

Highly Enantioselective Synthesis of Optically Active Ketones by Iridium-Catalyzed Asymmetric Hydrogenation**

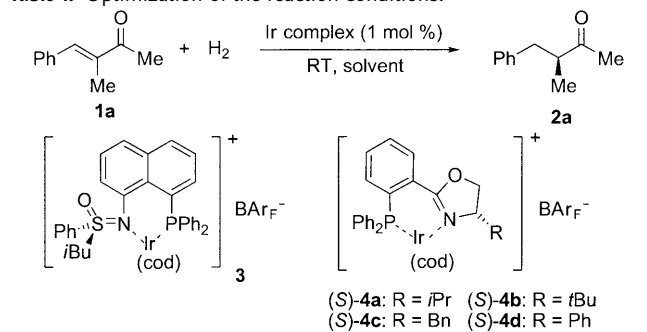
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Strategies for controlling the absolute configuration at the α position of a ketonic carbonyl compound usually rely on enantioselective protonations of achiral enolates or enol equivalents,^[1] asymmetric α alkylations using chiral auxiliaries,^[2] or enantioselective reductions of enones.^[3] However, most of the reported methods are limited in substrate scope, only a few are catalytic, and overall they do not provide a general solution for the preparation of optically active ketones. A highly enantioselective catalytic method for achieving this goal is most desirable, but has remained undiscovered to date.

As a consequence of their high efficiency, atom economy, and operational simplicity, asymmetric hydrogenations of properly selected prochiral starting materials provide highly practical and powerful routes to enantiomerically enriched compounds.^[4] Bearing this in mind, we realized that the hydrogenation of readily accessible α -substituted enones would be one of the most straightforward and simplest ways to prepare α -substituted chiral ketones. While there has been significant progress in the asymmetric hydrogenation of cyclic compounds of this type,^[5,6] to the best of our knowledge, there is no example of such a reduction with acyclic compounds.^[7,8] Herein, we report the first general method for the asymmetric synthesis of α -substituted ketones by the hydrogenation of enones which is applicable for both cyclic and acyclic substrates.^[9,10]

Initially, we examined the hydrogenation reaction of (*E*)-3-methyl-4-phenyl-3-buten-2-one ((*E*)-**1a**) in the presence of iridium complexes bearing chiral sulfoximine-type ligands, which had proven to be highly efficient for the asymmetric hydrogenation of β,β -disubstituted linear enones.^[11,12] The reduction proceeded well with **1a** as substrate and complex **3** as catalyst (under a hydrogen pressure of 2 bar at room temperature for 2 h), but the resulting ketone **2a** had only 55% *ee* (Table 1, entry 1). When the iridium-phosphinooxazoline (phox) complex **4a** was applied under the same conditions, the hydrogenation gave **2a** with 84% *ee* (Table 1, entry 2). To our surprise, in both cases the major product (\geq

Table 1: Optimization of the reaction conditions.^[a]



Entry	Complex	Solvent	H ₂ [bar]	t [h]	<i>ee</i> of 2a [%] ^[b]
1	3	toluene	2	12	55
2	4a	toluene	2	12	84
3	4a	toluene	10	1	83
4	4a	CH ₂ Cl ₂	10	1	78
5	4a	toluene	5	1	84
6	4a	toluene	2	3	85
7	4b	toluene	2	3	98
8	4c	toluene	2	3	69
9	4d	toluene	2	3	25
10	4b	toluene	10	16	99 ^[c]

[a] Reactions conditions: **1a** (0.25 mmol), catalyst (1 mol%), solvent (1.0 mL). All the reactions were carried out under argon at room temperature. The conversion was greater than 95% in all cases (as determined by ¹H NMR spectroscopy). [b] *ee* values were determined by HPLC on a Chiralcel OJ column. The *S* enantiomer of the product was formed in excess. [c] A catalyst loading of 0.1 mol% was used, and the yield was 98% on a 2.5 mmol scale of **1a**. Bn = benzyl.

98%) was the saturated ketone 3-methyl-4-phenyl-2-butanone (**2a**), thus indicating that complex **4a** induced a much better chemoselectivity than in the hydrogenation of β,β -disubstituted linear enones.^[11] At this point, we focused our attention on the effect of the solvent, the hydrogen pressure, and the reaction time on the reduction of **1a**, with **4a** used as the catalyst. The results revealed that the reaction was slightly more enantioselective in toluene than in dichloromethane (Table 1, entries 3 and 4). The hydrogenation pressure and the reaction time had no clear effect on the conversion and enantioselectivity: almost the same results (83–85% *ee*) were obtained when the hydrogen pressure was varied from 2 to 10 bar and the reaction time was changed from 1 to 12 h (Table 1, entries 2, 3, 5, and 6). On the basis of these observations, the conditions described in Table 1, entry 6 (2 bar H₂, 3 h reaction time) were selected for the following reactions.

Three other Ir complexes with phox-type ligands were next tested. The results indicated that the enantioselectivity in

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the asymmetric reduction of enone **1a** was greatly affected by the properties of the substituents on the oxazoline moiety. Although the conversions were complete in all cases, the reaction with *tert*-butyl-substituted complex **4b** (Table 1, entry 7) gave a much higher enantioselectivity (98% *ee*) than **4a** (R = *i*Pr, 85% *ee*; Table 1, entry 6), **4c** (R = Bn, 69% *ee*; Table 1, entry 8), and **4d** (R = Ph, 25% *ee*; Table 1, entry 9). The reaction was also performed with 2.5 mmol **1a** and a catalyst loading of 0.1 mol% (Table 1, entry 10), using **4b** as the catalyst. The high yield (98%) and excellent enantioselectivity (99% *ee*) were maintained despite the higher pressure and longer reaction time.

With the optimized reaction conditions in hand, the scope and limitations of the hydrogenations were investigated. The results are summarized in Table 2. The reductions of enones **1a–c** revealed that changing the substitution pattern of the ketonic moiety has no apparent effect on the conversion and enantioselectivity. The hydrogenation of both the ethyl- and the phenyl-substituted analogues of **1a** (enones **1b** and **1c**, respectively) gave full conversion and excellent enantioselectivities (99% *ee*) after 3 h under a H₂ pressure of 2 bar (Table 2, entries 2 and 3). Replacing the methyl group at the α position of the enone by ethyl, propyl, or phenyl (to give substrates **1d**, **1e**, and **1f**, respectively) affected neither the conversion nor the enantioselectivity of the reaction, and gave the corresponding products with similar selectivity (Table 2, entries 4–6; full conversion and 98–99% *ee*).

Substrate **1g**, in which the phenyl group at the β position of **1c** has been replaced with an ethyl group, was reduced with lower enantioselectivity (87% *ee*) under the same conditions (Table 2, entry 7 versus 3). In contrast, enone **1h**, with phenyl groups at both the α and the β positions, showed excellent activity and enantioselectivity (full conversion, 99% *ee*; Table 2, entry 8). For substrate **1i**, with no substituent other than hydrogen at the β position, a higher pressure (10 bar) was needed to obtain full conversion, and the enantioselectivity was lower (86% *ee*; Table 2, entry 9). The reduction of (*E,E*)-5-(4-methoxy-phenyl)-2-methyl-1-phenyl-1,4-pentadien-3-one (**1j**; Table 2, entry 10), which possesses two C=C double bonds, led to three different products after 3 h under 2 bar H₂ pressure. The major product (50%) was the unsaturated ketone with the C=C bond at the 1,2-position reduced, along with 23% of the fully saturated ketone (**2j**) and 27% of the other enone with the 4,5-C=C bond reduced. When the H₂ pressure was raised to 10 bar, both C=C double bonds were reduced and saturated ketone **2j** with 98% *ee* was produced.

β -Aryl-substituted enones bearing electron-donating and electron-withdrawing groups at the *ortho*, *meta*, or *para* positions of the arene were equally reactive and were hydrogenated with similar results (full conversion, 98–99% *ee*, Table 2, entries 11–20). All these results support the conclusion that this catalyst system has a high tolerance to the substitution pattern and electronic properties of the substrates.

To demonstrate the potential of the catalyst system in the asymmetric synthesis of α -substituted chiral ketones, the hydrogenation of 3-ethyl-4-(3-nitrophenyl)-3-buten-2-one (**5**) was carried out on a gram scale (1.480 g, 6.7 mmol) with **4b**

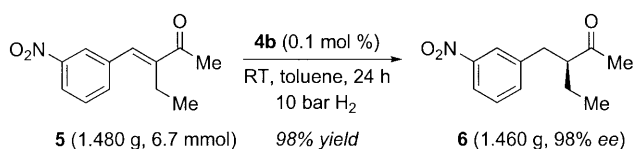
Table 2: Hydrogenation of α -substituted acyclic enones using complex **4b**.^[a]

Entry	Substrate	Product	Yield [%] ^[b]	<i>ee</i> [%] ^[c] Config. ^[d]
1		1a , R = Me	91	98 (S)
2		1b , R = Et	90	99 (S)
3		1c , R = Ph	96	99 (S)
4		1d , R = Et	86	98 (S)
5		1e , R = Pr	88	99 (S)
6		1f , R = Ph	94	98 (R)
7		1g	89	87 (S)
8		1h	93	99 (R)
9		1i	84 ^[e]	86 (R)
10		1j	91 ^[f]	98 (S)
11		1k , R = 2-Me	89	98 (S)
12		1l , R = 2-MeO	90	99 (S)
13		1m , R = 2-Cl	89	98 (S)
14		1n , R = 3-MeO	93	99 (S)
15		1o , R = 3-Cl	92	98 (S)
16		1p , R = 3-NO ₂	91	98 (S)
17		1q , R = 4-Me	90	98 (S)
18		1r , R = 4-MeO	97	98 (S)
19		1s , R = 4-Cl	92	99 (S)
20		1t , R = 4-NO ₂	88	99 (S)

[a] All reactions were carried out with 0.25 mmol substrates and 1 mol% complex **4b** in toluene (1 mL) for 3 h under argon at room temperature, unless otherwise specified. [b] All reactions gave complete conversion unless otherwise specified. The yields are based on enone conversions. The yields refer to the amount of isolated product. [c] Determined by HPLC analysis, see the Supporting Information. [d] The absolute configurations were assigned by comparison of the optical rotations with literature values or assuming analogous reaction pathways. [e] Reaction was carried out at a H₂ pressure of 10 bar for 18 h. [f] Reaction was carried out at a H₂ pressure of 10 bar for 3 h. The product was the fully saturated ketone.

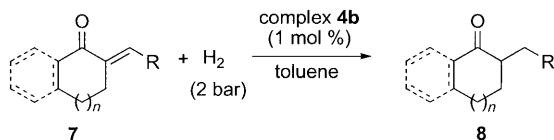
(substrate/catalyst = 870:1) under 10 bar H₂ pressure for 24 h (Scheme 1). Product **6** was isolated in 98% yield and 98% *ee*.

Encouraged by the results obtained with the linear enones, we also tested complex **4b** in the asymmetric hydrogenation of cyclic substrates. Pleasingly, all aryl-substituted *exo*-cyclic enones, regardless of the ring size (Table 3, entries 1–4) or the substitution pattern of the aryl ring



Scheme 1.

Table 3: Hydrogenation of α -substituted cyclic enones using complex 4b.^[a]



Entry	Substrate	Yield [%]	ee [%]	Config.
1		91	92	S
2		93	94	S
3		91	99	S
4		94	97	S
5		94	97	S
6		97	98	S
7		96	99	S
8		96	99	S
9		89	91 ^[b]	S
10		94	89 ^[c]	R

[a] The reaction conditions and methods of analysis are the same as those of Table 2 unless otherwise specified. [b] The reaction was carried out at a H₂ pressure of 5 bar for 24 h. [c] Using complex 3 as the catalyst and a H₂ pressure of 5 bar for 20 h. Complex 4b gave 56% conversion and 70% ee under the same conditions.

(Table 3, entries 5–7), afforded the corresponding products with full conversion and excellent enantioselectivity (92–99% ee). Somewhat lower activities and ee values were observed in the hydrogenation of alkyl-substituted tetralone derivatives (Table 3, entries 9 and 10). In contrast, substrate 7h, with a phenyl group, underwent complete conversion with excellent enantioselectivity (Table 3, entry 8, 99% ee).

In conclusion, we have discovered a simple and highly efficient asymmetric synthesis of α -substituted ketones. Both acyclic and cyclic enones undergo smooth catalytic enantioselective hydrogenations on application of an iridium complex bearing a phox ligand. In contrast to other methods, the protocol tolerates a wide variety of substituents^[15] and delivers products with excellent enantioselectivity in high yields under mild reaction conditions.

Experimental Section

General procedure for the hydrogenation: Complex 4b (3.9 mg, 0.0025 mmol) and substrate 1 (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. Toluene (1.0 mL) was added to the mixture under an argon atmosphere. The autoclave was then closed, purged three times with hydrogen (less than the pressure needed), and finally pressurized to the required value. 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 ¹H NMR

spectroscopic analysis of the crude reaction mixture, and the product was purified by chromatography using a pentane/ethyl acetate mixture (10:1) as eluent. Enantiomeric ratios were determined by HPLC on a Chiralcel column. The HPLC conditions and the spectral data of all compounds are provided in the Supporting Information.

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