Asymmetric Synthesis

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A Synthesis of Tamiflu by Using a Barium-Catalyzed Asymmetric Diels–Alder-Type Reaction**

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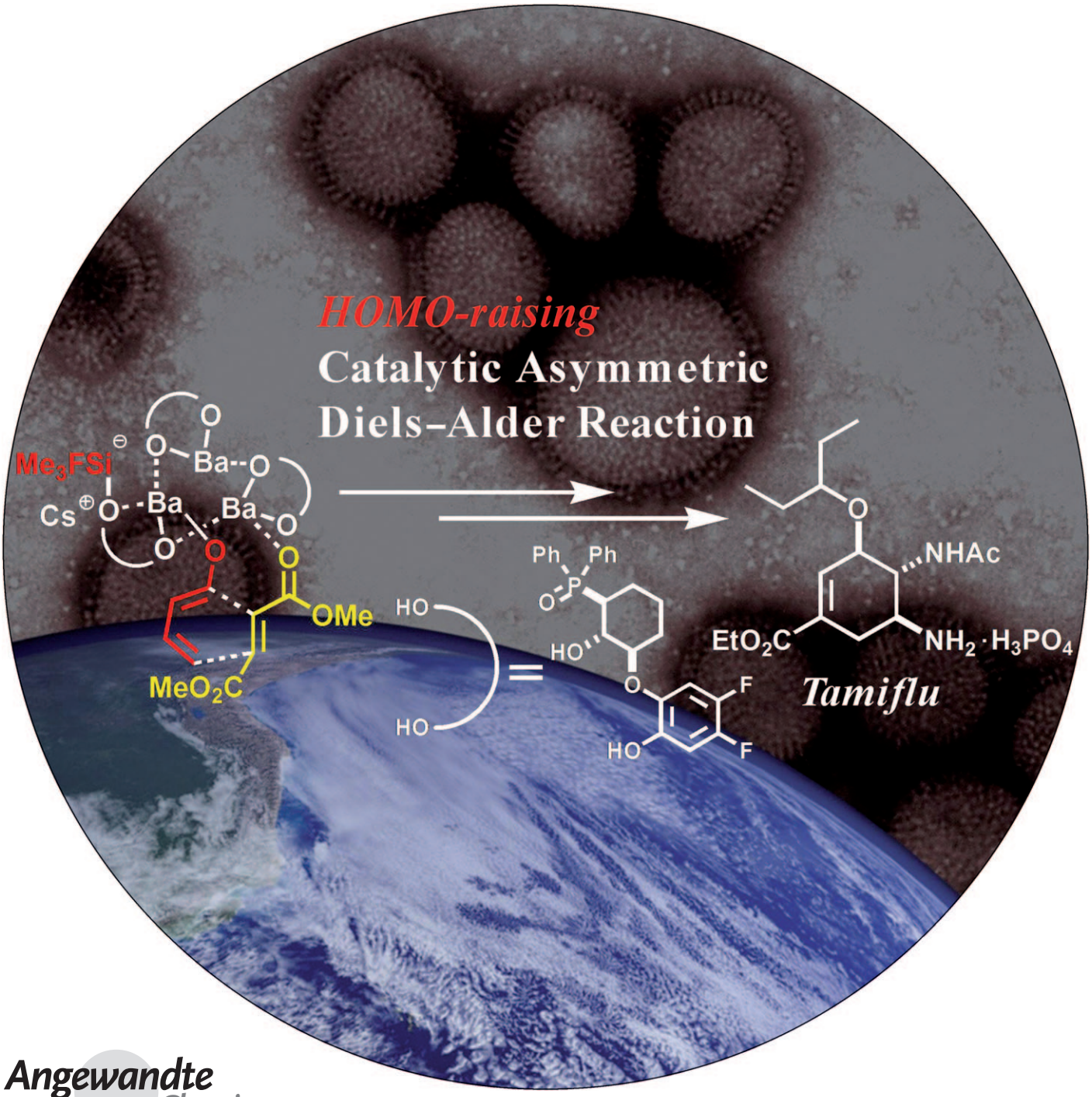
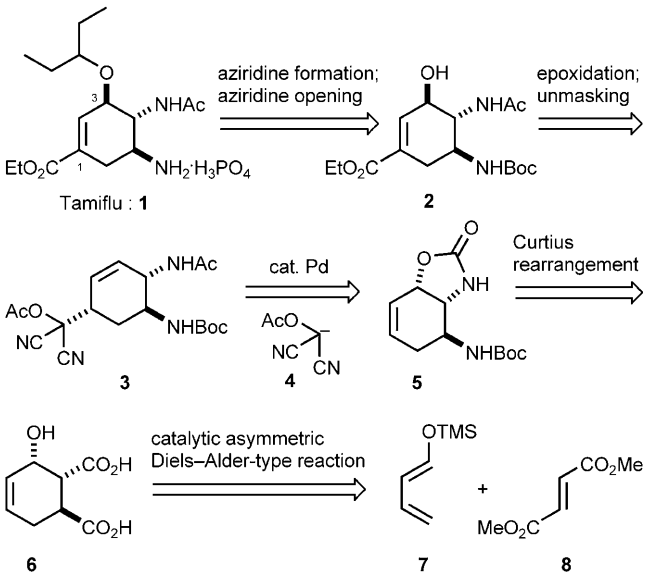


Influenza viruses pose a serious threat to world public health. Two of the drugs currently used to treat influenza patients are Tamiflu (**1**; (−)-oseltamivir phosphate)[1] and Relenza (zanamivir),[2] both of which inhibit viral neuraminidase. Currently, Tamiflu is produced and supplied by Roche using (−)-shikimic acid as the starting material.[3] The production of (−)-shikimic acid with consistent purity, however, requires a lot of time and is costly. In addition, the dependence on a single synthetic route for the supply of such an important drug is unwise. Therefore there is an urgent demand for the development of alternative practical syntheses of Tamiflu, starting from easily available starting materials.[4,5] We report herein a new synthesis of Tamiflu which features a novel asymmetric Diels–Alder-type reaction catalyzed by a barium/F_2-FujiCAPO complex.

Our retrosynthetic analysis is shown in Scheme 1. The 3-pentyloxy group at C3 should be introduced at a late stage by a ring-opening reaction of an *N*-acetyl aziridine[4a] produced from β-alcohol **2** under Mitsunobu conditions. In our previous reports,[4b,d,e] we utilized a cyanide group as a precursor for the ester group at C1, however, its introduction and conversion into an ethoxycarbonyl group afforded only moderate yields of the desired product. Therefore, we sought



Scheme 1. Retrosynthetic analysis.

an alternative ester surrogate which led to the identification of protected hydroxy malononitrile anion **4**, developed by Nemoto and Yamamoto et al.,[6] as a promising candidate. The introduction of **4** to cyclic carbamate **5** by a palladium-catalyzed allylic substitution would produce cyclohexene derivative **3**, which in turn would be converted into β-alcohol **2** by epoxidation and subsequent unveiling of the masked ester equivalent. Cyclic carbamate **5** would be obtained from hydroxy dicarboxylic acid **6** by using the Curtius rearrangement. A catalytic asymmetric Diels–Alder-type reaction between diene **7** and dienophile **8**[7] should produce a precursor of **6**. Thus, the first step was to develop such a key reaction.

Although a number of Lewis acid catalyzed asymmetric Diels–Alder reactions have been reported to date,[8] including those using ketone-derived siloxy dienes (such as Danishefsky's diene),[9] none of them utilize **7** because of the lability of **7** under acidic conditions. Indeed, **7** readily polymerized in the presence of representative chiral Lewis acid catalysts. Therefore, we examined a conceptually distinct catalytic asymmetric Diels–Alder-type reaction that was not dependent on acid catalysis. We envisioned that metal alkoxides (or phenoxides) might activate the siloxy diene through the formation of a hypervalent silicate or transmetalation (HOMO-raising mechanism; HOMO = highest occupied molecular orbital).[10] Table 1 shows the initial optimization results. First we used (*R*)-binol (**11**; binol = 2,2′-dihydroxy-1,1′-binaphthyl) as the chiral ligand, and examined several metal isopropoxides as catalytic metal sources (30 mol%) in CH_2Cl_2 at room temperature (Table 1, entries 1–4). Among the metal isopropoxides examined, $Ba(OiPr)_2$ afforded the desired products in moderate yield (Table 1, entry 2; isomers **9** and **10** were inseparable by silica gel column chromatography),[11] however a meaningful enantioselectivity was not induced. The effects of several chiral ligands on the enantioselectivity were examined at −20 °C (Table 1, entries 5–10). Whereas the reaction did not proceed at all using (*R*)-binol at this low temperature, products were obtained in 97% yield within 30 minutes by using taddol (**12**; Table 1, entry 5). Unfortunately, enantioinduction was also not observed in this case. Careful analysis of the reaction mixture revealed that the ligand was partially silylated (see below), suggesting that the chiral ligand was partially dissociated from the barium metal. This observation may explain why meaningful enantioinduction was not realized, even with the use of privileged chiral ligands. We therefore used multidentate ligands **13–15** which were developed in our laboratory,[12] anticipating that an effective chiral environment would be retained even after partial ligand silylation.[13] Initial promising enantioselectivity of desired product **9** was attained using F_2-GluCAPO (**13**); the products were produced in 72% combined yield (**9**/**10** 3:1) and with 77% *ee* for **9** (Table 1, entry 6). When the amount of catalyst used was reduced to 20 mol%, however, the reaction was sluggish and the enantiomeric excess of **9** decreased to 61% *ee* (Table 1, entry 7). In contrast, when the barium/FujiCAPO (**14**) complex was used, the reaction proceeded quickly and desired product **9** was obtained with 73% *ee*. However, several unidentified products were also produced, resulting in a moderate combined yield of **9** and **10** (34%;

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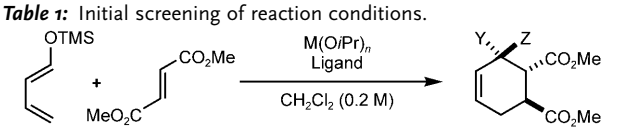
Table 1: Initial screening of reaction conditions.

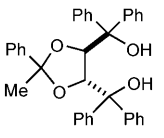


7 3 equiv; **8**

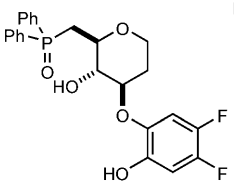
9: Y = OTMS (and OH), Z = H (*endo*: desired)
10: Y = H, Z = OTMS (and OH) (*exo*: undesired)

Entry	M	Ligand	*t* [h]	Combined yield [%]	d.r.[a] (**9**:**10**)	*ee* [%] of **9**[a]
1[b,c,e]	Mg	**11**	17	0	–	–
2[b,c,e]	Ba	**11**	17	45	3:1	4
3[b,c,e]	Sc	**11**	17	0	–	–
4[b,c,e]	Gd	**11**	17	0	–	–
5[c,f]	Ba	**12**	0.5	97	4:1	1
6[c,f]	Ba	**13**	2.5	72	3:1	77
7[d,f]	Ba	**13**	42	74	3:1	61
8[d,f]	Ba	**14**	1.5	34	5:1	73
9[d,f]	Ba	**15**	17	62	6:1	73
10[d,f,g]	Ba	**15**	23	64	3:1	88

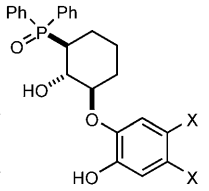
[a] Determined by chiral GC analysis. [b] Added 4 Å molecular sieves (500 mg per mmol **8**). [c] Metal (30 mol%), ligand (30 mol%). [d] Metal (20 mol%), ligand (20 mol%). [e] RT. [f] −20°C. [g] THF was used as the solvent. TMS = trimethylsilyl.



TADDOL (**12**)

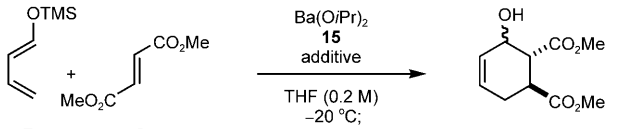


F_2-GluCAPO (**13**)



FujiCAPO (**14**): X = H
F_2-FujiCAPO (**15**): X = F

Table 2: Additive metal fluoride effects.



7 3 equiv; **8**

9: α-OH
10: β-OH

Entry	Additive	*t* [h]	Combined yield [%]	d.r.[a] (**9**:**10**)	*ee* [%] of **9**[a]
1[b]	–	23	64	3:1	88
2[b]	KF	38	79	3:1	87
3[b]	LaF_3	18.5	74	3:1	85
4[b]	ZnF_2	12	67	3:1	19
5[b]	CsF	0.5	>99	2:1	96
6[c]	CsF	0.5	>99	2:1	93
7[d]	CsF	36	91	4:1	97
8[d,e]	CsF	36	88	4:1	94
9[d,f]	CsF	96	91	5:1	95
10[g]	CsF[h]	24	>99	5:1	91

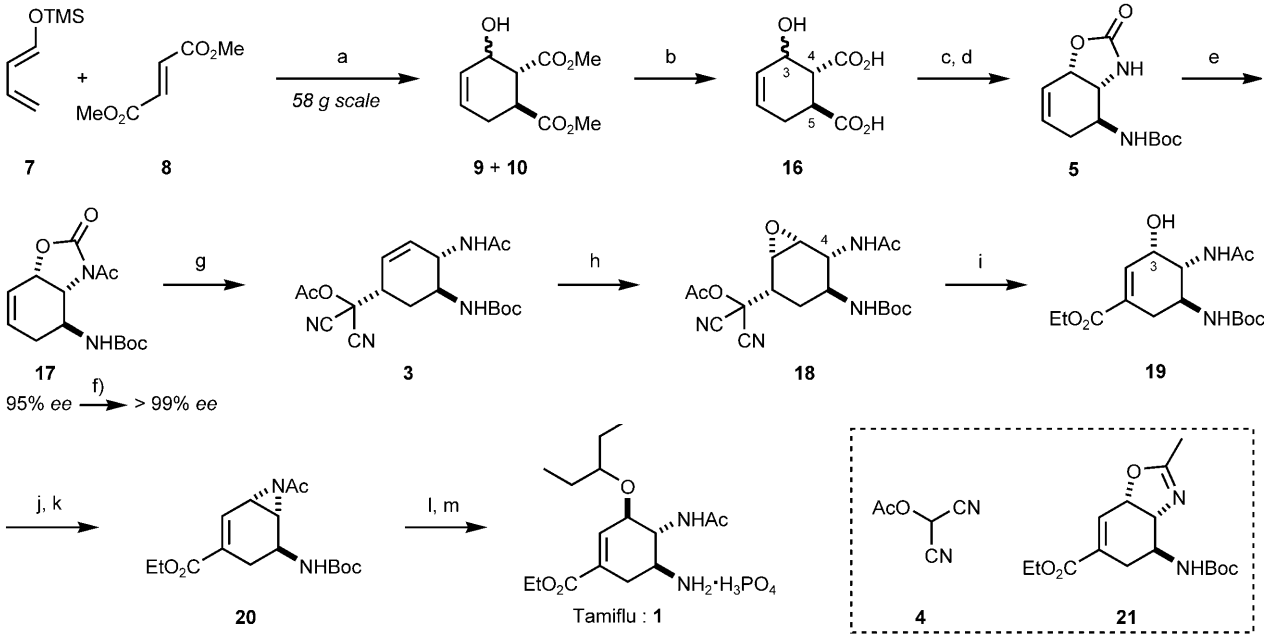
[a] Determined by chiral GC analysis. [b] $Ba(OiPr)_2$ (20 mol%), **15** (20 mol%). [c] $Ba(OiPr)_2$ (10 mol%), **15** (10 mol%). [d] $Ba(OiPr)_2$ (2.5 mol%), **15** (2.5 mol%), 0.67 M of **8**. [e] 12 g scale. [f] 58 g scale. [g] $Ba(OiPr)_2$ (1 mol%), **15** (1 mol%). [h] CsF = 5 mol%. In other entries, the same mol% of additives as those of Ba and **15** was used.

Table 1, entry 8). The catalyst derived from F_2-FujiCAPO (**15**) was the most effective in terms of reactivity, enantioselectivity, and diastereoselectivity, affording **9** with 73% *ee* (Table 1, entry 9). The enantiomeric excess of **9** was improved to 88% *ee* when THF was used as the solvent (Table 1, entry 10).

The reactivity and enantioselectivity of the Diels–Alder-type reaction were additionally improved, such that the reaction could be run on large scale, by optimizing the additives (Table 2). Thin layer chromatography analysis of the progress of the reaction (Table 1) revealed that the reaction mixture contained significant amounts of unsilylated products, even under strictly anhydrous conditions. This result suggested that the silicon transfer step from **7** to the secondary alkoxide products intervened in the catalytic cycle (see below), and that this step was catalyst turnover-limiting. The silicon transfer should be accelerated by the formation of a pentavalent silicate with Lewis base additives,[14] therefore we examined the additive effects of catalytic metal fluorides (20 mol%, Table 2).

Although the addition of KF had no effect on the reaction (Table 2, entry 2), the addition of LaF_3, ZnF_2, and CsF facilitated the reaction (Table 2, entries 3–5). Specifically, CsF had a remarkable effect (Table 2, entry 5); the reaction was complete within 30 minutes and the desired **9** was obtained with significantly higher enantioselectivity (96% *ee*), but the diastereomeric ratio was less satisfactory (2:1). The catalyst loading was reduced to 2.5 mol% under more concentrated conditions (Table 2, entry 7),[15] and the products were afforded in 91% combined yield with a higher diastereomeric ratio of 4:1. The enantiomeric excess of **9** was maintained (97% *ee*). The reaction is practical, and a 12 gram scale reaction was conducted without altering its efficiency (Table 2, entry 8). On a 58 gram scale, both the enantiomeric excess and the diastereomeric ratio were almost constant (Table 2, entry 9), though the reaction was slower, possibly because of the less satisfactory stirring efficiency. The reaction can be performed in the presence of 1 mol% of barium/**15** and 5 mol% of CsF to afford the products (**9** and **10**) in greater than 99% yield (d.r. 5:1) with 91% *ee* of **9** (Table 2, entry 10). We have established a practical catalytic asymmetric Diels–Alder-type reaction, which is the key methodology used for our Tamiflu synthesis.

Having established the key catalytic asymmetric Diels–Alder-type reaction, we investigated the synthesis of Tamiflu. Our optimized route is summarized in Scheme 2. The hydrolysis of the Diels–Alder products (5:1 mixture of **9** and **10**) proceeded uneventfully to afford dicarboxylic acids **16**, and treatment of **16** with DPPA[16] and Et_3N cleanly produced the corresponding hydroxy diacyl azide derived from **9**. In this step, the reaction temperature had to be strictly maintained below 4°C to prevent spontaneous Curtius rearrangement, which would diminish the yield of the desired products. Products derived from the minor isomer (*exo*-**10**) decomposed during this transformation. The desired diacyl azide was roughly isolated, after silica gel column chromatography in approximately 95% yield in two steps from **9**.[17] Next, the Curtius rearrangement was performed to construct the two neighboring nitrogen functionalities of Tamiflu. A solution of the diacyl azide in anhydrous *t*BuOH was heated



Scheme 2. Catalytic asymmetric synthesis of Tamiflu. Reagents and conditions: a) $Ba(OiPr)_2$ (2.5 mol%), F_2-FujiCAPO (**15**, 2.5 mol%), CsF (2.5 mol%), THF, −20°C, 36–96 h; aq. 1 M HCl (91%, 5:1, 95% *ee* for **9**); b) aq. 2 M NaOH (10 equiv), MeOH, 60°C, 10 h; c) DPPA (3 equiv), Et_3N (3 equiv), THF, 0°C, 21 h (95% (2 steps from **9**)); d) *t*BuOH, 80°C, 13 h; e) Ac_2O (2 equiv), Et_3N (4 equiv), DMAP (10 mol%), CH_2Cl_2, RT, 2.5 h (ca. 98% (2 steps)); f) Recrystallization from CH_2Cl_2/cyclopentyl methyl ether (1:2; 80%); g) **4** (1.2 equiv), $[Pd_2(dba)_3]\cdot CHCl_3$ (2 mol%), dppf (4 mol%), toluene, 60°C, 30 min (85%); h) TFAA (10 equiv), urea/H_2O_2 (20 equiv), Na_2HPO_4 (15 equiv), CH_2Cl_2, 4°C, 2 h; i) K_2CO_3 (5 equiv), EtOH, RT, 5 h; j) DEAD (2 equiv), PPh_3 (2 equiv), *p*-nitrobenzoic acid (2 equiv), THF, −20°C, 1.5 h; LiOH (3 equiv), EtOH, −20°C, 15 min (65% (3 steps); k) DIAD (2.1 equiv), Me_2PPh (2.1 equiv), Et_3N (21 mol%), CH_2Cl_2, 4°C, 10 min (76%); l) $BF_3\cdot OEt_2$ (1.5 equiv), 3-pentanol, −20°C, 15 min (75%); m) TFA; H_3PO_4 (73%). DPPA = diphenylphosphoryl azide; DMAP = 4-dimethylaminopyridine; dba = dibenzylideneacetone; dppf = bis(diphenylphosphanyl)ferrocene; TFAA = trifluoroacetic anhydride; DEAD = diethyl azodicarboxylate; DIAD = diisopropylazodicarboxylate; TFA = trifluoroacetic acid; Boc = *tert*-butoxycarbonyl; Ac = acetyl.

at 80°C for 13 hours. The Curtius rearrangement and subsequent intramolecular trapping of the resulting C4 isocyanate group by the *cis*-C3 hydroxy group, as well as the intermolecular addition of *t*BuOH to the C5 isocyanate group proceeded in one pot to afford cyclic carbamate **5**. Thus, the two amino functionalities were successfully differentiated by this sequence. Treatment of **5** with Ac_2O and Et_3N selectively installed an acetyl group on the cyclic carbamate nitrogen atom, producing **17** in 98% yield in two steps from the diacyl azide. Enantiomerically pure **17** was obtained in 80% yield after recrystallization of the crude product from CH_2Cl_2/cyclopentyl methyl ether (1:2).

Although the conversions of **16** into **17** were high yielding, it was desirable to develop more practical procedures such that the isolation of the potentially explosive azide compound could be avoided. Such a protocol was established: after completion of the diacyl azide formation from **16** was confirmed by TLC analysis, the reaction was quenched with 1 M HCl and the excess Et_3N and the diphenylphosphate byproduct were removed in an aqueous workup,[17] which was essential for clean conversion in the next Curtius rearrangement.[18] Neither additional purification of the diacyl azide nor complete removal of the extraction solvent (AcOEt) was necessary in this protocol, which was very advantageous considering the potentially explosive characteristics of neat forms of azide compounds.[19] After the Curtius rearrangement, **5** was isolated in 72% yield from the desired Diels–Alder-type product **9** (ca. 95% yield of **5** was isolated from the treatment of **9** by the above-described procedure using the isolated diacyl azide).

Among many reported C_1 acyl anion equivalents,[20] protected hydroxy malononitrile **4**, developed by Nemoto and Yamamoto et al.,[6] was effective. Thus, regioselective allylic substitution proceeded when cyclic carbamate **17** was heated with **4** in the presence of 2 mol% of $[Pd_2(dba)_3]\cdot CHCl_3$ and 4 mol% of dppf in toluene at 60°C, and product **3** was obtained in 85% yield. Epoxidation of **3** with in situ generated trifluoroperacetic acid[21] afforded α-epoxide **18** as the sole product.[22] This exclusive α-face selectivity is a result of the directing effect of the neighboring acetamide moiety at C4.[23] Treatment of **18** with K_2CO_3 in EtOH converted the acetoxydicyanomethyl unit into an ethoxycarbonyl group,[6] and subsequent E2 epoxide opening proceeded concomitantly to produce α-allyl alcohol **19** in one pot.

The final task was to install the 3-pentyloxy group at C3. After conversion of the C3 hydroxy group of **19** into a better leaving groups (such as triflate, mesylate, chloride, and cyclic sulfamidate), S_N2 inversion with the 3-pentyloxy anion was unsuccessfully attempted.[24] Therefore, we focused on the formation of *N*-acyl aziridine and the subsequent aziridine-opening process.[1,3,4a,b,d–g,j] Mitsunobu esterification of α-alcohol **19** with *p*-nitrobenzoic acid, and one-pot ethanolysis of the resulting ester produced C3 β-alcohol **2**, which was

isolated in 65% yield over 3 steps from **3**.[25] A Mitsunobu aziridine synthesis from **2** was successfully performed using Me_2PPh and DIAD in the presence of 21 mol% of Et_3N, producing **20** in 76% yield. Phosphines had a significant influence in this reaction, and oxazoline **21** was the major byproduct when using other phosphines. The ring-opening reaction of **20** with 3-pentanol was best performed using $BF_3{\cdot}OEt_2$ to afford Boc-protected (−)-oseltamivir in 75% yield. Cleavage of the Boc group with TFA and salt formation with phosphoric acid produced Tamiflu (**1**) in 73% yield. All the analytical data matched those reported in the literature.[3a] By using the synthetic route described above, we achieved a gram-scale synthesis of Tamiflu.

Success in developing this new synthesis of Tamiflu depended on the novel barium-catalyzed asymmetric Diels–Alder-type reaction. Preliminary mechanistic studies indicated that a chiral barium dienolate is generated through transmetalation from siloxy diene **7**, and the barium dienolate is the active species in this reaction. Two experimental results support this mechanism.[26] 1) when the barium/**15** complex was treated with 30 equivalents of **7** in the absence of dienophile **8**, trimethylsilylated ligand **22** was observed in the ESI-MS analysis.[27] This result suggests that transmetalation between **7** and the barium/**15** complex occurred. 2) A competitive experiment using **7** (3 equiv), 1-methoxy-1,3-butadiene (**23**; 3 equiv), and **8** (1 equiv) in the presence of 10 mol% barium/**15** complex and CsF afforded products **9** and **10** derived from siloxy diene **7** in 99% combined yield. Products **24** derived from **23** were not detected, therefore **7** is much more reactive than **23** under the current catalysis. A LUMO-lowering (LUMO = lowest occupied molecular orbital) mechanism does not explain this result. Together, these two results suggest that the barium-catalyzed asymmetric Diels–Alder-type reaction is likely promoted through a HOMO-raising mechanism, possibly via transmetalation.[28,29]

Next, catalyst constitution was determined based on ESI-MS studies. Two MS peaks corresponding to complexes of barium/**15** = 3:3 and 3:4 were observed in the catalyst solution.[26] The 3:4 complex, however, was labile and converted into the 3:3 complex by a tandem MS/MS experiment. The isotope distribution completely matched with the calculated pattern. Therefore, the 3:3 complex **25** should be the active catalyst for the asymmetric Diels–Alder-type reaction.

On the basis of the above results, we propose a catalytic cycle for the asymmetric Diels–Alder-type reaction (Figure 1). First, the active barium dienolate **27** is generated through transmetalation between catalyst **25** and siloxy diene **7**. In this step, the chiral ligand is partially silylated (**27**). The co-catalyst, CsF, would facilitate the generation of **27** through the formation of pentavalent silicate **26**.[30] Barium dienolate **27** should be reactive enough, and cyclization with **8** occurs in either a concerted manner (Diels–Alder pathway) or a stepwise manner (Michael-aldol pathway), producing intermediate barium alkoxide **29**.[31] Because of the existence of multiple barium metals of different electronic characteristics in a catalyst molecule, it is possible that the catalyst promotes the reaction through an intramolecular transfer of the barium dienolate to an activated dienophile by a Lewis acidic barium

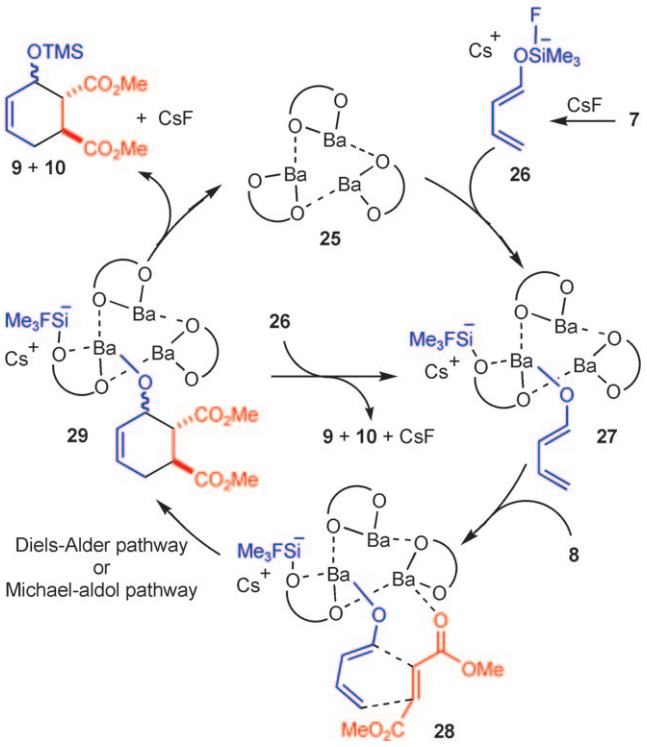


Figure 1. Postulated catalytic cycle of the asymmetric Diels–Alder-type reaction.

(**28**: dual activation mechanism[32]). Finally, the product barium alkoxide in **29** attacks the trimethylsilyl group attached to the ligand, and catalyst **25** is regenerated while silylated products **9** and **10** are liberated from the catalytic cycle. Alternatively, **29** reacts with another molecule of siloxy diene **26**, liberating the products while regenerating active barium dieonolate **27**. Given the synthetic usefulness of siloxy dienes[33] but their lability to strongly Lewis acidic conditions, the HOMO-raising activation mode of siloxy dienes induced by the barium complex will have great potential for the development of new asymmetric catalyses.

In summary, we developed a novel barium-catalyzed asymmetric Diels–Alder-type reaction between 1-trimethylsiloxy-1,3-butadiene (**7**) and dimethyl fumarate (**8**) to access the cyclohexene framework of Tamiflu. This methodology led to the establishment of a new synthetic route of Tamiflu by using the Curtius rearrangement and a palladium-catalyzed allylic substitution reaction using the C_1 acyl anion equivalent, as key steps. Each conversion in the synthetic scheme is easily conducted, and almost all the intermediates are crystalline compounds, which could minimize the need for column chromatography purification. Additional improvement of the synthetic efficiency, especially by the development of a novel methodology for the epoxide opening reaction of **18** with 3-pentanol, is currently ongoing in our laboratory.

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[1] C. U. Kim, W. Lew, M. A. Williams, H. Liu, L. Zhang, S. Swaminathan, N. Bischofberger, M. S. Chen, D. B. Mendel, C. Y. Tai, G. Laver, R. C. Stevens, *J. Am. Chem. Soc.* **1997**, *119*, 681.

[2] M. von Itzstein, W.-Y. Wu, G. B. Kok, M. S. Pegg, J. C. Dyason, B. Jin, T. V. Phan, M. L. Smythe, H. F. White, S. W. Oliver, P. M. Colman, J. N. Varghese, D. M. Ryan, J. M. Woods, R. C. Bethell, V. J. Hotham, J. M. Cameron, C. R. Penn, *Nature* **1993**, *363*, 418.

[3] a) J. C. Rohloff, K. M. Kent, M. J. Postich, M. W. Becker, H. H. Chapman, D. E. Kelly, W. Lew, M. S. Louie, L. R. McGee, L. M. Prisbe, R. H. Yu, L. Zhang, *J. Org. Chem.* **1998**, *63*, 4545; b) M. Federspiel, R. Fischer, M. Hennig, H.-J. Mair, T. Oberhauser, G. Rimmler, T. Albiez, J. Bruhin, H. Estermann, C. Gandert, V. Göckel, S. Götzö, U. Hoffmann, G. Huber, G. Janatsch, S. Lauper, O. Röckel-Stäbler, R. Trussardi, A. G. Zwahlen, *Org. Process Res. Dev.* **1999**, *3*, 266; c) S. Abrecht, P. Harrington, H. Iding, M. Karpf, R. Trussardi, B. Wirz, U. Zutter, *Chimia* **2004**, *58*, 621; d) S. Abrecht, M. C. Federspiel, H. Estermann, R. Fisher, M. Karpf, H.-J. Mair, T. Oberhauser, G. Rimmler, R. Trussardi, U. Zutter, *Chimia* **2007**, *61*, 93.

[4] a) Y.-Y. Yeung, S. Hong, E. J. Corey, *J. Am. Chem. Soc.* **2006**, *128*, 6310; b) Y. Fukuta, T. Mita, N. Fukuda, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 6312; c) X. Cong, Z.-J. Yao, *J. Org. Chem.* **2006**, *71*, 5365; d) T. Mita, N. Fukuda, F. X. Roca, M. Kanai, M. Shibasaki, *Org. Lett.* **2007**, *9*, 259; e) K. Yamatsugu, S. Kamijo, Y. Suto, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2007**, *48*, 1403; f) K. M. Bromfield, H. Graden, D. P. Hagberg, T. Olsson, N. Kann, *Chem. Commun.* **2007**, 3183; g) N. Satoh, T. Akiba, S. Yokoshima, T. Fukuyama, *Angew. Chem.* **2007**, *119*, 5836; *Angew. Chem. Int. Ed.* **2007**, *46*, 5734; h) J.-J. Shie, J.-M. Fang, S.-Y. Wang, K.-C. Tsai, Y.-S. E. Cheng, A.-S. Yang, S.-C. Hsiao, C.-Y. Su, C.-H. Wong, *J. Am. Chem. Soc.* **2007**, *129*, 11892; i) N. T. Kipassa, H. Okamura, K. Kina, T. Hamada, T. Iwagawa, *Org. Lett.* **2008**, *10*, 815; j) B. M. Trost, T. Zhang, *Angew. Chem.* **2008**, *120*, 3819; *Angew. Chem. Int. Ed.* **2008**, *47*, 3759; k) U. Zutter, H. Iding, P. Spurr, B. Wirz, *J. Org. Chem.* **2008**, *73*, 4895; l) J.-J. Shie, J.-M. Fang, C.-H. Wong, *Angew. Chem.* **2008**, *120*, 5872; *Angew. Chem. Int. Ed.* **2008**, *47*, 5788.

[5] For reviews, see: a) V. Farina, J. D. Brown, *Angew. Chem.* **2006**, *118*, 7488; *Angew. Chem. Int. Ed.* **2006**, *45*, 7330; b) M. Shibasaki, M. Kanai, *Eur. J. Org. Chem.* **2008**, 1839.

[6] a) H. Nemoto, Y. Kubota, Y. Yamamoto, *J. Org. Chem.* **1990**, *55*, 4515; b) H. Nemoto, X. Li, R. Ma, I. Suzuki, M. Shibuya, *Tetrahedron Lett.* **2003**, *44*, 73.

[7] Diene **7** is commercially available, or it can be prepared on a large scale from inexpensive crotonaldehyde ($ 40/500 mL) by treatment with TMSCl, Et_3N, and $ZnCl_2$ (0.9 mol%) in Et_2O (O. Gaonac'h, J. Maddaluno, J. Chauvin, L. Duhamel, *J. Org. Chem.* **1991**, *56*, 4045. Also see the Supporting Information). Dimethyl fumarate (**8**) is also readily available ($ 80/500 g).

[8] For a review of the catalytic asymmetric Diels–Alder reaction, see: E. J. Corey, *Angew. Chem.* **2002**, *114*, 1724; *Angew. Chem. Int. Ed.* **2002**, *41*, 1650.

[9] For examples of the use of ketone-derived siloxy dienes in asymmetric Diels–Alder reactions, see: a) A. N. Thadani, A. R. Stankovic, V. H. Rawal, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5846; b) D. E. Ward, J. Shen, *Org. Lett.* **2007**, *9*, 2843; c) H. Usuda, A. Kuramochi, M. Kanai, M. Shibasaki, *Org. Lett.* **2004**, *6*, 4387; d) D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 9626; e) D. Liu, E. Canales, E. J. Corey, *J. Am. Chem. Soc.* **2007**, *129*, 1498; f) Y. Sudo, D. Shirasaki, S. Harada, A. Nishida, *J. Am. Chem. Soc.* **2008**, *130*, 12588.

[10] For examples of nucleophile activation through transmetalation from silicon enolates to chiral catalytic metal enolates, see: a) M. Sodeoka, K. Ohrai, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 2648; b) J. Krüger, E. M. Carreira, *J. Am. Chem. Soc.* **1998**, *120*, 837; c) K. Oisaki, D. Zhao, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 7164.

[11] For chiral barium aryloxide catalysis, see: a) Y. M. A. Yamada, M. Shibasaki, *Tetrahedron Lett.* **1998**, *39*, 5561; b) S. Saito, S. Kobayashi, *J. Am. Chem. Soc.* **2006**, *128*, 8704; c) A. Yamaguchi, N. Aoyama, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2007**, *9*, 3387.

[12] Ligands **13** and **15** are commercially available from Junsei Chemical Co., Ltd. (shiyaku-t@junsei.co.jp).

[13] Rare-earth metal complexes of **13**–**15** are versatile asymmetric catalysts for cyanation and azidation. The catalysts activate the nucleophile (TMSCN or $TMSN_3$) through transmetalation. Therefore, an effective chiral environment is still constructed after partial silylation (or protonation). For reviews of the utility and mechanism of the catalysts derived from those chiral ligands, see: a) M. Shibasaki, M. Kanai, *Org. Biomol. Chem.* **2007**, *5*, 2027; b) M. Kanai, N. Kato, E. Ichikawa, M. Shibasaki, *Synlett* **2005**, 1491.

[14] a) V. Gutmann, *The Donor-Acceptor Approach to Molecular Interactions*; Plenum, New York, **1978**; b) S. E. Denmark, G. L. Beutner, T. Wynn, M. D. Eastgate, *J. Am. Chem. Soc.* **2005**, *127*, 3774; c) Y. Zhao, J. Rodrigo, A. H. Hoveyda, M. L. Snapper, *Nature* **2006**, *443*, 67. Also see reference [10c].

[15] 0.67 M is the saturating concentration of dimethyl fumarate in THF at room temperature. The reaction mixture was a suspension at −20 °C.

[16] T. Shioiri, K. Ninomiya, S. Yamada, *J. Am. Chem. Soc.* **1972**, *94*, 6203.

[17] Although the reason is unclear, the diacyl azide is more stable during aqueous workup or purification by silica gel column chromatography rather than under the reaction conditions of the acyl azide formation (in the presence of DPPA and Et_3N).

[18] The Curtius rearrangement of the hydroxy diacyl azide in the presence of Et_3N afforded a complex reaction mixture.

[19] Detailed characterization of the pyrolytic properties of the diacyl azide is currently ongoing.

[20] For reviews, see: a) T. A. Hase, J. K. Koskimies, *Aldrichimica Acta* **1982**, *15*, 35; b) T. A. Hase, *Umpoled synthons*, Wiley, USA, **1987**; c) H. Nemoto, *J. Synth. Org. Chem. Jpn.* **2004**, *62*, 347.

[21] D. Wiktelius W. Berts, A. J. Jensen, J. Gullbo, S. Saitton, I. Csöreghd, K. Luthman, *Tetrahedron* **2006**, *62*, 3600.

[22] The C=C bond of **3** is poorly reactive, and other oxidation methods using *m*CPBA, CH_3CO_3H, *m*CPBA, and a radical inhibitor at 80 °C (Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugiura, H. Kakoi, *Chem. Commun.* **1972**, 64), MMPP (P. Brougham, M. S. Cooper, D. A. Cummerson, H. Heaney, N. Thompson, *Synthesis* **1987**, 1015), and oxone did not afford the desired product.

[23] For a comprehensive review of substrate-directed chemical reactions, see: A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307.

[24] Preliminary attempts at epoxide-opening reactions of **18** using 3-pentanol were not successful.

[25] To eliminate this Mitsunobu inversion step, it is desirable for the oxidation of **3** to proceed from the β face. Such conditions were identified: dihydroxylation of **3** with $NaIO_4$ in the presence of catalytic $RuCl_3$ and H_2SO_4 (B. Plietker, M. Niggemann, *Org. Lett.* **2003**, *5*, 3353) afforded the corresponding *cis*-β-diol. However, the chemical yield was only approximately 50%.

[26] See the Supporting Information for the details.

[27] Isolation of **22** was not successful, possibly because of the lability of the phenol-derived trimethylsilyl ether. On the basis of our previous studies of cyanosilylation using a gadolinium/Glu-CAPO catalyst (GluCAPO = **13**; TMSCN as a stoichiometric

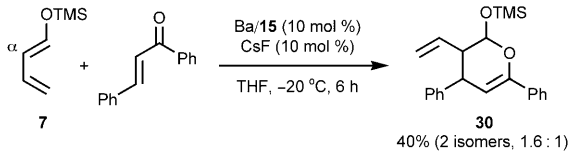
nucleophile: K. Yabu, S. Masumoto, S. Yamasaki, Y. Hamashima, M. Kanai, W. Du, D. P. Curran, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 9908), and the fact that the electron density of catechol significantly influenced the catalyst activity (Table 1, entry 8 versus 9), we assume that the phenolic oxygen atom is the silylation site (**22**).

[28] A HOMO-raising mechanism going through barium silicate formation cannot be completely excluded. In the presence of 10 mol% TBAT (tetrabutylammonium difluorotriphenylsilicate), however, the reaction between **7** and **8** produced only trace amounts of the cyclized products in THF at −20°C. Therefore, we assume that a barium dienolate generated through transmetalation is the actual active species in the barium-catalyzed asymmetric Diels–Alder-type reaction.

[29] Bienaymé and Longeau utilized **7** in a racemic Diels–Alder reaction via transmetalation to the corresponding aluminum enolate by the successive treatment of **7** with stoichiometric amounts of MeLi and Me_2AlCl. See: H. Bienaymé, A. Longeau, *Tetrahedron* **1997**, *53*, 9637.

[30] For related co-catalyst effects on the facilitation of the transmetalation step, see: a) R. Wada, T. Shibuguchi, S. Makino, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 7687; b) R. Wada, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 6536.

[31] At present, we cannot determine which pathway is operative. Therefore, we call the present reaction a Diels–Alder-type reaction. Preliminary application of the asymmetric barium catalyst to a reaction between **7** and chalcone produced compound **30** through conjugate addition of the barium dienolate at the α position and subsequent trapping of the enolate oxygen atom by the aldehyde. This result suggests that the reaction proceeds through a stepwise mechanism.



[32] M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem.* **1997**, *109*, 1290; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236. See also reference [13].

[33] For selected recent examples, see: a) V. B. Birman, S. J. Danishefsky, *J. Am. Chem. Soc.* **2002**, *124*, 2080; b) K. Tiefenbacher, V. B. Arion, J. Mulzer, *Angew. Chem.* **2007**, *119*, 2744; *Angew. Chem. Int. Ed.* **2007**, *46*, 2690; c) J. Yamaguchi, I. B. Seiple, I. S. Young, D. P. O'Malley, M. Maue, P. S. Baran, *Angew. Chem.* **2008**, *120*, 3634; *Angew. Chem. Int. Ed.* **2008**, *47*, 3578.

