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

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ABSTRACT

Chiral triazolium salts bearing a pyridine ring were developed as *N*-heterocyclic carbene precursors. In the presence of the chiral triazolium salt and a base, the catalytic asymmetric benzoin condensation proceeded to afford the product in high level of chemical yield and enantioselectivity. A wide range of aromatic aldehydes were applicable to this reaction.

1. Introduction

The broad application of *N*-heterocyclic carbenes (NHCs) in organic synthesis has been dramatically demonstrated since Bertrand, Arduengo and co-workers reported the first stable nucleophilic carbene around 1990.[1,2] Ukai and co-workers reported in 1943 that co-factor thiamine (vitamin B_1) catalyzed the benzoin condensation.[2a] The mechanism of the thiazolium catalyzed benzoin condensation was elucidated by Breslow in 1958.[3] The first catalytic asymmetric benzoin condensation reaction was developed by Sheehan and Hunnemann in 1966, however, the enantioselectivity was low.[4a] Although they reported that the second generation thiazolium salt promoted benzoin condensations of benzaldehyde more selectively, the product was obtained in only 6% yield with 52% ee.[4b] Even though several groups later attempted to improve the performance through the design of mono- and bicyclic thiazolium salt derivatives,[5] stereoselectivities of the products were lower than that reported by Sheehan. Enders achieved the dramatic improvement in 1996, which was the first design of chiral triazolium precatalyst for the benzoin condensation, giving the product up to 86% ee.[6a] Leeper also reported a bicyclic carbene catalyst by synthesizing the chiral triazolium salt.[7] Enders made improvements through a design of conformationally restricted triazolium salts in 2002.[6b] Furthermore, they reported the development of the pyroglutamic acid-derived precatalyst, which gave the product in 66% yield with 95% ee in 2008.[6c] As shown in previous literature of the asymmetric benzoin condensations, chemical yield, and enantioselectivity of the product were highly dependent on the steric and electronic characteristics of the aromatic aldehydes used, that is, aromatic aldehydes bearing electron-withdrawing group afforded the products in high chemical yield but with low enantioselectivity. On the other hand, aromatic aldehydes bearing electron-donating group showed low reactivity but realized high enantioselectivity. Very recently, hydrogen bond-donating carbene catalysts have been developed by Connon and were applied to benzoin condensation.[8] Although a number of enantioselective variants of the benzoin condensation have been reported, this reaction remains as a good model to test newly developed NHC catalysts. To the best of our knowledge, no example of chiral triazolium precatalyst bearing a pyridine ring has ever been reported in the literatures.[9]

2. Results and discussions

In the NHC catalyzed asymmetric benzoin condensation, it was elucidated that conformational control of the key intermediate, so called the Breslow intermediate, is significant to obtain the product with high enantioselectivity.[6,7] Thus, we expected that if the chiral triazolium salt possesses a Lewis basic moiety, OH group of the Breslow intermediate could make intramolecular hydrogen bond with the Lewis base affording more rigid intermediate for the benzoin condensation giving the product with higher stereoselectivity (Scheme 1).[2f,10] We therefore designed and synthesized a various kinds of chiral triazolium salts bearing a pyridine ring (Fig. 1). Our initial attempt of benzoin condensation of

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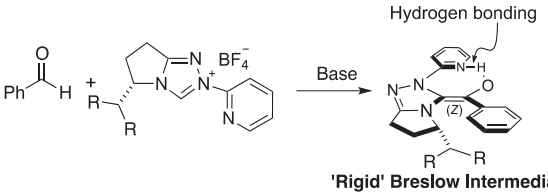
benzaldehyde (**1a**) was performed using 10 mol % of triazolium salt **3** and potassium *tert*-butoxide



Scheme 1. Working hypothesis.

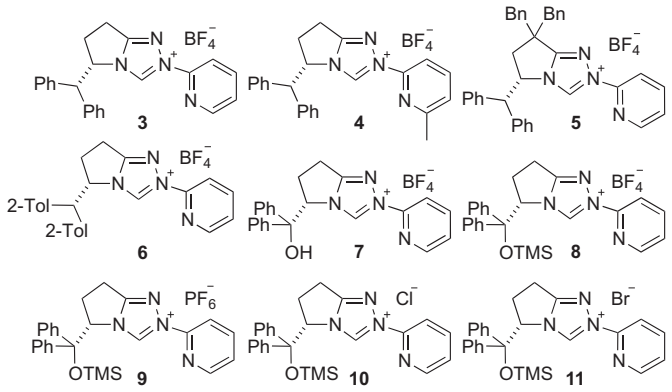
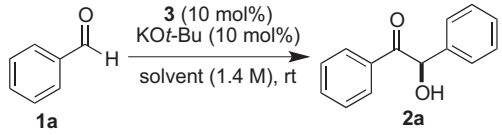


Fig. 1. Chiral triazolium salts bearing a pyridine ring.

(KO*t*-Bu) as a base to generate a carbene catalyst in toluene, and the corresponding benzoin **2a** was obtained in 10% yield with 34% ee in the preference of (*R*)-enantiomer after 19 h (Table 1, entry 1). In the case of dichloromethane or diethyl ether was used as a solvent, the reaction proceeded more efficiently to afford the product **2a** in 80% and 99% yields, respectively. However, enantioselectivity was still low (43% ee, 18% ee) (entries 2 and 3). Remarkable improvement of the enantioselectivity was observed when cyclic ether, such as THF or 1,4-dioxane was used to furnish **2a** with 51% ee and 65% ee, respectively (entries 4 and 5). Polar solvents (DMF and DMSO) were also effective in this reaction, giving the product with moderate enantioselectivity (entries 6 and 7).

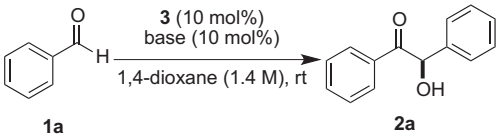
Table 1
Effect of solvents for the catalytic asymmetric benzoin condensation



Entry	Solv	Time (h)	Yield (%)	ee (%)
1	Toluene	19	10	34
2	CH_2Cl_2	24	80	43
3	Et_2O	20	99	18
4	THF	17	32	51
5	1,4-Dioxane	14	87	65
6	DMF	18	58	56
7	DMSO	18	91	58

Based on the above results, other bases beside KO*t*-Bu were then evaluated to generate carbene for the asymmetric benzoin condensation in 1,4-dioxane as a solvent (Table 2). The organolithium reagents and lithium amide were ineffective in this reaction (entries 1–3). In the cases of NaO*t*-Bu, KHMDS, and $CsCO_3$, benzoin **2a** was obtained with the comparable enantioselectivity as in the case of KO*t*-Bu, but yields were lower (entries 4–7). The use of DBU

Table 2
Effect of base and additives for the catalytic asymmetric benzoin condensation



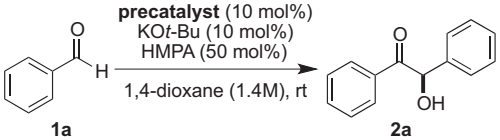
Entry	Base	Additive	Time (h)	Yield (%)	ee (%)
1	*n*-BuLi	—	15	nr	—
2	*t*-BuLi	—	15	nr	—
3	LHMDS	—	16	18	27
4	NaO*t*-Bu	—	16	42	69
5	KO*t*-Bu	—	14	87	65
6	KHMDS	—	22	75	65
7	Cs_2CO_3	—	15	38	69
8	DBU	—	15	46	54
9	KO*t*-Bu	KBr[a]	22	78	56
10	KO*t*-Bu	HMPA[b]	15	87	71

[a] KBr (100 mol %) was added.
[b] HMPA (50 mol %) was used.

afforded the product with moderate yield and enantioselectivity (entry 8). From these results, KO*t*-Bu proved to be a base of choice for this reaction system (entry 5). To assess the effect of potassium cation that comes from the base, some additives were examined. When 100 mol % of KBr was added to the reaction, the yield and enantioselectivity were decreased to give the product in 78% yield with 56% ee (entry 9). The use of 50 mol % HMPA coordinatable to the potassium cation improved the enantioselectivity to 71% ee (entry 10).

We turned our attention to the structure of chiral triazolium salts (Table 3). Introduction of a methyl group onto the C6-position of the pyridine ring (**4**), dibenzyl group onto the pyrrolidine ring (**5**), and replacement of the phenyl groups in **3** to 2-tolyl groups (**6**) lowered the enantioselectivity (entries 2–4). We found that catalytic efficiency of chiral triazolium salt is highly dependent on the bulkiness of the substituent on the diphenylmethyl group. Dramatic improvement of the enantioselectivity was realized up to 98% ee with the precatalyst **7**, in which a hydroxyl group was introduced on the diphenylmethyl carbon (entry 5). Finally, it was found that the enantioselectivity was enhanced to 99% ee when 10 mol % *O*-silylated triazolium salt **8** was used together with KO*t*-Bu in the presence of HMPA (entry 6). We have found that BF_4^- is suitable as a counter anion of the triazolium salt in this reaction, whereas the reaction using the chiral triazolium salts bearing PF_6^- **9**, Cl^- **10**, and Br^- **11** lowered chemical yields and/or enantioselectivities (entries 7–9).

Table 3
Effect of precatalyst

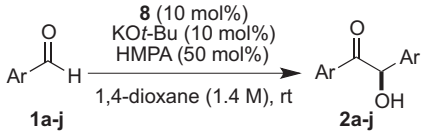


Entry	Precatalyst	Time (h)	Yield (%)	ee (%)
1	**3**	15	87	71
2	**4**	15	89	66
3[a]	**5**	15	8	42
4	**6**	21	96	22
5	**7**	22	64	98
6	**8**	14	75	99
7	**9**	24	15	97
8	**10**	18	61	88
9	**11**	17	61	98

[a] HMPA was not employed in this reaction.

Under the optimized reaction conditions using the highly active and selective precatalyst **8**, the scope of the catalytic enantioselective benzoin condensation was demonstrated with various aromatic aldehydes (Table 4). We were delighted to find that our catalytic system was applicable to a wide range of aromatic aldehydes when the reactions were conducted by using 10 mol % of **8** and 10 mol % of KO*t*-Bu in the presence of 50 mol % HMPA in 1,4-dioxane at room temperature. 2-Naphthaldehyde (**1b**) was found to be a good substrate, and the product **2b** was obtained in 56% yield with 93% ee (entry 2). We examined the substituted benzaldehydes bearing an electron-withdrawing group at the *para*-position of the phenyl group. 4-Bromobenzaldehyde (**1c**) and 4-chlorobenzaldehyde (**1d**) showed almost same reactivities, but the enantioselectivities were completely different (30% ee and 85% ee, respectively) (entries 3 and 4).[11] 4-Fluorobenzaldehyde (**1e**) bearing a stronger electron-withdrawing group on the aromatic ring showed low reactivity but high stereoselectivity was achieved (entry 5). In the case of 4-(trifluoromethyl)benzaldehyde (**1f**), the racemic product was obtained in 74% yield (entry 6). 2-Chlorobenzaldehyde (**1g**) showed poor reactivity and selectivity, probably due to the steric factor of the substituent at the *ortho*-position (entry 7). The reactions of relatively deactivated 4-methylbenzaldehyde (**1h**) and 4-methoxybenzaldehyde (**1i**) were sluggish to furnish the corresponding products **2h** and **2i** in lower yields but with excellent enantioselectivities (entries 8 and 9). Heteroaromatic aldehyde, furfural (**1j**), showed moderate reactivity to afford the product in 69% yield with 39% ee (entry 10).

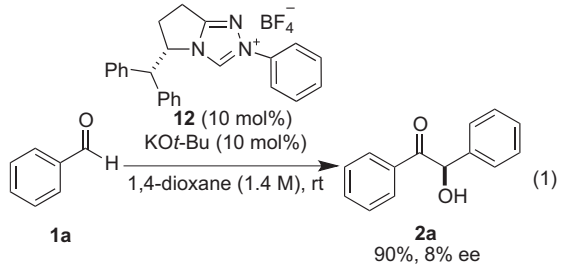
Table 4
Scope of substrates



Entry	Ar	Time (h)	Yield (%)	ee (%)
1	Ph (**1a**)	15	75 (**2a**)	99
2	2-Naphthyl (**1b**)	16	56 (**2b**)	93
3	4-BrC_6H_4 (**1c**)	23	83 (**2c**)	30
4	4-ClC_6H_4 (**1d**)	19	80 (**2d**)	85
5[a]	4-FC_6H_4 (**1e**)	12	31 (**2e**)	99
6	4-$CF_3C_6H_4$ (**1f**)	22	74 (**2f**)	0
7	2-ClC_6H_4 (**1g**)	23	11 (**2g**)	67
8	4-MeC_6H_4 (**1h**)	14	10 (**2h**)	95
9	4-MeOC_6H_4 (**1i**)	17	3 (**2i**)	99
10	2-Furyl (**1j**)	16	69 (**2j**)	39

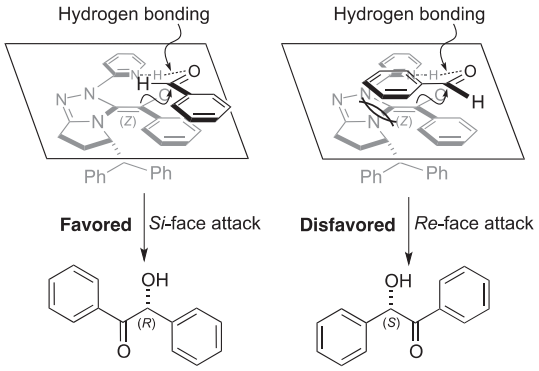
[a] Catalyst **8** (30 mol %) and KOt-Bu (30 mol%) were used.

To reveal the efficiency of the pyridine ring of the precatalyst, we conducted the asymmetric benzoin condensation of benzaldehyde (**1a**) by using the triazolium salt **12**.[6c] The reaction proceeded smoothly giving the product **2a** in 90% yield with 8% ee and this result clearly indicated that the pyridinyl group plays an important role to realize the high stereoselectivity (Eq. 1).



The absolute stereochemistry of the major isomer of the benzoin **2a** was determined to be *R* by comparison of its optical rotation with that reported in the literature.[6a]

The diphenylmethyl group shields the *Re* face of the Breslow intermediate, whose geometry was controlled by intramolecular hydrogen bonding between hydroxyl group and pyridine ring. Therefore, the attack to the incoming second aldehyde molecule occurs from the less hindered *Si* face, that is, the Breslow intermediate favorably approaches to the *Si* face of the second aldehyde leading to an *R* configuration at the newly formed stereogenic center.[2f] On the other hand, *Re* face attack by the Breslow intermediate may be disfavored due to the steric repulsion between the heterocyclic moiety of the Breslow intermediate and the aromatic ring of the second aldehyde (Scheme 2).



Scheme 2. Stereochemical model for benzoin condensation.

3. Conclusion

In summary, we have developed the chiral triazolium salts bearing a pyridine ring and could optimize the reaction procedure, which led to the catalytic asymmetric benzoin condensation in an excellent level. A wide range of aromatic aldehydes were applicable to this reaction. The precise mechanism of the stereoinduction is now further investigated in our laboratory.

4. Experimental section

4.1. General

^{1}H NMR was recorded on a JEOL ECS 400 (400 MHz) NMR spectrometer. Chemical shifts δ are reported in parts per million 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 JEOL ECS 400 (100 MHz) NMR spectrometer. The chemical shifts were determined in the δ-scale relative to $CDCl_3$ (δ=77.0 ppm). The IR spectra were measured on JASCO FT/IR-230 spectrometer. The MS spectra were recorded with Hitachi M-80 and JEOL SX-102A mass spectrometers. HPLC was performed using chiral column with JASCO PU2800 plus, HITACHI 650A and HITACHI D2500 chromato-integrater. Optical rotations were measured on a JASCO DIP370. All of the melting points were measured with YANAGIMOTO micro melting point apparatus. Toluene was dried and distilled over sodium. THF, Et_2O, and 1,4-dioxane were freshly distilled from sodium diphenylketyl. All other solvents were distilled and stored over drying agents. All anhydrous solvents used in the present experiment were degassed by freeze-thaw (3 cycles) prior to use. Thin-layer chromatography (TLC) and flash column chromatography were performed by using Merck silica gel 60 PF_{254} (Art. 7749) and silica gel 60N, spherical neutral (37563-84), respectively.

4.2. Catalytic asymmetric benzoin condensation; general procedure

To a suspension of chiral triazolium salt (0.1 mmol, 10 mol %), hexamethylphosphoramide (HMPA) (0.09 mL, 50 mol %) and aromatic aldehyde (1.0 mmol) in 1,4-dioxane (0.3 mL), the suspension of KO*t*-Bu (10 mol %) in 1,4-dioxane (0.4 mL) was added dropwise at room temperature. The reaction mixture was stirred at room temperature, quenched by adding water (2 mL) and diluted by $CHCl_3$ (5 mL). Aqueous layer was separated and extracted with $CHCl_3$ (5 mL×3). Combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel flash column chromatography.

Chiral triazolium salt **8** was used as a precatalyst in the following experiments.

*4.2.1. (R)-2-Hydroxy-1,2-diphenylethanone (**2a**)*[6a]. Silica gel column chromatography (hexane/ethyl acetate=10/1–4/1) gave **2a** (79 mg, 75% yield) as a white solid of mp=131.0–131.9 °C and $[\alpha]_D^{25}$ −150.1 (*c* 0.56, MeOH). Lit.[6a]: $[\alpha]_D^{25}$ −108.4 (*c* 1.0, MeOH) for *R* enantiomer with 75% ee. The ee was determined to be 99% by HPLC (Daicel Chiralpac IA, hexane/*i*-PrOH=9/1, 0.5 mL/min, 254 nm, major 28.9 min and minor 31.7 min). ^{1}H NMR ($CDCl_3$): 4.57 (br s, 1H), 5.96 (s, 1H), 7.27–7.33 (m, 7H), 7.52 (t, *J*=8.2 Hz, 1H), 7.92 (d, *J*=8.2 Hz, 2H).

*4.2.2. (R)-2-Hydroxy-1,2-di(naphthalen-2-yl)ethanone (**2b**)*[8b]. Silica gel column chromatography (hexane/ethyl acetate=10/1–4/1) gave **2b** (88 mg, 56% yield) as a white solid of mp=117.2–117.8 °C and $[\alpha]_D^{25}$ +52.4 (*c* 0.37, MeOH). The ee was determined to be 93% by HPLC (Daicel Chiralpac IA, hexane/*i*-PrOH=4/1, 1.0 mL/min, 254 nm, major 21.5 min and minor 15.1 min). ^{1}H NMR ($CDCl_3$): 4.82 (br s, 1H), 6.27 (s, 1H), 7.39–7.54 (m, 5H), 7.72–7.99 (m, 8H), 8.48 (s, 1H).

*4.2.3. (R)-1,2-Bis(4-bromophenyl)-2-hydroxyethanone (**2c**)*[6a]. Silica gel column chromatography (hexane/ethyl acetate=10/1–4/1) gave **2c** (149 mg, 83% yield) as a white solid of mp=96.8–97.5 °C and $[\alpha]_D^{25}$ −4.4 (*c* 0.63, $CHCl_3$). The ee was determined to be 30% by HPLC (Daicel Chiralpac IA, hexane/*i*-PrOH=9/1, 0.5 mL/min, 254 nm, major 31.2 min and minor 33.5 min). ^{1}H NMR ($CDCl_3$): 4.50 (br s, 1H), 5.85 (s, 1H), 7.18 (d, *J*=8.2 Hz, 2H), 7.46 (d, *J*=8.2 Hz, 2H), 7.55 (d, *J*=8.2 Hz, 2H), 7.73 (d, *J*=8.2 Hz, 2H).

*4.2.4. (R)-1,2-Bis(4-chlorophenyl)-2-hydroxyethanone (**2d**)*[8b]. Silica gel column chromatography (hexane/ethyl acetate=10/1–4/1) gave **2d** (85 mg, 80% yield) as a white solid of mp=89.6–90.1 °C and $[\alpha]_D^{25}$ −30.5 (*c* 0.66, $CHCl_3$). The ee was determined to be 85% by HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH=95/5, 0.6 mL/min, 220 nm, major 46.4 min and minor 42.0 min). ^{1}H NMR ($CDCl_3$): 4.55 (br s, 1H), 5.92 (s, 1H), 7.25 (d, *J*=8.2 Hz, 2H), 7.30 (d, *J*=8.2 Hz, 2H), 7.39 (d, *J*=8.2 Hz, 2H), 7.82 (d, *J*=8.2 Hz, 2H).

*4.2.5. (R)-1,2-Bis(4-fluorophenyl)-2-hydroxyethanone (**2e**)*[6a]. Silica gel column chromatography (hexane/ethyl acetate=10/1–4/1) gave **2e** (26 mg, 31% yield) as a yellow solid of mp=80.5–80.9 °C and $[\alpha]_D^{25}$ −128.2 (*c* 0.24, $CHCl_3$). The ee was determined to be 99% by HPLC (Daicel Chiralpac IA, hexane/*i*-PrOH=9/1, 0.5 mL/min, 254 nm, major 27.1 min and minor 29.1 min). ^{1}H NMR ($CDCl_3$): 4.53 (br s, 1H), 5.90 (s, 1H), 6.99–7.10 (m, 4H), 7.29 (m, 2H), 7.93 (m, 2H).

*4.2.6. (R)-2-Hydroxy-1,2-bis(4-(trifluoromethyl)phenyl)ethanone (**2f**)*[6a]. Silica gel column chromatography (hexane/ethyl acetate=10/1–4/1) gave **2f** (128 mg, 74% yield) as a yellow solid of mp=90.8–91.2 °C. The ee was determined to be almost 0% by HPLC (Daicel Chiralpac IA, hexane/*i*-PrOH=9/1, 0.5 mL/min, 254 nm, 17.8 min and 19.5 min). ^{1}H NMR ($CDCl_3$): 4.51 (br s, 1H), 6.03 (s, 1H), 7.45 (d, *J*=8.0 Hz, 2H), 7.60 (d, *J*=8.0 Hz, 2H), 7.69 (d, *J*=8.4 Hz, 2H), 8.00 (d, *J*=8.4 Hz, 2H).

*4.2.7. (R)-1,2-Bis(2-chlorophenyl)-2-hydroxyethanone (**2g**)*[8b]. Silica gel column chromatography (hexane/ethyl acetate=10/1–4/1) gave **2g** (16 mg, 11% yield) as a yellow solid of mp=60.6–61.2 °C and $[\alpha]_D^{25}$ −36.6 (*c* 0.13, $CHCl_3$). The ee was determined to be 67% by HPLC (Daicel Chiralpac IA, hexane/*i*-PrOH=9/1, 0.5 mL/min, 254 nm, major 21.3 min and minor 19.1 min). ^{1}H NMR ($CDCl_3$): 4.39 (br s, 1H), 6.35 (s, 1H), 7.17–7.36 (m, 8H).

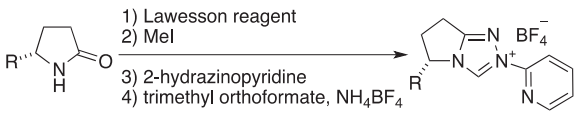
*4.2.8. (R)-2-Hydroxy-1,2-di(p-tolyl)ethanone (**2h**)*[8b]. Silica gel column chromatography (hexane/ethyl acetate=10/1–4/1) gave **2h** (12 mg, 10% yield) as a yellow solid of mp=88.5–89.1 °C and $[\alpha]_D^{25}$ −65.4 (*c* 0.14, $CHCl_3$). The ee was determined to be 95% by HPLC (Daicel Chiralpac IA, hexane/*i*-PrOH=9/1, 0.5 mL/min, 254 nm, major 16.1 min and minor 20.7 min). ^{1}H NMR ($CDCl_3$): 2.28 (s, 3H), 2.35 (s, 3H), 4.57 (br s, 1H), 5.89 (s, 1H), 7.11 (d, *J*=8.0 Hz, 2H), 7.17–7.22 (m, 4H), 7.81 (d, *J*=8.0 Hz, 2H).

*4.2.9. (R)-2-Hydroxy-1,2-bis(4-methoxyphenyl)ethanone (**2i**)*[8b]. Silica gel column chromatography (hexane/ethyl acetate=10/1–4/1) gave **2i** (4 mg, 3% yield) as a yellow solid of mp=119.0–119.9 °C and $[\alpha]_D^{25}$ −43.8 (*c* 0.05, $CHCl_3$). The ee was determined to be 99% by HPLC (Daicel Chiralpac IA, hexane/*i*-PrOH=4/1, 0.95 mL/min, 254 nm, major 26.5 min and minor 29.1 min). ^{1}H NMR ($CDCl_3$): 3.76 (s, 3H), 3.82 (s, 3H), 5.84 (s, 1H), 6.83–6.87 (m, 4H), 7.26 (m, 2H), 7.90 (d, *J*=9.1 Hz, 2H). OH proton was not observed clearly.

*4.2.10. (R)-1,2-Di(furan-2-yl)-2-hydroxyethanone (**2j**)*[8b]. Silica gel column chromatography (hexane/ethyl acetate=4/1–1/1) gave **2j** (66 mg, 69% yield) as a yellow solid of mp=135.1–135.7 °C and $[\alpha]_D^{25}$ −13.7 (*c* 0.47, $CHCl_3$). The ee was determined to be 39% by HPLC (Daicel Chiralpac IA, hexane/*i*-PrOH=9/1, 0.8 mL/min, 254 nm, major 26.0 min and minor 17.6 min). ^{1}H NMR ($CDCl_3$): 4.15 (br s, 1H), 5.80 (s, 1H), 6.35 (m, 1H), 6.49 (m, 1H), 6.53 (dd, *J*=1.8, 3.6 Hz, 1H), 7.25 (m, 1H), 7.37 (m, 1H), 7.61 (m, 1H).

4.3. Preparation of chiral triazolium salts

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 column chromatography to afford the corresponding thiolactam (Scheme 3, step 1).



Scheme 3. General synthesis of precatalysts.

To a solution of the thiolactam in benzene, excess amount 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).

*4.3.1. (S)-5-Benzhydryl-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo [2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (**3**).* Silica gel column chromatography ($CHCl_3$/MeOH=10/1) gave **3** as a brown viscous liquid of $[\alpha]_D^{25}$ +12.9 (*c* 0.23, $CHCl_3$). ^1H NMR ($CDCl_3$): 2.57 (m, 1H), 3.07 (m, 1H), 3.21 (m, 1H), 3.37 (m, 1H), 4.20 (d, *J*=11.4 Hz, 1H), 6.04 (m, 1H), 7.27–7.53 (m, 12H), 7.92 (m, 1H), 8.36 (s, 1H), 8.38 (d, *J*=4.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): 21.4, 32.9, 56.1, 64.4, 114.0, 125.7, 127.8, 127.9, 128.2, 128.6, 129.4, 129.9, 135.3, 138.8, 139.6, 139.9, 147.1, 148.9, 163.3. IR (neat): 3030, 2960, 1590, 1470, 1250 cm^{-1}. HRMS–FAB (*m*/*z*): calcd for $C_{23}H_{21}N_4$ $[M-BF_4]^+$: 353.1766. Found: 353.1769.

*4.3.2. (S)-5-Benzhydryl-2-(6-methylpyridin-2-yl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (**4**).* Silica gel column chromatography ($CHCl_3$/MeOH=10/1) gave **4** as a brown solid of mp=119.7–120.1 °C and $[\alpha]_D^{25}$ +4.3 (*c* 0.28, $CHCl_3$). ^1H NMR ($CDCl_3$): 2.47 (s, 3H), 2.57 (m, 1H), 3.07 (m, 1H), 3.18 (m, 1H), 3.34 (m, 1H), 4.20 (d, *J*=11.0 Hz, 1H), 6.03 (m, 1H), 7.25–7.52 (m, 11H), 7.66 (d, *J*=7.7 Hz, 1H), 7.79 (t, *J*=7.7 Hz, 1H), 8.30 (s, 1H). ^{13}C NMR ($CDCl_3$): 21.4, 23.8, 32.8, 55.8, 64.4, 110.6, 125.3, 127.8, 128.3, 128.4, 129.3, 129.8, 134.9, 138.9, 146.4, 158.9, 163.2. IR (KBr): 3020, 2960, 1590, 1210, 1060 cm^{-1}. HRMS–FAB (*m*/*z*): calcd for $C_{24}H_{23}N_4$ $[M-BF_4]^+$: 367.1923. Found: 367.1928.

*4.3.3. (S)-3,3-Bis(phenylmethyl)-5-benzhydryl-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (**5**).* Silica gel column chromatography ($CHCl_3$/MeOH=10/1) gave **5** as a brown solid of $[\alpha]_D^{25}$ +17.1 (*c* 0.70, $CHCl_3$) and mp=68.5–69.0 °C. ^1H NMR ($CDCl_3$): 2.47 (dd, *J*=5.5, 11.8 Hz, 1H), 2.72 (d, *J*=11.8 Hz, 1H), 3.07 (m, 2H), 3.35 (m, 2H), 3.46 (d, *J*=13.7 Hz, 1H), 5.45 (m, 1H), 7.00 (d, *J*=7.8 Hz, 2H), 7.05 (m, 2H), 7.16 (d, *J*=7.8 Hz, 2H), 7.21–7.48 (m, 15H), 7.85 (s, 1H), 7.92 (d, *J*=8.2 Hz, 1H), 7.99 (t, *J*=8.2 Hz, 1H), 8.40 (d, *J*=5.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): 42.0, 43.8, 45.5, 46.9, 54.7, 62.5, 113.9, 125.9, 127.4, 127.5, 127.6, 128.0, 128.1, 128.3, 128.4, 128.8, 129.1, 129.4, 129.6, 130.5, 130.8, 134.8, 135.5, 136.4, 138.7, 139.8, 140.0, 147.1, 148.9, 166.5. IR (KBr): 3030, 2930, 2860, 1570, 1470, 1190 cm^{-1}. HRMS–FAB (*m*/*z*): calcd for $C_{37}H_{33}N_4$ $[M-BF_4]^+$: 533.2705. Found: 533.2711.

*4.3.4. (S)-5-[Di(o-tolyl)methy]-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (**6**).* Silica gel column chromatography ($CHCl_3$/MeOH=10/1) gave **6** as a white solid of mp=236.1–236.9 °C and $[\alpha]_D^{25}$ +15.8 (*c* 0.16, $CHCl_3$). ^1H NMR ($CDCl_3$): 2.08 (s, 3H), 2.29 (s, 3H), 2.58 (m, 1H), 3.25 (m, 2H), 3.37 (m, 1H), 4.58 (d, *J*=11.4 Hz, 1H), 5.90 (m, 1H), 7.17–7.54 (m, 9H), 7.94 (m, 2H), 8.22 (s, 1H), 8.41 (d, *J*=4.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): 19.9, 27.3, 28.4, 47.9, 62.0, 107.9, 114.3, 126.0, 126.3, 126.6, 127.0, 127.3, 130.7, 131.0, 136.3, 136.7, 138.0, 139.3, 139.6, 146.3, 158.9. IR (KBr): 3060, 2960, 1600, 1470, 1190, 1060 cm^{-1}. HRMS–FAB (*m*/*z*): calcd for $C_{25}H_{25}N_4$ $[M-BF_4]^+$: 381.2074. Found: 381.2085.

*4.3.5. (S)-5-[Diphenyl(trimethylsilyloxy)methyl]-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (**8**).* Silica gel column chromatography ($CHCl_3$/MeOH=10/1) gave **8** as a viscous liquid of $[\alpha]_D^{25}$ −138.4 (*c* 0.51, $CHCl_3$). ^1H NMR ($CDCl_3$): −0.05 (s, 9H), 2.00 (m, 1H), 2.70 (m, 1H), 2.96 (m, 1H), 3.49 (m, 1H), 6.14 (d, *J*=7.7 Hz, 1H), 7.22–7.50 (m, 11H), 7.92 (d, *J*=8.2 Hz, 1H), 8.02 (m, 1H), 8.59 (d, *J*=4.1 Hz, 1H), 9.49 (s, 1H). ^{13}C NMR ($CDCl_3$): 1.52, 21.0, 29.5, 68.4, 82.3, 113.8, 125.9, 128.4, 128.8, 128.9, 129.3, 136.4, 139.6, 139.8, 140.1, 147.2, 149.1, 163.5. IR (neat): 3040, 2960, 1590, 1470, 1190, 1050 cm^{-1}. HRMS–FAB (*m*/*z*): calcd for $C_{26}H_{29}N_4OSi$ $[M-BF_4]^+$: 441.2111. Found: 441.2116.

*4.3.6. (S)-5-[Hydroxy(diphenyl)methy]-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (**7**).* To a solution of **8** (100 mg, 0.19 mmol) in THF (1.0 mL), tetrafluoroboric acid (0.95 mmol) was added. The whole was stirred at room temperature for 3 h, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=10/1) to give **7** (58 mg, 67%) as a yellow viscous liquid of $[\alpha]_D^{25}$ −119.6 (*c* 0.28, $CHCl_3$). ^1H NMR ($CDCl_3$): 2.52 (m, 1H), 2.78 (m, 1H), 3.01 (m, 1H), 3.23 (m, 1H), 4.14 (br s, 1H), 6.17 (m, 1H), 7.26–7.52 (m, 11H), 7.88 (m, 1H), 7.97 (m, 1H), 8.47 (m, 1H), 9.26 (s, 1H). ^{13}C NMR ($CDCl_3$): 21.4, 29.7, 67.9, 79.0, 113.8, 125.7, 126.0, 126.4, 128.0, 128.5, 128.7, 129.1, 136.2, 139.9, 141.6, 142.5, 147.2, 148.9, 164.0. IR (neat): 3490, 3040, 2960, 1590, 1470, 1190, 1060 cm^{-1}. HRMS–FAB (*m*/*z*): calcd for $C_{23}H_{21}N_4O$ $[M-BF_4]^+$: 369.1715. Found: 369.1708.

*4.3.7. (S)-5-[Diphenyl(trimethylsilyloxy)methyl]-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium hexafluorophosphate (**9**).* Silica gel column chromatography ($CHCl_3$/MeOH=10/1) gave **9** as a brown solid of mp=189.5–194.2 °C and $[\alpha]_D^{25}$ −151.2 (*c* 0.78, $CHCl_3$). ^1H NMR ($CDCl_3$): −0.03 (s, 9H), 2.09 (m, 1H), 2.76 (m, 1H), 2.98 (m, 1H), 3.45 (m, 1H), 6.07 (d, *J*=8.5 Hz, 1H), 7.26–7.61 (m, 11H), 7.93 (d, *J*=8.5 Hz, 1H), 8.05 (m, 1H), 8.61 (d, *J*=3.7 Hz, 1H), 9.43 (s, 1H). ^{13}C NMR ($CDCl_3$): 1.41, 20.9, 29.4, 68.5, 82.2, 113.6, 126.1, 127.8, 128.0, 128.4, 128.6, 128.9, 129.4, 135.9, 139.1, 139.6, 140.2, 147.0, 149.1, 163.4. IR (KBr): 3040, 2960, 1590, 1470, 1260, 1070 cm^{-1}. HRMS–FAB (*m*/*z*): calcd for $C_{26}H_{29}N_4OSi$ $[M-PF_6]^+$: 441.2111. Found: 441.2115.

*4.3.8. (S)-5-[Diphenyl(trimethylsilyloxy)methyl]-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium chloride (**10**).* Silica gel column chromatography ($CHCl_3$/MeOH=10/1) gave **10** as a brown viscous liquid of $[\alpha]_D^{25}$ −125.5 (*c* 0.55, $CHCl_3$). ^1H NMR ($CDCl_3$): −0.11 (s, 9H), 1.92 (m, 1H), 2.61 (m, 1H), 2.90 (m, 1H), 3.51 (m, 1H), 6.48 (d, *J*=7.7 Hz, 1H), 7.16–7.36 (m, 10H), 7.44 (m, 1H), 7.80 (d, *J*=7.7 Hz, 1H), 7.93 (m, 1H), 8.44 (m, 1H), 9.59 (s, 1H). ^{13}C NMR ($CDCl_3$): 1.45, 21.1, 29.8, 68.4, 82.2, 125.6, 128.0, 128.2, 128.6, 129.0, 136.6, 139.6, 139.8, 139.9, 147.1, 148.9, 163.5. IR (neat): 3150, 2920, 1590, 1470, 1250, 1070 cm^{-1}. HRMS–FAB (*m*/*z*): calcd for $C_{26}H_{29}N_4OSi$ $[M-Cl]^+$: 441.2111. Found: 441.2118.

*4.3.9. (S)-5-[Diphenyl(trimethylsilyloxy)methyl]-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium bromide (**11**).* Silica gel column chromatography ($CHCl_3$/MeOH=10/1) gave **11** as a brown viscous liquid of $[\alpha]_D^{25}$ −81.0 (*c* 0.55, $CHCl_3$). ^1H NMR ($CDCl_3$): −0.01 (s, 9H), 2.04 (m, 1H), 2.74 (m, 1H), 3.04 (m, 1H), 3.63 (m, 1H), 6.58 (d, *J*=8.0 Hz, 1H), 7.27–7.49 (m, 10H), 7.56 (m, 1H), 7.93 (d, *J*=8.0 Hz, 1H), 8.04 (m, 1H), 8.58 (m, 1H), 9.67 (s, 1H). ^{13}C NMR ($CDCl_3$): 1.39, 21.1, 29.6, 68.5, 82.1, 113.5, 125.7, 127.5, 127.8, 128.2, 128.6, 129.0, 136.3, 139.4, 139.6, 139.9, 146.9, 148.9, 163.4. IR (neat): 3050, 2970, 1590, 1500, 1250, 1100, 1070 cm^{-1}. HRMS–FAB (*m*/*z*): calcd for $C_{26}H_{29}N_4OSi$ $[M-Br]^+$: 441.2111. Found: 441.2109.

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Supplementary data

A supplementary data file (^1H and ^{13}C NMR) of newly synthesized chiral triazolium salts (**3**–**11**) is available. Supplementary data

associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.11.028.

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10. In our case, (*Z*)-enolamine might be preferentially generated because of intramolecular hydrogen-bonding and furthermore one of the four transition states of the (*Z*)-enolamine, derived from chiral triazolium precatalyst, might be preferred based on the Houk's study. See, Dudding, T.; Houk, K. N. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5770–5775.
11. Under the optimized conditions, when the reaction of **1c** was quenched after 3 h or 9 h, the product **3c** was obtained in 58% and 76% yields with 92% ee and 70% ee, respectively. These results suggest that the low enantioselectivity of the products **3** with aldehydes bearing an electron-withdrawing group is due to the partial racemization by deprotonation–protonation at the α-position of products **3**.