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

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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 stereo-selective 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 the drop weight test (DWT) has also demonstrated the feasibility of carrying out this iron-catalyzed olefin diazidation for large-scale Tamiflu synthesis.
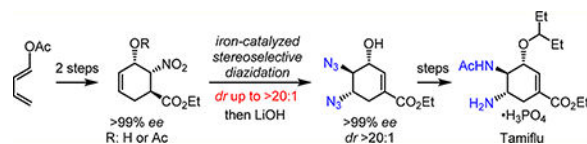
INTRODUCTION

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]

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 oxazabor- olidinium-catalyzed asymmetric Diels—Alder method for the synthesis of a chiral cyclohexene **7**, which then underwent several transformations, including iodo-lactamization 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).[3] 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 *a*-alkyoxyaldehyde **14** with a nitro-olefin **15** in an efficient synthesis of 1 (Scheme 2f).[3g,h] Notably, Ma independently reported the asymmetric conjugate addition of **14** with (Z)-2-nitroethenamide **16** in another expedient synthesis of Tamiflu (Scheme 2g).[3i]

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 to the previous syntheses.

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.

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 diazida- tion, 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).

The enantioselective synthesis of both 1,4-cyclohexadiene **17** and cyclic allylic alcohol **18** has not been reported; however, Danishefsky's pioneering studies of a Diels—Alder reaction between a siloxy diene **21a** and a nitroacrylate **22** have laid the foundation for the synthesis of 18 as a racemate (Scheme 5).[10a] Since nitroacrylate **22** tends to decompose under the reaction conditions, 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$_2$O 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 g 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 enantiose-lective 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 enantiopurity.

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 enantioenriched 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 enantiopure form (40% yield, >99% ee).[9]

To our surprise, neither of the aforementioned iron- catalyzed diazidation methods 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 **19**a 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]

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 toward $TMSN_3$ without an iron catalyst (Scheme 7).[8] These results suggest that competing reaction pathways do exist and they presumably proceed through the iron-promoted nonproductive 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 nonproductive 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 nonproductive 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).

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).

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 the Drop Weight Test (DWT) has been routinely applied to detect the sensitivity of a chemical toward 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 until 189 °C,[9] 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 g scale without compromising the yield and dr of the product (Scheme 8).[9]

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 carboradical **29a**, a putative intermediate reversibly generated from (+)-**25,** is likely more reactive than β-azido-C4 carboradical **29b** toward the rate-determining oxidative C—N$_3$ bond formation; there-fore, we suspect that the *dr* at C3 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 the C3 position *(dr* 4.8:1).[9] We thereby investigated the possibility of achieving enhanced stereo-selectivity via substrate control.

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 C3 (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 C3 and C4 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 the C3 and C4 positions in **36** and **37**). Again, a small amount of TMS- protected allyl silyl ether **38** was also obtained *(dr* >20:1).

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—$(Fe(\mathbf{L1})(N_3)_2)_n$ (Scheme 11).[14] In addition 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** becomes 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.

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 the C4 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 longer exist. If R is a less sterically demanding group, such as hydrogen or an 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 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 $(Fe(\mathbf{L1})(N_3)_2)_n$ **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 the rate-determining step may be too high for this electronically deactivated substrate.

Based upon our mechanistic studies,[7] we envision that the $Fe(NTf_2)_2$-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 the *tert*-butoxyl radical may thereby be rapidly sequestered by HN_3 to liberate the 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]

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 the enantiopure **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.

The gram-scale preparation of *trans,trans*-diazido alcohol **28** in short steps and high enantiopurity have 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 toward 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 toward **28.** We subsequently discovered that a catalytic amount of TfOH promotes the alkylation of diazido allylic alcohol **28;** however, a small amount of regioisomeric 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

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 uniquely effective for the stereoselective diazidation. Process safety assessment using both differential scanning calorimetry. (DSC) and the drop weight test (DWT) has also demonstrated the feasibility of carrying out this iron-catalyzed olefin diazidation for large-scale Tamiflu synthesis.

Supplementary Material

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ACKNOWLEDGMENTS

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(15). For a selected reference of characterized monomeric iron-azide complexes and their IR measurements, see: Grove LE; Hallman JK; Emerson JP; Halfen JA; Brunold TC Inorg. Chem 2008, 47, 5762. [PubMed: 18533647]

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(19). Konno F; Arai T; Zhang M-R; Hatori A; Yanamoto K; Ogawa M; Ito G; Odawara C; Yamasaki T; Kato K; Suzuki K Bioorg. Med. Chem. Lett 2008, 18, 1260. [PubMed: 18226899]
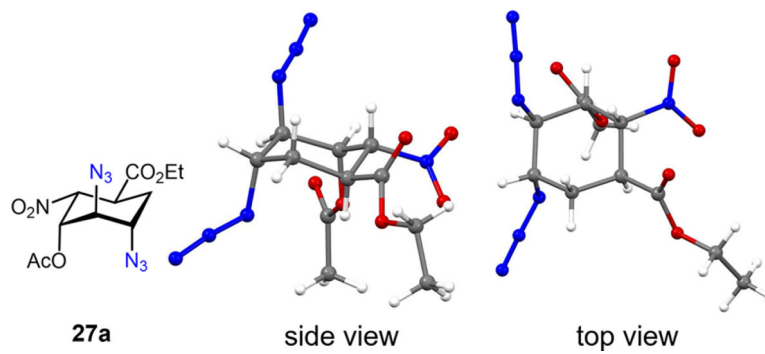
Figure 1.
X-ray crystallographic analysis of diazide 27a.
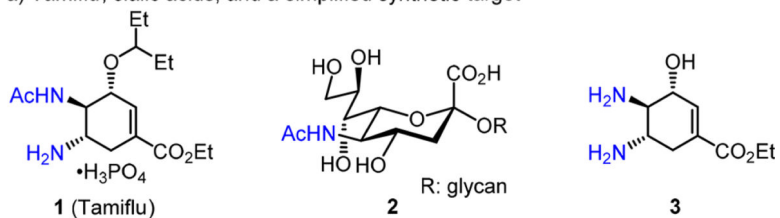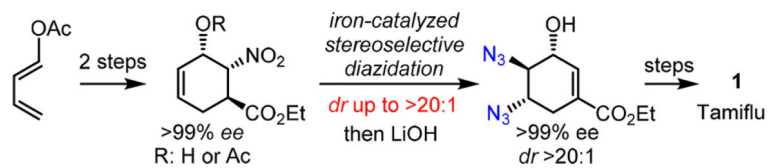
Scheme 1.
Enantioselective Synthesis of Tamiflu via the Iron-Catalyzed Stereoselective Olefin Diazidation
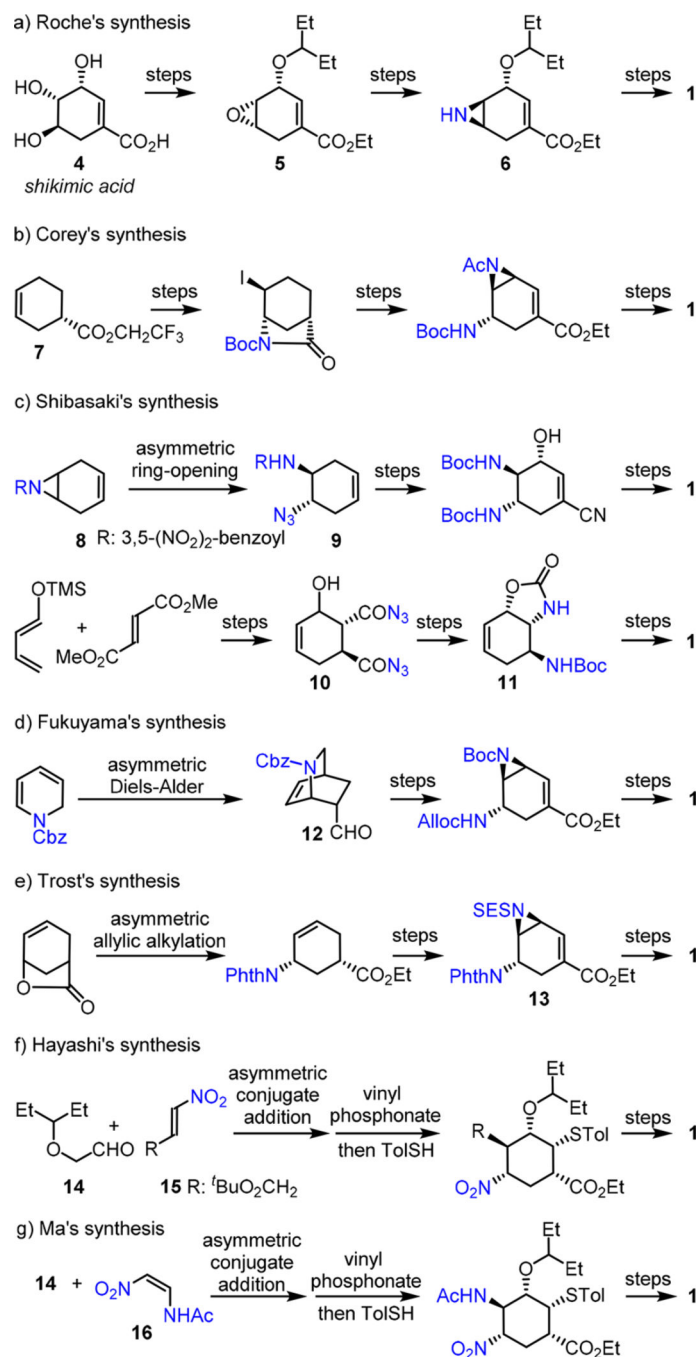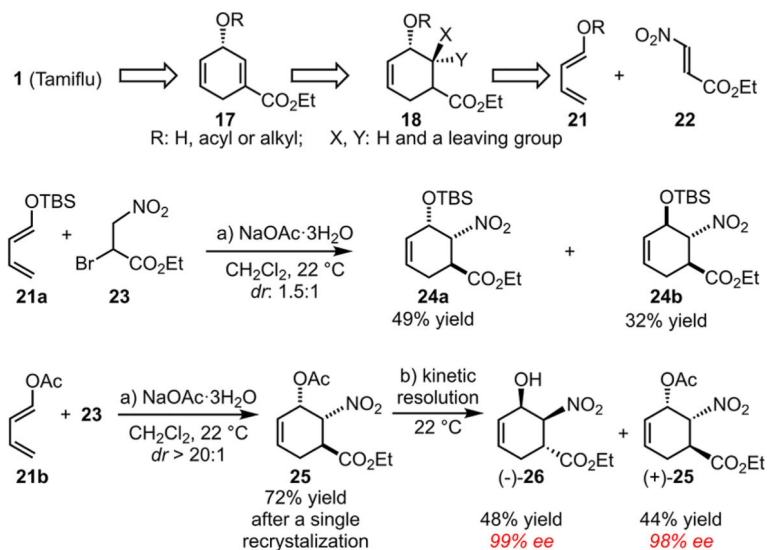
Scheme 2.
Selected Examples of the Previous Tamiflu Syntheses
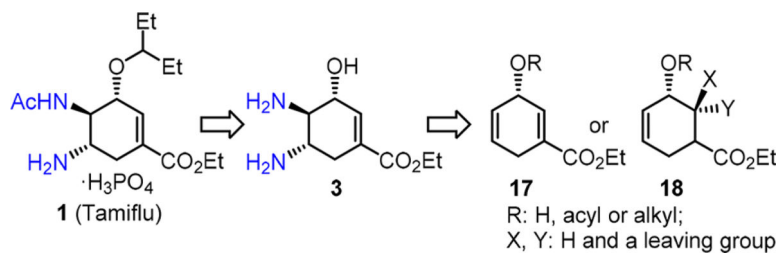
Scheme 3.
Retrosynthetic Analysis Based upon the Iron- Catalyzed Stereoselective Olefin Diazidation
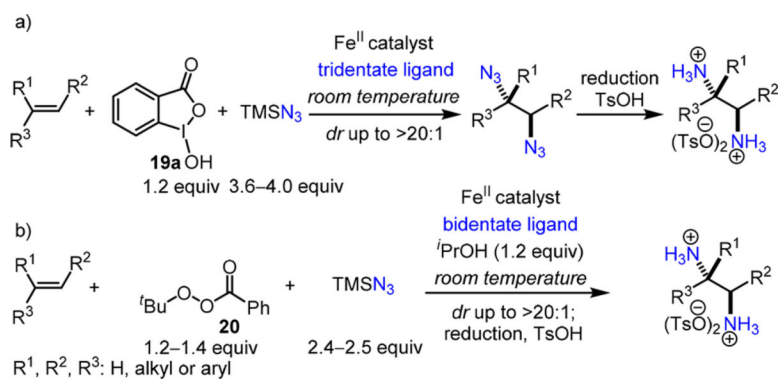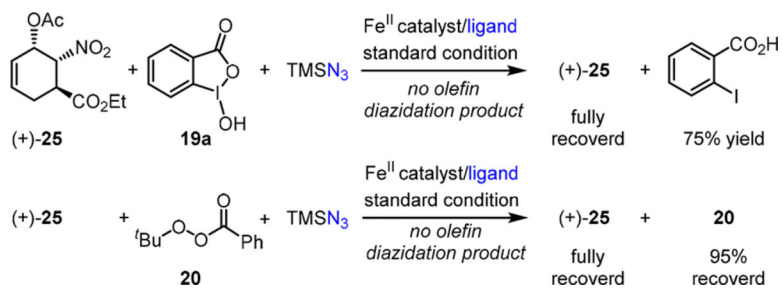
Scheme 4.
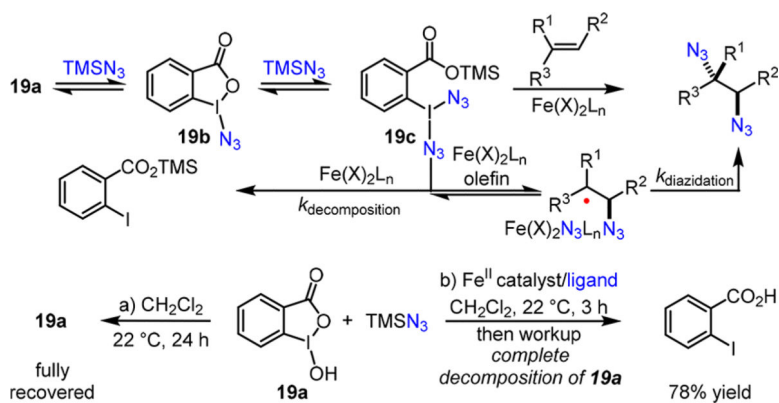Iron-Catalyzed Direct Olefin Diazidation Methods

^{a}NaOAc·3H$_2$O, CH$_2$Cl$_2$, 22 °C, 48 h. ^{b}Amano Lipase from *Pseudomonas fluorescens* (20,000 U/g, 50 wt %), aq. Na$_2$HPO$_4$ buffer, 22 °C, 26 h; (+)-**25** (40% yield, >99% *ee*) after a single recrystallization.

Scheme 5.
Enantioselective Synthesis of Highly Functionalized Cyclic Allylic Alcohols for the Iron-Catalyzed Olefin Diazidation

Scheme 6.
Initial Attempts for the Direct Diazidation of (+)-25 Using the Standard Iron-Catalyzed Diazidation Procedures

Scheme 7.
Mechanistic Analysis of the Iron-Catalyzed Olefin Diazidation Using Benziodoxole 19a
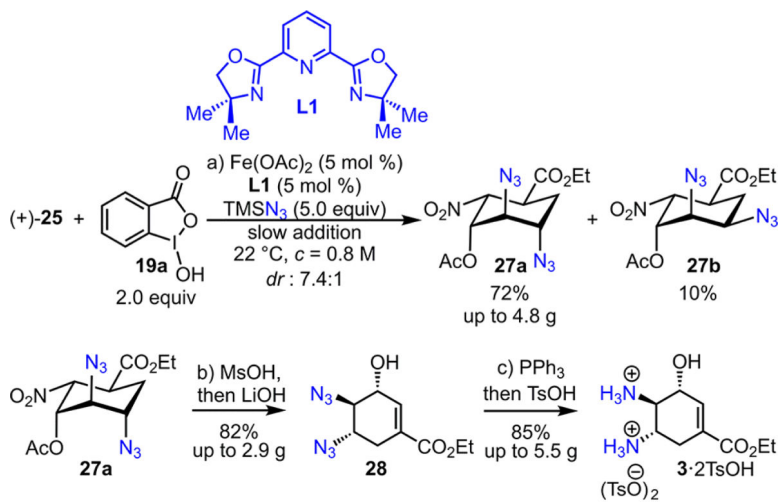
^{a}Fe(OAc)$_2$ (5 mol %), **L1** (5 mol %), **19a** (2 equiv), CH$_2$Cl$_2$/MeCN (10:1), 0.8 M, 22 °C, TMSN$_3$ (5 equiv) added gradually within 8 h and subsequently quenched with saturated NaHCO$_3$ solution. ^{b}MsOH, EtOH, 55 °C, 7 h, then LiOH·H$_2$O, EtOH, 0 °C, 0.5 h. ^{c}PPh$_3$, H$_2$O, THF, 22 °C, 8 h, then TsOH·H$_2$O, 1 h. Standard safety precautions about handling TMSN$_3$ should be taken; see SI for details.

Scheme 8.
Iron-Catalyzed Stereoselective Diazidation of (+)-25 for the Expedient Synthesis of 3 2TsOH
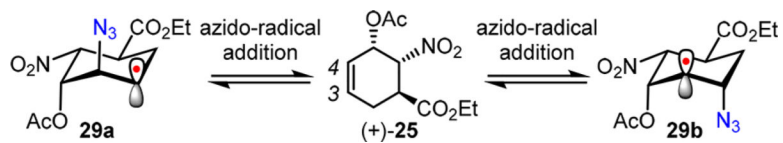
Scheme 9.
Proposed Reversible Azido-Radical Addition Step during the Diazidation of (+)-25
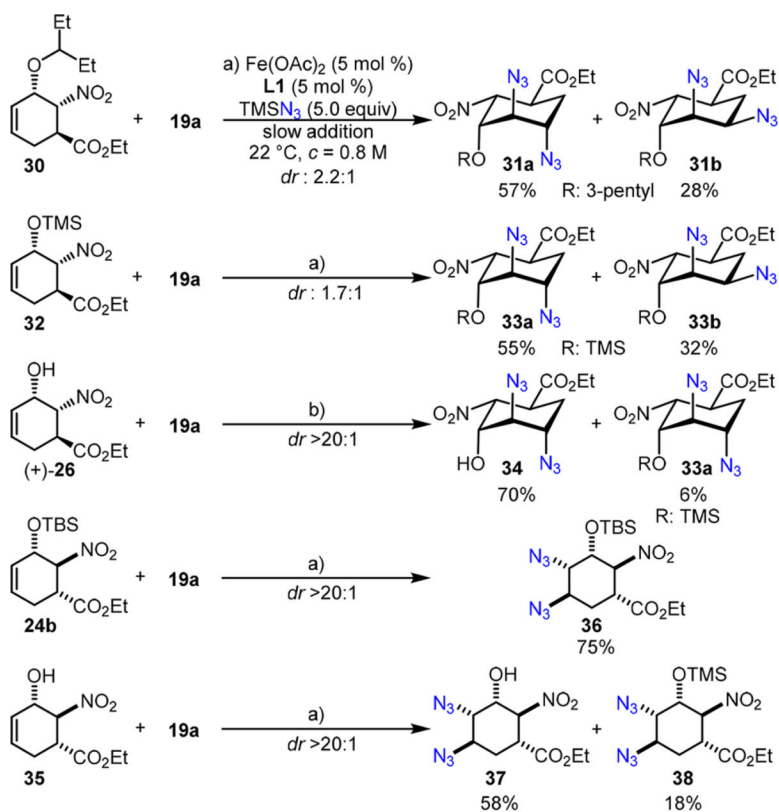
Fe(OAc)₂ (5 mol %), **L1** (5 mol %), **19a** (2 equiv), CH₂Cl₂/MeCN (10:1), 0.8 M, 22 °C, TMSN₃ (5 equiv) added gradually within 8 h. ᵇFe(OAc)₂ (5 mol %), **L1** (5 mol %), **19a** (1.5 equiv), CH₂Cl₂/MeCN (10:1), 0.8 M, 22 °C, TMSN₃ (3.6 equiv) added gradually within 8 h. The reactions were subsequently quenched with saturated NaHCO₃ solution.

Scheme 10.
Substrate Structure-Stereoselectivity Relationship Studies for the Iron-Catalyzed Olefin Diazidation
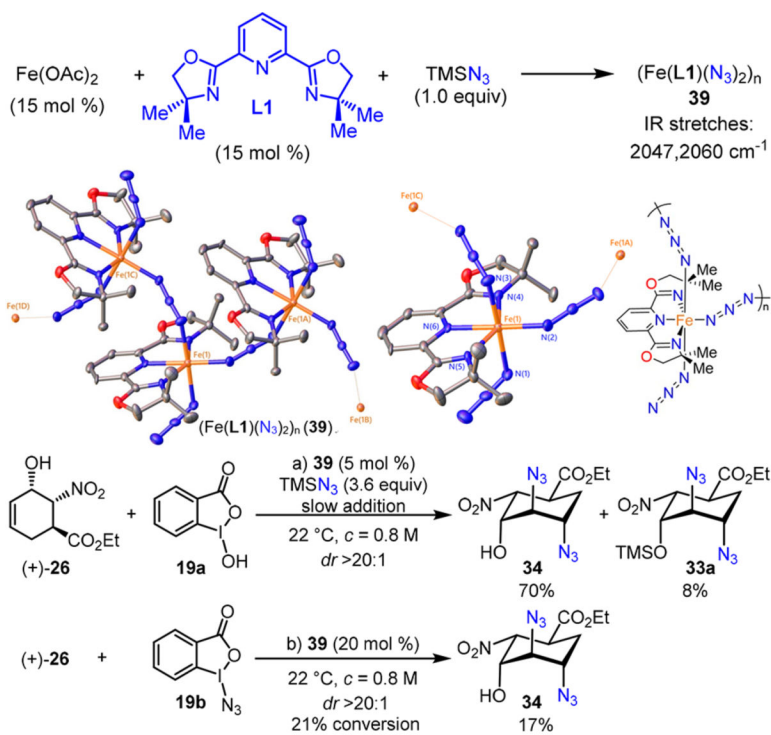
^{a}**39** (5 mol %), **19a** (1.5 equiv), CH_2Cl_2/MeCN (10:1), 0.8 M, 22 °C, TMSN$_3$ (3.6 equiv) added gradually within 8 h. ^{b}**39** (20 mol %), **19b** (1.5 equiv), CH_2Cl_2/MeCN (10:1), 0.8 M, 22 °C.

Scheme 11.
Catalyst Structure—Reactivity Relationship Studies of the Polymeric Iron—Azide Complex (Fe(L1)(N$_3$)$_2$)$_n$
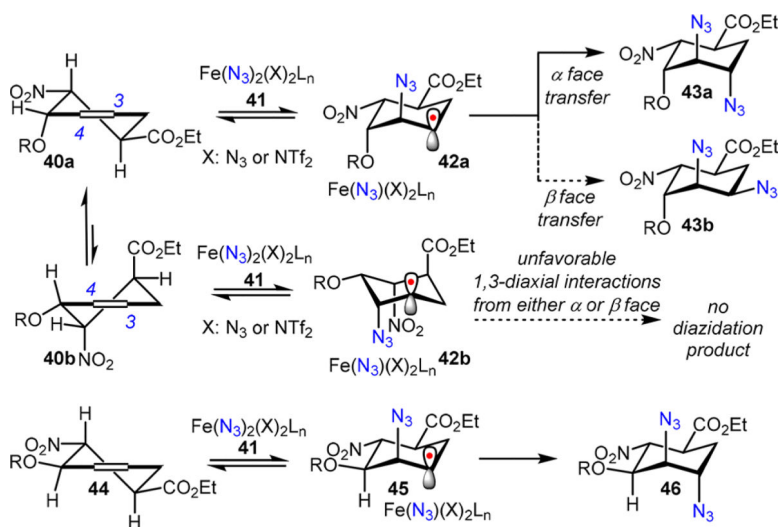
Scheme 12.
Proposed Stereochemical Model for the Iron- Catalyzed Olefin Diazidation of Cyclic Allylic Alcohols
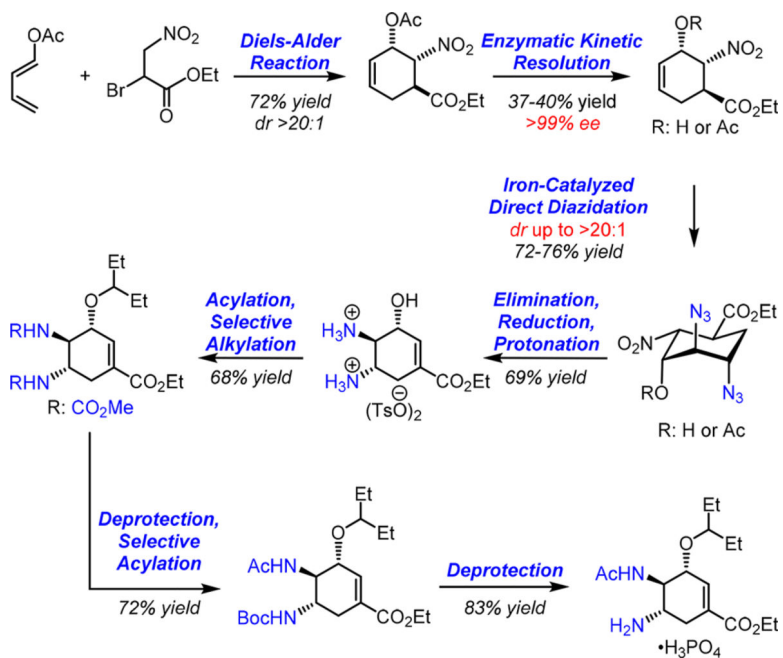
Scheme 13.
(a) Mechanistic Working Hypothesis of the Fe(NTf$_2$)$_2$-Catalyzed Olefin Diazidation Using Peroxyesters and (b) Iron-Catalyzed Peroxyester Activation for Diazidation of (+)-25
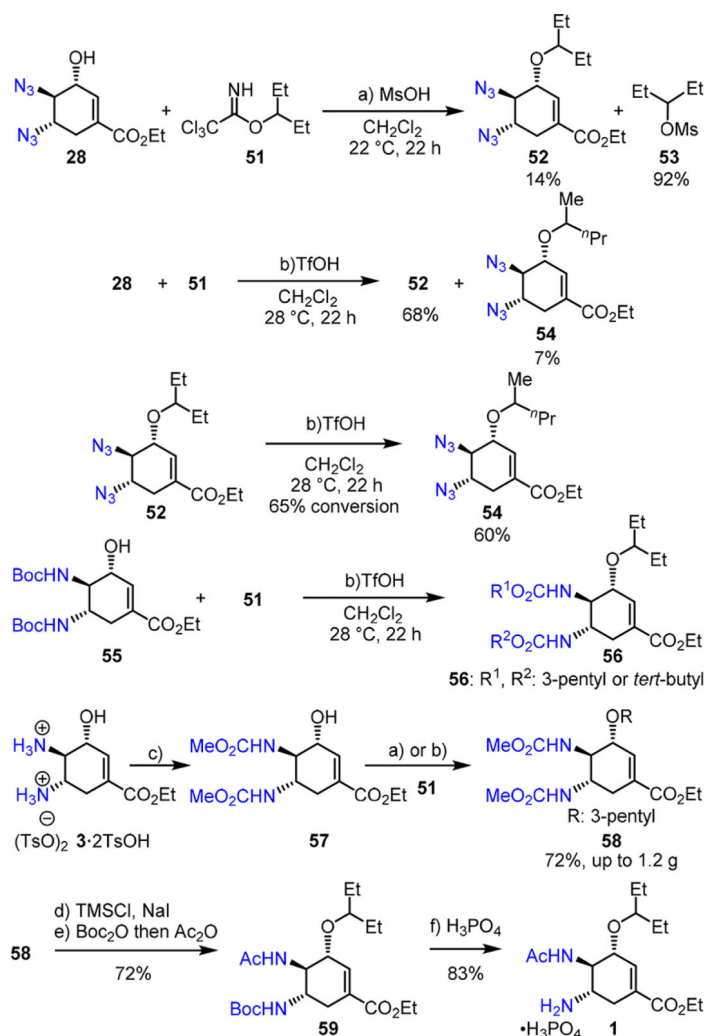
Scheme 14.
Expedient Tamiflu Synthesis from 3 2TsOH

Scheme 15.
Summary of the Enantioselective Synthesis of Tamiflu via the Iron-Catalyzed Stereoselective Olefin Diazidation