

# Asymmetric amidation of saturated C–H bonds catalysed by chiral ruthenium and manganese porphyrins

Xiang-Ge Zhou, Xiao-Qi Yu, Jie-Sheng Huang and Chi-Ming Che\*

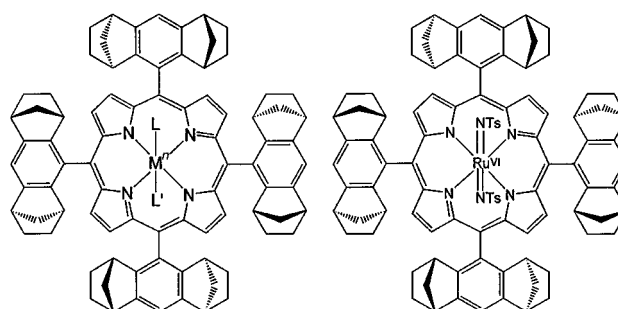
Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong. E-mail: cmche@hkucc.hku.hk

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Chiral ruthenium(II) and manganese(III) porphyrins catalyse the asymmetric amidation of saturated C–H bonds of ethylbenzene and ethylnaphthalenes to form the corresponding amides in up to 85% yield with 45–58% ee.

In the context of developing new protocols for asymmetric functionalisation of saturated C–H bonds, amidation *via* reactive metal–imido species is preferred over hydroxylation by reactive metal–oxo complexes because the latter usually suffers from further oxidation to give side products such as ketones. However, in contrast to the large number of investigations on the hydroxylation of saturated C–H bonds catalysed by both cytochrome P-450 and its chemical model systems such as iron and manganese porphyrins,<sup>1</sup> metalloporphyrin-catalysed amidations of saturated C–H bonds are rare.<sup>2–6</sup> Herein we describe the enantioselective amidation of saturated C–H bonds with chiral metalloporphyrin catalysts or directly by a chiral metal–imido complex (Scheme 1). Prior to this work, there was only one report on metal-mediated asymmetric amidation of saturated C–H bonds, with up to 31% ee obtained for indane,<sup>7</sup> despite the recent advances in metal-catalysed asymmetric aziridination of alkenes.<sup>8</sup>

The chiral porphyrin H<sub>2</sub>Por\* [Por\* = 5,10,15,20-tetrakis(1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimethanoanthracen-9-yl)porphyrinato dianion] was synthesised by Halterman's method.<sup>9</sup> Its complexes with ruthenium(II) and manganese(III) ions, [Ru<sup>II</sup>(Por\*)(CO)(EtOH)] **1**<sup>10</sup> and [Mn<sup>III</sup>(Por\*)(OH)(MeOH)] **2**,<sup>9,11</sup> respectively, were prepared according to the published procedures. Both complexes were found to be effective catalysts for asymmetric amidation of saturated C–H bonds by PhI=NTs.<sup>†</sup> The results obtained for a series of substrates containing saturated C–H bonds, at a catalyst: PhI=NTs: substrate molar ratio of 1:100:500 with yields based on starting PhI=NTs, are summarised in Table 1. In each case, TsNH<sub>2</sub> was detected as a side product; the total yields of TsNH<sub>2</sub> and the amidation product were close to 100%. As can be seen from Table 1, both the yield and ee increase considerably with increasing temperature (entries 1–3; 4, 5; 8, 9), and less sterically demanding substrates could be amidated with higher ees. For example, the ee obtained for 2-ethylnaphthalene (48%, entry 13) is higher than that obtained for the more sterically demanding substrates 1-ethylnaphthalene (23%, entry 15) and indane (10%, entry 9). Mass balance studies were carried out in the case of ethylbenzene, which resulted in conversions of 14 (catalyst **1**) and 47% (catalyst **2**) for this substrate at a



- 1** M = Ru, *n* = II, L = CO, L' = EtOH  
**2** M = Mn, *n* = III, L = HO<sup>−</sup>, L' = MeOH

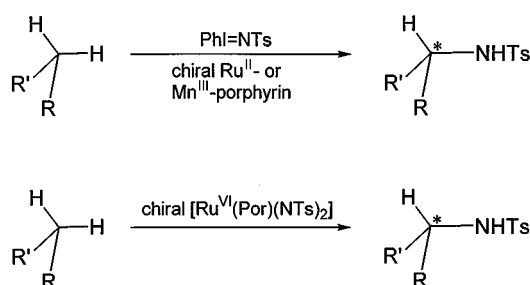
catalyst:ethylbenzene:PhI=NTs molar ratio of 1:75:150 (CH<sub>2</sub>Cl<sub>2</sub>, 40 °C, 2 h), with the yields of 1-tosylamino-1-phenylethane being 84 and 76%, respectively, based on the amount of ethylbenzene consumed.

Under the same conditions, the manganese catalyst **2** exclusively afforded the amidation product in a considerably higher yield (>70% in all the cases except entries 4 and 16) than the ruthenium catalyst **1**. The highest yield obtained was 85% for 2-ethylnaphthalene (entry 14). Increasing the amount of **2** used considerably improved the yield but only slightly enhanced the chiral induction (entries 16 and 17). Interestingly, the manganese catalyst **2** also gave higher ees than the ruthenium catalyst **1**, except for tetrahydronaphthalene. The

**Table 1** Asymmetric amidation of saturated C–H bonds by PhI=NTs catalysed by **1** and **2**<sup>a</sup>

Entry	R <sup>1</sup> —CH <sub>2</sub> —R <sup>2</sup>		Catalyst	Yield (%) <sup>b</sup>	Ee (%) <sup>c</sup>	T/°C
	R <sup>1</sup>	R <sup>2</sup>				
1	Ph	Me	<b>1</b>	16	34	0
2	Ph	Me	<b>1</b>	18	35	20
3	Ph	Me	<b>1</b>	23	43	40
4	Ph	Me	<b>2</b>	52	42	20
5	Ph	Me	<b>2</b>	72	45	40
6	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Me	<b>1</b>	45	33	40
7	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Me	<b>2</b>	82	47	40
8	1,2-C <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>2</sub>		<b>1</b>	28	6	20
9	1,2-C <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>2</sub>		<b>1</b>	34	10	40
10	1,2-C <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>2</sub>		<b>2</b>	72	12	40
11	1,2-C <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>3</sub>		<b>1</b>	47	31	40
12	1,2-C <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>3</sub>		<b>2</b>	78	26	40
13	2-naphthyl	Me	<b>1</b>	45	48	40
14	2-naphthyl	Me	<b>2</b>	85	53	40
15	1-naphthyl	Me	<b>1</b>	24	23	40
16	1-naphthyl	Me	<b>2</b>	62	50	40
17 <sup>d</sup>	1-naphthyl	Me	<b>2</b>	72	54	40

<sup>a</sup> Reaction conditions: PhI=NTs:substrate = 1:5 (molar ratio), CH<sub>2</sub>Cl<sub>2</sub>, 2 h (40 °C), 12 h (20 °C), 24 h (0 °C); 1 mol% catalyst (based on starting PhI=NTs). <sup>b</sup> Defined relative to starting PhI=NTs. <sup>c</sup> Determined by HPLC with chiral column. <sup>d</sup> 5 mol% catalyst (based on starting PhI=NTs) was used.



**Scheme 1**

**Table 2** Asymmetric amidation of saturated C–H bonds by complex **3**<sup>a</sup>

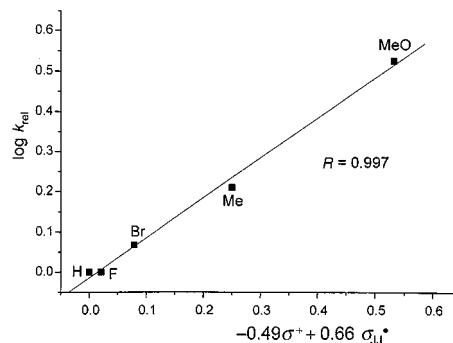
Entry	R <sup>1</sup>	R <sup>2</sup>	Yield (%) <sup>b</sup>	Ee (%) <sup>c</sup>	T/°C
1	Ph	Me	42	37	20
2	Ph	Me	54	43	40
3	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Me	68	33	40
4		1,2-C <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>2</sub>	70	15	40
4		1,2-C <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>3</sub>	75	32	40
6	2-naphthyl	Me	78	58	40
7	1-naphthyl	Me	58	35	40

<sup>a</sup> Reaction conditions: CH<sub>2</sub>Cl<sub>2</sub>, 2 h (40 °C), 12 h (20 °C). <sup>b</sup> Defined relative to complex **3**. <sup>c</sup> Determined by HPLC with chiral column.

highest ee obtained in the catalytic amidations was 54% for 1-ethylnaphthalene (entry 17).

Efforts have been made to ascertain the active species in the ruthenium-catalysed amidation reactions. Treatment of complex **1** with 2 equiv. of PhI=NTs in CD<sub>2</sub>Cl<sub>2</sub> at room temperature completely converted **1** into a bis(tosylimido)ruthenium(vi) complex, [Ru<sup>VI</sup>(Por\*)(NTs)<sub>2</sub>] **3**, which was characterised by the following spectral methods. The <sup>1</sup>H NMR spectrum<sup>‡</sup> of **3**, typical of a diamagnetic ruthenium porphyrin, shows *ortho*- and *meta*-proton resonances of axial tosyl groups, and the H<sub>β</sub> resonances of the chiral porphyrinato ligand at δ 4.89, 6.19 and 8.76, respectively, with an integration ratio of 1 : 1 : 2. The UV–VIS spectrum of **3** exhibits Soret and β bands at 422 and 537 nm, respectively, both of which are red-shifted by ca. 8 nm when compared with the carbonyl complex **1**. All these spectral features strongly resemble those of [Ru<sup>VI</sup>(Por\*)(NTs)<sub>2</sub>] (Por = achiral *meso*-tetraarylporphyrinato dianion).<sup>6</sup> Further, the positive ion electrospray mass spectrum of **3** shows a prominent cluster peak at *m/z* 1579.8 that can be attributed to the parent ion of **3**. Complex **3** constitutes the first example of a chiral imido metalloporphyrin, and, importantly, it was found to be reactive towards saturated C–H bonds, leading to an enantioselective insertion of the NTs group into these bonds.<sup>§</sup> The results are listed in Table 2. Under identical conditions, the ees obtained for the stoichiometric amidation by complex **3** and for the catalytic amidation by **1**, except for substrates 1- and 2-ethylnaphthalene, are rather similar, suggesting that complex **3** likely functions as the active species responsible for the asymmetric amidation reactions. Notably, the amidation of 2-ethylnaphthalene by **3** gave 58% ee (entry 6), which represents the highest ee obtained in this work.

For the manganese catalysed reactions, we found that the positive ion electrospray mass spectrum of a reaction mixture of **2** and PhI=NTs in CH<sub>2</sub>Cl<sub>2</sub> showed a prominent cluster peak at *m/z* 1569.1 ascribable to the fragment [Mn(Por\*)(PhINTs)]<sup>+</sup>. This suggests the involvement of a manganese tosylamido reactive intermediate and suggests that different types of active species may be involved in the ruthenium and manganese catalyses. To probe the nature of the intermediates formed in the rate-limiting step during the amidation catalysed by **2**, we examined substitution effect by measuring the amidation rates (*k*<sub>rel</sub>) of substituted ethylbenzenes *p*-YC<sub>6</sub>H<sub>4</sub>Et (Y = MeO, Me, F, Br) relative to that of ethylbenzene, which reveals that both electron-donating and -withdrawing substituents promote the amidation process. A dual-parameter (σ<sup>+</sup>, σ<sub>JJ</sub><sup>+</sup>) fitting of log *k*<sub>rel</sub>, as established by Jiang and co-workers,<sup>12</sup> through multiple regression gave rise to excellent linearity (Fig. 1), with ρ<sup>+</sup> and ρ<sub>JJ</sub><sup>+</sup> values of –0.49 and 0.66, respectively, suggesting that the amidation reactions should proceed *via* a benzylic radical intermediate, which possibly resulted from H-atom abstraction from the substrates by the manganese tosylamido active intermediate.



**Fig. 1** Plot of log *k*<sub>rel</sub> vs. (σ<sup>+</sup>, σ<sub>JJ</sub><sup>+</sup>) for the amidation of substituted ethylbenzenes *p*-YC<sub>6</sub>H<sub>4</sub>Et (Y = MeO, Me, F, H, Br) by PhI=NTs catalysed by manganese catalyst **2**. The *R* value for the multiple regression is indicated.

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## Notes and references

<sup>†</sup> *General procedure* for the amidation reactions: To a Schlenk flask containing the complex (5 μmol) and molecular sieves (4 Å) (150 mg) was added a solution of substrate (2.5 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (5 ml) *via* syringe. The mixture was stirred for 10 min at room temperature under argon. PhI=NTs (0.5 mmol) was then added against a positive pressure of argon. The reaction was maintained at 40 °C for 2 h. After cooling, the molecular sieves were filtered off and washed with CH<sub>2</sub>Cl<sub>2</sub>. The filtrate and washings were evaporated to dryness and the organic product, purified by column chromatography, was identified by <sup>1</sup>H and <sup>13</sup>C NMR, and high-resolution MS, along with melting point.

<sup>‡</sup> *Selected data* for **3**: δ<sub>H</sub> (300 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 8.76 (s, 8H), 7.37 (s, 4H), 6.19 (d, 4H), 4.89 (d, 4H), 3.54 (s, 8H), 2.69 (s, 8H), 1.97 (m, 8H), 1.84 (m, 14H), 1.34 (m, 24H), 1.07 (m, 8H).

<sup>§</sup> The general procedure for the stoichiometric amidation of saturated C–H bonds by complex **3** is the same as that for the catalytic amidation by **1** and **2**, except that 0.25 mmol of **3**, formed *in situ* by treating **1** with 2 equiv. of PhI=NTs, was used instead of **1** and **2**, and no additional PhI=NTs was added.

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