Tetrahedron: *Asymmetry* 25 (2014) 1031–1037

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

8-Amino-5,6,7,8-tetrahydroquinolines as ligands in iridium(III) catalysts for the reduction of aryl ketones by asymmetric transfer hydrogenation (ATH)

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ARTICLE INFO

Article history:
Received 20 May 2014
Accepted 6 June 2014

ABSTRACT

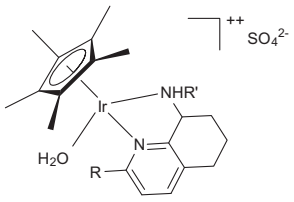
Aqua iridium(III) complexes with 8-amino-5,6,7,8-tetrahydroquinolines CAMPY **L1** and its derivatives as chiral ligands proved to be very efficient catalysts for the reduction of a wide range of prochiral aryl ketones, revealing a variety of behaviours in terms of reaction rate and stereoselectivity. As standard substrates, differently substituted acetophenones were studied and good enantioselectivity (86% ee) was achieved in the reduction of 1-(*o*-tolyl)ethan-1-one **6**. Particularly interesting was the ATH reaction in the case of β-amino keto esters, precursors of β-lactams and azetidinones. The best results were obtained with [Cp*Ir(H_2O)(**L1**)]SO_4 affording the corresponding diastereomeric alcohols in an (*R,S*)-configuration with an excellent 99% ee in the reduction of *2*-(benzamido methyl)-3-oxo-3-(4-(trifluoromethyl)phenyl) propanoate **12**.

1. Introduction

One of the most significant applications of asymmetric transfer hydrogenation (ATH) is the reduction of different substituted aryl ketones. Over the last decade, many approaches have been reported and many types of catalysts were used especially when the metal was ruthenium(II).[1–4] Our research group developed optically active ruthenium(II) catalysts based on complexes between diphosphines and a well-known chiral diamine DPEN, or a new chiral diamine CAMPY, with good results.[5,6] Recently, the possibility of using iridium complexes has been demonstrated as a valid alternative to the use of classical ruthenium systems.[7–17] In particular Carreira et al. reported that chiral aqua iridium(III) complexes bearing DPEN and its derivatives were very promising catalysts in the reduction of 2-cyanoacetophenones and β-keto esters.[18,19] Herein we report the use of a [Cp*Ir(H_2O)$_3$]SO_4 complex and 8-amino-5,6,7,8-tetrahydroquinoline, CAMPY hereafter, as a source of chirality, its derivative 2-methyl-5,6,7,8-tetrahydroquinolin-8-amine Me-CAMPY, and the corresponding NH-CH_3 diamines (Scheme 1).

The asymmetric reduction of ketones is a synthetically relevant reaction as the corresponding chiral alcohols are precursors of a wide range of bioactive compounds.

L1 R = R' = H; CAMPY
L2 R = CH_3; R' = H; Me-CAMPY
L3 R = H; R' = CH_3; CAMPY-NHMe
L4 R = R' = CH_3; Me-CAMPY-NHMe



Scheme 1. Catalysts used for ATH.

β-Amino keto esters are an important class for the synthesis of unnatural β-aminoacids which are used in the preparation of peptide mimetics and azetidinones.[20] The most common azetidinone precursor, used for the preparation of carbapenems, is ethyl 2-(benzamidomethyl)-3-oxobutanoate in which the methyl group is in α position to the carbonyl moiety.[21,22] In recent years the influence of different substituents at the α-position to the carbonyl group was studied.[23,24] With regard to the unique pharmacological properties attributed to the fluorine in helping absorption of the drug through the cell wall, selectively fluorinated organic intermediates still remain challenging targets for the synthesis of β-lactam antibiotic precursors.[25] Herein we focused our attention on the stereoselective reduction of different aromatic ketones and β-amino keto esters bearing either an electron donating or an electron withdrawing substituent.

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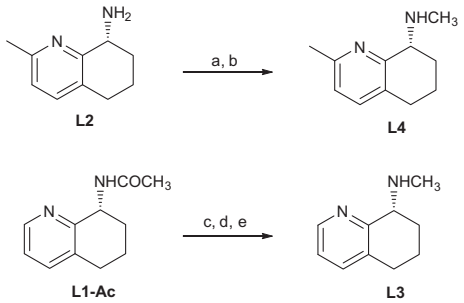
http://dx.doi.org/10.1016/j.tetasy.2014.06.003
0957-4166/

2. Results and discussion

The approach used for the synthesis of **L3** and **L4** is outlined in Scheme 2. Enantiomerically pure CAMPY **L1** and Me-CAMPY **L2** were obtained as salts by crystallization of racemic amines with enantiomerically pure tartaric acids.



Scheme 2. Synthesis of ligands **L3** and **L4**. Reagents and conditions: (a) K_2CO_3, ClCOOEt, THF/H_2O, 0 °C to rt; (b) $LiAlH_4$, THF, 0 °C to reflux; (c) NaH, THF, rt to reflux; (d) CH_3I, THF, 0 °C to rt; (e) HCl 6 M, reflux.

The absolute configuration of Me-CAMPY **L2** ligand was assigned by single-crystal X-ray diffraction studies of the $PtCl_4$((*S*)-(+)-Me-CAMPY)·H_2O salt (Fig. 1). This contains the **L2** ligand protonated on both nitrogen atoms (Fig. 2), a square planar $PtCl_4^{2-}$ counterion and one water molecule. $PtCl_4^{2-}$ and H_2O interact with **L2** through intramolecular hydrogen bonds [N1···H3 N-Ow 139(3)°, N1···Ow 2.982(6) Å; N2···H2-Ow 167.5(3)°, N2···Ow 2.772(7) Å; N1···H1 N-Cl2 165(5)°, N1···Cl2 3.184(6) Å] involving the hydrogens bonded to the two nitrogen atoms. The C1–C6 ring displays an envelope conformation with a deviation of the C3 atom from the meanplane defined by C2, C1, C6, C5 and C4 atoms of 0.310 Å and with the following torsion angles: C4–C5–C6–C1 –2.9° and C2–C1–C6–C5 –4.0°.

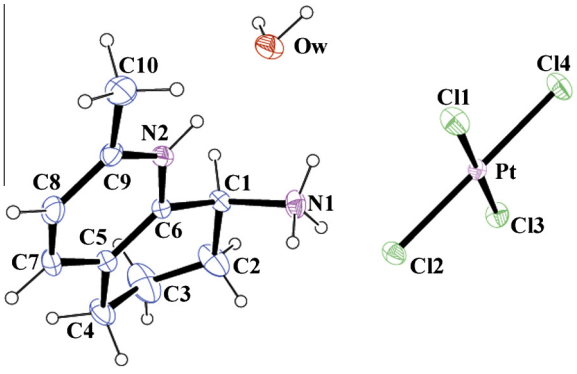
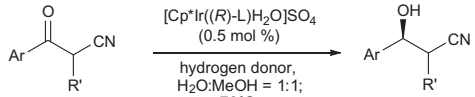


Figure 1. A perspective view of the $PtCl_4$((*S*)-(+)-Me-CAMPY)·H_2O salt. Selected interatomic distances (Å) are: Pt–Cl1 2.302(2), Pt–Cl2 2.299(2), Pt–Cl3 2.304(2), Pt–Cl4 2.305(2), C1–N1 1.508(6), C1–C2 1.533(7), C2–C3 1.430(10), C3–C4 1.516(11), C4–C5 1.510(7), C5–C6 1.373(6), C1–C6 1.511(6).

CAMPY and its derivatives were used as ligands for the one-pot synthesis of iridium(III) complexes after reaction with [Cp*Ir(H_2O)$_3$]SO_4, which could be used directly in ATH reactions. Screening was carried out for the reduction of different types of aryl ketones. The results obtained for 2-cyanoacetophenone and its heteroaromatic analogues are reported in Table 1.

The conversion of substrates **1**, **2** and **3** into the corresponding alcohols was achieved for all of the complexes in only 3 h with the exception of the complexes with ligands **L3** and **L4** in the reduction of substrate **1** (entries 9, 11 and 12). For substrate **1**, the best results were obtained with **L1** in the presence of HCOOH as the hydrogen donor (62% ee, entry 1). For substrate **2**, the azeotropic mixture of HCOOH/TEA gave 75% ee with [Cp*Ir(H_2O)(**L2**)]SO_4 (entry 18). In the case of substrate **3**, data did not show any appreciable difference in terms of reaction conditions or cata-

Table 1
ATH reaction of 2-cyanoacetophenones



1 Ar = Ph; R'= H
2 Ar = thienyl; R'= H
3 Ar = furyl; R'= H
4 Ar = Ph; R'= CH_2CH_3

1a Ar = Ph; R'= H
2a Ar = thienyl; R'= H
3a Ar = furyl; R'= H
4a Ar = Ph; R'= CH_2CH_3

Entry[a]	Sub.	L	Hydrogen donor	Conv.[b] (%)	ee (%)	de (%)
1	**1**	**L1**	HCOOH	100	62 (*S*)	
2			HCOONa	100	47 (*S*)	
3			HCOOH/TEA	100	53 (*S*)	
4		**L2**	HCOOH	100	57 (*S*)	
5			HCOONa	100	56 (*S*)	
6			HCOOH/TEA	100	48 (*S*)	
7		**L3**	HCOOH	100	40 (*S*)	
8			HCOONa	98	45 (*S*)	
9			HCOOH/TEA	82	24 (*S*)	
10		**L4**	HCOOH	100	44 (*S*)	
11			HCOONa	47	60 (*S*)	
12			HCOOH/TEA	33	51 (*S*)	
13	**2**	**L1**	HCOOH	100	50 (*S*)	
14			HCOONa	100	46 (*S*)	
15			HCOOH/TEA	100	46 (*S*)	
16		**L2**	HCOOH	100	61 (*S*)	
17			HCOONa	100	73 (*S*)	
18			HCOOH/TEA	100	75 (*S*)	
19		**L3**	HCOOH	100	61 (*S*)	
20			HCOONa	100	34 (*S*)	
21			HCOOH/TEA	100	19 (*S*)	
22		**L4**	HCOOH	100	48 (*S*)	
23			HCOONa	100	44 (*S*)	
24			HCOOH/TEA	100	54 (*S*)	
25	**3**	**L1**	HCOOH	100	34 (*S*)	
26			HCOONa	100	40 (*S*)	
27			HCOOH/TEA	100	34 (*S*)	
28		**L2**	HCOOH	100	50 (*S*)	
29			HCOONa	100	37 (*S*)	
30			HCOOH/TEA	100	41 (*S*)	
31		**L3**	HCOOH	100	48 (*S*)	
32			HCOONa	100	48 (*S*)	
33			HCOOH/TEA	100	49 (*S*)	
34		**L4**	HCOOH	100	50 (*S*)	
35			HCOONa	100	45 (*S*)	
36			HCOOH/TEA	100	56 (*S*)	
37	**4**	**L1**	HCOOH	100	94 (*R,S*); 68 (*S,S*)	38 *syn*
38			HCOONa	46	89 (*R,S*); 65 (*S,S*)	37 *syn*
39			HCOOH/TEA	100	84 (*R,S*); 62 (*S,S*)	20 *syn*
40		**L2**	HCOOH	100	90 (*R,S*); 75 (*S,S*)	40 *syn*
41			HCOONa	72	93 (*R,S*); 80 (*S,S*)	40 *syn*
42			HCOOH/TEA	100	68 (*R,S*); 53 (*S,S*)	16 *syn*
43		**L3**	HCOOH	68	88 (*R,S*); 64 (*S,S*)	55 *syn*
44			HCOONa	11	84 (*R,S*); 62 (*S,S*)	53 *syn*
45			HCOOH/TEA	100	30 (*R,S*); 22 (*S,S*)	22 *syn*
46		**L4**	HCOOH	70	74 (*R,S*); 55 (*S,S*)	55 *syn*
47			HCOONa	8	84 (*R,S*); 80 (*S,S*)	65 *syn*
48			HCOOH/TEA	100	16 (*R,S*); 7 (*S,S*)	14 *syn*

[a] Reactions were carried out at 70 °C using 0.5 mmol of substrate with 0.5 mol % of iridium complex in 2 mL of MeOH/water = 1:1 mixture when HCOOH or HCOONa was used as hydrogen donors, while an HCOOH/TEA azeotropic mixture was used neat.

[b] Conversion and ee were determined by GC after 3 h for substrate **1** while for substrates **2** and **3** they were determined by HPLC after 3 h, for substrate **4** after 24 h by HPLC (OD-H Chiralcel column).

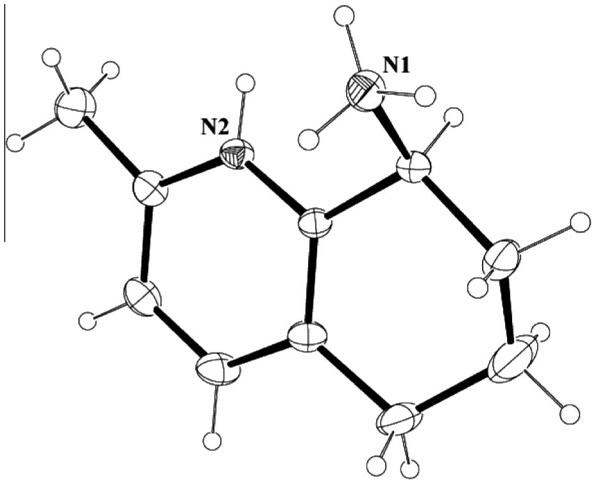


Figure 2. A perspective view of the Me-CAMPY **L2** dication.

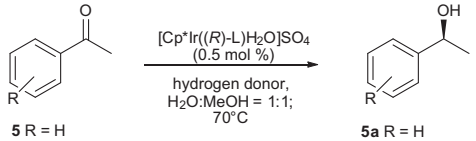
lyst used. The presence of an additional racemic stereogenic centre as in substrate **4** allowed the reaction to reach high stereoselectivity (90–94% ee) even with moderate diastereoselectivity (40% de) (entries 37 and 40). The best results were achieved using HCOOH as the hydrogen donor with complexes in which the diamines carried a primary amino group **L1** and **L2**. When the ATH reductions were carried out in the presence of HCOONa, the conversion decreased dramatically (entries 38, 44 and 47).

Generally, acetophenone was used as the standard substrate to study the catalytic behaviour of catalysts in ATH. We decided to investigate a range of substituted acetophenones with the aim of determining the influence of different groups on the aromatic ring in terms of electronic properties and steric hindrance (substrates 6, 7 and 8). The results are reported in Table 2. In the case of substituted acetophenones **6**, **7** and **8**, $[Cp^*Ir(H_2O)(\mathbf{L1})]SO_4$ in the presence of HCOOH generally gave the best results (entries 13, 25 and 37). In fact when there was a steric hindrance at the *ortho*-position with respect to ketone **6**, 86% ee was obtained with **L1** (entry 13); instead for acetophenone **5**, 74% ee was obtained using diamine ligand **L2** (entry 4).

Generally when the steric hindrance of the substrate was increased by the introduction of a group at the *ortho*-position, the stereoselectivity was increased. In our case, this behaviour suggested that the ideal matching between the ligand and the substrate was realized in the presence of a methyl group either on the substrate or on the backbone of the ligand. In the case of substrates **7** and **8**, the presence of a *meta*-methoxy group or a *para*-trifluoromethyl group improved the catalytic performance compared to acetophenone **5** (66% ee vs 46% ee, entries 1, 25 and 37, Table 2). These results, in terms of reaction rate, confirmed that the withdrawing properties of both substituents favoured the keto form over the enolic one, thus increasing the reaction rate and the stereoselectivity. For all of the substrates, when a secondary amine on the amino stereogenic centre of the ligands **L3** and **L4** was present, the reduction did not proceed well, either in terms of conversion or in terms of stereoselectivity. The same behaviour was observed under azeotropic mixture conditions.

As reported in previous work this type of catalyst was also applied to the reduction of β-ketoesters such as ethyl 3-oxo-3-phenylpropanoate **9** utilizing a monosulfonylated diamine as a ligand.[19] First screening with the monotosylated CAMPY derivatives did not lead to appreciable results with lower conversion and selectivity (data not reported), probably due to the excessive steric hindrance and the electronic effect of the tosyl group depleting the primary amine present in our ligands. For this reason, we decided to apply the non-sulfonylated catalysts, reported herein

Table 2
ATH reaction of acetophenones



5 R = H
6 R = *o*-CH_3
7 R = *p*-CF_3
8 R = *m*-OCH_3

5a R = H
6a R = *o*-CH_3
7a R = *p*-CF_3
8a R = *m*-OCH_3

Entry[a]	Sub.	L	Hydrogen donor	Conv.[b] (%)	ee (%)
1	**5**	**L1**	HCOOH	88	46 (*S*)
2			HCOONa	46	48 (*S*)
3			HCOOH/TEA	49	45 (*S*)
4		**L2**	HCOOH	74	74 (*S*)
5			HCOONa	59	30 (*S*)
6			HCOOH/TEA	48	27 (*S*)
7		**L3**	HCOOH	71	43 (*S*)
8			HCOONa	38	33 (*S*)
9			HCOOH/TEA	8	23 (*S*)
10		**L4**	HCOOH	37	21 (*S*)
11			HCOONa	10	31 (*S*)
12			HCOOH/TEA	50	0
13	**6**	**L1**	HCOOH	73	86 (*S*)
14			HCOONa	58	83 (*S*)
15			HCOOH/TEA	29	70 (*S*)
16		**L2**	HCOOH	17	31 (*S*)
17			HCOONa	19	47 (*S*)
18			HCOOH/TEA	23	10 (*S*)
19		**L3**	HCOOH	37	58 (*S*)
20			HCOONa	7	35 (*S*)
21			HCOOH/TEA	10	15 (*S*)
22		**L4**	HCOOH	5	9 (*S*)
23			HCOONa	3	51 (*S*)
24			HCOOH/TEA	9	0
25	**7**	**L1**	HCOOH	100	65 (*S*)
26			HCOONa	77	57 (*S*)
27			HCOOH/TEA	63	61 (*S*)
28		**L2**	HCOOH	98	46 (*S*)
29			HCOONa	96	38 (*S*)
30			HCOOH/TEA	92	41 (*S*)
31		**L3**	HCOOH	67	43 (*S*)
32			HCOONa	13	25 (*S*)
33			HCOOH/TEA	24	16 (*S*)
34		**L4**	HCOOH	31	27 (*S*)
35			HCOONa	32	29 (*S*)
36			HCOOH/TEA	58	6 (*S*)
37	**8**	**L1**	HCOOH	89	66 (*S*)
38			HCOONa	50	62 (*S*)
39			HCOOH/TEA	49	61 (*S*)
40		**L2**	HCOOH	81	34 (*S*)
41			HCOONa	81	30 (*S*)
42			HCOOH/TEA	67	45 (*S*)
43		**L3**	HCOOH	44	43 (*S*)
44			HCOONa	37	32 (*S*)
45			HCOOH/TEA	4	13 (*S*)
46		**L4**	HCOOH	45	47 (*S*)
47			HCOONa	11	45 (*S*)
48			HCOOH/TEA	78	18 (*S*)

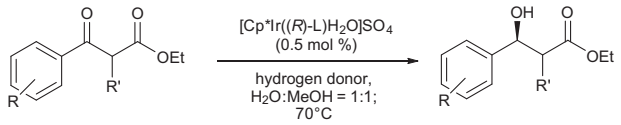
[a] Reactions were carried out at 70 °C using 0.5 mmol of substrate with 0.5 mol% of iridium complex in 2 mL of MeOH/water = 1:1 mixture when HCOOH or HCOONa were used as hydrogen donors, while an HCOOH/TEA azeotropic mixture was used neat.
[b] Conversion and ee were determined by GC after 6 h.

to different substituted β-keto esters. In particular we focused our attention on the reduction of β-lactam precursors. Starting from substrate **9**, we synthesized the corresponding β-amino keto ester **10** and its substituted *p*-OMe and *p*-CF_3 derivatives **11** and **12**. The results are reported in Table 3.

The reduction of ethyl 3-oxo-3-phenylpropanoate **9** proceeded with modest enantiomeric excesses except for complex bearing **L1** in the presence of HCOOH with 73% ee (entry 1). The reactions

carried out with $[Cp^*Ir(H_2O)(\mathbf{L3})]SO_4$ and $[Cp^*Ir(H_2O)(\mathbf{L4})]SO_4$, did not lead to the complete formation of the corresponding alcohols as expected on the basis of the results with the monotosylated CAMPY derivatives. Regarding substrates **10**, **11** and **12** our expectations were confirmed. The presence of an electron donor group at the *para*-position in the ketone moved the keto–enol equilibrium towards the enolic form, thus decreasing the conversion of substrate **11** even if the stereoselectivity remained acceptable. Conversely, when the aromatic moiety was substituted with an electron-withdrawing group, at the *para*-position, complete conversion was observed during the majority of the experiments mirroring the results obtained in the reduction of **10**. For substrates **10** and **12** when the reactions were conducted in the presence of a base (with HCOONa), a variable amount of by-products was detected, which

Table 3
ATH reaction of β-ketoesters



9 R = H; R' = H
10 R = H; R' = -$CH_2NHCOPh$
11 R = *p*-OCH_3; R' = -$CH_2NHCOPh$
12 R = *p*-CF_3; R' = -$CH_2NHCOPh$

9a R = H; R' = H
10a R = H; R' = -$CH_2NHCOPh$
11a R = *p*-OCH_3; R' = -$CH_2NHCOPh$
12a R = *p*-CF_3; R' = -$CH_2NHCOPh$

Entry[a]	Sub.	L	Hydrogen donor	Conv.[b] (%)	ee (%)	de (%)
1	**9**	**L1**	HCOOH	100	73 (*S*)	
2			HCOONa	100	48 (*S*)	
3			HCOOH/TEA	100	36 (*S*)	
4		**L2**	HCOOH	100	19 (*S*)	
5			HCOONa	100	21 (*S*)	
6			HCOOH/TEA	100	18 (*S*)	
7		**L3**	HCOOH	100	47 (*S*)	
8			HCOONa	17	48 (*S*)	
9			HCOOH/TEA	10	49 (*S*)	
10		**L4**	HCOOH	52	27 (*S*)	
11			HCOONa	24	50 (*S*)	
12			HCOOH/TEA	100	0	
13	**10**	**L1**	HCOOH	100	73 (*S*,*S*); 81 (*R*,*S*)	13 *anti*
14			HCOONa	100[c]	68 (*S*,*S*); 80 (*R*,*S*)	25 *anti*
15			HCOOH/TEA	100	42 (*S*,*S*); 51 (*R*,*S*)	0
16		**L2**	HCOOH	57	75 (*S*,*S*); 83 (*R*,*S*)	0
17			HCOONa	100[c]	9 (*S*,*S*); 18 (*R*,*S*)	9 *anti*
18			HCOOH/TEA	100	15 (*S*,*S*); 26 (*R*,*S*)	34 *anti*
19		**L3**	HCOOH	100	78 (*S*,*S*); 80 (*R*,*S*)	0
20			HCOONa	100[c]	20 (*S*,*S*); 42 (*R*,*S*)	10 *anti*
21			HCOOH/TEA	10	23 (*S*,*S*); 50 (*R*,*S*)	0
22		**L4**	HCOOH	29	57 (*S*,*S*); 78 (*R*,*S*)	17 *anti*
23			HCOONa	50	63 (*S*,*S*); 75 (*R*,*S*)	34 *anti*
24			HCOOH/TEA	100	0 (*S*,*S*); 0 (*R*,*S*)	34 *anti*
25	**11**	**L1**	HCOOH	71	81 (*S*,*S*); 32 (*R*,*S*)	37 *anti*
26			HCOONa	92	89 (*S*,*S*); 76 (*R*,*S*)	32 *anti*
27			HCOOH/TEA	40	76 (*S*,*S*); 63 (*R*,*S*)	57 *anti*
28		**L2**	HCOOH	32	86 (*S*,*S*); 69 (*R*,*S*)	32 *anti*
29			HCOONa	48	88 (*S*,*S*); 62 (*R*,*S*)	20 *anti*
30			HCOOH/TEA	79	56 (*S*,*S*); 44 (*R*,*S*)	8 *anti*
31		**L3**	HCOOH	11	96 (*S*,*S*); 78 (*R*,*S*)	23 *anti*
32			HCOONa	13	94 (*S*,*S*); 78 (*R*,*S*)	16 *anti*
33			HCOOH/TEA	13	73 (*S*,*S*); 53 (*R*,*S*)	0 *anti*
34		**L4**	HCOOH	13	67 (*S*,*S*); 52 (*R*,*S*)	4 *anti*
35			HCOONa	14	36 (*S*,*S*); 47 (*R*,*S*)	19 *anti*
36			HCOOH/TEA	72	0 ; 0	29 *anti*
37	**12**	**L1**	HCOOH	100	83 (*S*,*S*); 99 (*R*,*S*)	18 *anti*
38			HCOONa	100[c]	64 (*S*,*S*); 91 (*R*,*S*)	0
39			HCOOH/TEA	100	70 (*S*,*S*); 99 (*R*,*S*)	15 *anti*
40		**L2**	HCOOH	100	92 (*S*,*S*); 99 (*R*,*S*)	20 *anti*
41			HCOONa	100[c]	73 (*S*,*S*); 86 (*R*,*S*)	0
42			HCOOH/TEA	100	86 (*S*,*S*); 99 (*R*,*S*)	13 *anti*
43		**L3**	HCOOH	38	70 (*S*,*S*); 98 (*R*,*S*)	23 *anti*
44			HCOONa	100[c]	70 (*S*,*S*); 25 (*R*,*S*)	25 *anti*
45			HCOOH/TEA	78	46 (*S*,*S*); 67 (*R*,*S*)	33 *anti*
46		**L4**	HCOOH	100	71 (*S*,*S*); 97 (*R*,*S*)	37 *anti*
47			HCOONa	100[c]	40 (*S*,*S*); 33 (*R*,*S*)	59 *anti*
48			HCOOH/TEA	100	69 (*S*,*S*); 93 (*R*,*S*)	56 *anti*

[a] Reactions were carried out at 70 °C using 0.5 mmol of substrate with 0.5 mol % of iridium complex in 2 mL of MeOH/water = 1:1 mixture when HCOOH or HCOONa were used as hydrogen donors, while an HCOOH/TEA azeotropic mixture was used neat.

[b] Conversion, ee and de were determined by HPLC (AD Chiralpak column) after 24 h.

[c] Under these conditions *N*-(3-oxo-3-phenylpropyl)benzamide and its reduction products were observed as in previous work.

were attributable to spontaneous decarboxylation after hydrolysis of the ethyl ester function as observed in the literature.[26]

For both substrates, the best catalytic performances were achieved in favour of the (*R*,*S*)-diastereomer with an ee of up to 99% for **12** (entries 37, 39, 40 and 42). On the contrary, the (*S*,*S*)-diastereomer was predominant for the reduction of substrate **11**. The preferential formation of the couple of diastereomers with an *anti*-configuration for this type of catalysts is noteworthy. In our previous work, only the *syn*-diastereomers were formed by using classical transition metal catalysts in which the source of chirality was an atropoisomeric diphosphine. Finally in all of the reductions of these substrates, an increase in the diastereomeric excess was obtained along with a decrease in stereoselectivity on the prochiral centre.

3. Conclusions

In conclusion a series of efficient iridium catalysts based on CAMPY derivatives has been studied in the reduction of different types of aryl ketones. A wide variety of behaviours was seen by changing the reaction conditions. In particular the presence of HCOOH as a hydrogen donor played an important role with regard to the stereoselectivity of the catalysts. In the case of ligands **L3** and **L4**, by changing the primary amino group into a secondary one, the catalytic performance was reduced. Finally ATH reactions on β-lactam precursors led to very high ee. Further investigations are currently underway with the aim of increasing the de without losing the excellent stereoselectivity obtained.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or D_2O on Bruker DRX Avance 300 MHz equipped with a non-reverse probe. Chemical shifts (in ppm) are referenced to residual solvent proton/carbon peak. FTIR spectra were collected by using a Perkin Elmer (MA, USA) FTIR Spectrometer 'Spectrum One' in the spectroscopic region between 4000 and 450 cm^{-1} and analysed by transmittance techniques with 32 scansions and 4 cm^{-1} resolution. Polarimetry analyses were carried out on Perkin Elmer 343 Plus equipped with Na/Hal lamp. MS analyses were performed by using a Thermo Finnigan (MA, USA) LCQ Advantage system MS spectrometer with an electronspray ionization source and an 'Ion Trap' mass analyser. The MS spectra were obtained by direct infusion of a sample solution in MeOH under ESI positive ionization. Catalytic reactions were monitored by gas chromatography analysis using a chiral stationary phase column (MEGA DMT β, 25 m, internal diameter 0.25 mm) or by HPLC analysis with Merck-Hitachi L-7100 equipped with Detector UV6000LP and a chiral column (OD-H Chiralcel or AD Chiralpak).

Commercially reagent grade solvents were dried according to standard procedures and freshly distilled under nitrogen before use. Unless otherwise stated, materials were obtained from commercial sources and used without further purification; enantiomerically pure (*R*)-(−)- and (*S*)-(+)-8-amino-5,6,7,8-tetrahydroquinolines (CAMPY) were obtained as reported in the literature;[6] *rac*-2-methyl-5,6,7,8-tetrahydroquinolin-8-amines (Me-CAMPY) were synthesized according to literature procedures.[27,28]

4.2. Synthesis of the ligands

4.2.1. (*R*)-2-Methyl-5,6,7,8-tetrahydroquinolin-8-amine ((*R*)-Me-CAMPY) L2

Rac-Me-CAMPY (486 mg, 3 mmol) was dissolved in EtOH (30 mL), then a solution of (*R*,*R*)-L-(+)-tartaric acid (225 mg, 1.5 mmol) in EtOH (20 mL) was added. The suspension was heated until the disappearance of the solid salt, cooled to room temperature and complete crystallization was obtained at −18 °C. Yield 273 mg of (*R*)-(−)-Me CAMPY/(*R*,*R*)-(+)-L-tartrate (0.87 mmol, 58% yield); ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.64–1.77 (m, 2H), 2.04–2.14 (m, 2H), 2.46 (s, 3H), 2.60–2.77 (m, 2H), 3.93 (t, J = 6.3 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 20.06, 24.00, 28.63, 31.89, 50.91, 121.64, 128.60, 137.77, 155.77, 157.75 ppm. FTIR ν = 3493, 3456, 3320, 2973, 2916, 1725, 1627, 1602, 1485, 1305, 1264, 1135, 1107, 1077, 1067, 680 cm^{-1} Elemental analysis of $C_{14}H_0N_2O_6$ calcd C 53.84 H 6.45 N 8.97; found C 53.85 H 6.66 N 8.82; MS (ESI) of $C_{10}H_{14}N_2$ (*m*/*z*): calcd 162.1, found 163.1 $[M+1]^+$. The enantiomeric excess of Me-CAMPY was evaluated using the corresponding acetylated derivatives by chiral GC analysis (conditions: 140 °C 10 min, 2 °C/min to 165 °C).

Crystal structure of $PtCl_4$((*S*)-(+)-Me-CAMPY)·H_2O: $C_{10}H_{18}Cl_4N_2$ OPt, M = 519.15, monoclinic, a = 12.6157(5), b = 8.2091(3), c = 15.4482(6) Å, β = 90.4678(5), U = 1599.8(1) Å^3, T = 294(2) K, space group *C*2 (No. 5), Z = 4, μ = (Mo-Kα) 9.427 mm^{-1}. 8475 reflections (4809 unique; Rint = 0.019) were collected at room temperature in the range 5.28° < 2θ < 62.92°, employing a 0.25 × 0.20 × 0.15 mm crystal mounted on a Bruker APEX II CCD diffractometer and using graphite-monochromatized Mo-Kα radiation (λ = 0.71073 Å). Datasets were corrected for Lorentz polarization effects and for absorption (SADABS).[29] The structure was resolved by direct methods (SIR-97)[30] and was completed by iterative cycles of full-matrix least squares refinement on Fo^2 and ΔF synthesis using the SHELXL-97[31] program (WinGX suite).[32] Hydrogen atoms located on the ΔF maps, were allowed to ride on the carbon atoms for the phenanthroline ligand and on N2, whereas the position of those bonded to the N1 atom and to the water molecule were refined without constraint. The presence of the anomalous X-ray scatterer platinum atom allowed us to unambiguously determine the absolute configuration, the Flack parameter was 0.017(8) which confirmed that the absolute structure given by the structure refinement was correct. Final R1 [wR2] values are 0.0199 [0.0584] on $I > 2\sigma(I)$ [all data].

CCDC-989123 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.

4.2.2. (*R*)-*N*-Methyl-5,6,7,8-tetrahydroquinolin-8-amine ((*R*)-NH Me-CAMPY) L3

(*R*)-*N*-Acetyl-5,6,7,8-tetrahydroquinolin-8-amine (141 mg, 0.74 mmol) and NaH (24 mg, 1 mmol) in anhydrous THF (5 mL) were refluxed for 1 h, cooled to 0 °C and CH_3I (142 mg, 1 mmol) was added dropwise. The reaction mixture was stirred at room temperature and monitored by TLC (CH_2Cl_2/MeOH 9:1). The solution was quenched with water and the aqueous layers were extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4. The crude product was purified by Kugelrohr distillation to give *N*-methyl-*N*-(5,6,7,8-tetrahydroquinolin-8-yl)acetamide (GC: *iso* 140 °C 10 min, 1 °C/min to 160 °C). The corresponding *N*-acetyl derivate was hydrolysed by refluxing in HCl 6 M (3 mL). The solution was cooled to room temperature, quenched with Na_2CO_3, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude oil was dissolved in hexane (10 mL) and filtered on a Celite pad to give the product as a pale yellow oil (100 mg, 0.62 mmol, 82% yield). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.69–1.81 (m, 2H), 1.93–2.01 (m, 1H), 2.10–2.18 (m, 1H), 2.53 (s, 3H), 2.50–2.78 (m, 3H), 3.67 (t, J = 5.2 Hz, 1H), 7.05 (dd, J = 7.7, 4.7 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 8.40 (d, J = 4.6 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 19.55, 27.82, 28.85, 34.26, 59.56, 121.86, 132.46, 136.89, 146.86, 157,23 ppm. FTIR ν = 3333.9, 3049.6, 2926.7, 2855.2, 2784.1, 1648.1, 1575.3, 1444.5, 1428.1, 1238.7, 1104.1, 782.2 cm^{-1}. MS (ESI) of $C_{10}H_{14}N_2$ (*m*/*z*): calcd 162.1, found 163.2 $[M+1]^+$. $[\alpha]_D^{20}$ = −20.8 (c 0.5, CH_2Cl_2).

4.2.3. (*R*)-(−)-*N*-2-Dimethyl-5,6,7,8-tetrahydroquinolin-8-amine ((*R*)-NHMe-Me-CAMPY) L4

To a solution of (*R*)-Me-CAMPY **L2** (121 mg, 0.75 mmol) in THF (5 mL), aqueous K_2CO_3 (1.5 mL, 1 M) and ethyl chloroformate (0.11 mL, 1.1 mmol) were added at 0 °C. The solution was warmed to room temperature and stirred for 2.5 h. The organic phase was dried and the solvent was removed in vacuo. The crude oil obtained was dissolved in anhydrous THF (5 mL) and added dropwise into a suspension of $LiAlH_4$ (46 mg, 1.2 mmol) in anhydrous THF (5 mL) at 0 °C, stirred at room temperature for 1 h and refluxed for 2 h. The reaction mixture was quenched by adding THF, aqueous KOH and extracted with diethyl ether (3 × 10 mL). The crude product was purified by Kugelrohr distillation to obtain a pale yellow oil (99 mg, 0.56 mmol; 56% yield). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.56–1.74 (m, 1H), 1.81–1.95 (m, 2H), 2.08 (s, 3H), 2.52 (s, 3H), 2.55–2.68 (m, 1H), 2.77 (t, J = 6.5 Hz, 2H), 4.76 (dd, J = 9.6, 4.9 Hz, 1H), 6.70 (br, 1H), 7.00 (d, J = 7.9 Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 20.29, 24.13, 24.35, 28.14, 29.56, 51.64, 122.49, 130.15, 137.96, 154.62, 155.75 ppm. FTIR ν = 3330, 2940, 2860, 2785, 1707, 1596, 1574, 1471, 1444, 1258, 1147, 1119, 1105, 1035, 850, 813, 783 cm^{-1}. MS (ESI) of $C_{11}H_{16}N_2$ (m/z): calcd 176.1, found 177.2 [M+1]$^+$. $[\alpha]_D^{20}$ = −52.5 (c 1, CH_2Cl_2).

4.3. General procedure for the synthesis of [Cp*Ir(H$_2$O)(L)]SO$_4$

The complexes were prepared according to a literature procedure.[18]

4.3.1. [Cp*Ir(H$_2$O)(L1)]SO$_4$

^{1}H NMR (D_2O, 300 MHz, 25 °C): δ = 1.63 (m, 2H), 1.72 (s, 15H), 2.04–2.06 (m, 1H), 2.45–2.48 (m, 1H), 2.85–2.99 (m, 2 H), 4.02–4.13 (m, 1H), 7.58 (dd, J = 5.9 Hz,1 H), 7.80 (d, J = 7.9 Hz,1 H), 8.70 (d, J = 5.5 Hz, 1H) ppm; ^{13}C NMR (D_2O, 75 MHz, 25 °C): δ = 10.24, 20.11, 29.39, 37.57, 51.79, 122.34, 132.17, 137.28, 147.39, 155.12 ppm. MS (ESI) of $C_{17}H_{27}IrN_2$ [M−SO$_4$−H$_2$O−H] (m/z): calcd 475.7, found 475.4.

4.3.2. [Cp*Ir(H$_2$O)(L2)]SO$_4$

^{1}H NMR (D_2O, 300 MHz, 25 °C): δ = 1.52 (s, 15H), 1.62–1.66 (m, 2H), 1.74–1.85 (m, 2H), 2.28–2.32 (m, 2H), 2.70 (s, 3H), 4.58–4.66 (m, 1H), 7.35 (d, J = 7.7 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H) ppm; ^{13}C NMR (D_2O, 75 MHz, 25 °C): δ = 8.76, 20.12, 26.61, 26.83, 31.74, 62.37, 87.85, 126.62, 133.89, 141.28, 157.86, 158.02 ppm. MS (ESI) of $C_{20}H_{29}IrN_2$ [M−SO$_4$−H$_2$O−H] (m/z): calcd 489.7, found 489.6.

4.3.3. [Cp*Ir(H$_2$O)(L3)]SO$_4$

^{1}H NMR (D_2O, 300 MHz, 25 °C): δ = 1.54 (s, 15H), 1.66–1.69 (m, 2H), 1.75–1.78 (m, 2H), 2.54–2.69 (m, 2H), 3.10 (d, J = 6.1 Hz, 3H), 3.93–4.2 (m, 1H), 7.38 (dd, J = 7.7 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 8.51 (d, J = 5.5 Hz, 1H) ppm; ^{13}C NMR (D_2O, 75 MHz, 25 °C): δ = 8.46, 14.07, 22.35, 23.38, 28.79, 54.09, 116.39, 126.99, 131.42, 141.39, 151.76 ppm. MS (ESI) of $C_{20}H_{29}IrN_2$ [M−SO$_4$−H$_2$O−H] (m/z): calcd 489.7, found 489.5.

4.3.4. [Cp*Ir(H$_2$O)(L4)]SO$_4$

^{1}H NMR (D_2O, 300 MHz, 25 °C): δ = 1.68 (s, 15H), 1.94–1.97 (m, 2H), 2.48–2.50 (m, 2H), 2.62–2.65 (m, 2H), 2.70 (s, 3H), 3.14 (d, J = 5.9 Hz, 3H), 3.99–4.04 (m, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H) ppm; ^{13}C NMR (D_2O, 75 MHz, 25 °C): δ = 8.81, 19.78, 26.58, 38.77, 69.15, 88.43, 126.87, 134.00, 141.43, 156.67, 158.30 ppm. MS (ESI) of $C_{21}H_{31}IrN_2$ [M−SO$_4$−H$_2$O−H] (m/z): calcd 503.7, found 503.4.

4.4. Synthesis of the substrates

4.4.1. Enzymatic synthesis of *rac*-2-benzoylbutanenitrile 4

Commercial Baker's yeast (50 g/L) was suspended in a phosphate buffer (200 mL, 0.1 M, pH 7) containing 50 g/L of glucose and 5 g/L of the substrate **1** was added. The biotransformation system was shaken with a mechanical stirrer at 28 °C. When total conversion was achieved, the cells were separated by centrifugation. Both the aqueous phases and the cell mixture were extracted with diethyl ether (3 × 50 mL), dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by flash chromatography (CH_2Cl_2/hexane/ethyl acetate = 4:1:1) to give 860 mg of **4** (86% yield). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.16 (t, J = 7.7 Hz, 3 H), 2.02–2.15 (m, 2H), 4.30 (dd, J = 6.2, 4.3 Hz, 1H), 7.49–7.56 (m, 2H), 7.65 (d, J = 7.6 Hz, 1H) 7.95 (d, J = 6.7 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 11.71, 23.77, 41.69, 117.41, 128.92–134.63, 170.91, 190.97 ppm. FTIR ν = 3467, 2975, 2936, 2249, 1694, 1597, 1449, 1265, 1233, 1208, 1000, 696 cm^{-1}. MS (ESI) of $C_{11}H_{11}NO$ (m/z): calcd 173.2, found 196.1 [M+Na$^+$].

Compound ***4a****:* ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.09 (t, J = 7.7 Hz, 3H, *anti*), δ = 1.17 (t, J = 7.6 Hz, 3H, *syn*), 1.51–1.69 (m, 2H), 2.76–2.83 (m, 2H, *anti*), 2.87–2.95 (m, 2H, *syn*), 4.79 (d, J = 6.2 Hz, 1H, *anti*), 4.83 (d, J = 6.6 Hz, 1H, *syn*), 7.33–7.56 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 9.84 (*syn*), 10.38 (*anti*), 24.86 (*anti*), 25.87 (*syn*), 76.86 (*syn*), 77.46 (*anti*), 127.04, 128.05 (*anti*), 128.22 (*syn*), 128.55 (*anti*), 128.69 (*syn*), 140.61 (*anti*) 141.42 (*syn*) ppm. FTIR ν = 3390, 2964, 1494, 1453, 160, 1103, 1038, 702 cm^{-1}. MS (ESI) of $C_{11}H_{11}NO$ (m/z): calcd 175.1, found 198.3 [M+Na$^+$]. Yield was evaluated by ^{1}H NMR analysis. HPLC data: OD-H Chiralcel, eluent: hexane: 2-propanol = 95:5, flow = 0.8 mL/min, λ = 216 nm. rt: (*R*, *S*) = 25.6 min, (*S*, *S*) = 26.5 min, (*S*, *R*) = 34.6 min, (*R*, *R*) = 36.0 min.

4.4.2. Ethyl-2-(benzamidomethyl)-3-oxo-phenylpropanoate 10

The substrate was prepared according to a literature procedure.[26] ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.18 (t, J = 6.9 Hz, 3H), 3.93–3.97 (m, 2H), 4.09–4.16 (m, 2H), 4.19 (q, J = 6.9 Hz, 2H), 4.87 (dd, J = 5.5, 3.7 Hz, 1H), 6.73 (br, 1H), 7.42–7.62 (m, 2H), 7.71 (dd, J = 8.0, 1.5 Hz, 4H), 8.10 (dd, J = 5.1, 2.2 Hz, 4H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 14.1, 39.2, 53.7, 62.03, 127.1–135.9, 167.9 (isomer), 169.2 (isomer), 194.8 ppm. FTIR ν = 3334, 1961, 1734, 1679, 1637, 1534, 1311, 1250, 1211, 1198, 1078, 694 cm^{-1}. MS (ESI) of $C_{19}H_{19}NO_4$ (m/z): calcd 325.1, found 348.5 [M+Na$^+$].

Compound ***10a****:* ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.01 (t, J = 7.0 Hz, 3H), 2.93–3.01 (m, 1H, *syn*), 3.15–3.24 (m, 1H, *anti*), 3.61–3.69 (m, 2H), 3.98 (q, J = 7.0 Hz, 2H), 4.12–4.19 (m, 2H), 4.95 (d, J = 7.3 Hz, 1H, *anti*), 4.96 (d, J = 7.3 Hz, 1H, *syn*), 6.72 (br, 1H), 7.29–7.53 (m, 4H), 7.77 (dd, J = 8.0, 1.5 Hz, 4H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 14.0, 37.9 (*syn*), 38.0 (*anti*), 53.0, 61.1, 72.6, 126.4–132.0, 164.31, 173.5 ppm. FTIR ν = 3364, 1948, 1724, 1649, 1607, 1535, 1301, 1246, 1111, 828 cm^{-1}. MS (ESI) of $C_{19}H_{21}NO_4$ (m/z): calcd 327.1, found 350.4 [M+Na$^+$]. (2*R*,3*R*) $[\alpha]_D^{20}$ = +33.2 (c 0.15, $CHCl_3$); (2*S*,3*S*) $[\alpha]_D^{20}$ = −11.0 (c 0.18, $CHCl_3$); (2*R*,3*S*) $[\alpha]_D^{20}$ = −11.3 (c 0.12, $CHCl_3$); Yield was evaluated by ^{1}H NMR analysis. HPLC data: AD Chiralpak, eluent hexane/2-propanol = 90:10, flow = 0.6 mL/min, λ = 230 nm. rt: (*R*, *R*) = 35.1 min, (*S*, *S*) = 37.1 min, (*S*, *R*) = 49.8 min, (*R*, *S*) = 68.8 min.

4.4.3. Ethyl 2-(benzamidomethyl)-3-(4-methoxyphenyl)-3-oxo-propanoate 11

The substrate was prepared according to the literature by starting from ethyl 3-(4-methoxyphenyl)-3-oxopropanoate.[26] ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ = 1.22 (t, J = 7.3 Hz, 3H); 3.78 (s, 3H); 3.86–4.93 (m, 1H); 4.01–4.13 (m, 1H); 4.15 (q, J = 5.9 Hz, 2H); 4.88 (dd, J = 5.9, 3.8 Hz, 1H); 6.88 (d, J = 8.8 Hz, 2H); 7.37–7.67

(m, 3H) 7.74 (d, J = 8.4 Hz, 2H); 8.09 (d, J = 8.8 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 13.92, 39.14, 53.23, 55.77, 62.19, 114.04, 127.17, 128.24, 128.78, 131.61, 134.25, 164.03, 167.96, 186.91, 192.70 ppm. FTIR ν = 3401, 2979, 1731, 1665, 1602, 1574, 1533, 1261, 1205, 1184, 1016, 838, 714 cm^{-1}. MS (ESI) of $C_{20}H_{21}NO_5$ (m/z): calcd 355.1, found 378.2 [M+Na$^+$].

Compound **11a**: ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 0.96 (t, J = 7.3 Hz, 3H, *syn*), 1.21 (t, J = 6.9 Hz, 3H, *anti*); 2.94–3.02 (m, 1H, *syn*); 3.10–3.24 (m, 1H, *anti*); 3.54–3.68 (m, 2H); 3.73 (s, 3H); 3.99 (q, J = 7.0 Hz, 2H, *syn*); 4.16 (q, J = 7.3 Hz, 2H, *anti*); 4.88 (dd, J = 6.8, 3.9 Hz, 1H, *syn*); 4.95 (dd, J = 6.9, 3.9 Hz, 1H, *anti*); 6.55–6.68 (br, NH); 6.88 (d, 2H); 7.43 (d, J = 2.7 Hz, 2H); 7.47–7.59 (m, 3H); 7.79 (d, J = 2.5 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 14.36, 39.55, 53.67, 56.23, 62.14, 71.63, 114.61, 128.03, 128.73, 129.25, 132.32, 134.60, 164.75, 168.03, 170.00 ppm. FTIR ν = 3371, 2940, 1724, 1635, 1544, 1513, 1308, 1245, 1114, 836 cm^{-1}. MS (ESI) of $C_{20}H_{23}NO_5$ (m/z): calcd 357.2, found 380.3 [M+Na$^+$]. Yield was evaluated by ^{1}H NMR analysis. HPLC data: AD Chiralpak, eluent: hexane/2-propanol = 80:20, flow = 1.0 mL/min, λ = 230 nm. rt: (*S*, *S*) = 9.7 min, (*R*, *R*) = 10.7 min, (*S*, *R*) = 14.9 min, (*R*, *S*) = 21.7 min.

4.4.4. Ethyl 2-(benzamidomethyl)-3-oxo-3-(4-(trifluoromethyl)-phenyl)propanoate 12

The substrate was prepared according to the literature by starting from ethyl 2-(benzamidomethyl)-4,4,4-trifluoro-3-oxobutanoate.[26] ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.17 (t, J = 7.0 Hz, 3H); 3.87–4.15 (m, 1H); 4.16–4.22 (q, J = 5.9 Hz, 2H); 4.91 (dd, J = 5.9, 3.7 Hz, 1H); 6.92–6.98 (br, NH), 7.35–7.54 (m, 3H), 7.71–7.77 (m, 4H); 8.20 (d, J = 8.0 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 14.17, 39.15, 53.50, 62.01, 115.52, 120.94, 126.06, 126.37, 127.13, 128.80, 129.41, 131.94, 134.09, 134.91, 135.59, 136.33, 138.70, 167.87, 168.81, 193.79 ppm. FTIR ν = 3258, 2986, 1740, 1730, 1633, 1542, 1325, 1293, 1192, 1166, 1129, 1112, 1067, 1014, 710, 696 cm^{-1}. MS (ESI) of $C_{20}H_{18}F_3NO_4$ (m/z): calcd 393.1, found 416.1 [M+Na$^+$].

Compound ***12a****:* ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 0.87 (t, J = 7.0 Hz, 3H, *syn*); 0.99 (t, J = 7.3 Hz, 3H, *anti*); 2.94–2.99 (m, 1H, *syn*); 3.17–3.27 (m, 1H, *anti*); 3.55–3.87 (m, 1H); 3.96 (q, J = 7.0 Hz, 2H, *syn*); 4.14 (q, J = 7.3 Hz, 2H, *anti*); 4.17–4.27 (m, 1H), 4.94 (d, J = 8.1 Hz, 1H, *syn*); 5.09 (d, J = 5.1 Hz, 1H, *anti*); 6.77–6.79 (br, NH, *anti*), 6.93–6.96 (br, NH, *syn*), 7.36–7.68 (m, 7H); 7.70 (d, J = 6.9 Hz, 2H, *anti*); 7.73 (d, J = 5.4 Hz, 2H, *syn*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 13.97, 37.82, 53.18, 61.39, 71.93, 121.47, 125.41, 126.96, 127.25, 127.44, 128.64, 129.98, 130.63, 131.32, 131.89, 133.64, 145.28, 168.87, 173.09 ppm. FTIR ν = 3368, 2980, 2937, 1728, 1644, 1536, 1514, 1304, 1248, 1112, 1033, 834 cm^{-1}. MS (ESI) of $C_{20}H_{20}F_3NO_4$ (m/z): calcd 395.1 found 418.2 [M+Na$^+$]. Yield was evaluated by ^{1}H NMR analysis. HPLC data: AD Chiralpak, eluent: hexane/2-propanol = 90:10, flow = 0.8 mL/min, λ = 230 nm. rt: (*S*, *S*) = 17.3 min, (*R*, *R*) = 18.3 min, (*R*, *S*) = 29.9 min, (*S*, *R*) = 31.8 min.

4.5. General procedure for the asymmetric transfer hydrogenation (ATH)

4.5.1. Method A

The ATH procedure when formic acid or sodium formate was used as the hydrogen donor. To a solution of the substrate (0.5 mmol) in a 1:1 mixture methanol and water (2 mL), [Cp*Ir(H_2O)(**L**)]SO_4 (0.0025 mmol) and hydrogen donor (2.5 mmol, 5 equiv) were added. The reaction mixture was stirred at 70 °C for a fixed time (3 h for 2-cyanoacetophenones, 6 h for acetophenones and 24 h for β-ketoesters). The reaction mixture was quenched with brine (4 mL) and extracted with ethyl acetate (2 × 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo.

4.5.2. Method B

The ATH procedure when the HCOOH/TEA azeotropic mixture (5:2) was used as the hydrogen donor. To a solution of the substrate (0.5 mmol) in 2 mL of HCOOH/TEA azeotropic mixture (5:2), [Cp*Ir(H_2O)(**L**)]SO_4 (0.0025 mmol) was added. The reaction mixture was stirred at 70 °C for a fixed time (3 h for 2-cyanoacetophenones, 6 h for acetophenones and 24 h for β-ketoesters). The reaction mixture was quenched with 5% $NaHCO_3$ solution (4 mL) and extracted with ethyl acetate (2 × 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo.

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