Asymmetric Synthesis

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Asymmetric Hydrogenation of α,α′-Disubstituted Cycloketones through Dynamic Kinetic Resolution: An Efficient Construction of Chiral Diols with Three Contiguous Stereocenters**

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Transition-metal-catalyzed asymmetric hydrogenation is one of the most environmentally benign, atom-efficient, and powerful methods for the synthesis of chiral organic compounds in optically active form.[1] A particularly useful method is the transition-metal-catalyzed asymmetric hydrogenation of configurationally labile substrates through dynamic kinetic resolution (DKR).[2] For example, the hydrogenation of racemic α-substituted ketones catalyzed by chiral ruthenium diphosphine/diamine complexes is a highly efficient method for the one-step preparation of chiral alcohols containing two vicinal stereocenters.[3] However, despite its great potential for the synthesis of chiral compounds such as natural products and biologically active compounds with multiple stereocenters, the asymmetric hydrogenation of racemic α,α′-disubstituted ketones to generate chiral alcohols with three contiguous stereocenters remains a challenge.[4]

Successful hydrogenation of α-substituted ketones through DKR depends on both the selectivity of the catalyst for hydrogenation of one of two enantiomers of the racemic ketones and the ability of the substrates to racemize under the reaction conditions. As α,α′-disubstituted ketones have four stereoisomers, enantiocontrol of the hydrogenation is extremely difficult. To address this challenge, we investigated the hydrogenation of cycloketones with an α-alkoxycarbonylalkyl group and an α′-aryl group. We expected that the enantioselective hydrogenation of these racemic α,α′-disubstituted ketones through DKR would produce chiral cycloalkanols with three contiguous stereocenters and that these cycloalkanols could serve as chiral intermediates for the synthesis of natural alkaloids such as lycorane[5] and hexahydroapoerysopine.[6] Herein, we report the highly enantioselective hydrogenation of this type of cycloketones through DKR to chiral diols with three contiguous stereocenters and the use of the reaction for the asymmetric total synthesis of (+)-γ-lycorane.

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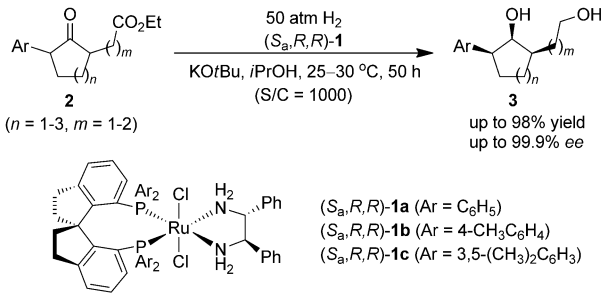
Recently, we reported highly efficient asymmetric hydrogenations of racemic α-substituted aldehydes and ketones through DKR, for the syntheses of chiral alcohols with one or two stereocenters catalyzed by [$RuCl_2$\{(*S*)-SDPs\}\{(*R*,*R*)-diamine\}] ((S_a,R,R)-**1**).[7] Herein, when we used (S_a,R,R)-**1** to catalyze the hydrogenation of racemic α-ethoxycarbonylalkyl-α′-arylcycloketones **2** at room temperature, the corresponding chiral diols **3** were obtained with excellent enantioselectivity and *cis*,*cis* selectivity (Scheme 1). Interestingly, the ester groups of **2** were hydrogenated to the corresponding

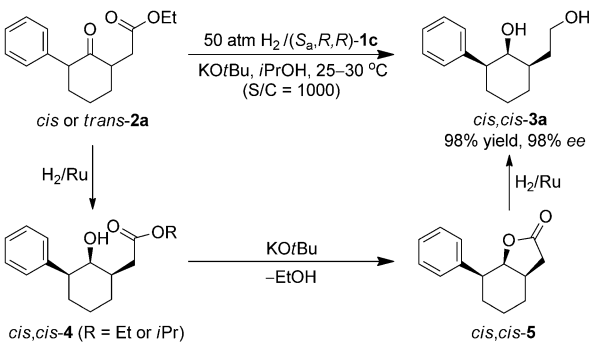


Scheme 1. [$RuCl_2$\{(*S*)-SDP\}\{(*R*,*R*)-DPEN\}]-catalyzed asymmetric hydrogenation of racemic α-ethoxycarbonylalkyl-α′-arylcycloketones by DKR.

alcohols at room temperature during the reaction, whereas previously reported examples of the hydrogenation of esters to primary alcohols required higher temperatures (> 80 °C).[8]

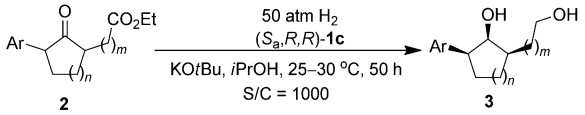
To evaluate chiral spiro ruthenium catalysts (S_a,R,R)-**1**, we selected *cis*-2-ethoxycarbonylmethyl-6-phenylcyclohexanone (*cis*-**2a**) as a substrate and we found that (S_a,R,R)-**1c**, which has 3,5-dimethylphenyl groups on the phosphorus atoms, was the best catalyst. When *cis*-**2a** was hydrogenated with 0.1 mol% of (S_a,R,R)-**1c** under 50 atm H_2 at room temperature (25–30 °C) in *i*PrOH containing 10 mol% of KO*t*Bu for 50 h, we were surprised to obtain diol *cis*,*cis*-**3a** in 98% yield with 98% *ee*, with none of the expected ketone reduction product, *cis*,*cis*-**4** (R = Et or *i*Pr; Scheme 2).[9] When we intentionally stopped the reaction after 12 h, we obtained *cis*,*cis*-**3a** in only 5% yield accompanied by lactone *cis*,*cis*-**5** (32% yield), but *cis*,*cis*-**4** was still not observed. This result indicates that diol *cis*,*cis*-**3a** was formed by hydrogenation of lactone *cis*,*cis*-**5**.

We used (S_a,R,R)-**1c** to catalyze the hydrogenation of various 2-ethoxycarbonylmethyl-6-arylcyclohexanones to the corresponding chiral diols (Table 1, entries 1–9). The substituent on the phenyl ring of the substrates had little effect on



Scheme 2. Asymmetric hydrogenation of racemic α,α′-disubstituted cycloketone **2a**.

Table 1: Asymmetric hydrogenation of racemic α,α′-disubstituted cycloketones **2**.[a]

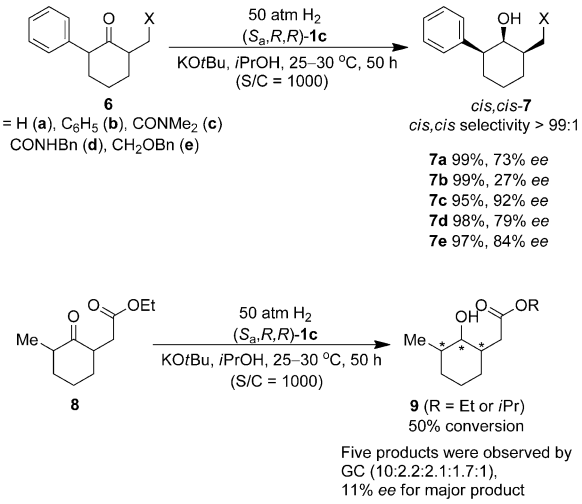


Entry	Ar	*n*	*m*	**3**	Yield [%][b]	*ee* [%][c]
1[d]	C_6H_5	2	1	**3a**	98	98
2[e]	C_6H_5	2	1	**3a**	97	98
3	4-MeC_6H_4	2	1	**3b**	93	97
4	4-$MeOC_6H_4$	2	1	**3c**	96	98
5	4-ClC_6H_4	2	1	**3d**	95	92
6	3-MeC_6H_4	2	1	**3e**	96	98
7	2-MeC_6H_4	2	1	**3f**	86	98
8	3,4-$(MeO)_2C_6H_4$	2	1	**3g**	96	99.6
9[f]	3,4-$(OCH_2O)C_6H_4$	2	1	**3h**	95	99.9
10	C_6H_5	2	2	**3i**	93	91
11	C_6H_5	1	1	**3j**	96	75
12	C_6H_5	3	1	**3k**	92	96

[a] Reaction conditions: (*S*a,*R*,*R*)-**1c**/**2**/*t*BuOK = 1/1000/100, [**2**] = 0.4 M, 50 atm H_2, 25–30 °C, 50 h, 100% conversion, the ratios of *cis*,*cis*-isomer to *cis*,*trans*-isomer are > 99:1, as determined by ^{1}H NMR spectroscopy. [b] Yield of the isolated product. [c] The *ee* value of the *cis*,*cis*-isomer was determined by HPLC or supercritical fluid chromatography (SFC) with chiral column. [d] *cis*-**2a** as a substrate. [e] *trans*-**2a** as a substrate. [f] The absolute configuration of product *cis*,*cis*-**3h** is (1*S*,2*S*,6*R*), as determined by X-ray analysis.

the yield and enantioselectivity of the reaction. All the hydrogenation reactions were complete within 50 h, and gave diols *cis*,*cis*-**3** in 93–98% yields with 91–99.9% *ee*. The best results were obtained with substrates **2g** and **2h**, which afforded *cis*,*cis*-**3g** and *cis*,*cis*-**3h** with 99.6 and 99.9% *ee*, respectively (entries 8 and 9). 2-Ethoxycarbonylethyl-6-phenylcyclohexanone (**2i**; $m = 2$) also could be hydrogenated to chiral diol *cis*,*cis*-**3i** in 93% yield with 91% *ee* (entry 10). The size of the cycloketone ring strongly affected the enantioselectivity of the reaction. Substrate **2k**, which has a seven-membered ring, yielded diol *cis*,*cis*-**3k** in 92% yield with 96% *ee* (entry 12), whereas **2j**, which has a five-membered ring, afforded *cis*,*cis*-**3j** with only moderate enantioselectivity (75% *ee*), although the yield was excellent (96%; entry 11). The absolute configuration of the hydrogenation product *cis*,*cis*-**3h** was determined by X-ray analysis of a single crystal, and indicated that catalyst (*S*a,*R*,*R*)-**1c** gave (1*S*,2*S*,6*R*)-products (see the Supporting Information).

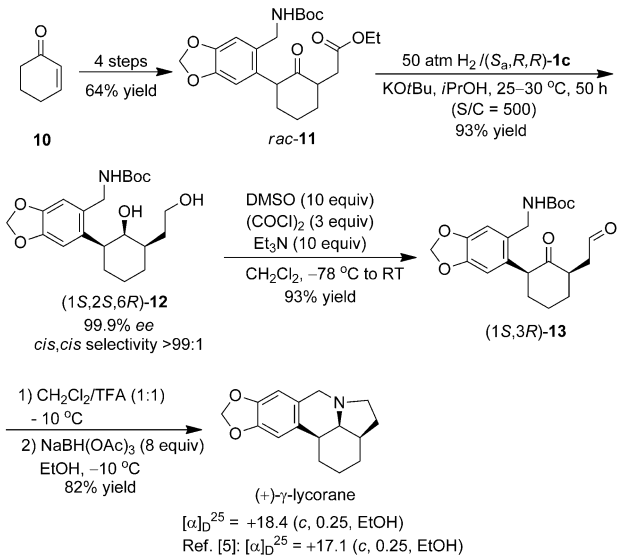
To investigate the effect of the ester group of the side chain on the reaction, we hydrogenated cyclohexanones **6** with various α-substituents (Scheme 3). When the ester group was replaced with an α-alkyl group such as a methyl group



Scheme 3. Asymmetric hydrogenation of other α,α′-disubstituted cyclohexanones. Bn = benzyl.

(**6a**; X = H) or a benzyl group (**6b**; X = C_6H_5), the enantioselectivity of the reaction dramatically decreased to 73 and 27% *ee*, respectively. Changing the ester group to an *N*,*N*-dimethylaminocarbonyl group (**6c**; X = $CONMe_2$) had little effect on the enantioselectivity (92% *ee*) and *cis*,*cis* selectivity (> 99%). However, introducing an *N*-benzylaminocarbonyl group (**6d**; X = CONHBn) or a benzyloxymethyl group (**6e**; X = CH_2OBn) lowered the enantioselectivity to 79 and 84% *ee*, respectively. When substrate **8**, which has a 2-methyl group instead of an aryl group, was hydrogenated, a mixture of five stereoisomers of alcohol **9** was obtained in a ratio of 10:2.2:2.1:1.7:1 (as indicated by GC), with the *ee* value of the major product being 11%. These results indicated that both the aryl group and the ester group of substrates **2** were necessary for high enantioselectivity.

To demonstrate the synthetic utility of this highly efficient strategy for producing chiral diols with three contiguous stereocenters in one step, we carried out an asymmetric total synthesis of (+)-γ-lycorane, which is a degradation product of the amaryllidaceae alkaloid lycorine.[5] Although this type of deoxygenated amaryllidaceae alkaloid skeleton has received much attention in recent years, a highly efficient catalytic asymmetric total synthesis of optically pure (+)-γ-lycorane is desirable.[10] We started the synthesis of (+)-γ-lycorane from commercially available cyclohex-2-enone (**10**; Scheme 4), which was converted into α,α′-disubstituted cyclohexanone **11** in 64% yield in 4 steps (see the Supporting Information). Hydrogenation of racemic ketone **11** catalyzed by (*S*a,*R*,*R*)-**1c** afforded chiral diol (1*S*,2*S*,6*R*)-**12** in 93% yield with 99.9% *ee*. The chiral diol was oxidized to aldehyde (1*S*,3*R*)-**13** in 93% yield by Swern oxidation. Removal of the *N*-*tert*-butyloxy-



Scheme 4. Catalytic enantioselective synthesis of (+)-γ-lycorane. DMSO = dimethylsulfoxide.

carbonyl (Boc) protecting group from (1*S*,3*R*)-**13** with trifluoroacetic acid (TFA) at −10 °C, followed by a reductive amination with sodium triacetoxyborohydride (NaBH(OAc)$_3$), afforded the target product, (+)-γ-lycorane, in 82 % yield. The optical rotation of the obtained product was consistent with the value reported for the natural product ($[\alpha]_D^{25} = +18.4$ ($c = 0.25$, EtOH); Ref. [5] $[\alpha]_D^{25} = +17.1$ ($c = 0.25$, EtOH)). Thus, we achieved a concise, catalytic, enantioselective total synthesis of (+)-γ-lycorane in 45 % overall yield from cyclohex-2-enone in 8 steps.

In conclusion, we have developed a strategy for the highly enantioselective ruthenium-catalyzed hydrogenation of racemic α,α′-disubstituted cycloketones through DKR for the one-step synthesis of chiral diols with three contiguous stereocenters. We used this new strategy for the enantioselective total synthesis of alkaloid (+)-γ-lycorane.

Experimental Section

General procedure for the asymmetric hydrogenation of α,α′-disubstituted cycloketones**:** [$RuCl_2$\{(S_a)-Xyl-SDP\}\{(*R*,*R*)-DPEN\}] ((S_a,*R*,*R*)-**1c**; 2.2 mg, 0.002 mmol) and anhydrous *i*PrOH (2.5 mL) were placed in a hydrogenation vessel. The vessel was placed in an autoclave and purged with hydrogen by pressurizing to 50 atm and releasing the pressure. The purging procedure was repeated three times, and then the solution was stirred under 50 atm of H_2 for 5 min. After the pressure was released, racemic cycloketone **2** (2.0 mmol in 1.5 mL *i*PrOH) and a solution of *t*BuOK in *i*PrOH (0.2 mmol mL^{-1}, 1.0 mL, 0.2 mmol) were added. The autoclave was purged with hydrogen and pressurized to 50 atm. The reaction mixture was stirred at room temperature (25–30 °C) until no obvious hydrogen pressure drop was observed (50 h). After the hydrogen pressure was released, the solution was concentrated in vacuo, and the residue was purified by column chromatography on silica gel with ethyl acetate/petroleum ether (1:15→1:1) as the eluent to provide the product. The enantioselectivity of the product was determined by HPLC or supercritical fluid chromatography (SFC) on a chiral column.

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