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# Direct Asymmetric Reductive Amination

Dietrich Steinhuebel,*,† Yongkui Sun,*,† Kazuhiko Matsumura,*,‡ Noboru Sayo,‡ and Takao Saito‡

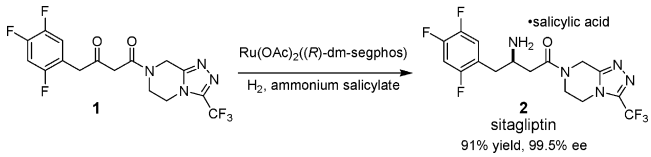
*Department of Process Research, Merck & Co., Inc., P.O. Box 2000, Rahway, New Jersey 07065, and Corporate Research & Development Division, Takasago International Corporation, 1-4-11 Nishi-yawata, Hiratsuka City, Kanagawa 254-0073, Japan*

Received June 22, 2009; E-mail: dietrich_steinhuebel@merck.com; yongkui_sun@merck.com; kazuhiko_matsumura@takasago.com

$\beta$-Amino acid derivatives are valuable chiral building blocks in the synthesis of pharmaceuticals.[1] Asymmetric hydrogenation of protected dehydroamino acid derivatives such as *N*-acyl enamines,[2a] along with other methods for chiral amine synthesis,[2b,c] has proven to be a valuable methodology for the preparation of these targets. However, from an efficiency standpoint, all of these methods require additional steps involving manipulation of the *N*-protecting group.

A highly efficient approach for an *unprotected* chiral amine would involve the direct asymmetric reductive amination of a ketone with *ammonia* or a suitable surrogate. However, there are very few reports of such an approach[3] and no reports on asymmetric reductive amination of $\beta$-keto amides to the unprotected $\beta$-amino amides. Because of the importance of $\beta$-amino amides in drug synthesis and our earlier work on asymmetric hydrogenation of unprotected $\beta$-enamine amides,[4] we were interested in such a direct approach. We now disclose the first general methodology for an efficient, catalytic, one-pot synthesis of unprotected $\beta$-amino amides via asymmetric reductive amination of readily accessible $\beta$-keto amides using simple ammonium salts as the nitrogen source. We have also applied this methodology to the highly enantioselective synthesis of sitagliptin (Scheme 1), a $\beta$-amino amide that is a potent DPP-IV inhibitor for the treatment of type-II diabetes.[5]

***Scheme 1***




We started our studies by investigating the asymmetric hydrogenation of preformed **3** (Scheme 2), a key intermediate in the reductive amination. Rh(I)-*t*-Bu-Josiphos catalyzes the reaction of **3** to give **2** with 95% ee.[4] Ru catalysts have been reported to catalyze asymmetric hydrogenation of unprotected $\beta$-enamine esters in high ee's[6] and reductive amination of the $\beta$-keto esters.[3b−d] Screening of Ru complexes with a series of bisphosphine chiral ligands revealed that Ru(OAc)$_2$((*R*)-dm-segphos) gave >99% ee, an enantioselectivity previously unachievable in the asymmetric hydrogenation of **3**.[4]

Further investigation of the Ru(OAc)$_2$((*R*)-dm-segphos) system (Table 1) showed that acid addition was necessary for the reactivity of Ru(OAc)$_2$((*R*)-dm-segphos) toward hydrogenation of **3** (entry 1 vs 2). The enantioselectivity also benefited greatly from the acid addition. However, acids such as acetic or benzoic acid promoted the generation of a considerable amount of dimer-like by-product **4** (entries 2, 3). Acid screening revealed that acids with a p$K_a \approx 2$, such as chloroacetic acid and salicylic acid, performed well. Salicylic acid was ultimately chosen for further focus because it suppressed the generation of **4** and enhanced the yield of **2** to 75% (entry 5). Finally, we found that addition of ammonium salicylate ($NH_4SA$) eliminated **4**, leading to 96% yield with nearly perfect enantioselectivity (99.5% ee; entry 6).

***Scheme 2***

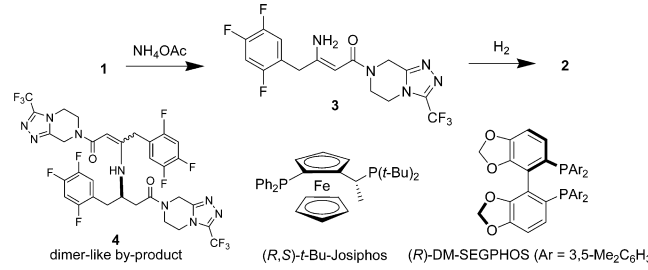



***Table 1.*** Asymmetric Hydrogenation of $\beta$-Enamine Amide **3** to **2**[a]

| | | (*R*)-**2** | |
|---|---|---|---|
| entry | additive(s) (equiv) | % yield[b] | % ee[c] |
| 1 | none | 2 | 86.9 |
| 2 | acetic acid (1) | 32 | 98.2 |
| 3 | benzoic acid (1) | 15 | 97.5 |
| 4 | $ClCH_2CO_2H$ (1) | 74 | >99 |
| 5 | salicylic acid (1) | 75 | 99.5 |
| 6 | salicylic acid (1) + $NH_4SA$ (3) | 96 | 99.5 |

[a] Conditions: 0.25 M substrate in MeOH, Ru(OAc)$_2$((*R*)-dm-segphos), S/C = 200, $H_2$ (290 psi), 80 °C, 15 h. [b] Assay yield of **2** by HPLC. [c] Assayed by chiral HPLC.

***Table 2.*** Asymmetric Reductive Amination of $\beta$-Keto Amide **1** to **2**[a]

| | | | | (*R*)-**2** | |
|---|---|---|---|---|---|
| entry | cat[b] | $NH_4X$ (equiv) | solvent | % yield[c] | % ee[d] |
| 1 | **I** | $NH_4SA$ (5) | MeOH | 91 | 99.5 |
| 2 | **I** | $NH_4SA$ (1) | MeOH | 43 | 99.6 |
| 3 | **I** | $NH_4SA$ (3) | MeOH | 85 | 99.6 |
| 4 | **I** | $NH_4OAc$ (5) | MeOH | 20 | 99.2 |
| 5 | **I** | $NH_4SA$ (5) | TFE | 74 | 98.1 |
| 6 | **II** | $NH_4OAc$ (5) | MeOH | 86 | 93.2 |
| 7 | **II** | $NH_4SA$ (5) | MeOH | 64 | 93.2 |

[a] Conditions: 0.25 M substrate in solvent, S/C = 100, $H_2$ (435 psi), 75 °C, 7 h. [b] **I**: Ru(OAc)$_2$((*R*)-dm-segphos). **II**: [RhCl(cod)]$_2$, (*R*,*S*)-*t*-Bu-Josiphos (1 equiv with respect to Rh). [c] Assay yield of **2** by HPLC. [d] Assayed by chiral HPLC.

We next examined the more complex one-pot reductive amination of **1** to **2** by hydrogenating the mixture of $\beta$-keto amide **1** and various ammonium salts in the presence of Ru(OAc)$_2$((*R*)-dm-segphos). The results are summarized in Table 2. As was suggested by Table 1, ammonium salicylate was the best among the ammonium salts tested.[7] With the addition of 5 equiv of ammonium salicylate, the reaction afforded $\beta$-amino amide **2** in 91% yield with 99.5% ee (entry 1).[8] Under these conditions, we observed only a small amount (<3%) of the $\beta$-hydroxyl amide resulting from direct hydrogenation of the $\beta$-keto amide **1**. Smaller amounts of ammonium salicylate (1−3 equiv) led to lower yields (entries 2, 3) due to higher levels of **4** and the

† Merck & Co., Inc.
‡ Takasago International Corporation.



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$\beta$-hydroxyl amide produced. The use of ammonium acetate led to slow hydrogenation, although still with >99% ee (entry 4). The use of 2,2,2-trifluoroethanol (TFE) as the solvent led to only slightly lower ee but a lower yield due to an elevated level of the $\beta$-hydroxyl amide (entry 5).

We also examined the use of Rh(I)-*t*-Bu-Josiphos, and contrary to the anticipation that the reductive amination would suffer from competitive hydrogenation of **1**,[3c] we observed excellent chemoselectivity to the $\beta$-amino amide with an ee as high as that observed for hydrogenation of preformed **3** (entry 6).[4] In this case, however, ammonium acetate was a better N source than ammonium salicylate, as the latter led to lower chemoselectivity due to the competitive keto hydrogenation (entry 6 vs 7).

A study of the effect of excess ammonium salicylate showed that the ammonium salicylate plays a dual role. In addition to its role in shifting the equilibrium toward **3** (Scheme 2), it also suppresses dimer formation and/or breaks up the dimer, releasing the product **2** along with **3** for hydrogenation. This becomes evident from the concentration profiles for hydrogenation of **3**. As shown in Figure 1, in the presence of salicylic acid only, the dimer builds up to significant levels and slowly hydrogenates to form **2** (Figure 1a). The additional 3 equiv of ammonium salicylate reduces the dimer concentration by a factor of 3 at its peak value and to zero at the end of the reaction (Figure 1b). The extra 3 equiv of ammonium salicylate lowers neither the rate nor the ee of the hydrogenation, demonstrating a remarkable tolerance of the Ru catalytic system toward high concentrations of ammonium ion.

The beneficial effect of the ammonium salicylate in breaking up the dimer was also observed for the asymmetric reductive amination

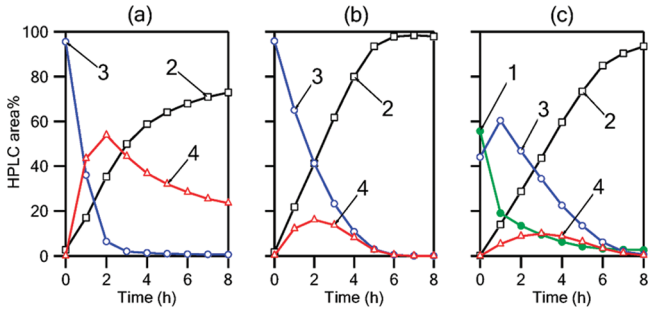
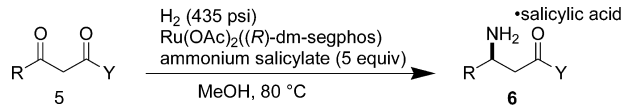



***Figure 1.*** Concentration profiles for (a, b) asymmetric hydrogenation of $\beta$-enamine amide **3** and (c) reductive amination of $\beta$-keto amide **1**. Additives: (a) salicylic acid (1 equiv); (b) salicylic acid (1 equiv) + $NH_4SA$ (3 equiv); (c) $NH_4SA$ (5 equiv). Conditions: 0.25 M substrate in MeOH; $Ru(OAc)_2$((*R*)-dm-segphos) (S/C = 100); (a, b) $H_2$ (290 psi), 75 °C; (c) $H_2$ (435 psi), 70 °C, set $t = 0$ when temperature reached 75 °C (a, b) or 70 °C (c).

***Table 3.*** Asymmetric Reductive Amination of $\beta$-Keto Amides[a]




**a**: R = Me; Y = NHPh
**b**: R = Et; Y = NHPh
**c**: R = *i*-Pr; Y = NHPh
**d**: R = Ph; Y = NHPh
**e**: R = 4-MeO-Ph; Y = NHPh
**f**: R = 4-F-Ph; Y = NHPh
**g**: R = Ph; Y = *N*-piperidyl
**h**: R = 2-thienyl; Y = NHPh

| entry | substrate | time (h) | % yield[b] | % ee[c] | configuration |
|---|---|---|---|---|---|
| 1 | **5a** | 15 | 91 | 94.7 | (−) |
| 2 | **5b** | 15 | 92 | 98.1 | (−) |
| 3 | **5c** | 15 | 89 | 98.9 | (−) |
| 4 | **5d** | 15 | 96 (91[d]) | 99.2 | (*S*) |
| 5 | **5e** | 15 | 95 | 99.6 | (+) |
| 6 | **5f** | 15 | 96 | 99.4 | (+) |
| 7 | **5g** | 15 | 81 | 97.9 | (−) |
| 8 | **5h** | 24 | 82 | 99.6 | (+) |

[a] Conditions: 0.25−0.5 M substrate in MeOH, S/C = 100, $H_2$ (435 psi), $NH_4SA$ (5 equiv with respect to **5**), 80 °C. [b] Assay yield of **6** by HPLC. [c] Assayed by chiral HPLC. [d] Isolated yield of the free $\beta$-amino amide.

of **1** to **2** (Figure 1c), leading to the formation of **2** with high yield and high ee (Table 2, entry 1). No dimer was observed at the end of the reaction (Figure 1c). Figure 1c also shows that the $\beta$-keto amide **1** coexists with the enamine **3** during the hydrogenation (e.g., $t = 1-5$ h) in a ratio of ~1:3.4. Nevertheless, the keto hydrogenation of **1** does not proceed to an appreciable degree (<3%). The remarkable tolerance to the high concentrations of ammonium ion, the high chemoselectivity (enamine vs keto hydrogenation), and the high enantioselectivity (99.5% ee) of the Ru catalyst system underlie the highly efficient asymmetric reductive amination of **1** to **2**. The quasi equilibrium between **1** and **3** during the hydrogenation suggests that the formation of **3** is not the rate-limiting step. The rate constant for direct reductive amination estimated from Figure 1c is ~50% that of the hydrogenation of preformed **3** estimated from Figure 1b (assuming a first-order rate dependence on the pressure), presumably because of the presence of the greater excess of ammonium ion in the case of direct reductive amination.

The scope of the Ru-catalyzed reductive amination was also explored. As shown in Table 3, a variety of alkyl- and aryl-substituted $\beta$-keto amides **5** were converted to the $\beta$-amino amides **6** in high yields and >94% ee's.

In summary, we have developed a new, high-yield, highly enantioselective reductive amination of $\beta$-keto amides to $\beta$-amino amides. The atom- and step economical methodology has a broad substrate scope and has been used to produce sitagliptin in 91% yield with unprecedented levels of asymmetric induction. The excellent performance of the methodology is attributable to the properties of the Ru catalyst (high chemoselectivity and nearly perfect enantioselectivity) and its remarkable tolerance to high concentrations of ammonium ion. We anticipate that direct reductive amination with simple ammonium salts will continue to be widely exploited in the synthesis of free amine derivatives.

**Acknowledgment.** We thank Dr. Yi Hsiao for screening with the Rh(I)-*t*-Bu-Josiphos system at an early stage of this study.

**Supporting Information Available:** Complete refs 4d and 5, experimental procedures, and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The use of ammonium benzoate and formate gave lower yields (19 and 42%, respectively).

(8) High yields and ee's were also observed using several other bisphosphine chiral ligands, such as BINAP (85% yield, 99.1% ee), xyl-binap (90% yield, 98.0% ee), and SEGPHOS (80% yield, 99.8% ee).

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