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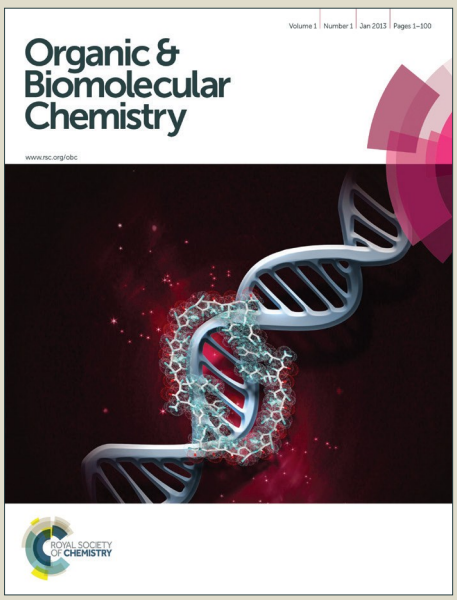

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Highly Efficient Asymmetric Hydrogenation of Cyano-substituted Acrylate Esters for Synthesis of Chiral γ-Lactams and Amino Acids†

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A highly efficient and enantioselective synthesis of γ-lactams and γ-amino acids by Rh-catalyzed asymmetric hydrogenation has been developed. Using the Rh-(*S*,*S*)-f-spiroPhos complex, under mild conditions a wide range of 3-cyano acrylate esters including both *E* and *Z*-isomers and β-cyano-α-aryl-α,β-unsaturated ketones were first hydrogenated with excellent enantioselectivities (up to 98% ee) and high turnover numbers (TON up to 10,000).

As a privileged structural skeleton, chiral lactams are found in a broad range of natural and biologically active molecules,[1] such as a number of widely employed medicinal agents, Penicillins, Cephalosporins, Carbapenems, Monobactams, Salinosporamide A, Rolipram and Bivaracetam. Although chiral β-lactams as the largest subclass of the lactam family are especially attractive as antibiotics, γ-lactams are also very important (Figure 1),[2] and widely exist in many natural products and pharmaceuticals.[3] For example, Bivaracetam, bearing a chiral γ-lactam has anticonvulsant effect by binding to the ubiquitous synaptic vesicle glycoprotein 2A(SV2A).[4] Particularly, enantiomerically pure γ-lactams, as key intermediates, are readily converted into pharmacologically important molecules, such as 2,3-disubstituted pyrrolidines.[5] Moreover, γ-lactams can also be easily hydrolyzed to the corresponding amino acids and their derivatives,[6] which are analogues of the neurotransmitter, γ-aminobutyric acid (GABAs) for the treatment of a series of central nervous system disorders.[7] Thus, a simple efficient method for synthesis of optically active γ-lactams is highly desirable.

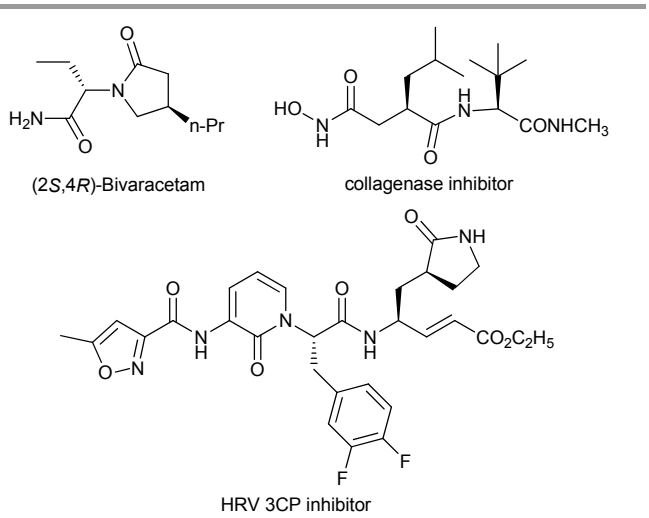

Figure 1. Structures of Biologically Active Compounds involving Lactam Moieties.

Despite a number of successful examples of asymmetric hydrogenation of other types of prochiral substrates,[8] to the best of our knowledge, the direct hydrogenation of cyano-substituted acrylate esters has not yet been reported.[9] The resulting hydrogenation products can be readily converted into the corresponding γ-lactams and amino acids.[6b,10] Recently, we reported the synthesis of chiral ferrocenyl diphosphine ligand, f-spiroPhos, combined with privileged spirobiindane skeleton, which was developed by Zhou and co-workers,[11] and proved its high efficiency in the asymmetric hydrogenation of nitroolefins.[12] It is the excellent performance exhibited in previous work that promotes us to evaluate the hydrogenation of cyano-substituted acrylate esters with Rh-(*S*,*S*)-f-spiroPhos complex. Herein, we report the first highly efficient and enantioselective hydrogenation of this kind of substrates, which provides a new efficient route to optically active γ-lactams as well as γ-amino acids (Scheme 1).[13]

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† Electronic Supplementary Information (ESI) available: General experimental procedures, compound characterization data and analysis of enantioselectivities of hydrogenation products. See DOI: 10.1039/x0xx00000x

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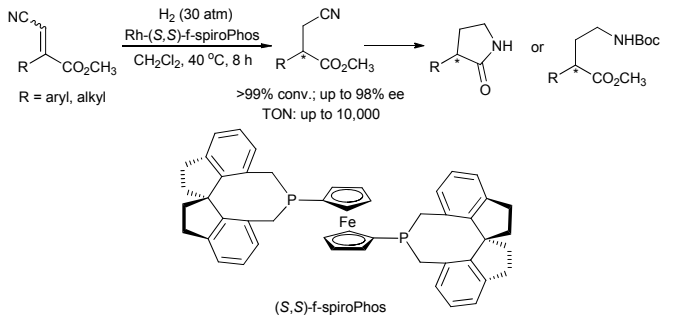


Scheme 1. Rh-Catalyzed Asymmetric Hydrogenation of Cyano-substituted Acrylate Esters.

Initially, asymmetric hydrogenation of (*Z*)-methyl 3-cyano-2-phenylacrylate **1a** was investigated by using the complex of (*S*,*S*)-f-spiroPhos and $[Rh(COD)_2]BF_4$ as the catalyst under 70 atm of H_2 in CH_2Cl_2 for 12 h. At room temperature, albeit excellent enantioselectivity, 98% ee, incomplete conversion was observed. When we used $[Rh(COD)Cl]_2$ as the metal precursor, only 9% conversion was achieved. Fortunately, an increase of the reaction temperature to 40 °C resulted in full conversion without any loss of ee value (Table 1, entries 1-2). Furthermore, a screening of other chiral phosphorus ligands available in our lab revealed that most of ligands including (*S*)-BINAP, (*S,R*)-DuanPhos, (*R*)-JosiPhos, (*S,S*)-f-Binaphane, (*R*)-DM-SegPhos and (*S*)-MonoPhos (figure 2), exhibited only low activity and poor enantioselectivity for this reaction (entries 3-8). Subsequently, the solvent effect was investigated and had significant influence on the conversion and enantioselectivity. Toluene, DME, Et_2O and MeOH gave only poor conversions and moderate enantioselectivities (entries 9, 12-14), while THF and dioxane provided full conversions and slightly lower enantioselectivities (entries 10, 11). Notably, under lower hydrogen pressure, 30 atm, the hydrogenation was complete in 8 h with unchanged enantioselectivity (entry 15). However, much lower hydrogen pressure would result in incomplete conversion.

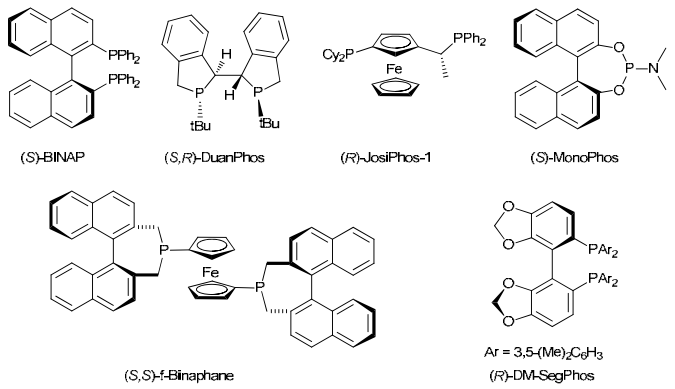
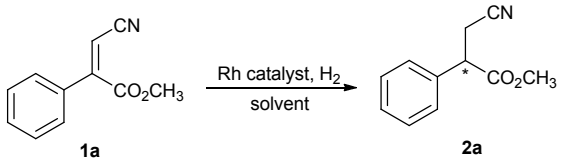


Figure 2. Structures of the ligands screened.

Table 1. Rh-catalyzed Asymmetric Hydrogenation of (*Z*)-methyl 3-Cyano-2-phenylacrylate 1a，Optimizing Reaction Conditions.[a]



1a **2a**

entry	ligands	T (°C)	solvent	conv. (%)[b]	ee. (%)[c]
1	(*S,S*)-f-spiroPhos	25	CH_2Cl_2	79	98
2	(*S,S*)-f-spiroPhos	40	CH_2Cl_2	>99	98
3	(*S*)-BINAP	40	CH_2Cl_2	<5	NA
4	(*S,R*)-DuanPhos	40	CH_2Cl_2	9	NA
5	(*R*)-JosiPhos-1	40	CH_2Cl_2	29	28
6	(*S,S*)-f-Binaphane	40	CH_2Cl_2	80	58
7	(*R*)-DM-SegPhos	40	CH_2Cl_2	7	NA
8	(*S*)-MonoPhos	40	CH_2Cl_2	65	0
9	(*S,S*)-f-spiroPhos	40	toluene	14	59
10	(*S,S*)-f-spiroPhos	40	THF	>99	93
11	(*S,S*)-f-spiroPhos	40	dioxane	97	97
12	(*S,S*)-f-spiroPhos	40	DME	31	89
13	(*S,S*)-f-spiroPhos	40	Et_2O	27	12
14	(*S,S*)-f-spiroPhos	40	MeOH	29	67
15[d]	(*S,S*)-f-spiroPhos	40	CH_2Cl_2	>99	98

[a] Unless otherwise mentioned, all reactions were carried out with a $Rh(COD)_2BF_4$ /phosphine /substrate ratio of 1 : 1.1 : 100, CH_2Cl_2, 70 atm H_2, 12 h. [b] Determined by ^1H NMR spectroscopy. [c] Determined by HPLC analysis using a chiral stationary phase. [d] 30 atm H_2, 8 h.

Encouraged by the promising result obtained in the hydrogenation of (*Z*)-methyl 3-cyano-2-phenylacrylate **1a**, a variety of (*Z*)-3-cyano-2-substituted acrylate esters **1** were examined under the optimized reaction conditions. As the results illustrated in table 2, the electronic properties of the substituent at the *meta* or *para*-position of the aromatic ring had no obvious influence on both the reactivity and enantioselectivity, and full conversions with excellent ee values, 95%-98% ee, were achieved (entries 1-10). However, presumably due to steric hindrance, substrates with a Me (**1k**) or MeO group (**1l**) at the *ortho*-position of the aromatic ring and with a 1-naphthyl group (**1m**) required longer reaction time for full conversion but without any erosion of enantioselectivity (entries 11-13). Gratifyingly, excellent enantioselectivities were also observed for the alkyl substrates (^{i}Pr and cyclohexyl), albeit with longer reaction time (entries 15-16).

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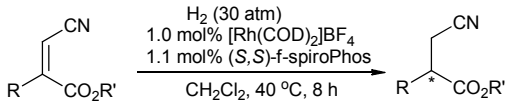
Table 2. Rh-catalyzed Asymmetric Hydrogenation of (*Z*)-3-Cyano-2-substituted Acrylate Esters 1.[a]

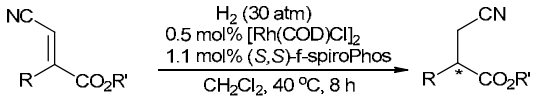


1 2

entry	R	R′	product	conv. (%)[b]	ee (%)[c]
1	C_6H_5(**1a**)	CH_3	**2a**	>99(98)	98(*R*)[d]
2	C_6H_5(**1b**)	C_2H_5	**2b**	>99(97)	96(-)
3	4-$CH_3C_6H_4$(**1c**)	CH_3	**2c**	>99(97)	96(-)
4	4-$CH_3OC_6H_4$(**1d**)	CH_3	**2d**	>99(96)	97(-)
5	4-FC_6H_4(**1e**)	CH_3	**2e**	>99(96)	97(-)
6	4-ClC_6H_4(**1f**)	CH_3	**2f**	>99(97)	98(-)
7	4-BrC_6H_4(**1g**)	CH_3	**2g**	>99(97)	97(-)
8	3-$CH_3C_6H_4$(**1h**)	CH_3	**2h**	>99(98)	97(-)
9	3-$CH_3OC_6H_4$(**1i**)	CH_3	**2i**	>99(96)	97(-)
10	3-FC_6H_4(**1j**)	CH_3	**2j**	>99(98)	97(-)
11[e]	2-$CH_3C_6H_4$(**1k**)	CH_3	**2k**	>99(97)	95(-)
12[f]	2-$CH_3OC_6H_4$(**1l**)	CH_3	**2l**	>99(95)	98(-)
13[e]	1-naphthyl(**1m**)	CH_3	**2m**	>99(98)	98(-)
14	2-naphthyl(**1n**)	CH_3	**2n**	>99(98)	97(-)
15[e]	^{i}Pr(**1o**)	CH_3	**2o**	>99(97)	97(-)
16[e]	cyclohexyl(**1p**)	CH_3	**2p**	99(95)	97(-)

[a] Unless otherwise mentioned, all reactions were carried out with a $[Rh(COD)_2]BF_4$ /(*S,S*)-f-spiroPhos/substrate ratio of 1 : 1.1 : 100, CH_2Cl_2, 30 atm H_2, 40 °C, 8 h. [b] Determined by ^{1}H NMR spectroscopy or GC analysis; data in parentheses are isolated yields. [c] Determined by HPLC analysis using a chiral stationary phase or chiral GC analysis. [d] The absolute configuration of (*R*)-**2a** was determined by comparison with optical rotation data for the reported literature.[6b] [e] 12 h. [f] 50 atm H_2, 24 h.

Table 3. Rh-catalyzed Asymmetric Hydrogenation of (*E*)-3-Cyano-2-substituted Acrylate Esters 1′.[a]



1' 2'

entry	R	R′	product	conv. (%)[b]	ee (%)[c]
1	C_6H_5(**1a′**)	CH_3	**2a′**	>99(98)	97(*S*)[d]
2	C_6H_5(**1b′**)	C_2H_5	**2b′**	>99(98)	97(+)
3	4-$CH_3C_6H_4$(**1c′**)	CH_3	**2c′**	>99(96)	97(+)
4	4-$CH_3OC_6H_4$(**1d′**)	CH_3	**2d′**	>99(96)	97(+)
5	4-FC_6H_4(**1e′**)	CH_3	**2e′**	>99(97)	97(+)
6	4-ClC_6H_4(**1f′**)	CH_3	**2f′**	>99(96)	96(+)
7	4-BrC_6H_4(**1g′**)	CH_3	**2g′**	>99(97)	96(+)
8	3-$CH_3C_6H_4$(**1h′**)	CH_3	**2h′**	>99(98)	96(+)
9	3-$CH_3OC_6H_4$(**1i′**)	CH_3	**2i′**	>99(98)	95(+)
10	3-FC_6H_4(**1j′**)	CH_3	**2j′**	>99(97)	96(+)
11	2-$CH_3C_6H_4$(**1k′**)	CH_3	**2k′**	>99(96)	98(+)
12	2-$CH_3OC_6H_4$(**1l′**)	CH_3	**2l′**	>99(96)	98(+)
13	1-naphthyl(**1m′**)	CH_3	**2m′**	>99(98)	95(+)
14	2-naphthyl(**1n′**)	CH_3	**2n′**	>99(98)	95(+)
15	^{i}Pr(**1o′**)	CH_3	**2o′**	>99(96)	96(+)
16	cyclohexyl(**1p′**)	CH_3	**2p′**	>99(96)	94(+)

[a] Unless otherwise mentioned, all reactions were carried out with a $[Rh(COD)Cl]_2$/(*S,S*)-f-spiroPhos/substrate ratio of 0.5 : 1.1 : 100, CH_2Cl_2, 30 atm H_2, 40 °C, 8 h. [b] Determined by ^{1}H NMR spectroscopy or GC analysis; data in parentheses are isolated yields. [c] Determined by HPLC analysis using a chiral stationary phase or chiral GC analysis. [d] The absolute configuration of (*R*)-**2a** was determined by comparison with optical rotation data for the reported literature.[6b]

Under the optimized conditions, the asymmetric hydrogenation of (*E*)-methyl 3-cyano-2-phenylacrylate **1a′** was also investigated. However, only moderate enantioselectivity, 73% ee, was reached with an opposite configuration, which was because the different olefin geometry often reacted from the opposite enantioface. Inspired by the research of halide effects in rhodium catalysts by Lautens and Fagnou,[14] we replaced the metal precursor with $[Rh(COD)Cl]_2$. To our delight, the ee value of the hydrogenation product **2a′** dramatically increased to 97 % ee with opposite configuration (Table 3, entry 1), which facilitated the access to the chiral cyano compound with any configuration. Subsequently, a series of (*E*)-substrates **1′** were smoothly hydrogenated with comparable results of (*Z*)-substrates. Regardless of the electronic property or position of the substituents in the phenyl moiety, no apparent effect on the reactivities and enantioselectivities was observed. For example, the substrates with a Me, MeO or F, Cl group at *meta*- or *para*-position of the phenyl ring afforded the corresponding products with 95%-97% ee values and full conversions (entries 3-10). Even for the sterically hindered *ortho*-substituted substrates, **1k′** and **1l′**, the highest enantioselectivity, 98% ee, was achieved (entries 11-12). Moreover, the substrate with an alkyl substituent (^{i}Pr and cyclohexyl) also afforded the desired products with full conversions and excellent enantioselectivities (entries 15 and 16).

Furthermore, besides 3-cyano acrylate esters, the Rh-(*S,S*)-f-spiroPhos catalyst is also very efficient for the asymmetric hydrogenation of β-cyano-α-aryl-α,β-unsaturated ketones. Under the optimized conditions, (*E*)-β-cyano-*α*-aryl-α,β-unsaturated ketones **3** were hydrogenated to the corresponding products **4** in full conversions with 91-95% ee, which could be further reduced to the desired products **5** in the presence of $NaBH_4$ with excellent diastereoselectivities, dr > 99:1, and unchanged enantioselectivities (Table 4).

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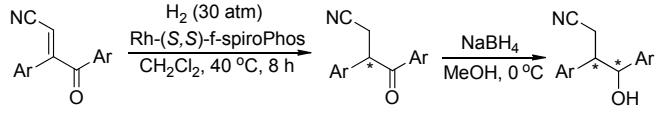
Table 4. Rh-catalyzed Asymmetric Hydrogenation of (*E*)-β-Cyano-α-Aryl-α,β-Unsaturated Ketones **3**.[a]

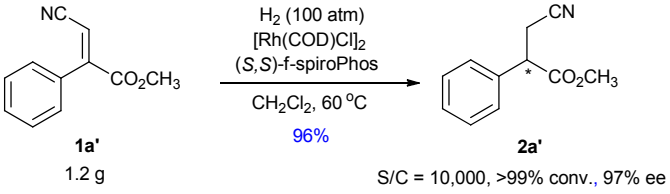


3 **4** **5**

entry	Ar	product	conv. (%)[b]	ee (%)[c]
1	C_6H_5(**3a**)	**4a**	>99(96)	95(+)
2	2-$CH_3OC_6H_4$(**3b**)	**4b**	>99(97)	96(+)
3	3-$CH_3C_6H_4$(**3c**)	**4c**	>99(95)	91(+)
4	4-$CH_3C_6H_4$(**3d**)	**4d**	>99(95)	92(+)
5	4-$CH_3OC_6H_4$(**3e**)	**4e**	>99(96)	94(+)
6	C_6H_5(**4a**)	**5a**	(92)	95(dr >99:1)
7	2-$CH_3OC_6H_4$(**4b**)	**5b**	(89)	96(dr >99:1)
8	3-$CH_3C_6H_4$(**4c**)	**5c**	(90)	90(dr >99:1)
9	4-$CH_3C_6H_4$(**4d**)	**5d**	(89)	92(dr >99:1)
10	4-$CH_3OC_6H_4$(**4e**)	**5e**	(91)	94(dr >99:1)

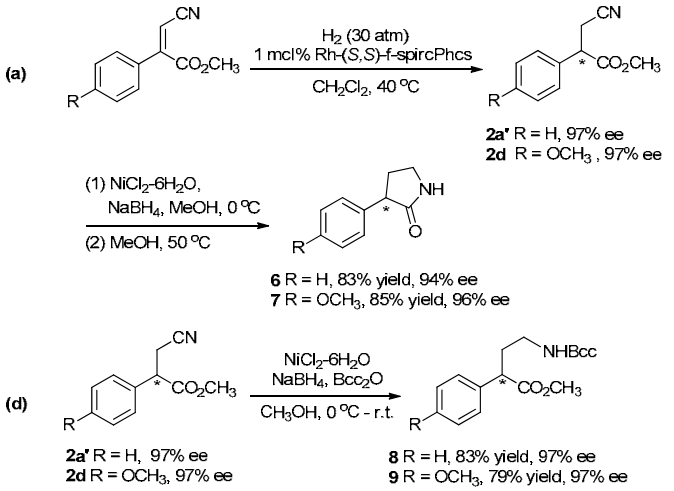
[a] Unless otherwise mentioned, all asymmetric hydrogenation of reactions were carried out with a $[Rh(COD)Cl]_2$/(*S,S*)-f-spiroPhos/substrate ratio of 0.5 : 1.1 : 100, CH_2Cl_2, 30 atm H_2, 40 °C, 8 h. [b] Determined by ^1H NMR spectroscopy; data in parentheses are isolated yields. [c] Determined by HPLC analysis using a chiral stationary phase; diastereomeric ratios were determined by ^1H NMR of crude products.

More importantly, the hydrogenation could be accomplished on gram scale and with much lower catalyst loading. With the Rh-(*S,S*)-f-spiroPhos catalyst, the hydrogenation of the substrate **1a′** was carried out on gram scale at a catalyst loading of 0.01 mol% under 100 atm of initial H_2 pressure, the desired product **2a′** was obtained in full conversion with 97% ee. The results indicated that this catalyst was exceptionally highly efficient for the asymmetric hydrogenation of these substrates and showed very high turnover numbers (TON) approaching 10,000 (Scheme 2).



Scheme 2. Asymmetric hydrogenation of **1a′** on gram scale under lower catalyst loading.

In addition, this catalyst system can also be successfully applied to the synthesis of important chiral pharmacophore fragments, γ-lactams and amino acids (Scheme 3).[6b] The hydrogenation products were further reduced and subsequent cyclized,[6a] γ-lactams and γ-amino esters were obtained in high yields and excellent enantioselectivities.



Scheme 3. Synthesis of γ-lactams and γ-amino esters.

In conclusion, we have developed a highly efficient and enantioselective hydrogenation of 3-cyano acrylate esters including both *E* and *Z*-isomers and β-cyano-α-aryl-α,β-unsaturated ketones to produce chiral cyano compounds with excellent enantioselectivities (up to 98% ee) and high turnover numbers (TON up to 10,000). Moreover, this method provides a new efficient route to optically active γ-lactams and γ-amino acids.

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