

## An Asymmetric, Bifunctional Catalytic Approach to Non-Natural α-Amino Acid Derivatives

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A catalytic, asymmetric process for the synthesis of 1,4benzoxazinones from *o*-benzoquinone imides and ketene enolates is reported. Addition of Lewis acids  $(Zn(OTf)_2, In(OTf)_3)$ , and in particular Sc(OTf)\_3) creates a bifunctional catalytic system that dramatically increases the reaction rate and the yield of these non-natural amino acid precursors while preserving the remarkable enantioselectivity inherent to the reaction. Cocatalyst Sc(OTf)\_3 increases the yield by up to 42% while producing products in >99% ee.

The use of asymmetric, bifunctional catalytic systems for the efficient synthesis of optically active compounds is an especially active area of research in modern asymmetric catalysis.<sup>1</sup> Systems that attempt to mimic enzymatic efficiency by the simultaneous activation of both substrates via the partnership of a Lewis acid and a Lewis base<sup>2</sup> are particularly attractive. The cooperative action of these dynamic catalysts promotes respectively electrophilicity and nucleophilicity in reactive partners. One obstacle is that, theoretically, most Lewis acid/base pairs should self-quench, yet when the right pair is combined, for example, a hard metal ion and a softer base, reaction rates may increase considerably.<sup>3</sup>





SCHEME 2. Simple Derivatization To Yield  $\alpha$ -Amino Acid Derivatives



Asymmetric, bifunctional catalytic systems that promote inverse electron demand hetero-Diels—Alder reactions are virtually unknown, excepting an initial communication from our lab.<sup>4</sup> We report a system in which a chiral nucleophile generates dienophile activity while an achiral Lewis acid enhances diene electrophilicity. These catalysts, working in tandem, promote the enantioselective reaction of ketene enolates with *o*-benzoquinone imides to produce optically active 1,4-benzoxazinones (**4**, Scheme 1) with greatly improved yield and excellent enantiomeric excess (>99% ee).

As previously described,<sup>5</sup> these 1,4-benzoxazinone products are readily converted into  $\alpha$ -amino acid derivatives by in situ methanolysis and a simple oxidation by ceric ammonium nitrate (CAN) in an acetonitrile/water mixture. This process affords the respective  $\alpha$ -amino acid derivatives in good yield and in virtually enantiomerically pure form (Scheme 2).

We had previously determined that the in situ methanolysis proceeds quantitatively; mass loss must occur during the formation of the 1,4-benzoxazines and may be a function of the sluggishness of the cycloaddition reaction. A faster reaction might therefore limit byproduct formation and increase the yield of the desired product. We reasoned that a Lewis acid might coordinate to the quinone imide, rendering it more electrophilic without detriment to the nucleophilic catalyst, thereby increasing the reaction rate and, subsequently, the chemical yield.

 <sup>(1) (</sup>a) Fujimori, I.; Mita, T.; Maki, K.; Shiro, M.; Sato, A.; Furusho, S.; Kanai, M.; Shibasaki, M. J. Am. Chem. Soc. 2006, 128 (51), 16438–16439.
 (b) Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. J. Am. Chem. Soc. 2007, 129 (4), 768–769.

<sup>(2) (</sup>a) DiMauro, E. F.; Mamai, A.; Kozlowski, M. C. Organometallics 2003, 22, 850–855. (b) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. J. Am. Chem. Soc. 2005, 127, 1206–1215. (c) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. Synlett 2005, 10, 1491– 1508.

<sup>(3)</sup> Pearson, R. G. J. Am. Chem. Soc. 1963, 85, 3533-3539.

<sup>(4)</sup> Abraham, C. J.; Paull, D. H.; Scerba, M. T.; Grebinski, J. W.; Lectka, T. J. Am. Chem. Soc. 2006, 128 (41), 13370–13371.

<sup>(5)</sup> Wolfer, J.; Bekele, T.; Abraham, C. J.; Dogo-Isonagie, C.; Lectka, T. Angew. Chem., Int. Ed. 2006, 45 (44), 7398-7400.

 TABLE 1. Metal Cocatalyst Effect on the [4+2] Cycloaddition

 Reaction



<sup>*a*</sup> Reactions run with the quinone imide (0.12 mmol), dihydrocinnamoyl chloride (0.12 mmol), Hünig's base (0.12 mmol), BQd (0.012 mmol), and metal triflate (0.012 mmol), followed by addition of MeOH; percent yield is for both steps. <sup>*b*</sup> Previously reported yield, ref 5.

For guidance, we drew on our previous experience with bifunctional catalytic systems, which focused on the cooperative action of Lewis acids and cinchona alkaloid based nucleophilic catalysts. One study screened Lewis acids for their ability to activate imino esters toward nucleophilic attack by cinchona alkaloid derived zwitterionic ketene enolates.<sup>2b</sup> This work identified several Lewis acids that worked well in tandem with our chiral nucleophilic catalyst, narrowing a range of metal co-catalysts to complexes of Al(III), Zn(II), Sc(III), and In(III). In another study, these same metals were found to activate *o*-benzo-quinone diimides and improve their reaction with chiral ketene enolates.<sup>4</sup> Though each reaction set prefers a different metal complex, both reports demonstrated that the Lewis acid acts through coordination with the respective electrophilic substrate.

On the basis of previous success, we tested the ability of these metals to enhance the reaction between *o*-benzoquinone imides and ketene enolates. We examined the effect of a metal cocatalyst on the overall yield of a standard reaction. Several metal triflates were screened in the reaction of the dichlorobenzoquinone imide (1) and dihydrocinnamoyl chloride (Table 1). Cocatalyst Sc(OTf)<sub>3</sub> provided a nearly 30% increase in yield relative to no metal. The strong Lewis acid activity of Sc(OTf)<sub>3</sub> is expected because of its hard character and electron-delocalizing triflate group.<sup>6</sup> Scandium has found considerable use in catalysis of Diels—Alder-type reactions, and is particularly known for catalyzing hetero-Diels—Alder cycloadditions.<sup>7</sup> The scandium complex promoted a faster, cleaner reaction than the other metals tested, thereby making it the best overall Lewis acid for this cycloaddition reaction.

Zinc(II) triflate was the second most efficient metal cocatalyst, effecting a 16% increase in yield, and indium promoted a more modest increase. It is not surprising that copper(II) triflate was detrimental to the reaction; copper is known to have an affinity for amines, and it is possible that this is an example of the selfquenching catalytic system discussed previously. Most importantly, there was no erosion of ee when any of these metal complexes were used as cocatalysts.

Having established that the  $Sc(OTf)_3$  cocatalyst was the best overall Lewis acid, we decided to screen several acid chloride substrates to study the scope of scandium's influence on the

CI		Ph-p-NO <sub>2</sub>	1. 10 m Hüni THF	nol% 3a ig's base -78 °C	HO-	
CI		0 R <sub>1</sub> U	2. MeC	р-N	O <sub>2</sub> -Ph R	
			no metal		10 mol % Sc(OTf) <sub>3</sub>	
entry		$R_1$	% ee	% yield <sup>a</sup>	% ee	% yield <sup>a,b</sup>
1	4a	Me	>99	69 <sup>c</sup>	>99	91
2	4b	Me	>99	$71^{d}$	>99	$92^d$
3	4c	Et	>99	$62^{c}$	>99	86
4	4d	<i>i</i> -Pr	>99	59	>99	84
5	4e	Ph	>99	66 <sup>c,e</sup>	>99	$92^e$
6	4f	Bn	>99	63 <sup>c</sup>	>99	81
7	4g	p-MeO-Ph	>99	83 <sup>e</sup>	>99	$87^e$
8	4h	CH <sub>2</sub> Phthalimide	>99	86	>99	90

<sup>*a*</sup> Reactions run with quinone imide (0.12 mmol), acid chloride (0.12 mmol), Hünig's base (0.12 mmol), and BQd (**3a**, 0.012 mmol), followed by addition of MeOH; percent yield is for both steps. <sup>*b*</sup> Reactions employed cocatalyst Sc(OTf)<sub>3</sub> (0.012 mmol). <sup>*c*</sup> Previously reported yield, ref 5. <sup>*d*</sup> Reactions employed BQ (**3b**, 0.012 mmol) instead of BQd and yielded the opposite enantiomer. <sup>*c*</sup> Reactions required slow addition of a solution of acid chloride over 6 h.

cycloaddition reaction (Table 2). The yields of the scandium cocatalyzed reactions are universally high. Generally, the addition of  $Sc(OTf)_3$  increased the reaction yields by an average of 28%, and up to a 42% increase (Table 2, entry 4). Only two reactions displayed less than a 29% increase: the reactions involving *p*-methoxyphenylacetyl chloride and 3-phthalimidopropionyl chloride each benefited from a scandium cocatalyst by a modest 5% increase in yield. However, these were by far the highest yielding no-metal reactions (Table 2, entries 7 and 8).

Each reaction shown in Table 2 (entries 1 and 3-8) gave the (R)-enantiomer in virtually enantiomerically pure form.<sup>8</sup> The (S)-enantiomer can be obtained in similarly high enantioselectivity and yield for every cycloaddition reaction when catalyst pseudoenantiomer BQ (3b) is utilized (Table 2, entry 2). This sense of induction is consistent with other asymmetric reactions that have employed these cinchona alkaloids to catalytically derive chiral ketene enolates.9 Importantly, the addition of the scandium cocatalyst did not degrade or change the enantioselectivity. In fact, in every chiral reaction assayed, the other enantiomer was not detected by chiral phase HPLC. The bifunctional catalytic system, employing scandium as a cocatalyst, provided faster, cleaner reactions-they were generally complete in less than half the time required for their no-metal counterparts. By coordinating with the quinone imide functionality, scandium renders it more electrophilic and more susceptible to nucleophilic attack by the catalytically derived chiral ketene enolate; thus, scandium creates the bifunctional catalytic system proposed in Scheme 3.

In conclusion, we have demonstrated an asymmetric, bifunctional catalytic method that vastly improves the yield and accessibility of non-natural  $\alpha$ -amino acid precursors, 1,4-

<sup>(6)</sup> Silvero, G.; Arévalo, M. J.; Bravo, J. L.; Ávalos, M.; Jiménez, J. L.; López, I. *Tetrahedron* **2005**, *61* (30), 7105–7111.

<sup>(7)</sup> Kobayashi, S. Eur. J. Org. Chem. 1999, 15-27.

<sup>(8)</sup> Absolute configurations were determined previously by correlation to several known  $\alpha$ -amino acid derivatives; see ref 5.

<sup>(9) (</sup>a) Bekele, T.; Shah, M. H.; Wolfer, J.; Abraham, C. J.; Weatherwax, A.; Lectka, T. J. Am. Chem. Soc. 2006, 128 (6), 1810–1811. (b) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. Acc. Chem. Res. 2004, 37 (8), 592–600. (c) France, S.; Weatherwax, A.; Lectka, T. Eur. J. Org. Chem. 2005, 475–479. (d) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. J. Am. Chem. Soc. 2002, 124 (23), 6626–6635.



SCHEME 3. Proposed Mechanism of Bifunctional Catalysis  $(R = CO-Ph-p-NO_2)$ 

benzoxazines, in virtually enantiomerically pure form. The catalyst used here,  $Sc(OTf)_3$ , reduces reaction times and increases chemical yield of the [4+2] cycloaddition by efficiently activating the quinone imide. Combined with methods previously reported,<sup>5</sup> the system presented here opens the door to a wide range of amino acids, both natural and non-natural, with selectable enantiomers, in exceptional enantioselectivity and high yields. The improved scope of this remarkably enantioselective methodology now provides unhindered access to this important class of chiral compounds that are otherwise difficult to synthesize.

## **Experimental Section**

Representative Procedure for Aliphatic Acid Chloride Reactions, (*R*)-Methyl 2-(*N*-(4,5-Dichloro-2-hydroxyphenyl)-4-nitrobenzamido)-3-(1,3-dioxoisoindolin-2-yl)propanoate (4h). A solution of quinone imide (1, 0.12 mmol in 1 mL THF) was added dropwise, at -78 °C, to a reaction flask containing benzoylquinidine (3a, 0.012 mmol), scandium(III) triflate (0.012 mmol, where indicated), Hünig's base (0.12 mmol), and 3-phthalimidopropionyl chloride (0.12 mmol) in 3 mL of THF. The reaction was stirred at -78 °C and monitored by TLC. When the reaction was complete, it was quenched with methanol (3 mL) and allowed to warm to room temperature overnight. The solvent was removed in vacuo and the crude residue was purified by column chromatography to yield pale yellow crystalline solid **4h**: yield 90%; % ee >99; mp 88 °C; [α]<sub>D</sub> 102.4° (*c* 0.9467, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.37 (s, 0.85H), 9.10 (s, 0.15H), 8.01 (m, 2H), 7.85 (m, 2H), 7.42 (m, 2H), 7.38 (2H), 6.85 (s, 1H), 6.29 (s, 1H), 4.93 (m, 1H), 4.24 (m, 2H), 3.93, (m, 2.6H), 3.73 (s, 0.4H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 172.5, 169.4, 168.2, 152.5, 148.5, 139.8, 134.8, 134.4, 131.4, 129.2, 128.7, 128.0, 123.9, 123.4, 122.9, 120.2, 64.4, 63.5, 54.5 ppm; IR (solvent) 3193, 1774, 1719, 1672 cm<sup>-1</sup>; HPLC (OD, 20% *i*-PrOH/hexanes, 1.0 mL/min) (*R*) 17.00, (*S*) 47.04; HRMS (ESI+) calcd for C<sub>25</sub>H<sub>17</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>8</sub>Na<sup>+</sup> 580.0285, found 580.0282.

**Representative Procedure for Arylacetyl Chloride Reactions,** (R)-Methyl 2-(N-(4,5-Dichloro-2-hydroxyphenyl)-4-nitrobenzamido)-2-(4-methoxyphenyl)acetate (4g). A solution of p-methoxyphenylacetyl chloride (0.12 mmol in 2 mL THF) was added via syringe pump over 6 h, at -78 °C, to a reaction flask containing benzoylquinidine (3a, 0.012 mmol), scandium(III) triflate (0.012 mmol, where indicated), Hünig's base (0.12 mmol), and quinone imide (1, 0.12 mmol) in 3 mL of THF. The reaction was stirred at -78 °C and monitored by TLC. When the reaction was complete, it was quenched with methanol (3 mL) and allowed to warm to room temperature overnight. The solvent was removed in vacuo and the crude residue was purified by column chromatography to yield white crystalline solid **4g**: yield 87%; % ee >99; mp 88 °C;  $[\alpha]_D = -10.9^\circ$  (c 1.14, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  9.72 (s, 1H), 8.07 (m, 2H), 7.47 (m, 2H), 6.98 (m, 2H), 6.84 (s, 1H), 6.78 (m, 2H), 6.35 (s, 1H), 6.23 (s, 1H), 3.91 (s, 3H), 3.76 (s, 3H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 175.7, 169.9, 160.7, 154.1, 148.5, 140.6, 134.2, 132.6, 130.9, 128.2, 125.1, 123.3, 122.7, 122.4, 119.6, 114.7, 64.3, 55.4, 54.2) ppm; IR (CH<sub>2</sub>Cl<sub>2</sub>) 3207, 1715, 1662 cm<sup>-1</sup>; HPLC (Whelk-01, 10% *i*-PrOH/hexanes, 1.0 mL/min) (R) 42.77, (S) 27.01; HRMS (ESI+) calcd for  $C_{23}H_{18}Cl_2N_2O_7Na^+$  527.0383, found 527.0379.

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**Supporting Information Available:** General procedures for the synthesis of catalysts, quinone imide, and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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