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ARTICLE

Iridium-Catalyzed Asymmetric Hydrogenation of Racemic α-Substituted Lactones to Chiral Diols

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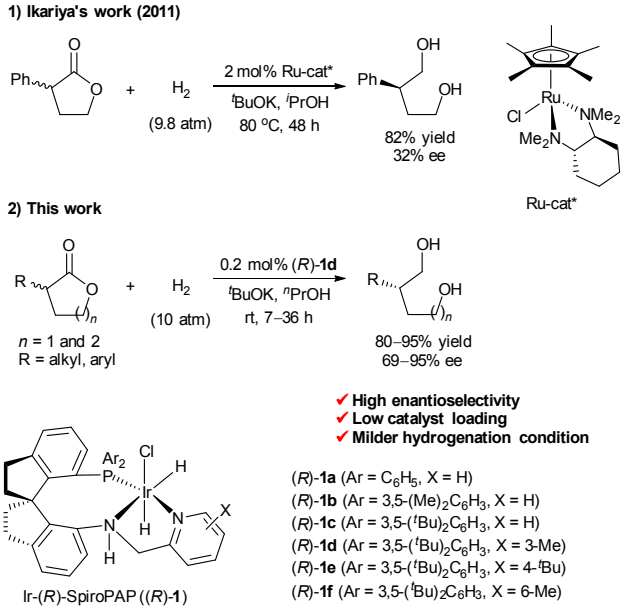
We report a protocol for highly efficient iridium-catalyzed asymmetric hydrogenation of racemic α-substituted lactones via dynamic kinetic resolution. With Ir-SpiroPAP (*R*)-**1d** as a catalyst, a wide range of chiral diols were prepared in high yield (80–95%) with high enantioselectivity (up to 95% ee) under mild reaction conditions. The protocol was used for enantioselective syntheses of (–)-preclamol and a chiral 2,5-disubstituted tetrahydropyran.

Introduction

Transition-metal-catalyzed asymmetric hydrogenation of ketones is an efficient and reliable method for the synthesis of optically active chiral secondary alcohols.[1] In contrast, the enantioselective synthesis of chiral primary alcohols by catalytic asymmetric hydrogenation of the corresponding aldehydes or esters is difficult, and work on the development of practical methods is underway. In 2007, we reported the first example of catalytic asymmetric hydrogenation of racemic α-branched aldehydes via dynamic kinetic resolution (DKR) for the synthesis of chiral primary alcohols.[2] Subsequently, List [3] and Lin [4] et al. also reported the synthesis of chiral primary alcohols, by means of ruthenium-catalyzed asymmetric hydrogenation of racemic α-substituted aldehydes. Although a wide range of catalysts have been developed for the hydrogenation of esters,[5] efficient chiral catalysts for asymmetric hydrogenation of racemic α-substituted esters via DKR are rare. The biggest challenge for direct asymmetric hydrogenation of racemic esters to form optically active primary alcohols is to find a catalyst that can discriminate the enantiomers of chiral esters and hydrogenate them to alcohols selectively. In 2011, Ikariya et al.[6] described the enantioselective hydrogenation of a racemic α-substituted γ-lactones to chiral 1,4-diol via DKR using chiral ruthenium catalysts bearing chiral 1,2-diamine ligands (Scheme 1). However, the enantioselectivity of the reaction was low (up to 32% ee). Recently, as part of our work on the asymmetric hydrogenation of ketones, we found that chiral Ru-SDPs/diamine catalysts and chiral Ir-SpiroPAP catalysts can also mediate the hydrogenation of ester groups.[7]



Scheme 1 Asymmetric hydrogenation of racemic α-substituted lactones via DKR.

In this communication, we report a protocol for Ir-SpiroPAP-catalyzed asymmetric hydrogenation of racemic α-substituted lactones to afford chiral diols in high yield (80–95%) with high enantioselectivity (up to 95% ee, Scheme 1).

Results and discussion

We initially performed the hydrogenation of racemic α-phenyl δ-valerolactone (**2a**) to evaluate the activity and enantioselectivity of various catalysts (Table 1). Under previously reported reaction conditions,[7b] that is, catalyst loading = 0.2 mol % (S/C = 500), [**2a**] = 0.25 M, [^{t}BuOK] = 0.04 M, EtOH, 10 atm H_2, 25–30 °C, no reaction occurred in the

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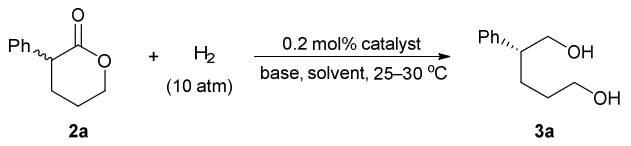
presence of catalyst (*R*)-**1d** (entry 1). However, when the concentration of ^{t}BuOK was increased to 0.06 M, the hydrogenation reaction occurred and provided (*R*)-**3a** in 15% yield with 91% ee (entry 2); and further increasing the concentration of ^{t}BuOK increased the reaction rate and the yield of **3a** substantially. For example, when 0.25 M ^{t}BuOK (**2a**/^{t}BuOK/(*R*)-**1d** = 500:500:1) was used, the reaction was complete within 10 h, providing (*R*)-**3a** in 91% yield with 92% ee (entry 3). The absolute configuration of (*R*)-**3a** was determined by comparison of the sign of its optical rotation with literature data.[8] Evaluation of various chiral Ir-SpiroPAP catalysts (*R*)-**1** revealed that the substituents on the pyridine and phenyl groups of the catalysts had little effect on the yield or enantioselectivity (entries 4–8), with (*R*)-**1d** giving the best results. Experiments with various solvents showed that ^{n}PrOH was suitable (entries 9–11): the reaction was complete within 10 h, affording (*R*)-**3a** in 92% yield with 93% ee. In addition to ^{t}BuOK, ^{t}BuONa also gave a high yield with high enantioselectivity, but the use of KOH, NaOH, or K_2CO_3 resulted in low yields (entries 12–15).

To evaluate the substrate scope of the reaction, we investigated a wide range of racemic α-substituted δ-valerolactones under the established reaction conditions (Table 2). For racemic α-aryl-substituted δ-valerolactones **2a-i** (entries 1–9), neither electron-donating nor electron-withdrawing groups on the phenyl ring of the substrates had much effect on the enantioselectivity of the reaction, but substrates with an electron-withdrawing group (entries 2, 5, and 8) showed a higher reaction rate than those with an electron-donating group.

Table 1 Asymmetric hydrogenation of **2a**. Optimizing reaction conditions.[a]

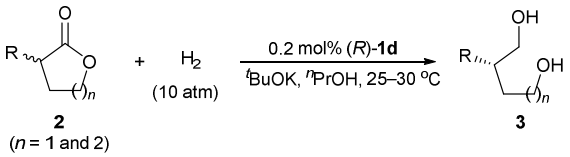


2a **3a**

Entry	Cat.	Base	[base]	Solvent	Time (h)	Yield (%)[b]	Ee (%)[c]
1	(*R*)-**1d**	^{t}BuOK	0.04	EtOH	24	ND	ND
2	(*R*)-**1d**	^{t}BuOK	0.06	EtOH	24	15	91
3	(*R*)-**1d**	^{t}BuOK	0.25	EtOH	10	91	92
4	(*R*)-**1a**	^{t}BuOK	0.25	EtOH	10	93	90
5	(*R*)-**1b**	^{t}BuOK	0.25	EtOH	10	92	90
6	(*R*)-**1c**	^{t}BuOK	0.25	EtOH	10	92	91
7	(*R*)-**1e**	^{t}BuOK	0.25	EtOH	17	91	90
8	(*R*)-**1f**	^{t}BuOK	0.25	EtOH	10	92	90
9	(*R*)-**1d**	^{t}BuOK	0.25	MeOH	7	10	86
10	(*R*)-**1d**	^{t}BuOK	0.25	^{n}PrOH	10	92	93
11	(*R*)-**1d**	^{t}BuOK	0.25	^{i}PrOH	8	89	74
12	(*R*)-**1d**	^{t}BuONa	0.25	^{n}PrOH	10	91	93
13	(*R*)-**1d**	KOH	0.25	^{n}PrOH	20	48	93
14	(*R*)-**1d**	NaOH	0.25	^{n}PrOH	20	36	93
15	(*R*)-**1d**	K_2CO_3	0.25	^{n}PrOH	20	21	92

[a] Reaction conditions: 1.0 mmol scale, [**2a**] = 0.25 M, 0.2 mol% of catalyst, solvent (4.0 mL), room temperature (25–30 °C). [b] Isolated yield. [c] Determined by HPLC using chiral column. The absolute configuration of **3a** is *R* determined by comparison of its optical rotation with the literature date (see Supporting Information).

Table 2 Asymmetric hydrogenation of racemic α-substituted lactones to chiral diols with (*R*)-**1d**.[a]



2 (*n* = 1 and 2) **3**

Entry	R	*n*	**3**	Time (h)	Yield (%)[b]	Ee (%)[c]
1[d]	C_6H_5	2	**3a**	10	92	93 (*R*)
2	4-ClC_6H_4	2	**3b**	7	93	93
3	4-MeC_6H_4	2	**3c**	9	92	93
4	4-$MeOC_6H_4$	2	**3d**	10	93	93
5	3-ClC_6H_4	2	**3e**	7	95	92
6	3-MeC_6H_4	2	**3f**	10	91	93
7	3-$MeOC_6H_4$	2	**3g**	10	93	92 (*R*)
8[d]	3,4-$Cl_2C_6H_3$	2	**3h**	7	94	92
9	3,4-$(MeO)_2C_6H_3$	2	**3i**	10	91	91
10	2-ClC_6H_4	2	**3j**	13	89	78
11	2-MeC_6H_4	2	**3k**	36	84	77
12	2-$MeOC_6H_4$	2	**3l**	20	88	86
13[d]	Me	2	**3m**	8	92	91 (*S*)
14	Et	2	**3n**	12	90	87
15[d]	^{i}Pr	2	**3o**	12	90	95 (*R*)
16[d]	CH_2=$CHCH_2CH_2$	2	**3p**	12	91	88 (*S*)
17	C_6H_5	1	**3q**	10	80	80 (*R*)
18	Me	1	**3r**	10	82	69 (*S*)

[a] Reaction conditions: 1.0 mmol scale, [substrate] = 0.25 M, [^{t}BuOK] = 0.25 M, 0.2 mol% of (*R*)-**1d**, ^{n}PrOH (4.0 mL), room temperature (25–30 °C). [b] Isolated yield. [c] Determined by HPLC using chiral column. [d] The absolute configuration of the product is determined by comparison of their optical rotation with the literature data (see Supporting Information)

In addition, owing to steric effects, substrates with an ortho-substituent on the phenyl ring gave lower reaction rates, yield, and enantioselectivity (entries 10–12). The hydrogenation of α-alkyl-substituted δ-valerolactones **2m-p** also worked well, affording corresponding 1,5-diols **3m-p** in high yield and high enantioselectivity (entries 13–16). Catalyst (*R*)-**1d** also catalyzed the hydrogenation of racemic α-substituted γ-butyrolactones **2q** and **2r**, providing 1,4-diols **3q** (80% ee) and **3r** (69% ee), respectively (entries 17 and 18).

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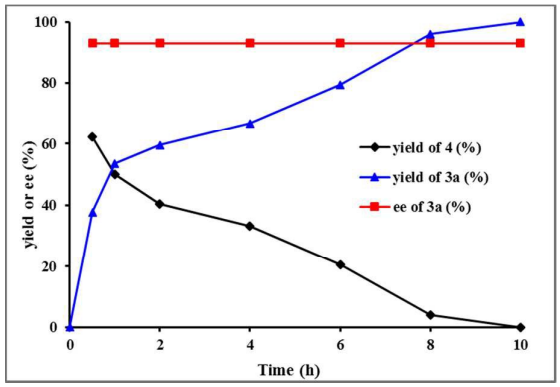
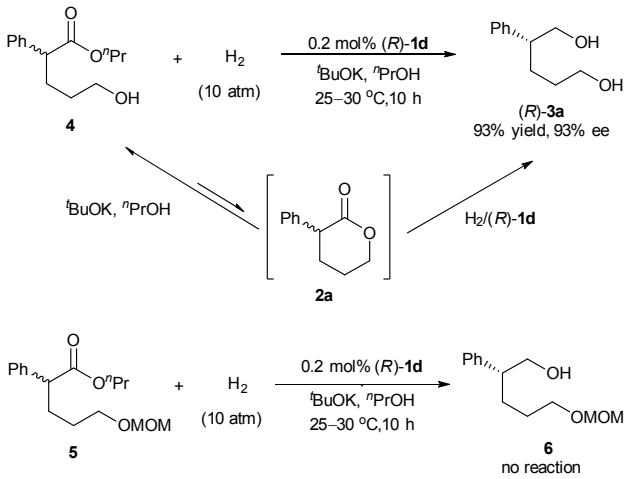


Fig. 1 The plots of the hydrogenation of *rac*-**2a** with (*R*)-**1d**.

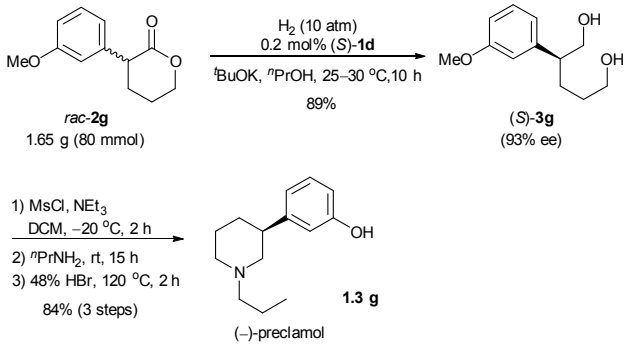
We investigated the pathway of the hydrogenation of racemic α-substituted lactones **2** by ^{1}H NMR. As shown in Fig. 1, after reaction for 0.5 h under the optimal reaction conditions, *rac*-**2a** was converted to hydroxyl ester **4**, propyl 5-hydroxy-2-phenylpentanoate, in 62.3% yield with no ee and diol **3a** in 37.7% yield with 93% ee. In the following 10 h, the hydroxyl esters **4** gradually decreased, and the diol **3a** increased. Only trace amount of lactone **2a** was detected from 2 min after reaction started.

Direct hydrogenation of hydroxyl ester **4** with catalyst (*R*)-**1d** provided diol **3a** in 93% yield with 93% ee, which is the same as the result obtained from the hydrogenation of lactone **2a** (Scheme 2). We also conducted the hydrogenation of the ester **5**, which has a δ-OCH_2OMe group instead of a δ-OH group as in hydroxyl ester **4**, and observed no reaction. These results indicated that the hydroxyl group of ester **4** is crucial for the hydrogenation. Thus, although lactone **2a** was readily alcoholized to hydroxyl ester **4** under the reaction conditions, the hydrogenation of **2a** occurred inevitably via lactone form (Scheme 2).[7b,c]

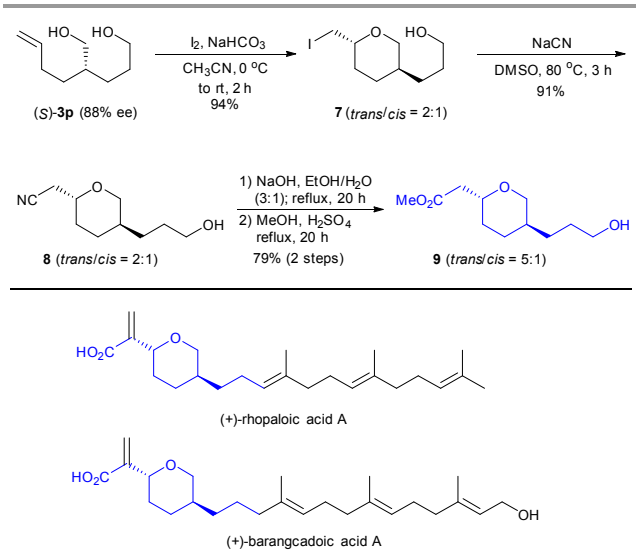
Chiral 3-aryl/alkyl substituted piperidines are of an important class of bioactive heterocyclic compounds,[9] but they are difficult to synthesize in optically active form.[10] By using catalyst



Scheme 2 Asymmetric hydrogenation of ester **4** and **5** with (*R*)-**1d**.



Scheme 3 Enantioselective synthesis of (–)-preclamol.



Scheme 4 Enantioselective synthesis of a chiral 2,5-disubstituted tetrahydropyran.

(*S*)-**1d**, we synthesized (–)-preclamol,[11] a candidate drug for treating neurological disorders such as Parkinson's disease.[12] The hydrogenation of *rac*-**2g** (1.65 g) catalyzed by (*S*)-**1d** afforded diol (*S*)-**2g** (89% yield, 93% ee), which was subsequently transformed to (–)-preclamol by activation with methanesulfonyl chloride, substitution/cyclization with *n*-propylamine, and demethylation with hydrobromic acid (84% yield over three steps, Scheme 3).

Diol (*S*)-**3p** is a useful building block for the synthesis of chiral 2,5-disubstituted tetrahydropyrans, which occur in many biologically active natural products such as the terpenoids rhopaloic acid A[13] and barangcadoic acid A[14] (Scheme 4), isolated from marine sponges. Iodoetherification of (*S*)-**3p** with iodine[15] produced tetrahydropyran **7** in 94% yield as a 2:1 *trans*/*cis* mixture. Nucleophilic substitution of tetrahydropyran **7** with NaCN afforded a nitrile **8** (*trans*/*cis* = 2:1). Hydrolysis of

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the nitrile **8** and subsequent esterification with MeOH afforded tetrahydropyran **9** in 72% yield with a higher *trans/cis* ratio (5:1). Thus, this protocol represents a potential method for the construction of the chiral core structure of rhopaloic acid A and barangcadoic acid A.[16]

Conclusions

In conclusion, we have developed a protocol for highly efficient iridium-catalyzed asymmetric hydrogenation of racemic α-substituted lactones *via* DKR. Using Ir-SpiroPAP catalyst, a series of racemic α-substituted lactones were hydrogenated to chiral diols in high yield with high enantioselectivity under mild reaction conditions. The protocol was used for enantioselective syntheses of (−)-preclamol and a chiral 2,5-disubstituted tetrahydropyran.

Experimental

General procedure for asymmetric hydrogenation of 2: To a 20 mL hydrogenation vessel in an autoclave was added racemic α-substituted δ-valerolactone **2** (1.0 mmol), a solution of iridium catalyst (*R*)-**1d** in ^{n}PrOH (dried with MS 4Å for 12 h, 0.002 mmol/mL, 1.0 mL, 0.002 mmol), a solution of ^{t}BuOK in ^{n}PrOH (0.5 mmol/mL, 2.0 mL, 1.0 mmol) and ^{n}PrOH (1.0 mL). The autoclave was purged with hydrogen by pressurizing to 5 atm and releasing the pressure. This procedure was repeated three times and then pressurized to 10 atm of H_2. The reaction mixture was stirred at room temperature (25−30 °C) until no obvious hydrogen pressure drop was observed. The reaction mixture was then quenched with saturated NH_4Cl (5 mL) and extracted with EtOAc (5 mL × 3). The combined extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silical gel with petroleum ether/ethyl acetate as an eluent to afford the chiral diols **3**. The ee values of the chiral diols **3** were determined by HPLC using chiral column.

Acknowledgements

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