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De Novo Synthesis of Tamiflu via a Catalytic Asymmetric Ring-Opening of meso-Aziridines with TMSN₃

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Due to the recent emergence of avian flu, which has the potential to infect humans, an outbreak of influenza virus is a serious worldwide concern. Tamiflu (oseltamivir phosphate 1) is an orally active anti-influenza drug that potently inhibits neuramidase, an enzyme crucial for the release and spread of the influenza virus from infected cells. Many nations have planned to stock a significant amount of 1 to protect against a possible influenza outbreak. The current commercial synthetic route of 1 uses naturally occurring (—)-shikimic acid as a starting material. For constant and large-scale supply of 1, however, a more reliable source is desired. We describe an asymmetric synthesis of 1 utilizing a general catalytic enantioselective ring-opening of *meso*-aziridines with TMSN₃.

Optically active 1,2-diamines are versatile chiral building blocks for many useful molecules, including pharmaceuticals and chiral ligands.³ Desymmetrization of *meso*-aziridines by a nitrogen nucleophile is a direct method to access these compounds. Only one catalytic enantioselective method has been reported in this category from Jacobsen's group using a tridentate Schiff base Cr(III) complex as a catalyst.⁴ Considering the high utility of the products, however, there remains room for improvement in terms of enantioselectivity, substrate generality, and catalyst loading.⁵ On the basis of our recent development of catalytic desymmetrization of *meso*-aziridines (CDMA) with TMSCN using a poly Gd complex derived from ligand 2,⁶ we investigated the possibility of extending this catalysis to using TMSN₃ as a nucleophile.

Previously optimized conditions for CDMA with TMSCN involve a catalytic amount of trifluoroacetic acid (TFA) and a stoichiometric amount of 2,6-dimethylphenol (DMP) as additives.⁶ We proposed that TFA tuned the catalyst by forming a TFAcontaining polymetallic complex, and DMP facilitated the catalyst turnover step. When those conditions were applied to a ring-opening reaction of N-4-nitrobenzoylaziridine (3a, optimum substrate for CDMA with TMSCN⁶) with TMSN₃, the reaction proceeded slowly, giving product 4a with only 46% ee (Table 1, entry 1). In the absence of any additives, enantioselectivity improved to 66% ee without changing the reaction rate (entry 3). To enhance the reactivity of the substrate, N-3,5-dinitrobenzoylaziridine 3b was used. Although the reaction time decreased little, enantioselectivity significantly improved to 85% ee (entry 4). Screening of rare earth alkoxides as the catalyst metal source (entries 5-9) indicated that Y(O'Pr)₃ was optimum, giving the product in 90% yield with 92% ee in 1 h (entry 9).

Table 1. Optimization of Reaction Conditions

M(O[/]Pr)₃ (10 mol %)
2 (20 mol %)
TMSN₃ (3 equiv)

additive
CH₃CH₂CN, rt

4a or 4b

		•				
entry	М	substrate	additive ^a	time (h)	yield (%) ^b	ee (%) ^c
1	Gd	3a	DMP, TFA	20	>99	46
2	Gd	3a	DMP	20	>99	64
3	Gd	3a	none	20	>99	66
4	Gd	3b	none	16	90	85
5	Dy	3b	none	16	93	90
6	Er	3b	none	16	89	89
7	Yb	3b	none	16	91	82
8	Sc	3b	none	16	90	63
9	Υ	3b	none	1	90	92

^a DMP = 2,6-dimethylphenol (1 equiv was used). TFA = trifluoroacetic acid (5 mol % was used). ^b Isolated yield. ^c Determined by chiral HPLC.

The optimized reaction conditions were then applied to various meso-aziridines (Table 2). High enantioselectivity was produced from a wide range of substrates, including cyclic and acyclic aziridines, using 1-10 mol % catalyst. Thus, this is the most general CDMA with TMSN₃ reported to date. The absolute configuration of products was the same as that of CDMA with TMSCN.⁶ Therefore, the present reaction should proceed through a mechanism similar to the previously reported CDMA with TMSCN.⁶ generation of a reactive yttrium azide from TMSN₃ through transmetalation⁷ and intramolecular transfer of the azide to an activated acylaziridine by a Lewis acidic yttrium in the same poly Y catalyst.⁸ Products were converted to optically active C_2 symmetric 1,2-diamines in excellent yield (Scheme 1).

Our next focus was to achieve a catalytic asymmetric synthesis of Tamiflu (1) using this reaction as a basic methodology (Scheme 2). We selected **4e** as a starting compound (Table 2, entry 5). The main tasks required for the synthesis of 1 from 4e were the introduction of an oxygen functionality at the allylic position and an ethoxycarbonyl group at the olefin. After obtaining enantiomerically enriched 4e by recrystallization, C_2 symmetric diamide 5 was synthesized in four steps. Allylic oxidation of 5 with SeO₂⁹ in the presence of Dess-Martin periodinane produced a mixture of enone 6 and allylic alcohol 7 (ca. 2:3),10 which was treated without purification by Dess-Martin periodinane, giving 6 in 68% yield. Enantiomerically pure (>99% ee) 6 was obtained at this stage by recrystallization. A 1,4-addition of TMSCN in the presence of 10 mol % of Ni(COD)₂¹¹ followed by treatment with NBS and Et₃N produced γ -keto nitrile 8, which was selectively reduced with a bulky aluminum reagent¹² to give alcohol 9. Aziridine formation under Mitsunobu conditions and BF3. EOEt2-mediated aziridine opening with 3-pentanol¹ afforded 10 in good yield. Treatment of 10 with TFA, followed by protection of the sterically less hindered

Table 2. Catalytic Enantioselective Desymmetrization of *meso*-Aziridines with TMSN₃

 a Isolated yield. b Determined by chiral HPLC. c Three equivalents of TMSN $_3$ was used. d The absolute configuration was determined as shown.

Scheme 1. Typical Conversion to 1,2-Diamines

amine with a Boc group, acetylation, conversion of the nitrile to ethoxycarbonyl in acidic ethanol concomitant with removal of Boc group, and $\rm H_3PO_4$ salt formation afforded 1. To our knowledge, this is the first enantioselective synthesis of Tamiflu using an artificial asymmetric catalyst.

In conclusion, we developed a general CDMA with $TMSN_3$ using a Y complex of chiral ligand 2. This reaction was applied to a catalytic asymmetric synthesis of Tamiflu. Further improvement of the synthetic efficacy of Tamiflu, particularly, in the allylic oxidation and the Ni-catalyzed cyanide conjugate addition, and investigation of an alternative route are currently ongoing.

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Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

Scheme 2. Catalytic Asymmetric Synthesis of Tamiflu^a

^a Reagents and conditions: (a) recrystallized from PrOH, 72%; (b) Boc₂O (1.5 equiv), DMAP (0.5 equiv), CH₃CN, rt, 3 h; (c) 4 M NaOH, rt, 2 h, 98% (2 steps); (d) Ph₃P (1.1 equiv), CH₃CN, 50 °C, 3 h; H₂O, 40 °C, 2 h; (e) Boc₂O (2 equiv), Et₃N (5 equiv), CH₂Cl₂, rt, 2 h, 90% (2 steps); (f) SeO₂ (1 equiv), Dess−Martin periodinane (1.5 equiv), dioxane, 80 °C, 15; (g) Dess−Martin periodinane (1.5 equiv), CH₂Cl₂, 4 °C, 68% (2 steps); recrystallized from Pr₂O−hexane, >99% ee, 62%; (h) Ni(COD)₂ (10 mol%), CDO (10 mol%), TMSCN (3 equiv), THF, 60 °C, 65 h; (i) NBS (1.05 equiv), THF, 20 min; Et₃N (14 equiv), 4 °C, 40 min; (j) LiAlH(O'Bu)₃ (5 equiv), THF, 4 °C, 30 min, 60% (>20:1) (3 steps); (k) DEAD (2.5 equiv), Ph₃P (2.5 equiv), THF, 4 °C, 1 h, 87%; (l) 3-pentanol, BF₃·OEt₂ (1.5 equiv), 4 °C, 1 h, 52%; (m) TFA (20 equiv), CH₂Cl₂, 4 °C to rt, 3 h; (n) Boc₂O (1.1 equiv), Et₃N (5 equiv), Ph₂P (2.5 equiv), DMAP (0.5 equiv), py, rt, 1 h, 84%; (p) 4.2 M HCl−EtOH, 60 °C, 4 h; H₂O, 4 °C, 3 h, 53%; (q) 85% H₃PO₄ (1 equiv), EtOH; cryst, 50%.

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