was stirred at room temperature. After 24 h, the whole was though silica gel and washed with ethyl acetate, then, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography.

(*S*)-1-Hydroxy-1,4-diphenylbutan-2-one (3aa)[12f]

Silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **3aa** (83 mg, 69% yield) as a colorless oil of $[\alpha]^{25}_D$ +49.6 (*c* 0.67, acetone) [lit[16a]. $[\alpha]^{25}_D$ –77.6 (*c* 1.5, acetone) for 85% ee, *R*-isomer]. The ee was determined to be 65% by HPLC (Daicel Chiralpac IB, hexane/*i*-PrOH = 50/1, 1.0 mL/min, 220 nm, major 18.3 min and minor 20.3 min). ^{1}H NMR ($CDCl_3$): 2.57–2.68 (m, 2H), 2.70–2.78 (m, 1H), 2.84–2.91 (m, 1H), 4.28 (brs, 1H), 5.02 (s, 1H), 7.03 (d, *J* = 7.2 Hz, 2H), 7.13–7.40 (m, 8H). ^{13}C NMR ($CDCl_3$): 29.6, 39.5, 79.9, 126.3, 127.4, 128.1, 128.5, 128.7, 129.0, 137.7, 140.1, 208.6.

(*S*)-1-Hydroxy-1-phenyl-4-(*p*-tolyl)butan-2-one (3ba)

Silica gel column chromatography (hexane/ethyl acetate = 5/1) gave **3ba** (83 mg, 66% yield) as a white solid of mp = 67–68 °C and $[\alpha]^{25}_D$ +83.3 (*c* 0.70, $CHCl_3$). The ee was determined to be 56% by HPLC (Daicel Chiralpac IB x 2, hexane/*i*-PrOH = 50/1, 1.0 mL/min, 220 nm, major 37.4 min and minor 34.2 min). ^{1}H NMR ($CDCl_3$): 2.21 (s, 3H), 2.48–2.66 (m, 3H), 2.67–2.79 (m, 1H), 4.25 (d, *J* = 4.0 Hz, 1H), 4.95 (d, *J* = 4.0 Hz, 1H), 6.86 (d, *J* = 7.2 Hz, 2H), 6.97 (d, *J* = 7.2 Hz, 2H), 7.18–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$): 20.9, 29.2, 39.6, 79.8, 127.3, 128.0, 128.6, 128.9, 129.1, 135.7, 137.0, 137.7, 208.7. IR (KBr): 3460, 2920, 1720, 1520, 1450, 1360, 1190, 1060 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{17}H_{19}O_2$ $[M+H]^+$: 255.1385. Found: 255.1394.

(*S*)-1-Hydroxy-4-(4-methoxyphenyl)-1-phenylbutan-2-one (3ca)

Silica gel column chromatography (hexane/ethyl acetate = 5/1) gave **3ca** (25 mg, 31% yield) as a colorless oil and $[\alpha]^{25}_D$ +74.2 (*c* 0.77, $CHCl_3$). The ee was determined to be 67% by HPLC (Daicel Chiralpac IA, hexane/ethyl acetate = 20/1, 1.0 mL/min, 254 nm, major 54.8 min and minor 69.2 min). ^{1}H NMR ($CDCl_3$): 2.51–2.71 (m, 3H), 2.78–2.82 (m, 1H), 3.74 (s, 3H), 4.29 (d, *J* = 4.0 Hz, 1H), 5.00 (d, *J*= 4.0 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 7.24–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$): 28.7, 39.7, 55.1, 79.8, 113.8, 127.3, 128.6, 128.9, 129.0, 132.1, 137.7, 157.9, 208.6. IR (KBr): 3450, 2930, 1720, 1510, 1250, 1040 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{17}H_{19}O_3$ $[M+H]^+$: 271.1334. Found: 271.1332.

(*S*)-1-Hydroxy-1-phenylbutan-2-one (3da)[12f]

Silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **3da** (19 mg, 23% yield) as a pale yellow oil and $[\alpha]^{25}_D$ +153.4 (*c* 0.05, $CHCl_3$) [lit[16b]. $[\alpha]^{25}_D$ –301.4 (*c* 1.5, $CHCl_3$) for 91% ee, *R*-isomer]. The ee was determined to be 60% by HPLC (Daicel Chiralpac IB, hexane/*i*-PrOH = 50/1, 1.0 mL/min, 220 nm, major 10.7 min and minor 12.5 min). ^{1}H NMR ($CDCl_3$): 0.93 (t, *J* = 7.6 Hz, 3H), 2.21–2.38 (m, 2H), 4.28 (brs, 1H), 5.03 (s, 1H), 7.24–7.33 (m, 5H). ^{13}C NMR ($CDCl_3$): 7.6, 31.2, 79.4, 128.7, 129.0, 138.3, 210.1.

(*S*)-1-Hydroxy-1-phenylnonan-2-one (3ea)[12f]

Silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **3ea** (64 mg, 55% yield) as a colorless oil and $[\alpha]^{25}_D$ +119.0 (*c* 0.35, $CHCl_3$). The ee was determined to be 59% by HPLC

(Daicel Chiralpac IC, hexane/*i*-PrOH = 50/1, 1.0 mL/min, 220 nm, major 16.2 min and minor 15.2 min). ^{1}H NMR ($CDCl_3$): 0.77 (t, *J* = 7.2 Hz, 3H), 1.04–1.19 (m, 8H), 1.37–1.46 (m, 2H), 2.18–2.33 (m, 2H), 4.32 (brs, 1H), 5.01 (s, 1H), 7.14–7.33 (m, 5H). ^{13}C NMR ($CDCl_3$): 14.0, 22.5, 23.6, 28.8, 28.9, 31.5, 37.6, 79.6, 127.4, 128.6, 128.9, 138.1, 209.7.

(*S*)-1-Hydroxy-4-methyl-1-phenylpentan-2-one (3fa)[12f]

Silica gel column chromatography (hexane/ethyl acetate = 5/1) gave **3ea** (23 mg, 24% yield) as a colorless oil and $[\alpha]^{25}_D$ +69.3 (*c* 0.11, $CHCl_3$). The ee was determined to be 17% by HPLC (Daicel Chiralpac IC, hexane/*i*-PrOH = 50/1, 1.0 mL/min, 220 nm, major 32.8 min and minor 31.5 min). ^{1}H NMR ($CDCl_3$): 0.67 (d, *J* = 6.4 Hz, 3H), 0.80 (d, *J* = 6.4 Hz, 3H), 1.97–2.23 (m, 3H), 4.32 (d, *J* = 4.4 Hz, 1H), 4.97 (d, *J* = 4.4 Hz, 1H), 7.22–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$): 22.2, 22.5, 24.6, 46.7, 80.0, 127.5, 128.6, 128.9, 137.9, 209.1.

(*S*)-1-Hydroxy-1-(naphthalen-1-yl)-4-phenylbutan-2-one (3ab)

Silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **3ab** (36 mg, 28% yield) as a colorless oil and $[\alpha]^{25}_D$ +54.5 (*c* 0.30, $CHCl_3$). The ee was determined to be 64% by HPLC (Daicel Chiralpac ID, hexane/*i*-PrOH = 50/1, 1.0 mL/min, 254 nm, major 37.5 min and minor 34.2 min). ^{1}H NMR ($CDCl_3$): 2.42–2.52 (m, 1H), 2.64–2.79 (m, 2H), 2.84–2.92 (m, 1H), 4.36–4.39 (m, 1H), 5.53 (d, *J* = 2.4 Hz, 1H), 6.97 (d, *J* = 7.2 Hz, 2H), 7.16–7.28 (m, 3H), 7.40–7.45 (m, 2H), 7.48–7.52 (m, 2H), 7.83–7.90 (m, 2H), 7.94–7.97 (m, 1H). ^{13}C NMR ($CDCl_3$): 29.7, 39.5, 79.1, 123.4, 125.3, 126.0, 126.2, 126.9, 127.8, 128.1, 128.4, 129.0, 129.7, 131.0, 133.1, 134.2, 140.0, 209.8. IR (KBr): 3450, 3030, 1710, 1600, 1510, 1500, 1450, 1350, 1170, 1050 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{20}H_{19}O_2$ $[M+H]^+$: 291.1385. Found: 291.1396.

(*S*)-1-Hydroxy-1-(naphthalen-1-yl)-4-phenylbutan-2-one (3ac)

Silica gel column chromatography (hexane/ethyl acetate = 5/1) gave **3ac** (111 mg, 76% yield) as a pale yellow oil and $[\alpha]^{25}_D$ +84.5 (*c* 0.52, $CHCl_3$). The ee was determined to be 67% by HPLC (Daicel Chiralpac ID, hexane/*i*-PrOH = 10/1, 1.0 mL/min, 254 nm, major 36.2 min and minor 30.0 min). ^{1}H NMR ($CDCl_3$): 2.57–2.97 (m, 4H), 4.45 (d, *J* = 4.0 Hz, 1H), 5.20 (d, *J* = 4.0 Hz, 1H), 7.01 (d, *J* = 6.8 Hz, 2H), 7.11–7.34 (m, 3H), 7.48–7.52 (m, 2H), 7.78–7.89 (m, 5H). ^{13}C NMR ($CDCl_3$): 29.5, 39.5, 79.9, 124.2, 126.2, 126.5, 127.2, 127.7, 128.0, 128.1, 128.3, 128.4, 129.0, 133.2, 133.3, 135.1, 140.0, 208.6. IR (neat): 3450, 2930, 1720, 1600, 1560, 1360 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{20}H_{19}O_2$ $[M+H]^+$: 291.1385. Found: 291.1396.

(*S*)-1-(2-Chlorophenyl)-1-hydroxy-4-phenylbutan-2-one (3ad)[12c]

Silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **3ad** (51 mg, 41% yield) as a pale yellow oil and $[\alpha]^{25}_D$ +26.8 (*c* 0.14, $CHCl_3$). The ee was determined to be 69% by HPLC (Daicel Chiralpac IB, hexane/*i*-PrOH = 10/1, 1.0 mL/min, 220 nm, major 11.5 min and minor 13.7 min). ^{1}H NMR ($CDCl_3$): 2.51–2.59 (m, 1H), 2.66–2.89 (m, 3H), 4.32 (brs, 1H), 5.47 (s, 1H), 6.98 (d, *J* = 7.2 Hz, 2H), 7.08–7.18 (m, 5H), 7.29–7.33 (m, 2H). ^{13}C NMR ($CDCl_3$): 29.6, 39.4, 76.2, 126.2, 127.5, 128.1, 128.5, 129.1, 129.9, 130.0, 133.4, 135.5, 140.0, 207.9.

(*S*)-1-(3-Chlorophenyl)-1-hydroxy-4-phenylbutan-2-one (3ae)[12c]

Silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **3ae** (66 mg, 50% yield) as a colorless oil and $[\alpha]^{25}_D$ +48.0 (*c* 0.08, $CHCl_3$). The ee was determined to be 39% by HPLC (Daicel Chiralpac ID, hexane/*i*-PrOH = 10/1, 1.0 mL/min, 220 nm, major 21.4 min and minor 19.9 min). ^{1}H NMR ($CDCl_3$): 2.52–2.66 (m, 2H), 2.74–2.87 (m, 2H), 4.26 (d, *J* = 4.0 Hz, 1H), 4.92 (d, *J* = 4.0 Hz, 1H), 6.98 (d, *J* = 6.8 Hz, 2H), 7.06–7.23 (m, 7H). ^{13}C NMR ($CDCl_3$): 29.5, 39.5, 79.1, 125.5, 126.4, 127.5, 128.1, 128.5, 128.9, 130.2, 134.9, 139.6, 139.9, 207.8.

(*S*)-1-(4-Chlorophenyl)-1-hydroxy-4-phenylbutan-2-one (3af)

Silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **3af** (60 mg, 43% yield) as a colorless oil and $[\alpha]^{25}_D$ +82.6 (*c* 0.32, $CHCl_3$). The ee was determined to be 69% by HPLC (Daicel Chiralpac IC, hexane/*i*-PrOH = 10/1, 1.0 mL/min, 230 nm, major 22.7 min and minor 19.5 min). ^{1}H NMR ($CDCl_3$): 2.50–2.60 (m, 2H), 2.69–2.84 (m, 2H), 4.22 (brs, 1H), 4.92 (s, 1H), 6.96 (d, *J* = 6.8 Hz, 2H), 7.09–7.27 (m, 7H). ^{13}C NMR ($CDCl_3$): 29.6, 39.4, 79.2, 126.3, 128.1, 128.5, 128.7, 129.2, 134.6, 136.2, 140.0, 208.0. IR (neat): 3450, 2930, 1720, 1590, 1490, 1460, 1400, 1190, 1090 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{16}H_{16}ClO_4$ $[M+H]^+$: 275.0839. Found: 275.0847.

(*S*)-1-(2-Bromophenyl)-1-hydroxy-4-phenylbutan-2-one (3ag)[12f]

Silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **3ag** (47 mg, 30% yield) as a colorless oil and $[\alpha]^{25}_D$ +52.0 (*c* 0.08, $CHCl_3$). The ee was determined to be 64% by HPLC (Daicel Chiralpac IB, hexane/*i*-PrOH = 10/1, 1.0 mL/min, 240 nm, major 25.0 min and minor 31.6 min). ^{1}H NMR ($CDCl_3$): 2.53–2.61 (m, 1H), 2.72–2.88 (m, 3H), 4.33 (d, *J* = 4.0 Hz, 1H), 5.50 (d, *J* = 4.0 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 2H), 7.06–7.21 (m, 6H), 7.52 (dd, *J* = 1.6, 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): 29.6, 39.5, 78.3, 123.7, 126.3, 128.2, 128.4, 129.1, 130.2, 133.4, 137.1, 140.0, 207.9.

(*S*)-1-(4-Bromophenyl)-1-hydroxy-4-phenylbutan-2-one (3ah)

Silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **3ah** (68 mg, 46% yield) as a colorless oil and $[\alpha]^{25}_D$ +19.0 (*c* 0.16, $CHCl_3$). The ee was determined to be 77% by HPLC (Daicel Chiralpac IC, hexane/*i*-PrOH = 10/1, 1.0 mL/min, 220 nm, major 21.1 min and minor 18.8 min). ^{1}H NMR ($CDCl_3$): 2.51–2.60 (m, 2H), 2.71–2.84 (m, 2H), 4.23 (brs, 1H), 4.91 (s, 1H), 6.95 (d, *J* = 6.8 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.09–7.24 (m, 3H), 7.39 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): 29.6, 39.4, 79.2, 122.8, 126.4, 128.1, 128.5, 128.9, 132.1, 136.7, 139.9, 207.9. IR (neat): 3450, 2910, 1720, 1560, 1510, 1490, 1070 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{16}H_{15}BrO_2$ $[M+H]^+$: 319.0334. Found: 319.0333.

Methyl (*S*)-4-(1-hydroxy-2-oxo-4-phenylbutyl)benzoate (3ai)[12f]

Silica gel column chromatography (hexane/ethyl acetate = 5/1) gave **3ai** (59 mg, 40% yield) as a pale yellow oil and $[\alpha]^{25}_D$ +30.6 (*c* 0.31, $CHCl_3$). The ee was determined to be 43% by HPLC (Daicel Chiralpac IB x 2, hexane/*i*-PrOH = 10/1, 1.0 mL/min, 230 nm, major 82.0 min and minor 77.7 min). ^{1}H NMR ($CDCl_3$): 2.52–2.80 (m, 4H), 3.82 (s, 3H), 4.31 (brs, 1H), 5.00 (s, 1H), 6.94 (d, *J* = 6.4 Hz, 2H), 7.09–7.18 (m, 3H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.94 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): 29.5, 39.5, 52.2, 79.5, 126.3, 127.3, 128.1, 128.3, 128.5, 130.2, 139.9, 142.5, 166.5, 207.7.

(*S*)-1-Hydroxy-1-(2-methoxyphenyl)-4-phenylbutan-2-one (3aj)[12f]

Silica gel column chromatography (hexane/ethyl acetate = 5/1) gave **3ai** (52 mg, 39% yield) as a pale yellow oil and $[\alpha]^{25}_D$ +91.5

(*c* 0.20, $CHCl_3$). The ee was determined to be 69% by HPLC (Daicel Chiralpac IB, hexane/ethyl acetate = 20/1, 1.0 mL/min, 254 nm, major 38.3 min and minor 41.0 min). ^{1}H NMR ($CDCl_3$): 2.50–2.67 (m, 2H), 2.70–2.86 (m, 2H), 3.71 (s, 3H), 4.14 (brs, 1H), 5.25 (s, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.87 (t, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 2H), 7.04–7.42 (m, 5H). ^{13}C NMR ($CDCl_3$): 29.7, 39.1, 55.4, 75.1, 111.1, 121.1, 126.1, 126.3, 128.1, 128.4, 129.0, 129.3, 130.0, 140.0, 156.8, 208.9.

(*S*)-1-Hydroxy-1-(3-methoxyphenyl)-4-phenylbutan-2-one (3ak) [12f]

Silica gel column chromatography (hexane/ethyl acetate = 5/1) gave **3ak** (89 mg, 66% yield) as a pale yellow oil and $[\alpha]^{25}_D$ +58.7 (*c* 0.20, $CHCl_3$). The ee was determined to be 68% by HPLC (Daicel Chiralpac IB, hexane/ethyl acetate = 20/1, 1.0 mL/min, 254 nm, major 47.3 min and minor 51.3 min). ^{1}H NMR ($CDCl_3$): 2.66–2.70 (m, 2H), 2.72–2.92 (m, 2H), 3.77 (s, 3H), 5.00 (s, 1H), 6.77 (t, *J* = 2.4 Hz, 1H), 6.85 (dd, *J* = 2.4, 8.0 Hz, 2H), 7.04 (d, *J* = 6.8 Hz, 2H), 7.14–7.31 (m, 4H). OH proton was not appeared clearly. ^{13}C NMR ($CDCl_3$): 29.5, 39.2, 55.1, 79.7, 112.5, 114.3, 119.8, 126.2, 128.1, 128.2, 128.4, 129.9, 139.2, 140.0, 159.9, 208.4.

(*S*)-1-Hydroxy-1-(4-methoxyphenyl)-4-phenylbutan-2-one (3al) [12f]

Silica gel column chromatography (hexane/ethyl acetate = 5/1) gave **3al** (26 mg, 19% yield) as a pale yellow oil and $[\alpha]^{25}_D$ +74.2 (*c* 0.17, $CHCl_3$). The ee was determined to be 64% by HPLC (Daicel Chiralpac IB, hexane/ *i*-PrOH = 50/1, 1.0 mL/min, 254 nm, major 49.4 min and minor 51.6 min). ^{1}H NMR ($CDCl_3$): 2.49–2.59 (m, 2H), 2.67–2.84 (m, 2H), 3.71 (s, 3H), 4.17 (d, *J* = 3.6 Hz, 1H), 4.91 (d, *J* = 3.6 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 7.07–7.20 (m, 5H). ^{13}C NMR ($CDCl_3$): 29.7, 39.4, 55.3, 79.3, 114.4, 126.2, 128.1, 128.5, 126.7, 129.8, 140.2, 159.9, 208.9.

(*S*)-1-Hydroxy-4-phenyl-1-(*m*-tolyl)butan-2-one (3an)

Silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **3an** (59 mg, 46% yield) as a colorless oil and $[\alpha]^{25}_D$ +69.8 (*c* 0.14, $CHCl_3$). The ee was determined to be 70% by HPLC (Daicel Chiralpac IB, hexane/ *i*-PrOH = 50/1, 1.0 mL/min, 230 nm, major 15.0 min and minor 18.2 min). ^{1}H NMR ($CDCl_3$): 2.25 (s, 3H), 2.55–2.89 (m, 4H), 4.21 (d, *J* = 3.6 Hz, 1H), 4.92 (d, *J* = 3.6 Hz, 1H), 6.96–7.18 (m, 9H). ^{13}C NMR ($CDCl_3$): 21.4, 29.6, 39.4, 79.8, 124.6, 126.3, 127.9, 128.2, 128.5, 128.8, 129.5, 137.7, 138.8, 140.2, 208.7. IR (neat): 3420, 2910, 1720, 1510, 1380, 1060 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{17}H_{19}O_2$ $[M+H]^+$: 255.1385. Found: 255.1383.

(*S*)-1-Hydroxy-4-phenyl-1-(*p*-tolyl)butan-2-one (3ao) [12f]

Silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **3an** (66 mg, 52% yield) as a colorless oil and $[\alpha]^{25}_D$ +72.6 (*c* 0.58, $CHCl_3$). The ee was determined to be 64% by HPLC (Daicel Chiralpac IB, hexane/ *i*-PrOH = 50/1, 1.0 mL/min, 254 nm, major 40.0 min and minor 31.4 min). ^{1}H NMR ($CDCl_3$): 2.35 (s, 3H), 2.63–2.99 (m, 4H), 4.30 (brs, 1H), 5.01 (s, 1H), 7.06 (d, *J* = 8.0 Hz, 2H), 7.16–6.30 (m, 7H). ^{13}C NMR ($CDCl_3$): 21.1, 29.6, 39.3, 79.6, 126.2, 127.3, 128.1, 128.4, 129.6, 134.8, 138.5, 140.1,208

Supplementary Material

A Supplementary Data file (^{1}H and ^{13}C NMR) of newly synthesized chiral triazolium salts (**7**–**15**) and chiral lactams (**16**–**18**) is available online.

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