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Detection and Elimination of Product Inhibition from the Asymmetric Catalytic Hydrogenation of Enamines

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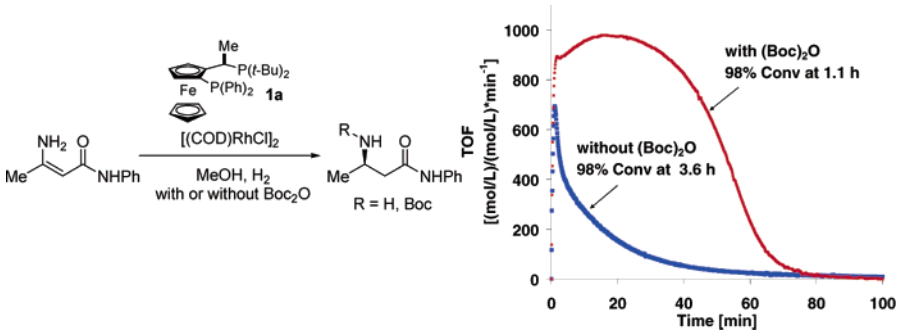
ABSTRACT



The catalytic asymmetric hydrogenation of enamine amides and esters with catalyst Rh-1a, prepared from ferrocenyl based ligand 1a or 1b and [(COD)RhCl]$_2$, has been shown through kinetic studies to suffer from product inhibition. Enamine ester substrates have also been shown to be incompatible with the amine products of the reaction in methanol. In situ protection of the amine products with di-*tert*-butyl dicarbonate eliminates functional group incompatibility of ester substrates and eliminates product inhibition in the reaction.

The catalytic asymmetric hydrogenation of enamine amides and esters with catalyst **Rh-1a**, prepared from ferrocenyl based ligand **1a** or **1b** and [(COD)RhCl]$_2$, is a powerful method for the synthesis of unprotected *β*-amino acid derivatives.[1] However, one of the most desirable aspects of this reaction, the direct formation of unprotected amino amides and esters, has the potential to limit the reaction performance. Amine compounds are known to have deleterious effects on the performance of heterogeneous[2] and homogeneous[3] hydrogenation systems. The basicity/nucleophillicity of the amine products may also render them unstable to the reaction conditions, especially in the case of amino ester compounds in methanol. This issue has been previously addressed by using the *N*-acyl enamine substrates for hydrogenation.[4] However, control of the enamine geometry in the synthesis of these substrates is difficult and the geometry can drastically affect the enantioselectivity of their reduction.[5] This Letter provides evidence that product inhibition occurs in the asymmetric hydrogenation of unprotected enamines and that the primary amine products are incompatible with ester substrates when the reaction is conducted in methanol instead of 2,2,2-trifluoroethanol. However, the deleterious effects of the amine products on the reaction can be eliminated by their in situ protection as they are formed.

(1) Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J. D., III.; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc*. **2004**, *126* (32), 9918−9919.

(2) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; John Wiley & Sons: New York, 2001; Chapter 2.2.1.

(3) (a) Marcazzan, P.; Patrick, B. O.; James, B. R. *Organometallics* **2003**, *22*, 1177−1179. (b) Marcazzan, P.; Patrick, B. O.; James, B. R. *Inorg. Chem.* **2004**, *43*, 6838−6841 and references therein. (c) Faller, J. W.; Tokunaga, M. *Tetrahedron Lett.* **1993**, *34*, 7359−7362

(4) Ma, J.-A. *Angew. Chem., Int. Ed.* **2004**, *42*, 4290−4299

(5) For an example of a system that performs the asymmetric reduction of *N*-acyl enamines with high ee, independent of the *E*/*Z* ratio of the enamine, see: Zhou, Y.-G.; Tang, W.; Wang, W.-B.; Li, W.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 4952−4953.

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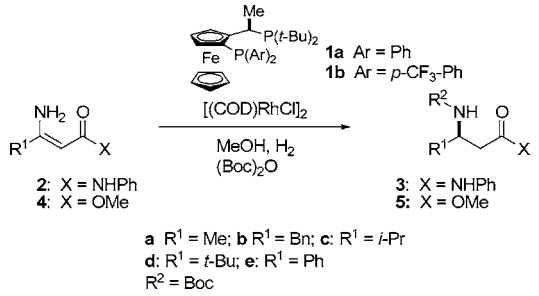
The potential for product inhibition was investigated by studying the hydrogenation of 3-amino-2-butenanilide **2a**, using reaction calorimetry (RC) (Scheme 1). The kinetics

Scheme 1. Asymmetric Hydrogenation of Enamine Amides and Enamine Esters



of the reduction of **2a** were monitored by performing it with 1.0 mol % of catalyst in a reaction calorimeter to measure the heat flow over the course of the reaction. A plot of the catalyst turnover frequency (TOF) as a function of time is shown in Figure 1, Reaction A. The plot shows that the rate

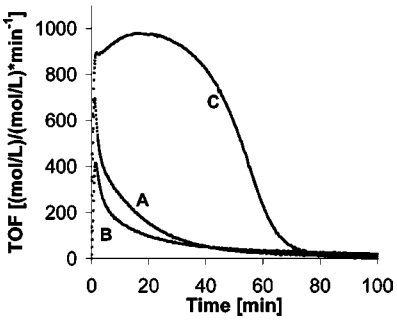


Figure 1. Rate profile for the hydrogenation of **2a**. Conditions: 8.5 mmol of **2a** in 15 mL of MeOH, 40 °C with (A) 1 mol % of **Rh-1a**, 479 psi of H_2, (B) 32 mol % of **3a** (R^2 = H), 1 mol % of **Rh-1a**, 479 psi of H_2, and (C) 0.2 mol % of **Rh-1a**, 2 equiv of $(Boc)_2O$, 459 psi of H_2.

reaches an early maximum and then slows as the reaction proceeds. The decrease in the turnover frequency over the course of the reaction is consistent with a rate dependence on substrate concentration and/or product inhibition occurring.

When the same reduction was performed with an initial charge of 32 mol % of product **3a** (R^2 = H), the heat flow profile showed a significant reduction in the TOF (Figure 1, Reaction B). Consistent with the rate reduction, the overall reaction time under these conditions increased from 3.6 h to 11.3 h (Table 1).[6]

Selective derivatization or protection of the amine products by acylation in situ could potentially attenuate or eliminate

(6) The reactions were judged complete when 98% of the total heat flow for the experiment was obtained.

Table 1. Selected Kinetic Data from the Asymmetric Hydrogenation of **2a**[a]

reaction	cat. loading, mol %	additive	time,[b] h	$TOF_{50\%}$[c]
A	1.0	none	3.6	220
B	1.0	0.31 equiv of **3a** (R^2 = H)	11.3	50
C	0.2	2 equiv of $(Boc)_2O$	1.1	950

[a] For reaction conditions see Figure 1. [b] Reaction time required to reach 98% of total heat flow for each experiment. [c] Turnover frequency at 50% thermal conversion.

the product inhibition observed in the reaction. Treatment of enamine **2a** with common acylating agents such as acetic anhydride, benzoyl chloride, or benzoic anhydride under the reaction conditions resulted in reaction of the substrate with the acylating agent directly or decomposition of the enamine to its ketone precursor. Alternatively, di-*tert*-butyl dicarbonate ($(Boc)_2O$)[7] reacted very slowly with enamine substrates, even at temperatures up to 50 °C. Since $(Boc)_2O$ reacts quickly with primary amines and forms relatively innocuous byproducts (CO_2[8] and *tert*-butyl alcohol), it was studied further as a potential means of eliminating product inhibition from the reaction.

The addition of $(Boc)_2O$ to the reaction was demonstrated by RC to have a favorable effect on the asymmetric hydrogenation of enamine amides. Hydrogenation of **2a** with 0.2 mol % of **Rh-1a** and 2 equiv of $(Boc)_2O$ resulted in the formation of the expected *N*-Boc β-amino amide **3** (R^2 = Boc). Performing the hydrogenation under these conditions also resulted in a reduction of the reaction time from 3.6 h to 1.1 h when compared to the control experiment, despite a 5-fold reduction in catalyst loading (Table 1). The reason for the dramatic difference in reaction rate can be seen from the TOF profile of the reaction (Figure 1, Reaction C), which shows the rate of the reaction in the presence of $(Boc)_2O$ is higher and only begins to slow toward the end of the reaction.[9] Indeed, the TOF at 50% conversion increased from 220 without Boc_2O to 950 when $(Boc)_2O$ was added to the hydrogenation (Table 1). Plotting the differential thermal % conversion as a function of thermal conversion[10] reveals that the reduction in the presence of $(Boc)_2O$ displays apparent zero-order kinetics for the majority of the reaction.[11] The apparent change in reaction order in Reaction C is consistent with the idea that the product inhibition observed in the hydrogenation of **2a** was eliminated by in situ protection with $(Boc)_2O$.

(7) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999; pp 518−525.

(8) Carbon dioxide has been demonstrated to facilitate the reduction of nitriles to amines by protecting the product as a carbamic acid. Xie, X.; Liotta, C. L.; Eckert, C. A. *Ind. Eng. Chem. Res.* **2004**, *43*, 7907−7911.

(9) A similar RC profile was obtained when this experiment was performed with 1.1 equiv of $(Boc)_2O$.

(10) This type of plot provides a graphical equivalent to the rate of reaction versus conversion. See: Landau, R. N.; Blackmond, D. G.; Tung, H.-H. *Ind. Eng. Chem. Res.* **1994**, *33*, 814−820.

(11) A plot of the differential % thermal conversion as a function of thermal conversion for reactions A, B, and C is contained in the Supporting Information.

The elimination of product inhibition from the reaction allows it to be performed under milder conditions with higher yields. Performing the reduction of **2a** with 0.4 mol % of catalyst at room temperature with 90 psig of H_2 resulted in only a 63% assay yield (Table 2, entry 1). However when

Table 2. Asymmetric Hydrogenation of Enamine Amides and Esters with $(Boc)_2O$[a]

entry	enamine R^1, X (#)	substrate	% yield[b]	% ee
1	Me, NHPh	**2a**	63[c]	97
2	Me, NHPh	**2a**	84	97
3	Bn, NHPh	**2b**	97	97
4[d]	Bn, NHPh	**2b**	99	97
5	Ph, NHPh	**2e**	98	98
6	Me, OMe	**4a**	<10[c,e]	
7	Me, OMe	**4a**	85[e]	96
8	Bn, OMe	**4b**	93	99
9[f]	*i*-Pr, OMe	**4c**	75[e]	95
10[f]	*t*-Bu, OMe	**4d**	62[e]	91
11	Ph, OMe	**4e**	15	97
12[g]	Ph, OMe	**4e**	57	97

[a] Reaction conditions: 0.5 M substrate in methanol, 1.1 equiv of $(Boc)_2O$, 0.2 mol % of $[(COD)RhCl]_2$, 0.41 mol % (*R*,*S*)-Josphios, 20 °C, 90−100 psig of H_2, 20 °C, 18 h. [b] HPLC assay yield. [c] $(Boc)_2O$ added after hydrogenation was complete. [d] Performed at 40 psig of H_2 on 5 mmol scale. [e] GC assay yield. [f] With 0.8 mol % of catalyst. [g] With 3.0 mol % of catalyst.

the same reaction was performed in the presence of 1.1 equiv of $(Boc)_2O$, an 84% assay yield of the desired *N*-Boc amino amide **Boc-3a** was obtained (Table 2, entry 2).

The effect of in situ protection was much more pronounced with enamine ester substrates **4**. While enamine amides are hydrogenated in high yield and enantioselectivity with **Rh-1a** in methanol, the corresponding methyl esters are poor substrates under the same conditions.[1] The reduction of methyl 3-aminocrotonate **4a** with complex **Rh-1a** in methanol at 20 °C proceeds with poor yield to the desired β-amino ester product **5** (Table 2, entry 6). Analysis of the reaction mixture showed that undesired dimeric compounds **6** and **7**, arising from acylation of the primary amine of **5a** by the ester of both product and starting material, are the major products of the reaction (Figure 2). Performing the reduction

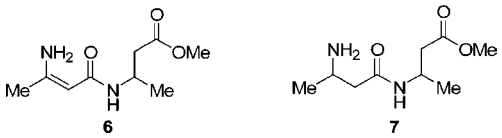


Figure 2. Byproducts of the asymmetric hydrogenation of **4a** with **Rh-1a** in methanol in the absence of $(Boc)_2O$.

of **4a** in the presence of 1.1 equiv of $(Boc)_2O$ results in the formation of the desired *N*-Boc product **Boc-5a** in nearly identical enantioselectivity and yield as the corresponding anilide (Table 2, entry 7).

The new conditions were applied to a variety of substrates and the results are summarized in Table 2. The reductions, which were performed at 20 °C with 0.4 mol % of catalyst at 90−100 psi of H_2, afforded the desired *N*-Boc amino ester or amides in good yields and excellent enantioselectivities. In the case of substrates **4c** or **4d**, the catalyst loading was increased to 0.8 mol % to obtain the desired product in reasonable yield, most likely due to the increased size of R^1. The phenyl substituted enamine ester **4e** was by far the poorest performing substrate that was examined: <20% conversion at 0.4 mol % of catalyst loading. However, by increasing the catalyst loading further to 3 mol %, a comparable yield to the other substrates in Table 2 was obtained. Comparison of the results obtained for ester **4e** with its anilide analogue, **2e**, reveals that amides are inherently more reactive substrates under identical conditions (entry 5 versus entry 11). This difference in reactivity may be due to the amide carbonyl binding more strongly to the catalyst than the corresponding ester.[12]

The beneficial effect of using $(Boc)_2O$ in the asymmetric hydrogenation of enamine amides and esters has implications for the use of this reaction on both large and small scale. Typically, to achieve selectivities and rates comparable to enamine amide substrates, enamine esters are reacted with the trifluoromethyl ligand **1b** in 2,2,2-trifluoroethanol (TFE) as reaction solvent.[1] One potential role of TFE, which is considerably more acidic than methanol, may be to stabilize the amino ester product by attenuating the nucleophilicity of the primary amine.[13] In situ protection of the product with $(Boc)_2O$ has a similar effect as TFE and allows for the more economical solvent, methanol, to be used as the reaction solvent for both ester and amide substrates.

Due to the enhanced catalyst performance, the reaction can be performed at lower pressures, eliminating the need for high-pressure equipment. For example, compound **2b** was hydrogenated at 40 psig of H_2[14] on 5 mmol scale with excellent ee and yield with use of a glass pressure bottle as a reactor (Table 2, entry 4).[15,16]

While the unreactive nature of the enamine substrates toward $(Boc)_2O$ supports the claim that carbamate formation occurs after hydrogenation of the unprotected enamine, the reduction of an *N*-Boc enamine, formed in small amounts during the reaction, cannot be ruled out. However, performing the reduction with D_2 in the presence of $(Boc)_2O$ resulted in incorporation of deuterium only in the β position. This result is consistent with the reaction proceeding by the same pathway as when the reaction is performed in the absence of $(Boc)_2O$.[17]

In conclusion, the reactive nature of the primary amine formed in the direct asymmetric hydrogenation of enamines

(12) Coordination of the substrate to catalyst **Rh-1a** has been proposed in this reaction. See ref 1.

(13) The pK_a values of TFE and MeOH are 23.5 and 29 in DMSO, respectively. Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.

(14) 40 psig can be maintained with a stopper on a glass bottle.

(15) A detailed reaction procedure is given in the Supporting Information.

(16) The *N*-Boc amino ester and amide products are easily purified by flash chromatography, in contrast to the unprotected products.

(17) The asymmetric hydrogenation of unprotected enamines has been proposed to proceed through the imine tautomer, which results in deuterium incorporation only in the β position of the product.

catalyzed by **Rh-1a** leads to substantial product inhibition as well as functional group incompatibility with ester substrates. A simple solution, the in situ formation of the easily removable *tert*-butyl carbamate with $(Boc)_2O$, solves both of these problems, resulting in milder and more general conditions to perform the reaction. This strategy may potentially be applied to other catalytic systems where the amine products produced are incompatible with the reaction conditions and/or are inhibitors of the catalyst.

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Supporting Information Available: Experimental details and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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