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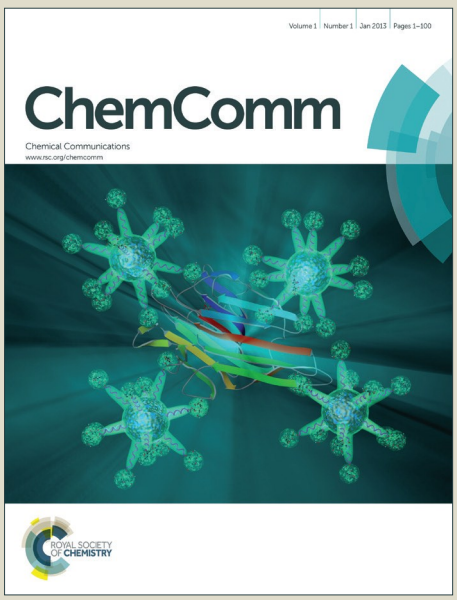

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Chiral Bicyclic NHC/Ir Complexes for Catalytic Asymmetric Transfer Hydrogenation of Ketones

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A diverse series of chiral bicyclic NHC/Ir complexes were prepared via a previously developed divergent synthesis of chiral imidazolium salts. Among the complexes, **8dz** was found to be an excellent catalyst precursor for the Ir-catalyzed asymmetric transfer hydrogenation of ketones. The reaction of ketones with **8dz** proceeded smoothly to give corresponding alcohols with high enantioselectivities (up to 98%) and productivities (TON up to 4,500).

Introduction

One of the important considerations in the development of new chiral ligands is whether the chiral ligands can be divergently prepared or not, because it is directly linked to the efficiency of finding an appropriate catalyst for each asymmetric reaction at the stage of catalyst screening.[1] In 2010, we reported a modular synthesis of chiral bicyclic imidazolium salts **2** and **3** based on the alkylation of newly prepared imidazoles **1** (Fig. 1).[2] We expected that the *N*-heterocyclic carbenes (NHCs)[3] generated from those salts would have superior asymmetric induction ability when used as chiral ligands, because the restriction of internal rotation around the N-C axis by the fused bicyclic molecular structure should be favorable for a chiral environment.[4] Unfortunately, scant attention has been given to the study of transition metal catalyzed asymmetric reactions using the bicyclic NHCs as chiral ligands, and therefore, little is known about the utility of those compounds as chiral ligands.[5] Taking advantage of our divergent synthetic procedure, we have investigated the performance of our ligands in transition metal catalyzed asymmetric reactions. Here we report the results of our attempt to accomplish the Ir-catalyzed asymmetric transfer hydrogenation of ketones.[6,7]

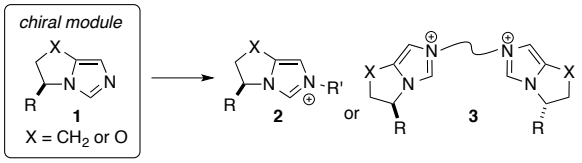
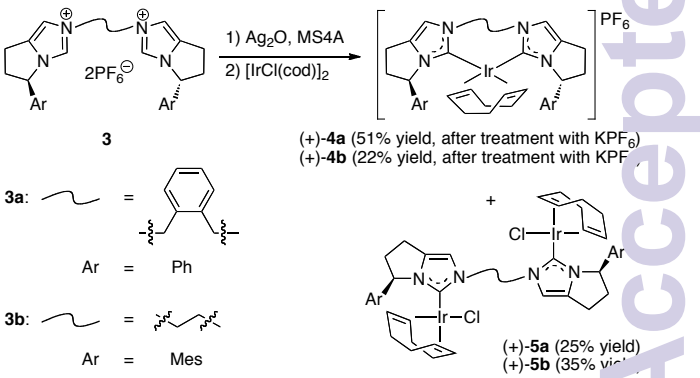


Fig. 1 Modular synthesis of chiral bicyclic imidazolium salts **2** and **3**.

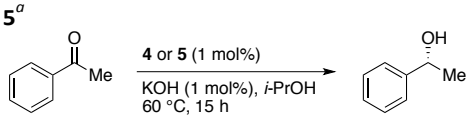
Results and discussion

As we were originally interested in the application of C$_2$-symmetric transition metal catalysts bearing chiral bis-NHC ligands, the conversion of our imidazolium salts **3** into chelating Ir complexes **4** was conducted (Scheme 1). In practice, desired Ir complexes **4a** and **4b** were obtained from **3a** and **3b** by the carbene transfer strategy through Ag-NHC complexes in 51% and 22% yields, respectively. The modest yields were mainly caused by the formation of by-products **5**, in which the ligands bridge two Ir units.



Scheme 1 Preparation of bis-NHC/Ir complexes **4**.

Table 1 Asymmetric transfer hydrogenation of **6a** with by **4** and **5**[a]



Entry	Ir complex	Yield[b] (%)	% Ee[c]
1	(*R*,*R*)-(+)-**4a**	77	0
2	(+)-**4b**	88	0
3	(*R*,*R*)-(+)-**5a**	70	8
4	(+)-**5b**	85	19

[a] The transfer hydrogenation was carried out with acetophenone (**6a**) in *i*-PrOH (65 eq) in the presence of KOH (1 mol%) and Ir complex **4** or **5** (1 mol%) at 60 °C for 15 h under N_2. [b] Isolated yield. [c] Determined by HPLC analysis with chiral stationary phase column.

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To our disappointment, the application of **4** to the transfer hydrogenation reaction of acetophenone (**6a**) was a failure, and no asymmetric induction was observed (Table 1, entries 1 and 2). Those results were, however, interpreted by the crystal structure of **4a** in which the *cis*-chelating bis-NHC ligand adopted the C_1 symmetric coordination mode toward the Ir center instead of the C_2 symmetric mode.[8] The ^{1}H-NMR spectra of **4a** measured at room temperature also demonstrated that the C_1 symmetric structure remained even in the solution state. A similar degradation of C_2 symmetry was also confirmed in the ^{1}H-NMR spectra of **4b**. We found, however, that dinuclear Ir complexes **5a** and **5b**, the by-products of **4** in Scheme 1, showed a certain degree of enantioselectivity, namely, (*R*)-**7a** having 8% and 19% ee was obtained, respectively (Table 1, entries 3 and 4).

The results inspired us to investigate an Ir-monodentate NHC system for this reaction. Parts of the structures of the new Ir complexes we prepared are shown in Fig. 2. Using our synthetic procedure, a variety of complexes having flexibility at the substituents R and R' were prepared.

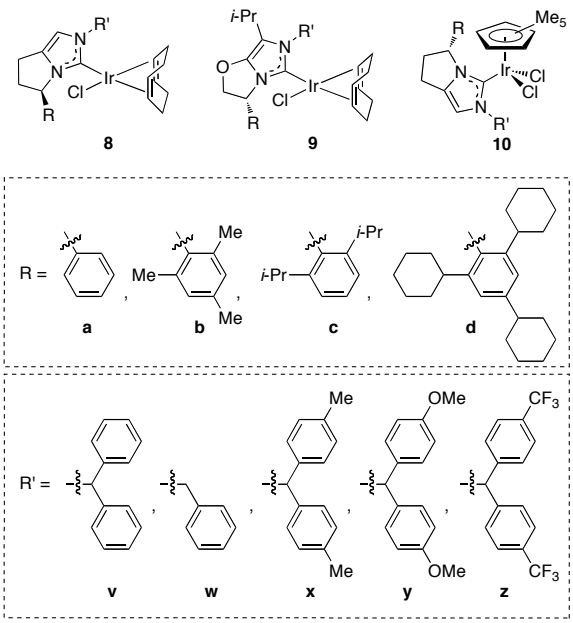
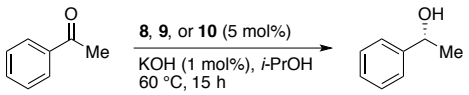


Fig. 2 Structures of NHC/Ir complexes for asymmetric transfer hydrogenation.

The results of catalyst screening for the asymmetric transfer hydrogenation are shown in Table 2. First, it was found that increasing the steric hindrance of the substituent R in the NHC ligand tended to increase the enantioselectivity of the reaction (entries 1-4). Second, as for the substituent R' in the ligand, replacement of the diphenylmethyl group with the less bulky benzyl group decreased the selectivity, whereas replacement with the bulkier di-*p*-tolylmethyl group increased the selectivity (entries 4-6). Use of the bis(*p*-methoxyphenyl)methyl group having an electron-donating *p*-methoxy group decreased the selectivity considerably (entry 7), whereas use of the bis(*p*-(trifluoromethyl)phenyl)methyl group having an electron-withdrawing *p*-trifluoromethyl group gave the best enantioselectivity in this screening (entry 8). Finally, the complex containing chiral oxazolidine-fused NHC **9** and Ir(III) complex **10** also exhibited catalyst activity. The results were, however, unsatisfactory from the viewpoint of enantioselectivity (entries 9 and 10).

Table 2 Catalyst screening for Ir-catalyzed asymmetric transfer hydrogenation of **6a**[a]



6a (*R*)-**7a**

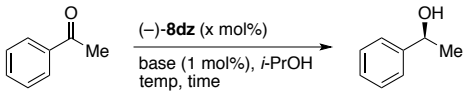
Entry	Ir complex	Yield[b] (%)	% Ee[c]
1	(*R*)-(+)-**8av**	80	22
2	(+)-**8bv**	43	38
3	(*R*)-(+)-**8cv**	79	53
4	(+)-**8dv**	80	60
5	(+)-**8dw**	89	55
6	(+)-**8dx**	83	68
7	(+)-**8dy**	40	30
8	(+)-**8dz**	78	73
9	(*R*)-**9aw**[d]	89	17[e]
10	(*R*)-**10cv**[f]	92	1

[a] The transfer hydrogenation was carried out with acetophenone (**6a**) in *i*-PrOH (65 eq) in the presence of KOH (1 mol%) and Ir complex **8**-**10** (5 mol%) at 60 °C for 15 h under N_2. [b] Isolated yield. [c] Determined by HPLC analysis with chiral stationary phase column. [d] The complex was generated by mixing an NHC/Ag complex and $[IrCl(cod)]_2$ in situ. [e] The absolute configuration was *S*. [f] An impure complex was used.

Optimization of the reaction conditions was then carried out using Ir complex **8dz**, which showed the best enantioselectivity in Table 2 (Table 3). Although the yield was decreased, a substantial improvement of the selectivity was observed when we shortened the reaction time from 15 h to 1 h, (entry 1 vs. 2). The results implied that the enantioselectivity is high at the beginning but worsens with time. Then, we tried to improve the reaction rate by raising the temperature from 60 to 70 °C. Although the enantioselectivity was decreased slightly, the product yield was high as expected (entry 2 vs. 3). Several bases were then screened to further optimize the reaction conditions, and *t*-BuOK was chosen as the base (entries 3-7). Reinvestigation of the temperature with the latter conditions revealed that 70 °C is the best after all (entries 7-9). Finally, we attempted to decrease the catalyst loading and found that almost the same yields and

enantioselectivities were achieved even when the catalyst loading was lowered from 5 mol% to 0.5 or 0.1 mol% (entries 7 vs. 10 and 11). To our surprise, further decrease of the catalyst loading to 0.05 mol% led to an even higher enantioselectivity (entry 12), and the enantioselectivity improvement was maintained even with 0.01 mol% of the catalyst loading to give the product with 97% ee (entry 13). Under the last set of conditions (S/C = 10,000), the turnover number (TON) of **8dz** was estimated to be 4,500.

Table 3 Optimization of reaction conditions with **8dz**[a]



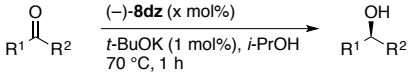
6a (*S*)-**7a**

Entry	x (mol%)	Base	Temp (°C)	Time (h)	Yield[b] (%) (Conv[c] (%))	% Ee[d]
1	5	KOH	60	15	78 (88)	73
2	5	KOH	60	1	50 (60)	88
3	5	KOH	70	1	90 (98)	85
4	5	CsOH	70	1	90 (97)	89
5	5	*i*-PrONa	70	1	88 (96)	90
6	5	*t*-BuONa	70	1	89 (98)	86
7	5	*t*-BuOK	70	1	90 (97)	92
8	5	*t*-BuOK	60	1	70 (82)	91
9	5	*t*-BuOK	80	1	90 (98)	89
10	0.5	*t*-BuOK	70	1	89 (96)	91
11	0.1	*t*-BuOK	70	1	95 (96)	91
12	0.05	*t*-BuOK	70	1	87 (88)	95
13[e]	0.01	*t*-BuOK	70	1	45 (45)	97

[a] The transfer hydrogenation was carried out with acetophenone (**6a**) in *i*-PrOH (65 eq) in the presence of base (1 mol%) and Ir complex (–)-**8dz** (0.01-5 mol%) under N_2. [b] Isolated yield. [c] Conversion based on ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis with a chiral stationary phase column. [e] 0.1 mol% of *t*-BuOK and 6.5 eq of *i*-PrOH were used.

Then, the asymmetric transfer hydrogenation of several ketones was accomplished. The results are summarized in Table 4. In all cases, new Ir complex **8dz** displayed high enantioselectivities, affording corresponding chiral alcohols. The important point is that the tendency of enantioselectivity increase with catalyst loading emerged distinctly as a general phenomenon (odd numbered entries vs. even numbered entries). Although the reason for the dilute catalyst condition is unclear at present, we expect that this would provide additional information on the mechanistic study of the reaction which is still under debate.[6b]

Table 4 Asymmetric transfer hydrogenation of ketones with **8dz**[a]



6 (*S*)-**7**

Entry	**6**	R^1	R^2	x (mol%)	Yield[b] (%)	% Ee[c]
1	**6b**	Ph	Et	0.1	95	96
2				0.05	93	97
3	**6c**	Ph	Pr	0.1	94	96
4				0.05	79	97
5	**6d**	Ph	Bu	0.1	87	95
6				0.05	15	97
7	**6e**	4-MeC_6H_4	Me	0.1	88	87
8				0.05	86	92
9	**6f**	3- MeC_6H_4	Me	0.1	65	83
10				0.05	20	83
11	**6g**	Ph	$PhCH_2$	0.1	98	96
12				0.05	66	98
13	**6h**	4-FC_6H_4	Me	0.1	95	89
14				0.05	90	92
15	**6i**	4-ClC_6H_4	Me	0.1	91	95
16				0.05	trace	-
17	**6j**	4-BrC_6H_4	Me	0.1	82	93
18				0.05	83	93
19	**6k**	4-IC_6H_4	Me	0.1	83	94
20				0.05	60	95
21	**6l**	4-MeOC_6H_4	Me	0.1	75	81
22				0.05	55	94
23	**6m**	2-Naphthyl	Me	0.1	55	77
24				0.05	37	83

[a] The transfer hydrogenation was carried out with ketone **6** in *i*-PrOH (65 eq) in the presence of *t*-BuOK (1 mol%) and Ir complex (–)-**8dz** (0.05-0.1 mol%) at 70 °C for 1 h under N_2. [b] Isolated yield. [c] Determined by HPLC analysis with a chiral stationary phase column.

Complexes **8** were obtained as light yellow solids sufficiently stable for purification by silica gel chromatography

and have high solubility in various organic solvents. As **8dz** that gave the best results in the present reaction is soluble even in hexane, we were unable to obtain good crystals of **8dz** for X-ray crystallography. However, the crystallization of **8av** and **8cv**, which have different substituents on the basic structure of **8**, was successful (Fig. 3).[9] The crystal structures revealed that the NHC ligands coordinated to the iridium center with the heterocyclic plane facing vertically toward the square planar coordination plane. Intriguingly, the two types of NHC ligands differed in spatial orientation on coordination to iridium: the diphenylmethyl group was observed at the lower side of the coordination plane in **8av**, whereas it was observed at the upper side in **8cv**. The ^{1}H-NMR spectra of **8av** indicated that conformational isomers derived from the restricted rotation around the carbene-Ir bond axis exist in a 2:1 ratio in the solution state. The rotation barrier was, however, not as high as to isolate one isomer from the other at room temperature,[10] because ^{1}H-NMR analysis of **8av** that was prepared by dissolving the same lot of crystals as that used for X-ray crystallography showed also a 2:1 ratio of the isomers. On the other hand, a single species was observed in the ^{1}H-NMR spectra of **8cv**, which has a bulkier substituent R than **8av**. We believe that controlling the equilibrium between conformational isomers, which is influenced by the bulkiness of the substituent R, would be related to the enantioselectivities in Table 1 (entries 1-4). Indeed, no conformational isomer was observed in the ^{1}H-NMR spectra of **8dz**, which gave the best enantioselectivity of the reaction.

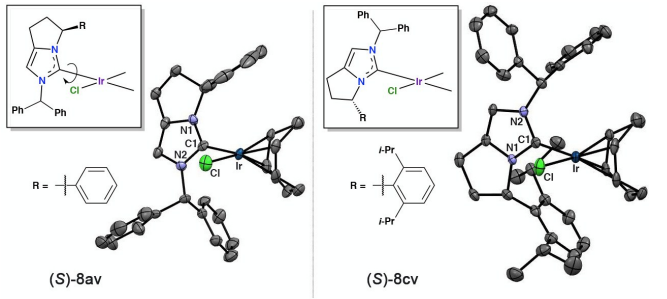


Fig. 3 Crystal structures of (*S*)-(–)-**8av** and (*S*)-(–)-**8cv**: Hydrogen atoms and CH_2Cl_2 (only for (*S*)-(–)-**8cv**) are omitted for clarity.

Conclusions

We have developed bench-stable, easily manipulable, and highly soluble NHC/Ir complex **8dz** as an excellent catalyst precursor for the asymmetric transfer hydrogenation. The present catalyst screening based on our synthesis of chiral bicyclic imidazolium salts is not limited to the Ir system. Investigations aimed at applying the screening procedure to other asymmetric reactions are in progress in our laboratory.

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