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# Highly Enantioselective Construction of the α-Chiral Center of Amides *via* Iridium-Catalyzed Hydrogenation of α,β-Unsaturated Amides

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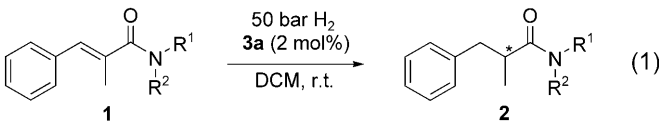
**Abstract:** The chiral center at the α-position of amides is installed in excellent enantioselectivity *via* the iridium-catalyzed asymmetric hydrogenation of α,β-unsaturated amides under mild conditions. Even aliphatic amides are suitable substrates. The presence of a hydrogen atom on the nitrogen of the amide is important for the enantioselectivity of the reaction.

**Keywords:** amides; enantioselectivity; hydrogenation; iridium; P,N ligands

Amides with an α-chiral center are an important class of compounds because not only are they widely present as important subunit in natural products[1] but also they can be transformed into many other useful compounds such as ketones, amines, etc.[2] Many procedures have been developed to install a chiral center at the α-position of amides *via* alkylation, however, chiral auxiliaries have been used in most cases.[2,3] A catalytic version of the enantioselective alkylation of amides with an α-chiral center has only been realized for a few examples,[4] one of the reasons is the racemization of the chiral carbon *via* enolization in strong basic conditions. A great challenge remains regarding the effective synthesis of chiral amides enantioselectively. One approach to address this challenge is the reaction under neutral conditions. In this regard, hydrogenation seems to be a good choice. The transition metal-catalyzed asymmetric hydrogenation as a practical protocol has attracted much attention in recent years.[5] Among them, chiral iridium complexes have shown their unique properties both in asymmetric induction and catalytic activity.[6–9] A variety of compounds have been used as substrates in Ir-catalyzed hydrogenation reaction, in particular, the α-chiral center of carbonyl compounds has been successfully established *via* Ir-catalyzed hydrogenation of α,β-unsaturated ketones as well as carboxylic acids.[8,9] However, only lower enantioselectivities were obtained when α,β-unsaturated amides were used.[10] Recently, Bolm[8b] and we[9] realized the Ir-catalyzed hydrogenation of α,β-unsaturated ketones in high enantioselectivity. Based upon the results, we investigated the hydrogenation of α,β-unsaturated amides. In this communication, we would like to report our preliminary results on the asymmetric hydrogenation of α,β-unsaturated amides with aromatic and/or aliphatic substituents at the α- and β-positions using chiral Ir complexes; a wide range of amides with an α-carbon chiral center in high enantioselectivity were obtained. The importance of the presence of hydrogen on the nitrogen of the amide group is also demonstrated.

Initially, the asymmetric hydrogenation of α,β-unsaturated amide **1a** was carried out by using 2 mol% of **3a** as catalyst in dichloromethane (DCM) under 50 bar of $H_2$ pressure at room temperature [Eq. (1)]. Chiral amide **2a** was obtained with completed conversion but the *ee* value was only 21%.

To improve the enantioselectivity, amides **1** with different substituents on nitrogen were tested (Table 1). The results showed that all reactions pro-




(1)

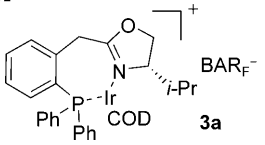


**Table 1.** The asymmetric hydrogenation of amides **1** with different substituents on N catalyzed by Ir complex **3a**.[a]

| Entry | **1**, $R^1$, $R^2$ | Conv. [%][b] | *ee* [%][c] |
|---|---|---|---|
| 1 | **a**, -$(CH_2CH_2)_2O$ | 100 | 21 |
| 2 | **b**, Et, Et | 100 | 30 |
| 3 | **c**, Ph, H | 100 | 54 |
| 4 | **d**, *n*-Bu, H | 100 | 42 |
| 5 | **e**, *i*-Bu, H | 100 | 55 |
| 6 | **f**, Bn, H | 100 | 49 |
| 7 | **g**, $CH_2CH_2OMe$, H | 100 | 45 |

[a] *Reaction conditions:* **1** (0.1 mmol), catalyst (2 mol%), $H_2$ (50 bar), DCM 2 mL. The reaction mixture was stirred at room temperature for 24 h.
[b] Determined by $^1$H NMR.
[c] Determined by chiral HPLC.

ceeded to complete conversion. Better enantioselectivities were realized when one substituent on nitrogen was H in spite of the other substituent being aromatic (entry 3) and aliphatic groups having different steric hindrance (entries 4–7) while amides **1a** and **1b** with two substituents on the nitrogen gave the products in lower *ee* (entries 1 and 2).

Based upon these results, the influence of different type of ligands on the enantioselectivity were investigated using amide **1e** as substrate (Figure 1, Table 2). The catalysts **4** derived from PHOX ligands[7b,11] provided product in better *ee* than the catalysts **3** derived from benzylic-substituted ligands developed by our group[12] (entries 3, 4 *vs.* entries 1, 2). Interestingly, the catalysts **5** derived from Fc-PHOX[13] gave even better results, among which **5b** and **5e** with a *t*-Bu group on the oxazoline ring and phenyl and 4-methoxyphenyl substitutents on P the atom, respectively, provided the product in 93% *ee*, the highest value among the catalysts screened (entries 6 and 10). Catalyst **5a** with an *i*-Pr substituent on the oxazoline ring

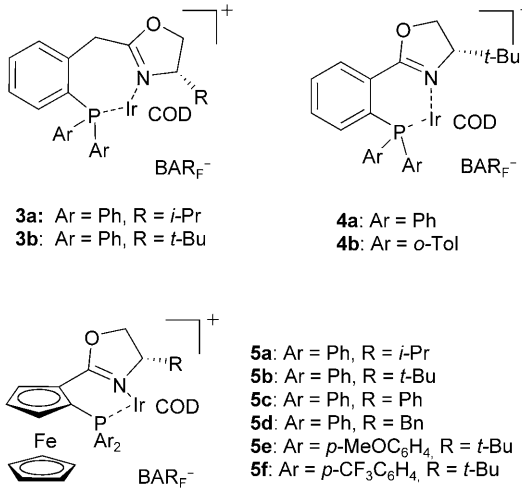



**Figure 1.** The structures of the catalysts.

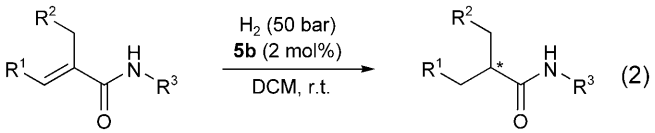
**Table 2.** The influence of ligands with different structure in the asymmetric hydrogenation of unsaturated amide **1e**.[a]

| Entry | Catalyst | Conv. [%][b] | *ee* [%][c] |
|---|---|---|---|
| 1 | **3a** | 100 | 55 |
| 2 | **3b** | 100 | 70 |
| 3 | **4a** | 100 | 81 |
| 4 | **4b** | 100 | 79 |
| 5 | **5a** | 100 | 79 |
| 6 | **5b** | 100 | 93 |
| 7[d] | **5b** | 100 | 90 |
| 8 | **5c** | 100 | 62 |
| 9 | **5d** | 100 | 62 |
| 10[d] | **5e** | 100 | 93 |
| 11 | **5e** | 94 | 86[e] |
| 12[d] | **5f** | 100 | 91 |
| 13 | **5f** | 41 | Nd.[e,f] |

[a] *Reaction conditions:* **1e** (0.1 mmol), catalyst (2 mol%), $H_2$ (50 bar) DCM 2 mL. The reaction mixture was stirred at room temperature for 24 h.
[b] Determined by $^1$H NMR.
[c] Determined by chiral HPLC.
[d] 0.6 mol% of catalyst was used.
[e] 0.1 mol% of catalyst was used.
[f] Not determined.

furnished product **2e** in 79% *ee* (entry 5), while **5c** and **5d** with Ph and Bn as substituents on the oxazoline ring provided chiral amide **2e** in 62% *ee* (entries 8 and 9). The electronic property of the substituent on the phenyl ring on the P atom has only a slight effect on the enantioselectivity. Catalysts **5e** and **5f** with MeO and $CF_3$ at the 4-position of phenyl ring, respectively, provided products with close *ee*s (entry 10 *vs.* entry 12). The studies on the effect of common solvents (toluene, $CHCl_3$, THF, AcOEt, $CH_2Cl_2$) using **1e** as substrate and **5b** as catalyst under the conditions of Eq. (1) revealed that toluene (93% *ee*), AcOEt (92% *ee*) and $CH_2Cl_2$ (93% *ee*) are suitable solvents (not showed in the Table 2).

Under the above reaction conditions, different substrates were subjected to the hydrogenation reaction using **5b** as catalyst [Eq. (2), Table 3]. All amides **1c–p** with different aromatic substituents at the β-posi-




1

**h**: $R^1$ = Ph, $R^2$ = *t*-Bu, $R^3$ = *i*-Bu
**i**: $R^1$ = Ph, $R^2$ = Bn, $R^3$ = *i*-Bu
**j**: $R^1$ = Ph, $R^2$ = naphthalenyl, $R^3$ = *i*-Bu
**k**: $R^1$ = *m*-$ClC_6H_4$, $R^2$ = Et, $R^3$ = *i*-Bu
**l**: $R^1$ = *p*-$MeOC_6H_4$, $R^2$ = Et, $R^3$ = *i*-Bu
**m**: $R^1$ = Ph, $R^2$ = Et, $R^3$ = *i*-Bu

2

**n**: $R^1$ = Ph, $R^2$ = *i*-Pr, $R^3$ = *i*-Bu
**o**: $R^1$ = Ph, $R^2$ = *n*-Bu, $R^3$ = *i*-Bu
**p**: $R^1$ = Ph, $R^2$ = MeO, $R^3$ = *i*-Bu
**q**: $R^1$ = *i*-Pr, $R^2$ = H, $R^3$ = Bn
**r**: $R^1$ = *n*-Pr, $R^2$ = H, $R^3$ = Bn
**s**: $R^1$ = *i*-Bu, $R^2$ = H, $R^3$ = Bn
**t**: $R^1$ = Me, $R^2$ = H, $R^3$ = Ph

**Table 3.** Asymmetric hydrogenation of α,β-unsaturated amide **1** catalyzed by **5b.**[a]

| Entry | Substrate | [Ir] (mol%) | Conv. [%][b] | *ee* [%][c] |
|---|---|---|---|---|
| 1 | **1c** | 2 | 100 | 96 |
| 2 | **1d** | 2 | 100 | 84 |
| 3 | **1e** | 2 | 100 | 93 |
| 4 | **1f** | 2 | 100 | 95 |
| 5 | **1g** | 2 | 100 | 90 |
| 6 | **1h** | 2 | 100 | 96 |
| 7 | **1i** | 2 | 100 | 97 |
| 8 | **1j** | 2 | 100 | 87 |
| 9 | **1k** | 2 | 100 | 98 |
| 10 | **1l** | 3 | 100 | 96 |
| 11 | **1m** | 2 | 100 | 97 |
| 12 | **1n** | 2 | 100 | 96 |
| 13 | **1o** | 2 | 100 | 95 |
| 14 | **1p** | 2 | 100 | 95 |
| 15 | **1q** | 2 | 100 | 93 |
| 16 | **1r** | 2 | 100 | 84 |
| 17 | **1s** | 2 | 100 | 87 |
| 18 | **1t** | 2 | 100 | 95 |
| 19 | **1u** | 2 | 100 | 75 |
| 20 | **1c** | 2 | 99 | 97[d] |
| 21 | **1t** | 2 | 85 | Nd.[d,e] |
| 22 | **1t** | 3 | 100 | 98[d] |

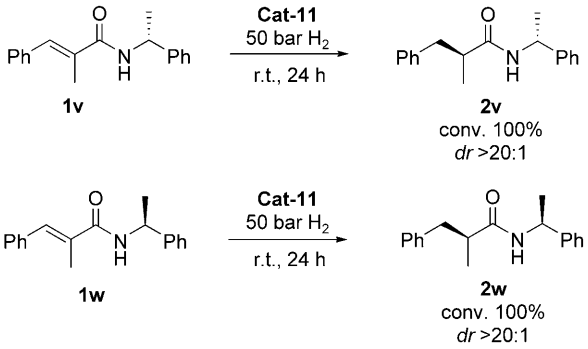
[a] *Reaction conditions:* **1** (0.1 mmol), catalyst (2 mol%), $H_2$ (50 bar), solvent 2 mL at room temperature. The reaction mixture was stirred for 24 h to assure the complete conversion of **1**.
[b] Determined by $^1$H NMR.
[c] Determined by chiral HPLC.
[d] The hydrogenation pressure is 1 atm.
[e] Not determined.

tion and with different aryl and alkyl or even heteroatom substituents at the α-position provided the corresponding amides with an α-chiral center in complete conversion and in high enantioselectivities (entries 1–14). It should be noted that amides with alkyl substituents at both the α- and β-positions are also suitable substrates to afford chiral aliphatic amides in complete conversion and in high *ee* (entries 15–19) while worse results were obtained by using the corresponding aliphatic α,β-unsaturated ketones as substrates.[8b,9]

The hydrogenation of amides **1c** and **1t** also proceeded smoothly under ambient $H_2$ pressure, providing the products in slightly increased *ee* (entries 20 and 22 *vs.* entries 1 and 18).

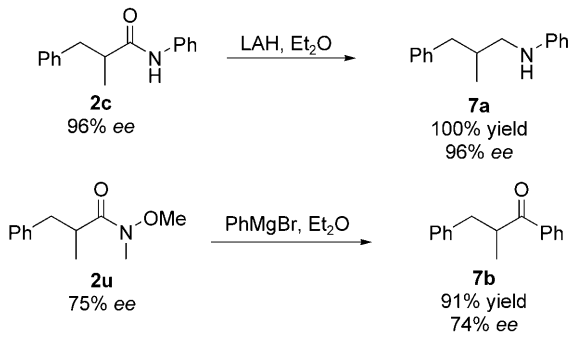
The hydrogenation can also be carried out on a gram-scale. When 1.314 g of **1t** (7.5 mmol) were hydrogenated with 0.2 mol% **5b** as catalyst under 50 bar hydrogen pressure at room temperature for 24 h, 1.276 g (96% yield) of **2t** were produced in 94% *ee*.

The stereochemistry of the substituent on nitrogen has little effect on the selectivity of the reaction. Hydrogenation of the amides **1v** and **1w** having chiral substituents with different configurations on the nitrogen provided products with the same configuration at the α-position of the amide [Eq. (3)].




(3)

The utilities of amides with an α-chiral center obtained from hydrogenation are demonstrated by the transformation of **2c** and **2u** into chiral amine **7a** and chiral ketone **7b** in high yields and with no decrease of the *ee* values [Eq. (4)].




(4)

The absolute configuration of α-carbon of amides **2t**,[14a] **2v** and **2w**[14b] was determined as (*S*) by comparison of their analytical data with those of authentic samples reported in the literature.[14]

In summary, the asymmetric hydrogenation of α,β-unsaturated amides has been realized by using a chiral Ir catalyst, providing amides with an α-chiral center in high enantioselectivity. Even aliphatic amides are suitable substrates. The presence of hydrogen on the nitrogen of the amide is important for the enantioselectivity of the reaction. The usefulness of these chiral amides with an α-chiral center has also been demonstrated. Investigation on the details of the reaction and the role of the H atom on the nitrogen atom of the amide are in progress.

## Experimental Section

### General Procedure for the Asymmetric Hydrogenation

A mixture of catalyst **5b** (0.002 mmol), substrate **1** (0.1 mmol), and DCM (2 mL) in a tube containing a mag-

netic stir bar was placed in an autoclave under air and the autoclave was sealed. The autoclave was pressurized to 50 bar with $H_2$ and the solution was stirred at room temperature for 24 h. The pressure was then carefully released and the reaction mixture was passed through a short column of silica gel with ethyl acetate/petroleum ether. The solution was then concentrated and the resulting oil or solid was analyzed.

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