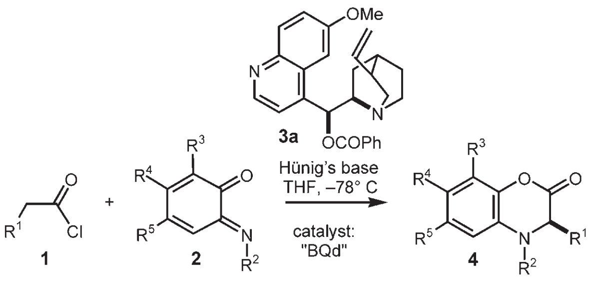
Amino Acids

DOI: 10.1002/ange.200602801

Catalytic, Asymmetric Synthesis of 1,4-Benzoxazinones: A Remarkably Enantioselective Route to α-Amino Acid Derivatives from *o*-Benzoquinone Imides**

*Jamison Wolfer, Tefsit Bekele, Ciby J. Abraham, Cajetan Dogo-Isonagie, and Thomas Lectka**

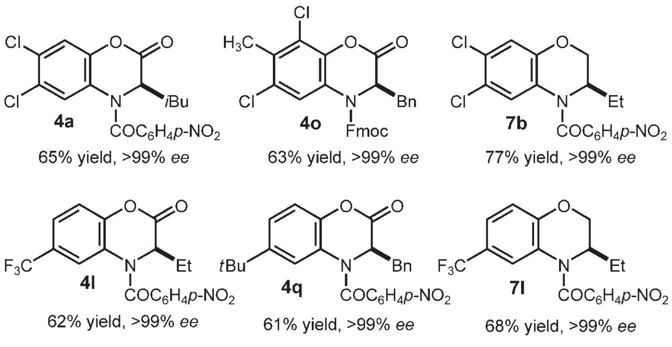
Molecules that serve as versatile branch points for the synthesis of pharmaceutically or biologically active products, besides being of interest in their own right, are especially valuable targets for asymmetric catalysis. The 1,4-benzoxazinone[1] and 1,4-benzoxazine[2] systems are intriguing because they are present in clinically significant pharmaceuticals and other biologically active molecules. On the basis of previous success in the preparation of α-oxygenated carboxylic acid derivatives from benzodioxinones,[3] we speculated that chiral 1,4-benzoxazinone intermediates could also serve as flexible precursors for the efficient synthesis of highly enantiomerically enriched α-amino acids and related derivatives.[4] Herein, we present the first catalytic, asymmetric synthesis of 1,4-benzoxazinones that relies on the highly enantioselective [4+2] cycloaddition of *o*-benzoquinone imides with chiral ketene enolates (derived from acid chlorides and cinchona alkaloid[5] catalysts; Scheme 1). These cycloadducts can be functionalized in situ to provide 1,4-benzoxazines and α-amino acid derivatives in good-to-excellent yields and with virtual enantiopurity, only rivaled by that of enzymatic amino acid synthesis. As a testament to the flexibility of this methodology, a variety of substituents and *N*-acyl groups can be incorporated into the products.



Scheme 1. Synthesis of 1,4-benzoxazinones.

We also highlight the synthesis of several biologically significant α-amino acid derivatives (e.g., α-fluoro,[6] β,γ-alkynyl,[7] and β,γ-alkenyl species) whose optically pure synthesis has not been solved by asymmetric catalysis and that are very difficult to prepare by using other methods.[8] For example, α-fluoro α-amino acid derivatives are of great value in the preparation of peptidomimetics and transition-state analogues of peptide-containing therapeutic agents.[9] Similarly, β,γ-alkynyl and β,γ-alkenyl α-amino acid derivatives display analogous activity, postulated to be caused by conformational constraint.[7]

We have had an interest in the catalytic, enantioselective reactions of α-imino esters, chemistry which provides a variety of useful products (β-lactams and α- or β-amino acids) with high enantioselectivity upon alkylation at the carbon atom.[10] Although we noted that *o*-benzoquinone imides share structural similarity to α-imino esters, they prefer to alkylate at the nitrogen atom instead, thus providing products in which the aromaticity is restored.[11] An approach employing chiral ketene enolates provides three points of modification: the quinone core, the N substituent, and the acid chloride. We noted that electron-withdrawing *N*-acyl groups should increase the reactivity of the quinone unit towards cycloaddition, besides serving as protecting groups that can subsequently be removed. Initially, we examined several N-acylated quinone imides[12] and chose experimental conditions that worked well for the asymmetric cycloaddition of ketene enolates and *o*-quinones.[3] We found that by employing 4-methylvaleryl chloride **1a** ($R^1 = i$Bu), imide **2a** ($R^2 = p$-NO_2PhCO, $R^3 = H$, $R^4 = R^5 = Cl$), 10 mol% benzoylquinidine (**3a**; BQd), and Hünig's base in THF at −78 °C, we formed cycloadduct **4a** in 65% yield with over 99% *ee* (Scheme 2).[13] Several other 1,4-benzoxazinones were synthesized from different quinone imides and acid chlorides to provide products in good yield with uniformly excellent enantiomeric excess.[14] One reaction of special interest would be the conversion of chiral 1,4-benzoxazinones into 1,4-benzoxazines, skeleta that are present in biologically relevant molecules, such as levofloxacin.[15] For example, benzoxazinone **4l** reacts smoothly with $BH_3{\cdot}SMe_2$[16] to provide the corresponding benzoxazine **7l** in 68% yield and with full preservation of the enantiomeric excess.



Scheme 2. Chiral 1,4-benzoxazinone and 1,4-benzoxazine products. Fmoc = 9-fluorenylmethoxycarbonyl, Bn = benzyl.

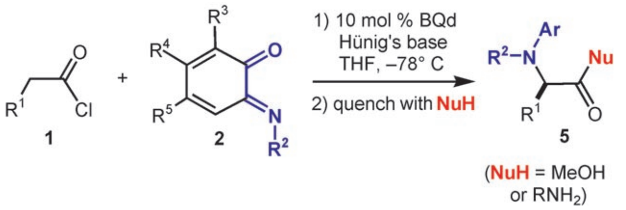
---

[*] J. Wolfer, T. Bekele, C. J. Abraham, C. Dogo-Isonagie, Prof. T. Lectka
Department of Chemistry
Johns Hopkins University
3400 North Charles Street, Baltimore, MD 21218 (USA)
Fax: (+1) 410-516-7044
E-mail: lectka@jhu.edu

[**] T.L. thanks the NIH (GM064559); the Sloan, Guggenheim, and Dreyfus Foundations; and Merck & Co. for support.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

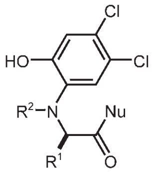
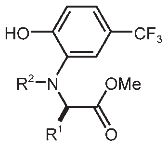
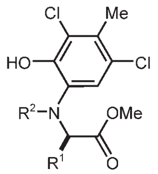
We discovered that cycloadduct **4a** undergoes rapid ring-opening methanolysis to afford ester **5a**, thus indicating that in situ transformation to α-amino acid derivatives by various nucleophiles would occur. Thus, we sought to convert the cycloadducts directly into the α-amino acids in one pot (Scheme 3).[17]



Scheme 3. One-pot amino acid synthesis.

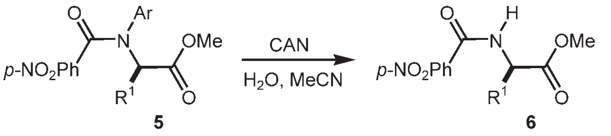
We chose *o*-benzoquinone imides derived from halogenated *o*-aminophenols as templates for α-amino acid synthesis for a variety of reasons—the starting materials are inexpensive and the electron-withdrawing groups in the 3- and 4-positions block undesired reactivity at the quinone ring and enhance the overall reactivity of the system.[18] Following the cycloaddition (ca. 5 h at −78 °C), MeOH was added to the reaction mixture, which was then warmed to room temperature to produce products **5** in high yield. Having chosen $R^2 = p\text{-}NO_2PhCO$ as the group that performed the best overall, we then screened a variety of R^1 substituents and cores, (Table 1, entries 1—13 and 16). In each case, the reaction occurred in good yield and with excellent enantiomeric excess.

Table 1: Synthesis of α-amino acid derivatives.

Entry	R²	R¹	Product[a]		*ee* [%]	Yield [%]
1[b]	*p*-NO₂PhCO	*i*Bu		**5a**	>99	73
2[b]	*p*-NO₂PhCO	Et		**5b**	>99	62
3[b]	*p*-NO₂PhCO	Me		**5c**	>99	69
4[b]	*p*-NO₂PhCO	Bn		**5d**	>99	63
5[b]	*p*-NO₂PhCO	Ph		**5e**	>99	66
6[b]	*p*-NO₂PhCO	PhOCH₂		**5f**	>99	72
7[b]	*p*-NO₂PhCO	CH₃CH₂C≡C		**5g**	>99	59
8[b]	*p*-NO₂PhCO	PhCH=CH		**5h**	>99	61
9[c]	*p*-NO₂PhCO	PhOCH₂		**5i**	>99	71
10[d]	*p*-NO₂PhCO	Et		**5j**	>99	90
11[b]	*p*-NO₂PhCO	Bn		**5k**	>99	83
12[b]	*p*-NO₂PhCO	Et		**5l**	>99	71
13[b]	*p*-NO₂PhCO	*i*Bu		**5m**	>99	73
14[e]	Fmoc	Et		**5n**	>99	59
15[e]	Fmoc	Bn		**5o**	>99	62
16[b]	*p*-NO₂PhCO	F		**5p**	>99	60

[a] Nu = OMe for all entries, except entry 9 ($Nu = NH_2$) and entry 10 (Nu = BnNH). [b] Reactions run with catalyst (10 mol %), Hünig's base (0.55 mmol), acid chloride (0.55 mmol), and quinone imide (0.55 mmol) at −78 °C followed by addition of MeOH and overnight stirring. Yield for cycloaddition and methanolysis. [c] Reaction quenched with NH_4OH to yield amide **5i**. [d] Reaction quenched with benzylamine in THF to yield **5j**. [e] Quinone imide formed in situ at −78 °C; yield for both steps.

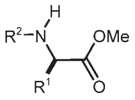
Most notably, we accomplished the synthesis of three biologically significant derivatives—β,γ-alkynyl acid **5g**, β,γ-alkenyl acid **5h**, and α-fluoro acid **5p** (Table 1, entries 7, 8, and 16, respectively)—all in good yield and with excellent enantiomeric excess. To our knowledge, α-fluoro α-amino acid derivatives have not heretofore been addressed by asymmetric catalysis.[6]



(1)

Finally, oxidation by using ceric ammonium nitrate (CAN)[19] removes the aryl group in good yield under mild conditions [Eq. (1)]; for example, see Table 2, entries 1 (conversion of **5o** into **6o**), 2 (**5k** into **6d**), 3 (**5d** into **6d**), 4 (**5e** into **6e**), 5 (**5f** into **6f**), and 6 (**5h** into **6h**).

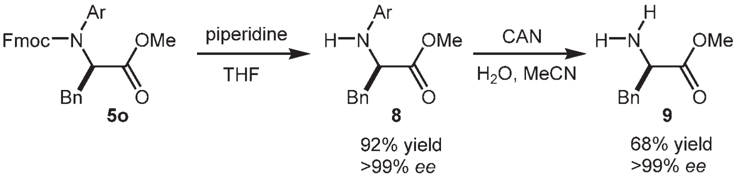
Table 2: Deprotection using CAN.

Entry	R²	R¹	Product		*ee* [%]	Yield[a] [%]
1	Fmoc	Bn		**6o**	>99	71
2	*p*-NO₂PhCO	Bn		**6d**	>99	71
3	*p*-NO₂PhCO	Bn		**6d**	>99	64
4	*p*-NO₂PhCO	Ph		**6e**	>99	58
5	*p*-NO₂PhCO	PhOCH₂		**6f**	>99	72
6	*p*-NO₂PhCO	PhCH=CH		**6h**	>99	74

[a] Reactions run with **5** (0.55 mmol) and CAN (1.65 mmol) in water/MeCN (1:3) at 0 °C. Yield after column chromatography.

We then screened other quinone imides in which the *N*-acyl group was varied (Table 1, entries 14 and 15). In particular, we were interested in highlighting a signature protecting group important in peptide synthesis, such as 9-fluorenylmethyl carbamate (Fmoc).[20] For example, when $R^1 = Bn$ and $R^2 = Fmoc$, the reaction occurs smoothly in THF at −78 ° C to form product **5o** in 62 % yield with greater than 99 % *ee*. The Fmoc group was then removed by piperidine to afford **8** in high yield (92 %) followed by deprotection with CAN to give **9** in good yield and without loss of optical activity (Scheme 4).[20]

In conclusion, we have illustrated the first highly enantioselective synthesis of 1,4-benzoxazinones and 1,4-benzoxazines. These products are readily con-



Scheme 4. Synthesis of N-deprotected α-amino esters.

verted into virtually optically pure α-amino acid esters. This study compares very favorably with other chiral α-amino acid syntheses because of the remarkably high enantioselectivities obtained and as it provides access important classes of chiral compounds that are otherwise difficult to synthesize.

Experimental Section

General procedure: A solution of the quinone imide (0.12 mmol) in THF (2 mL) was added to a reaction flask containing an acid chloride (0.12 mmol), Hünig's base (0.12 mmol), and BQd (**3a**; 0.012 mmol) at −78 °C. After stirring for 6 h, the reaction was concentrated in vacuo and the crude residue was purified by column chromatography. Additional procedures and characterization data are presented in the Supporting Information.

Received: July 14, 2006

Keywords: amino acids · asymmetric catalysis · benzoxazines · benzoxazinones · cycloaddition

---

[1] Benzoxazinones are known as antitumor agents and protease inhibitors: a) S. K. Sengupta, D. H. Trites, M. S. Madhavarao, W. R. Beltz, *J. Med. Chem.* **1979**, *22*, 797; b) R. L. Jarvest, S. C. Connor, J. G. Gorniak, L. J. Jennings, H. T. Serafinowska, A. West, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1733; c) F. Bihel, J.-L. Kraus, *Org. Biomol. Chem.* **2003**, *1*, 793.

[2] Benzoxazines are active as antioxidative neuroprotectants and antibiotics: a) M. Largeron, B. Lockhart, B. Pfeiffer, M.-B. Fleury, *J. Med. Chem.* **1999**, *42*, 5043; b) Y.-G. Zhou, P.-Y. Yang, X.-W. Han, *J. Org. Chem.* **2005**, *70*, 1679; c) J. Ilas, P. S. Anderluh, M. S. Delenc, D. Kikelj, *Tetrahedron* **2005**, *61*, 7325.

[3] T. Bekele, M. H. Shah, J. Wolfer, C. J. Abraham, A. Weatherwax, T. Lectka, *J. Am. Chem. Soc.* **2006**, *128*, 1810.

[4] For recent examples of asymmetric α-amino acid synthesis, see: a) T. Abellan, R. Chinchilla, N. Galindo, G. Guillena, C. Najera, J. M. Sansano, *Eur. J. Org. Chem.* **2000**, 2689; b) J. Kobayashi, M. Nakamura, Y. Mori, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 9192; c) T. Belser, M. Stohr, A. Pfaltz, *J. Am. Chem. Soc.* **2005**, *127*, 8720.

[5] K. Kacprzak, J. Gawronski, *Synthesis* **2001**, *7*, 961.

[6] a) D. P. Huber, K. Stanek, A. Togni, *Tetrahedron: Asymmetry* **2006**, *17*, 658; b) B. Mohar, J. Baudoux, J.-C. Plaquevent, D. Cahard, *Angew. Chem.* **2001**, *113*, 4666; *Angew. Chem. Int. Ed.* **2001**, *40*, 4214.

[7] P. Meffre, F. Le Goffic, *Amino Acids* **1996**, *11*, 313.

[8] Presumably, these amino acids are not very amenable to synthesis through asymmetric hydrogenation (that is, **5g** and **5h** by virtue of their unsaturation), through the chiral phase-transfer synthesis (that is, **5g** and **5h** as no suitable S_N2 substrates exist), or the Strecker reaction (that is, the conditions for the hydrolysis of the nitrile group can be harsh for **5g**, **5h**, and **5p**).

[9] V. P. Kukhar in *Fluorine-Containing Amino Acids, Synthesis and Properties (*Ed.: V. A. Soloshonok), Wiley, Chichester, **1995**.

[10] a) D. Ferraris, B. Young, T. Dudding, T. Lectka, *J. Am. Chem. Soc.* **1998**, *120*, 4548; b) A. E. Taggi, A. M. Hafez, H. Wack, B. Young, W. J. Drury III, T. Lectka, *J. Am. Chem. Soc.* **2000**, *122*, 7831.

[11] For a detailed study of *o*-quinone imide cycloadditions: K. C. Nicolaou, K. Sugita, P. S. Baran, Y.-L. Zhong, *J. Am. Chem. Soc.* **2002**, *124*, 2221.

[12] In some cases, the quinone imides were isolated, in other cases, they were generated in situ by simple $Pb(OAc)_4$ oxidation.

[13] The opposite *S* enantiomer products can be made in comparable selectivity with benzoylquinine (BQ, **3b**) as the catalyst.

[14] Absolute configurations were determined by correlation to several known α-amino acid derivatives; the sense of induction observed was consistent with that obtained in other cinchona alkaloid catalyzed reactions (see Reference [10]).

[15] K. F. Croom, K. L. Goa, *Drugs* **2003**, *63*, 2769.

[16] P. Verma, S. Singh, D. K. Dikshit, R. Suprabhat, *Synthesis* **1987**, *1*, 68.

[17] Reactions were quenched with a THF solution of the desired nucleophile at room temperature.

[18] R. Adams, J. M. Stewart, *J. Am. Chem. Soc.* **1952**, *74*, 5876.

[19] For an example of dearylation by using CAN, see: S. Kobayashi, J. Kobayashi, H. Ishiani, M. Ueno, *Chem. Eur. J.* **2002**, *8*, 4185.

[20] For a review, see: L. A. Carpino, *Acc. Chem. Res.* **1987**, *20*, 401.