ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 1698–1700

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Asymmetric hydrogenolysis of racemic tertiary alcohols, 3-substituted 3-hydroxyisoindolin-1-ones†

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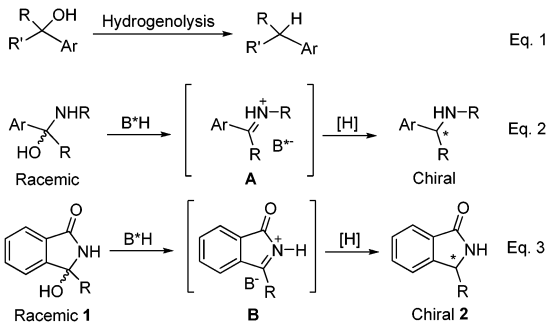
Received 4th November 2011, Accepted 28th November 2011
DOI: 10.1039/c2cc16832d

Asymmetric hydrogenolysis of racemic tertiary alcohols, 3-substituted 3-hydroxyisoindolin-1-ones, was developed using chiral phosphoric acid as catalyst and a Hantzsch ester as the hydrogen source with up to 95% ee. The reaction process of this asymmetric transfer hydrogenation may occur directly through the acyliminium ion intermediate.

Hydrogenolysis of alcohols and their derivatives is an important transformation (eqn (1), Scheme 1), which is widely used in pharmaceutical synthesis, biomass conversion, environmental application and organic synthesis.[1] In general, most of the hydrogenolysis reactions were carried out in the presence of a transition-metal catalyst[2a–g] and/or acid[2h–j,3] to synthesize the corresponding compounds in racemic form. To the best of our knowledge, hitherto the asymmetric version of hydrogenolysis reactions has received very little attention in previous experimental and theoretical investigations.[4]

In the presence of Brønsted acids, alcohols can readily dehydrate to *in situ* give a carbonium ion, which is not very stable and prone to undergo some side reactions, such as rearrangement,[5a–c] olefin formation[5d] and etherification.[5e,f] Whereas the introduction of a heteroatom at the center of carbonium can generate a stable form with positive charge on the heteroatom, such as introduction of a N atom can make the carbonium ion into a stabler iminium ion (**A**). The hydrogenolysis of this key intermediate might afford chiral products in the proper chiral environment (eqn (2), Scheme 1).



Scheme 1 Asymmetric transfer hydrogenation of 3-substituted 3-hydroxyisoindolin-1-ones.

Racemic tertiary alcohols, 3-hydroxy-substituted isoindolin-1-ones, can readily dehydrate to *in situ* form acyliminium ions (eqn (3), Scheme 1) in the presence of Brønsted acids,[3] which have been successfully applied in various asymmetric organocatalytic carbon–carbon bond formations.[6] C=N can be successfully reduced after transformation to iminium ions in the presence of chiral Brønsted acids using a Hantzsch ester as the hydrogen source.[7,8] Hence, we envisioned that it would be possible to obtain chiral 3-substituted isoindolinones through transfer hydrogenolysis of the achiral acyliminium intermediates (**B**) using chiral phosphoric acid as catalyst and a Hantzsch ester as the hydrogen source. In addition, hydrogenolysis products, chiral 3-substituted isoindolinones, have attracted much attention from the scientific community since they represent the core unit of numerous biologically active molecules and naturally-occurring alkaloids.[9] Though several approaches to the synthesis of 3-substituted isoindolinones have been developed in the past decades, most of these methods need a chiral auxiliary derived to control the diastereoselectivity of this reaction.[10–12] Herein, we have reported the enantioselective synthesis of 3-substituted isoindolin-1-ones by a chiral phosphoric acid catalyzed asymmetric hydrogenolysis of 3-hydroxysubstituted isoindolin-1-ones with a Hantzsch ester as the hydrogen source.

3-Butyl-3-hydroxyisoindolin-1-one (**1a**) was selected as a model substrate, (*S*)-Binol derived chiral phosphoric acid and diethyl Hantzsch ester were used as the catalyst and hydrogen source, respectively. Initially, full conversion was obtained with the desired product **2a** and the sole byproduct alkene **2a′** in a ratio of 39 : 61 in $CHCl_3$ (Table 1, entry 1). Subsequently, different solvents were examined, and it was found that solvent effect played a crucial role in reactivity, chemoselectivity and enantioselectivity, CH_2Cl_2 was the best choice (Table 1, entries 1–4). Then, some commercially available chiral phosphoric acids were tested (Table 1, entries 5–7), and it clearly showed that VAPOL-derived phosphoric acid displayed better chemoselectivity and enantioselectivity. The reaction rate dramatically decreased when 4 Å MS was added to remove the trace amount of water during the hydrogenolysis reaction (Table 1, entry 8). Next, screening of the effect of Hantzsch esters revealed that the di-*tert*-butyl Hantzsch ester provided the highest enantioselectivity (Table 1, entries 9–12).

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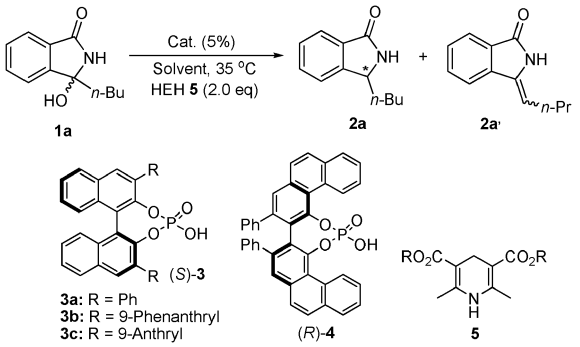
† Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/c2cc16832d

Table 1 The evaluation of reaction parameters[a]



Entry	Solvent	Catalyst	R of **5**	**2a**/**2a'**[b]	ee[c] (%)
1	$CHCl_3$	**3a**	Et (**5a**)	39/61	35
2	Toluene	**3a**	Et (**5a**)	31/69	24
3	THF	**3a**	Et (**5a**)	—/ > 95	/
4	CH_2Cl_2	**3a**	Et (**5a**)	63/37	43
5	CH_2Cl_2	**3b**	Et (**5a**)	60/40	4
6	CH_2Cl_2	**3c**	Et (**5a**)	51/49	43
7	CH_2Cl_2	**4**	Et (**5a**)	81/19	72
8[d]	CH_2Cl_2	**4**	Et (**5a**)	52/48	71
9	CH_2Cl_2	**4**	Me (**5b**)	62/38	60
10	CH_2Cl_2	**4**	*i*-Pr (**5c**)	71/29	72
11	CH_2Cl_2	**4**	*t*-Bu (**5d**)	70/30	85
12	CH_2Cl_2	**4**	Bn (**5e**)	67/33	67
13[e]	CH_2Cl_2	**4**	*t*-Bu (**5d**)	68/32	86

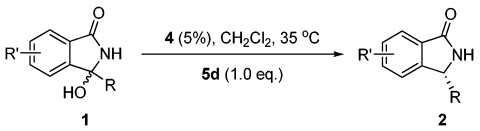
[a] The reaction was carried out with **1a** (0.05 mmol), catalyst (0.0025 mmol), **5** (0.10 mmol), and 3 mL solvent under 35 °C for 24 h. Full conversions were obtained for all cases. [b] Determined by ^{1}H NMR. [c] ee was determined by HPLC analysis. [d] 4 Å MS was added as an additive. [e] 3,5-di-*tert*-Butyl-Hantzsch ester (0.05 mmol).

Lowering the amount of Hantzsch ester to 1.0 equivalent did not affect the enantioselectivity (Table 1, entry 13). Therefore, the optimal conditions were established as phosphoric acid **4** (5%), Hantzsch ester **5d** (1 equiv.), CH_2Cl_2, 35 °C.

With the optimal reaction conditions in hand, we explored the scope of the chiral phosphoric acid catalyzed asymmetric transfer hydrogenolysis of 3-substituted 3-hydroxyisoindolin-1-ones. As expected, various aliphatic substituents at the 3-position of **1** worked well under the standard conditions with moderate to good enantioselectivities (Table 2, entries 1–14). Prolonging alkyl chains led to a significant improvement in enantioselectivity and the steric hindrance of alkyl chains did not affect the enantioselectivity (Table 2, entries 3–6). Notably, 3-benzyl substituted 3-hydroxyisoindolin-1-one afforded the products with excellent enantioselectivities (91–95% ee, Table 2, entries 9–12). Then, the effect of substituents on the benzene ring on the activity and enantioselectivity was also investigated. For 4-methyl and 7-methyl substituted isoindolinones **1m** and **1n**, 82% and 90% ee were obtained, respectively (Table 2, entries 13 and 14). In addition, 3-aryl substituted isoindolinone **1o** was also examined under the standard conditions, giving moderate 61% ee (Table 2, entry 15).

Acyliminium ions formed from the dehydration of 3-substituted 3-hydroxyisoindolin-1-ones in the presence of Brønsted acids can isomerize to the corresponding enamine,[3c] 3-alkylidene isoindolinones, which might be hydrogenated to give the chiral target molecule. So, 3-butylideneisoindolin-1-one was synthesized and subjected to asymmetric transfer hydrogenation under the above standard conditions; no desired product **2a** was obtained. Transfer hydrogenolysis of the *N*-methyl protected 3-butyl-3-hydroxy-isoindolin-1-one (**1p**) was investigated, but no reaction occurred. The above experiments clearly indicated that the reaction process of this asymmetric transfer hydrogenation may occur directly through the acyliminium ion intermediate (Scheme 2), and the tautomerization between the imine and enamine might be irreversible.

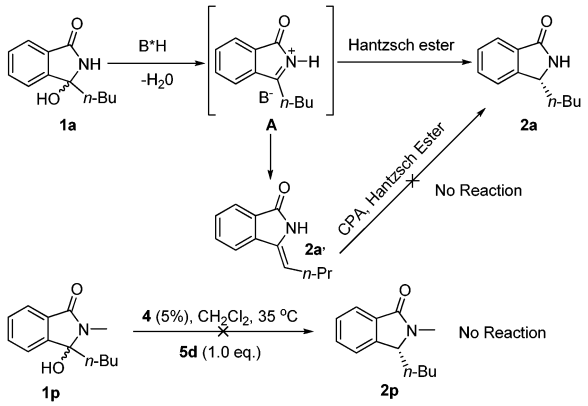
Table 2 Chiral phosphoric acid catalyzed asymmetric transfer hydrogenolysis of **1**[a]



Entry	R	R′	Yield[b] (%)	ee[c] (%)
1	*n*-Bu	H	62 (**2a**)	86 (*R*)
2	Me	H	64 (**2b**)	65 (*R*)
3	Et	H	56 (**2c**)	86 (*R*)
4	*n*-Pr	H	60 (**2d**)	83 (*R*)
5[d]	*i*-Pr	H	66 (**2e**)	88 (*R*)
6	*n*-Hexyl	H	71 (**2f**)	86 (*R*)
7[d]	Cy	H	54 (**2g**)	76 (*R*)
8	$PhCH_2CH_2$	H	38 (**2h**)	78 (*R*)
9	Bn	H	47 (**2i**)	95 (*R*)
10[d]	4-Me-$C_6H_4CH_2$	H	57 (**2j**)	94 (*R*)
11[d]	3-Me-$C_6H_4CH_2$	H	49 (**2k**)	91 (+)
12[d]	4-F-$C_6H_4CH_2$	H	50 (**2l**)	93 (+)
13	*n*-Bu	4-Me	62 (**2m**)	82 (+)
14	*n*-Bu	7-Me	71 (**2n**)	90 (+)
15[e]	Ph	H	43 (**2o**)	61 (*R*)

[a] The reaction was carried out with **1** (0.20 mmol), **4** (0.01 mmol), Hantzsch ester **5d** (0.20 mmol), and 12 mL CH_2Cl_2 under 35 °C for 24 h. [b] Isolated yield. [c] ee was determined by HPLC analysis. [d] 48 h. [e] 72 h.

In summary, we have successfully developed an organocatalytic enantioselective synthesis of chiral 3-substituted isoindolin-1-ones through the chiral phosphoric acid catalyzed transfer hydrogenolysis of easily accessible racemic 3-substituted 3-hydroxyisoindolin-1-ones with a Hantzsch ester as the hydrogen source with up to 95% ee.[13] Our ongoing experiments are focused on exploring other asymmetric hydrogenation reactions of iminium salts/acyliminium ions.



Scheme 2 Proposed pathway for hydrogenolysis of **1**.

This work was financially supported by National Natural Science Foundation of China (21032003 & 20872140), and National Basic Research Program of China (2010CB833300).

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