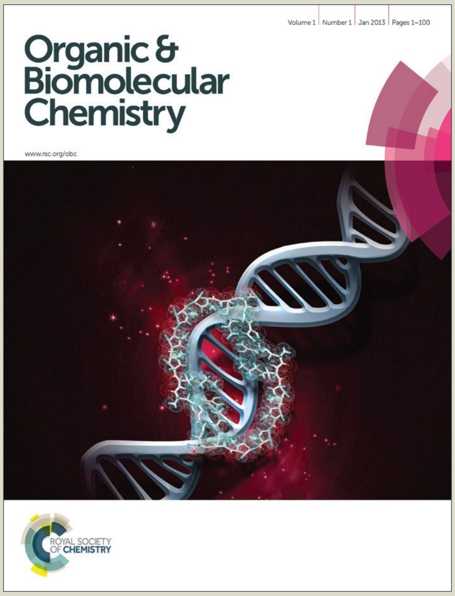
Organic & Biomolecular Chemistry

Accepted Manuscript



Volume 1 | Number 1 | Jan 2013 | Pages 1–100

Organic & Biomolecular Chemistry

www.rsc.org/obc

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Journal Name RSCPublishing

ARTICLE

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

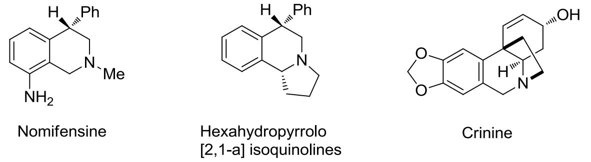
Enantioselective Synthesis of 4-Substituted Tetrahydroisoquinolines *via* Palladium-Catalyzed Intramolecular Friedel-Crafts Type Allylic Alkylation of Phenols

Zheng-Le Zhao,[a,b] Qing-Long Xu,[b] Qing Gu,[b] Xin-Yan Wu[a,*] and Shu-Li You[a,b,*]

Palladium-catalyzed asymmetric intramolecular Friedel-Crafts type allylic alkylation reaction of phenols has been developed under mild conditions. In the presence of $Pd_2(dba)_3$ with (1*R*, 2*R*)-DACH-phenyl Trost ligand (**L2**) in toluene at 50 °C, the reaction provides various C4 substituted tetrahydroisoquinolines with moderate to excellent yields, regioselectivity and enantioselectivity.

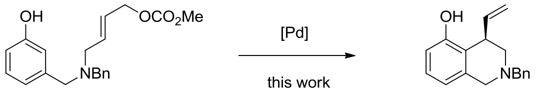
Introduction

Tetrahydroisoquinolines are important scaffolds widely distributed in natural alkaloids and biologically active compounds, and are also commonly used as key intermediates in organic synthesis and medicinal chemistry (Scheme 1).[1] Therefore, considerable efforts have been devoted to the synthesis of chiral tetrahydroisoquinolines (THIQs) and their derivatives. In this regard, many elegant works have been reported mainly focusing on the asymmetric synthesis of 1-substituted tetrahydroisoquinolines by Pictet-Spengler reaction, hydrogenation of isoquinoline, cross dehydrogenative coupling and nucleophilic addition to C=N bond of isoquinoline.[2] However, limited success on the synthesis of chiral 4-substituted tetrahydroisoquinolines was achieved despite of their unique structure and diverse biological properties.[3] Accordingly, the development of a general and straightforward synthetic method towards 4-substituted THIQs is in high demand.



Scheme 1. Selected pharmaceuticals and natural product containing 4-substituted THIQs

Transition-metal-catalyzed allylic substitution reactions[4] of phenols have been widely investigated in the past two decades. However, in most cases the reactions proceed as *O*-allylation.[5-8] There are only limited examples of *C*-allylation in which phenols react as *C*-nucleophiles. In addition, highly enantioselective Friedel-Crafts type transition-metal-catalyzed allylic allylation reactions remain rare and poor regioselectivity is often observed.[9-11] Recently, we reported an Ir-catalyzed intramolecular asymmetric Friedel-Crafts type allylic alkylation reaction of phenols by tethering the allylic carbonate at the *meta*-position, providing a facile access to tetrahydroisoquinolines with a C4 stereogenic center in excellent yields and ee.[12] About the same time, an elegant report on asymmetric intramolecular Friedel-Crafts allylic alkylation of phenols under Pd catalysis has been reported by Hamada and coworkers.[9] Inspired by their work, we explored the asymmetric synthesis of THIQs by Pd catalysis. In this paper, we report such a Pd-catalyzed asymmetric intramolecular allylic alkylation reaction of phenols for the synthesis of highly enantioenriched THIQs. (Scheme 2).

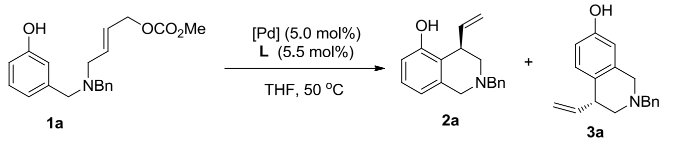


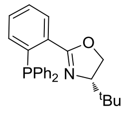
Scheme 2. Pd-catalyzed asymmetric Friedel-Crafts type allylic alkylation of phenols.

Results and discussion

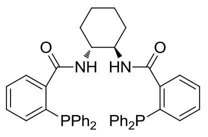
At the outset of our study, we chose the allyl carbonate tethered phenol **1a** as a model substrate, $Pd(PPh_3)_4$ (5 mol%) as the catalyst and THF as the solvent. To our delight, our first attempt of this reaction at 50 °C gave the allylic alkylation product **2a** and **3a** in 72% combined yield (Table 1, entry 1). Encouraged by this preliminary result, we screened several readily available chiral ligands (**L1**-**L5**) together with $[Pd(C_3H_5)Cl]_2$. The results are summarized in Table 1. (1*R*, 2*R*)-DACH-phenyl Trost ligand (**L2**) proved to be the most efficient ligand, affording product **2a** as a single regioisomer in 85% yield and 65% ee (Table 1, entry 3). The significant decrease of the enantioselectivity and yields with ligands **L4** and **L5** indicated that the steric effect of the chiral ligands plays a critical role for the reaction outcome. It is remarkable that almost no allylic alkylation product **3a** at the *para*-position was found. When the palladium precursor was switched from $[Pd(C_3H_5)Cl]_2$ to $Pd_2(dba)_3$ with ligand **L2**, product **2a** was obtained with significantly improved enantiomeric excess (67% yield, 88% ee) (Table 1, entry 7).

Table 1. Screening different ligands and palladium precursors[a]

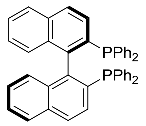




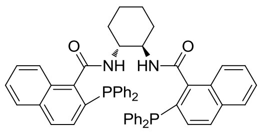
L1: (*S*)-^{i}Pr-PHOX



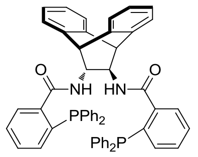
L2: (1*R*, 2*R*)-DACH-phenyl Trost ligand



L3: (*R*)-BINAP



L4: (1*R*, 2*R*)-DACH-naphthyl Trost ligand



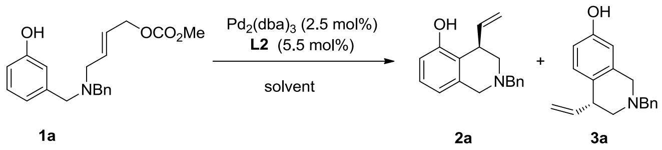
L5: (1*R*, 2*R*)-ANDEN-phenyl Trost ligand

Entry	[Pd]	L	Time (h)	2a/3a[b]	Yield (%)[c]	Ee (%)[d]
1	$Pd(PPh_3)_4$	-	16	2/3	28/44	0
2	$[Pd(C_3H_5)Cl]_2$	**L1**	16	-	trace	-
3	$[Pd(C_3H_5)Cl]_2$	**L2**	1	**2a**	85	65
4	$[Pd(C_3H_5)Cl]_2$	**L3**	5	3/5	30/50	41
5	$[Pd(C_3H_5)Cl]_2$	**L4**	45	-	trace	-
6	$[Pd(C_3H_5)Cl]_2$	**L5**	45	-	trace	-
7	$Pd_2(dba)_3$	**L2**	1	**2a**	67	88
8	$Pd_2(dba)_3$	**L4**	1	4/1	49	14
9	$Pd_2(dba)_3$	**L5**	1	5/1	68	41

[a] Reaction conditions: [Pd] (5 mol%), **L** (5.5 mol%), **1a** (0.3 mmol) in THF (2 mL) at 50 °C. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Isolated yields of **2a** and **3a**. [d] Determined by HPLC analysis.

With the optimized ligand (**L2**) and palladium precursor $[Pd_2(dba)_3]$ in hand, we further examined the solvent effect. The results are summarized in Table 2. Various solvents such as THF, Et_2O, DCM and 1,4-dioxane could be tolerated in the reaction to afford the desired product **2a** in moderate to good yields and good to excellent enantioselectivity except CH_3CN, in which only trace amount of product was observed. The reaction in toluene gave the best result (73% yield, 92% *ee*, Table 2, entry 6). Varying other reaction parameters such as temperature (Table 2, entries 7-9) and substrate concentration (Table 2, entries 10-11) gave no improvement in terms of yield and ee value of the product.

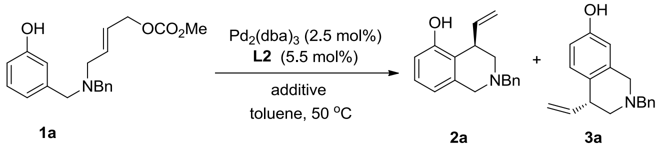
Table 2. Screening solvents, temperatures and substrate concentrations[a]



Entry	Solvent	T (°C)	Time (h)	2a/3a[b]	Yield (%)[c]	Ee (%)[d]
1	THF	50	1	**2a**	67	88
2	Et_2O	reflux	6	**2a**	35	90
3	DCM	reflux	0.5	10/1	57	82
4	1,4-dioxane	50	1	25/1	43	79
5	CH_3CN	50	1	-	trace	-
6	toluene	50	0.25	**2a**	73	92
7	toluene	rt	1.5	**2a**	52	91
8	toluene	0	15	**2a**	42	88
9	toluene	80	0.1	**2a**	67	86
10[e]	toluene	50	0.25	**2a**	70	92
11[f]	toluene	50	0.25	**2a**	69	91

[a] Reaction conditions: $Pd_2(dba)_3$ (2.5 mol%), **L2** (5.5 mol%), **1a** (0.3 mmol) in solvent (2 mL) at 50 °C. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Isolated yield of **2a.** [d] Determined by HPLC analysis. [e] 3 mL toluene was used. [f] 6 mL toluene was used.

Table 3. Screen of the different bases and additives[a]



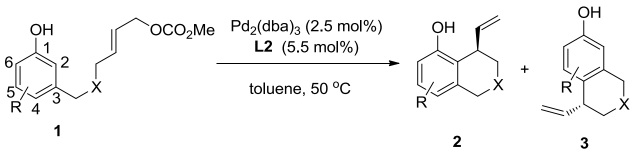
Entry	Additive	Time (h)	2a/3a[b]	Yield (%)[c]	Ee (%)[d]
1	none	0.25	**2a**	73	92
2	K_3PO_4	50	**2a**	7	85
3	Cs_2CO_3	50	**2a**	5	89
4	DMAP	24	-	NR	-
5	DBU	0.25	**2a**	38	75
6	Et_3N	0.25	**2a**	67	90
7	4Å MS	20	**2a**	64	87
8	5Å MS	0.25	**2a**	70	90

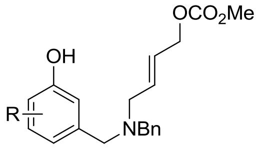
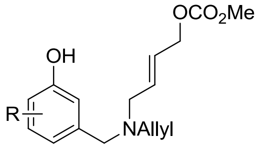
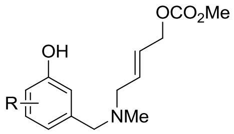
[a] Reaction conditions: $Pd_2(dba)_3$ (2.5mol%), **L2** (5.5mol%), **1a** (0.3 mmol), MS (150 mg), base (200 mol%) in toluene (2 mL) at 50 °C. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Isolated yield of **2a.** [d] Determined by HPLC analysis.

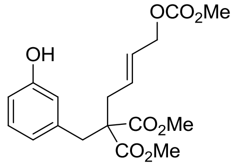
Under the above conditions (Table 2, entry 6), several bases and additives were further evaluated. The results are summarized in Table 3. These results indicated that external base is not necessary in this allylic alkylation reaction (Table 3, entries 1-6). Moreover, the addition of molecular sieves did not give better results (Table 3, entries7 and 8). Thus the optimized conditions were obtained as the following: 2.5 mol% $Pd_2(dba)_3$, 5.5 mol% **L2** in 2 mL toluene at 50 ^{o}C.

Under the optimized reaction conditions, various substrates were tested to examine the scope of the reaction. The results are summarized in Table 4. In general, all substrates varying substituents on the phenol ring and benzyl group on the linked nitrogen atom proceeded well to deliver the Friedel-Crafts alkylation products in moderate to excellent enantioselectivity. When electron-donating substituent was introduced on the phenol ring, a single isomer of **2** was exclusively obtained with good to excellent yields and ee values (Table 4, entry 3, 4-Br, 6-OMe, 80% yield, 90% ee; entry 6, 5-OH, 93% yield, 66% ee; entry7, 5-OH, 6-OMe, 86% yield, 72% ee). For the substrate bearing 6-OMe group, the alkylation product was obtained in 83% yield with 2.6/1 regioselectivity favouring the *ortho* alkylated product **2b** (Table 4, entry 2). With a strong electron-withdrawing group (6-NO_2), an appreciable decreased yield was obtained but with excellent enantioselectivity (Table 4, entry 5, 30% yield, 92% ee). It was noteworthy that when a substituent was introduced at the 2-position of the phenol, the allylic alkylation reaction proceeded smoothly to afford a single regioisomer by alkylation at the *para*-position but with a sharply decreased ee value (Table 4, entry 8, 20% ee; entry 9, 3% ee). Interestingly, protecting groups such as allyl and methyl on the linked nitrogen atom could also afford alkylation products in excellent enantioselectivity (Table 4, entries 10-14, 38-91% yields, 84-99% ee). The carbon-tethered phenol was also a suitable substrate in this reaction, affording the corresponding product in 50% yield and 38% ee (Table 4, entry 15). The absolute configuration of the product was assigned by comparison with the specific rotation value in our previous work.[3g]

Table 4. The substrates scope[a]



Entry		**1**, R	Time (h)	Yield (%)[b]	**2**/**3**[c]	Ee (%)[d]
1		**1a**, H	0.25	73	**2a**	92
2		**1b**, 6-MeO	0.25	83	2.6/1	85/15[f]
3		**1c**, 4-Br, 6-MeO	0.25	80	**2c**	90
4		**1d**, 4-Br	0.25	61	**2d**	91
5		**1e**, 6-NO_2	4	30	**2e**	92
6[e]		**1f**, 5-OH	3	93	**2f**	66
7[e]		**1g**, 5-OH, 6-MeO	3	86	**2g**	72
8		**1h**, 2-MeO	0.25	73	**3h**	20
9		**1i**, 2-Cl	0.25	61	**3i**	3
10		**1j**, H	0.5	75	**2j**	91
11		**1k**, 4-Br	1	38	**2k**	92
12		**1l**, H	1	71	**2l**	99
13		**1m**, 6-OMe	1.5	91	**2m**	84
14		**1n**, 4-Br	1.5	43	**2n**	90

15		**1o**	0.25	50	**2o**	38

[a] Reaction conditions: $Pd_2(dba)_3$ (2.5 mol%), **L2** (5.5 mol%), **1** (0.3 mmol), toluene (2 mL). [b] Isolated yields of **2** and **3**. [c] Determined by ^1H NMR of the crude reaction mixture. [d] Determined by HPLC analysis. [e] 0 ºC. [f] Ee value of **3b**.

Experimental Section

General Methods

Unless stated otherwise, all reactions were carried out in flame-dried glassware under a dry argon atmosphere. All solvents were purified and dried according to standard methods prior to use.

^1H and ^{13}C NMR spectra were recorded on a Varian instrument (300, 400 MHz and 75, 100 MHz, respectively) and internally referenced to tetramethylsilane signal or residual protio solvent signals. Data for ^1H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad singlet, coupling constant (s) in Hz, integration). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm).

Trost ligands,[13] substituted phenol amines, (*E*)-4-bromo-but-2-enyl methyl ester[14] and substrates **1a-j**, **1o**[12] were prepared according to the reported procedures.

General procedure for synthesis of the substituted allylic carbonates (1k-1n)

To a solution of the corresponding substituted phenol amine (2.0 mmol, 1.0 equiv) and Et_3N (0.33 mL, 2.4 mmol, 1.2 equiv) in dry THF (25 mL)was added carbonic acid (*E*)-4-bromo-but-2-enyl methyl ester (836 mg, 4.0 mmol, 2.0 equiv) at 0 ℃. Then the reaction was stirred at room temperature for 6-12 h. After the reaction was complete (monitored by TLC), the crude reaction mixture was filtrated through a pad of celite and washed with EtOAc. The solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography (PE/EA = 6/1) to afford the desired product **1**.

1k, colorless oil, 75% yield. ^1H NMR (300 MHz, $CDCl_3$) δ7.33 (d, *J* = 9.0 Hz, 1H), 7.05 (d, *J* = 3.0 Hz, 1H), 6.60 (dd, *J* = 3.0, 8.4 Hz, 1H), 5.73-5.91 (m, 3H),5.54 (br s, 1H), 5.13-5.24 (m, 2H), 4.61 (d, *J* = 5.1 Hz, 2H), 3.78 (s, 3H), 3.59 (s, 2H), 3.13 (d, *J* = 5.7 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 139.0, 134.8, 133.2, 132.6, 126.4, 118.1, 117.6, 116.0, 113.7, 67.9, 56.8, 56.7, 54.9, 54.8; IR (film): v_{max}/cm^{-1}=2962, 1748,1575, 1442, 1259, 1088, 1018, 794, 700; ESI-HRMS (m/z): Exact mass calcd. for$C_{16}H_{21}BrNO_4$ $[M+H]^+$: 370.0648. Found: 370.0657.

1l, colorless oil, 77% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.10-7.16 (m, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 6.75 (d, *J* = 2.0 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 5.74-5.93 (m, 2H), 4.60 (d, *J* = 6.0 Hz, 2H), 3.78 (s,3H), 3.45 (s, 2H), 3.06 (d, *J* = 6.4 Hz, 2H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 155.6, 139.3, 132.4, 129.4, 127.0, 121.2, 116.6, 114.8, 67.9, 61.4, 58.6, 54.8, 41.9; IR (film): v_{max}/cm^{-1}=3023, 2955, 2793, 1746, 1588, 1485, 1445, 1380, 1366, 1256, 1157, 1124, 1084, 977, 942, 899, 876, 849, 788, 757, 696, 650; ESI-HRMS (m/z): Exact mass calcd. for$C_{14}H_{20}NO_4$ $[M+H]^+$: 266.1387. Found: 266.1390.

1m, yellow oil, 74% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 1H), 6.75-6.81 (m, 2H), 5.85-5.93 (m, 1H), 5.72-5.80 (m, 1H), 4.62 (d, *J* = 6.4 Hz, 2H), 3.87 (s,3H), 3.78 (s, 3H), 3.39 (s, 2H), 3.01 (d, *J* = 6.0 Hz, 2H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ155.5, 145.6, 145.4, 133.5, 131.8, 126.1, 120.4, 115.4, 110.3, 68.0, 61.2, 58.5, 55.9, 54.7, 41.9; IR (film): v_{max}/cm^{-1}=3446, 2955, 2789, 1745, 1590, 1509, 1441, 1365, 1257, 1126, 1027, 977, 940, 879, 792, 757, 636 ; ESI-HRMS (m/z): Exact mass calcd. for$C_{15}H_{22}NO_5$ $[M+H]^+$: 296.1493. Found: 296.1483.

1n, yellow oil, 77% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.8 Hz, 1H), 6.91 (d, *J* = 3.2 Hz, 1H), 6.60 (dd, *J* = 3.2, 8.8 Hz, 1H), 5.75-5.93 (m, 2H), 4.61 (d, *J* = 5.6 Hz, 2H), 3.78 (s,3H), 3.54 (s, 2H), 3.12 (d, *J* = 6.4 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ155.7, 155.6, 138.3, 133.5, 132.3, 127.0, 118.1, 116.6, 114.3, 67.9, 60.4, 59.0, 54.9, 42.1; IR (film): v_{max}/cm^{-1}=3405, 2956, 1746, 1591, 1574, 1441, 1381, 1257, 1165, 1111, 1018, 975, 942, 877, 851, 791, 754, 698, 626; ESI-HRMS (m/z): Exact mass calcd. for$C_{14}H_{19}BrNO_4$ $[M+H]^+$: 344.0492. Found: 344.0488.

General procedure for palladium-catalyzed intramolecular enantioselective allylic alkylation reaction

To a flame-dried Schlenk tube under argon, $Pd_2(dba)_3$ (6.9 mg, 0.0075 mmol, 2.5 mol%), (*R*, *R*)-DACH-phenyl Trost ligand(**L2**) (12 mg, 0.018 mmol, 5.5 mol%), and toluene (1 mL) were added. The reaction mixture was heated at 50 ℃ for 30 min, after that allyl carbonate **1** (0.30 mmol, dissolved in 1.0 mL toluene) was added. The reaction mixture was stirred at 50 ℃. After the reaction was complete (monitored by TLC), the crude reaction mixture was filtrated through a pad of celite and washed with EtOAc. Then the solvent was removed under reduced pressure. The **2**/**3** ratio was determined by ^1H NMR of the crude reaction mixture. The residue was purified by silica gel column chromatography (PE/EA = 8/1) to afford the desired products **2** and **3**.

2a/**3a**>19/1. **2a**,[12] colorless oil, 73% yield, 92% ee. [Daicel Chiralcel OJ-H (0.46 cmx 25 cm); *n*-hexane/2-propanol = 90/10; flow rate = 0.7 mL/min; detection wavelength = 230 nm; t_R = 15.68 (major), 20.03 (minor) min]. $[\alpha]_D^{20}$ = -39.8 (c = 0.5, $CHCl_3$).^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.39 (m, 5H), 7.07 (t, *J* = 7.8 Hz, 1H),6.69 (d, *J* = 7.8 Hz, 1H), 6.63 (d, *J* = 7.8 Hz, 1H), 6.03-6.16 (m, 1H), 5.31 (br s, 1H), 5.23-5.31 (m, 2H), 3.46-3.77 (m, 5H), 2.74 (d, *J* = 4.2 Hz, 2H).

2b/**3b** = 2.6/1. 83% yield, **2b**,[12] colorless oil, 85% ee. [Daicel Chiralpak IC (0.46 cmx 25 cm); *n*-hexane/2-propanol = 80/20; flow rate = 0.5 mL/min; detection wavelength = 230 nm; t_R = 10.10 (major), 9.25 (minor) min]. $[\alpha]_D^{20}$ = -18.8 (c = 0.5, $CHCl_3$).^1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.41 (m, 5H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.54 (d, *J* = 8.1 Hz, 1H), 6.06-6.18 (m, 1H), 5.68 (s, 1H), 5.05-5.10 (m, 2H), 3.79-3.86(m, 4H), 3.72 (AB, J_{AB} = 13.2 Hz, 1H), 3.66

(s, 1H), 3.59 (BA, J_{BA} = 13.8 Hz, 1H),3.34 (d, J= 15.0 Hz, 1H), 2.91 (d, J = 11.1 Hz, 1H), 2.54 (dd, J = 4.2, 11.4 Hz, 1H). **3b**,[12] colorless oil, 15% ee. [Daicel Chiralpak AD-H (0.46 cmx 25 cm); *n*-hexane/2-propanol= 90/10; flow rate = 1.0 mL/min; detection wavelength = 254 nm; t_R = 9.78 (major), 13.50 (minor) min]. $[\alpha]_D^{20}$ = 4.3 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.40 (m, 5H), 6.64 (s, 1H), 6.56 (s, 1H), 5.79-5.92 (m, 1H), 5.08-5.19 (m, 2H), 3.83 (s, 3H), 3.47-3.67 (m, 5H), 2.86 (dd, J = 5.7, 11.4 Hz, 1H), 2.48 (dd, J = 4.8, 11.4 Hz, 1H).

2c,[12] colorless oil, 80% yield, 90% ee. [Daicel Chiralpak AD-H (0.46 cmx 25 cm); *n*-hexane/2-propanol = 90/10; flow rate = 0.6 mL/min; detection wavelength = 230 nm; t_R = 9.62 (major), 11.86 (minor) min]. $[\alpha]_D^{20}$ = -54.7 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.39 (m, 5H), 6.94 (s, 1H), 6.01-6.10 (m, 1H), 5.64 (br s, 1H), 5.01-5.08 (m, 2H), 3.93 (AB, J_{AB} = 15.2 Hz, 1H), 3.84 (AB, J_{AB} = 13.6 Hz, 1H), 3.83 (s, 3H), 3.63-3.61 (m,1H), 3.57 (BA, J_{BA} = 13.2 Hz, 1H), 3.20 (BA, J_{BA} = 15.6 Hz, 1H), 2.87 (d, J = 11.2 Hz,1H), 2.43 (dd, J = 4.0, 11.2 Hz, 1H).

2d,[12] colorless oil, 61% yield, 91% ee. [Daicel Chiralpak AD-H (0.46 cmx 25 cm); *n*-hexane/2-propanol = 85/15; flow rate = 0.5 mL/min; detection wavelength = 230 nm; t_R = 14.91 (major), 18.69 (minor) min]. $[\alpha]_D^{20}$ = -63.5 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.25-7.38 (m, 6H), 6.63 (d, J = 8.8 Hz, 1H), 6.00-6.10 (m, 1H), 5.31 (br s, 1H), 5.20-5.26 (m, 2H), 3.83 (AB, J_{AB} = 16.0 Hz, 1H),3.81 (AB, J_{AB}= 13.2 Hz, 1H),3.63 (BA, J_{BA} = 13.6 Hz, 1H),3.48-3.51 (m, 1H), 3.40 (BA, J_{BA} = 16.4 Hz, 1H), 2.75 (dd, J = 4.0,11.2 Hz,1H), 2.61 (dd, J = 4.4,11.2 Hz, 1H).

2e/**3e**>19/1.**2e**,[12] colorless oil, 30% yield, 92% ee. [Daicel Chiralpak AS-H (0.46 cmx 25 cm); *n*-hexane/2-propanol = 95/5; flow rate = 0.5 mL/min; detection wavelength = 230 nm; t_R = 9.62 (major), 10.94 (minor) min]. $[\alpha]_D^{20}$ = 3.7 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ11.13 (br s, 1H), 7.90 (d, J = 9.0 Hz, 1H), 7.26-7.39 (m, 5H), 6.64 (d,J = 9.0 Hz, 1H), 6.03-6.15 (m, 1H), 5.06-5.13 (m, 2H), 3.92 (AB, J_{AB} = 17.1 Hz, 1H), 3.63-3.76 (m, 3H), 3.37 (BA, J_{BA}= 16.8 Hz, 1H), 3.01 (d, J = 11.4 Hz, 1H), 2.54 (dd, J = 3.9, 11.4 Hz, 1H).

2f,[12] colorless oil, 93% yield, 66% ee. [Daicel Chiralpak IC (0.46 cmx 25 cm); *n*-hexane/2-propanol = 80/20; flow rate = 0.5 mL/min; detection wavelength = 230 nm; t_R = 16.54 (major), 12.03 (minor) min]. $[\alpha]_D^{20}$ = -31.5 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.38 (m, 5H), 6.20 (d, J = 1.8 Hz,1H), 5.97-6.10 (m,2H), 5.22-5.32 (m, 2H), 3.58-3.72 (m, 3H), 3.39-3.53 (m, 2H), 2.76 (dd, J = 5.4, 12.0 Hz, 1H), 2.66 (dd, J = 5.1, 12.9 Hz, 1H).

2g,[12] white solid, 86% yield, 72% ee. [Daicel Chiralpak AD-H (0.46 cmx 25 cm); *n*-hexane/2-propanol = 70/30; flow rate = 0.5 mL/min; detection wavelength = 214 nm; tR = 21.01 (major), 15.02 (minor) min]. $[\alpha]_D^{20}$ = -37.5 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.39 (m, 5H), 6.22 (s, 1H), 6.02-6.14 (m, 1H), 5.36 (br s, 2H), 5.15-5.23 (m, 2H), 3.86 (s,3H), 3.49-3.71 (m, 4H), 3.35 (d, J= 14.7 Hz, 1H), 2.75 (dd, J = 3.9, 11.7 Hz, 1H), 2.63 (dd, J = 4.2, 11.4 Hz, 1H).

3h,[12] colorless oil, 73% yield, 21% ee. [Daicel Chiralpak IC (0.46 cmx 25 cm); *n*-hexane/2-propanol= 90/10; flow rate = 0.6 mL/min; detection wavelength = 230 nm; t_R = 22.66 (major), 10.78 (minor) min]. $[\alpha]_D^{20}$ = 9.3 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.40 (m, 5H), 6.85 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 8.4 Hz,1H), 5.77-5.87 (m, 1H), 5.05-5.15 (m, 2H), 3.77 (AB, J_{AB} = 14.8 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 2H), 3.59 (BA, J_{BA} = 15.6 Hz, 1H), 3.50-3.55 (m, 1H), 2.84 (dd, J = 5.2, 11.2 Hz, 1H), 2.47 (dd, J = 7.6, 11.6 Hz, 1H).

3i,[12] colorless oil, 61% yield, 3% ee. [Daicel Chiralpak IC (0.46 cmx 25 cm); *n*-hexane/2-propanol = 90/10; flow rate = 0.5 mL/min; detection wavelength = 230 nm; t_R = 8.94 (major), 11.60 (minor) min]. $[\alpha]_D^{20}$ = -2.9 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.44 (m, 5H), 7.03 (d, J = 8.7 Hz, 1H), 6.87 (d, J = 8.4 Hz,1H), 5.75-5.88 (m, 1H), 5.53 (br s, 1H), 5.07-5.16 (m, 2H), 3.57-3.74 (m, 4H), 3.47-3.55 (m, 1H), 2.81 (dd, J = 4.8, 11.4 Hz, 1H), 2.48 (dd, J = 6.9,11.4 Hz, 1H).

2j/**3j**>19/1. **2j**,[12] white solid, 75% yield, 91% ee. [Daicel Chiralpak IC (0.46 cmx 25 cm); *n*-hexane/2-propanol = 90/10; flow rate = 0.5 mL/min; detection wavelength = 230 nm; t_R = 8.80 (major), 8.14 (minor) min]. $[\alpha]_D^{20}$ = -86.9 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (t, J = 7.5 Hz, 1H), 6.65-6.72 (m, 2H), 5.84-6.14 (m, 2H), 5.44 (br s, 1H), 5.18-5.35 (m, 4H), 3.72 (AB, J_{AB} = 14.7 Hz, 1H), 3.55-3.63 (m,1H), 3.48 (BA, J_{BA} = 15.0 Hz, 1H), 3.20 (dd, J = 6.0, 13.8 Hz, 1H), 3.08 (dd, J = 6.6,13.5 Hz, 1H), 2.72-2.75 (m,2H).

2k/**3k**>19/1. **2k**, white solid, mp110-111°C, 38% yield, 92% ee. [Daicel Chiralpak AS-H (0.46 cmx 25 cm); *n*-hexane/2-propanol = 90/10; flow rate = 0.5 mL/min; detection wavelength = 254 nm; t_R = 9.25 (major), 10.59 (minor) min]. $[\alpha]_D^{20}$ = -73.6 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.28 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 6.01-6.14 (m, 1H), 5.84-5.96 (m, 1H), 5.55 (br s, 1H), 5.19-5.31 (m, 4H), 3.76 (AB, J_{AB} = 16.4 Hz, 1H), 3.52-3.57 (m,1H), 3.38 (BA, J_{BA} = 16.0 Hz, 1H), 3.27 (dd, J = 6.0, 13.6 Hz, 1H), 3.12 (dd, J = 6.4,13.6 Hz, 1H),2.78 (dd, J = 3.6, 10.8 Hz, 1H), 2.63 (dd, J = 4.0, 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 138.0, 133.1, 132.5, 129.1, 122.2, 116.1, 115.1, 113.6, 111.2, 58.6, 55.0, 53.1, 37.7; IR (film): v_{max}/cm^{-1}=2934, 2903, 2819, 2780, 1857, 1749, 1642, 1576, 1434, 1359, 1332, 1285, 1244, 1181, 1140, 1068, 1045, 992, 914, 811, 732, 654, 627; ESI-HRMS (m/z): Exact mass calcd. for$C_{14}H_{17}BrNO$ $[M+H]^+$: 294.0488. Found: 294.0494.

2l/**3l**>19/1. **2l**, white solid, mp 142-144°C, 71% yield, 99% ee. [Daicel Chiralcel OJ-H (0.46 cmx 25 cm); *n*-hexane/2-propanol= 85/15; flow rate = 0.4 mL/min; detection wavelength = 254 nm; t_R = 14.48 (major), 20.93 (minor) min]. $[\alpha]_D^{20}$ = -63.9 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (t, J = 7.6 Hz, 1H), 6.64-6.69 (m, 2H), 6.02-6.12 (m, 1H), 5.63 (br s, 1H), 5.23-5.28 (m, 2H), 3.72 (AB, J_{AB} = 14.8 Hz, 1H), 3.57-3.63 (m,1H), 3.39 (BA, J_{BA} = 14.8 Hz, 1H), 2.66-2.71 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ154.5, 140.5, 136.0, 127.3, 120.9, 118.6, 116.7, 113.8, 58.8, 58.0, 45.8, 39.1; IR (film): v_{max}/cm^{-1}=3068, 2977, 2948, 2853, 2818, 2794, 2682, 2357, 1915, 1827, 1737, 1635, 1610, 1587, 1511, 1460, 1446, 1416, 1390, 1369, 1346, 1306, 1281, 1260, 1187, 1150, 1128, 1115, 1080, 1060, 1028, 983, 912, 860, 813, 777, 746, 724, 708, 639; ESI-HRMS (m/z): Exact mass calcd. for$C_{12}H_{16}NO$ $[M+H]^+$: 190.1226. Found: 190.1232.

2m/**3m**>19/1. **2m**, white solid, mp 110-112°C, 91% yield, 84% ee. [Daicel Chiralpak IC (0.46 cmx 25 cm); *n*-hexane/2-propanol = 85/15; flow rate = 0.7 mL/min; detection wavelength = 230 nm; t_R = 20.01 (major), 12.79 (minor) min]. $[\alpha]_D^{20}$ = -65.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, J = 8.0 Hz, 1H), 6.57 (d, J = 8.4 Hz, 1H), 6.04-6.13 (m, 1H),5.10 (dt, J = 1.6, 10.4 Hz,1H), 5.05 (dt, J = 1.6, 17.2 Hz,1H), 3.85 (s, 3H), 3.79 (AB, J_{AB} = 14.4 Hz, 1H), 3.66-3.67 (m,1H), 3.22 (BA, J_{BA} = 14.4 Hz, 1H), 2.84 (dd, J = 2.8, 11.6 Hz, 1H), 2.50 (dd, J = 4.4, 11.2 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ144.5, 143.4, 140.7, 128.3, 121.9, 117.0, 114.5, 109.0, 58.5, 57.8, 56.0, 46.4, 38.2; IR (film): v_{max}/cm^{-1}=3673, 2972, 2903, 2349, 2325, 1610, 1494, 1456, 1438, 1410, 1378, 1326, 1284, 1235, 1186, 1151, 1130, 1069, 1035, 987, 892, 826, 784, 753, 695, 659; ESI-HRMS (m/z): Exact mass calcd. for$C_{13}H_{18}NO_2$ [M+H]$^+$: 220.1332. Found: 220.1323.

2n, white solid, mp 174-176°C, 43% yield, 90% ee. [Phenomenex Amylose-2 (0.46 cmx 25 cm); *n*-hexane/2-propanol= 98/2; flow rate = 0.8 mL/min; detection wavelength = 240 nm; t$_R$ = 21.46 (minor), 27.00 (major) min]. $[\alpha]_D^{20}$ = -113.8 (c = 0.5, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.30 (d, *J* = 8.4 Hz, 1H), 6.63 (d, *J* = 8.8 Hz, 1H), 6.01-6.11 (m, 1H), 5.46 (br s, 1H), 5.22-5.30 (m,1H), 3.75 (AB, J_{AB}= 16.4 Hz, 1H), 3.53-3.58 (m,1H), 3.26 (BA, J_{BA} = 16.0 Hz, 1H), 2.72 (dd, *J* = 3.6, 11.6 Hz, 1H), 2.63 (dd, *J* = 4.8, 11.6 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ153.8, 140.1, 131.2, 123.8, 117.2, 115.7, 113.1, 58.9, 58.1, 45.9, 39.7; IR (film): v_{max}/cm^{-1}=3673, 2986, 2973, 2902, 1990, 1945, 1451, 1407, 1252, 1229, 1068, 1054, 894, 881, 801; ESI-HRMS (m/z): Exact mass calcd. for$C_{12}H_{15}BrNO$ [M+H]$^+$: 268.0332. Found: 268.0321.

2o/**3o**>19/1.**2o**,[12] colorless oil, 50% yield, 38% ee. [Daicel Chiralpak IC (0.46 cmx 25 cm); *n*-hexane/2-propanol= 90/10; flow rate = 0.6 mL/min; detection wavelength = 230 nm; t$_R$ = 14.05 (major), 15.01 (minor) min]. $[\alpha]_D^{20}$ = -22.2 (c = 1.0, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$) δ7.08 (t, *J* = 7.8 Hz, 1H), 6.74 (d, *J* = 7.5 Hz, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 5.83-5.96 (m, 1H), 5.58 (br s, 1H), 5.26-5.32 (m, 2H), 3.71-3.80 (m, 4H), 3.66 (s, 3H),3.19-3.33 (m, 2H), 2.62 (dd, *J* = 7.2,13.8 Hz, 1H), 2.12 (dd, *J* = 8.1, 14.1 Hz, 1H).

Conclusions

In summary, we have developed a Pd-catalyzed intramolecular Friedel-Crafts type allylic alkylation reaction of phenols under mild conditions. This method provides a facile access to various tetrahydroisoquinolines bearing a stereogenic center at the C4-position with moderate to excellent yields, good regio- and enantioselectivity, serving as a complementary approach for the previously reported Ir-catalytic system.

Acknowledgements

We thank the National Basic Research Program of China (973 Program 2015CB856600) and National Natural Science Foundation of China (21272253, 21332009, 21421091) for generous financial support.

Notes and references

[a] Key Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, Shanghai 200237, China

[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

* xinyanwu@ecust.edu.cn or slyou@sioc.ac.cn

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

1 (a) J. D. Scott and R. M. Williams, *Chem. Rev.* 2002, **102**, 1669.(b) K.W. Bentley, *Nat. Prod. Rep.* 2006, **23**, 444.(c) K. Bhadra and G. S. Kumar, *Med. Res. Rev.* 2011, **31**, 821.

2 For reviews, see: (a) J. Stökigt, A. P. Antonchick, F. Wu and H. Waldmann, *Angew. Chem. Int. Ed.* 2011, **50**, 8538. (b) Y.-G. Zhou, *Acc. Chem. Res.*2007, **40**, 1357. (c) D.-S. Wang, Q.-A. Chen, S.-M. Lu and Y.-G. Zhou, *Chem. Rev.* 2012, **112**, 2557. For selected examples, see: (d) Z. Li and C.-J. Li, *Org. Lett.* 2004, **6**, 4997. (e) M. S. Taylor, N. Tokunaga and E. N. Jacobsen, *Angew. Chem. Int. Ed.* 2005, **44**, 6700. (f) N. Sasamoto, C. Dubs, Y. Hamashima and M. Sodeoka, *J. Am. Chem. Soc.* 2006, **128**, 14010. (g) A. M. Taylor and S. L. Schreiber, *Org. Lett.* 2006, **8**, 143. (h) T. Itoh, M. Miyazaki, H. Fukuoka, K. Nagata and A. Ohsawa, *Org. Lett.* 2006, **8**, 1295. (i) S.-M. Lu, Y.-Q. Wang, X.-W. Han and Y.-G. Zhou, *Angew. Chem. Int. Ed.* 2006, **45**, 2260.(j) F. Berhal, Z. Wu, Z. Zhang, T. Ayad and V. Ratovelomanana-Vidal, *Org. Lett.* 2012, **14**, 3308. (k) G. Zhang, Y. Ma, S. Wang, Y. Zhang and R. Wang, *J. Am. Chem. Soc.* 2012, **134**, 12334. (l) J. Zhang, B. Tiwari, C. Xing, X. Chen and Y. R. Chi, *Angew. Chem. Int. Ed.* 2012, **51**, 3649.(m) W. Lin, T. Cao, W. Fan, Y. Han, J. Kuang, H. Luo, B. Miao, X. Tang, Q. Yu, W. Yuan, J. Zhang, C. Zhu and S. Ma, *Angew. Chem. Int. Ed.* 2014, **53**, 277.

3 (a) L. Belvisi, C. Gennari, G. Poli, C. Scolastico and B. Salom, *Tetrahedron: Asymmetry* 1993, **4**, 273.(b) M. Kihara, M. Ikeuchi, S. Adachi, Y. Nagao, H. Moritoki, M. Yamaguchi and Z. Taira, *Chem. Pharm. Bull.* 1995, **43**, 1543. (c) N. Philippe, V. Levacher, G. Dupas, G. Quéguiner and J. Bourguignon, *Org. Lett.*2000, **2**, 2185. (d) L. F. Tietze, K. Thede, R. Schimpf and F. Sannicol, *Chem. Commun.* 2000, 583.(e) M. Yamashita, K. Yamada and K. Tomioka, *J. Am. Chem. Soc.* 2004, **126**, 1954.(f) D. W. Low, G. Pattison, M. D. Wieczysty, G. H. Churchill and H. W. Lam, *Org. Lett.* 2012, **14**, 2548. (g) Z. Chen, Z. Wang and J. Sun, *Chem. Eur. J.* 2013, **19**, 8426.

4 (a) B. M. Trost and D. L. Van Vranken, *Chem. Rev.* 1996, **96**, 395. (b)B. M. Trost, *Acc. Chem. Res.*2002, **35**, 695. (c) B. M. Trost and M. L. Crawley, *Chem. Rev.* 2003, **103**, 2921. (d) Z. Lu and S. Ma, *Angew. Chem. Int. Ed.* 2008, **47**, 258.

5 For Pd: (a) B. M. Trost and F. D. Toste, *J. Am. Chem. Soc.* 1998, **120**,815. (b) B. M. Trost and F. D. Toste, *J. Am. Chem. Soc.* 1999, **121**, 4545. (c)B. M. Trost, H. C. Shen, L. Dong and J.-P. Surivet, *J. Am. Chem. Soc.* 2003, **125**, 9276. (d) B. M. Trost, H. C. Shen, L. Dong, J.-P. Surivet and C. Sylvain, *J. Am. Chem. Soc.* 2004, **126**, 11966. (e) Y. Uozumi and M. Kimura, *Tetrahedron: Asymmetry*2006, **17**, 161. (f) S. F. Kirsch, L. E. Overman and N. S. White, *Org. Lett.*2007, **9**, 911.

6 For Rh: (a) P. A. Evans and D. K. Leahy, *J. Am. Chem. Soc.* 2000, **122**, 5012. (b) P. A. Evans and D. K. Leahy, *J. Am. Chem. Soc.* 2002, **124**, 7882.

7 For Ru: (a) B. M. Trost, P. L. Fraisse and Z. T. Ball, *Angew. Chem. Int. Ed.* 2002, **41**, 1059. (b) M. D. Mbaye, J. L. Renaud, B. Demerseman and C. Bruneau, *Chem. Commun.* 2004, 1870. (c) M. D. Mbaye, B. Demerseman, J.-L. Renaud, L. Toupet and C. Bruneau, *Adv. Synth. Catal.* 2004, **346**, 835. (d) C. Bruneau, J.-L. Renaud and B. Demerseman, *Chem.-Eur. J.* 2006, **12**, 5178. (e) K. Onitsuka, H. Okuda and H. Sasai, *Angew. Chem. Int. Ed.* 2008, **47**,

1454. (f) J. A. van Rijn, M. Lutz, L. S. von Chrzanowski, A. L. Spek, E. Bouwman and E. Drent, *Adv. Synth. Catal.* 2009, **351**, 1637. (g) J. A. van Rijn, M. A. Siegler, A. L. Spek, E. Bouwman and E. Drent, *Organometallics*2009, **28**, 7006. (h)J. A. van Rijn, E. van Stapele, E. Bouwman and E. Drent, *J. Catal.* 2010, **272**, 220. (i) J. A. van Rijn, A. den Dunnen, E. Bouwman and E. Drent, *J. Mol. Catal. A Chem.* 2010, **329**, 96. (j) J. A. van Rijn, E. Bouwman andE. Drent, *J. Mol. Catal. A Chem.* 2010, **330**, 26. (k) M. Austeri, D. Linder and J. Lacour, *Adv. Synth. Catal.* 2010, **352**, 3339. (l) J. A. van Rijn,M. C. Guijt, E. Bouwman and E. Drent, *Appl. Organometal. Chem.*2011, **25**, 207. (m) Z. Sahli, N. Derrien, S. Pascal, B. Demerseman, T. Roisnel, F. Barrière, M. Achard and C. Bruneau, *Dalton Trans.* 2011, **40**, 5625.

8 For Ir: (a) F. Lopez, T. Ohmura and J. F. Hartwig, *J. Am. Chem. Soc.* 2003, **125**, 3426. (b) C. Welter, A. Dahnz, B. Brunner, S. Streiff,P. Dübon and G. Helmchen, *Org. Lett.*2005, **7**, 1239. (c) M. Kimura and Y. Uozumi, *J. Org. Chem.*2007, **72**, 707.

9 Y. Suzuki, T. Nemoto, K. Kakugawa, A. Hamajima and Y. Hamada, *Org. Lett.*2012, **14**, 2350.

10 (a) T. Nemoto, Y. Ishige, M. Yoshida, Y. Kohno, M. Kanematsu and Y. Hamada, *Org. Lett.* 2010, **12**, 5020. (b) M. Yoshida, T. Nemoto, Z. Zhao, Y. Ishige and Y. Hamada, *Tetrahedron: Asymmetry*2012, **23**, 859. (c) T. Nemoto, Z. Zhao, T. Yokosaka, Y. Suzuki, R. Wu and Y. Hamada, *Angew. Chem. Int. Ed.* 2013, **52**, 2217. (d) Q.-F. Wu, W.-B. Liu, C.-X. Zhuo, Z.-Q. Rong, K.-Y. Ye and S.-L. You, *Angew. Chem. Int. Ed.* 2011, **50**, 4455. (e) C.-X. Zhuo and S.-L. You, *Angew. Chem. Int. Ed.* 2013, **52**, 10056. (f) C.-X. Zhuo and S.-L. You, *Adv. Synth. Catal.* 2014, **356**, 2020.

11 (a) M. Kimura, M. Fukasaka and Y. Tamaru, *Synthesis*2006, **21**, 3611. (b) A. V. Malkov, S. L. Davis, I. R. Baxendale, W. L. Mitchell and P. Kočovský, *J. Org. Chem.* 1999, **64**, 2751. (c) A. V. Malkov, P. Spoor, V. Vinader and P. Kočovský, *J. Org. Chem.*1999, **64**, 5308. (d) Y. Yamamoto and K. Itonaga, *Org. Lett.* 2009, **11**, 717.(e) I. Fernández, R. Hermatschweiler, F. Breher, P. S. Pregosin, L. F. Veiros and M. J. Calhorda, *Angew. Chem. Int. Ed.* 2006, **45**, 6386. (f) I. Fernández, D. Schott, S. Gruber and P. S. Pregosin, *Helv. Chim. Acta* 2007, **90**, 271. (g) N. Tsukada, Y. Yagura, T. Sato and Y. Inoue, *Synlett* 2003, 1431. (h) W. Rao and P. W. H. Chan, *Org. Biomol. Chem.* 2008, **6**, 2426. (i) V. Vece, J. Ricci, S. Poulain-Martini, P. Nava, Y. Carissan, S. Humbel and E. Duñach, *Eur. J. Org. Chem.* 2010, 6239.

12 Q.-L. Xu, L.-X. Dai and S.-L. You, *Org. Lett.* 2012, **14**, 2579.

13 (a) B. M. Trost, D. L. Van Vranken and C. Bingel, *J. Am.Chem. Soc.* 1992, **114**, 9327. (b) B. M. Trost, and D. L. Van Vranken, *Angew. Chem., Int. Ed. Engl.* 1992, **31**, 228.

14 B. M. Trost, K. L. Sacchi, G. M. Schroeder and N. Asakawa, *Org. Lett.* 2002, **4**, 3427.