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Highly enantioselective Friedel–Crafts alkylation of indoles with α,β-unsaturated ketones with simple Cu(II)–oxazoline–imidazoline catalysts

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ABSTRACT

A series of novel chiral ligands **L1**–**L4** with an imidazoline–oxazoline framework have been developed as new type of non-symmetric *N*,*N*-bidentate ligands. All the chiral ligands were prepared from 2,2-diethylmalonic acid and enantiomerically pure (*S*)-2-amino-3-methyl-1-butanol in four steps with excellent optical purity. These newly developed ligands efficiently affect the copper-catalyzed enantioselective addition of indole to α,β-unsaturated ketones, yielding the corresponding adducts in good yield and high enantiomeric excess. The fine-tuning capability of these ligands plays a significant role in achieving high enantioselectivity in the asymmetric alkylation (up to 99% ee). The higher enantioselectivity of the reaction could be due to the activation and asymmetric induction of chiral Lewis acid metal complex coordinated by enones through a concerted mechanism of 1,4-metal bonding model.

1. Introduction

Asymmetric catalysis catalyzed by Lewis acid metal complexes of chiral ligands, has attracted synthetic chemists, owing to its efficacy in producing enantiopure compounds.[1] The development of various chiral ligands has become a vast expanding research area in this field. Recently the preparation and application of C_2-symmetric bisoxazoline ligands that have two oxazoline rings separated by a single carbon atom with two identical substituents, have been reported by several authors.[2] Moreover the box type chiral bisoxazolines provide an advantageous combination of structural diversity and outstanding enantioselectivity for a wide variety of reactions. These types of ligands have shown excellent potential for the construction of new stereogenic C–C bonds through Lewis acid catalyzed Friedel–Crafts alkylation reaction.[3] Throughout the literature, enantioselective Friedel–Crafts alkylation reaction of indole with α,β-unsaturated-R-ketoesters (R=alkyl, aryl),[4] R-hydroxy enones (R=alkyl, aryl),[5] nitroalkenes,[6] alkylidene malonates,[7] acyl phosphonates,[8] and acyl heterocyclic compounds[9,10] remains of interest. Although, a large variety of chiral bisoxazolines have been reported from malonate,[11] tartrate,[5] ferrocene[12] or cyclohexane,[6b,13] biphenyl or binaphthyl,[14] pyridine,[15] cyclopropane framework,[16] and other derivatives. However, very little research work has been reported in the recent literature for the synthesis and application of non-symmetric imidazoline–oxazoline box ligands. This new class of imidazoline–oxazoline chiral ligands could be useful for the asymmetric allylic substitutions,[17] enantioselective addition of diethylzinc to acyclic enones,[18] asymmetric cyclopropanation,[19] Diels–Alder reactions,[20] asymmetric Henry reactions.[21] To the best of our knowledge, only one example has been reported in the recent literature for the synthesis and application of non-symmetric imidazoline–oxazoline ligand.[22] Therefore, designing, syntheses, and the evaluation of non-symmetric box type novel imidazoline–oxazoline ligands remains a tremendous challenge.[23] Moreover the Lewis acid-catalyzed enantioselective Friedel–Crafts reaction of prochiral α,β-unsaturated enones building blocks is one of the most important and straightforward strategies to access structurally elaborated and optically pure molecules. Herein, as part of our ongoing interest toward the development of enantioselective catalysis, we report a series of diethylmalonate-derived oxazoline–imidazoline ligands **L1**–**L4** with isopropyl stereogenic center on both imidazoline and

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oxazoline ring and their Cu(II) complexes in the highly enantioselective Friedel–Crafts alkylation of indole with enones.

2. Result and discussion

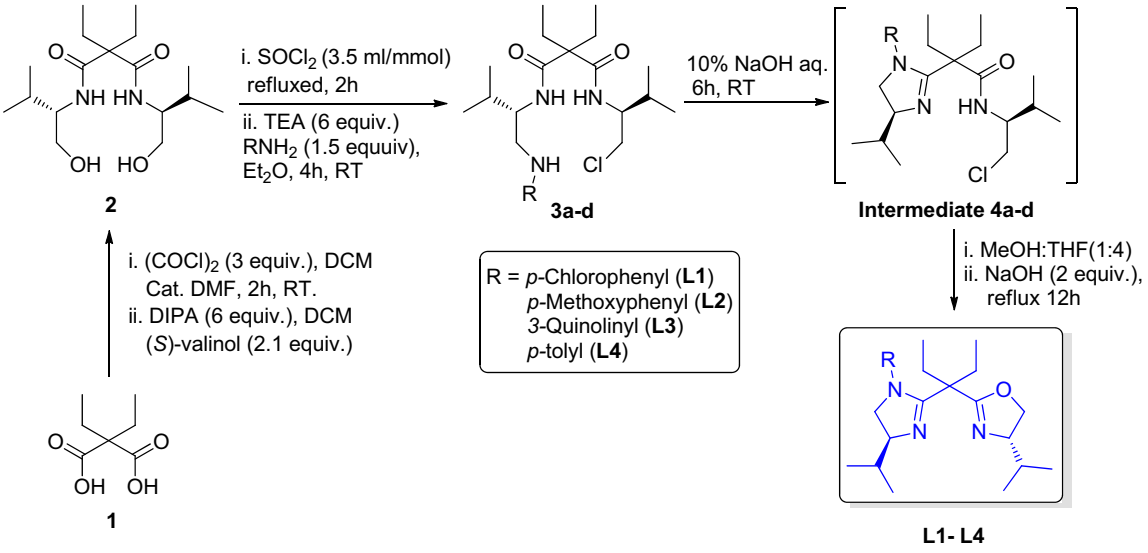
2.1. Synthesis of chiral imidazoline–oxazoline ligands

A set of four non-symmetric oxazoline–imidazoline type ligands **L1**–**L4** with sp^2 hybridized two coordinating N atoms were synthesized from commercially available and cheap material 2,2-diethylmalonic acid **1** and (*S*)-valinol by following the procedure reported by Xin-Qi Hao et al. as illustrated in Scheme 1.[22] The chemistry for synthesizing bisoxazoline compounds starting from dicarboxylic acid is well known, but to synthesize one imidazoline ring and another oxazoline ring selectively was a challenging task. At the outset, 2,2-diethylmalonic acid **1** was converted into dicarbonyl chloride, via oxalyl chloride in the presence of catalytic amount of dimethylformamide (DMF), followed by subsequent reaction with (*S*)-valinol in the presence of excess diisopropylamine (DIPA) produced 2,2-diethyl-N^1,N^3-bis((*S*)-1-hydroxy-3-methylbutan-2-yl)malonamide **2** with overall 92% yield. The compound bis-amidoalcohol **2** (2 mmol) was then refluxed with thionylchloride to obtain bis-amidochloride, which was then treated with different aromatic amines (3 mmol) (*p*-chloroaniline, *p*-methoxyaniline, 3-quinolin, and *p*-toluidine) in presence of triethylamine leading to the formation of corresponding products **3a**–**d**. Then the intermediates **3a**–**d** resulted in imidazoline ring closure by using 10% aqueous solution of sodium hydroxide to afford crude product **4a**–**d**, mainly containing imidazoline–amidochloride with some expected imidazoline–oxazoline product (intermediates **4a**–**d**, Scheme 1).

2.2. Catalytic asymmetric Friedel–Crafts alkylation of indole with a variety of enones

Initial findings of Friedel–Crafts alkylation reaction between (*E*)-chalcone **6a** and indole **5** as the model substrates in the presence of chiral oxazoline–imidazoline ligand **L1**. L/Cu $(OTf)_2$ ratio (10:11 mol %) were used, aiming at screening the optimal conditions, and the results of these experiments are summarized in Table 1. By screening different solvents, such as toluene, benzene, tetrahydrofuran (THF), ethanol, dichloromethane (CH_2Cl_2), acetonitrile, and mixture of THF/^{i}PrOH (1:1), we found that CH_3CN was the best solvent for this asymmetric Friedel–Crafts alkylation, affording the corresponding product **7a** with 49–58% chemical yield and in 93%, 89%, and 92% ee at room temperature within 24 h, 36 h, and 40 h, respectively (Table 1, entries 7, 10, 11). Upon lowering the reaction temperature to 0 °C, a remarkable lowering of yield (13%) could be observed after 24 h, with only 3% increment in enantioselectivity (96%) (Table 1, entry 8). On the other hand, upon raising the reaction temperature to 45 °C, the chemical yield increased dramatically to 87% and only 7% enantioexcess were obtained. But in case of other solvents like toluene, benzene, dichloromethane only trace amount of product formation was observed (Table 1, entries 1, 2, 6), while using polar solvent, such as THF, ethanol, and ^{i}PrOH, 11–21% yield and 29–43% ee were obtained (Table 1, entries 2–5).

To elucidate the catalytic activity of imidazoline–oxazoline ligands at different L/Cu$(OTf)_2$ mole ratio, ligands **L1**–**L4** were screened for the asymmetric Friedel–Crafts alkylation of indole **5** with (*E*)-chalcone **6a**, affording the corresponding adduct **7a** and the results are depicted in Table 1. All the ligands **L1**–**L4** showed outstanding catalytic activity in producing chiral compounds **7a**

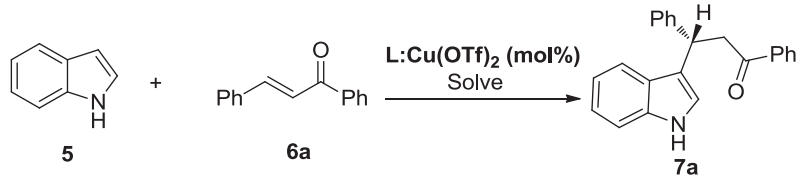


Scheme 1. Synthesis of chiral oxazoline–imidazoline ligands **L1**–**L4**.

The isolation of these intermediates **4a**–**d** was very difficult by column chromatography because of their high polarity. To circumvent this obstacle, crude intermediates were taken into next step without further purification for the oxazoline ring closer reaction. Thus, the ligands **L1**–**L4** were obtained by refluxing the crude intermediates **4a**–**d** with NaOH (4 mmol) in THF/MeOH mixture (4:1) for 12 h. The overall isolated yield of the ligands in four steps was obtained in the range of 45–59%. The bis-amidoalcohol and the ligands **L1**–**L4** were fully characterized by ^{1}H NMR, ^{13}C NMR, and mass spectroscopy techniques.

with high enantioexcess 95–99.9% ee and moderate to good chemical yields 67–86%, by simply using 5–10 mol % ligands and 10–30 mol % Cu$(OTf)_2$. Although ligand **L1** and **L2** gave the best result for enantioselectivity (Table 1, entries 12–16) as compared to **L3** and **L4** (Table 1, entries 17 and 18). Best result was achieved with 86% yield and 99.9% ee by using 10:20 mol % of **L2**/Cu$(OTf)_2$ (Table 1, entry 15). No significant changes were observed in enantioselectivity by increasing the percentage of ligands from 5 to 10% and Cu$(OTf)_2$ from 15 to 30 mol %, but the chemical yields increased from 39% to 86% (Table 1, entries 12–15).

Table 1
Screening of conditions for the Friedel–Crafts alkylation reaction of model substrate **6l**



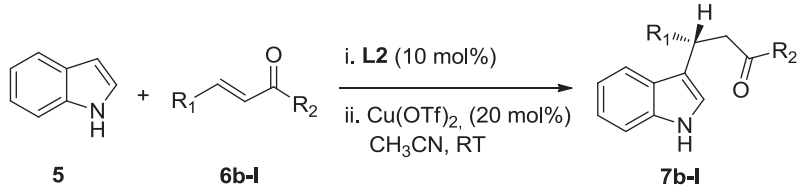
#	L:Cu(OTf)$_2$ (mol %)	Ligands (L)	T [°C]	Solvent	t [h]	Yield[a] [%]	ee [%][b]
1	10:11	**L1**	rt	Toluene	36	—	—
2	10:11	**L1**	rt	Benzene	36	—	—
3	10:11	**L1**	rt	THF	30	11	29
4	10:11	**L1**	rt	Ethanol	30	23	43
5	10:11	**L1**	rt	THF/^{i}PrOH	40	21	37
6	10:11	**L1**	rt	CH_2Cl_2	40	—	—
7	10:11	**L1**	rt	CH_3CN	24	49	93
8	10:11	**L1**	0	CH_3CN	24	13	96
9	10:11	**L1**	45	CH_3CN	24	87	7
10	10:11	**L1**	rt	CH_3CN	36	58	89
11	10:11	**L1**	rt	CH_3CN	40	55	92
12	5:10	**L2**	rt	CH_3CN	36	39	99.8
13	10:15	**L1**	rt	CH_3CN	24	67	99.9
14	10:15	**L2**	rt	CH_3CN	24	73	99.9
15	**10:20**	**L2**	**rt**	CH_3CN	**24**	**86**	**99.9**
16	10:30	**L2**	rt	CH_3CN	24	83	98.6
17	10:20	**L3**	rt	CH_3CN	32	81	96.7
18	10:20	**L4**	rt	CH_3CN	32	84	94.9

Bold represents highest enantiomeric excess (ee 99.92) achieved in this set of condition for reaction optimization process.
[a] The reactions were performed on a 0.425 mmol scale and the isolated yield after column purification.
[b] Determined by chiral HPLC analysis.

To illustrate the generality of this asymmetric Friedel–Crafts alkylation of indole **5**, with various substrates (**6b**–**l**), eleven examples were carried out with ligand **L2** 10 mol % and 20 mol % of Cu(OTf)$_2$ in CH_3CN at room temperature and the results are shown in Table 2.

strong $+I$ effect on the benzene ring, gave the corresponding products **7d**, **7e**, and **7f** in very low yields 40%, 22%, and 27%, respectively, which could be attributed to the poor solubility of the substrate but high selectivity was observed 93–97% ee values, suggesting that the electron donating group on the benzene ring,

Table 2
Highly enantioselective Friedel–Crafts reactions of indole with α,β-unsaturated enones (**6a**–**k**) catalyzed by ligand **L2** (10 mol %)–Cu(OTf)$_2$ (20 mol %) in acetonitrile at room temperature



#	**6**	R^1	R^2	Time (h)	Yield[d] (%)	ee (%)[e]
1	**6a**	*p*-ClPh	Ph	24	84	93.8(*S*)
2	**6b**	*p*-ClPh	Napthyl	24	81	95.6(*S*)
3[a]	**6c**	2,4,6-$(CH_3)_3$Ph	Ph	36	40	96.0(*S*)
4[b]	**6d**	2,4,6-$(CH_3)_3$Ph	Napthyl	36	22	97.8(*S*)
5	**6e**	Tolyl	Ph	24	73	95.7(*S*)
6	**6f**	Tolyl	Napthyl	30	27	93.4(*S*)
7	**6g**	*p*-MeOPh	Ph	24	89	96.4(*S*)
8	**6h**	*p*-MeOPh	Napthyl	24	66	90.8(*S*)
9	**6i**	Ph	Napthyl	24	47	95.5(*S*)
10	**6j**	Thiophene	Ph	24	65	89.7(*R*)
11[c]	**6k**	Ferrocene	Ph	48	8	87.7(*R*)

[a] 15 mol % of **L2** and 30 mol % of Cu(OTf)$_2$ has been used in this run.
[b] 20 mol % of **L2** and 30 mol % of Cu(OTf)$_2$ has been used in this run.
[c] Temperature raised up to 40 °C and 20 mol % of **L2** and 30 mol % of Cu(OTf)$_2$ has been used in this run.
[d] Isolated yield after column purification.
[e] Determined by chiral HPLC analysis and the configuration was assigned by comparison of the optical rotation sign of all compounds with literature data.[23]

As can be seen, by using substrate **6b**, **6c**, **6f**, **6h**, **6i**, and **6k**, the corresponding Friedel–Crafts alkylation products **7b**, **7c**, **7f**, **7h**, **7i**, and **7k** were obtained in moderate to good chemical yields 65–89% and excellent enantioselectivity 89–97% ee (Table 2, entries 1, 2, 5, 7, 8, and 10). At the same time, using substrate **6d**, **6e**, and **6f** with

does not have a significant impact on the enantioselectivity (Table 2, entries 3, 4, and 6). However the L/Cu(OTf)$_2$ ratio (15:30 mol % and 20:30 mol %) has been applied in case of **6d**, **6e** accordingly, in order to increase the yield, unfortunately no improvement in chemical yield were observed. Moreover, the lowest yield was

noticed in case of substrate **6l** affording only 8% of product **7l** with 87% ee value under the most harsh conditions, again the reason for this low yield could be attributed to the poor solubility of compound **6l** (Table 2, entry 11).

The absolute configuration of the stereogenic center (*S*) in compound **7a** was determined by comparison of its optical rotation with those reported in the literature.[23] The configurations of the rest of the products (**7b**–**j**) and (**7k**–**l**) were assigned as (*S*) and (*R*), respectively, on the assumption of a uniform mechanistic pathway[23] (Fig. 1).

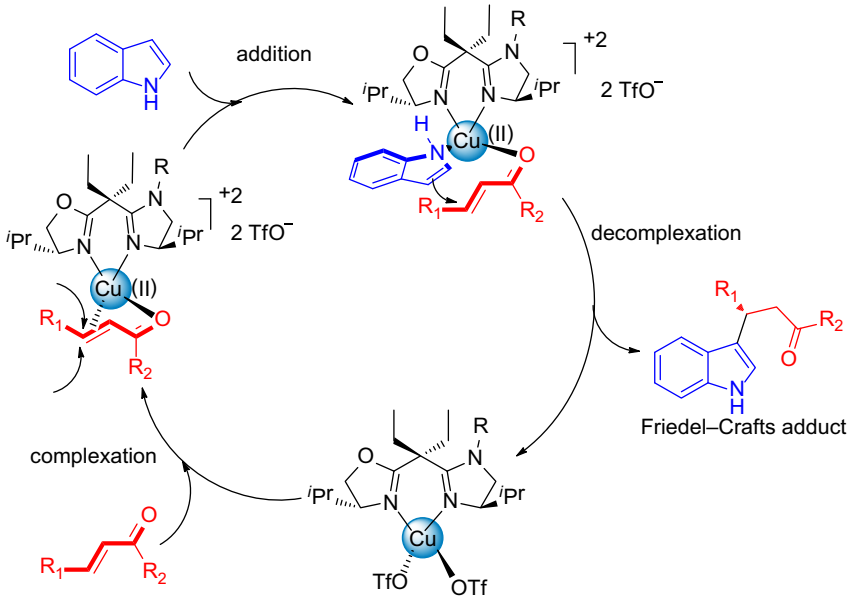


Fig. 1. Activation mechanism and stereo chemical model.

3. Conclusion

In summary, we have developed a Cu(II) oxazoline–imidazoline catalyst, which enables the enantioselective Friedel–Crafts alkylation of indole with enones. The non C_2-symmetric oxazoline–imidazoline ligands **L1**–**L4** were prepared from enantiopure (*S*)-valinol with overall satisfactory yield and excellent optical purity. These ligands were proven to be highly potent in inducing chirality in the Friedel–Crafts alkylation reactions. With 10:20 mol % of the Cu(II) oxazoline–imidazoline catalyst in acetonitrile at ambient temperature, up to 99% ee could be achieved for a variety of substrates. The application of this new catalyst to other reactions, such as asymmetric allylic substitutions and Henry reactions, involving olefin and alkyne π-bond activation is currently being investigated.

4. Experimental

4.1. General remarks

Glassware was oven-dried overnight at 120 °C before use. Reactions were performed under an inert atmosphere using an argon filled glove box and standard Schlenk-line techniques. All the reactions were monitored by TLC analysis using Merck Silica Gel 60 F_{254} thin layer plates. Column chromatography was performed on silica gel 100–200 mesh.

4.1.1. Materials. Petroleum ether (PE), hexane, and ethyl acetate for column chromatography were distilled prior to use. CH_2Cl_2, EtOH were distilled from P_2O_5 and Mg, respectively, and stored on 4 Å molecular sieves. Diethyl ether, tetrahydrofuran, benzene, toluene were distilled from sodium benzophenone ketyl. Acetonitrile and dimethylformamide were dried by distillation over calcium hydride. Triethylamine and diisopropylamine were dried over sodium hydroxide. (*S*)-(+)-2-Amino-3-methyl-1-butanol, aromatic amines, oxalyl chloride, and indole were commercially obtained and used as purchased without further purification. Enones **6a**–**l** were prepared according to procedures reported in the literature.[24]

4.1.2. Instrumentation. NMR spectra were recorded with a Jeol spectrometer at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR). The chemical shifts (δ in parts per million) were reported down field from tetramethylsilane (TMS, δ scale) with the deuterated solvent resonance referenced as internal standard. Specific optical rotations were measured on a highly sensitive automatic 'A. KRÜSS OPTRONOCS' polarimeter using sodium light (D line 589 nm). Elemental analyses were performed on a Perkin Elmer 2400 Elemental Analyzer. Chiral HPLC analyses were performed in an ultra-flow liquid chromatography (UFLC) SHIMADZU instrument equipped with a PDA detector using chiral stationary Chiralcel OD-H column, hexane/isopropanol (80:20). IR spectra were obtained using Perkin Elmer FTIR-800 Model. Mass spectrometric analysis was conducted by using ESI mode on AGILENT Technologies 6410-triple quad LC/MS instrument.

4.2. Synthesis of ligands

*4.2.1. Synthesis of 2,2-diethyl-N^1,N^3-bis((S)-1-hydroxy-3-methylbutan-2-yl)malonamide (**2**).* In a 100 mL round bottom flask compound **1** (5.00 g, 31.3 mmol) was suspended in dry CH_2Cl_2 (75 mL) and a catalytic amount of DMF (three drops) was added. Then oxalyl chloride (11.9 g, 93.8 mmol) was added dropwise to the reaction mixture at room temperature. The reaction mixture was stirred at ambient temperature for 1.5 h and gave a light yellow solution of acid chloride. Then the solvent was removed under reduced pressure to afford the crude acid chloride (6.15 g, ~100%) (crude). IR (cm^{-1}): 1802 cm^{-1} (C=O str.), (absence of OH str. frequency at 3451 cm^{-1}). Then the solution of acid chloride (6.15 g, 31.3 mmol) in CH_2Cl_2 (60 mL), was added slowly to

a solution of amine (6.77 g, 65.6 mmol, 2.1 equiv) and diisopropylamine (19.0, 26.5 mL, 187 mmol, 6 equiv) at 0–5 °C. Then the reaction mixture was allowed to stir at ambient temperature for 4 h. TLC analyses (10% MeOH/CH_2Cl_2) showed complete consumption of the starting material. The reaction mixture was then quenched with a saturated aqueous solution of ammonium chloride (50 mL) and extracted with chloroform (5×100 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to afford the crude product, which was washed with diethyl ether to afford pure amide **2** (9.5 g, 92%) as a white solid; mp 76–78 °C; $[\alpha]_D^{25}$ +19.9 (*c* 0.45, $CHCl_3$); [Anal. Calcd for $C_{17}H_{34}N_2O_4$: C, 61.79; H, 10.37; N, 8.48; found C, 61.39; H, 10.63; N, 8.43]; IR (KBr): 3319 (br s, OH str.), 2963, 1637, 1071, 1545 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 0.70 (t, 6H, *J*=3.6 Hz, CH_3CH_2), 0.81–0.87 (m, 12H, $(CH_3)_2CH$), 1.74–1.87 (m, 6H, CH_3CH_2, & $(CH_3)_2CH$), 3.35–3.39 (m, 4H, $CHCH_2OH$), 3.65–3.67 (m, 2H, CH_2OH), 4.55–4.65 (m, 2H, $NHCH(CH_2OH)$), 8.26 (d, 2H, *J*=8.8 Hz, CONH); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 8.9 (CH_3CH_2), 19.0 ($(CH_3)_2CH$), 19.8 ($(CH_3)_2CH$), 27.3 ($(CH_3)_2CH$), 29.0 (CH_3CH_2), 57.3 (NHCH), 58.6 ((CO)CCH_2), 63.8 (CH_2OH), 173.9 (CONH); LC/MS (ESI): M^+, found 330.23, $C_{17}H_{34}N_2O_4$ requires 330.25.

*4.2.2. General procedure for the synthesis of chiral oxazoline–imidazoline ligands **L1**–**L4** (**GP1**).* Bis-amidoalcohol **2** (2 mmol) was treated with thionylchloride (6 mL) at reflux for 2 h. Excess thionylchloride was removed under reduced pressure and the residue was dissolved in diethyl ether (20 mL). To this solution triethylamine (1.6 mL, 12 mmol) and RNH_2 (3 mmol) were added. The reaction mixture was then stirred for 4 h at room temperature. 10% aqueous NaOH solution (8.3 mL) was then added and the reaction mixture was stirred for further 6 h. Then the aqueous layer was extracted with CH_2Cl_2 (2×20 mL) and the combined organic phases were washed with brine (25 mL) and dried over anhydrous magnesium sulfate. Then the organic part was concentrated under reduced pressure to afford the crude product mainly containing imidazoline–amidochloride with some expected oxazoline–imidazoline product (Intermediate **4a**–**d**, Scheme 1). The imidazoline–amidochloride was cyclized to oxazoline by treating with 10% NaOH (160 mg, 4 mmol) in MeOH/THF (3 mL/12 mL) at reflux for 12 h. The solvent was then removed and ligands were isolated by column chromatography using 100–200 mesh silica gel.

*4.2.3. (S)-2-(3-((S)-1-(4-Chlorophenyl)-4-isopropyl-4,5-dihydro-1H-imidazol-2-yl)pentan-3-yl)-4-isopropyl-4,5-dihydrooxazole (**L1**).* This ligand was prepared from bis-amidoalcohol **2** (660 mg, 2.0 mmol) and *p*-chloroaniline (381 mg, 3.0 mmol) according to **GP1** as described above. Light yellow colored oily product **L1** (392 mg, 48.6%, over three steps) was isolated after purification by silica gel chromatography (EtOAc/Pet. Ether/Et_3N=1:1:0.02, R_f=0.2). $[\alpha]_D^{25}$ +93.7 (*c* 0.5, $CHCl_3$); [Anal. Calcd for $C_{23}H_{34}ClN_3O$: C, 68.38; H, 8.48; N, 10.40; found C, 68.47; H, 8.67; N, 10.23]; IR (KBr): 2960, 1660, 1606, 1491, 1381, 1231, 1092, 983, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.54–1.03 (m, 18H, CH_3CH_2 & $(CH_3)_2CH$), 1.48–1.63 (m, 1H, $(CH_3)_2CH$, imidazole), 1.63–1.82 (m, 1H, $(CH_3)_2CH$, oxazole), 1.82–2.10 (m, 4H, CH_3CH_2), 3.30–3.42 (m, 1H, $NCH_{2(a)}CH$, imidazole), 3.42–3.51 (m, 1H, $NCH_{2(b)}CH$, imidazole), 3.61–3.71 (m, 1H, $OCH_{2(a)}CH$, oxazole), 3.71–3.80 (m, 1H, $OCH_{2(b)}CH$, oxazole), 3.62–3.98 (m, 1H, $OCH_2CH(CH_3)_2$, oxazole), 4.01–4.13 (m, 1H, $NCH_2CH(CH_3)_2$, imidazole), 7.08 (d, 2H, *J*=8.8 Hz, ArH), 7.26 (d, 2H, *J*=8.8 Hz, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 7.94 (CH_3CH_2), 17.97 ($(CH_3)_2CH$), 18.33 ($(CH_3)_2CH$), 19.35 (CH_3CH_2), 19.54 (CH_3CH_2), 28.01 ($(CH_3)_2CH$), 32.52 ($C(CH_2CH_3)_2$), 46.55 (NCH_2, imidazole), 58.88 ($NCH_2CH(CH_3)_2$, imidazole), 69.57 (OCH_2, oxazole), 72.40 ($OCH_2CH(CH_3)_2$, oxazole), 129.22 (ArC_2), 129.83 (ArC_3), 135.94 (ArC_4Cl), 141.88 (ArC_1N), 163.00 (NCN), 167.01 (OCN); LC/MS (ESI): M^+, 403.25, $C_{23}H_{34}ClN_3O$ requires 403.24.

*4.2.4. (S)-4-Isopropyl-2-(3-((S)-4-isopropyl-1-(4-methoxyphenyl)-4,5-dihydro-1H-imidazol-2-yl)pentan-3-yl)-4,5-dihydrooxazole (**L2**).* The ligand **L2** was prepared from bis-amidoalcohol **2** (660 mg, 2.00 mmol) and *p*-anisidine (369 mg, 3.00 mmol) according to **GP1** as described above. Light yellow colored oily product **L2** (470 mg, 58.9%, over three steps) was isolated after purification by silica gel chromatography (EtOAc/Pet. Ether/Et_3N=1:1:0.02, R_f=0.25). $[\alpha]_D^{25}$ +121.3 (*c* 0.5, $CHCl_3$); [Anal. Calcd for $C_{24}H_{37}N_3O_2$: C, 72.14; H, 9.33; N, 10.52; found C, 71.93; H, 9.11; N, 10.45]; IR (KBr): 2959, 2875, 1658, 1607, 1511, 1485, 1241, 1037, 984, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.71–0.99 (m, 18H, CH_3CH_2 & $(CH_3)_2CH$), 1.59–1.72 (m, 1H, $(CH_3)_2CH$, imidazole), 1.73–1.85 (m, 1H, $(CH_3)_2CH$, oxazole), 1.85–2.10 (m, 4H, CH_3CH_2), 3.38–3.50 (m, 2H, NCH_2CH, imidazole), 3.58–3.72 (m, 1H, $OCH_{2(a)}CH$, oxazole), 3.72–3.77 (m, 1H, $OCH_{2(b)}CH$, oxazole), 3.79 (s, 3H, $ArOCH_3$), 3.87–3.96 (m, 1H, $OCH_2CH(CH_3)_2$, oxazole), 4.06–4.19 (m, 1H, $NCH_2CH(CH_3)_2$, imidazole), 6.80 (d, 2H, *J*=8.8 Hz, ArH), 7.06 (d, 2H, *J*=8.8 Hz, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 7.9 (CH_3CH_2), 8.0 (CH_3CH_2), 17.9 ($(CH_3)_2CH$, imidazole), 18.2 ($(CH_3)_2CH$, oxazole), 19.4 (CH_3CH_2), 19.6 (CH_3CH_2), 32.4 ($(CH_3)_2CH$, imidazole), 32.8 ($(CH_3)_2CH$, oxazole), 46.4 ($C(CH_2CH_3)_2$), 55.5 (NCH_2, imidazole), 59.0 ($ArOCH_3$), 69.2 (OCH_2, oxazole), 72.0 ($(NCH_2CH(CH_3)_2$, imidazole)), 72.4 ($OCH_2CH(CH_3)_2$, oxazole), 114.2 (ArC_2), 129.9 (ArC_3), 135.3 (ArC_4OMe), 158.4 (ArC_1N), 163.4 (NCN), 167.2 (OCN); LC/MS (ESI): M^+, found 399.30, $C_{24}H_{37}N_3O_2$ requires 399.29.

*4.2.5. (S)-4-Isopropyl-2-(3-((S)-4-isopropyl-1-(quinolin-3-yl)-4,5-dihydro-1H-imidazol-2-yl)pentan-3-yl)-4,5-dihydrooxazole (**L3**).* The ligand **L3** was prepared from bis-amidoalcohol **2** (660 mg, 2.00 mmol) and quinolin-3-amine (432 mg, 3.00 mmol) according to **GP1** as described above. Light yellow colored oily product **L3** (410 mg, 48.8%, over three steps) was isolated after purification by silica gel chromatography (EtOAc/Pet. Ether/Et_3N=1:1:0.02, R_f=0.3). $[\alpha]_D^{25}$ +76.5 (*c* 0.5, $CHCl_3$); [Anal. Calcd for $C_{26}H_{36}N_4O$: C, 74.25; H, 8.63; N, 13.32; found C, 74.41; H, 8.38; N, 12.97]; IR (KBr): 2960, 2874, 1660, 1601, 1516, 1489, 1418, 1382, 1238, 1114, 787, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.58–0.79 (m, 6H, CH_3CH_2), 0.79–1.06 (m, 12H, $(CH_3)_2CH$), 1.52–1.71 (m, 2H, $(CH_3)_2CH$, oxazole & imidazole), 1.72–2.11 (m, 4H, CH_3CH_2), 3.11–3.16 (m, 1H, $NCH_{2(a)}CH$, imidazole), 3.16–3.34 (m, 1H, $NCH_{2(b)}CH$, imidazole), 3.57–3.67 (m, 1H, $OCH_{2(a)}CH$, oxazole), 3.67–3.71 (m, 1H, $OCH_{2(b)}CH$, oxazole), 3.72–3.83 (m, 1H, OCH_2CH, oxazole), 4.03–4.12 (m, 1H, NCH_2CH, imidazole), 7.25 (s, 1H, ArH), 7.54–8.05 (m, 4H, ArH),7.50–7.59 (m, 1H, ArH), 7.64–7.79 (m, 2H, ArH), 8.06 (d, *J*=7.4 Hz, 1H, ArH), 8.70 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 7.9 (CH_3CH_2), 8.0 (CH_3CH_2), 18.1 ($(CH_3)_2CH$, imidazole), 19.4 ($(CH_3)_2CH$, oxazole), 25.3 (CH_3CH_2), 25.9 (CH_3CH_2), 32.3 ($(CH_3)_2CH$, imidazole), 32.9 ($(CH_3)_2CH$, oxazole), 46.7 ((NCH_2, imidazole), 59.1 (OCH_2, oxazole), 69.9 (NCH_2CH, imidazole), 72.1 ((OCH_2CH, oxazole), 127.2 (ArC), 127.7 (ArC), 128.1 (ArC), 129.2 (ArC), 129.7 (ArC), 134.4 (ArC), 136.2 (ArC), 146.7 (ArC), 151.6 (ArC), 162.7 (NCN), 166.8 (OCN); LC/MS (ESI): M^+, found 420.27, $C_{26}H_{36}N_4O$ requires 420.29.

*4.2.6. (S)-4-Isopropyl-2-(3-((S)-4-isopropyl-1-(p-tolyl)-4,5-dihydro-1H-imidazol-2-yl)pentan-3-yl)-4,5-dihydrooxazole (**L4**).* The ligand **L4** was prepared from bis-amidoalcohol **2** (660 mg, 2.00 mmol) and *p*-toluidine (321 mg, 3.00 mmol) according to the described procedure **GP1**. Light yellow colored oily product **L4** (345 mg, 45%, over three steps) was isolated after purification by silica gel chromatography (EtOAc/Pet. Ether/Et_3N=1:1:0.02, R_f=0.25). $[\alpha]_D^{25}$ 111.7 (*c* 0.5, $CHCl_3$); [Anal. Calcd for $C_{24}H_{37}N_3O$: C, 75.15; H, 9.72; N, 10.95; found C, 75.27; H, 9.53; N, 11.12]; IR (KBr): 2959, 2874, 1660, 1596, 1515, 1466, 1382, 1236, 1110, 1035, 985, 824, 751 cm^{-1}; ^1H NMR

($CDCl_3$, 400 MHz) δ 0.65–0.10 (m, 18H, CH_3CH_2 & $(CH_3)_2CH$), 1.69–2.07 (m, 6H, CH_3CH_2, & $(CH_3)_2CH$), 2.30 (s, 3H, $ArCH_3$), 3.32–3.43 (m, 1H, $NCH_{2(a)}CH$, imidazole), 3.43–3.53 (m, 1H, $NCH_{2(b)}CH$, imidazole), 3.62–3.71 (m, 1H, $OCH_{2(a)}CH$, oxazole), 3.71–3.79 (m, 1H, $OCH_{2(b)}CH$, oxazole), 3.79–3.98 (m, 1H, $OCH_2CH(CH_3)_2$, oxazole), 4.01–4.15 (m, 1H, $NCH_2CH(CH_3)_2$, imidazole), 7.03 (d, 2H, J=8.0 Hz, Ar*H*), 7.09 (d, 2H, J=8.0 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 7.9 (CH_3CH_2), 17.9 ($(CH_3)_2CH$, imidazole), 18.3 ($(CH_3)_2CH$, oxazole), 19.4 (CH_3CH_2), 21.7 ($ArCH_3$), 32.3 ($(CH_3)_2CH$, imidazole), 32.8 ($(CH_3)_2CH$, oxazole), 46.5 ($C(CH_2CH_3)_2$), 58.9 (NCH_2, imidazole), 69.1 (OCH_2, oxazole), 69.3 ($NCH_2CH(CH_3)_2$, imidazole)), 72.4 ($OCH_2CH(CH_3)_2$, oxazole), 128.4 (ArC_2), 129.7 (ArC_3), 136.9 (ArC_4Me), 140.0 (ArC_1N), 163.3 (NCN), 167.2 (OCN); LC/MS (ESI): M^+, found 383.29, $C_{24}H_{37}N_3O$ requires 383.29.

4.3. Asymmetric Friedel–Craft's alkylation

*4.3.1. General procedure for enantioselective addition of conjugated enones with indole (**GP2**).* A solution of $Cu(OTf)_2$ (15 mg, 0.042 mmol, 20 mol %) and chiral ligand **L2** (17 mg, 0.042 mmol, 10 mol %) in dry CH_3CN (2 mL) was stirred for 1 h at room temperature under the argon atmosphere. To this resulting blue-green solution, a solution of indole **5** (50 mg, 0.425 mmol) and conjugated ketones (**6a**–**l**) (0.425 mmol) in dry CH_3CN (1 mL) was added via syringe. The reaction was then stirred at ambient temperature for 24–48 h. The reaction mixture was monitored by TLC until the starting material was completely consumed, then the solvent was removed under vacuum. Water (10 mL) was added and the mixture was extracted with EtOAc (2×25 mL), washed with brine (10 mL), and dried over $MgSO_4$. The product was purified by column chromatography.

*4.3.2. (S)-3-(1H-Indol-3-yl)-1,3-diphenylpropan-1-one (**7a**).* Oxazoline–imidazoline ligand **L2** (17 mg, 0.042 mmol, 10 mol %), $Cu(OTf)_2$ (15 mg, 0.042 mmol, 20 mol %), indole **5** (50 mg, 0.425 mmol), and chalcone **6a** (89 mg, 0.425 mmol) in CH_3CN (3 mL) were reacted according to **GP2**. Purification by chromatography on silica (EtOAc/hexane 1:9) yielded **7a** as a white solid (119 mg, 86%). This is a known compound.[23a] Enantiomeric excess was determined by chiral HPLC (Chiracel OD-H column), hexane/*i*-PrOH 80:20, 0.4 mL/min, λ=220 nm, t_R (minor)=8.73 min, t_R (major)=9.68 min, to be 99.92%; mp 147–149 °C, $[\alpha]_D^{25}$ +29.6 (c 0.45, $CHCl_3$) [lit.[23a] mp 148–152 °C, $[\alpha]_D^{25}$ +25.3 (c 0.3, $CHCl_3$)]; [Anal. Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30; found C, 85.17; H, 5.63; N, 4.42]; IR (cm^{-1}): 3413, 1679, 1597, 1451, 745, 698; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.73–3.80 (m, 2H, $COCH_2$), 5.07 (t, 1H, J=6.6 Hz, $ArCHCH_2$), 6.99 (s, 1H, CHNH), 7.25–7.44 (m, 11H, Ar*H*), 7.92 (d, J=7.3 Hz, 1H of 4*H*-indole & 2H of $COPh H_{ortho}$), 7.96 (s, 1H, N*H* of Indole); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 38.29, 45.28, 111.18, 119.4, 119.5, 119.6, 121.5, 122.2, 126.4, 126.5, 127.9, 128.2, 128.5, 128.7, 133.1, 136.6, 137.1, 144.3, 198.62; LC/MS (ESI): M^+, found 325.15, $C_{23}H_{19}NO$ requires 325.15.

*4.3.3. (S)-3-(4-Chlorophenyl)-3-(1H-indol-3-yl)-1-phenylpropan-1-one (**7b**).* Oxazoline–imidazoline ligand **L2** (17 mg, 0.042 mmol, 10 mol %), $Cu(OTf)_2$ (15 mg, 0.042 mmol, 20 mol %), indole **5** (50 mg, 0.425 mmol), and enone **6b** (103 mg, 0.425 mmol) in CH_3CN (3 mL) were reacted according to **GP2**. Purification by chromatography on silica (EtOAc/hexane 1:9, R_f=0.75) yielded **7b** as a light yellow solid (128.5 mg, 84%). Enantiomeric excess was determined by chiral HPLC (Chiracel OD-H column), hexane/*i*-PrOH 80:20, 0.4 mL/min, λ=220 nm, t_R (minor)=8.84 min, t_R (major)=9.74 min, to be 93.85%; mp 189–192 °C, $[\alpha]_D^{25}$ +23.7 (c 0.45, $CHCl_3$); [Anal. Calcd for $C_{23}H_{18}ClNO$: C, 76.77; H, 5.04; N, 3.89; found C, 76.92; H, 5.12; N, 3.71]; IR (cm^{-1}): 3369, 1677, 745, 582, 502; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.64–3.38 (m, 2H, $COCH_2$), 5.04 (t, 1H, J=7.3 Hz, $ArCHCH_2$), 6.93–7.11 (m, 2H, Ar*H* & 1H of NC*H* of Indole), 7.12–7.63 (m, 8H, Ar*H*), 7.92 (d, J=7.3 Hz, 1H of 4*H*-indole & 2H of $COPh H_{ortho}$), 7.99 (s, N*H* of Indole); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.8, 45.0, 113.3, 119.0, 119.9, 121.2, 123.3, 126.5, 128.1, 128.2, 128.6, 128.7, 132.0, 133.8, 136.7, 137.0, 140.0, 142.8, 198.3; LC/MS (ESI): M^+, found 359.10, $C_{23}H_{18}ClNO$ requires 359.11.

*4.3.4. (S)-3-(4-Chlorophenyl)-3-(1H-indol-3-yl)-1-(naphthalen-2-yl) propan-1-one (**7c**).* Oxazoline–imidazoline ligand **L2** (17 mg, 0.042 mmol, 10 mol %), $Cu(OTf)_2$ (15 mg, 0.042 mmol, 20 mol %), indole **5** (50 mg, 0.425 mmol), and enone **6c** (124 mg, 0.425 mmol) in CH_3CN (3 mL) were reacted according to **GP2**. Purification by chromatography on silica (EtOAc/hexane 1:9) yielded **7c** as a light yellow solid (141 mg, 81%). Enantiomeric excess was determined by chiral HPLC (Chiracel OD-H column), hexane/*i*-PrOH 80:20, 0.4 mL/min, λ=220 nm, t_R (minor)=8.80 min, t_R (major)=9.73 min, to be 95.6%; mp 237–241 °C, $[\alpha]_D^{25}$ +19.1 (c 0.45, $CHCl_3$); [Anal. Calcd for $C_{27}H_{20}ClNO$: C, 79.11; H, 4.92; N, 3.42; found C, 79.35; H, 5.02; N, 3.59]; IR (KBr): 3409, 2923, 1677, 815, 744, 476 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.75–3.86 (m, 1H, $COCH_{2(a)}$), 3.86–3.98 (m, 1H, $COCH_{2(b)}$), 5.09 (t, 1H, J=7.3 Hz, $ArCHCH_2$), 7.01–7.07 (m, 2H, Ar*H*), 7.14–7.38 (m, 7H, Ar*H*), 7.38–7.46 (m, 1H, Ar*H*), 7.48–7.66 (m, 2H, Ar*H*), 7.83–7.91 (m, 2H, Ar*H*), 7.91–7.99 (m, 2H, Ar*H*), 8.42 (s, 1H, N*H* of Indole); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.5, 45.0, 111.1, 119.0, 119.5, 121.1, 122.0, 123.9, 124.6, 126.5, 128.1, 128.2, 128.6, 128.7, 129.3, 132.0, 133.8, 134.1, 135.2, 136.7, 137.0, 139.8, 142.7, 199.9; LC/MS (ESI): M^+, found 409.09, $C_{27}H_{20}ClNO$ requires 409.12.

*4.3.5. (S)-3-(1H-Indol-3-yl)-3-mesityl-1-phenylpropan-1-one (**7d**).* Oxazoline–imidazoline ligand **L2** (25 mg, 15 mol %), $Cu(OTf)_2$ (22 mg, 30 mol %), indole **5** (50 mg, 0.425 mmol), and enone **6d** (107 mg, 0.425 mmol) in CH_3CN (3 mL) were reacted according to **GP2**. Purification by chromatography on silica (EtOAc/hexane 1:9) yielded **7d** as a light yellow solid (63 mg, 40%). Enantiomeric excess was determined by chiral HPLC (Chiracel OD-H), hexane/*i*-PrOH 80:20, 0.4 mL/min, λ=220 nm, t_R (minor)=18.9 min, t_R (major)=23.0 min, to be 96%; mp 169–171 °C, $[\alpha]_D^{25}$ +11.5 (c 0.45, $CHCl_3$); [Anal. Calcd for $C_{26}H_{25}NO$: C, 84.98; H, 6.86; N, 3.81; found C, 85.11; H, 6.73; N, 3.75]; IR (KBr): 3409, 2921, 1677, 1451, 744, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.27 (s, 9H, $ArCH_3$), 3.57–3.63 (m, 1H, $COCH_{2(a)}$), 4.05–4.12 (m, 1H, $COCH_{2(a)}$), 5.49 (t, 1H, J=6.6 Hz, $ArCHCH_2$), 6.81 (s, 2H, Me_3PhH), 6.85–6.94 (m, 1H, Ar*H*), 6.94–7.02 (m, 1H, Ar*H*), 7.02–7.15 (m, 1H, Ar*H*), 7.20–7.36 (m, 2H, Ar*H*),7.41–7.50 (m, 2H, Ar*H*), 7.50–7.59 (m, 1H, Ar*H*), 7.90 (s, 1H, N*H* of Indole), 7.98 (d, J=7.3 Hz, 2H, $ArH_{(orthoproton)}$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.9, 21.4, 29.8, 33.2, 43.0, 111.09, 117.8, 118.7, 119.1, 119.9, 121.7, 122.1, 127.0, 128.2, 128.3, 128.8, 130.0, 138.8, 136.8, 137.2, 137.3, 199.24; LC/MS (ESI): M^+, found 367.17, $C_{26}H_{25}NO$ requires 367.19.

*4.3.6. (S)-3-(1H-Indol-3-yl)-3-mesityl-1-(naphthalen-2-yl)propan-1-one (**7e**).* Oxazoline–imidazoline ligand **L2** (34 mg, 20 mol %), $Cu(OTf)_2$ (22 mg, 30 mol %), indole **5** (50 mg, 0.425 mmol), and enone **6e** (129 mg, 0.425 mmol) in CH_3CN (3 mL) were reacted according to **GP2**. Purification by chromatography on silica (EtOAc/hexane 1:9) yielded **7e** as a yellow solid (39 mg, 22%). Enantiomeric excess was determined by chiral HPLC (Chiracel OD-H), hexane/*i*-PrOH 80:20, 0.4 mL/min, λ=220 nm, t_R (minor)=18.8 min, t_R (major)=22.9 min, to be 97.8%; mp 227–229 °C, $[\alpha]_D^{25}$ +17.3 (c 0.45, $CHCl_3$); [Anal. Calcd for $C_{30}H_{27}NO$: C, 86.30; H, 6.52; N, 3.35; found C, 86.19; H, 6.61; N, 3.49]; IR (KBr): 3410, 3319, 2652, 1653, 1619, 1590, 1457, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.27 (s, 9H, $ArCH_3$), 3.68–3.78 (m, 1H, $COCH_{2(a)}$), 4.17–4.23 (m, 1H, $COCH_{2(b)}$), 5.54 (t, 1H, J=6.6 Hz, $ArCHCH_2$), 6.79–6.92 (m, 3H, Ar*H*), 7.92–7.20 (m, 2H, Ar*H*), 7.20–7.38 (m, 3H, Ar*H*), 7.50–7.68 (m, 2H, Ar*H*), 7.84–7.98 (m, 3H, Ar*H*), 8.05–8.08 (m, 1H, Ar*H*), 8.47 (s, 1H, N*H* of Indole); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.4, 21.5, 29.8, 33.4, 43.0, 111.0, 115.8, 116.2, 117.6, 119.1, 119.3, 120.0, 121.5, 122.0, 123.2, 124.1,

125.5, 127.1, 128.0, 128.5, 129.6, 131.0, 132.8, 134.6, 135.9, 137.0, 137.3, 199.1; LC/MS (ESI): M^+, found 417.22, $C_{30}H_{27}NO$ requires 417.21.

*4.3.7. (S)-3-(1H-Indol-3-yl)-1-phenyl-3-(p-tolyl)propan-1-one (**7f**).* Oxazoline–imidazoline ligand **L2** (17 mg, 0.042 mmol, 10 mol %), $Cu(OTf)_2$ (15 mg, 0.042 mmol, 20 mol %), indole **5** (50 mg, 0.425 mmol), and enone **6f** (95 mg, 0.425 mmol) in CH_3CN (3 mL) were reacted according to **GP2**. Purification by chromatography on silica (EtOAc/hexane 1:9) yielded **7f** as a yellow solid (105 mg, 73%). Enantiomeric excess was determined by chiral HPLC (Chiracel OD-H), hexane/*i*-PrOH 80:20, 0.4 mL/min, λ=220 nm, t_R (minor)=27.3 min, t_R (major)=31.2 min, to be 95.8%; mp 153–155 °C, $[\alpha]_D^{25}$ +14.6 (*c* 0.45, $CHCl_3$); [Anal. Calcd for $C_{24}H_{21}NO$: C, 84.92; H, 6.24; N, 4.13; found C, 84.66; H, 6.15; N, 3.97]; IR (KBr): 3413, 1680, 1452, 743, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.26 (s, 3H, ArC*H*$_3$), 3.65–3.78 (m, 1H, COC*H*$_{2(a)}$), 3.78–3.89 (m, 1H, COC*H*$_{2(b)}$), 5.02 (t, 1H, *J*=7.4 Hz, ArC*H*CH$_2$), 6.98–7.61 (m, 12H, Ar*H*), 7.89 (s, 1H, N*H* of Indole), 7.93 (d, *J*=7.3 Hz, 2H of COPh*H*$_{ortho}$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.1 (ArCH$_3$), 37.9 (ArCHCH$_2$), 45.4 (ArCHCH$_2$), 111.2, 119.4, 119.5, 119.6, 121.6, 122.2, 126.9, 127.8, 128.2, 128.7, 129.4, 133.3, 135.8, 136.7, 137.1, 141.3, 198.71; LC/MS (ESI): M^+, found 339.19, $C_{24}H_{21}NO$ requires 339.16.

*4.3.8. (S)-3-(1H-Indol-3-yl)-1-(naphthalen-2-yl)-3-(p-tolyl)propan-1-one (**7g**).* Oxazoline–imidazoline ligand **L2** (17 mg, 0.042 mmol, 10 mol %), $Cu(OTf)_2$ (15 mg, 0.042 mmol, 20 mol %), indole **5** (50 mg, 0.425 mmol), and enone **6g** (116 mg, 0.425 mmol) in CH_3CN (3 mL) were reacted according to **GP2**. Purification by chromatography on silica (EtOAc/hexane 1:9) yielded **7g** as a yellowish solid (45 mg, 27%). Enantiomeric excess was determined by chiral HPLC (Chiracel OD-H), hexane/*i*-PrOH 80:20, 0.4 mL/min, λ=220 nm, t_R (minor)=7.6 min, t_R (major)=9.7 min, to be 93.4%; mp 174–177 °C, $[\alpha]_D^{25}$ +9.1 (*c* 0.45, $CHCl_3$); [Anal. Calcd for $C_{28}H_{23}NO$: C, 86.34; H, 5.95; N, 3.60; found C, 86.24; H, 6.09; N, 3.37]; IR (KBr): 3413, 2923, 2854, 1676, 1625, 1461, 816, 748, 476 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.27 (s, 3H, ArC*H*$_3$), 3.76–3.88 (m, 1H, COC*H*$_{2(a)}$), 3.89–3.98 (m, 1H, COC*H*$_{2(b)}$), 5.08 (t, 1H, *J*=7.3 Hz, ArC*H*CH$_2$), 6.87–7.45 (m, 7H, Ar*H*), 7.55–7.71 (m, 3H, Ar*H*), 7.83–8.02 (m, 6H, Ar*H*), 8.42 (s, 1H, N*H* of Indole); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.1, 38.1, 45.4, 111.2, 116.1, 118.0, 119.5, 122.2, 123.8, 124.2, 125.8, 126.7, 127.8, 128.4, 129.2, 129.8, 132.2, 134.1, 135.9, 136.8, 138.2, 139, 8, 141.1, 197.8; LC/MS (ESI): M^+, found 389.18, $C_{28}H_{23}NO$ requires 389.18.

*4.3.9. (S)-3-(1H-Indol-3-yl)-3-(4-methoxyphenyl)-1-phenylpropan-1-one (**7h**).* Oxazoline–imidazoline ligand **L2** (17 mg, 0.042 mmol, 10 mol %), $Cu(OTf)_2$ (15 mg, 0.042 mmol, 20 mol %), indole **5** (50 mg, 0.425 mmol), and enone **6h** (101 mg, 0.425 mmol) in CH_3CN (3 mL) were reacted according to **GP2**. Purification by chromatography on silica (EtOAc/hexane 1:9) yielded **7h** as a yellow solid (134 mg, 89%). Enantiomeric excess was determined by HPLC (Chiracel OD-H), hexane/*i*-PrOH 80:20, 0.4 mL/min, λ=220 nm, t_R (minor)=20.1 min, t_R (major)=24.0 min, to be 96.4%; mp 134–136 °C, $[\alpha]_D^{25}$ +21.4 (*c* 0.45, $CHCl_3$); [Anal. Calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94; found C, 80.79; H, 5.86; N, 4.07]; IR (KBr): 3412, 2923, 1674, 1509, 1245, 1177, 746, 476 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.73 (s, 3H, ArOC*H*$_3$), 3.77–3.85 (m, 1H, COC*H*$_{2(a)}$), 3.85–3.98 (m, 1H, COC*H*$_{2(b)}$), 5.06 (t, 1H, *J*=7.4 Hz, ArC*H*CH$_2$), 6.78–7.83 (m, 2H, Ar*H*), 6.97–7.05 (m, 2H, Ar*H*), 7.11–7.19 (m, 1H, Ar*H*), 7.22–7.62 (m, 6H, Ar*H*), 7.84–8.01 (m, 3H, Ar*H*), 8.42 (s, 1H, N*H* of Indole); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.8, 45.5, 55.3, 111.3, 113.9, 119.7, 121.5, 122.0, 124.0, 126.8, 127.8, 128.5, 128.8, 129.6, 132.4, 134.9, 135.8, 136.7, 158.1, 198.8; LC/MS (ESI): M^+, found 355.19, $C_{24}H_{21}NO_2$ requires 355.16.

*4.3.10. (S)-3-(1H-Indol-3-yl)-3-(4-methoxyphenyl)-1-(naphthalen-2-yl)propan-1-one (**7i**).* Oxazoline–imidazoline ligand **L2** (17 mg, 0.042 mmol, 10 mol %), $Cu(OTf)_2$ (15 mg, 0.042 mmol, 20 mol %), indole **5** (50 mg, 0.425 mmol), and enone **6i** (123 mg, 0.425 mmol) in CH_3CN (3 mL) were reacted according to **GP2**. Purification by chromatography on silica (EtOAc/hexane 1:9) yielded **7i** as an off white solid (112 mg, 66%). Enantiomeric excess was determined by chiral HPLC (Chiracel OD-H), hexane/*i*-PrOH 80:20, 0.4 mL/min, λ=220 nm, t_R (major)=39.4 min, t_R (minor)=49.1 min, to be 90.8%; mp 159–162 °C, $[\alpha]_D^{25}$ +17.5 (*c* 0.45, $CHCl_3$); [Anal. Calcd for $C_{28}H_{23}NO_2$: C, 82.94; H, 5.72; N, 3.45; found C, 83.22; H, 5.61; N, 3.73]; IR (KBr): 3413, 3007, 2930, 1679, 1610, 1509, 1246, 1177, 1032, 745, 544 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.65–3.82 (m, 2H+3H, COC*H*$_2$ & ArOC*H*$_3$), 5.01 (t, 1H, *J*=7.3 Hz, ArC*H*CH$_2$), 6.75–6.83 (m, 2H, Ar*H*), 6.97–7.07 (m, 2H, Ar*H*), 7.11–7.20 (m, 1H, Ar*H*), 7.21–7.48 (m, 8H, Ar*H*), 7.49–7.56 (m, 1H, Ar*H*), 7.91 (s, 1H, N*H* of Indole), 7.93 (s, 2H. Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.5, 45.5, 55.3, 111.4, 113.8, 116.2, 118.1, 119.7, 119.9, 121.6, 122.1, 123.4, 126.7, 127.0, 128.3, 128.9, 130.1, 130.4, 131.9, 133.3, 135.2, 136.4, 136.7, 137.2, 158.0, 198.8; LC/MS (ESI): M^+, found 405.18, $C_{28}H_{23}NO_2$ requires 405.17.

*4.3.11. (S)-3-(1H-Indol-3-yl)-1-(naphthalen-2-yl)-3-phenylpropan-1-one (**7j**).* Oxazoline–imidazoline ligand **L2** (17 mg, 0.042 mmol, 10 mol %), $Cu(OTf)_2$ (15 mg, 0.042 mmol, 20 mol %), indole **5** (50 mg, 0.425 mmol), and enone **6j** (110 mg, 0.425 mmol) in CH_3CN (3 mL) were reacted according to **GP2**. Purification by chromatography on silica (EtOAc/hexane 1:9) yielded **7j** as a white solid (75 mg, 47%). Enantiomeric excess was determined by chiral HPLC (Chiracel OD-H), hexane/*i*-PrOH 80:20, 0.4 mL/min, λ=220 nm, t_R (minor)=12.0 min, t_R (major)=14.9 min, to be 95.5%; mp 166–169 °C, $[\alpha]_D^{25}$ +24.2 (*c* 0.45, $CHCl_3$); [Anal. Calcd for $C_{27}H_{21}NO$: C, 86.37; H, 5.64; N, 3.73; found C, 85.98; H, 5.87; N, 3.93]; IR (KBr): 3415, 1677, 1597, 1456, 746, 476 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.83–3.91 (m, 1H, COC*H*$_{2(a)}$), 3.91–3.95 (m, 1H, COC*H*$_{2(b)}$), 5.13 (t, 1H, *J*=7.3 Hz, ArC*H*CH$_2$), 7.00–7.11 (m, 3H, Ar*H*), 7.11–7.23 (m, 2H, Ar*H*), 7.23–7.50 (m, 6H, Ar*H*), 7.50–7.63 (m, 2H, Ar*H*), 7.95–8.19 (m, 4H, Ar*H*), 8.43 (s, 1H, N*H* of Indole); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 38.3, 45.3, 111.2, 116.0, 119.4, 119.5, 119.6, 121.5, 122.2, 123.3, 125.1, 126.4, 126.6, 127.9, 128.2, 128.5, 128.7, 129.4, 131.0, 133.0, 136.5, 137.1, 141.1, 144.3, 198.6; LC/MS (ESI): M^+, found 375.15, $C_{27}H_{21}NO$ requires 375.16.

*4.3.12. (R)-3-(1H-Indol-3-yl)-1-phenyl-3-(thiophen-2-yl)propan-1-one (**7k**).* Oxazoline–imidazoline ligand **L2** (17 mg, 0.042 mmol, 10 mol %), $Cu(OTf)_2$ (15 mg, 0.042 mmol, 20 mol %), indole **5** (50 mg, 0.425 mmol), and enone **6k** (91 mg, 0.425 mmol) in CH_3CN (3 mL) were reacted according to **GP2**. Purification by chromatography on silica (EtOAc/hexane 1:9) yielded **7k** as a white solid (91 mg, 65%). Enantiomeric excess was determined by chiral HPLC (Chiracel OD-H), hexane/*i*-PrOH 80:20, 0.4 mL/min, λ=220 nm, t_R (minor)=3.1 min, t_R (major)=8.6 min, to be 89.8%; mp 112–115 °C, $[\alpha]_D^{25}$ +6.3 (*c* 0.45, $CHCl_3$); [Anal. Calcd for $C_{21}H_{17}NOS$: C, 76.10; H, 5.17; N, 4.23; found C, 75.89; H, 5.31; N, 4.43]; IR (KBr): 3419, 1676, 1594, 1456, 741, 576 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.84 (t, *J*=6.6 Hz, 2H, COC*H*$_2$), 5.37 (t, 1H, *J*=6.6 Hz, ArC*H*CH$_2$), 6.85–6.98 (m, 2H, Ar*H*), 7.02–8.65, (m, 9H, Ar*H*), 7.92–7.94 (m, 2H, Ar*H*), 7.99 (s, N*H* of Indole); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 33.6, 46.2, 111.3, 116.1, 119.5, 119.6, 121.9, 122.3, 123.5, 124.3, 126.6, 128.2, 128.7, 133.2, 136.0, 136.4, 143.9, 148.8, 198.1; LC/MS (ESI): M^+, found 331.11, $C_{21}H_{17}NOS$ requires 331.10.

*4.3.13. (R)-3-(1H-Indol-3-yl)-1-phenyl-3-(ferrocene-2-yl)-propan-1-one (**7l**).* Oxazoline–imidazoline ligand **L2** (17 mg, 0.042 mmol, 10 mol %), $Cu(OTf)_2$ (15 mg, 0.042 mmol, 20 mol %), indole **5** (50 mg, 0.425 mmol), and enone **6l** (91 mg, 0.425 mmol) in CH_3CN (3 mL) were reacted according to **GP2**. Purification by chromatography on silica (EtOAc/hexane 1:9) yielded **7l** as a white solid (15 mg, 8%). Enantiomeric excess was determined by chiral HPLC (Chiracel OD-H), hexane/*i*-PrOH 80:20, 0.4 mL/min, λ=220 nm, t_R (major)=16.5 min, t_R (minor)=22.6 min, to be 89.8%; mp 273–275 °C, $[\alpha]_D^{25}$ +8.1 (*c* 0.45, $CHCl_3$); [Anal. Calcd for $C_{27}H_{23}FeNO_2$: C, 74.83; H, 5.31;

N, 3.23; found C, 74.61; H, 5.17; N, 3.51]; IR (KBr): 3409, 3011, 2934, 1678, 1615, 1503, 1247, 1179, 1031, 743, 541 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.61–3.73 (m, 1H, $COCH_{2(a)}$), 3.73–3.85 (m, 1H, $COCH_{2(b)}$), 4.06 (s, 5H, protons of **Cp**), 4.09-4.31 (m, 4H, protons of **Cp**), 4.90 (t, 1H, J=7.36 Hz, $CpCHCH_2$), 7.04–7.09 (m, 1H, Ar*H*), 7.10–7.16 (m, 1H, Ar*H*), 7.23–7.30 (m, 2H, Ar*H*), 7.35–7.44 (m, 2H, Ar*H*), 7.48–7.53 (m, 1H, Ar*H*), 7.61–7.68 (m, 1H, Ar*H*), 7.87–7.98 (m, 2H of Ar*H* & 1H of Indole); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.8, 45.8, 67.1, 67.3, 68.7, 111.2, 115.9, 119.3, 119.9, 121.8, 126.4, 128.2, 128.5, 131.3, 133.0, 137.1, 137.4, 199.1; LC/MS (ESI): M^+, found 433.22, $C_{27}H_{23}FeNO_2$ requires 433.23.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.04.063.

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