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Published on Web 04/25/2006

De Novo Synthesis of Tamiflu via a Catalytic Asymmetric Ring-Opening of *meso*-Aziridines with $TMSN_3$

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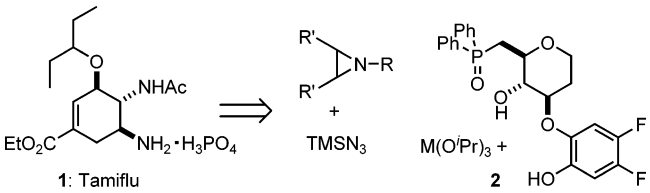
Due to the recent emergence of avian flu, which has the potential to infect humans, an outbreak of influenza virus is a serious worldwide concern. Tamiflu (oseltamivir phosphate **1**) is an orally active anti-influenza drug that potently inhibits neuramidase, an enzyme crucial for the release and spread of the influenza virus from infected cells.[1] 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.[2] 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 $TMSN_3$.



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 $TMSN_3$ 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 TFA-containing 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 TMSCN[6]) with $TMSN_3$, 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 $Y(O^iPr)_3$ was optimum, giving the product in 90% yield with 92% ee in 1 h (entry 9).

Table 1. Optimization of Reaction Conditions

entry	M	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	Y	**3b**	none	1	90	92

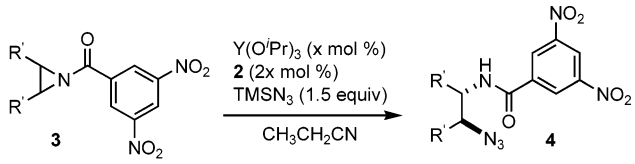
[a] DMP = 2,6-dimethylphenol (1 equiv was used). TFA = trifluoroacetic acid (5 mol % was used). [b] Isolated yield. [c] Determined by chiral HPLC.

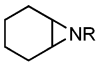
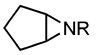
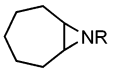
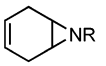
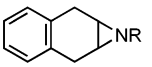
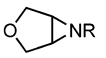
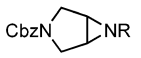
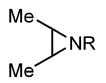
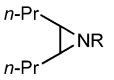
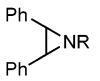
The optimized reaction conditions were then applied to various *meso*-aziridines (Table 2). High enantioselectivity was produced from a wide range of substrates, including cyclic and acyclic aziridines, using 1−10 mol % catalyst. Thus, this is the most general CDMA with $TMSN_3$ reported to date. The 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 $TMSN_3$ through transmetalation[7] 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 SeO_2[9] 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 $Ni(COD)_2$[11] followed by treatment with NBS and Et_3N produced γ-keto nitrile **8**, which was selectively reduced with a bulky aluminum reagent[12] to give alcohol **9**. Aziridine formation under Mitsunobu conditions and $BF_3{\cdot}EOEt_2$-mediated aziridine opening with 3-pentanol[1] afforded **10** in good yield. Treatment of **10** with TFA, followed by protection of the sterically less hindered

10.1021/ja061696k CCC: $33.50

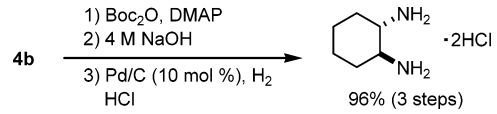
Table 2. Catalytic Enantioselective Desymmetrization of *meso*-Aziridines with $TMSN_3$



entry	substrate (R = 3,5-$(NO_2)_2$-Bz)		temp. (°C)	catalyst (x mol %)	time (h)	yield (%)[a]	ee (%)[b]
1[c]		**3b**	0	1	36	97	92[d]
2		**3c**	r.t.	5	36	>99	94
3		**3d**	40	10	20	94	86
4			40	5	48	93	83
5		**3e**	r.t.	2	48	96	91[d]
6		**3f**	r.t.	2	48	98	91
7		**3g**	40	10	18	>99	96
8		**3h**	r.t.	5	48	>99	94
9		**3i**	r.t.	1	48	94	95[d]
10		**3j**	r.t.	5	48	>99	87
11		**3k**	r.t.	2	48	>99	93

[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



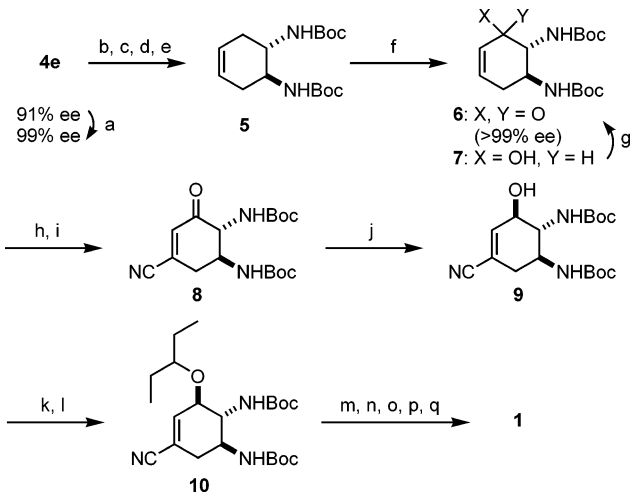
amine with a Boc group, acetylation, conversion of the nitrile to ethoxycarbonyl in acidic ethanol concomitant with removal of Boc group, and H_3PO_4 salt formation afforded **1**. To our knowledge, this is the first enantioselective synthesis of Tamiflu using an artificial asymmetric catalyst.

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.

Acknowledgment. Financial support was provided by a Grant-in-Aid for Specially Promoted Research of MEXT.

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 ^{i}PrOH, 72%; (b) Boc_2O (1.5 equiv), DMAP (0.5 equiv), CH_3CN, rt, 3 h; (c) 4 M NaOH, rt, 2 h, 98% (2 steps); (d) Ph_3P (1.1 equiv), CH_3CN, 50 °C, 3 h; H_2O, 40 °C, 2 h; (e) Boc_2O (2 equiv), Et_3N (5 equiv), CH_2Cl_2, rt, 2 h, 90% (2 steps); (f) SeO_2 (1 equiv), Dess−Martin periodinane (1.5 equiv), dioxane, 80 °C, 12 h; (g) Dess−Martin periodinane (1.5 equiv), CH_2Cl_2, 4 °C, 68% (2 steps); recrystallized from $^iPr_2O$−hexane, >99% ee, 62%; (h) $Ni(COD)_2$ (10 mol %), COD (10 mol %), TMSCN (3 equiv), THF, 60 °C, 65 h; (i) NBS (1.05 equiv), THF, 20 min; Et_3N (14 equiv), 4 °C, 40 min; (j) $LiAlH(O^tBu)_3$ (5 equiv), THF, 4 °C, 30 min, 60% (>20:1) (3 steps); (k) DEAD (2.5 equiv), Ph_3P (2.5 equiv), THF, 4 °C, 1 h, 87%; (l) 3-pentanol, BF_3·OEt_2 (1.5 equiv), 4 °C, 1 h, 52%; (m) TFA (20 equiv), CH_2Cl_2, 4 °C to rt, 3 h; (n) Boc_2O (1.1 equiv), Et_3N (5 equiv), CH_2Cl_2, 4 °C, 30 min, 63% (2 steps); (o) Ac_2O (2 equiv), DMAP (0.5 equiv), py, rt, 1 h, 84%; (p) 4.2 M HCl−EtOH, 60 °C, 4 h; H_2O, 4 °C, 3 h, 53%; (q) 85% H_3PO_4 (1 equiv), EtOH; cryst, 50%.

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JA061696K