Synthetic Methods

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# Highly Regio- and Enantioselective Synthesis of γ,δ-Unsaturated Amido Esters by Catalytic Hydrogenation of Conjugated Enamides**

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***Abstract:*** *An efficient and highly regio- and enantioselective catalytic asymmetric hydrogenation of α,γ-dienamido esters to γ,δ-unsaturated amido esters has been achieved using Rh/TangPhos as the catalyst. A series of γ,δ-unsaturated amido acids were furnished in excellent yields with up to 99 % ee. This effective methodology was applied in the asymmetric synthesis of key intermediate of Ramipril, an ACE inhibitor.*

Enantiomerically pure γ,δ-unsaturated amido acids and their derivatives are versatile intermediates in organic synthesis. They can be readily converted into a variety of useful building blocks in nonproteinogenic amino acids, antibiotics, and other biologically active molecules, such as trapoxin A,[1] Ramipril,[2] isostatine,[3] 7-epicylindrospermopsin,[4] pin1 inhibitors,[5] barmumycin,[6] etc. (Figure 1). In addition to their catalytic application,[7] transformation of the enantiomerically pure γ,δ-unsaturated amido esters derivatives led to diversity in combinatorial chemistry.[8] However, the cost of enantiomerically pure γ,δ-unsaturated amino acids is too high (such as allylglycine, 1500 $ g$^{-1}$, Sigma–Aldrich) and greatly limited their applications. Therefore, to develop an efficient method to synthesis of γ,δ-unsaturated amino acids is highly desired.

In the past decades, asymmetric hydrogenation of enamides using chiral ligands (Figure 2) on either rhodium or iridium has proven to be a robust and readily accessible route for synthesis of chiral amines.[9,10] However, in the case of asymmetric synthesis of γ,δ-unsaturated amino acid derivatives,[3,11] little progress has been made. In 1998, Burk and coworkers reported their pioneering work on Rh/DuPhos-catalyzed asymmetric hydrogenation of α,γ-dienamido esters,[12] thus affording γ,δ-unsaturated amido esters in good yields and excellent enantioselectivities. However, over-reduction products were unavoidable in their catalytic system even with reduction of the catalyst loading and shortening of the reaction time. Later, Jiang and co-workers[13] tried to improve the results through Rh$^{I}$/(*R*)-H$_8$-Mono-Phos-catalyzed asymmetric hydrogenation, but failed to achieve the goal. Recently, some advances in the synthesis

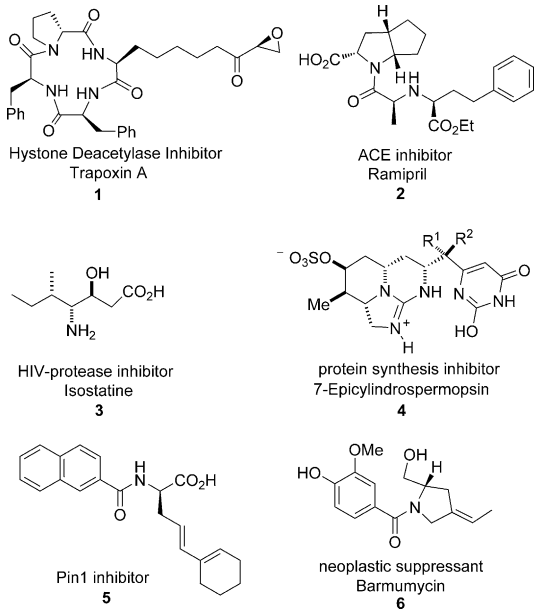


***Figure 1.*** Selected examples of biologically active products derived from amido acid moiety.

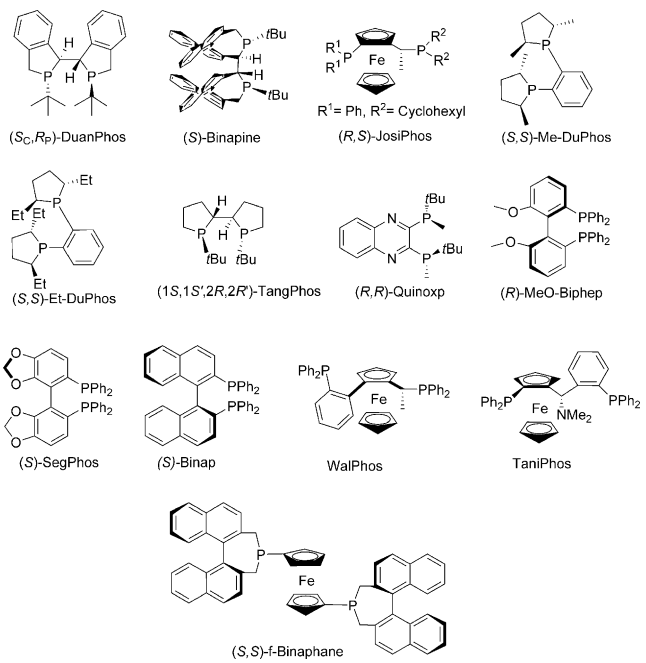


***Figure 2.*** Structures of the phosphine ligands for hydrogenation of α,γ-dienamide esters.

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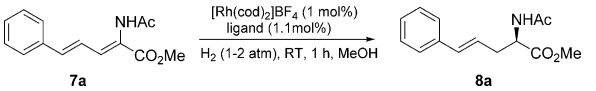
of γ, δ-unsaturated amido esters have been achieved and the synthesis of vinylglycine analogues with high diastereoselectivities and high yields has been reported. Unfortunately, the reaction turnover number (TON) is very low, and greatly hinders their use in practical applications.[14] Herein we report an efficient approach to the synthesis of γ,δ-unsaturated amido acid derivatives with high yields and excellent enantioselectivities as well as high TONs.

Initially, the conjugated enamide (*Z*)-**7a** was chosen as a model substrate for optimization of the reaction conditions for the hydrogenation. When $[Rh(cod)_2]BF_4$/(*R*,*S*)-DuanPhos was employed as the catalyst, we were delighted to find that the reaction was complete in 1 hour under 1–2 atm $H_2$ pressure at room temperature and gave the product **8a** with full conversion and 99% *ee* (Table 1, entry 1). Further screening of ligands indicated that highly electron-donating bisphosphine ligands, such as (*S*)-Binapine, (*R*,*S*)-JosiPhos, (*S*,*S*)-Me-DuPhos, (*S*,*S*)-Et-DuPhos, and (*S*,*S*,*R*,*R*)-TangPhos led to quantitative conversion and good *ee* values (86–99.3%; entries 2–6). When Rh/TangPhos was employed, the reaction provided the target product in 99.3% *ee*, which is slightly better than that of the Rh/DuPhos catalytic system reported by Burk and co-workers.[13] When (*R*,*R*)-Quinoxp was used, it was found that an over-reduction process occurred even under low $H_2$ pressure over a shorter reaction time (entry 7). Meanwhile, chiral biaryl bisphosphorus ligands such as (*R*)-MeO-Biphep, (*S*)-SegPhos, and (*S*)-Binap were also employed and gave high conversions but poor *ee* values (20–52%; entries 8–10). In addition, the complexes with chiral ferrocene ligands, such as Rh/WalPos, Rh/TaniPhos, and Rh/f-Binaphane, were also evaluated and afforded the γ,δ-unsaturated amido ester with good conversions and low enantioselectivities (entries 11–13).

Subsequently, we evaluated the solvent effect on the transformation and the results are summarized in Table 2. It

***Table 1:*** Ligand screening for rhodium-catalyzed asymmetric hydrogenation of conjugated enamides.[a]

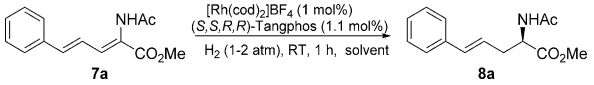



**7a** **8a**

| Entry | Ligand | Conversion [%][b] | *ee* [%][c] |
|---|---|---|---|
| 1 | (*R*,*S*)-DuanPhos | >99 (99) | 99 |
| 2 | (*S*)-Binapine | >99 (99) | 86 |
| 3 | (*R*,*S*)-JosiPhos | >99 (98) | 93.5 |
| 4 | (*S*,*S*)-Me-DuPhos | >99 (99) | 97.5 |
| 5 | (*S*,*S*)-Et-DuPhos | >99 (99) | 96.2 |
| 6 | (*S*,*S*,*R*,*R*)-TangPhos | >99 (99) | 99.3 |
| 7 | (*R*,*R*)-Quinoxp | >99 (23) | 13 |
| 8 | (*R*)-MeO-Biphep | >99 (99) | 51 |
| 9 | (*S*)-SegPhos | 94 (94) | 71 |
| 10 | (*S*)-Binap | >99 (99) | 20 |
| 11 | (*S*)-WalPhos | >99 (99) | 9 |
| 12 | TaniPhos | >99 (99) | 78 |
| 13 | (*S*,*S*)-f-Binaphane | 93 (93) | 41 |

[a] Unless otherwise mentioned, all reactions were carried out with a $[Rh(cod)_2]BF_4$/ligand/substrate ratio of 1:1.1:100, in methanol at room temperature under hydrogen (1–2 atm) for 1 h. [b] Determined by $^1H$ NMR spectroscopy. Data within parentheses are the yields of the isolated product based on starting material. [c] Determined by HPLC analysis using a chiral stationary phase. cod = 1,5-cyclooctadiene.

***Table 2:*** Solvent screening for rhodium-catalyzed asymmetric hydrogenation of conjugated enamides.[a]




**7a** **8a**

| Entry | Solvent | Conversion [%][b] | *ee* [%][c] |
|---|---|---|---|
| 1 | 1,4-dioxane | >99 (99) | 99.2 |
| 2 | ethyl acetate | >99 (99) | 99.5 |
| 3 | oxolane | >99 (99) | 99 |
| 4 | propan-2-ol | >99 (98) | 99 |
| 5 | ethanol | >99 (23) | 99.4 |
| 6 | toluene | >99 (99) | 99 |
| 7 | 1,2-dichloroethane | 92.8 (91) | 92 |
| 8 | trifluoroethanol | 95.2 (93) | 95 |
| 9 | dichloromethane | >99 (99) | 99.9 |
| 10[d] | dichloromethane | >99 (99) | 99.9 |

[a] Unless otherwise mentioned, all reactions were carried out with a $[Rh(cod)_2]BF_4$/(*S*,*S*,*R*,*R*)-TangPhos/substrate ratio of 1:1.1:100, at room temperature under hydrogen (1–2 atm) for 1 h. [b] Determined by $^1H$ NMR spectroscopy. Data in parentheses are the yields of the isolated products based on starting material. [c] Determined by HPLC analysis using a chiral stationary phase. [d] S/C = 3000, 1 h.

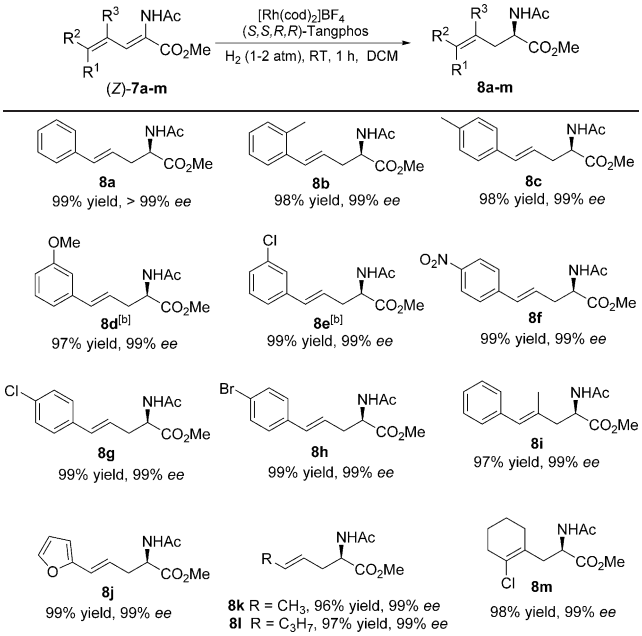
appears that the conversion is not sensitive to the solvent when the Rh/TangPhos complex is employed as catalyst, but a very low yield of the isolated product was obtained with ethanol because of the over-reduction of **7a**. (entry 5). When dichloromethane was used as the solvent, the reaction proceeded smoothly and an excellent results were achieved in terms of both yield and enantioselectivity under mild reaction conditions (99% yield and 99.9% *ee*; entry 9). Increasing the ratio of substrate to catalyst (S/C = 3000) had no effect on the reaction and afforded **8a** with the same conversion and *ee* value (entry 10).

Under the optimized reaction conditions, the scope of γ,δ-unsaturated enamides was examined (Table 3). It was found that a broad range of conjugated enamides could be hydrogenated smoothly. More importantly, the position and electronic properties of the substituents on the phenyl rings had no effect on the reaction and gave products in high yields with excellent regio- and enantioselectivities in all the cases(**8b**–**h**). The γ-substituted dienamide was also a good substrate for this reaction (**8i**). Replacement of the aryl groups with a heteroaryl group also worked very well (**8j**). Notably, δ-alkyl-substituted dienamides could also readily participate in this reaction and all the examined δ-alkyl-dienamides gave the desired products (**8k**–**m**) in high yields and excellent enantioselectivities (99% *ee*).

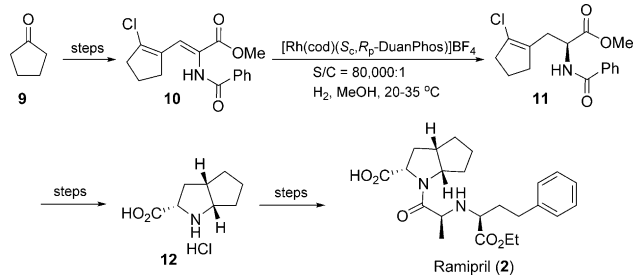
To demonstrate the practical utility of the current methodology, we cooperated with Chiral Quest Inc. to achieved the highly enatioselective synthesis of the key intermediate **11** [precursor to Ramipril (**2**)] by employing asymmetric hydrogenation of **10** on a ton scale with up to 80000 for a TON (Scheme 1). The process was patented by Chiral Quest Inc.[2] To the best of our knowledge, this process represents one of the most concise and economical routes for synthesis of Ramipril, and the turnover number is also the best one for hydrogenation of conjugated enamides for synthesis of chiral γ,δ-unsaturated amino acid derivatives.

***Table 3:*** Rhodium-catalyzed enantioselective hydrogenation of α,γ-dienamido esters.[a]




[a] Unless otherwise mentioned, all reactions were carried out with a $[Rh(cod)_2]BF_4$/(*S*,*S*,*R*,*R*)-TangPhos/substrate ratio of 1:1.1:3000, at room temperature under hydrogen (1–2 atm) for 1 h. Yields of isolated products are given. The enantioselectivities were determined by HPLC using a chiral stationary phase. Chiral assignment was determined by comparison of sign of optical rotation and order of elution, from an HPLC using a chiral stationary phase, with configurationally defined sample. [b] 1 atm.




***Scheme 1.*** An environmentally friendly route to a Ramipril intermediate by an asymmetric hydrogenation protocol.

In summary, we developed a Rh/TangPhos-catalyzed asymmetric hydrogenation of α,γ-dienamido esters to afford γ,δ-unsaturated amido esters in high yield with good regioselectivities and excellent enantioselectivities. More importantly, the methodology exhibits excellent TONs, which made it successful for making a key intermediate in Ramipril synthesis. Further investigation into catalytic asymmetric hydrogenation for synthesis of high bioactivity and value-added compounds are in progress.

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