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Article

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J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 24 Jul 2018

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Enantioselective Synthesis of Oseltamivir Phosphate (Tamiflu) via the Iron-Catalyzed Stereoselective Olefin Diazidation

Hongze Li,‡ Shou-Jie Shen,‡ Cheng-Liang Zhu, and Hao Xu*

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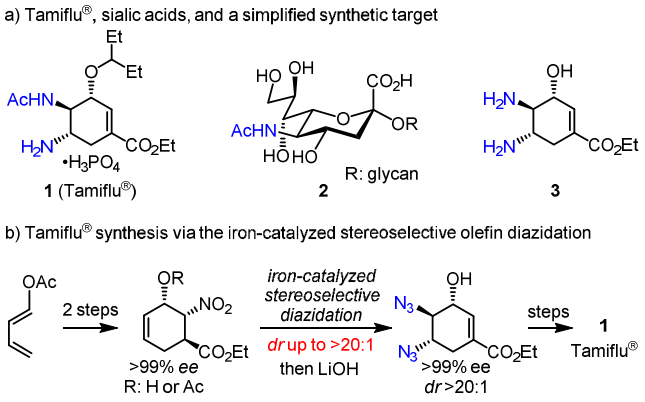
ABSTRACT: We herein report a gram-scale, enantioselective synthesis of Tamiflu, in which the key *trans*-diamino moiety has been efficiently installed via an iron-catalyzed stereoselective olefin diazidation. This significantly improved, iron-catalyzed method is uniquely effective for highly functionalized yet electronically deactivated substrates that have been previously problematic. Preliminary catalyst structure–reactivity–stereoselectivity relationship studies revealed that both the iron catalyst and the complex substrate cooperatively modulate the stereoselectivity for diazidation. Safety assessment using both differential scanning calorimetry (DSC) and drop weight test (DWT) has also demonstrated the feasibility of carrying out this iron-catalyzed olefin diazidation for large-scale Tamiflu synthesis.

INTRODUCTION

Oseltamivir phosphate **1** (Tamiflu), the pro-drug of a potent viral neuraminidase inhibitor, has been used as an effective medicine to treat and prevent influenza A and influenza B.[1a] Designed and developed by scientists at Gilead and Hoffman–La Roche, it effectively mimics the transition state of enzymatic hydrolysis of terminal sialic acids **2** from cell-surface glycoconjugates, a step postulated to be necessary for elution of newly formed viruses from infected cells (Scheme 1a). From a synthetic chemistry perspective, the structure of Tamiflu can be simplified to a functionalized *trans*, *trans*-diamino cyclic allylic alcohol **3**, in which the stereochemical alignment of three contiguous stereogenic centers is critical for Tamiflu's antiviral activity;[1b] however, *the stereoselective synthesis of* **3** *from a readily available starting material is not straightforward*. As a result, numerous efforts have been devoted to search for an expedient strategy to produce Tamiflu and a range of efficient Tamiflu syntheses have been reported (Scheme 2).[2,3]

Scheme 1. Enantioselective synthesis of Tamiflu via the iron-catalyzed stereoselective olefin diazidation



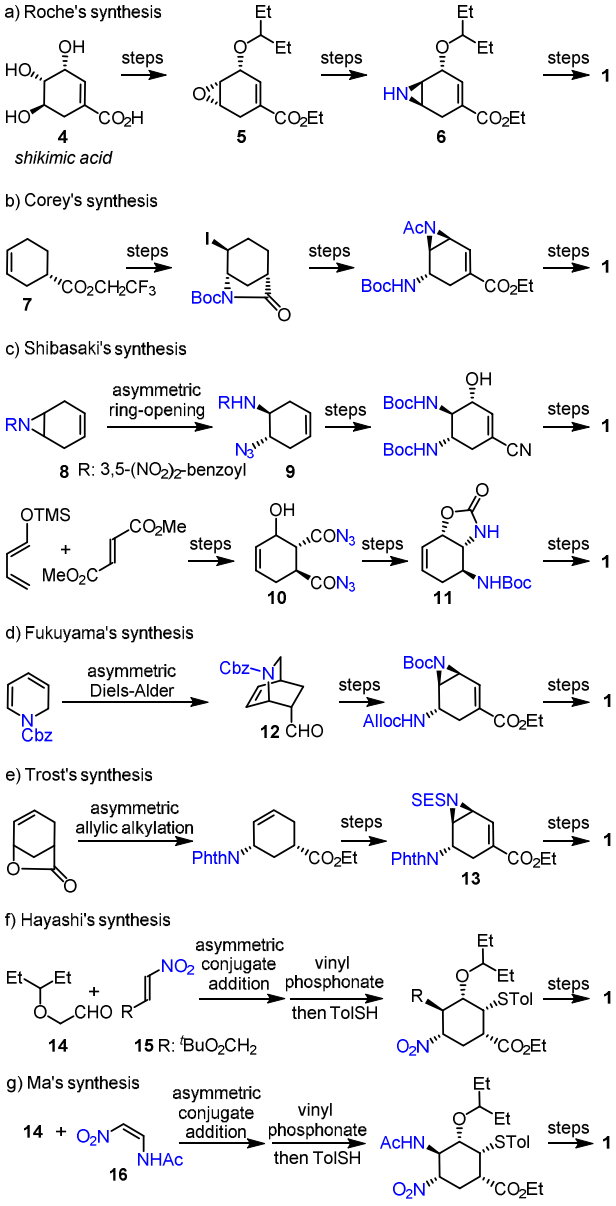
In Roche's Tamiflu production route, the starting material, shikimic acid **4**, is converted to a key homoallylic epoxide intermediate **5** (Scheme 2a).[2] The *trans*-diamino moiety in Tamiflu is installed through the stereoselective ring-opening of both epoxide **5** and a homoallylic *N*-H aziridine **6** using NaN_3 (Scheme 2a).[2] Azide-free procedures were later developed from **5** as well; however, additional epimerization steps are necessary.[2c-d] To search for an efficient synthetic strategy from readily available achiral starting materials, chemists have also extensively investigated the de novo enantioselective synthesis of Tamiflu.[3]

Among these efforts, Corey developed a chiral oxazaborolidinium-catalyzed asymmetric Diels–Alder method for the synthesis of a chiral cyclohexene **7**, which then underwent several transformations, including iodolactamization and *N*-acyl aziridine ring-opening, to furnish **1** (Scheme 2b).[3a] Shibasaki reported an enantioselective Tamiflu synthesis that involves an asymmetric ring-opening of a *meso N*-acyl aziridine **8** to provide the key *trans*-amino azide intermediate **9** (Scheme 2c).[3b] During development of several generations of synthetic strategies, he also capitalized on a barium-catalyzed asymmetric Diels–Alder reaction and a stereospecific Curtius rearrangement of a *trans*-diacyl azide intermediate **10** to afford the key oxazolidinone intermediate **11**, which was later converted to **1** (Scheme 2c).[3d]

In Fukuyama's Tamiflu synthesis,[3e] an organo-catalytic acrolein Diels–Alder reaction was applied to assemble a chiral 2-azabicyclo[2.2.2]octene building block **12** (Scheme 2d). Furthermore, a palladium-catalyzed asymmetric allylic alkylation and a rhodium-catalyzed dienoate aziridination were used to prepare a key intermediate **13** in Trost's synthesis of Tamiflu (Scheme 2e).[3f] Moreover, Hayashi developed an organo-catalytic conjugate addition of an α-alkyoxyaldehyde **14** with a nitro-olefin **15** in an efficient synthesis of **1** (Scheme 2f).[3g-h] Notably, Ma inde-

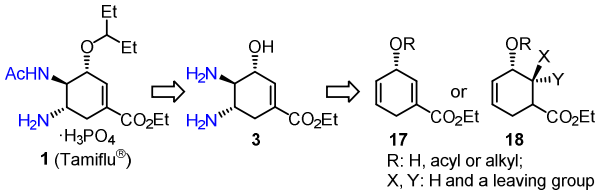
pendently reported the asymmetric conjugate addition of **14** with (*Z*)-2-nitroethenamide **16** in another expedient synthesis of Tamiflu (Scheme 2g).[3i]

Scheme 2. Selected examples of the previous Tamiflu syntheses



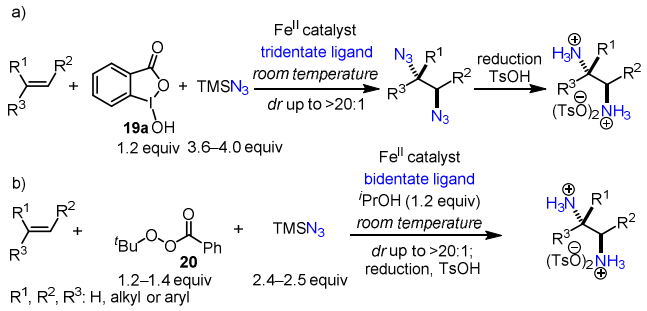
These existing Tamiflu syntheses have showcased the power of catalytic reactions in assembling stereochemically complex synthetic targets; however, a strategically unique synthetic approach has not been reported that can directly install the *trans*-diamino moiety within Tamiflu via stereoselective diamination or diazidation of a highly functionalized synthetic intermediate, such as **17** or **18** (Scheme 3). Implementation of this diazidation–diamination strategy will provide a mechanistically distinct approach for an efficient synthesis of Tamiflu in complement of the previous syntheses.

Scheme 3. Retrosynthetic analysis based upon the iron-catalyzed stereoselective olefin diazidation



In 2015, we reported an iron-catalyzed direct diazidation method for a broad range of olefins, in which an iron catalyst activates $TMSN_3$ in the presence of bench-stable benziodoxole **19a**[4] to achieve direct olefin diazidation (Scheme 4a).[5] This reaction occurs at room temperature and it is effective for a wide variety of olefins, including those that are incompatible with the previously reported diazidation methods.[6] Coupled with facile reduction, it readily provides an array of valuable vicinal primary diamines. Recently, we disclosed a second iron-catalyzed olefin diazidation method via ligand-promoted activation of bench-stable peroxyesters.[7] In this method, nearly a stoichiometric amount of commercially available *tert*-butyl perbenzoate **20** and $TMSN_3$ are sufficient for high-yielding diazidation of a wide variety of olefins and N-heterocycles (Scheme 4b).[7] These and other concurrent olefin diazidation methods[8] add useful tools in the repertoire of synthetic chemists.

Scheme 4. Iron-catalyzed direct olefin diazidation methods



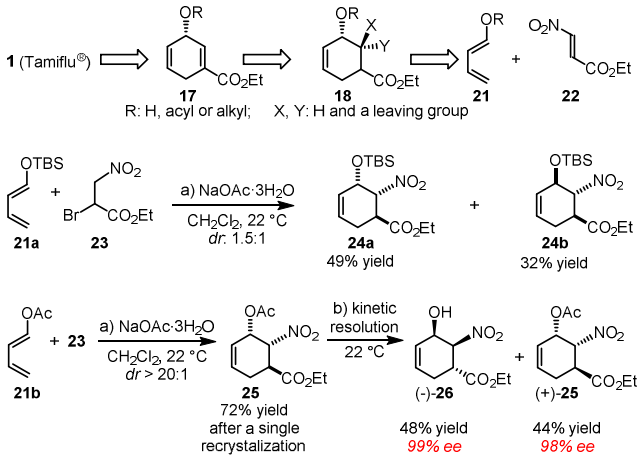
Our initial attempts to directly apply these two methods under the standard conditions to a range of designed late-stage intermediates for Tamiflu synthesis were not successful. Most of these complex substrates, including **18**, suffer from lack of reactivity, while functionalized 1,4-cyclohexadiene **17** readily undergoes aromatization.[9] Guided by mechanistic analysis, we have improved these iron-catalyzed methods such that they become effective with these highly functionalized substrates. Herein, we disclose these new discoveries that have enabled the iron-catalyzed stereoselective diazidation of these previously challenging substrates and thereby facilitated a gram-scale, enantioselective synthesis of Tamiflu in short steps (Scheme 1b).

RESULTS AND DISCUSSION

To explore the feasibility of achieving an expedient Tamiflu synthesis via the iron-catalyzed stereoselective

olefin diazidation, we initially chose a chiral 1,4-cyclohexadiene **17** as a possible substrate (Scheme 5). Since **17** readily underwent aromatization under the diazidation conditions,[9] we further targeted a functionalized chiral cyclic allylic alcohol **18** as an alternative substrate and expected that facile elimination under mild conditions would unveil the key enoate moiety within Tamiflu (Scheme 3).

Scheme 5. Enantioselective synthesis of highly functionalized cyclic allylic alcohols for the iron-catalyzed olefin diazidation



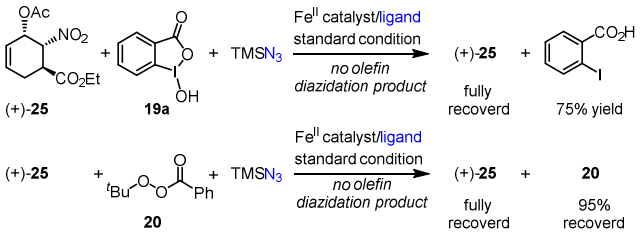
[a]NaOAc·3H_2O, CH_2Cl_2, 22 °C, 48 h. [b]Amano Lipase from *Pseudomonas fluorescens* (20,000 U/g, 50 wt. %), aq. Na_2HPO_4 buffer, 22 °C, 26 h; (+)-**25** (40% yield, >99% *ee*) after a single recrystallization.

The enantioselective synthesis of both 1,4-cyclohexadiene **17** and cyclic allylic alcohol **18** has not been reported; however, the pioneering Danishefsky's studies of a Diels–Alder reaction between a siloxy diene **21** and a nitroacrylate **22** have laid the foundation for the synthesis of **18** as racemate (Scheme 5).[10a] Since nitroacrylate **22** tends to decompose under the reaction condition, we speculated that a more efficient cycloaddition could be achieved when **22** was gradually generated in situ from its precursor, bromo-3-nitropropanoate **23** (Scheme 5). As a promising lead, we discovered that solid NaOAc·3H_2O effectively promotes the reaction between siloxy diene **21a** and **23** at room temperature, which readily affords the Diels–Alder products **24a** and **24b** in a high combined yield, albeit with a low *dr*. Inspired by this observation, we further discovered that acetoxy diene **21b** undergoes a highly *endo*-selective Diels–Alder reaction, delivering **25** as a single diastereomer. Notably, this reaction has been consistently scaled up to 30 gram-scale and **25** can be easily purified through recrystallization (Scheme 5).[9]

To search for an enantioselective variant of this transformation, we have explored a range of catalytic enantioselective strategies which prove less effective, presumably due to the high reactivity associated with nitroacrylate **22**. Therefore, as an alternative strategy, we envision that an efficient kinetic resolution of **25** may provide both of its enantiomers with high enantio-purity.

Although the chemo- and enzymatic kinetic resolution of cyclic allylic alcohols have been precedented,[11] the kinetic resolution of highly functionalized substrates with three contiguous stereogenic centers has not been reported. We thereby investigated an array of chemo- and enzymatic catalysts for the proposed kinetic resolution and discovered that Amano Lipase from *Pseudomonas fluorescens* is uniquely effective (Scheme 5): the highly enantio-enriched product (–)-**26** (>99% *ee*) was isolated in 48% yield and the starting material (+)-**25** was recovered in a good yield and excellent *ee* (44% yield, 98% *ee*). A single recrystallization affords (+)-**25** essentially in its enantio-pure form (40% yield, >99% *ee*).[9]

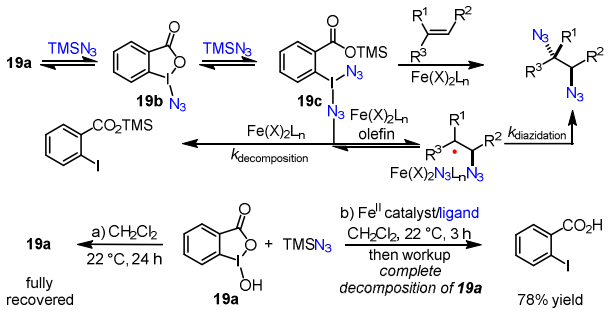
Scheme 6. Initial attempts for the direct diazidation of (+)-**25** using the standard iron-catalyzed diazidation procedures



To our surprise, neither of the aforementioned iron-catalyzed diazidation method was effective for the highly functionalized (+)-**25** when it was directly applied under the standard reaction conditions (Scheme 6). In the benziodoxole-mediated diazidation,[5] (+)-**25** was fully recovered while benziodoxole **19a** completely decomposed to *o*-iodobenzoic acid.[9] Notably, both (+)-**25** and *tert*-butyl perbenzoate **20** were largely recovered using the iron-catalyzed, peroxyester-based[8] diazidation method.[9]

In order to significantly improve these iron-catalyzed methods such that they can become effective with (+)-**25**, we carried out detailed mechanistic analysis of both iron-catalyzed olefin diazidation reactions.[5,7] The mechanistic studies[5] have uncovered that $TMSN_3$ may reversibly convert otherwise insoluble benziodoxole **19a** to azidoiodinane **19b**, and then to a transient iodine(III)–diazide species **19c**, with which an iron catalyst may be oxidized to a high-valent iron-azide species that promotes the stepwise olefin diazidation (Scheme 7). A variety of experiments suggest that *the iron–ligand complexes are involved in the second C–N_3 bond forming step which is rate-determining*.[5]

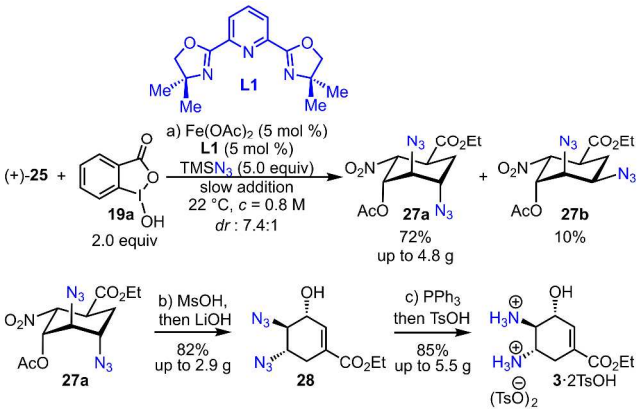
Scheme 7. Mechanistic analysis of the iron-catalyzed olefin diazidation using benziodoxole **19a**



Furthermore, we observed that, *in the absence of an olefin*, an iron catalyst completely decomposes benziodoxole **19a** together with $TMSN_3$ (Scheme 7), while **19a** is stable towards $TMSN_3$ without an iron catalyst (Scheme 7).[8] These results suggest that competing reaction pathways do exist and they presumably proceed through the iron-promoted non-productive decomposition of iodine(III)–diazide species **19c** (Scheme 7).[8] These competing pathways may become particularly detrimental for electronically deactivated substrates that are less reactive.

Based upon this analysis, we envision that the rate of olefin diazidation may have an order-dependence on both [iron catalyst] and [olefin] since the first C–N_3 bond forming step is reversible and the second C–N_3 bond forming step is rate-limiting (Scheme 7). Furthermore, the rate of iron-mediated non-productive decomposition of **19c** is likely dependent on both [**19c**] and [iron catalyst] (Scheme 7). Therefore, we suspect that an effective diazidation of (+)-**25** may be achieved if a high concentration of (+)-**25** and a low concentration of **19c** can be maintained at the same time through the reaction such that non-productive decomposition of **19c** can be largely suppressed. Built upon this mechanistic proposal, we have drastically modulated the previously reported method: to increase the concentration of (+)-**25** up to 0.8 M and to decrease the concentration of $TMSN_3$ through slow addition (up to 8 h, Scheme 8).

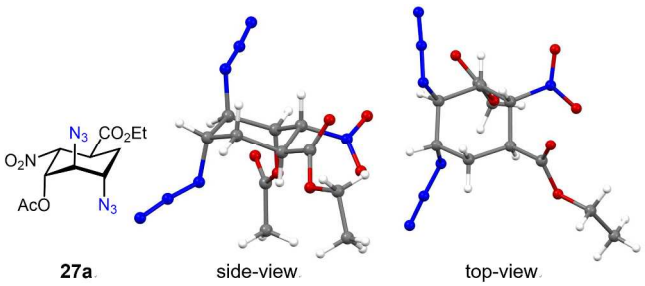
Scheme 8. Iron-catalyzed stereoselective diazidation of (+)-**25** for the expedient synthesis of **3**·2TsOH



[a]$Fe(OAc)_2$ (5 mol %), **L1** (5 mol %), **19a** (2 equiv), CH_2Cl_2/MeCN (10:1), 0.8 M, 22 °C, $TMSN_3$ (5 equiv) added gradually within 8 h and subsequently quenched with saturated $NaHCO_3$ solution. [b]MsOH, EtOH, 55 °C, 7 h, then LiOH·H_2O, EtOH, 0 °C, 0.5 h. [c]PPh_3, H_2O, THF, 22 °C, 8 h, then TsOH·H_2O, 1 h. Standard safety precautions about handling $TMSN_3$ should be taken; see SI for details.

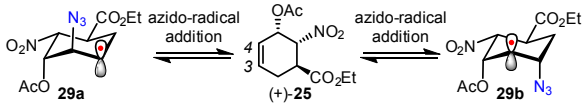
We discovered that the $Fe(OAc)_2$–**L1** catalyst (5 mol %) effectively promotes the stereoselective diazidation of (+)-**25** with a good combined yield and excellent *dr* (*dr*: 7.4:1). Notably, an array of control experiments revealed that deviation from the newly discovered condition leads to an incomplete reaction. The desired *trans*, *trans*-diazide **27a** can be readily separated from the *cis*, *trans*-diazide **27b** through either recrystallization or flash-column chromatography. Their structures were initially assigned with 2D–NMR experiments and later corroborated by X-ray crystallographic analysis of **27a** (Figure 1).[9] A straightforward hydrolysis–elimination procedure converts **27a** to *trans*, *trans*-diazido alcohol **28**, which can be easily converted to *trans*, *trans*-hydroxyl diaminium tosylates **3**·2TsOH via a standard reduction–protonation procedure (Scheme 8).

Figure 1. X-ray crystallographic analysis of diazide **27a**



Organic azides, especially those with lower molecular weights, may present potential safety concerns for their handling, with regard to their thermo- and mechanical impact stabilities.[12] In order to explore the feasibility of the iron-catalyzed olefin diazidation for Tamiflu production on a larger scale, it is imperative to carry out chemical hazard assessment of this olefin diazidation process. A reactive chemical hazard assessment refers the identification and possibly quantification of dangerous energy release scenarios for a chemical process of interest. Differential Scanning Calorimetry (DSC) is one of the most commonly applied thermal stability testing methods for organic compounds, while Drop Weight Test (DWT) has been routinely applied to detect the sensitivity of a chemical towards mechanical impact. In 2017, we reported a process safety assessment of the iron-catalyzed olefin diazidation using benziodoxole **19a**.[13] DSC analysis of the corresponding reagents, intermediates presented in sufficient concentrations, and a list of representative diazide products revealed that all of them are thermal stable at the reaction temperature.[13] Based upon these results, we carried out DSC analysis of **27a** and observed that it does not decompose occur until 189 °C, which allows for a convenient operating margin in carrying out the diazidation at room temperature. Most notably, the diazide **27a** is insensitive to mechanical impact during DWT studies. Encouraged by these results, this iron-catalyzed diazidation has been consistently scaled up to 5 gram-scale without compromising the yield and *dr* of the product (Scheme 8).[9]

Scheme 9. The proposed reversible azido-radical addition step during the diazidation of (+)-**25**

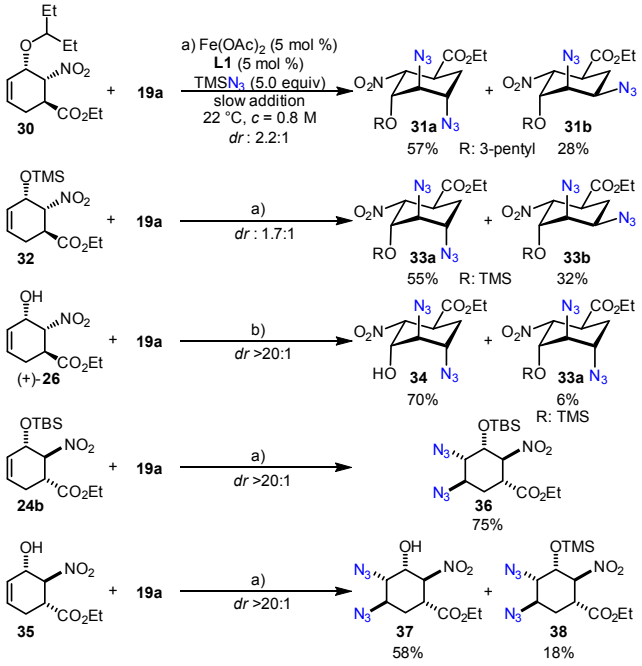


The observed promising stereoselectivity at both C3 (*dr*: 7.4:1) and C4 (*dr* >20:1) positions is mechanistically interesting. During the diazidation (Scheme 9), we envision that, based upon electronic effect, β-azido-C3 carboradi-

cal **29a**, a putative intermediate reversibly generated from (+)-**25**, is likely more reactive than β-azido-C_4 carboradical **29b** towards the rate-determining oxidative C–N_3 bond formation; therefore, we suspect that the *dr* at C_3 may be further improved through structural modulation of both iron catalysts and substrates.

Extensive explorations of a range of iron catalysts and ligands for the diazidation of (+)-**25** provided modest improvement over the *dr*: notably, the Fe(NTf_2)$_2$–ligand complexes induced an even lower *dr* at C_3 position (*dr*: 4.8:1).[9] We thereby investigated the possibility of achieving enhanced stereoselectivity via substrate control.

Scheme 10. Substrate structure–stereoselectivity relationship studies for the iron-catalyzed olefin diazidation

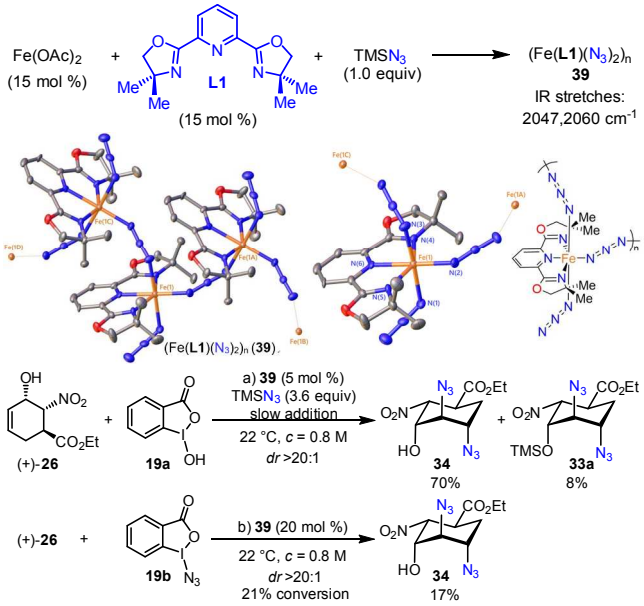


[a]Fe($OAc)_2$ (5 mol %), **L1** (5 mol %), **19a** (2 equiv), CH_2Cl_2/MeCN (10:1), 0.8 M, 22 °C, $TMSN_3$ (5 equiv) added gradually within 8 h. [b]Fe($OAc)_2$ (5 mol %), **L1** (5 mol %), **19a** (1.5 equiv), CH_2Cl_2/MeCN (10:1), 0.8 M, 22 °C, $TMSN_3$ (3.6 equiv) added gradually within 8 h. The reactions were subsequently quenched with saturated $NaHCO_3$ solution.

The diazidation of a 3-pentyl-substituted allylic ether **30** was first evaluated since it could lead to a more streamlined Tamiflu synthesis (Scheme 10). We observed that the Fe($OAc)_2$–**L1** catalyst promotes an efficient diazidation of **30**, albeit with a low *dr* at C_3 (*dr*: 2.2:1). Considering the β-branch effect that might be associated with **30**, we further explored the reaction with a TMS-protected allyl silyl ether **32**; however, a modest level of *dr* was again observed (*dr*: 1.7:1). To our surprise, the iron catalyst promotes a highly stereoselective diazidation with an unprotected allylic alcohol (+)-**26**, affording a *trans*, *trans*-diazido alcohol **34** and a small amount of its TMS-protected ether **33a** with excellent *dr* (*dr* >20:1 at both C_3 and C_4 positions in **33a** and **34**). It is worth noting that (+)-**26** is evidently more reactive than (+)-**25** and acid workup readily converts **33a** back to **34**. Since $TMSN_3$ is gradually released under the diazidation condition, **33a** is likely derived from **34** by the residue $TMSN_3$ and it is unlikely the diazidation product from **32**.

The excellent stereoselectivity achieved with (+)-**26** urged us to further evaluate **24b** and **35**, two *exo*-Diels–Alder products, for the diazidation (Scheme 10). Interestingly, both **24b** and **35** present excellent reactivity and stereoselectivity, affording either a *trans*, *cis*-diazido silyl ether **36** or an alcohol **37** as a single diastereomer (*dr* >20:1 at both C_3 and C_4 positions in **36** and **37**). Again, a small amount of TMS-protected allyl silyl ether **38** was also obtained (*dr* >20:1).

Scheme 11. Catalyst structure–reactivity relationship studies of the polymeric iron-azide complex (Fe(**L1**)($N_3)_2$)$_n$

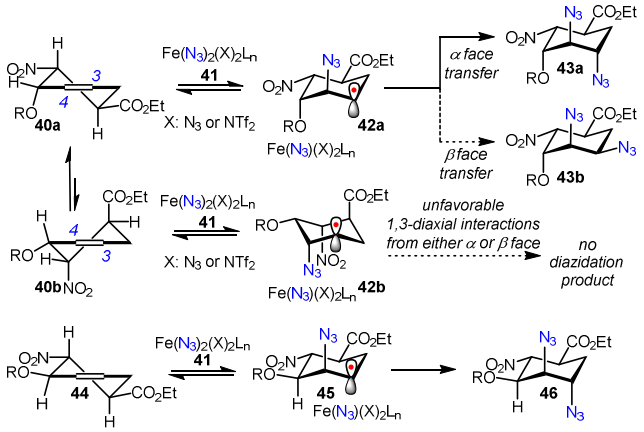


[a]**39** (5 mol %), **19a** (1.5 equiv), CH_2Cl_2/MeCN (10:1), 0.8 M, 22 °C, $TMSN_3$ (3.6 equiv) added gradually within 8 h. [b]**39** (20 mol %), **19b** (1.5 equiv), CH_2Cl_2/MeCN (10:1), 0.8 M, 22 °C.

These observations evidently suggest that both iron catalysts and substrates cooperatively influence the stereoselectivity of the diazidation. In order to propose a plausible stereochemical model, the possible structure of a catalytically active iron complex needs to be considered. Our mechanistic studies have revealed that the Fe($OAc)_2$–**L1** complex readily reacts with $TMSN_3$, furnishing an iron-azide complex **39** (Scheme 11).[14] IR analysis of **39** uncovered strong azido group absorptions (2047 and 2060 cm^{-1}) shifted to lower energy in comparison to free azide, characteristic of iron-azide complexes.[15] Subsequent X-ray crystallographic analysis of **39** revealed a unique iron coordination polymer with all iron centers equivalent and generated by symmetry–(Fe(**L1**)($N_3)_2$)$_n$ (Scheme 11).[14] In additional to the rigid tridentate ligand **L1**, three remaining coordination sites of the iron center are occupied by three azides with one being terminal and the other two azides *cis* to each other bridging adjacent iron centers to form the coordination polymer.[14] *Importantly, this polymeric iron catalyst* ***39*** *is catalytic active and it catalyzes the diazidation of* (+)-**26** *with essentially the same yield*

and dr (Scheme 11). *Surprisingly,* ***39*** *can also promote diazidation of (+)-****26*** *with* ***19b*** *in the absence of* $TMSN_3$*, albeit with a low yield* (Scheme 11, 17% yield, *dr* >20:1). Therefore, it is likely that iron-azide complex **39** gets oxidized to a high-valent iron-azide species that facilitates the olefin diazidation and that the terminal iron–azide bond in **39** may be involved in the rate-limiting azido-group transfer.

Scheme 12. Proposed stereochemical model for the iron-catalyzed olefin diazidation of cyclic allylic alcohols



Based upon these catalyst structure–reactivity relationship studies, a plausible stereochemical model that fits the observations is presented in Scheme 12. We envision that the *endo*-Diels-Alder product **40** can adopt either of the two conformations (**40a** and **40b**) that may be in rapid equilibrium. Since the azido-radical addition to **40** is reversible and it likely occurs at C_4 position from the axial trajectory in order to avoid a twist-boat conformation (Scheme 9),[16] β-azido carboradical species **42a** and **42b** may be two reactive intermediates in equilibrium. In the subsequent rate-determining C–N_3 bond forming step, the bulky iron(III) azide species derived from **39** may oxidize **42a** or **42b** through direct azido-ligand transfer from the iron center.[5,7] Considering the significant unfavorable 1,3-diaxial interactions that may build up in **42b** (between the iron-azide complex and the CO_2Et or NO_2 group) along the reaction trajectory, it is less likely that this oxidation occurs with **42b** from either the α or β face.

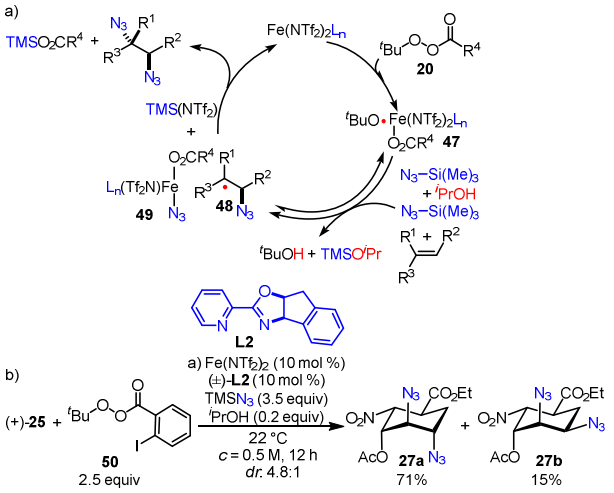
However, the azido-group transfer may occur with **42a** in which these unfavorable interactions no long exist. If R is a less-sterically demanding group, such as hydrogen or acetyl group, the iron complex may readily deliver the azido-group to **42a** from the α face.[16] The axial hydroxyl group may also direct the iron catalyst to achieve an enhanced α-selectivity. Alternatively, when R becomes more sterically demanding, the iron complex may thereby be forced to deliver the azido-group from the β face. Therefore, excellent stereoselectivity can be achieved with an unprotected allylic alcohol (+)-**26** using a bulky polymeric iron-azide catalyst (Fe(**L1**)$(N_3)_2)_n$ **39**.

This proposed model can also rationalize the excellent stereoselectivity observed with *exo*-Diels–Alder product **44** (Scheme 12). Locked in a conformation where the OR, CO_2Et, and NO_2 groups all reside in equatorial positions, the polymeric iron(III)-azide intermediate should be able to approach the β-azido carboradical species **45** from its α face regardless of the R substituent.

With the success of this improved diazidation method using benziodoxole **19a**, we further explored the possibility of developing a new peroxyester-based diazidation approach for the synthesis of *trans*, *trans*-diazido alcohol **28**. Under the standard peroxyester-based diazidation conditions, both (+)-**25** and *tert*-butyl perbenzoate **20** were largely recovered (Scheme 6), which suggests that the energy barrier of rate-determining step may be too high for this electronically deactivated substrate.

Based upon our mechanistic studies,[7] we envision that $Fe(NTf_2)_2$–ligand complex may reductively cleave the O–O bond in a peroxyester **20** to generate a *tert*-butoxyl radical that is associated with a high-valent iron complex **47** (Scheme 13a). ^{i}PrOH presumably facilitates gradual release of HN_3 from $TMSN_3$, and *tert*-butoxyl radical may thereby be rapidly sequestered by HN_3 to liberate azido radical. The azido radical may reversibly add to an olefin to afford carbo-radical species **48** and $TMSN_3$ may also convert the iron(III) species **47** to a high-valent iron-azide species **49**, which presumably mediates the rate-determining azido-group transfer to the carbo-radical species **48** and afford the diazidation product.[7]

Scheme 13. a) Mechanistic working hypothesis of the $Fe(NTf_2)_2$-catalyzed olefin diazidation using peroxyesters and b) iron-catalyzed peroxyester activation for diazidation of (+)-**25**

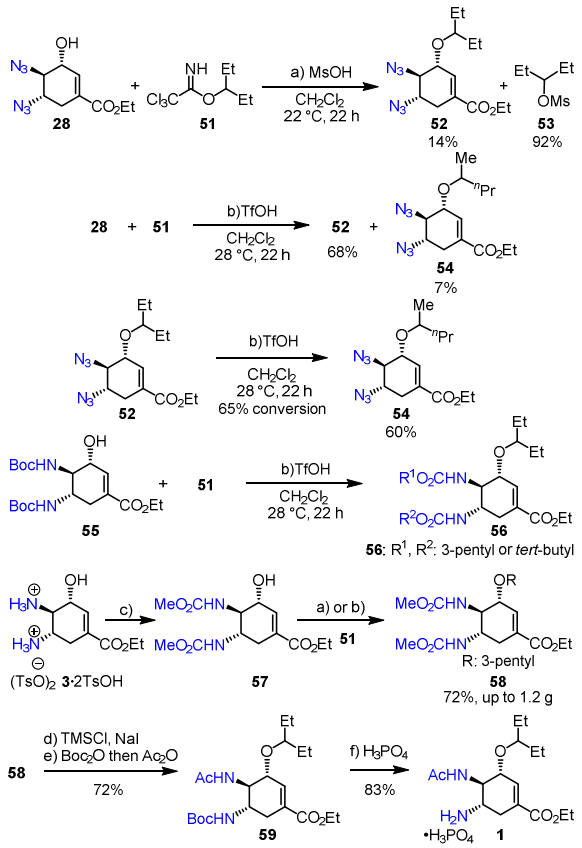


[a]$Fe(NTf_2)_2$ (10 mol %), (±)-**L2** (10 mol %), **50** (2.5 equiv), ^{i}PrOH (0.2 equiv), $TMSN_3$ (3.5 equiv), CH_2Cl_2/MeCN (9:1), 0.5 M, 22 °C, 12 h. The reactions were subsequently quenched with saturated NaHCO3 solution.

Since the O–O bond cleavage is unlikely rate-determining, we suspect that a more electron-deficient iron(III) species **49** may accelerate the rate-determining C–N_3 bond forming step. Therefore, we evaluated peroxyester **50** with a more-electron-withdrawing acyl group and observed that the $Fe(NTf_2)_2$–racemic **L2** catalyst promotes an efficient diazidation with (+)-**25**, affording **27** in an excellent yield albeit moderate *dr* (Scheme 13b). It is worth noting that no significant match/mismatch effect was observed using enantio-pure **L2** ligand,[9] and that a

high concentration of $TMSN_3$ is necessary for the reactivity. Further evaluation of the unprotected allylic alcohol (+)-**26** under the newly discovered condition furnished decreased stereoselectivity, presumably due to the readily conversion of (+)-**26** to its TMS-protected ether **32** in situ.

Scheme 14. Expedient Tamiflu synthesis from **3**·2TsOH



[a]MsOH, **51**, CH_2Cl_2, 22 °C, 22 h. [b]TfOH (0.4 equiv), **51**, 5 Å MS, CH_2Cl_2, 28 °C, 22 h. [c]Methyl chloroformate, $NaHCO_3$, H_2O, 22 °C, 2 h. [d]TMSCl, NaI, CH_3CN, 40 °C, 12 h. [e]Boc_2O, CH_2Cl_2, 0 °C, 1.5 h then Ac_2O, Et_3N, DMAP, 22 °C, 2 h. [f]H_3PO_4, EtOH, 0.5 M, 78 °C, 12 h.

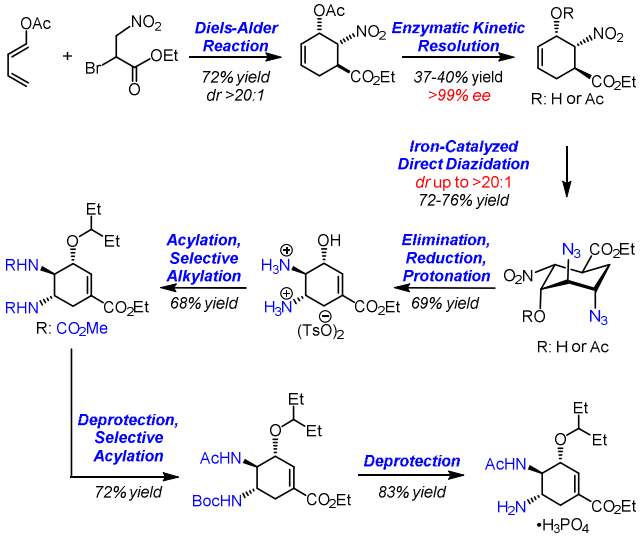
The gram-scale preparation of *trans*, *trans*-diazido alcohol **28** in short steps and high enantio-purity has allowed us to explore the selective incorporation of both 3-pentyl and acetyl groups for a short Tamiflu synthesis (Scheme 14). Although a list of standard 3-pentyl-derived electrophiles are unreactive towards this diazido cyclic allylic alcohol **28**, alkylation with trichloroacetimidate **51** proves uniquely effective under acidic conditions.[17]

We observed that MsOH promotes the difficult alkylation of **28** to afford **52**, albeit in a low yield (Scheme 14); however, 3-pentylmesylate **53**, generated in situ, is an ineffective electrophile towards **28**. We subsequently discovered that a catalytic amount of TfOH promotes the alkylation of diazido allylic alcohol **28**; however, a small amount of regio-isomeric 2-pentyl-alkylation product **54** was formed as an inseparable mixture with **52**.[9] We suspected that **54** may be generated from **52** via TfOH-catalyzed rearrangement, which was confirmed by a subsequent experiment (Scheme 14).

Given the pitfalls of alkylation with diazido alcohol **28**, we further evaluated bis-carbamates that are more nucleophilic. Straightforward reduction of **28** and *N*-Boc protection affords **55**, which demonstrates excellent reactivity in the acid-catalyzed alkylation with trichloroacetimidate **51**; however, *N*-Boc groups surprisingly participate in the alkylation as well (Scheme 14). Fortunately, bis-methyl carbamate **57** can be engaged in this alkylation and it was converted to **58** in an excellent yield (Scheme 14). White crystalline solid **58** can be further converted to **59**, the penultimate synthetic target, via a gram-scale procedure that involves TMSCl–NaI-mediated carbamate deprotection[18] and selective *N*-acylation[19] of both Boc and Ac groups. Subsequently, *N*-Boc deprotection of **59** using H_3PO_4 in hot EtOH readily affords Tamiflu **1** (Scheme 14).

CONCLUSIONS

Scheme 15. Summary of the enantioselective synthesis of Tamiflu via the iron-catalyzed stereoselective olefin diazidation



In conclusion, we have reported a gram-scale, enantioselective Tamiflu synthesis, in which the key *trans*-diamino moiety within Tamiflu has been efficiently installed via an iron-catalyzed stereoselective olefin diazidation (Scheme 15). This improved, iron-catalyzed method is effective for highly functionalized yet electronically deactivated substrates that have been otherwise problematic. Preliminary catalyst structure–reactivity–stereoselectivity relationship studies revealed that both the iron catalyst and the complex substrate cooperatively modulate the stereoselectivity for diazidation. Most notably, an oligomeric iron-azide catalyst proves unique effective for the stereoselective diazidation. Process safety assessment using both differential scanning calorimetry (DSC) and drop weight test (DWT) has also demonstrated the feasibility of carrying out this iron-catalyzed olefin diazidation for large-scale Tamiflu synthesis.

ASSOCIATED CONTENT

Supporting Information

Experimental procedure, characterization data for all new compounds, selected NMR spectra and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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Funding Sources

This research was supported by the National Institutes of Health (GM110382).

Notes

The subject matter described in this article is included in patent applications filed by Georgia State University.

ACKNOWLEDGMENT

We thank Luca Arosio, Dr. Roberto Villa, and Professor Marino Nebuloni for the DSC and DWT safety assessment of compound **27a**. We thank Peijing Jia and Naixin Qian for their assistance in lipase-catalyzed kinetic resolution of **25**. P. J. and N. Q. were supported by a Li-Yun Summer Undergraduate Research Scholarship.

REFERENCES

(1) a) Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, W. G.; Stevens, R. C. "Influenza Neuraminidase Inhibitors Possessing a Novel Hydrophobic Interaction in the Enzyme Active Site: Design, Synthesis, and Structural Analysis of Carbocyclic Sialic Acid Analogues with Potent Anti-Influenza Activity." *J. Am. Chem. Soc.* **1997**, *119*, 681; b) Hajzer, V.; Fisera, R.; Latika, A.; Durmis, J.; Kollar, J.; Frecer, V.; Tucekova, Z.; Miertus, S.; Kostolansky, F.; Vareckova, E.; Sebesta, R. "Stereoisomers of Oseltamivir - Synthesis, in silico Prediction and Biological Evaluation." *Org. Biomol. Chem.* **2017**, *15*, 1828.

(2) For selected references of Tamiflu synthesis from shikimic acid, see: (a) Rohloff, J. C.; Kent, K. M.; Postich, M. J.; Becker, M. W.; Chapman, H. H.; Kelly, D. E.; Lew, W.; Louie, M. S.; McGee, L. R.; Prisbe, E. J.; Schultze, L. M.; Yu, R. H.; Zhang, L. "Practical Total Synthesis of the Anti-Influenza Drug GS-4104." *J. Org. Chem.* **1998**, *63*, 4545; (b) Federspiel, M.; Fischer, R.; Hennig, M.; Mair, H.-J.; Oberhauser, T.; Rimmler, G.; Albiez, T.; Bruhin, J.; Estermann, H.; Gandert, C.; Göckel, V.; Götzö, S.; Hoffmann, U.; Huber, G.; Janatsch, G.; Lauper, S.; Röckel-Stäbler, O.; Trussardi, R.; Zwahlen, A. G. "Industrial Synthesis of the Key Precursor in the Synthesis of the Anti-Influenza Drug Oseltamivir Phosphate (Ro 64-0796/002, GS-4104-02): Ethyl (3*R*,4*S*,5*S*)-4,5-epoxy-3-(1-ethyl-propoxy)-cyclohex-1-ene-1-carboxylate." *Org. Process Res. Dev.* **1999**, *3*, 266; (c) Karpf, M.; Trussardi, R. "New, Azide-Free Transformation of Epoxides into 1,2-Diamino Compounds: Synthesis of the Anti-Influenza Neuraminidase Inhibitor Oseltamivir Phosphate (Tamiflu)." *J. Org. Chem.* **2001**, *66*, 2044; (d) Harrington, P. J.; Brown, J. D.; Foderaro, T.; Hughes, R. C. "Research and Development of a Second-Generation Process for Oseltamivir Phosphate, Prodrug for a Neuraminidase Inhibitor." *Org. Process Res. Dev.* **2004**, *8*, 86; (e) Karpf, M.; Trussardi, R. "Efficient Access to Oseltamivir Phosphate (Tamiflu) via the *O*-Trimesylate of Shikimic Acid Ethyl Ester." *Angew. Chem., Int. Ed.* **2009**, *48*, 5760.

(3) For selected references of Tamiflu synthesis from academic labs, see: (a) Yeung, Y. Y.; Hong, S.; Corey, E. J. "A Short Enantioselective Pathway for the Synthesis of the Anti-Influenza Neuramidase Inhibitor Oseltamivir from 1,3-Butadiene and Acrylic Acid." *J. Am. Chem. Soc.* **2006**, *128*, 6310; (b) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. "De Novo Synthesis of Tamiflu via a Catalytic Asymmetric Ring-Opening of *meso*-Aziridines with $TMSN_3$." *J. Am. Chem. Soc.* **2006**, *128*, 6312; (c) Mita, T.; Fukuda, N.; Roca, F. X.; Kanai, M.; Shibasaki, M. "Second Generation Catalytic Asymmetric Synthesis of Tamiflu: Allylic Substitution Route." *Org. Lett.* **2007**, *9*, 259; (d) Yamatsugu, K.; Yin, L.; Kamijo, S.; Kimura, Y.; Kanai, M.; Shibasaki, M. "A Synthesis of Tamiflu by Using a Barium-Catalyzed Asymmetric Diels–Alder-Type Reaction." *Angew. Chem., Int. Ed.* **2009**, *48*, 1070; (e) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. "A Practical Synthesis of (–)-Oseltamivir." *Angew. Chem., Int. Ed.* **2007**, *46*, 5734; (f) Trost, B. M.; Zhang, T. "A Concise Synthesis of (–)-Oseltamivir." *Angew. Chem., Int. Ed.* **2008**, *47*, 3759; (g) Ishikawa, H.; Suzuki, T.; Hayashi, Y. "High-Yielding Synthesis of the Anti-Influenza Neuramidase Inhibitor (–)-Oseltamivir by Three "One-Pot" Operations." *Angew. Chem., Int. Ed.* **2009**, *48*, 1304; (h) Hayashi, Y.; Ogasawara, S. "Time Economical Total Synthesis of (–)-Oseltamivir." *Org. Lett.* **2016**, *18*, 3426; (i) Zhu, S.; Yu, S.; Wang, Y.; Ma, D. "Organocatalytic Michael Addition of Aldehydes to Protected 2-Amino-1-Nitroethenes: The Practical Syntheses of Oseltamivir (Tamiflu) and Substituted 3-Aminopyrrolidines." *Angew. Chem., Int. Ed.* **2010**, *49*, 4656; (j) Shie, J.-J.; Fang, J.-M.; Wang, S.-Y.; Tsai, K.-C.; Cheng, Y.-S. E.; Yang, A.-S.; Hsiao, S.-C.; Su, C.-Y.; Wong, C.-H. "Synthesis of Tamiflu and its Phosphonate Congeners Possessing Potent Anti-Influenza Activity." *J. Am. Chem. Soc.* **2007**, *129*, 11892; (k) Sullivan, B.; Carrera, I.; Drouin, M.; Hudlicky, T. "Symmetry-Based Design for the Chemoenzymatic Synthesis of Oseltamivir (Tamiflu) from Ethyl Benzoate." *Angew. Chem., Int. Ed.* **2009**, *48*, 4229; (l) Bromfield, K. M.; Graden, H.; Hagberg, D. P.; Olsson, T.; Kann, N. "An Iron Carbonyl Approach to the Influenza Neuraminidase Inhibitor Oseltamivir." *Chem Commun* **2007**, 3183; (m) Matveenko, M.; Willis, A. C.; Banwell, M. G. "A Chemoenzymatic Synthesis of the anti-Influenza Agent Tamiflu." *Tetrahedron Lett.* **2008**, *49*, 7018; (n) Mandai, T.; Oshitari, T. "Efficient Asymmetric Synthesis of Oseltamivir from *d*-Mannitol." *Synlett* **2009**, *2009*, 783; (o) Osato, H.; Jones, I. L.; Chen, A.; Chai, C. L. L. "Efficient Formal Synthesis of Oseltamivir Phosphate (Tamiflu) with Inexpensive *d*-Ribose as the Starting Material." *Org. Lett.* **2010**, *12*, 60; (p) Zutter, U.; Iding, H.; Spurr, P.; Wirz, B. "New, Efficient Synthesis of Oseltamivir Phosphate (Tamiflu) via Enzymatic Desymmetrization of a *meso*-1,3-Cyclohexanedicarboxylic Acid Diester." *J. Org. Chem.* **2008**, *73*, 4895. See also: (q) Cong, X.; Yao, Z.-J. "Ring-Closing Metathesis-Based Synthesis of (3*R*,4*R*,5*S*)-4-Acetylamino-5-amino-3-hydroxy-cyclohex-1-ene-carboxylic Acid Ethyl Ester: A Functionalized Cycloalkene Skeleton of GS4104." *J. Org. Chem.* **2006**, *71*, 5365.

(4) Zhdankin, V. V.; Krasutsky, A. P.; Kuehl, C. J.; Simonsen, A. J.; Woodward, J. K.; Mismash, B.; Bolz, J. T. "Preparation, X-ray Crystal Structure, and Chemistry of Stable Azidoiodinanes Derivatives of Benziodoxole." *J. Am. Chem. Soc.* **1996**, *118*, 5192.

(5) Yuan, Y.-A.; Lu, D.-F.; Chen, Y.-R.; Xu, H. "Iron-Catalyzed Direct Diazidation for a Broad Range of Olefins." *Angew. Chem., Int. Ed.* **2016**, *55*, 534.

(6) For selected examples of diazidation that are effective for limited types of olefins reported prior to 2015, see: (a) Minisci, F.; Galli, R. "Influence of the Electrophilic Character on the Reactivity of Free Radicals in Solution Reactivity of Alkoxy, Hydroxy, Alkyl and Azido Radicals in Presence of Olefins." *Tetrahedron Lett.* **1962**, *3*, 533; (b) Fristad, W. E.; Brandvold, T. A.; Peterson, J. R.; Thompson, S. R. "Conversion of Alkenes to 1,2-Diazides and 1,2-Diamines." *J. Org. Chem.* **1985**, *50*, 3647; (c) Moriarty, R. M.; Khosrowshahi, J. S. A Versatile Synthesis of Vicinal Diazides Using Hypervalent Iodine. *Tetrahedron Lett.* **1986**, *27*, 2809; (d) Arimoto, M.; Yamaguchi, H.; Fujita, E.; Nagao, Y.; Ochiai, M. Diazidation of Allylsilanes with a Combination of Iodosylbenzene and Trimethylsilyl Azide, and Synthesis of Allyl Azides. *Chem. Pharm. Bull.* **1989**, *37*, 3221; (e) Magnus, P.; Lacour, J. New Trialkylsilyl Enol Ether Chemistry. Direct β-Azido Functionalization of Triisopropylsilyl Enol Ethers. *J. Am. Chem. Soc.* **1992**, *114*, 767; (f) Chung, R.; Yu, E.; Incarvito, C. D.; Austin, D. J. Hypervalent Iodine-Mediated Vicinal *Syn* Diazidation: Application to the Total Synthesis of (±)-Dibromophakellstatin. *Org. Lett.* **2004**, *6*, 3881.

(7) Shen, S.-J.; Zhu, C.-L.; Lu, D.-F.; Xu, H. "Iron-Catalyzed Direct Olefin Diazidation via Peroxyester Activation Promoted by Nitrogen-Based Ligands." *ACS Catal.* **2018**, *8*, 4473.

(8) For selected concurrent olefin diazidation methods, see: a) Fu, N.; Sauer, G. S.; Saha, A.; Loo, A.; Lin, S. Metal-Catalyzed Electrochemical Diazidation of Alkenes. *Science* **2017**, *357*, 575; b) Peng, H.; Yuan, Z.; Chen, P.; Liu, G. Palladium-Catalyzed Intermolecular Oxidative Diazidation of Alkenes. *Chin. J. Chem.* **2017**, *35*, 876; c) Zhou, H.; Jian, W.; Qian, B.; Ye, C.; Li, D.; Zhou, J.; Bao, H. Copper-Catalyzed Ligand-Free Diazidation of Olefins with $TMSN_3$ in CH_3CN or in H_2O. *Org. Lett.* **2017**, *19*, 6120. For a recent review for olefin azidation, see: d) Wu, K.; Liang, Y.; Jiao, N. Azidation in the Difunctionalization of Olefins. *Molecules* **2016**, *21*, 352; e) Sauer, G. S.; Lin, S. "An Electrocatalytic Approach to the Radical Difunctionalization of Alkenes." *ACS Catal.* **2018**, *8*, 5175.

(9) For experimental details, see Supporting Information.

(10) (a) Danishefsky, S.; Prisbylla, M. P.; Hiner, S. "The Use of *trans*-Methyl-β-nitroacrylate in Diels–Alder Reactions." *J. Am. Chem. Soc.* **1978**, *100*, 2918; see also: (b) J. Stoodley, R.; Yuen, W.-H. "Enhancement of *endo* Selectivity in Diels–Alder Reactions of Methyl (*E*)-3-nitroacrylate with (*E*)-1-Oxybuta-1,3-dienes." *Chem. Commun.* **1997**, 1371.

(11) For selected example of asymmetric synthesis of chiral cyclic allylic alcohols via kinetic resolution methods, see: (a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. "Kinetic Resolution of Racemic Allylic Alcohols by Enantioselective Epoxidation. A Route to Substances of Absolute Enantiomeric Purity?" *J. Am. Chem. Soc.* **1981**, *103*, 6237; (b) Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R.; Takaya, H. "Kinetic Resolution of Racemic Allylic Alcohols by BINAP-Ruthenium(II) Catalyzed Hydrogenation." *J. Org. Chem.* **1988**, *53*, 708; (c) Lüssem, B. J.; Gais, H.-J. "Palladium-Catalyzed Deracemization of Allylic Carbonates in Water with Formation of Allylic Alcohols: Hydrogen Carbonate Ion as Nucleophile in the Palladium-Catalyzed Allylic Substitution and Kinetic Resolution." *J. Am. Chem. Soc.* **2003**, *125*, 6066; (d) Lihammar, R.; Millet, R.; Bäckvall, J.-E. "Enzyme- and Ruthenium-Catalyzed Dynamic Kinetic Resolution of Functionalized Cyclic Allylic Alcohols." *J. Org. Chem.* **2013**, *78*, 12114. For an enzymatic kinetic resolution to obtain enantio-enriched acyclic allylic alcohols, see: (e) Burgess, K.; Jennings, L. D. "Enantioselective Esterifications of Unsaturated Alcohols Mediated by a Lipase Prepared from *Pseudomonas sp*." *J. Am. Chem. Soc.* **1991**, *113*, 6129.

(12) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. "Organic Azides: An Exploding Diversity of a Unique Class of Compounds." *Angew. Chem., Int. Ed.* **2005**, *44*, 5188.

(13) Zhu, H.-T.; Arosio, L.; Villa, R.; Nebuloni, M.; Xu, H. "Process Safety Assessment of the Iron-Catalyzed Direct Olefin Diazidation for the Expedient Synthesis of Vicinal Primary Diamines." *Org. Process Res. Dev.* **2017**, *21*, 2068.

(14) Zhu, C.-L.; Wang, C.; Qin, Q.-X.; Yruegas, S.; Martin, C. D.; Xu, H. "Iron(II)-Catalyzed Azidotrifluoromethylation of Olefins and N-Heterocycles for Expedient Vicinal Trifluoromethyl Amine Synthesis." *ACS Catal.* **2018**, *8*, 5032.

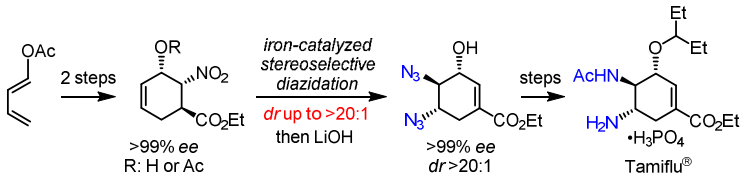
(15) For a selected reference of characterized monomeric iron-azide complexes and their IR measurements, see: Grove, L. E.; Hallman, J. K.; Emerson, J. P.; Halfen, J. A.; Brunold, T. C. "Synthesis, X-Ray Crystallographic Characterization, and Electronic Structure Studies of a Di-Azide Iron(III) Complex: Implications for the Azide Adducts of Iron(III) Superoxide Dismutase." *Inorg. Chem.* **2008**, *47*, 5762.

(16) For selected references of torsional effects in addition reactions to cyclic olefins and allylic alcohol derivatives, see (a) Rondan, N. G.; Paddon-Row, M. N.; Caramella, P.; Houk, K. N. "Nonplanar Alkenes and Carbonyls: a Molecular Distortion Which Parallels Addition Stereoselectivity." *J. Am. Chem. Soc.* **1981**, *103*, 2436; (b) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. "Staggered Models for Asymmetric Induction: Attack Trajectories and Conformations of Allylic bonds from ab initio Transition Structures of Addition Reactions." *J. Am. Chem. Soc.* **1982**, *104*, 7162.

(17) For selected examples of using trichloroacetimidates in organic synthesis, see: a) Overman, L. E. "A General Method for the Synthesis of Amines by the Rearrangement of Allylic Trichloroacetimidates. 1,3 Transposition of Alcohol and Amine Functions." *J. Am. Chem. Soc.* **1976**, *98*, 2901; b) Schmidt, R. R.; Josef, M. "Facile Synthesis of α- and β-O-Glycosyl Imidates; Preparation of Glycosides and Disaccharides." *Angew. Chem., Int. Ed.* **1980**, *19*, 731; c) Zhang, Q.; Stockdale, D. P.; Mixdorf, J. C.; Topczewski, J. J.; Nguyen, H. M. "Iridium-Catalyzed Enantioselective Fluorination of Racemic, Secondary Allylic Trichloroacetimidates." *J. Am. Chem. Soc.* **2015**, *137*, 11912.

(18) Jung, M. E.; Lyster, M. A. "Conversion of Alkyl Carbamates into Amines via Treatment with Trimethylsilyl Iodide." *J. Chem. Soc., Chem. Commun.* **1978**, 315.

(19) For a similar selective acylation procedure for semi-synthesis of radio-labeled Tamiflu, see: Konno, F.; Arai, T.; Zhang, M.-R.; Hatori, A.; Yanamoto, K.; Ogawa, M.; Ito, G.; Odawara, C.; Yamasaki, T.; Kato, K.; Suzuki, K. "Radiosyntheses of two Positron Emission Tomography probes: [^{11}C]Oseltamivir and its active metabolite [^{11}C]Ro 64-0802." *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1260.


OAc
2 steps
OR
NO2
CO2Et
>99% ee
R: H or Ac
iron-catalyzed
stereoselective
diazidation
dr up to >20:1
then LiOH
OH
N3
N3
CO2Et
>99% ee
dr >20:1
steps
Et
O
Et
AcHN
H2N
CO2Et
•H3PO4
Tamiflu®