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Authors: Jun Gong, Shi-Wu Li, Saira Qurban, and QIANG KANG

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Highly Enantioselective Mannich Reaction Employing 1,3,5-Triaryl-1,3,5-Triazinanes Catalyzed by Chiral-at-Metal Rhodium Complexes

Jun Gong,[a,b] Shi-Wu Li,[a,b] Saira Qurban,[a,b] and Qiang Kang*[a]

Abstract: Chiral-at-metal Rh(III) complexes catalyzed highly efficient enantioselective Mannich reaction of 2-acyl imidazoles with 1,3,5-triazinanes is developed, affording the corresponding adducts in 81-99% yields with up to >99% enantioselectivities. This protocol performs with 0.1 mol % of Rh(III) complex on gram scale without loss in enantioselectivity.

Introduction

The Mannich reaction is an efficient method for the preparation of *β*-amino carbonyl compounds and therefore a very important carbon-carbon bond-formation reaction.[1] Specifically, the asymmetric Mannich reaction[2] has received considerable attention since the Kobayashi group reported the first catalytic enantioselective Mannich-type reactions of aldimines with silylenolates using a novel chiral zirconium catalyst.[3] In complement to one-pot three-component reaction, preformed imines were extensively employed in the asymmetric Mannich reaction.[4] However, such preformed Mannich reagents have some defects such as low activity and instability despite its important synthetic value.

As the promising and stable surrogates for aryl imines, 1,3,5-triaryl-1,3,5-triazinanes, which are readily prepared through the condensation of paraformaldehyde with aromatic amines,[5] have been utilized as effective reagents in organic synthesis. For example, Krische and co-workers reported the hydroaminomethylation of allenes and 1,3-dienes with 1,3,5-triazinanes in ruthenium-catalyzed processes.[6] The Sun group developed a series of gold-catalyzed [4+1]/[4+3], [2+2+2] and [3+2+2]-cycloadditions employing 1,3,5-triazinanes.[7] However, the application of 1,3,5-triazinanes in asymmetric synthesis is quite limited. Only recently, the Feng group realized the first asymmetric Mannich reaction using 1,3,5-triazinanes as the Mannich reagents catalyzed by chiral *N*,*N'*-dioxide-metal complexes, and optically active *β*-amino compounds with all-carbon quaternary stereocenters were obtained (Scheme 1a).[8]

[a] J. Gong, S.-W. Li, S. Qurban, Prof. Dr. Q. Kang
Key Laboratory of Coal to Ethylene Glycol and Its Related Technology, Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences
155 Yangqiao Road West, Fuzhou, 350002, China
E-mail:kangq@fjirsm.ac.cn
http://www.fjirsm.cas.cn/research/R1/kangqianggroup/
[b] J. Gong, S.-W. Li, S. Qurban
University of Chinese Academy of Sciences
Beijing, 100049, China

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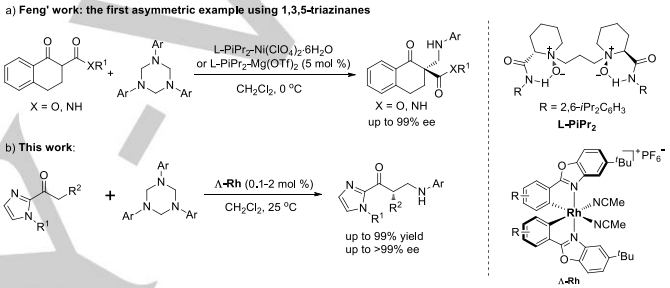
Inspired by these works and as a continuation of our interest in chiral-at-metal Lewis acid catalysts,[9-12] herein we report an asymmetric Mannich reaction of 2-acyl imidazoles with 1,3,5-triazinanes catalyzed by chiral-at-metal rhodium complexes, delivering the corresponding *β*-amino derivatives in high yields with good to excellent enantioselectivities (Scheme 1b).



Scheme 1. Previous asymmetric report and our work involving utilization of 1,3,5-triaryl-1,3,5-triazinanes.

Results and Discussion

We started our studies on this topic by investigating the reaction of 2-acyl imidazole **1a** with the 1,3,5-triphenyl-1,3,5-triazinane **2a** in the presence of chiral-at-metal rhodium complex **Δ-Rh1** (2 mol%) developed by the Meggers group.[11a] The reaction performed smoothly to afford the desired product **3aa** in good yield (80%), but with poor enantioselectivity (-32% ee) (Table 1, entry 1). Replacing the methyl substituent of the imidazole moiety with phenyl (**1b**) and *o*-tolyl (**1c**) improved the enantioselectivity to 83% and 93%, respectively (entries 2-3). Then we attempted to modify the catalyst by introducing 3,5-dimethyl phenyl ring at the two R' sites shown in Table 1. To our delight, **Λ-Rh2** provided a further increase in yield and enantioselectivity (95% yield, 95% ee, entry 4). Replacing the solvent CH_2Cl_2 with 1,2-dichlorethane (DCE) or $CHCl_3$ provided slightly reduced yields and enantioselectivities (entries 5-6), while other tested solvents such as toluene and THF did not provide satisfactory results (entries 7-8). Remarkably, reducing the catalyst loading to 1 mol% still afforded the product **3ca** in 95% yield with 95% ee (entry 9). Control experiment in the absence of catalyst fail to provide any product, thereby demonstrating that this reaction crucially depends on the chiral-at-metal rhodium complexes (entry 10).

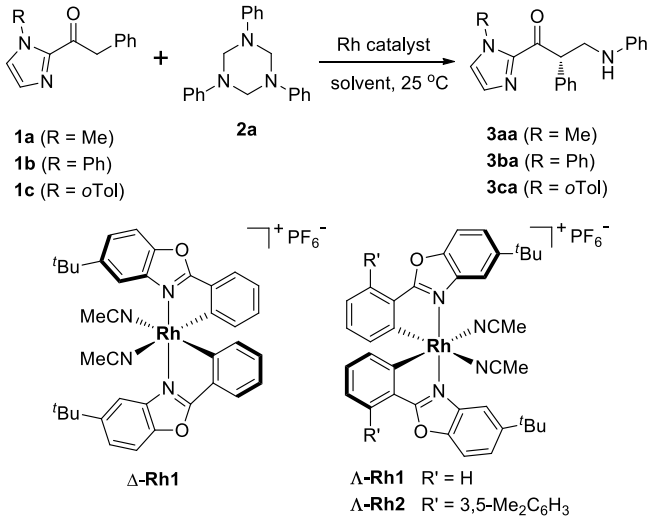
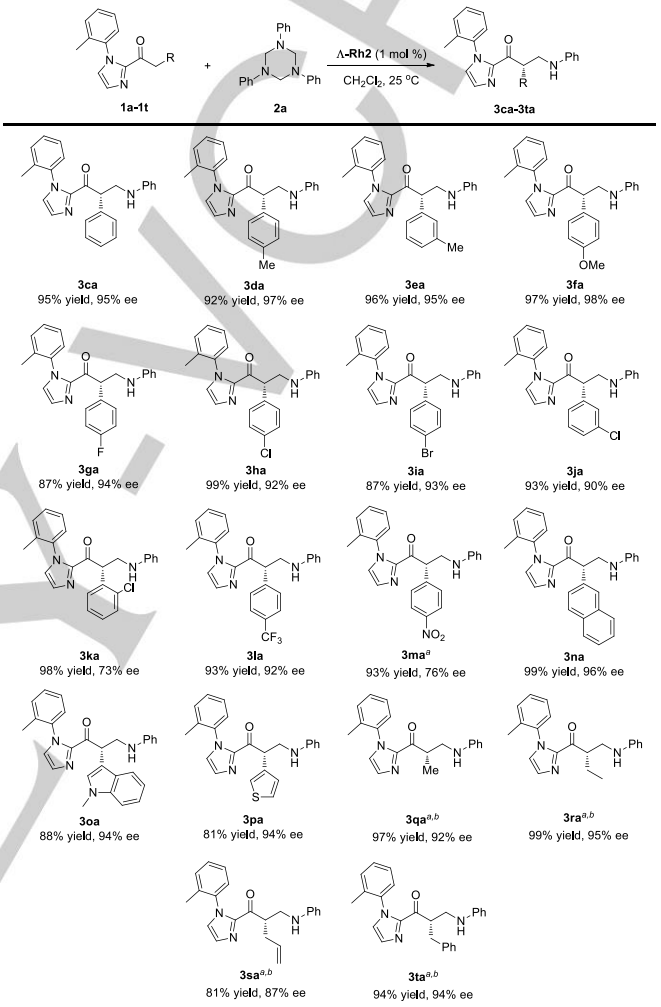


Table 1. Initial experiments and optimization of the reaction conditions.[a]

Entry	R	Catalyst	Solvent	Time [h]	Yield [%][b]	ee [%][c]
1	Me	**Δ-Rh1**	CH_2Cl_2	24	80	-32
2	Ph	**Λ-Rh1**	CH_2Cl_2	16	81	83
3	*o*Tol	**Λ-Rh1**	CH_2Cl_2	16	87	93
4	*o*Tol	**Λ-Rh2**	CH_2Cl_2	16	95	95
5	*o*Tol	**Λ-Rh2**	DCE	12	93	94
6	*o*Tol	**Λ-Rh2**	$CHCl_3$	12	94	93
7	*o*Tol	**Λ-Rh2**	toluene	12	85	84
8	*o*Tol	**Λ-Rh2**	THF	12	83	83
9[d]	*o*Tol	**Λ-Rh2**	CH_2Cl_2	16	95	95
10	*o*Tol	none	CH_2Cl_2	16	0	n.d.

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.08 mmol) and catalyst (0.004 mmol, 2.0 mol%) in solvent (0.4 mL) at 25 °C under argon. [b] Isolated yield. [c] Determined by HPLC analysis using chiral stationary phase, n.d.= not determined. [d] 1.0 mol% of catalyst was used.

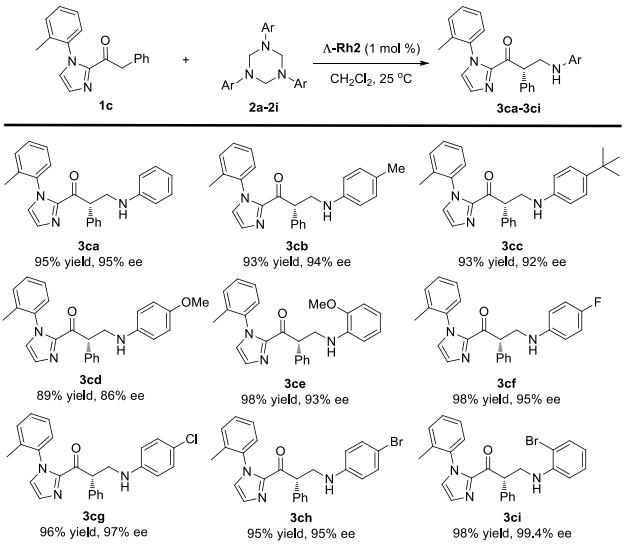
With the optimized reaction conditions in hand, we next investigated the scope of 2-acyl imidazoles in this reaction (Scheme 2). Electron-donating methyl group or methoxy group on the phenyl ring had little influence on both the yields and enantioselectivities (92-97% yields, 95-98% ee; **3da**-**3fa**). Substrates equipped with electron-withdrawing groups such as halogen atoms, trifluoromethyl group or nitro group on the phenyl ring were also tolerable, affording the corresponding products with good yields and enantioselectivities, although the ee values of **3ka** and **3ma** were diminished (87-99% yields, 73-94% ee; **3ga**-**3ma**). Ring-condensed **1n** and heteroaromatic**1o** or **1p** were all well converted in good yields with excellent ee (81-99% yield, 94-96% ee; **3na**-**3pa**). Moreover, substrates with aliphatic methyl, ethyl, allyl and benzyl groups in α-position to the carbonyl group were also suitable substrates for the reaction, offering products in good yields with good to excellent ee (81-99% yields, 87-95% ee; **3qa**-**3ta**).



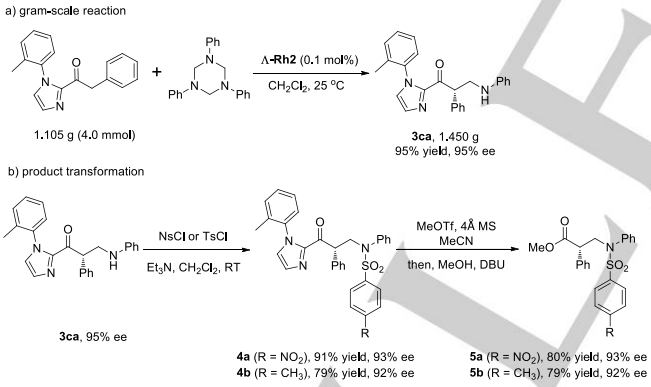
Scheme 2. Substrate scope of 2-acyl imidazoles. Reaction conditions: **1** (0.20 mmol), **2a** (0.08 mmol) and **Λ-Rh2** (0.002 mmol, 1.0 mol%) in CH_2Cl_2 (0.4 mL) at 25 °C under argon atmosphere. All isolated yields were based on substrate **1**. ee values were determined by HPLC analysis using chiral stationary phase. [a] 2.0 mol% of **Λ-Rh2** was used. [b] The reaction was conducted at 50 °C in 1,2-dichlorethane under argon atmosphere.

Next, 1,3,5-triaryl-1,3,5-triazinanes derived from substituted aromatic amines were investigated. As it shown in Scheme 3, alkyl substituted 1,3,5-triazinanes **2b** and **2c** performed smoothly under the optimized reaction conditions to give the products in high yields with good ee (93% yield, 92-94% ee; **3cb**-**3cc**). Notably, the 4-methoxyl substituted 1,3,5-triazinane **2d** showed a slight decrease in yield and enantioselectivity compared with 2-methoxyl substituted 1,3,5-triazinane **2e** (89-98% yields, 86-93% ee; **3cd**-**3ce**). Furthermore, 1,3,5-

triazinanes equipped with electron-withdrawing halogen groups were tolerable, affording corresponding products in high yields with excellent enantioselectivities (95-98% yields, 95->99% ee; **3cf**-**3ci**).



Scheme 3. Substrate scope of 1,3,5-triaryl-1,3,5-triazinanes. Reaction conditions: **1c** (0.20 mmol), **2a-2i** (0.08 mmol) and **Λ-Rh2** (0.002 mmol, 1.0 mol%) in CH_2Cl_2 (0.4 mL) at 25 °C under argon atmosphere. All isolated yields were based on substrate **1c**. ee values were determined by HPLC analysis using chiral stationary phase.



Scheme 4. Gram-scale reaction and product transformation.

It is noteworthy that a gram-scale reaction with **1c** (1.1 g) was also conducted at a lower catalyst loading (0.1 mol%), and the product **3ca** was obtained in 95% yield without loss in enantioselectivity (95% ee), which highlights the synthetic potential of current methodology (Scheme 4a). On the other hand, the product **3ca** could be converted into optically active *N*-protected *β*-amino methyl ester **5a** and **5b** by protection with NsCl or TsCl followed by the removal of imidazole moieties, albeit with a little loss in enantiomeric excess (Scheme 4b).

On the basis of previous related investigations,[11a,11b,14] a putative mechanism is proposed as shown in Figure 1. The acyl imidazole substrate can be activated by coordinating to the rhodium catalyst in a bidentate fashion, thus forming a nucleophilic enolate complex after deprotonation. The *Si*-face of coordinated substrate is effectively shielded by one of the *tert*-butyl groups. The highly selective approach of the *in situ* generated *N*-aryl formaldimine toward the *Re*-face of coordinated substrate leads to the desired product with *S* configuration, which is consistent with the observed absolute configuration of **3ba** determined by a single-crystal X-ray analysis (for details, see the Supporting Information).[13]

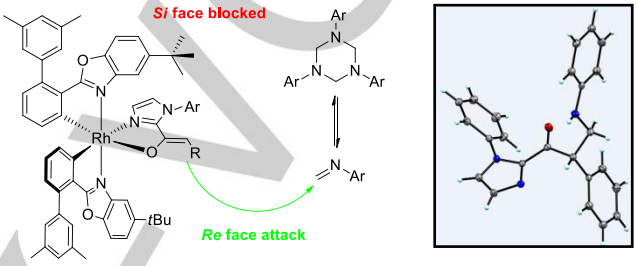


Figure 1. Proposed mechanism and the X-ray structure of **3ba** with thermal ellipsoids shown at the 35% probability level.

Conclusions

In conclusion, we have developed a highly enantioselective Mannich reaction of 2-acyl imidazoles with 1,3,5-triaryl-1,3,5-triazinanes as *N*-aryl formaldimine precursors. In the presence of chiral-at-metal rhodium complexes (0.1-2.0 mol%), a variety of optically active *β*-amino derivatives were obtained in high yields (up to 99%) with good to excellent enantioselectivities (up to >99% ee). Further studies focused on asymmetric reactions catalyzed by chiral-at-metal rhodium complexes are underway in our laboratory.

Experimental Section

General Procedure: A dried 25 mL Schlenk tube was charged with 2-acyl imidazole **1** (0.20 mmol, 1.0 equiv), 1,3,5-triaryl-1,3,5-triazinane **2** (0.08 mmol, 0.4 equiv) and chiral catalysts **Δ-Rh1**, **Λ-Rh1**, or **Λ-Rh2** (1.0-2.0 mol%). The tube was purged with argon and anhydrous CH_2Cl_2 or 1,2-dichloroethane (0.4 mL) was added via syringe. The reaction mixture was stirred at 25 °C (CH_2Cl_2 as solvent) or 50 °C (1,2-dichloroethane as solvent) for the indicated time (monitored by TLC) under argon atmosphere. Afterwards, the mixture was subjected to a silica gel flash chromatography (petroleum ether/ EtOAc = 20:1 to 10:1) to afford chiral products. The ee values were determined by chiral HPLC chromatography using a Daicel Chiralpak IC column (250 x 4.6 mm).

(*R*)-1-(1-methyl-1H-imidazol-2-yl)-2-phenyl-3-(phenylamino)propan-1-one (3aa): light yellow oil (49.0 mg, yield: 80%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 32% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 0.5 mL/min, 40 °C, t_r(minor) = 27.47 min, t_r(major) = 28.37 min).

$[\alpha]_D^{25}$ = +6.0° (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 7.1 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.27-7.23 (m, 1H), 7.16-7.12 (m, 3H), 6.97 (s, 1H), 6.70-6.66 (m, 1H), 6.62 (d, *J* = 1.0 Hz, 1H), 6.60 (d, *J* = 0.9 Hz, 1H), 5.48 (dd, *J* = 6.4 Hz, 8.5 Hz, 1H), 3.98 (dd, *J* = 8.5 Hz, 12.7 Hz, 1H), 3.94 (s, 3H), 3.52 (dd, *J* = 6.4 Hz, 12.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.25, 147.78, 142.88, 137.18, 129.52, 129.26, 128.83, 128.76, 127.56, 127.47, 117.56, 113.04, 52.51, 46.64, 36.27. IR (KBr): *v* (cm^{-1}) 3054, 3026, 2954, 1670, 1602, 1507, 1402, 1317, 1289, 1257, 749, 694. HRMS (ESI, *m*/*z*) calcd for $C_{19}H_{19}N_3NaO$ $[M+Na]^+$: 328.1420, found: 328.1427.

(*S*)-2-phenyl-1-(1-phenyl-1H-imidazol-2-yl)-3-(phenylamino)propan-1-one (3ba): yellow solid (60.0 mg, yield: 81%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 83% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 8.18 min, t_r(minor) = 11.34 min). **3ba** can be recrystallized from a mixed solvent (*n*-hexane/*i*-PrOH = 4:1). After recrystallization, enantiomeric excess of **3ba** was determined by HPLC analysis using a Chiralpak IC column, ee = 95% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 8.65 min, t_r(minor) = 11.70 min). $[\alpha]_D^{20}$ = -55.5° (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45-7.41 (m, 5H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.28-7.24 (m, 1H), 7.22 (s, 1H), 7.17-7.11 (m, 5H), 6.68 (t, *J* = 7.2 Hz, 1H), 6.59 (d, *J* = 7.8 Hz, 2H), 5.48 (t, *J* = 7.9 Hz, 1H), 3.92-3.87 (m, 2H), 3.47 (dd, *J* = 6.2 Hz, 13.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.84, 147.73, 142.80, 138.30, 137.07, 130.06, 129.33, 129.08, 128.97, 128.86, 128.82, 127.56, 127.43, 125.78, 117.53, 113.02, 52.93, 46.45. IR (KBr): *v* (cm^{-1}) 3053, 3027, 2923, 2853, 1683, 1601, 1505, 1491, 1454, 1444, 1399, 1312, 1259, 909, 761, 749, 692. HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{21}N_3NaO$ $[M+Na]^+$: 390.1577, found: 390.1574.

(*S*)-2-phenyl-3-(phenylamino)-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3ca): light yellow oil (72.5 mg, yield: 95%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 95% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 8.99 min, t_r(minor) = 12.57 min). $[\alpha]_D^{25}$ = -59.5° (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41-7.21 (m, 9H), 7.16-7.12 (m, 2.5H), 7.01 (d, *J* = 1.4 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 0.5H), 6.67 (t, *J* = 7.2 Hz, 1H), 6.58 (d, *J* = 8.1 Hz, 2H), 5.46 (t, *J* = 7.2 Hz, 1H), 3.91-3.83 (m, 2H), 3.48-3.42 (m, 1H), 1.98 (s, 1.4H), 1.63 (s, 1.6H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.82, 189.78, 147.68, 143.23, 137.83, 136.98, 136.94, 134.59, 134.41, 130.79, 130.74, 130.26, 130.23, 129.29, 129.19, 129.15, 128.88, 128.85, 128.75, 127.48, 126.72, 126.66, 126.63, 126.44, 126.19, 117.51, 117.46, 112.95, 52.77, 46.53, 46.07, 17.30, 16.74 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3308, 3056, 3025, 2952, 1680, 1602, 1504, 1454, 1402, 909, 747, 693. HRMS (ESI, *m*/*z*) calcd for $C_{25}H_{23}N_3NaO$ $[M+Na]^+$: 404.1733, found: 404.1729.

(*S*)-3-(phenylamino)-2-(p-tolyl)-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3da): colorless oil (72.5 mg, yield: 92%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 97% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 9.80 min, t_r(minor) = 13.04 min). $[\alpha]_D^{25}$ = -77.4° (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40-7.22 (m, 6.5H), 7.16-7.11 (m, 4H), 7.01 (s, 1H), 6.93 (d, *J* = 7.7 Hz, 0.5H), 6.67 (t, *J* = 7.2 Hz, 1H), 6.58 (d, *J* = 7.9 Hz, 2H), 5.41 (s, 1H), 3.87-3.83 (m, 2H), 3.44-3.42 (m, 1H), 2.31 (s, 3H), 1.99 (s, 1.4H), 1.66 (s, 1.6H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.96, 189.92, 147.74, 143.24, 137.89, 137.85, 137.16, 137.13, 134.59, 134.45, 133.93, 133.87, 130.78, 130.73, 130.23, 130.19, 129.61, 129.57, 129.28, 129.17, 129.13, 128.61, 128.59, 126.65, 126.44, 126.20, 117.46, 117.41, 112.96, 52.37, 46.49, 46.12, 21.13, 17. 31, 16.83 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3397, 3051, 3024, 2922, 2861, 1681, 1602, 1503, 1461, 1401, 1317, 1261, 910, 764, 749, 692. HRMS (ESI, *m*/*z*) calcd for $C_{26}H_{25}N_3NaO$ $[M+Na]^+$: 418.1890, found: 418.1885.

(*S*)-3-(phenylamino)-2-(m-tolyl)-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3ea): yellow oil (75.7 mg, yield: 96%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 95% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 4.49 min, t_r(minor) = 5.19 min). $[\alpha]_D^{25}$ = -50.6° (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40-7.12 (m, 9H), 7.07-7.05 (m, 1H), 7.01 (d, *J* = 2.3 Hz, 1H), 6.93 (d, *J* = 7.7 Hz, 0.5H), 6.68 (t, *J* = 7.2 Hz, 1H), 6.58 (d, *J* = 8.3 Hz, 2H), 5.42-5.39 (m, 1H), 3.83 (s, 2H), 3.45-3.43 (m, 1H), 2.31 (d, *J* = 2.8 Hz, 3H), 1.99 (s, 1.4H), 1.67 (s, 1.5H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.93, 189.88, 147.73, 143.32, 143.27, 138.55, 138.49, 137.89, 137.85, 136.90, 136.80, 134.63, 134.41, 130.79, 130.75, 130.27, 130.22, 129.35, 129.29, 129.20, 129.15, 128.75, 128.73, 128.31, 128.27, 126.67, 126.61, 126.49, 126.21, 125.83, 117.47, 117.42, 112.95, 52.76, 52.71, 46.57, 46.15, 21.47, 17.32, 16.76 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3420, 3053, 2924, 2864, 1681, 1602, 1503, 1460, 1403, 1304, 1265, 763, 744, 701. HRMS (ESI, *m*/*z*) calcd for $C_{26}H_{25}N_3NaO$ $[M+Na]^+$: 418.1890, found: 418.1891.

(*S*)-2-(4-methoxyphenyl)-3-(phenylamino)-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3fa): yellow oil (80.0 mg, yield: 97%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 98% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 13.42 min, t_r(minor) = 17.61 min). $[\alpha]_D^{25}$ = -92.5° (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.22 (m, 6H), 7.17-7.12 (m, 2.5H), 7.02 (s, 1H), 6.93 (d, *J* = 7.8 Hz, 0.5H), 6.84 (dd, *J* = 2.6 Hz, 8.7 Hz, 2H), 6.67 (t, *J* = 7.2 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 2H), 5.42-5.38 (m, 1H), 3.81 (br, 2H), 3.77 (s, 3H), 3.45-3.42 (m, 1H), 1.99 (s, 1.4H), 1.65 (s, 1.5H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.04, 189.98, 158.95, 147.77, 143.24, 137.89, 137.85, 134.59, 134.42, 130.78, 130.74, 130.22, 130.18, 129.85, 129.29, 129.18, 129.13, 128.94, 128.88, 126.66, 126.62, 126.42, 126.20, 117.47, 117.43, 114.29, 114.25, 112.97, 55.26, 51.85, 46.47, 46.05, 17.31, 16.81 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3392, 3051, 2952, 2924, 2855, 1681, 1602, 1509, 1461, 1401, 1249, 763, 747. HRMS (ESI, *m*/*z*) calcd for $C_{26}H_{25}N_3NaO_2$ $[M+Na]^+$: 434.1839, found: 434.1837.

(*S*)-2-(4-fluorophenyl)-3-(phenylamino)-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3ga): colorless oil (69.2 mg, yield: 87%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 94% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 6.72 min, t_r(minor) = 9.16 min). $[\alpha]_D^{25}$ = -52.9° (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40-7.23 (m, 6H), 7.16-7.13 (m, 2.5H), 7.04 (dd, *J* = 0.8 Hz, 3.2 Hz, 1H), 7.02-6.94 (m, 2.5H), 6.70-6.67 (m, 1H), 6.58 (d, *J* = 8.3 Hz, 2H), 5.48-5.44 (m, 1H), 3.82 (br, 2H), 3.44-3.42 (m, 1H), 1.98 (s, 1.4H), 1.65 (s, 1.5H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.69, 189.63, 163.41, 160.97, 147.56, 143.07, 137.76, 134.56, 134.32, 132.74, 132.71, 132.66, 132.63, 130.81, 130.76, 130.39, 130.31, 129.31, 129.25, 129.21, 126.89, 126.70, 126.66, 126.40, 126.14, 117.63, 117.58, 115.84, 115.82, 115.63, 115.61, 112.95, 51.84, 46.58, 46.12, 17.26, 16.76 (Contained the rotamer). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -114.97 and -115.01. IR (KBr): *v* (cm^{-1}) 3410, 3110, 3052, 3025, 2961, 2926, 2858, 1681, 1602, 1507, 1461, 1401, 1317, 1305, 1264, 1224,1159, 910, 764, 749, 692. HRMS (ESI, *m*/*z*) calcd for $C_{25}H_{23}N_3FO$ $[M+H]^+$: 400.1820, found: 400.1820.

(*S*)-2-(4-chlorophenyl)-3-(phenylamino)-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3ha): light yellow oil (83.0 mg, yield: 99%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 92% (HPLC: Chiralpak column IC, λ = 254 nm,

n-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 6.66 min, t_r(minor) = 8.65 min). $[\alpha]_D^{25}$ = -95.5° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41-7.23 (m, 8H), 7.17-7.13 (m, 2.5H), 7.04 (d, *J* = 1.6 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 0.5H), 6.69 (t, *J* = 7.2 Hz, 1H), 6.57 (d, *J* = 7.6 Hz, 2H), 5.48-5.44 (m, 1H), 3.88-3.82 (m, 2H), 3.45-3.41 (m, 1H), 1.98 (s, 1.4H), 1.67 (s, 1.6H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.41, 189.36, 147.51, 143.02, 137.74, 137.72, 135.58, 135.46, 134.56, 134.35, 133.40, 130.83, 130.79, 130.39, 130.36, 130.14, 129.34, 129.28, 129.24, 129.03, 129.01, 126.97, 126.72, 126.69, 126.40, 126.16, 117.68, 117.64, 112.97, 52.04, 52.01, 46.46, 46.08, 17.28, 16.86 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3336, 3109, 3053, 3025, 2955, 2924, 2858, 1681, 1602, 1503, 1491, 1461, 1400, 1304, 1259, 1090, 1015, 910, 767, 749, 692. HRMS (ESI, *m*/*z*) calcd for $C_{25}H_{22}ClN_3NaO$ $[M+Na]^+$: 438.1344, found: 438.1346.

(*S*)-2-(4-bromophenyl)-3-(phenylamino)-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3ia): light yellow oil (80.2 mg, yield: 87%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 93% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 6.75 min, t_r(minor) = 8.79 min). $[\alpha]_D^{25}$ = -93.3° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.4 Hz, 2H), 7.41-7.23 (m, 6H), 7.17-7.13 (m, 2.5H), 7.04 (d, *J* = 1.3 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 0.5H), 6.69 (t, *J* = 7.2 Hz, 1H), 6.57 (d, *J* = 7.4 Hz, 2H), 5.44 (br, 1H), 3.88-3.81 (m, 2H), 3.45-3.41 (m, 1H), 1.98 (s, 1.4H), 1.68 (s, 1.6H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.31, 189.26, 147.47, 142.99, 137.73, 136.11, 135.98, 134.55, 134.35, 131.97, 131.95, 130.82, 130.78, 130.50, 130.48, 130.39, 130.36, 129.34, 129.28, 129.24, 126.97, 126.71, 126.69, 126.39, 126.15, 121,56, 117.68, 117.64, 112.96, 52.10, 52.07, 46.39, 46.03, 17.27, 16.87 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3412, 3051, 3025, 2959, 2925, 2858, 1680, 1602, 1503, 1487, 1461, 1400, 1304, 1260, 1073, 1011, 944, 910, 766, 749, 692. HRMS (ESI, *m*/*z*) calcd for $C_{25}H_{22}BrN_3NaO$ $[M+Na]^+$: 482.0838, found: 482.0838.

(*S*)-2-(3-chlorophenyl)-3-(phenylamino)-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3ja): light yellow oil (77.0 mg, yield: 93%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 90% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 7.15 min, t_r(minor) = 8.89 min). $[\alpha]_D^{25}$ = -64.4° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41-7.37 (m, 2H), 7.34-7.21 (m, 6H), 7.17-7.13 (m, 2.5H), 7.05 (d, *J* = 4.4 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 0.5H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.58 (d, *J* = 8.3 Hz, 2H), 5.48-5.43 (m, 1H), 3.84 (s, 2H), 3.45-3.42 (m, 1H), 1.97 (s, 1.4H), 1.69 (s, 1.5H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.23, 189.15, 147.46, 143.08, 143.02, 139.07, 138.94, 137.70, 137.69, 134.60, 134.55, 134.36, 130.82, 130.43, 130.39, 130.06, 129.34, 129.29, 129.25, 128.78, 128.72, 127.72, 127.07, 127.00, 126.71, 126.43, 126.20, 117.69, 117.64, 112..96, 112.95, 52.36, 52.28, 46.55, 46.12, 17.25, 16.77 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3308, 3051, 3022, 2927, 2862, 1681, 1602, 1503, 1400, 1317, 1303, 1258, 911, 763, 749, 692. HRMS (ESI, *m*/*z*) calcd for $C_{25}H_{23}ClN_3O$ $[M+H]^+$: 416.1524, found: 416.1521.

(*S*)-2-(2-chlorophenyl)-3-(phenylamino)-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3ka): light yellow oil (81.2 mg, yield: 98%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 73% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 7.97 min, t_r(minor) = 11.05 min). $[\alpha]_D^{25}$ = -55.6° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43-7.23 (m, 6H), 7.20-7.12 (m, 4.5H), 7.04-7.03 (m, 1.5H), 6.67 (t, *J* = 7.3 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 2H), 5.95-5.90 (m, 1H), 4.10 (s, 1H), 3.81-3.73 (m, 1H), 3.51-3.47 (m, 1H), 1.97 (s, 1.5H), 1.83 (s, 1.5H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.74, 189.65, 147.63, 143.28, 143.24, 137.83, 135.34, 135.28, 134.74, 134.48, 134.44, 134.42, 130.84, 130.75, 130.59, 130.53, 130.09, 129.28, 129.22, 128.91, 128.85, 128.59, 127.06, 126.97, 126.83, 126.68, 126.66, 126.63, 126.22, 117.44, 117.40, 112.81, 49.54, 49.52, 45.88, 45.78, 17.29, 17.07 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3397, 3059, 3028, 2919, 2863, 1681, 1614, 1521,1492, 1453, 1402, 1317, 1303, 1256, 944, 910, 808, 762, 699. HRMS (ESI, *m*/*z*) calcd for $C_{25}H_{22}ClN_3NaO$ $[M+Na]^+$: 438.1344, found: 438.1342.

(*S*)-3-(phenylamino)-1-(1-(o-tolyl)-1H-imidazol-2-yl)-2-(4-(trifluoromethyl)phenyl)propan-1-one (3la): colorless oil (83.2 mg, yield: 93%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 92% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 5.11 min, t_r(minor) = 6.17 min). $[\alpha]_D^{25}$ = -60.3° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58-7.51 (m, 4H), 7.41-7.24 (m, 4H), 7.17-7.14 (m, 2.5H), 7.06 (dd, *J* = 0.8 Hz, 3.1 Hz, 1H), 6.97 (d, *J* = 7.7 Hz, 0.5H), 6.70 (ddd, *J* = 0.9 Hz, 7.3 Hz, 1H), 6.58 (dd, *J* = 1.0 Hz, 7.6 Hz, 2H), 5.58-5.54 (m, 1H), 3.93-3.83 (m, 2H), 3.49-3.45 (m, 1H), 1.98 (s, 1.4H), 1.68 (s, 1.5H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.05, 189.00, 147.37, 147.36, 142.96, 141.18, 141.04, 137.66, 134.53, 134.31, 130.84, 130.80, 130.49, 130.46, 129.36, 129.32, 129.29, 129.14, 129.12, 127.12, 126.74, 126.72, 126.39, 126.14, 125.77, 125.75, 125.71, 117.78, 117.74, 112.95, 52.53, 52.46, 46.55, 46.18, 17.23, 16.82 (Contained the rotamer). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.53 and -62.54. IR (KBr): *v* (cm^{-1}) 3308, 3107, 3056, 3025, 2927, 1682, 1603, 1504, 1403, 1325, 1166, 1123, 1068, 1019, 910, 764, 750. HRMS (ESI, *m*/*z*) calcd for $C_{26}H_{23}F_3N_3O$ $[M+H]^+$: 450.1788, found: 450.1785.

(*S*)-2-(4-nitrophenyl)-3-(phenylamino)-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3ma): brown oil (79.3 mg, yield: 93%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 76% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 12.61 min, t_r(minor) = 18.54 min). $[\alpha]_D^{25}$ = -87.3° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 1.8 Hz, 8.5 Hz, 2H), 7.58 (t, *J* = 7.7 Hz, 2H), 7.41-7.24 (m, 4H), 7.17-7.13 (m, 2.5H), 7.07 (d, *J* = 3.0 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 0.5H), 6.70 (t, *J* = 7.3 Hz, 1H), 6.58 (dd, *J* = 2.7 Hz, 7.7 Hz, 2H), 5.66-5.61 (m, 1H), 3.95-3.89 (m, 2H), 3.52-3.47 (m, 1H), 1.97 (s, 1.5H), 1.69 (s, 1.5H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.43, 188.37, 147.28, 147.20, 147.18, 144.70, 144.52, 142.82, 142.79, 137.54, 134.51, 134.23, 130.90, 130.84, 130.64, 130.61, 129.73, 129.71, 129.40, 127.37, 126.80, 126.77, 126.37, 126.10, 123.96, 117.95, 117.90, 112.96, 52.59, 52.51, 46.53, 46.21, 17.21, 16.91 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3052, 3023, 2917, 2850, 1680, 1602, 1518, 1399, 1345, 1316, 1304, 909, 762, 749, 693. HRMS (ESI, *m*/*z*) calcd for $C_{25}H_{22}N_4NaO_3$ $[M+Na]^+$: 449.1584, found: 449.1586.

(*S*)-2-(naphthalen-2-yl)-3-(phenylamino)-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3na): light yellow oil (86.0 mg, yield: 99%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 96% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 10.53 min, t_r(minor) = 13.51 min). $[\alpha]_D^{25}$ = -142.5° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.2 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 3H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.48-7.43 (m, 2H), 7.41-7.13 (m, 7H), 7.01 (s, 1H), 6.90 (d, *J* = 7.8 Hz, 0.5H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.60 (d, *J* = 7.1 Hz, 2H), 5.63 (t, *J* = 7.3 Hz, 1H), 3.96 (br, 1H), 3.85 (s, 1H), 3.56 (br, 1H), 2.02 (s, 1.4H), 1.61 (s, 1.5H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.72, 189.68, 147.69, 147.67, 143.26, 143.20, 137.86, 137.79, 134.64, 134.55, 134.42, 134.40, 133.57, 132.73, 130.80, 130.77, 130.33, 130.27, 129.33, 129.24, 129.19, 128.64, 128.62, 127.92, 127.80, 127.68, 126.78, 126.74, 126.69, 126.64, 126.61, 126.46, 126.22, 126.01, 117.57, 117.53, 113.01, 52.87, 46.44, 46.14, 17.35, 16.83 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3050, 2924, 2854, 1681, 1601,

1504, 1454, 1403, 763, 747, 692. HRMS (ESI, *m*/*z*) calcd for $C_{29}H_{25}N_3NaO$ $[M+Na]^+$: 454.1890, found: 454.1886.

(*S*)-2-(1-methyl-1H-indol-3-yl)-3-(phenylamino)-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3oa): pale yellow solid (76.2 mg, yield: 88%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 94% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 11.97min, t_r(minor) = 13.99 min). $[\alpha]_D^{25}$ = -80.0° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.0 Hz, 1H), 7.38-7.07 (m, 11H), 7.01 (d, *J* = 0.8 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 0.5H), 6.67 (t, *J* = 7.3 Hz, 1H), 6.58 (d, *J* = 7.2 Hz, 2H), 5.76 (t, *J* = 7.2 Hz, 1H), 3.94-3.88 (m, 2H), 3.73 (s, 3H), 3.60-3.54 (m, 1H), 1.99 (s, 1.5H), 1.58 (s, 1.5H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.40, 190.29, 147.98, 143.45, 137.96, 137.91, 136.96, 136.93, 134.63, 134.48, 130.73, 130.67, 130.10, 130.04, 129.24, 129.10, 129.06, 128.12, 127.24, 126.65, 126.61, 126.59, 126.52, 126.33, 121.80, 119.76, 119.30, 117.33, 117.28, 112.96, 109.88, 109.76, 109.30, 109.26, 46.24, 46.03, 44.31, 44.26, 32.86, 17.32, 16.78 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3392, 3109, 3051, 2929, 1681, 1602, 1504, 1462, 1403, 1329, 909, 742, 692. HRMS (ESI, *m*/*z*) calcd for $C_{28}H_{27}N_4O$ $[M+H]^+$: 435.2179, found: 435.2175.

(*S*)-3-(phenylamino)-2-(thiophen-3-yl)-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3pa): yellow oil (62.6 mg, yield: 81%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 94% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 8.93 min, t_r(minor) = 11.98 min). $[\alpha]_D^{25}$ = -40.3° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.25 (m, 6H), 7.16-7.13 (m, 3.5H), 7.06 (d, *J* = 3.5 Hz, 1H), 6.98 (d, *J* = 7.7 Hz, 0.5H), 6.68 (t, *J* = 7.3 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 2H), 5.63 (s, 1H), 3.85 (s, 2H), 3.51-3.44 (m, 1H), 1.97 (s, 1.5H), 1.67 (s, 1.5H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.47, 189.37, 147.65, 143.15, 137.77, 137.01, 136.98, 134.56, 134.37, 130.79, 130.76, 130.24, 129.29, 129.21, 129.16, 127.73, 127.69, 126.91, 126.88, 126.66, 126.37, 126.20, 125.89, 123.21, 123.14, 117.57, 117.52, 112.98, 48.10, 48.05, 46.50, 45.92, 17.23, 16.68 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3392, 3108, 3051, 2952, 1681, 1602, 1503, 1402, 1317, 1303, 909, 764, 750, 692. HRMS (ESI, *m*/*z*) calcd for $C_{23}H_{21}N_3NaOS$ $[M+Na]^+$: 410.1298, found: 410.1294.

(*S*)-2-methyl-3-(phenylamino)-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3qa): colorless oil (62.2 mg, yield: 97%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 92% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 7.71 min, t_r(minor) = 8.94 min). $[\alpha]_D^{25}$ = +118.9° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.24 (m, 4.5H), 7.13 (t, *J* = 7.7 Hz, 2H), 7.09 (d, *J* = 4.3 Hz, 1H), 7.02 (d, *J* = 7.8 Hz, 0.5H), 6.66 (t, *J* = 7.3 Hz, 1H), 6.56 (d, *J* = 6.6 Hz, 2H), 4.27-4.19 (m, 1H), 4.05 (s, 1H), 3.45-3.43 (m, 1H), 3.28-3.24 (m, 1H), 1.97 (s, 1.5H), 1.87 (s, 1.4H), 1.25 (t, *J* = 6.6 Hz, 3H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.86, 193.79, 148.06, 143.25, 143.20, 137.97, 137.92, 134.61, 134.27, 130.81, 130.71, 130.02, 129.99, 129.21, 129.15, 129.11, 126.70, 126.66, 126.62, 126.40, 126.17, 117.22, 117.18, 112.73, 47.28, 46.97, 41.56, 41.34, 17.17, 17.08, 15.22, 15.05 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3392, 3050, 2967, 2933, 1680, 1603, 1504, 1460, 1405, 1302, 953, 912, 763, 748, 692. HRMS (ESI, *m*/*z*) calcd for $C_{20}H_{22}N_3O$ $[M+H]^+$: 320.1757, found: 320.1760.

(*S*)-2-((phenylamino)methyl)-1-(1-(o-tolyl)-1H-imidazol-2-yl)butan-1-one (3ra): colorless oil (65.8 mg, yield: 99%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 95% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 6.36 min, t_r(minor) = 7.48 min). $[\alpha]_D^{25}$ = +85.5° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.23 (m, 4H), 7.15-7.08 (m, 3.5H), 7.02 (d, *J* = 7.4 Hz, 0.5H), 6.66 (t, *J* = 7.3 Hz, 1H), 6.54 (d, *J* = 8.5 Hz, 2H), 4.16-4.08 (m, 1H), 4.02 (s, 1H), 3.45-3.40 (m, 1H), 3.30 (dd, *J* = 4.7 Hz, 12.1 Hz, 1H), 1.97 (s, 1.5H), 1.91-1.79 (m, 2.5H), 1.69-1.62 (m, 1H), 0.96-0.91 (m, 3H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.82, 193.66, 148.17, 143.91, 143.80, 137.96, 134.68, 134.22, 130.79, 130.67, 129.99, 129.18, 129.17, 129.13, 129.11, 126.74, 126.67, 126.60, 126.47, 126.17, 117.18, 117.14, 112.70, 48.36, 48.16, 45.72, 45.55, 23.08, 23.04, 17.15, 17.06, 11.97, 11.91 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3392, 3109, 3052, 3025, 2964, 2930, 2875, 1680, 1603, 1503, 1460, 1320, 1302, 1265, 1149, 948, 763, 748, 692. HRMS (ESI, *m*/*z*) calcd for $C_{21}H_{24}N_3O$ $[M+H]^+$: 334.1914, found: 334.1911.

(*S*)-2-((phenylamino)methyl)-1-(1-(o-tolyl)-1H-imidazol-2-yl)pent-4-en-1-one (3sa): colorless oil (56.0 mg, yield: 81%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 87% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 7.04 min, t_r(minor) = 8.09 min). $[\alpha]_D^{25}$ = +85.0° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.23 (m, 4H), 7.14-7.08 (m, 3.5H), 7.02 (d, *J* = 7.7 Hz, 0.5H), 6.66 (t, *J* = 7.3 Hz, 1H), 6.54 (dd, *J* = 1.5 Hz, 8.4 Hz, 2H), 5.86-5.74 (m, 1H), 5.08-5.03 (m, 1H), 5.00 (d, *J* = 10.2 Hz, 1H), 4.33-4.25 (m, 1H), 4.04 (s, 1H), 3.46-3.41 (m, 1H), 3.34-3.31 (m, 1H), 2.62-2.52 (m, 1H), 2.39-2.32 (m, 1H), 1.94 (s, 1.5H), 1.87 (s, 1.4H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.95, 192.77, 148.04, 143.61, 143.53, 137.88, 135.34, 135.25, 134.62, 134.31, 130.78, 130.68, 130.07, 130.05, 129.18, 129.14, 126.82, 126.65, 126.59, 126.43, 126.26, 117.25, 117.21, 117.13, 112.74, 46.27, 46.12, 45.49, 45.44, 34.17, 34.14, 17.20, 17.09 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3410, 3108, 3053, 3025, 2979, 1679, 1603, 1506, 1405, 1302, 1260, 1149, 910, 763, 749. HRMS (ESI, *m*/*z*) calcd for $C_{22}H_{24}N_3O$ $[M+H]^+$: 346.1914, found: 346.1913.

(*S*)-2-benzyl-3-(phenylamino)-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3ta): colorless oil (74.6 mg, yield: 94%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 94% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 7.69 min, t_r(minor) = 8.30 min). $[\alpha]_D^{25}$ = +42.1° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.14 (m, 9H), 7.10 (t, *J* = 7.8 Hz, 2H), 7.05 (dd, *J* = 0.8 Hz, 7.2 Hz, 1H), 6.98 (dd, *J* = 7.0 Hz, 15.0 Hz, 1H), 6.66-6.63 (m, 1H), 6.47 (d, *J* = 7.7 Hz, 2H), 4.57-4.46 (m, 1H), 4.11 (s, 1H), 3.45-3.41 (m, 1H), 3.31-3.28 (m, 1H), 3.18-3.12 (m, 1H), 2.84 (dd, *J* = 7.6 Hz, 13.8 Hz, 1H), 1.86 (s, 1.4H), 1.73 (s, 1.5H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.95, 192.66, 148.06, 148.02, 143.66, 143.59, 139.19, 139.10, 137.83, 137.81, 134.62, 134.38, 130.76, 130.65, 130.10, 130.08, 129.22, 129.18, 129.16, 128.42, 126.78, 126.76, 126.61, 126.56, 126.40, 126.35, 126.32, 117.23, 117.20, 112.74, 48.42, 48.34, 45.58, 45.46, 35.75, 35.64, 17.10, 16.86 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3308, 3056, 3025, 2922, 2856, 1679, 1602, 1503, 1454, 1405, 1302, 940, 910, 763, 747, 693. HRMS (ESI, *m*/*z*) calcd for $C_{26}H_{26}N_3O$ $[M+H]^+$: 396.2070, found: 396.2067.

(*S*)-2-phenyl-1-(1-(o-tolyl)-1H-imidazol-2-yl)-3-(p-tolylamino)propan-1-one (3cb): light yellow oil (73.8 mg, yield: 93%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 94% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 11.11 min, t_r(minor) = 15.37 min). $[\alpha]_D^{25}$ = -43.3° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40-7.22 (m, 9H), 7.16 (d, *J* = 7.5 Hz, 0.5H), 7.02 (d, *J* = 1.7 Hz, 1H), 6.96-6.92 (m, 2.5H), 6.51 (d, *J* = 7.8 Hz, 2H), 5.45 (t, *J* = 6.9 Hz, 1H), 3.88-3.81 (m, 1H), 3.68 (br, 1H), 3.46-3.40 (m, 1H), 2.22 (s, 3H), 1.99 (s, 1.4H), 1.63 (s, 1.6H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.92, 189.87, 145.42, 143.26, 137.86, 137.07, 137.03, 134.60, 134.42, 130.79, 130.74, 130.25, 130.21, 129.79, 129.18, 129.14, 128.86, 128.83, 128.78, 127.45, 126.69, 126.65, 126.63, 126.45, 126.19, 113.22, 52.78, 52.75,

46.99, 46.52, 20.44, 17.32, 16.75 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3397, 3059, 3028, 2919, 2863, 1681, 1614, 1521, 1492, 1453, 1402, 1317, 1303, 1256, 944, 910, 808, 762, 699. HRMS (ESI, *m*/*z*) calcd for $C_{26}H_{25}N_3NaO$ $[M+Na]^+$: 418.1890, found: 418.1896.

(*S*)-3-((4-(tert-butyl)phenyl)amino)-2-phenyl-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3cc): light yellow oil (81.7 mg, yield: 93%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 92% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 10.21 min, t_r(minor) = 13.82 min). $[\alpha]_D^{25}$ = -43.9° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41-7.21 (m, 9H), 7.18-7.15 (m, 2.5H), 7.02 (dd, *J* = 0.8 Hz, 3.0 Hz, 1H), 6.93 (d, *J* = 7.2 Hz, 0.5H), 6.54 (dd, *J* = 1.3 Hz, 8.5 Hz, 2H), 5.44 (t, *J* = 7.2 Hz, 1H), 3.89-3.82 (m, 1H), 3.73 (br, 1H), 3.47-3.41 (m, 1H), 1.99 (s, 1.4H), 1.64 (s, 1.6H), 1.26 (s, 9H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.87, 189.84, 145.35, 145.33, 143.25, 140.23, 140.17, 137.87, 137.84, 137.08, 137.05, 134.61, 134.42, 130.79, 130.74, 130.23, 130.19, 129.18, 129.14, 128.87, 128.83, 128.77, 127.45, 126.69, 126.66, 126.63, 126.45, 126.19, 126.07, 112.70, 112.67, 52.93, 52.89, 46.78, 46.32, 33.87, 31.60, 17.35, 16.76 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3308, 3056, 3028, 2960, 2902, 2866, 1681, 1614, 1519, 1492, 1454, 1403, 1303, 1261, 909, 821, 762, 699. HRMS (ESI, *m*/*z*) calcd for $C_{29}H_{31}N_3NaO$ $[M+Na]^+$: 460.2359, found: 460.2356.

(*S*)-3-((4-methoxyphenyl)amino)-2-phenyl-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3cd): light yellow oil (72.9 mg, yield: 89%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 86% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 21.77 min, t_r(minor) = 30.75 min). $[\alpha]_D^{25}$ = -31.3° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38-7.26 (m, 9H), 7.17 (d, *J* = 7.6 Hz, 0.5H), 7.02 (s, 1H), 6.93 (d, *J* = 7.5 Hz, 0.5H), 6.75 (d, *J* = 8.3 Hz, 2H), 6.55 (d, *J* = 8.3 Hz, 2H), 5.45-5.43 (m, 1H), 3.86-3.79 (m, 1H), 3.74 (s, 3H), 3.54 (br, 1H), 3.43-3.40 (m, 1H), 1.99 (s, 1.4H), 1.63 (s, 1.6H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.92, 189.87, 152.20, 143.26, 141.90, 137.85, 137.82, 137.05, 136.99, 134.59, 134.41, 130.78, 130.74, 130.23, 130.19, 129.18, 129.14, 128.85, 128.82, 128.78, 127.45, 126.72, 126.64, 126.62, 126.43, 126.18, 114.92, 114.46, 55.82, 52.81, 52.76, 47.67, 47.21, 17.31, 16.74 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3362, 3056, 3028, 2929, 2831, 1681, 1513, 1453, 1401, 1236, 1035, 909, 819, 762, 699. HRMS (ESI, *m*/*z*) calcd for $C_{26}H_{25}N_3NaO_2$ $[M+Na]^+$: 434.1839, found: 434.1834.

(*S*)-3-((2-methoxyphenyl)amino)-2-phenyl-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3ce): colorless oil (81.0 mg, yield: 98%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 93% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 11.81 min, t_r(minor) = 16.87 min). $[\alpha]_D^{25}$ = -67.3° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41-7.21 (m, 9H), 7.16 (d, *J* = 7.6 Hz, 0.5H), 7.01 (s, 1H), 6.95 (d, *J* = 7.8 Hz, 0.5H), 6.89-6.84 (m, 1H), 6.72-6.70 (m, 2H), 6.66-6.61 (m, 1H), 5.52-5.46 (m, 1H), 4.41 (s, 1H), 3.97-3.89 (m, 1H), 3.72 (d, *J* = 1.8 Hz, 3H), 3.48-3.43 (m, 1H), 1.97 (s, 1.4H), 1.64 (s, 1.6H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.87, 189.80, 146.89, 146.86, 143.33, 137.90, 137.77, 137.71, 137.18, 137.14, 134.68, 134.42, 130.77, 130.73, 130.21, 129.16, 129.11, 128.82, 128.79, 128.74, 128.73, 127.39, 126.63, 126.61, 126.49, 126.19, 121.42, 116.54, 116.48, 110.07, 109.96, 109.63, 109.58, 55.40, 55.36, 52.86, 52.78, 46.34, 45.98, 17.16, 16.78 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3064, 2952, 1681, 1601, 1514, 1454, 1403, 1249, 1221, 1028, 909, 762, 739, 699. HRMS (ESI, *m*/*z*) calcd for $C_{26}H_{25}N_3NaO_2$ $[M+Na]^+$: 434.1839, found: 434.1833.

(*S*)-3-((4-fluorophenyl)amino)-2-phenyl-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3cf): colorless oil (78.3 mg, yield: 98%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 95% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 7.99 min, t_r(minor) = 10.57 min). $[\alpha]_D^{25}$ = -65.6° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40-7.16 (m, 9.5H), 7.03 (dd, *J* = 0.8 Hz, 2.2 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 0.5H), 6.85 (t, *J* = 8.5 Hz, 2H), 6.53-6.49 (m, 2H), 5.46-5.42 (m, 1H), 3.87-3.80 (m, 1H), 3.71 (s, 1H), 3.44-3.39 (m, 1H), 1.99 (s, 1.3H), 1.62 (s, 1.7H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.77, 189.72, 157.04, 154.71, 144.04, 144.03, 143.22, 137.81, 137.77, 136.88, 136.83, 134.55, 134.41, 130.79, 130.77, 130.29, 130.25, 129.23, 129.18, 128.91, 128.88, 128.76, 127.55, 126.82, 126.66, 126.41, 126.19, 115.80, 115.58, 113.92, 113.85, 52.70, 52.68, 47.26, 46.80, 17.29, 16.72 (Contained the rotamer). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -127.98 and -128.03. IR (KBr): *v* (cm^{-1}) 3392, 3056, 3031, 2927, 1681, 1510, 1453, 1402, 1303, 1221, 909, 821, 762, 699. HRMS (ESI, *m*/*z*) calcd for $C_{25}H_{22}FN_3NaO$ $[M+Na]^+$: 422.1639, found: 422.1640.

(*S*)-3-((4-chlorophenyl)amino)-2-phenyl-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3cg): colorless oil (80.0 mg, yield: 96%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 97% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 7.33 min, t_r(minor) = 8.89 min). $[\alpha]_D^{25}$ = -47.2° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.19 (m, 9H), 7.16 (d, *J* = 7.7 Hz, 0.5H), 7.08 (d, *J* = 8.2 Hz, 2H), 7.03 (d, *J* = 1.4 Hz,1H), 6.93 (d, *J* = 8.0 Hz, 0.5H), 6.50 (dd, *J* = 1.6 Hz, 8.6 Hz, 2H), 5.44 (t, *J* = 7.9 Hz, 1H), 3.85 (s, 2H), 3.43 (s, 1H), 1.98 (s, 1.3H), 1.62 (s, 1.6H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.65, 189.62, 146.24, 143.18, 137.77, 137.74, 136.76, 136.71, 134.53, 134.40, 130.79, 130.77, 130.33, 130.28, 129.24, 129.19, 129.10, 128.92, 128.90, 128.73, 127.58, 126.84, 126.66, 126.40, 126.18, 122.01, 121.96, 114.04, 52.59, 46.60, 46.14, 17.28, 16.72 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3309, 3057, 3029, 2955, 2925, 2854, 1681, 1599, 1501, 1454, 1403, 1315, 1258, 1088, 944, 909, 816, 762, 740, 699. HRMS (ESI, *m*/*z*) calcd for $C_{25}H_{22}ClN_3NaO$ $[M+Na]^+$: 438.1344, found: 438.1338.

(*S*)-3-((4-bromophenyl)amino)-2-phenyl-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3ch): colorless oil (87.5 mg, yield: 95%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 95% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 7.49 min, t_r(minor) = 8.96 min). $[\alpha]_D^{25}$ = -30.1° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.20 (m, 11H), 7.15 (d, *J* = 7.6 Hz, 0.5H), 7.03 (d, *J* = 1.4 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 0.5H), 6.45 (dd, *J* = 1.8 Hz, 8.6 Hz, 2H), 5.44 (t, *J* = 7.4 Hz, 1H), 3.87-3.80 (m, 2H), 3.43-3.40 (m, 1H), 1.98 (s, 1.3H), 1.62 (s, 1.7H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.62, 189.59, 146.65, 143.16, 137.76, 137.73, 136.73, 136.68, 134.52, 134.39, 131.96, 130.80, 130.77, 130.33, 130.29, 129.24, 129.19, 128.93, 128.90, 128.72, 127.59, 126.85, 126.67, 126.39, 126.18, 114.53, 109.05, 108.99, 52.54, 46.47, 46.02, 17.28, 16.72 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3308, 3029, 2955, 2924, 2854, 1681, 1594, 1493, 1454, 1402, 1313, 1258, 909, 813, 762, 699. HRMS (ESI, *m*/*z*) calcd for $C_{25}H_{22}BrN_3NaO$ $[M+Na]^+$: 482.0838, found: 482.0841.

(*S*)-3-((2-bromophenyl)amino)-2-phenyl-1-(1-(o-tolyl)-1H-imidazol-2-yl)propan-1-one (3ci): colorless oil (90.5 mg, yield: 98%). Enantiomeric excess was determined by HPLC analysis using a Chiralpak IC column, ee = 99.4% (HPLC: Chiralpak column IC, λ = 254 nm, *n*-hexane/*i*-PrOH = 98:2, flow rate: 1.0 mL/min, 40 °C, t_r(major) = 5.85 min, t_r(minor) = 6.43 min). $[\alpha]_D^{25}$ = -54.8° (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41-7.23 (m, 10H), 7.18-7.16 (m, 1.5H), 7.04 (s, 1H), 6.97(d, *J* = 7.7 Hz, 0.5H), 6.74-6.71 (m, 1H), 6.54 (t, *J* = 7.5 Hz, 1H), 5.52-5.46 (m, 1H), 4.52-4.45 (m, 1H), 3.97-3.90 (m, 1H), 3.53-3.43 (m, 1H), 1.98 (s, 1.5H),

1.68 (s, 1.4H) (Contained the rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.50, 144.49, 144.44, 143.21, 137.82, 136.73, 134.78, 134.38, 132.46, 130.79, 130.73, 130.36, 129.22, 129.18, 128.94, 128.92, 128.67, 128.60, 127.60, 126.85, 126.70, 126.60, 126.52, 126.14, 117.89, 117.87, 111.46, 111.31, 109.88, 109.78, 52.38, 46.42, 46.13, 17.37, 16.84 (Contained the rotamer). IR (KBr): *v* (cm^{-1}) 3402, 3060, 3029, 2926, 2858, 1681, 1597, 1502, 1454, 1403, 1317, 1019, 909, 762, 740, 699. HRMS (ESI, *m/z*) calcd for $C_{25}H_{22}BrN_3NaO$ $[M+Na]^+$: 482.0838, found: 482.0839.

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[13] CCDC 1547735 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] Three-component Mannich reaction of 2-acyl imidazole, aldehyde and primary amine catalyzed by **Λ-Rh2** in CH_2Cl_2 were examined, affording desired product **3ca** in 82% yield with 69% ee. Further control experiment showed that in the absence of catalyst, the three-component Mannich reaction could afford *rac*-**3ca** in 33% yield in 12 hours (for details, see the Supporting Information).

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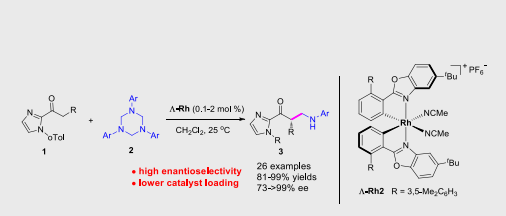

Highly efficient enantioselective Mannich reaction of 2-acyl imidazoles with 1,3,5-triazinanes catalysed by Chiral-at-metal Rh(III) complexes is developed, affording the corresponding adducts in good yields with excellent enantioselectivities.

Key Topic*

*Jun Gong, Shi-Wu Li, Saira Qurban, and Qiang Kang**

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*Chiral-at-metal rhodium complex for highly efficient enantioselective Mannich reaction.