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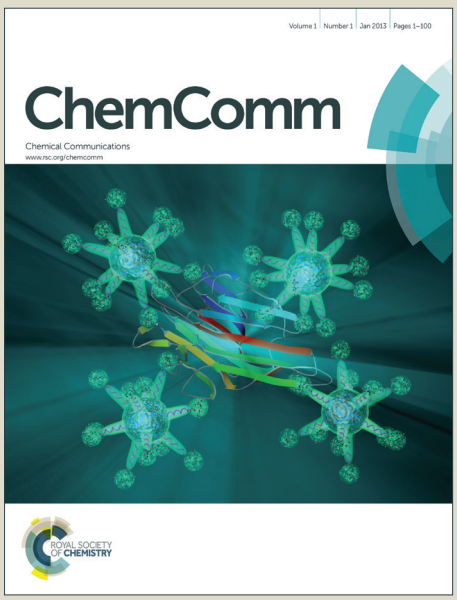

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Palladium-Catalyzed Asymmetric Hydrogenation of 3-Phthalimido Substituted Quinolines

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Xian-Feng Cai, Wen-Xue Huang, Zhang-Pei Chen and Yong-Gui Zhou*

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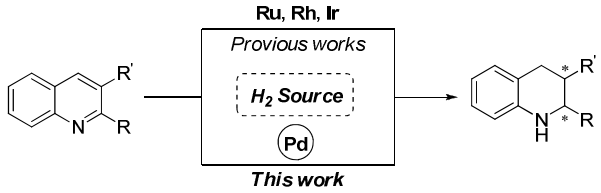
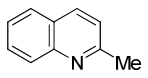
Homogeneous Pd-catalyzed asymmetric hydrogenation of 3-phthalimido substituted quinolines was successfully developed, providing a facile access to chiral substituted tetrahydroquinolines bearing two contiguous stereogenic centers with up to 90% ee.

Palladium complexes have been extensively employed as catalysts for a wide range of reactions, especially for carbon–carbon and carbon–heteroatom coupling reactions.[1] In addition, heterogeneous palladium catalysts (e.g., Pd/C) have been used extensively in the hydrogenation of unsaturated double bonds. The interest towards homogeneous palladium catalyzed asymmetric hydrogenation was generated in 2001, when the first example of Pd-catalyzed homogeneous hydrogenation of imino esters was reported by Amii and co-workers by using a $Pd(OCOCF_3)_2$-Binap complex.[2] Over the past two decades, Pd has gradually become a new and popular metal used in homogeneous asymmetric hydrogenation, and much progress has been successfully achieved in the catalytic asymmetric reduction of imines, enamines, olefins, ketones and heteroarenes,[3-7] as well as asymmetric hydrogenolysis of hydroxyl groups.[8] However, compared to the traditional Ru, Rh and Ir catalysts, the substrate scope of the Pd-catalyzed asymmetric hydrogenation was still limited and needed to be further extended.



Scheme 1. Metal-Catalyzed Asymmetric Hydrogenation of Quinolines

Optically pure tetrahydroquinolines exist as key structural elements in many natural alkaloids which display a wide range of physiological activities. In addition, they are useful building blocks for asymmetric synthesis in pharmaceutical and agrochemical industries and for the total synthesis of natural products.[9] Due to simplicity and atom efficiency, asymmetric reduction of quinolines represents a significant approach to get these compounds. In 2003, our group reported the first example of highly enantioselective hydrogenation of quinolines with combined chiral catalyst system, which consists of $[Ir(cod)Cl]_2$ with bisphosphine ligand and I_2, since then, numerous catalytic systems involve various chiral transition-metal catalysts and organocatalysts have been developed for this transformation.[10-12] It is well known that the success of transition metal-catalyzed asymmetric hydrogenation owes much to the proper combination of a metal and a ligand. Nevertheless, compared with the wide range of chiral ligands,[13] the choice of the metal for the asymmetric hydrogenation of quinolines was limited within the platinum group metals Ru, Rh and Ir. Herein, we report the first homogeneous palladium-catalyzed asymmetric hydrogenation of substituted quinolines, affording the chiral substituted tetrahydroquinolines bearing two continguous stereogenic centers in high yields and stereoselectivities (Scheme 1).



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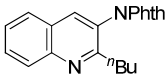


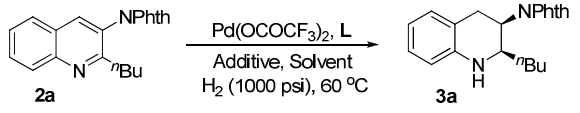
2a

Initially, 2-methylquinoline (**1**) was selected as model substrate. The original hydrogenation experiment was conducted in trifluoroethanol with $(Pd(OCOCF_3)_2/(S,S,Rax)$-C_3*-TunePhos and L-CSA as catalyst and activator[14] (1000 psi hydrogen gas, 60 °C, 18 h). Unfortunately, no reaction was observed. Very recently, we have reported the asymmetric reduction of aromatic quinolin-3-amines[15] and 3-phthalimido substituted quinoline (**2a**) has been studied.[15a] We envisioned that **2a** could be hydrogenated by the palladium catalyst due to the electron-withdrawing group at the C3 position, which could activate the substrates through decreasing the electron density of the aromatic ring. Thus, **2a** was then tested. To our delight, the reaction could proceed, though the conversion and stereoselectivity were low (52% conversion, 45% ee and 4:1 d.r.; entry 1, Table 1). So, the next step is how to improve the activity and stereoselectivity.

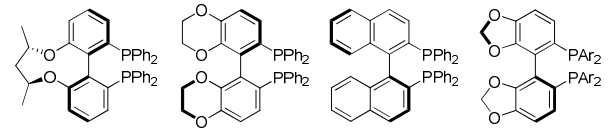
The first survey of different additives showed that better results were found when TFA was used in terms of both conversion and diasteroselectivity (85% conversion and 8:1 d.r.;

entry 5, Table 1). Then, the effect of the reaction medium were screened (entries 6-8, Table 1), the results indicated that the reaction could not proceed in toluene or THF (entrie 6 and 7, Table 1), and obvious improvement of enantioselectivity was realized when CH_2Cl_2 was employed (78% ee; entry 8, Table 1). From the survey of different ligands (entries 9-11, Table 1), the best enantio- and diastereoselectivity was obtained with 93% conversion when the electron-rich bisphosphine ligand **L4** was used (90% ee and >20:1 d.r.; entry 11, Table 1). By elevating the temperture to 70 °C, we were glad to find that the reaction could proceeded well with >95% conversion (entry 12, Table 1). Thus, the optimized conditions were established as follows: $Pd(OCOCF_3)_2$/**L4**, TFA (60 mol%), H_2 (1000 psi), CH_2Cl_2, 70 °C.

Table 1. The Evaluation of Reaction Parameters[a]



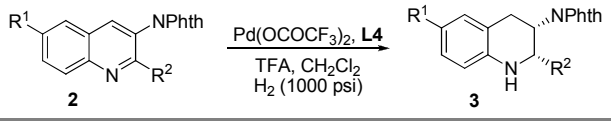
Entry	Additive	L	Solvent	Conv. (%)	Ee (%)[b]	D.r.
1	L-CSA	**L1**	TFE	52	45	4:1
2	TsOH·H_2O	**L1**	TFE	53	46	4:1
3	D-CSA	**L1**	TFE	45	46	4:1
4	$PhCO_2H$	**L1**	TFE	9	--	1:1
5	TFA	**L1**	TFE	85	47	8:1
6	TFA	**L1**	PhMe	<5	--	--
7	TFA	**L1**	THF	<5	--	--
8	TFA	**L1**	CH_2Cl_2	>95	78	14:1
9	TFA	**L2**	CH_2Cl_2	>95	80	>20:1
10	TFA	**L3**	CH_2Cl_2	72	78[d]	15:1
11	TFA	**L4**	CH_2Cl_2	93	90[d]	>20:1
12[c]	TFA	**L4**	CH_2Cl_2	>95	90[d]	>20:1



[a] Reaction conditions: **2a** (0.05 mmol), $Pd(OCOCF_3)_2$ (5.0 mol%) and **L** (6.0 mol%), additive (60 mol%), solvent (2 mL), H_2 (1000 psi), 60 °C, 18 h. Reaction conversion and d.r. were determined by ^{1}H NMR spectroscopy. [b] Determined by HPLC using a chiral stationary phase. [c] 70 °C. [d] The opposite enantiomer was obtained. L-CSA: L-Camphorsulfonic acid. TsOH·H_2O: *p*-Toluenesulfonic acid monohydrate. D-CSA: D-Camphorsulfonic acid. TFA: Trifluoroacetic acid. TFE: 2,2,2-Trifluroroethanol.

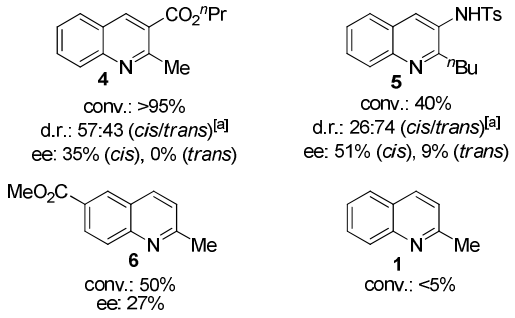
In order to probe the generality of the catalytic system, a series of 3-phthalimido substituted quinolines were subjected to hydrogenation under the optimized conditions, and the results were summarized in Table 2. A variety of substrates bearing an alkyl group at the 2-position were hydrogenated smoothly with high yields and 79-90% ee, regardless of the length of the side chain (entries 1-10, Table 2). Notably, there appears to be a trend toward increased enantiocontrol as the relative length of the alkyl increases when the alkyl group were linear carbon chains with less than four carbon atoms (R = Me, 81% ee; R = Et, 85% ee; R = ^{n}Pr, 87% ee; R = ^{n}Bu, 90% ee; entries 1-4, Table 2). The phenyl substituted substrate **2k** could be transformed smoothly under standard conditions with low enantioselectivity (14% ee; entry 11, Table 2). The C=C double bond in the side chain of substrate **2l** and **2m** could also be hydrogenated and high enantioselectivity was observed (90% and 88% ee; entries 12 and 13, Table 2).

Table 2. Catalytic Asymmetric Hydrogenation of Quinolines **2**[a]



Entry	2	R^1 / R^2	T (°C)	Yield (%)[b]	Ee (%)[c]
1	**2a**	H / ^{n}Bu	70	91 (**3a**)	90 (*S,S*)[e]
2	**2b**	H / Me	70	86 (**3b**)	81 (-)
3	**2c**	H / Et	80	93 (**3c**)	85 (-)
4	**2d**	H / ^{n}Pr	80	97 (**3d**)	87 (-)
5	**2e**	H / ^{c}Pr	80	72 (**3e**)	80 (-)
6	**2f**	H / ^{i}Bu	80	94 (**3f**)	90 (-)
7	**2g**	H / ^{i}Pentyl	80	91 (**3g**)	90 (-)
8	**2h**	H / ^{n}Hexyl	70	86 (**3h**)	90 (-)
9	**2i**	H / Phenethyl	80	95 (**3i**)	90 (-)
10	**2j**	F / ^{n}Bu	80	97 (**3j**)	79 (-)
11	**2k**	H / Ph	70	83 (**3k**)	14 (-)
12	**2l**	H / (*E*)-Styryl[d]	80	99 (**3i**)	90 (-)
13	**2m**	H / (*E*)-4-Fluorostyryl[d]	80	86 (**3m**)	88 (-)

[a] Reaction conditions: **2** (0.10 mmol), $Pd(OCOCF_3)_2$ (5.0 mol%) and **L4** (6.0 mol%), TFA (60 mol%), CH_2Cl_2 (4 mL), H_2 (1000 psi), 18 h. The d.r. of the products wad determined by ^{1}H NMR spectroscopy. In all cases the d.r. >20:1. [b] Isolated yield. [c] Determined by HPLC using a chiral stationary phase. [d] The conjugated double bond was also hydrogenated. [e] The absolute configuration of **3a** was determined to be *cis*-(*S,S*) by comparison of the ^{1}H NMR, HPLC and optical rotation with our earlier reported data.[15a]



Scheme 2. Palladium-Catalyzed Asymmetric Hydrogenation of Other Substituted Quinolines. [a] The Relative Configura-tions were Determined by Comparison of the ^{1}H NMR with Our Previous Reported Data.[15a,16]

This methodology can also be applied in the asymmetric hydrogenation of several other substituted quinolines (Scheme 2). 3-Carbalkoxy substituted substrate **4** could be hydrogenated smoothly with poor diastereoselectivity and moderate enantioselectivity. The reduction of 3-*p*-toluenesulfonamido substituted quinoline **5** gave the corresponding product with 40% conversion and low distereoselectivity. It is noteworthy that the substrate **6** with a carbalkoxy group at the C6 position could also be transformed, moderate 50% conversion and 27% ee was obtained. Unfortunately, this catalyst system still has no catalytic activity on simple 2-methylquinoline **1**.

Conclusions

In conclusion, we have described the first example of homogeneous palladium-catalyzed asymmetric hydrogenation of substituted quinolines, providing a facile access to chiral substituted 1,2,3,4-tetrahydroquinolines bearing two contiguous stereogenic centers with up to 90% ee. This reaction broadens the application scope of palladium catalysts in asymmetric hydrogenation. Our ongoing experiments are focused on homogeneous palladium-catalyzed asymmetric hydrogenation of other aromatics.

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Notes and references

State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China
E-mail: ygzhou@dicp.ac.cn; Homepage: http://www.lac.dicp.ac.cn/

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