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COMMUNICATION

Highly enantioselective intermolecular carbene insertion to C–H and Si–H bonds catalyzed by a chiral iridium(III) complex of a D_4-symmetric Halterman porphyrin ligand†‡

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The chiral iridium porphyrin [Ir((−)-D_4-Por*)(Me)(EtOH)] displays excellent reactivity and stereoselectivity towards carbene insertion to C–H and Si–H bonds, affording corresponding products in high yields (up to 96%) and high enantioselectivities (up to 98% ee).

Direct functionalization of C–H bonds is an appealing strategy for C–C, C–N and C–O bond formation due to the abundance of C–H bonds in organic compounds and the high atom-economy of this methodology.[1] In these endeavours, much attention has been devoted to develop transition metal-catalyzed carbene insertion to C–H bonds.[2] Chiral rhodium carboxamidates and carboxylates have been proven to be effective catalysts for highly enantioselective intramolecular carbene C–H bond insertion reactions.[2] However, the asymmetric intermolecular version remains a formidable challenge as facile formation of dimer product(s) from a metal–carbene moiety and low chemo- and regioselectivity are usually encountered. A notable achievement in this area is the rhodium prolinate complex [Rh_2(DOSP)$_4$]-catalyzed carbene C–H insertion with aryl- or vinyldiazoacetates to give products in high enantioselectivity.[3] Recently, we reported a chiral rhodium complex bearing the D_4-symmetric Halterman porphyrin ligand to achieve a highly enantioselective carbene C–H insertion of alkanes with methyl phenyldiazoacetate.[4] Apart from rhodium complexes, few transition metal complexes are known to efficiently catalyze intermolecular carbene C–H insertion with high enantioselectivity.

Metalloporphyrin complexes of ruthenium, iron, rhodium, osmium and cobalt are known to catalyze a variety of carbene transfer reactions giving products with high stereoselectivity and high product turnovers under mild conditions.[5] However, only few metalloporphyrin complexes are known to catalyse carbene C–H insertion with high enantioselectivity.[4] Very recently, Suematsu and Katsuki reported a chiral iridium(III) Schiff-base complex which can catalyze carbene C–H insertion with diazo esters in high enantioselectivity at low temperature.[6] Herein, we report the first chiral iridium porphyrin-catalyzed enantioselective carbene C–H and Si–H bond insertion reactions featuring high enantio- and diastereo-selectivity and high product turnovers.

Complex **1** [Ir(TTP)(Me)(L)] (L = solvent molecule, H_2O) was synthesized in 50% yield by heating [Ir(COD)Cl]$_2$ with tetrakis(*p*-tolyl)porphyrin (TTP) in 1,2,4-trichlorobenzene at 190 °C, followed by treatment with $NaBH_4$ and MeI.[7] The complex [Ir((−)-D_4-Por*)(Me)(L)] (L = solvent molecule, H_2O) bearing the D_4-symmetric Halterman porphyrin ligand (H_2(D_4-Por*) = *meso*-tetrakis-{(1*R*,4*S*,5*S*,8*R*)-1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimethano-anthracen-9-yl}porphyrin) was prepared in 64% yield *via* a similar procedure. Recrystallisation in a THF/EtOH mixture gave [Ir((−)-D_4-Por*)(Me)(EtOH)] **2**, the structure of which has been determined by X-ray crystal analysis (Fig. 1).

With complexes **1** and **2**, we examined their reactivity towards intermolecular carbene C–H insertion of 1,4-cyclohexadiene **4** with methyl phenyldiazoacetate **3a** (Table 1). Treatment of **4** with **3a** in the presence of 1 mol% [Ir(TTP)(CO)Cl] at room temperature for 24 h gave the C–H insertion product **5a** in 35% isolated yield and 61% substrate conversion (entry 1). [Ir(TTP)(Me)(L)] displayed a much higher activity than [Ir(TTP)(CO)Cl] with the reaction reaching completion in 5 min giving **5a** in 90% yield under the

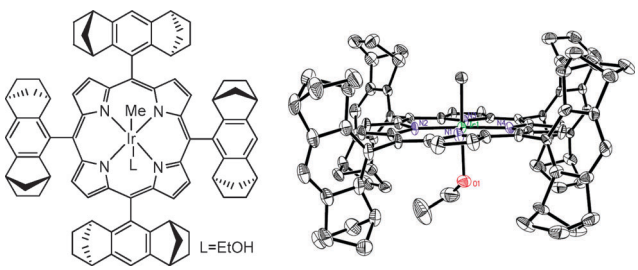

Fig. 1 Structure of [Ir((−)-D_4-Por*)(Me)(EtOH)] **2**.

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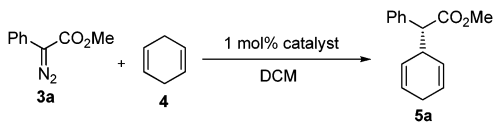
Table 1 C–H insertion reactions of 1,4-cyclohexadiene with methyl phenyldiazoacetate catalyzed by iridium porphyrins



Entry[a]	Catalyst	Temp./°C	Time/h	Yield[b] (%)	ee[c] (%)
1	[Ir(TTP)(CO)Cl]	23	24	35	
2	**1**	23	<0.1	90	
3	**2**	23	<0.1	90	91
4	**2**	−40	16	90	95
5	**2**	−78	24	90	93

[a] Reaction conditions: **4** (4 mmol), **3a** (0.4 mmol), catalyst (0.004 mmol), DCM (4 mL). [b] Isolated yield. [c] Determined by chiral HPLC.

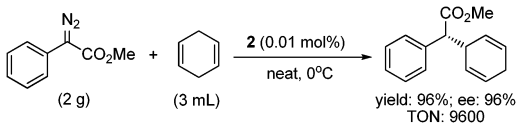
same conditions (entry 2). When [Ir((−)-D_4-Por*)(Me)(EtOH)] **2** was used, **5a** was obtained in 90% yield and 91% ee (entry 3). Lowering the reaction temperature to −40 °C extended the reaction time to 16 h and led to **5a** in 95% ee (entry 4). When the reaction was performed at −78 °C **5a** was obtained in 93% ee (entry 5). It is noteworthy that the **2**-catalyzed carbene C–H insertion was performed in a one-pot fashion; neither a dimer nor a cyclopropanation product was found in the reaction mixture.

With the optimized conditions, we examined the substituent effect of methyl aryldiazoacetates on the reaction. As shown in Table 2, both electron donating and electron withdrawing groups on the phenyl ring led to C–H insertion products in high yields and excellent enantioselectivities (Table 2, entries 1–4). Moreover, all of the reactions were accomplished in a one-pot manner without the need of slow addition of diazo compounds. Probably due to the steric hindrance of an *o*-substituted chloro group, no reaction of methyl *o*-Cl-phenyldiazoacetate with **4** was observed (entry 5). Changing a phenyl to naphthyl group did not affect neither the reaction yield nor enantioselectivity (entry 6). It is noteworthy that **2** also efficiently catalyzed the C–H insertion of **4** with α-thienyl substituted diazoacetate in high enantioselectivity (entry 7). Under the same reaction conditions, the ruthenium analogue [Ru(D_4-Por*)(CO)(EtOH)] failed to effect similar carbene C–H insertion. The **2**-catalyzed C–H insertion protocol can

Table 2 C–H insertion reactions of 1,4-cyclohexadiene with methyl aryldiazoacetate catalyzed by **2**

Entry[a]	Ar	Yield[b] (%)	ee[c] (%)
1	*p*-MeO–C_6H_4	**5b**, 94	96
2	*p*-Br–C_6H_4	**5c**, 91	96
3	*p*-Cl–C_6H_4	**5d**, 82	98
4	*m*-Cl–C_6H_4	**5e**, 90	86
5	*o*-Cl–C_6H_4	NR	—
6	2-Naphthyl	**5f**, 85	95
7	3-Thienyl	**5g**, 62	96

[a] Reaction conditions: **4** (4 mmol), **3** (0.4 mmol), **2** (0.004 mmol), DCM (4 mL), −40 °C. [b] Isolated yield. [c] Determined by chiral HPLC, the absolute configuration of the products is determined to be *R* by comparing the optical rotation with the literature.



Scheme 1

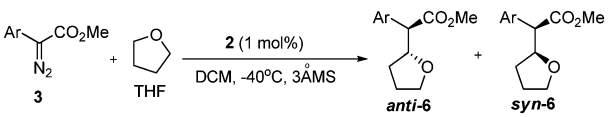
be scaled up. Slow addition of a solution of **3a** (2 g, 11.4 mmol) in **4** (1 mL) to a mixture of **2** (0.01 mol%) and **4** (2 mL) for 1 h at 0 °C afforded C–H insertion products in 96% isolated yield and 96% ee with a product turnover number of 9600 (Scheme 1).

The **2**-catalyzed C–H bond insertion of THF with methyl aryldiazoacetate was also examined. With 1 mol% **2** as catalyst, the one-pot reaction of THF with methyl phenyldiazoacetate proceeded smoothly in DCM at −40 °C giving C–H insertion products *anti*-**6a** and *syn*-**6a** in overall 82% yield with an *anti*/*syn* ratio of 10 : 1, the enantiomeric excess of the major isomer *anti*-**6a** was determined to be 90% (Table 3, entry 1). In most cases, all of the other aryl substituted diazo compounds **3** reacted with THF efficiently at −40 °C to give C–H insertion products in good to high yields with high diastereoselectivities (up to *anti*/*syn* = 20 : 1) and excellent enantioselectivities (up to 97% ee). Electron-donating group MeO led to low product yield and diastereoselectivity, but retained high enantio-induction for *anti*-isomer (entry 5). It is noteworthy that the *syn*-selectivity is favorable in the similar reaction catalyzed by rhodium carboxylates and iridium(III) Schiff-base complexes,[3,6] thus the chiral iridium(III) porphyrin **2** catalyzed carbene C–H insertion provides the first efficient method for the enantioselective synthesis of *anti*-isomer **6**. No reaction was observed with [Ru(D_4-Por*)(CO)(EtOH)] as catalyst under the same conditions.

The Si–H bond insertion catalyzed by **2** was also investigated.[8] As shown in Table 4, **2** catalyzed carbene Si–H bond insertion with various diazo compounds even at −80 °C to give products in high yields and good to high enantioselectivities. Among the diazo compounds examined, methyl *p*-bromophenyldiazoacetate was proven to be the most effective giving products in 93% yield and 91% ee (Table 4, entries 2 and 5).

We also examined the reactivity and stereoselectivity of **2**-catalysed cyclopropanation of styrene with EDA. With as low

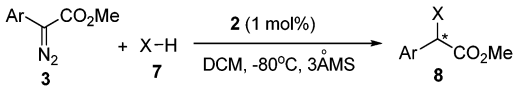
Table 3 C–H insertion reactions of THF with methyl aryldiazoacetate catalyzed by **2**



Entry[a]	Ar	Yield[b] (%)	*anti* : *syn*[c]	ee[d] (%)
1	Ph	**6a**, 82	10 : 1	90
2	*p*-Br–C_6H_4	**6b**, 96	>20 : 1	97
3	*p*-Cl–C_6H_4	**6c**, 86	16.9 : 1	97
4	*p*-Me–C_6H_4	**6d**, 74	14.6 : 1	96
5	*p*-MeO–C_6H_4	**6e**, 22	2.5 : 1	92
6	*m*-Cl–C_6H_4	**6f**, 86	13.7 : 1	81
7	2-Naphthyl	**6g**, 76	9.3 : 1	92
8	3-Thienyl	**6h**, 23	>20 : 1	91

[a] Reaction conditions: **3** (0.4 mmol), THF (4 mmol), **2** (0.004 mmol), DCM (4 mL), −40 °C. [b] Isolated yield. [c] Determined by analysis of the crude reaction mixture, with ^{1}H NMR spectroscopy. [d] Determined by chiral HPLC.

Table 4 Si–H insertion reaction with methyl aryl-diazoacetate catalyzed by **2**



Entry[a]	Ar	X	Yield[b] (%)	ee[c] (%)
1	Ph	$PhMe_2Si$	**8a**, 92	72
2	*p*-Br–C_6H_4	$PhMe_2Si$	**8b**, 93	91
3	*p*-Cl–C_6H_4	$PhMe_2Si$	**8c**, 75	78
4	Ph	Et_3Si	**8d**, 75	75
5	*p*-Br–C_6H_4	Et_3Si	**8e**, 93	91
6	*p*-Cl–C_6H_4	Et_3Si	**8f**, 94	82
7	2-Naphthyl	Et_3Si	**8g**, 92	75

[a] Reaction conditions: **3** (0.4 mmol), X–H substrate (0.48 mmol), **2** (0.004 mmol), DCM (4 mL), −80 °C, 24 h. [b] Isolated yield. [c] Determined by chiral HPLC.

as 0.01 mol% **2** as catalyst, the reaction proceeded smoothly in DCM at −78 °C to afford the *trans* cyclopropyl ester **9** as the major product in 80% yield with 88% ee and a TON of 8000 (Scheme 2). Upon comparing this result with that catalyzed by [Ru(D_4-Por*)(CO)(EtOH)][9] which effected styrene cyclopropanation at room temperature, the change from ruthenium(II) to iridium(III) greatly speeds up the catalysis.

We performed DFT calculation on [Ir(TPP)(Me)]-catalyzed carbene C–H insertion of **4** with **3a** *via* two potential intermediates **I** and **II** as shown in Scheme 3. The transformation of intermediate **I** to **III** *via* transition state $\mathbf{TS_{I–III}}$ requires 19.9 kcal mol^{-1} and this process is endergonic by 10.6 kcal mol^{-1}. Whereas carbene insertion to **4** from intermediate **II** has an overall activation barrier of only 16.2 kcal mol^{-1} *via* $\mathbf{TS_{II–IV}}$, which is 3.7 kcal mol^{-1} lower than the energy required in the intermediate **I** pathway. The formation of product **IV** is significantly exothermic by 43.9 kcal mol^{-1}. Intermediate **II** has a longer Ir–C(carbene) bond length than **I**, (2.06 Å *vs.* 1.90 Å for **II** *vs.* **I**), revealing that **II** is more facile to undergo the C–H insertion.

To get further information on the reaction mechanism, we monitored the [Ir(TTP)(Me)(L)] **1**-catalyzed carbene C–H insertion of **4** with **3a** by UV-visible absorption and ^{1}H NMR spectroscopies. When **3a** was added to a CH_2Cl_2 solution of **1**, a shift of the Soret band from 407 nm to 419 nm was observed. Upon addition of **4**, the Soret band shifted back to 407 nm. By ^{1}H NMR spectroscopy, addition of **3a** to a $CDCl_3$ solution of **1** caused a downfield shift of the ligated methyl group from −6.30 ppm to −5.71 ppm. The signal then shifted to −6.45 ppm upon addition of excess **4**. These findings revealed that **1** catalyzed carbene C–H insertion proceeded through a short-lived intermediate.

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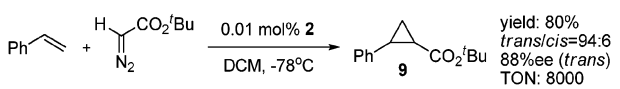
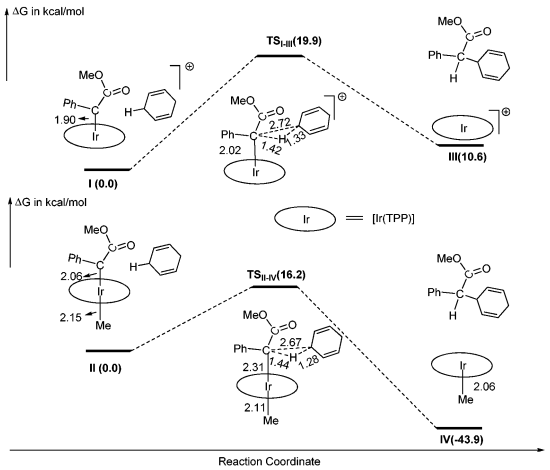


Scheme 2



Scheme 3 The calculated potential energy surfaces of intermolecular carbene insertion reaction pathway of I and II to the 1,4-cyclohexadiene at the B3LYP/6-31G(d):LAN2DZ level.

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