

A Convenient Synthesis and the Asymmetric Hydrogenation of *N*-Phthaloyl Dehydroamino Acid Esters

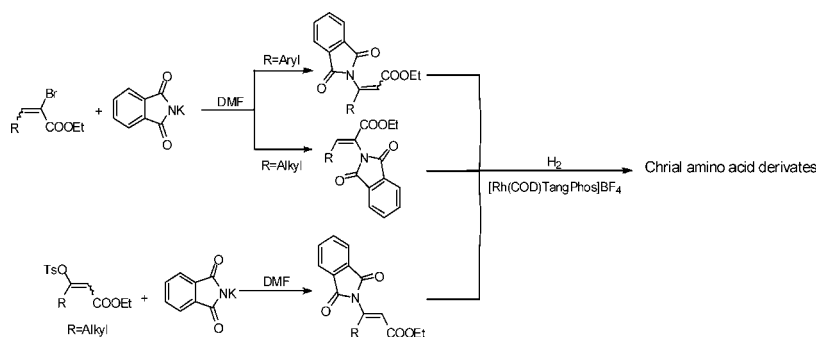
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ABSTRACT



A convenient synthetic method was reported for the preparation of *N*-phthaloyl dehydroamino acid esters from easily accessible vinyl bromides (or vinyl tosylate) and potassium phthalimide. Rh-catalyzed asymmetric hydrogenation of these substrates with TangPhos gave the products with good to excellent enantioselectivities (up to 99% ee).

In transition metal mediated asymmetric hydrogenation¹ of functionalized substrates, a secondary chelating group near the unsaturated double bond is important to achieve high reactivity as well as excellent enantioselectivity. For example, both dehydroamino acids and enamides possess an amide moiety, which not only masks the amine but also participates in chelation with metal during hydrogenation reactions. So far the most applied *N*-protecting groups are acyl groups, such as acetyl and benzoyl. After hydrogenation, these groups can be removed under carefully controlled condition to afford

the free amino group for further transformations. In contrast, other potentially useful protecting groups have received little attention. A recent work by Feringa and co-workers demonstrated the formyl group as an effective *N*-protecting group for α -dehydroamino acids, and excellent ee's were obtained in the hydrogenation of these new substrates.² Moreover, the formyl group can be removed under milder conditions than acetyl group. In our studies on new substrates for asymmetric hydrogenation,³ we conceived phthalimide as a valuable protecting group for primary amines, which can be cleaved under mild conditions without racemization. A number of interesting substrates containing such functionality have been developed and subjected to hydrogenation with

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(1) (a) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis I–III*; Springer: Berlin, New York, 1999. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (c) Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley-VCH: New York, 2000. (d) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.

(2) Panella, L.; Aleixandre, A. M.; Kruidhof, G. J.; Robertus, J.; Feringa, B. L.; de Vries, J. G.; Minnaard, A. J. *J. Org. Chem.* **2006**, *71*, 2026.

(3) Zhang, W.; Chi, Y.; Zhang, X. *Acc. Chem. Res.* **2007**, *40*, 1278.

excellent enantioselectivities, including amino ketone **1** and enamides **2** and **3** (Figure 1).⁴ Recently, others have also

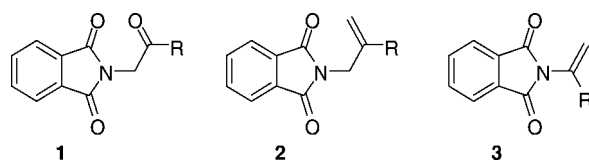


Figure 1. Functional groups of phthalimido.

succeeded in asymmetric hydrogenation of phthalimide-bearing olefins.⁵ To further expand this usage, we herein report a novel synthesis of *N*-phthaloyl dehydroamino acid esters **6** and **7** via the reaction of vinyl bromide **4** or vinyl tosylates **9** with potassium phthalimide **5**. To our knowledge, so far there is only one report concerning the synthesis of such phthalimide-bearing substrates.⁶ As a complementary approach, our present method enables convenient preparation of new *N*-phthaloyl substrates in good to excellent yields. Asymmetric hydrogenation with a Rh-TangPhos system afforded the products with excellent ee's (up to 99% ee).

Although intensive efforts have been made for the synthetic route to *N*-acyl enamides,⁷ fewer studies have focused on the *N*-phthaloyl counterpart. This is not surprising in view of its less basic nitrogen atom stabilized by the neighboring two carbonyl groups. In a pioneering study, Trost reported the use of catalytic PPh₃ to activate the alkynoate regioselectively at the α -position prior to nucleophilic addition of phthalimide, leading to **7** (R = aryl or H) in excellent yields.⁶ However, asymmetric hydrogenation of this type of substrates was not pursued. Furthermore, aliphatic analogues cannot be prepared via this route because of competitive side reactions.

To gain full access to these structurally interesting compounds, it is necessary to explore alternative methods. We chose vinyl bromide as starting material, which can be easily prepared in a few steps via Wittig reaction.⁸ The coupling of sp²-bromide with amide has been extensively studied, usually involving transition metal catalyst.⁹ Instead of resorting to those metal catalysts, we looked for a simple conversion to the desired product. To our delight, it was found through various tests that simply heating the solution of **4a** and **5** in DMF gave the product **6a** (Table 1, entry 1). Its configuration was determined as *Z* via X-ray diffraction experiment (Figure 2).

(4) (a) Lei, A.; Wu, S.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2004**, *126*, 1626. (b) Wang, C.-J.; Sun, X.; Zhang, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 4933. (c) Yang, Q.; Gao, W.; Deng, J.; Zhang, X. *Tetrahedron Lett.* **2006**, *47*, 821.

(5) (a) Huang, H.; Liu, X.; Deng, J.; Qiu, M.; Zheng, Z. *Org. Lett.* **2006**, *8*, 3359. (b) Deng, J.; Duan, Z.-C.; Huang, J.-D.; Hu, X.-P.; Wang, D.-Y.; Yu, S.-B.; Xu, X.-F.; Zheng, Z. *Org. Lett.* **2007**, *9*, 4825.

(6) Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7595.

(7) Zhao, H.; Vandenbossche, C. P.; Koenig, S. G.; Singh, S. P.; Bakale, R. P. *Org. Lett.* **2008**, *10*, 505, and references therein.

(8) See Supporting Information for details.

(9) (a) Coleman, R. S.; Liu, P.-H. *Org. Lett.* **2004**, *6*, 577. (b) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667. (c) Shen, R.; Porco, J.A., Jr. *Org. Lett.* **2000**, *2*, 1333. (d) Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* **1991**, 1443.

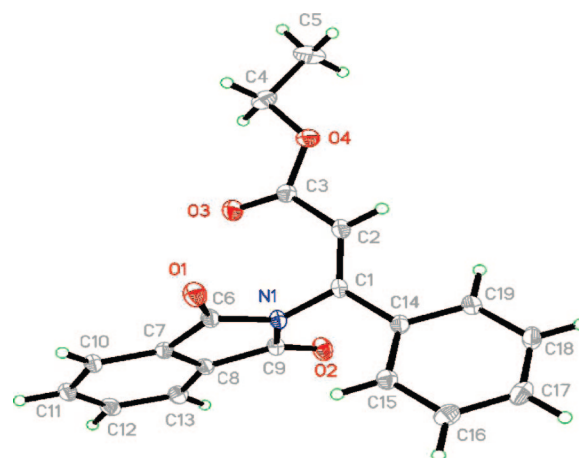
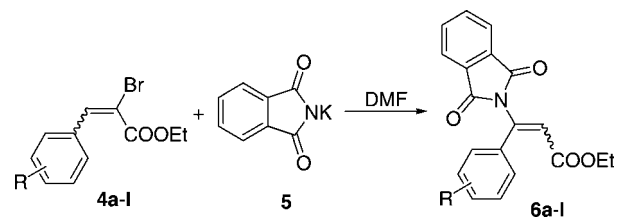


Figure 2. ORTEP representation of **6a** (50% probability for the drawing of thermal ellipsoids).

Despite the moderate yield (43%), this transformation is unique in that, unlike a typical metal-catalyzed coupling reaction, the phthalimide unit is assembled at the β -position with concomitant elimination of an α -bromo group, presumably through a tandem Michael addition–elimination reaction sequence.¹⁰ To study its scope, a variety of β -aryl β -dehydroamino acid esters **4a–l** were prepared under similar conditions. As shown in Table 1, substitution on the phenyl ring has a remarkable effect on the separation yield of **6**. While electron-withdrawing NO₂ enhances the reaction (entries 2 and 3), those bearing an electron-donating sub-

Table 1. Preparation of β -Aryl β -*N*-Phthaloyl **6a–l**^a



entry	R	T (°C)/time (h)	6	yield ^b (%)	<i>Z:E</i> ^c
1	H	150/12	6a	43	>50:1 ^d
2	4-NO ₂	90/1	6b	92	>50:1 ^d
3	3-NO ₂	60/1	6c	95	>50:1 ^d
4	4-Cl	120/4	6d	87	>50:1 ^d
5	2-Cl	150/6	6e	58	1.1:1
6	2-Br	120/12	6f	40	1.2:1
7	3-Br	120/12	6g	45	>50:1 ^d
8	2,4-di-Cl	120/12	6h	67	1.5:1
9	4-NMe ₂	120/12	6i	62	>50:1 ^d
10	4- <i>t</i> -Bu	130/12	6j	80	>50:1 ^d
11	4-Et	130/12	6k	76	3.7:1
12	4-Me-O	130/12	6l	67	>50:1 ^d

^a All reactions were carried out with 10 mmol of **4** and 15 mmol of **5** in 30 mL of DMF. ^b Isolated yield. ^c Determined by ¹H NMR. ^d Estimated on the basis of the detection limit of proton NMR.

stituent gave lower yield (entries 9–12). Sterically, an *ortho*-substituent (entries 5, 6, and 8) usually resulted in relatively low yield compared with *para*-substituted substrates (entries 4, 9–12). The existence of a *meta*-bromo group also lowered the yield considerably. With the help of ¹H NMR analysis, the configuration of **6** can be assigned unambiguously. It was found that most of the product **6** exist predominantly as the (*Z*)-isomer except for **6e**, **6f**, **6h**, and **6k**.

Intrigued by this highly efficient reaction, we wondered whether it could be applied to aliphatic vinyl bromides. Thus **4m–4o** were prepared from the corresponding aldehydes and subjected to the same reaction condition in the presence of **5**. To our surprise, this time α -*N*-phthaloyl products **7a–7c** were obtained as the only major product (Table 2). When

Table 2. Preparation of β -Alkyl α -*N*-Phthaloyl **7a–c**^a



entry	R	7	yield ^b (%)	<i>Z</i> : <i>E</i> ^c
1	<i>n</i> -C ₃ H ₇ -	7a	82	>50:1 ^d
2	<i>n</i> -C ₅ H ₁₁ -	7b	63	>50:1 ^d
3	<i>n</i> -C ₉ H ₁₉ -	7c	62	>50:1 ^d

^a All reactions were carried out with 10 mmol of **4** and 15 mmol of **5** in 30 mL of DMF at 90°C for an hour. ^b Isolated yield. ^c Determined by ¹H NMR. ^d Estimated on the basis of the detection limit of proton NMR.

the alkyl chain becomes longer, the yield drops considerably. Their major (*Z*)-configuration was assigned by ¹H NMR analysis and X-ray diffraction experiments (Figure 3).

Since our initial attempt to prepare the aliphatic analogues of **6** failed, we switched to β -tosylates **9** as starting materials,

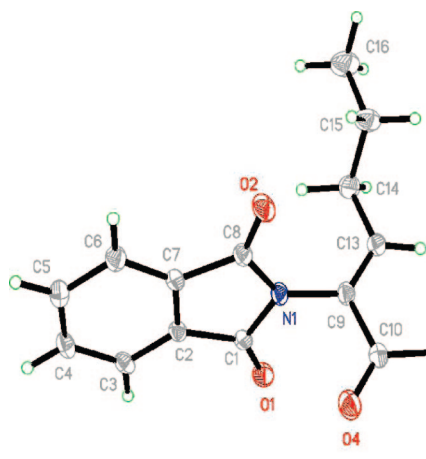
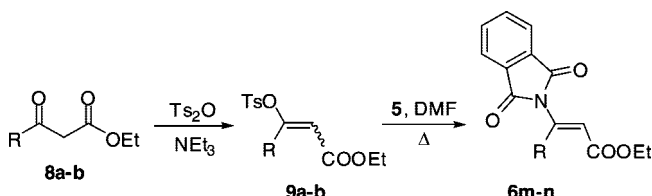


Figure 3. ORTEP representation of **7a** (50% probability for the drawing of thermal ellipsoids).

in the hope that a similar tandem Michael addition–elimination strategy could be implemented. Compared with vinyl bromide **4**, **9** is readily available from β -keto esters **8**. To our delight, the desired products **6m,n** were obtained in moderate yield after column chromatography (Table 3). From X-ray

Table 3. Preparation of β -Alkyl β -*N*-Phthaloyl **6m,n**^a



entry	R	6	yield ^b (%)	<i>E</i> : <i>Z</i> ^c
1	Me	6m	23	>50:1 ^d
2	<i>n</i> -propyl	6n	25	>50:1 ^d

^a All reactions were carried out with 1.4 mmol of **9** and 2.0 mmol of **5** in 5 mL of DMF at 90°C for 12 h. ^b Isolated yield. ^c Determined by ¹H NMR. ^d Estimated on the basis of the detection limit of proton NMR.

diffraction experiment, their predominant configuration was determined as *E* (Figure 4).

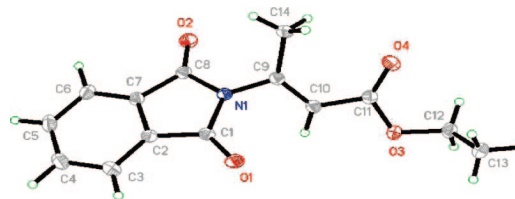
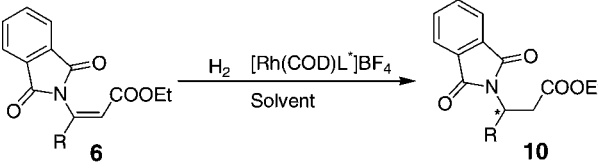


Figure 4. ORTEP representation of **6m** (50% probability for the drawing of thermal ellipsoids).

With all of these interesting substrates **6** and **7** at hand, we performed brief asymmetric hydrogenation reactions. Initial screening of chiral ligands for the substrate **6l**, a typical (*Z*)- β -dehydroamino acid ester, revealed TangPhos^{11a} as the most selective among several well-established ligands, including DuanPhos^{11b} and DuPhos.^{11c} A number of common organic solvents were screened, which showed that EtOAc was the solvent of choice. As seen from the selected hydrogenation results (Table 4), all substrates have been hydrogenated with excellent enantioselectivities by the Rh/TangPhos system (up to 98% ee). In contrast, substrates **6e**, **6f**, **6h** bearing *ortho* chloro or bromo groups deactivate the catalyst, probably through phthalimide-assisted oxidative addition of Rh into the C–X bond.¹² Finally, this catalyst was applied in the hydrogenation of α -dehydroamino acid ester **7b** and **7c**, affording the product in 97% and >99% ee, respectively (Table 5).

In summary, a series of *N*-phthaloyl dehydroamino acid esters have been prepared via a novel reaction of vinyl

(10) See Supporting Information for discussion of the mechanism.

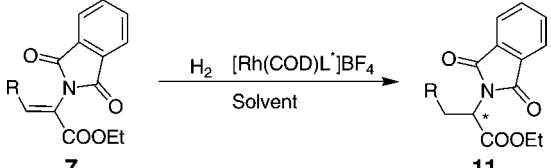
Table 4. Rh-Catalyzed Asymmetric Hydrogenation of **6** under Various Conditions


entry ^a	6	L*	solvent	10	conv (%) ^e	ee (%) ^{f,g} (config)
1	6l	L1 ^b	EtOAc	10b	100	88
2	6l	L2 ^c	EtOAc	10b	100	85
3	6l	L3	EtOAc	10b	100	97 (–)
4	6l	L3 ^d	CH ₂ Cl ₂	10b	100	96
5	6l	L3	acetone	10b	33	89
6	6l	L3	THF	10b	100	87
7	6l	L3	EtOH	10b	100	96
8	6l	L3	<i>i</i> -PrOH	10b	100	96
9	6l	L3	MeCN	10b	0	n.a.
10	6l	L3	toluene	10b	14	97
11	6a	L3	EtOAc	10a	100	95 (–)
12	6j	L3	EtOAc	10c	100	94 (–)
13	6k	L3	EtOAc	10d	100	92 (–)
14	6m	L3	EtOAc	10e	100	98 (+)

^a All reactions were carried out with 0.1 mmol of substrate at room temperature under a H₂ pressure of 30 bar in 3 mL of solvent for 20 h with a substrate/[Rh(COD)L*]BF₄ ratio of 1/0.01. ^b L1 = Et-DuPhos. ^c L2 = (S_cR_p)-DuanPhos. ^d L3 = (S,S,R,R)-TangPhos. ^e Conversion was determined by ¹H NMR. ^f The ee values were determined by HPLC on a chiral column (see Supporting Information for details). ^g Absolute configuration not determined.

bromide or vinyl tosylate with potassium bromide. Depending on the nature of the substituent (aryl or alkyl) on **7**, the phthalimide moiety can be selectively attached to either the α- or β-position, thereby providing an efficient synthesis of

(11) (a) Tang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 1612. (b) Liu, D.; Zhang, X. *Eur. J. Org. Chem.* **2005**, 646. (c) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363.

Table 5. Rh-Catalyzed Asymmetric Hydrogenation of **7** under Various Conditions


entry ^a	7	L*	solvent	11	conv (%) ^e	ee (%) ^{f,g} (config)
1	7b	L3 ^b	EtOAc	11a	100	97 (+)
2	7c	L3	EtOAc	11b	100	>99 (+)

^a All reactions were carried out with 0.1 mmol of substrate at room temperature under a H₂ pressure of 30 bar in 3 mL of the EtOAc for 20 h with a substrate/[Rh(COD)L*]BF₄ ratio of 1/0.01. ^b L3 = (S,S,R,R)-TangPhos. ^e Conversion was determined by ¹H NMR. ^f The ee values were determined by HPLC on a chiral column (see Supporting Information for details). ^g Absolute configuration not determined.

these structurally interesting compounds. Asymmetric hydrogenation with a Rh/TangPhos system gave excellent results.

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Supporting Information Available: Synthesis of substrates, hydrogenation, spectroscopic data, and experimental details, including a file in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>. OL800996J

(12) No reduction by Rh/TangPhos was observed even at 60 °C under 120 bar hydrogen pressure.