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Highly Chemo- and Enantioselective Hydrogenation of Linear α,β-Unsaturated Ketones

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Asymmetric hydrogenation of olefins is one of the most powerful transformations in asymmetric catalysis. In reductions of unfunctionalized substrates, chiral iridium complexes with N-heterocyclic carbene ligands or P,N-ligands have revealed high activities and excellent enantioselectivities under relatively mild reaction conditions.[1] Catalytic asymmetric hydrogenations of functionalized olefins such as α-(acylamino) acrylic acids, enamides, α,β-unsaturated carboxylic acids and esters, allylic and homoallylic alcohols have also been widely investigated, and they can most successfully be performed with chirally modified ruthenium, rhodium and iridium complexes.[2] In contrast, enone-to-ketone hydrogenations are less studied, which is surprising considering the synthetic importance of compounds with stereogenic centers at the α- or β-position to a carbonyl group.[3]

Generally, the chemoselectivity is a key issue in the hydrogenation of α,β-unsaturated ketones, since both double bonds can react. Commonly, in catalytic hydrogenations C=C double bonds are more reactive than C=O ones.[4] Important exceptions are Noyori's Ru^{II}–diamine–diphosphine[5a–c] and Takaya's Ir^{I}–BINAP[5d] catalyst systems, which preferentially reduce carbonyl groups faster than C=C double bonds. Effective catalysts for enantioselective C=C bond hydrogenations of unsaturated ketones, especially those applicable for linear substrates, are still rare.[6] The following examples shall illustrate the current status.

As early as 1983, Maux and Simonneaux investigated asymmetric hydrogenations of α,β-unsaturated ketones catalyzed by chiral $[Co_2(CO)_8]$/phosphine complexes giving saturated ketones with 1–16% *ee*.[7] Later, the enantioselectivity was improved to 62% *ee* by using a chiral ruthenium complex as the catalyst,[8] but only 2% *ee* were achieved in asymmetric hydrogenations of linear α,β-unsaturated ketones. In 1995, Takaya and co-workers employed Ru^{II}–BINAP complexes as catalysts to hydrogenate *exo*-cyclic enones, and they obtained 2-alkyl-substituted cyclic ketones with up to 98% *ee*.[9] However, the conversion of a 2-aryl-substituted substrate provided a product with only 9% *ee*, and furthermore, to achieve full conversion, it was necessary to employ both high pressure (100 bar) and elevated temperature (50 °C). A few selected examples of hydrogenations of *endo*-cyclic enones were reported by Consiglio[10] and Genet.[11] The former obtained (two) products with up to 76% *ee* and the latter focused on a synthesis of (+)-*cis*-methyl dihydrojasmonate, which was finally prepared with 88% *ee*. In 2005, Hilgraf and Pfaltz investigated the hydrogenation of 3-methyl cyclohexenone using iridium/P,N-ligand complexes as catalysts, and a moderate enantioselectivity (58% *ee*) was obtained under high pressure (100 bar) using a 4 mol% catalyst loading.[12] Subsequently, MacMillan[13] and List[14] found organocatalytic transfer hydrogenation of enones using Hantzsch esters as hydrogen sources. Excellent enantioselectivities (up to 98% *ee*) were obtained in the conjugate reduction of *endo*-cyclic enones. However, linear enones were less suitable and an ee_{max} of only 70% was obtained.[14] The most recent developments stem from Mashima and co-workers, who used a cationic Rh^{I}/DTBM-SegPhos/$(CH_2CH_2PPh_3Br)_2$ catalyst system to hydrogenate *endo*-cyclic enones providing products with up to 98% *ee*.[15] Heterogeneous hydrogenations of *exo*-cyclic enones have also been investigated,[16] but only moderate enantioselectivities were achieved.

Recently, we reported the synthesis of sulfoximine-derived P,N-ligands and their applications in iridium-catalyzed asymmetric hydrogenation reactions.[17,18] As part of our continued interest in the area and with the goal to explore the general reactivity pattern of this catalyst family (see below, complexes **1** and **2**), we focused our efforts now on the hydrogenation of α,β-unsaturated ketones.

We began the study using linear β,β-disubstituted 1,3-diphenyl-2-butenone [(*E*)-**4a**] as model substrate and iridium

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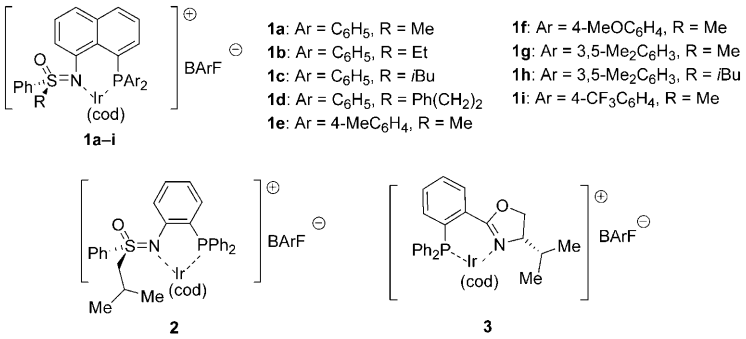
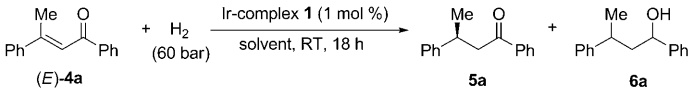


complex **1a** as catalyst (1 mol%). To our delight, full conversion and excellent chemoselectivity resulted at 60 bar hydrogen pressure in a reaction performed at room temperature in toluene for 18 h. The major product (≥95%) was saturated ketone **5a** (1,3-diphenyl-butan-1-one) with 76% *ee,* and only traces of the corresponding saturated alcohol **6a** (≤5%) could be detected (Table 1, entry 1). No allylic alcohol was formed. These results were surprising and indicated the discovery of a complementary catalysts system to that of Noyori, whose Ru^{II}–diamine–diphosphine complexes provided unsaturated alcohols from α,β-unsaturated ketones.[5] When the reaction was carried out with complex **2**, incomplete conversion of enone (*E*)-**4a** (75%) resulted, and larger quantities (15%) of saturated alcohol **6a** were formed (Table 1, entry 2). Although the conversion of the reaction with complex **3** was complete, the enantioselectivity was low giving **5a** with 26% *ee*. Furthermore, a significant amount of **6a** was found (entry 3).

In order to improve the catalyst system, the effect of the solvent and the structural details of complex **1** were studied.

Table 1. Enantioselective hydrogenation of 1,3-diphenyl-2-butenone [(*E*)-**4a**].[a]



Entry	Solvent	Complex	Conversion [%][b]	*ee* of **5a** [%][c]
1	toluene	**1a**	>95	76
2	toluene	**2**	75 (60)[d]	n.d.
3	toluene	**3**	>95 (69)[d]	26
4	CH_2Cl_2	**1a**	>95	76
5	THF	**1a**	35	n.d.
6	toluene	**1b**	>95	75
7	toluene	**1c**	>95	81
8	toluene	**1d**	>95	80
9	toluene	**1e**	>95	78
10	toluene	**1f**	>95	75
11	toluene	**1g**	>95	75
12	toluene	**1h**	>95	71
13	toluene	**1i**	>95	54

[a] Reactions conditions: (*E*)-**4a** (0.5 mmol), catalyst **1** (1 mol%), solvent (1.5 mL), 18 h reaction time, under argon at room temperature. [b] Measured by ^{1}H NMR. [c] Enantiomer ratios were determined by HPLC by using a Chiralcel OJ column. The *S* enantiomer of the product was formed in excess; n.d. = not determined. [d] The values in parentheses refer to the detected amount of saturated ketone **5a**.

Complete conversion and formation of ketone **5a** with 76% *ee* were found when the reaction was carried out in dichloromethane (Table 1, entry 4). In THF the conversion was low (35%; entry 5). By using toluene as solvent, hydrogenations of (*E*)-**4a** catalyzed by complexes **1b–i** proceeded well as indicated by the results shown in Table 1, entries 6–13. All complexes were highly effective leading to full conversion and the predominate formation of ketone **5a** (>95%). The alkyl substituents of the sulfoximidoyl moiety and the substitution pattern of the phenyl group at the phosphorus atom had no obvious effect on the performance of the resulting catalysts. All (complexes **1a–h**) provided **5a** with similar enantioselectivity (in the range of 71–81% *ee*, Table 1, entries 1 and 6–12), and only complex **1i** led to **5a** with a significantly lower *ee* (54%; entry 13). The best result (>95% conversion, 81% *ee*) was obtained, when complex **1c** was used as catalyst.

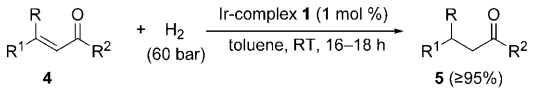
Encouraged by the results achieved in the asymmetric hydrogenation of (*E*)-**4a** catalyzed by complexes **1**, various other β,β-disubstituted enones were applied (Table 2). Generally, the substrate conversions were high. The reactions with enones (*E*)-**4a–d** revealed that increasing the size of the alkyl group at the β-position of the carbonyl group had a positive effect on the enantioselectivity. Thus, methyl substituted (*E*)-**4a** was hydrogenated with **1c** as catalyst to give a product with 81% *ee* (Table 2, entry 1). Under the same conditions, the ethyl-, isopropyl, and cyclohexyl-substituted analogues [(*E*)-**4b**, (*E*)-**4c**, and (*E*)-**4d**] gave the corresponding ketones (**5b–d**) with 89, 97 and 97% *ee*, respectively (Table 2, entries 5, 10, and 17).

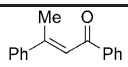
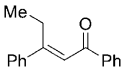
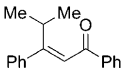
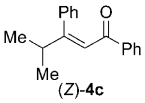
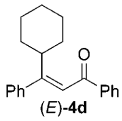
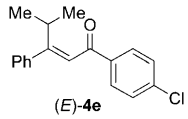
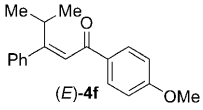
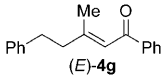
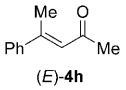
For the hydrogenation of enone (*Z*)-**4c**, which differed from (*E*)-**4c** by its altered olefin geometry, both conversion and enantioselectivity were slightly lower (compared with the analogous reaction of its diastereomeric counterpart). The absolute configuration of the product (ketone **5c**) was reversed (entries 14–16), which indicated that the catalyst approached the olefin from the same face. Consequently, the ratio of the (*Z*)- and (*E*)-isomers will greatly affect the enantioselectivity of the product. From a practical point of view, this offers a convenient access to both enantiomers of a ketone by using the same catalyst if isomerically pure substrates are available.

Changing the substitution pattern on the ketonic phenyl group affected both conversion and enantioselectivity only to a small degree. Thus, hydrogenations of chloro- and methoxy-substituted enones (*E*)-**4e** and (*E*)-**4f** with **1d** as catalyst led to almost identical results (>95% conversion in both cases; 96% *ee* for **5e** and 97% *ee* for **5f**) as conversions of (*E*)-**4c**.

In order to test if the aryl groups of the substrates were essential for efficient asymmetric hydrogenations, enone

Table 2. Enantioselective hydrogenations of linear α,β-unsaturated ketones.[a]



Entry	Substrates	Catalyst	Yield [%][b]	*ee* [%][c] configuration[d]
1		**1c**	89	81 (*S*)
2		**1d**	94	80 (*S*)
3	(*E*)-**4a**	**1f**	91	75 (*S*)
4		**1a**	92	86 (*S*)
5		**1c**	94	89 (*S*)
6		**1d**	88	87 (*S*)
7	(*E*)-**4b**	**1f**	92	88 (*S*)
8		**1h**	92	85 (*S*)
9		**1a**	90	96 (+)
10		**1c**	94	97 (+)
11		**1d**	93	97 (+)
12	(*E*)-**4c**	**1f**	93	96 (+)
13		**1g**	90	96 (+)
14		**1c**	86	92 (−)
15		**1d**	80[e]	87 (−)
16	(*Z*)-**4c**	**1g**	93	93 (−)
17		**1c**	88	97 (+)
18		**1d**	89	97 (+)
19	(*E*)-**4d**	**1g**	91	97 (+)
20		**1c**	91	95 (−)
21		**1d**	93	96 (−)
22	(*E*)-**4e**	**1g**	93	94 (−)
23		**1c**	93	97 (−)
24		**1d**	91	97 (−)
25	(*E*)-**4f**	**1g**	90	97 (−)
26		**1c**	93	81 (+)
27		**1d**	94	80 (+)
28	(*E*)-**4g**	**1h**	89	77 (+)
29		**1a**	65[f]	80 (*S*)
30		**1c**	70[f]	79 (*S*)
31		**1d**	74[f]	81 (*S*)
32	(*E*)-**4h**	**1g**	75[f]	79 (*S*)

[a] Reactions conditions: substrate (0.25 mmol), catalyst **1** (1 mol %), toluene (1.0 mL), 16–18 h reaction time. All the reactions were carried out under argon at room temperature and full conversion were obtained for all reaction unless otherwise specified. [b] Yield of isolated product based on α,β-unsaturated ketone. [c] Determined by HPLC analysis; see Supporting Information. [d] Absolute configurations assigned by comparison of optical rotations with literature values. For unknown compounds, the sign of optical rotation is noted. [e] Only 80 % conversion in this reaction. [f] The value in parentheses indicates the amount of saturated ketone.

(*E*)-**4g** having a ketonic phenyl group and two alkyl substituents at the olefinic β-positions was used as starting material (Table 2, entries 26–28). Furthermore, methyl ketone (*E*)-**4h** with a β-methyl and β-phenyl substituent was applied (Table 2, entries 29–32). For both substrates the conversions were complete and the enantioselectivities in the formation of the corresponding saturated ketones (**5g** and **5h**, respectively) were comparable to the one observed in the reaction with enone (*E*)-**4a**. Noteworthy is that the hydrogenation of (*E*)-**4h** also generated a significant amount of saturated alcohol (fully reduced product; not shown), which was formed with moderate *ee* (57–66 %). These results allow the conclusion that the aryl groups were not required for conversion and enantioselectivity, but that the presence of a ketonic aryl group positively affected the chemoselectivity of the reaction.

In summary, we discovered and developed catalysts for the enantioselective hydrogenation of linear enones providing saturated ketones with up to 97 % *ee*. The application of the catalyst system to other substrates is currently under investigation.

Experimental Section

General procedure for hydrogenation: Complex **1a** (4.1 mg, 0.0025 mmol) and substrate **4** (0.25 mmol) were placed in a 5 mL vial equipped with a stirrer bar. This vial was then put into an argon-filled steel autoclave. To the mixture was added toluene (1.0 mL) under an argon atmosphere. The autoclave was then closed, purged three times with hydrogen (less than the pressure needed) and finally pressurized to the value needed. The reaction mixture was stirred for the indicated period of time, and then the hydrogen gas slowly released. The conversion of the substrate was determined by ^{1}H NMR spectroscopy of the crude reaction mixture, and the product was purified by chromatography with pentane/ethyl acetate 10:1. Enantiomeric ratios were analyzed with HPLC by using a Chiralcel column. The synthetic procedures for the substrate preparations, HPLC conditions, and the spectral data of new compounds are provided in Supporting Information.

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Keywords: enantioselectivity · hydrogenation · iridium · ketones · sulfoximines

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