Catalytic Amidomethylative [2+2+2] Cycloaddition of Formaldimine and Styrenes toward *N*-heterocycles

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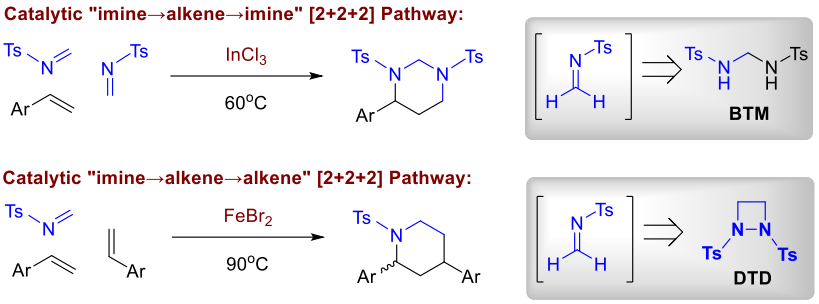
This paper is dedicated to the 20th Anniversary of the Professor Peter Zhang Group.



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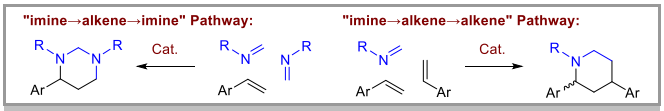
Abstract Chemo-switchable catalytic [2+2+2] cycloaddition of alkenes with formaldimines has been reported. Bis(tosylamido)methane (BTM) and 1,2-ditosyl-1,2-diazetidine (DTD), two bench-stable precursors for highly reactive tosylformaldimine, have been identified to be effective. BTM worked as a selective releaser of the formaldimine for catalytic [2+2+2] reactions toward hexahydropyrimidine products via a presumable "imine-alkene-imine" addition. A unique catalytic retro-[2+2] reaction of DTD was used and has enabled a proposed "imine-alkene-alkene" pathway with high chemoselectivity for the synthesis of 2,4-diarylpyperidine derivatives. The two alternative processes were catalyzed by simple and environmentally benign catalysts $InCl_3$ and $FeBr_2$, respectively.

Key words [2+2+2] cycloaddition, aza-Prins, chemoselective, formaldimine, *N*-heterocycles, diazetidine, controlled release.

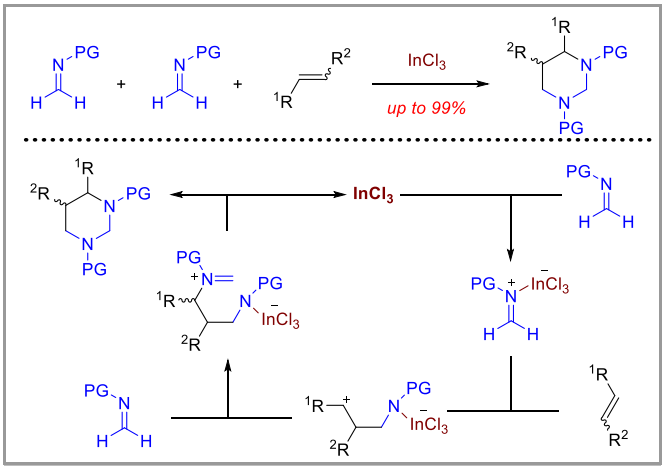
The synthetic demand for new nitrogen-containing molecules has been dramatically increasing, especially for their wide applications in biology and pharmaceuticals.[1] Among U.S. FDA-approved drugs, over 59% of small-molecule drugs contain one to multiple nitrogen atoms.[2] Selective construction of nitrogen-containing structures, especially cyclic compounds, has thus been one of the central topics in modern synthetic chemistry.[3] Among different approaches, Aminomethylation and amidomethylation reactions occupy a unique place in organic synthesis for the construction of C–C and C–X bonds, which have been found highly applicable in pharmaceutical chemistry and natural product synthesis.[4] Departing from the classical aminomethylation of C–H acidic compounds, namely Mannich reactions,[5] various amidomethylating and amidoalkylating reagents based on imines and iminiums has been developed for a number of transformations with different nucleophiles.[6] Being the most important class, a variety of *C*-nucleophiles have been employed in these processes. While C–H acidic compounds, organometallic reagents, and carbon-based anions are generally reactive,[7] effective π-nucleophiles mainly limit to silyl enoles, vinyl ethers, enamines, and alkynyl ethers. Recently, transition metal catalysts have enabled new reaction patterns for the aminoalkylation of unsaturated hydrocarbons.[8] With this highly desirable chemistry continuing to grow, significant challenges still exist to be addressed for new synthetic opportunities.

Catalytic amidomethylation reactions of simple alkenes are among the least developed although they are among the most available materials.[9] Moreover, current systems primarily allow for the installation of one aminomethyl unit, which limits the rapid increase of molecular complexity. From simple and available starting materials, it is hard to reach multifunctionalized products without multi-step syntheses. To address these challenges, ongoing research in our lab has initiated a focus on amidomethylation-triggered new catalytic cyclization processes, which build complex structures directly from simple unsaturated hydrocarbons.



Scheme 1 Alternative Pathways of Catalytic [2+2+2] Cycloaddition of Alkenes with Formaldimines

Saturated six-membered *N*-heterocyclic compounds are important structural motifs that commonly present as backbones in a number of natural products and drugs, [10] as well as a diverse range of biologically active molecules.[11] Among several strategies,[12] the [2+2+2] cycloaddition reaction provides one of the most effective and direct approaches for constructing six-membered rings from some of the simplest building blocks, including widely available olefin starting materials.[13] A well-organized catalytic [2+2+2] pathway involving alkene and imines would allow for one-step syntheses of different saturated six-membered *N*-heterocycles (Scheme 1). Specifically, if one molecule of alkene is controlled to react with two molecules of imines, hexahydropyrimidines (HHPs) are to be synthesized. If two molecules of alkene are controlled to react with one molecule of imines, piperidine derivatives will be accessible.

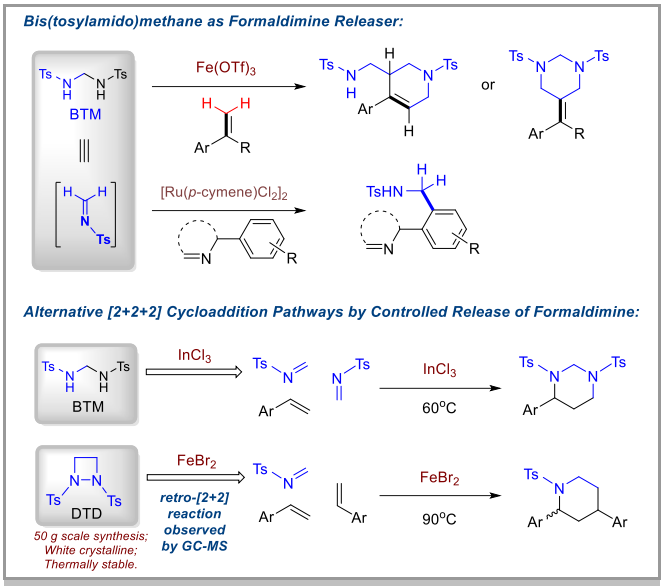


Scheme 2 Catalytic [2+2+2] Cycloaddition of Alkenes with Formaldimines toward Hexahydropyrimidines.

While catalytic systems based on low-valent transition metals, such as Rh(I),[14] Ni(0),[14g, 15] Co(I),[14g, 16] resulted in effective involvement of alkenes as reaction partners through oxidative metallacyclization, [2+2+2] reactions that only use simple alkenes to form totally saturated N-heterocycles are still rare.[14g, 15d, 15e, 17] Alternatively, Lewis acid or Brønsted acid-catalyzed [2+2+2] cyclization provides a different approach for the synthesis of saturated six-membered *N*-heterocycles. Recently, we have developed a catalytic intermolecular [2+2+2] cycloaddition reaction of imines and olefins for the direct construction of HHPs (Scheme 2).[18] While the intramolecular aza-Prins reactions are well documented[6c, 19] and widely applicable in syntheses,[20] catalytic intermolecular aza-Prins processes are highly challenging due to the insufficient nucleophilicity of the iminium species.[6c, 19e, 21] Using an $InCl_3$-catalyzed intermolecular aza-Prins reaction with formaldimines as highly reactive reagents, this catalytic [2+2+2] system is capable of employing alkenes and allenes with a broad scope of electronic and steric properties.

While this "imine→alkene→imine" [2+2+2] cycloaddition represents one of the few systems for the catalytic intermolecular aza-Prins reaction of imines and alkenes, the new reactivity under mild conditions encouraged us to continue exploring new [2+2+2] pathways. As an unexplored reactivity, the alternative "imine-alkene-alkene" sequence would allow for a direct transformation of two molecules of alkenes into piperidine derivatives, "the most frequent nitrogen heterocycles in U.S. FDA approved drugs".[22] However, this process may be much more challenging. The key to the switch of the chemoselectivity is presumably the second electrophilic addition step of the cationic intermediate from the intermolecular aza-Prins step. In the presence of imine species, the second addition to an imine may be much more favored than the addition to alkenes. With a highly reactive formaldimine species that enables effective intermolecular aza-Prins step, the selectivity would be even less toward the non-polarized alkenes. This is in accord with the absence of any detectable piperidine products in the existing "imine→alkene→imine" [2+2+2] system.[18]

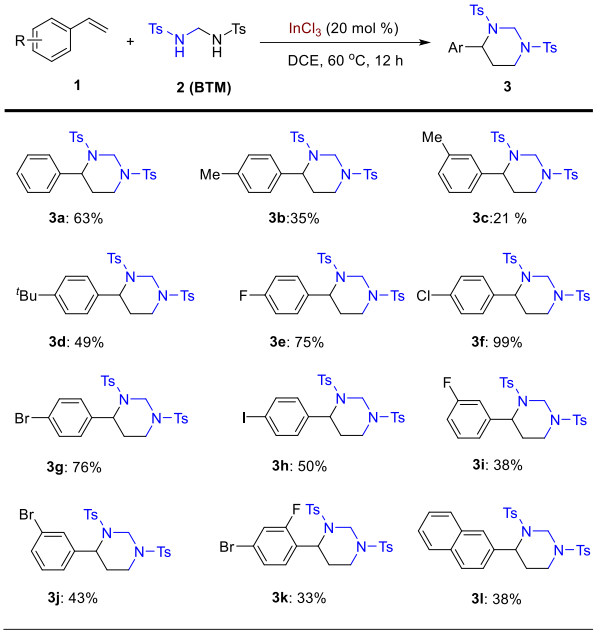
While formaldimines can be freshly prepared and used in solution, bench-stable precursors that generate formaldimines in situ have been known. If these releasers were able to catalytically generates the formaldimine species at a slow rate, it would control a low concentration of the formaldimine during the reaction. We hypothesize that if a proper catalytically controlled releaser for formaldimine can be identified, it would switch the [2+2+2] cycloaddition from an "imine→alkene→imine" pathway to "imine-alkene-alkene" sequence due to the largely suppressed concentration of the formaldimine. In addition to the potential chemo-switch, the releaser would also provide further practicality of the processes, and possibly solve the issues of lifetime and homo- side reactions of the formaldimine species, especially in the reactions with weak π-nucleophiles.



Scheme 3 Controlled Release of Formaldimines for Alternative [2+2+2] Pathways.

Our recent work has adopted bis(tosylamido)methane (BTM), a bench-stable releaser for the labile tosylformaldimine, as an effective amidomethylating reagent for ruthenium(II)-catalyzed C–H amidomethylation reactions[23] and iron(III)-catalyzed tandem cyclization reactions with alkenes (Scheme 3).[24] While the freshly prepared tosylformaldimine was shown to be ineffective, BTM was rationalized to have a properly controlled rate of the release of the formaldimine, which may match the rates of the C–H amidomethylation process to enable the reaction. On the other hand, recently we have developed a practical synthesis of 1,2-ditosyl-1,2-diazetidine (DTD, Scheme 3, **I**).[25] The one-step synthesis was demonstrated to produce this thermally stable diazetidine in 78% yield without the need of column chromatographic purification at 50 gram scale. Our most recent efforts in studying the reactivity of the DTD have revealed that Fe(II) species is able to catalyze a retro-[2+2] reaction of DTD, forming *N*-tosylformaldimine with the cleavage of both the C–C and N–N bonds (Scheme 3). While the formed formaldimine species were not stable enough to be isolated, analysis of the reaction mixture by GC-MS was able to detect a M^+ peak at 183.15, which is consistent with the tosylformaldimine species (see experimental section and supporting information). This unexpected new reactivity has provided another potential bench-stable formaldimine releaser for the proposed chemo-switch in the [2+2+2] cycloaddition reactions. In this report, we herein report the employment of bis(tosylamido)methane (BTM) and 1,2-ditosyl-1,2-diazetidine (DTD) as bench-stable precursors for the controlled release of the tosylformaldimine species in their [2+2+2] cycloaddition reactions with styrenes. BTM was proven to be effective for the "imine→alkene→imine" pathway to form HHPs in moderate to high yields with $InCl_3$ as the Lewis acid catalyst. In contrast, DTD with simple $FeBr_2$ as the catalyst was shown to switch the pathway completely to an "imine-alkene-alkene" sequence, which produced 2,4-disubstituted piperidine derivatives in up to 90 % yield.

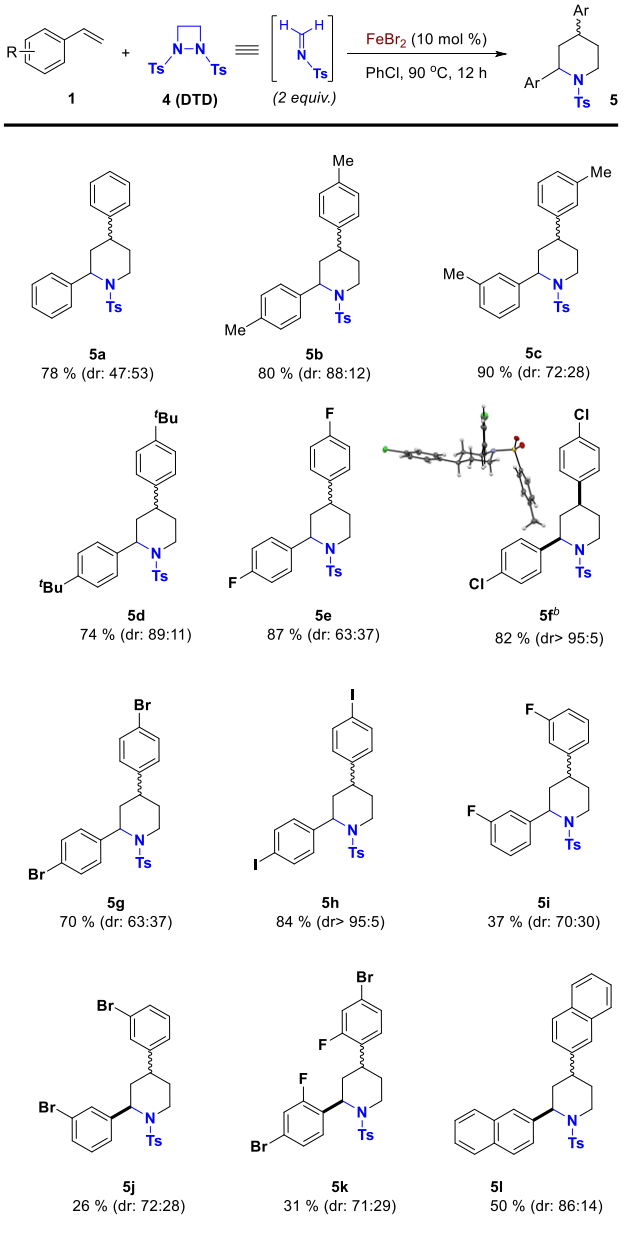
Table 1 $InCl_3$-catalyzed [2+2+2] cycloaddition of styrene derivatives with BTM (imine→alkene→imine).[a]



[a]Carried out with 1 (0.1 mmol), BTM (0.3 mmol) and $InCl_3$ (20 mol %) in 1 mL anhydrous 1,2-dichloroethane (DCE), 60 °C for 12 h. Yields are reported based on flash column chromatography.

While our reported [2+2+2] cycloaddition employed freshly prepared *N*-sulfonyl formaldimine solution as the reagent, we explored the catalytic reaction with BTM (**2**) as a bench-stable solid releaser for the process (table 1). As a simple and environmentally benign Lewis acid, $InCl_3$ was employed as the catalysts for both the decomposition of the BTM and the subsequent cycloaddition. Under the standard conditions, including 4 equivalents of styrenes, 20 mol % $InCl_3$ as the catalyst in dichloroethane (DCE) at 60°C for 12 hours, the reaction produced HHP **3a** in 63% yield. While BTM has been proven to be an effective bench-stable formaldimine precursor for this cycloaddition reaction, there was no indication of the formation of piperidine product from the hypothesized "imine-alkene-alkene" pathway. Employment of substituted styrene derivatives continued to indicate the effectiveness of HHP formation by the BTM-based system. For example, alkyl groups with varied steric hindrance at the *para*- and *meta*- positions of the styrenes are suitable substrates that formed the corresponding HHPs **3b**-**3d** in moderate yields. It is worth to note that the alkenes were fully converted, resulting in side reactions including possible alkene polymerization. Halogenated styrene derivatives were examined with an emphasis on the potential synthetic utility of the haloarene units for further transformations. All halogen atoms at the *para*- positions of the styrenes resulted in productive reactions, affording HHPs **3e**-**3h** in 50%-99% yields. When the halogen atoms, such as both fluorine and the bulky bromine, are at the *meta*- positions, cycloaddition reactions were also able to produce the HHPs **3i** and **3j**. While the *para*- and *meta*-substituted styrenes were shown to be suitable substrates, the scope of *ortho*-substituted styrenes appeared to be limited. Among a few attempts, only *ortho*-fluoro substitution was shown to be productive for the formation of **3k**, which might indicate an increased steric at the *ortho*- position of the styrene would significantly decrease the reactivity. In addition, expanded aromatic olefin 2-vinylnaphthalene was employed to afford HHP **3l** in 38 % yield.

Table 2 $FeBr_2$-catalyzed [2+2+2] cycloaddition of styrene derivatives with DTD (imine→alkene→alkene).[a]



[a]Carried out with 1 (0.3 mmol), DTD (0.05 mmol) and $FeBr_2$ (10 mol %), in 1 mL anhydrous chlorobenzene (PhCl), 90 °C for 12 h. Yields are reported based on flash column chromatography. Diastereomeric ratio was determined by crude ^1H NMR. [b]The structure was determined by X-ray analysis on the single crystal of **5f**.

Although BTM was shown productive as a more practical and bench-stable precursor, it demonstrated the same chemoselectivity as the original [2+2+2] cycloaddition system. This might be related to the facile decomposition of the BTM under the reaction condition, which was not able to sufficiently suppress the concentration of the formaldimine. Given the observation that the retro-[2+2] reaction of the DTD occurred above 80°C, together with the fact that the catalytic HHP formation needs a much lower temperature, we envision that the release of formaldimine from the retro-[2+2] reaction of DTD would be much slower and might be the rate-determining step. In this case, the lack of formaldimine in the system might drive the second addition reaction only to another molecule of alkene, resulting in a switch to the "imine-alkene-alkene" pathway.

Given the detection of the tosylformaldimine by GC-MS when DTD was treated with $FeBr_2$, we tried to use styrene as a π-nucleophile to trap the formed formaldimine intermediate (table 2). It was found that the retro-[2+2] reaction of DTD occurred smoothly in nonpolar solvents, such as DCE and common aromatic solvents. At 80°C, the conversation of DTD was observed at a slow rate, and 90°C was found to be a suitable temperature for the process. The standard conditions were set to be 10 mol % of $FeBr_2$ as the catalyst in chlorobenzene at 90°C for 12 hours. A 1:6 ratio of DTD and styrene was adopted, making the formaldimine/styrene ratio to be 1:3 since the retro-[2+2] of the DTD presumably generates two equivalents of the formaldimine. Substrate scope study has indicated that DTD, presumably working as a slow releaser of the formaldimine, with simple $FeBr_2$ catalyst performed effective [2+2+2] reactions and switched the chemoselectivity to a "imine-alkene-alkene" pathway. 2,4-Diphenyl-1-tosylpiperidine (**5a**) in its diastereomeric mixture was isolated in 78% overall yield with a trace amount of the HHP product detected. The chemoselective process was proven to be effective for the conversation of styrene derivatives with *para*- and *meta*- methyl substituents, as well as a tert-butyl group at the *para*- position of the arene. 2,4-Diarylpiperidines **5b**-**5d** have been isolated in up to 90% yield with varied diastereomeric ratios. While further study is needed, the diversified diastereomeric ratios were believed to be controlled kinetically and largely impacted by the substituents of the styrene derivatives. Subsequently, halogenated styrene derivatives were examined. To our delight, *para*-substituted styrenes with all four common halogen atoms have resulted in highly chemoselective formation of the corresponding piperidines **5e**-**5h**. The major diastereomer of the 2,4-bis(4-chlorophenyl)-1-tosylpiperidine (**5f**) was isolated and determined to be a *cis*-substitution pattern by the X-ray analysis on its single crystals (see supporting information). Interestingly, when fluorine and bromine atoms are at the *meta*- positions of the styrenes, the yields of the piperidine products, **5i** and **5j**, were shown to be significantly decreased. While HHP products were still observed at a trace amount in these reactions, a crude ^1H NMR study suggested possible polymer formation. Moreover, disubstituted styrene was employed to catalytically produce **5k** in 31% yield. As an example of expanded aromatic olefin, 2-vinylnaphthalene was examined in this [2+2+2] process to afford piperidine **5l** in 50 % yield. Similar to the BTM-based system, alkenes were fully converted even in the low-yielding reactions.

In summary, the development of chemo-switchable catalytic [2+2+2] cycloaddition of alkenes with formaldimines has resulted in the identification of bis(tosylamido)methane (BTM) and 1,2-ditosyl-1,2-diazetidine (DTD), two bench-stable releasers for highly reactive tosylformaldimine. Instead of the formaldimine solution that must be freshly prepared, BTM worked as a practical and selective precursor for a "imine-alkene-imine" addition reaction for the formation of hexahydropyrimidines derivatives. Depending on a catalytic retro-[2+2] reaction of DTD, a "imine-alkene-alkene" pathway was identified with high chemoselectivity for the synthesis of 2,4-diarylpyperidine derivatives. The alternative processes were catalyzed by simple and environmentally benign catalysts $InCl_3$ and $FeBr_2$, respectively. While examples of both catalytic reactions are documented in this report, mechanisms of the unique iron-catalyzed retro-[2+2] reactions of DTD, together with a more detailed kinetic study on its presumable role as a controlled releaser of the formaldimine, are to be studied. More broadly, we hope these pathways would stimulate further exploration of the underdeveloped intermolecular aza-Prins reaction and the totally intermolecular cycloaddition reactions for the synthesis of saturated *N*-heterocyclic compounds.

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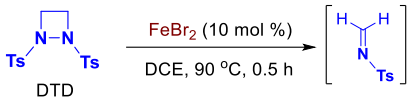
Materials: Unless otherwise indicated, starting catalysts and materials were obtained from Sigma Aldrich, Oakwood, Strem, or Acros Co. Ltd. Moreover, commercially available reagents were used without additional purification.

Instrumentation: NMR spectra were recorded at 500 MHz or 300 MHz(1H NMR) and 125 MHz (13C NMR) using TMS as an internal standard. Chemical shifts are given relative to TMS or CDCl3 (0 ppm for 1H NMR, 77.16 ppm for 13C NMR). Data are represented as follows: chemical shift (multiplicity, coupling constant (s) in Hz, integration). Multiplicities are denoted as follows: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectroscopy data of the products were collected on an HRMS-TOF instrument using ESI or APCI ionization.

GC/MS observation for retro-[2+2] ring opening of 1,2-ditosyl-1,2-diazetidine (DTD)



An oven dried Schlenk tube was charged with catalyst $FeBr_2$ (10 mol %) and 1,2-ditosyl-1,2-diazetadine. The Schlenk tube was then vacuumed to remove air and followed by filled with nitrogen. The Teflon screw cap was replaced with a rubber septum and 1mL of 1,2-dichloroethane was added to the Schlenk tube. The Schlenk tube was then purged with nitrogen for 1 minute and the rubber septum was replaced with a Teflon screw cap. The reaction mixture was then stirred at 90 °C for 30 min. Reaction mixture was analyzed by GC/MS with temperature program of 30.0 °C as starting temperature with 1 min holding time. Final temperature was 275 °C and with gradient increment of temperature 5 °C/min and 8 min holding time at final temperature. Injection temperature was 250 °C and split injection mode was used to inject the sample to column. Helium was used as carrier gas with 1.88 mL/min flow rate and Rtx-5MS GC capillary column was used with dimension of 0.25 mm diameter and length 30.0 m thickness 0.25µm Electron ionization method was used in mass spectrometer with threshold voltage of 1000 kV. A peak for 4-methyl-*N*-methalenebenzenesulfonamide, m/z =183.15(Calcd for $C_8H_9NO_2S$ [M^+]: 183.04), was observed at 8.66 min.

General procedure for preparation of 4-phenyl-1,3-ditosylhexahydropyrimidine (3a)

An oven dried Schlenk tube was charged with catalyst $InCl_3$ (20 mol %) and bis(tosulamido)methane (BTM) (0.3 mmol). The Schlenk tube was vacuumed to remove air and filled with nitrogen. The Teflon screw cap was replaced with a rubber septum and styrene (0.1 mmol) and 1 mL of 1,2-dicloroethane (DCE) were added to the Schlenk tube and followed by purged with nitrogen for 1 minute and the rubber septum was replaced with a Teflon screw cap. The reaction mixture was then stirred at 60 °C for12 h. Desire product was isolated by column chromatography with 3:1 hexane and ethyl acetate as mobile phase and isolated yield was 63%. Final structure was confirmed according to the characterization details in previous report by Cui et al.[18]

Synthesis of **4-p-tolyl-1, 3-ditosylhexahydropyrimidine (3b)** was followed general procedure and percentage yield of reaction between BMT and 4-methylstyrene was 35%. Final structure was confirmed according to the characterization details in previous report.[18]

Synthesis of **4-p-tolyl-1, 3-ditosylhexahydropyrimidine (3c)** was followed general procedure and percentage yield of reaction between BMT and 3-methylstyrene was 21%. Final structure was confirmed according to the characterization details in previous report.[18]

Synthesis of **4-p-tolyl-1, 3-ditosylhexahydropyrimidine (3d)** was followed general procedure and percentage yield of reaction between BMT and 4-tert-butylstyrene 49 %. Final structure was confirmed according to the characterization details in previous report.[18]

Synthesis of **4-(4-fluorophenyl)-1, 3-ditosylhexahydropyrimidine (3e)** was followed general procedure and percentage yield of reaction between BMT and 4-fluorostyrene was 75%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.27 – 7.25 (m, 4H), 6.98 (t, *J* = 8.6 Hz, 2H), 5.67 (ABq, *J* = 13.1 Hz, 1H), 5.05 (d, *J* = 5.2 Hz, 1H), 3.66 (ABq, *J* = 13.1 Hz, 1H), 3.46 – 3.42 (m, 1H), 2.49 (td, *J* = 12.3, 2.5 Hz, 1H), 2.47 (s, 3H), 2.40 (s, 3H), 2.07 – 2.02 (m, 1H), 1.61 – 1.58 (m, 1H); ^{13}C NMR (126 MHz, CDCl) δ $_3$162.1 (d, *J* = 245.5 Hz), 144.1 (d, *J* = 14.9 Hz), 136.7, 134.0, 132.4(d, *J* = 3.0 Hz), 130.0, 129.9, 128.7, 128.6, 128.0, 127.2, 115.8 (d, *J* = 21.3 Hz), 56.9, 53.0, 41.2, 24.8, 21.7, 21.6; HRMS (ESI) Calcd. for $C_{24}H_{26}N_2O_4S_2F$ [M+H]: 489.1312, found: 489.1312.

Synthesis of **4-(4-chlorophenyl)-1, 3-ditosylhexahydropyrimidine (3f)** was followed general procedure and percentage yield of reaction between BMT and 4-chlorostyere was 99%. Final structure was confirmed according to the characterization details in previous report.[18]

Synthesis of **4-(4-bromophenyl)-1, 3-ditosylhexahydropyrimidine (3g)** was followed general procedure and percentage yield of reaction between BMT and 4-bromosyrene was 76%. Final structure was confirmed according to the characterization details in previous report.[18]

Synthesis of **4-(4-iodophenyl)-1, 3-ditosylhexahydropyrimidine (3h)** was followed general procedure and percentage yield of reaction between BMT and 4-iodostyrene was 50%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.7 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 5.67 (ABq, *J* = 13.2 Hz, 1H), 5.01 (d, *J* = 4.8 Hz, 1H), 3.64 (ABq, *J* = 13.2 Hz, 1H), 3.47 – 3.39 (m, 1H), 2.50 – 2.45 (m, 1H), 2.47 (s, 3H), 2.41 (s, 3H), 2.06 – 1.97 (m, 1H), 1.64 – 1.58 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.2, 144.1, 138.0, 136.7, 136.6, 134.0, 130.0, 129.9, 128.9, 128.0, 127.2, 93.3, 57.0, 53.2, 41.2, 24.7, 21.7, 21.5; HRMS (ESI) Calcd for $C_{24}H_{25}IN_2KO_4S_2$ [M+K]: 634.9932, found: 634.9932.

Synthesis of **4-(3-fluorophenyl)-1, 3-ditosylhexahydropyrimidine (3i)** was followed general procedure and percentage yield of reaction between BMT and 3-fluorostyerene was 38%. Final structure was confirmed according to the characterization details in previous report.[18]

Synthesis of **4-(3-bromophenyl)-1, 3-ditosylhexahydropyrimidine (3j)** was followed general procedure and percentage yield of reaction between BMT and 3-bromostyrene was 43%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.38 – 7.36 (m, 4H), 7.29 – 7.26 (m, 2H), 7.23 – 7.15 (m, 2H), 5.69 (ABq, *J* = 13.3 Hz, 1H), 5.04 (d, *J* = 4.6 Hz, 1H), 3.71 (ABq, *J* = 13.3 Hz, 1H), 3.47 –3.39 (m, 1H), 2.54 – 2.44 (m, 1H), 2.47 (s, 3H), 2.40 (s, 3H), 2.06 – 1.98 (m, 1H), 1.65 – 1.58 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.3, 142.2, 137.4, 134.7, 132.2, 129.0, 128.6, 128.1, 128.0, 126.0, 125.3, 123.7, 121.4, 114.5, 55.1, 51.2, 39.3, 23.0, 19.8, 19.7; HRMS (ESI) Calcd. for $C_{24}H_{26}N_2O_4S_2BrNa$ [M+Na]: 571.0331, found: 571.0313.

Synthesis of **4-(4-brormo-2-fluorophenyl)-1, 3-ditosylhexahydropyrimidine (3k)** was followed general procedure and percentage yield of reaction between BMT and 4-bromo-2-fluorostyrene was 33%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.34 – 7.30 (m, 4H), 7.19 – 7.09 (m, 2H), 7.06 (t, J = 8.2 Hz, 11H), 5.58 (ABq, *J* = 13.1 Hz, 1H), 4.96 (t, *J* = 5.6 Hz, 1H), 4.29 (ABq, *J* = 13.1 Hz, 1H), 3.21 – 3.14 (m, 1H), 2.76 (ddd, *J* = 12.4, 9.4, 3.4 Hz, 1H), 2.46 (s, 3H), 2.44 (s, 3H), 2.00 – 1.90 (m, 1H), 1.82 – 1.70 (m, 1H); ^{13C} NMR (75 MHz, $CDCl_3$) δ 144.3 (d, J = 13.1 Hz), 135.9, 134.6, 130.3, 130.2, 130.1, 130.0, 127.9, 127.8 (d, *J* = 3.5 Hz), 127.5, 125.3 (d, *J* = 11.8 Hz), 122.0, 119.8 (d, *J* = 25.8 Hz), 57.5, 51.6, 41.7, 29.9, 27.7, 21.8, 21.7. HRMS (ESI) Calcd for $C_{24}H_{24}IN_2O_4S2Na$ [M+Na]: 589.0237, found: 589.0222.

Synthesis of **4-(naphthalen-2-yl)-1, 3-ditosylhexahydropyrimidine (3l)** was followed general procedure and percentage yield of reaction between BMT and 2-vinylnapthalene was 38%. Final structure was confirmed according to the characterization details in previous report.[18]

General procedure for preparation of 2,4-diphenyl-1-tosylpiperidine (5a)

An oven dried Schlenk tube was charged with catalyst $FeBr_2$ (10 mol%) and 1,2-ditosyl-1,2-diazetadine (DTD) (0.05 mmol). The Schlenk tube was vacuumed to remove air and filled with nitrogen. The Teflon screw cap was replaced with a rubber septum and styrene (0.3 mmol) and 1 mL of chlorobenzene were added to the Schlenk tube and followed by purged with nitrogen for 1 minute and the rubber septum was replaced with a Teflon screw cap. The reaction mixture was then stirred at 90 °C for12 h. The reaction mixture was purified by column chromatography with 5:1 hexane and ethyl acetate as mobile phase. Isolated product was white powder and percentage yield was 78% with dr ratio 53:47 ratio and two isomers isolated by preparative TLC. For major isomer:^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.36 (dt, *J* = 10.8, 7.5 Hz, 6H), 7.27 (dt, *J* = 13.3, 4.2 Hz, 2H), 7.20 – 7.16 (m, 1H), 5.46 (d, *J* = 4.7 Hz, 1H), 4.13 – 3.97 (m, 1H), 3.14 (ddd, *J* = 14.6, 13.1, 3.0 Hz, 1H), 2.69 (tt, *J* = 12.6, 3.3 Hz, 1H), 2.47 (s, 3H), 2.44 – 2.41 (m, 1H), 2.41 – 2.39 (m, 1H), 1.90 – 1.78 (m, 1H), 1.47 (ddd, *J* = 25.7, 12.9, 4.5 Hz, 1H). 13C NMR (125 MHz, $CDCl_3$) δ 144.6, 143.1, 141.7, 135.6, 129.2, 128.6, 128.0, 127.8, 127.4, 127.4, 126.6, 126.6, 62.3, 46.3, 42.0, 40.6, 31.9, 21.5. HRMS (ESI) [M+H] Calcd for $C_{24}H_{26}NO_2S$: 392.1678, found 392.1679. For minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.3 Hz, 1H), 7.29 – 7.23 (m, 3H), 7.23 – 7.15 (m, 3H), 7.13 – 7.08 (m, 1H), 4.17 (dd, *J* = 11.1, 4.6 Hz, 1H), 4.06 (dt, *J* = 12.8, 5.2 Hz, 1H), 3.17 (ddd, *J* = 13.2, 9.0, 4.5 Hz, 1H), 2.60 – 2.51 (m, 1H), 2.42 (s, 3H), 2.15 – 2.06 (m, 1H), 2.06 – 2.03 (m, 1H), 2.02 (td, J = 4.5, 2.1 Hz, 1H), 1.86 (dddd, J = 13.6, 11.6, 9.0, 4.9 Hz, 1H).^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 138.6, 138.5, 129.8, 128.8, 128.6, 127.1, 127.0, 126.8, 126.6, 126.5, 55.4, 41.8, 36.5, 34.2, 31.7, 21.6. HRMS (ESI) Calcd for $C_{24}H_{26}NO_2S$ [M+H]: 392.1678, found 392.1679.

Synthesis of **2,4-di-p-tolyl-1-tosylpiperidine (5b)** was followed general procedure and percentage yield of reaction between DTD and 4-methylstyrene was 80% with 88: 12 dr ratio. For the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 7.9 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.06 (d, *J* = 7.9 Hz, 2H), 6.86 (d, *J* = 8.1 Hz, 2H), 5.41 (d, *J* = 4.0 Hz, 1H), 4.02 – 3.98 (m, 1H), 3.12 (m, 1H), 2.66 (tt, *J* = 12.5, 3.2 Hz, 1H), 2.46 (s, 3H), 2.39 (d, *J*=13.0, 1H) 2.35 (s, 3H), 2.29 (s, 3H), 1.78 (td, *J* = 13.5, 5.3 Hz, 1H), 1.55 (s, 1H) 1.44 (ddd, *J* = 25.6, 12.8, 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 142.2, 138.7, 136.6, 136.1, 135.4, 129.8, 129.5, 129.2, 127.1, 126.7, 126.4, 55.2, 41.8, 36.0, 34.2, 31.8, 21.5, 21.0; HRMS (ESI) calcd for $C_{26}H_{30}NO_2S$ [M+Na]: 442.1811, Found 442.1809.

Synthesis of **2,4-di-m-tolyl-1-tosylpiperidine (5c)** was followed general procedure and percentage yield of reaction between DTD and 3-methylstyrene was 90% with 72: 28 cis: dr ratio. For the major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.16 – 7.12 (m, 3H), 7.07 (d, J = 7.7 Hz, 1H), 7.00 (d, J = 7.4 Hz, 1H), 6.78- 6.76 (m, 2H), 5.42 (d, *J* = 4.6 Hz, 1H), 4.05 – 4.01 (m, 1H), 3.17 – 3.11 (m, 1H), 2.65 (tt, *J* = 12.6, 3.5 Hz, 1H), 2.47 (s, 3H), 2.37 (d,

J = 13.7 Hz, 1H), 2.32 (s, 3H), 2.29 (s, 3H), 1.82 (td, *J* = 13.7, 5.5 Hz, 1H), 1.55 (m, 1H), 1.48 (td, *J* = 12.6, 4.5 Hz, 1H);.^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2, 143.1, 138.8, 138.5, 138.4, 138.1, 129.8, 128.6, 128.5, 127.7, 127.5, 127.4, 127.3, 127.2, 123.8, 123.6, 55.4, 41.9, 36.4, 34.1, 31.8, 21.6, 21.5, 21.4. HRMS (ESI) Calcd for $C_{26}H_{29}NO_2SNa$ [M+Na]: 442.1811, found 442.1814

Synthesis of **2,4-bis(4-(tertbutyl)phenyl)-1-tosylpiperidine (5d)** was followed general procedure and percentage yield of reaction between DTD and 4-tert-butylstyrene was 74% with 89: 11 dr ratio. For the trans isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 6.93 (d, *J* = 8.3 Hz, 2H), 5.41 (d, *J* = 4.5 Hz, 1H), 4.02 – 3.99 (m, 1H), 3.18- 3.12 (m, 1H), 2.71 (tt, *J* = 12.5, 3.3 Hz, 1H), 2.46 (s, 3H), 2.40 (d, *J* = 11.2 Hz, 1H), 1.81 (td, *J* = 13.5, 5.3 Hz, 1H), 1.56 (s, 1H), 1.50 – 1.41 (m, 1H), 1.32 (s, 9H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8, 149.3, 143.1, 142.2, 138.8, 135.5, 129.8, 127.1, 126.5, 126.2, 125.7, 125.4, 55.3, 41.9, 35.9, 34.4, 34.4, 34.1, 31.9, 31.4, 21.6. HRMS (ESI) Calcd for $C_{32}H_{42}NO_2S$ [M+H]: 504.2931, found 504.2932.

Synthesis of **2,4-bis(4-flurophenyl)-1-tosylpiperidine (5e)** was followed general procedure and percentage yield of reaction between DTD and 4-fluorostyrene was 87% with 63: 37 dr ratio. For the major isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.31 (m, 4H), 7.06 – 7.031 (m, 2H), 6.96 – 6.90 (m, 4H), 5.42 (d, i = 4.1 Hz, 1H), 4.04 – 4.00 (m, 1H), 3.12 – 3.06 (m, 1H), 2.65 (tt, *J* = 12.6, 3.1 Hz, 1H), 2.47 (s, 3H), 2.33 (d, *J* = 14.2 Hz, 1H), 1.79 (td, *J* = 13.3, 5.3 Hz, 1H), 1.58 (s, 1H), 1.42 (ddd, *J* = 26.0, 12.9, 4.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.9 (d, *J* = 244.8 Hz), 161.6 (d, *J* = 243.3 Hz), 143.4, 140.6 (d, *J* = 3.2 Hz), 138.5, 134.1 (d, *J* = 3.1 Hz), 129.9, 128.5 (d, *J* = 8.0 Hz), 127.9 (d, *J* = 7.8 Hz), 127.1, 115.7 (d, *J* = 21.3 Hz), 115.4 (d, *J* = 21.1 Hz), 54.9, 41.7, 35.8, 34.5, 31.9, 21.6. HRMS (ESI) Calcd for $C_{24}H_{23}F_2NO_2SK$[M+K]: 466.1050, found 466.108.

Synthesis of **2,4-bis(4-chlorophenyl)-1-tosylpiperidine (5f)** was followed general procedure and percentage yield of reaction between DTD and 4-chlorostyrene was 82%.with dr ratio > 95:5. For the major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.0 Hz, 2H), 7.26 – 7.21 (m, 4H), 7.14 (s, 4H), 7.05 (d, *J* = 8.0 Hz, 2H), 4.11 – 4.08 (m, 2H), 3.14 – 3.09 (m, 1H), 2.57 (tt, *J* = 12.0, 4.1 Hz, 1H), 2.43 (s, 3H), 2.10 – 2.06 (m, 1H), 1.98 – 1.95 (m, 1H), 1.91 – 1.86 (m, 1H), 1.84 – 1.79 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.4, 142.8, 139.7, 135.5, 133.2, 132.3, 129.3, 129.0, 128.7, 128.1, 128.0, 127.8, 61.8, 46.5, 41.9, 40.3, 32.0, 21.5; HRMS (ESI) Calcd for $C_{24}H_{23}Cl_2NO_2SNa$ [M+Na]: 482.0718, found 482.0704.

Synthesis of **2,4-bis(4-bromophenyl)-1-tosylpiperidine (5g)** was followed general procedure and percentage yield of reaction between DTD and 4-bromostyrene was 70% with 63:37 dr ratio. For the major isomer: ^{1}H NMR (500 MHz,$CDCl_3$) δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.0 Hz,2H), 6.83 (d, *J* = 8.5 Hz, 2H), 5.90 (d, *J* = 4.5 Hz, 1H), 4.04 – 4.00 (m, 1H), 3.11 – 3.05 (m, 1H), 2.59 (m, 1H), 2.47 (s, 3H), 2.31 (dd, *J* = 13.9, 1.3 Hz, 1H), 1.78 (td, *J* = 13.5, 5.3 Hz, 1H) , 1.58 (s, 1H) 1.42 (ddd, *J* = 25.7, 12.9, 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 143.5, 138.4, 137.5, 132.0, 131.7, 129.9, 128.6, 128.3, 127.1, 121.2, 120.4, 55.0, 41.7, 36.1, 34.2, 31.6, 21.6; HRMS (ESI) Calcd for $C_{24}H_{23}Br_2NO_2SNa$ [M+Na]: 569.9708, found 569.708.

Synthesis of **2,4-bis(4-iodophenyl)-1-tosylpiperidine (5h)** was followed general procedure and percentage yield of reaction between DTD and 4-iodostyrene was 84% with dr ratio >95:5. For the major isomer:. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.71 (d, *J* = 8.5 Hz, 2H), 5.38 (d, *J* = 4.0 Hz, 1H), 4.01 (d, *J* = 13.0 Hz, 1H), 3.10 – 3.04 (m, 1H), 2.57 (tt, *J* = 12.5, 3.5 Hz, 1H), 2.47 (s, 3H), 2.29 (d, *J* = 14.0 Hz, 1H), 1.57 (s, 1H), 1.78 (td, *J* = 13.5, 5.5 Hz, 1H), 1.42 (ddd, *J* = 25.7, 12.9, 4.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.4, 143.5, 138.3, 138.3, 138.0, 137.7, 129.9, 128.8, 128.6, 127.1, 92.7, 91.7, 55.0, 41.7, 36.2, 34.0, 31.6, 21.6. HRMS (ESI) Calcd for $C_{24}H_{24}I_2NO_2S$[M+H]: 643.9611, found 643.9606.

Synthesis of **2,4-bis(3-fluorophenyl)-1-tosylpiperidine (5i)** was followed general procedure and percentage yield of reaction between DTD and 3-fluorostyrene was 50% 70:30 dr ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.22 – 7.17 (m, 2H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.91 – 6.86 (m, 4H), 6.80 (dt, *J* = 9.8, 2.0 Hz, 1H), 4.20 (dd, *J* = 11.5, 4.5 Hz, 1H), 4.03 (dt, *J* = 13.5, 5.2 Hz, 1H), 3.22 – 3.17 (m, 1H), 2.59 – 2.52 (m, 1H), 2.43 (s, 3H), 2.12 – 2.01 (m, 1H), 1.92 – 1.84 (m, 1H), 1.86 – 1.78 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9 (d, *J* = 207.5 Hz), 161.8 (d, *J* = 206.0 Hz), 146.9 (d, *J* = 27.0 Hz), 144.0 (d, *J* = 27.5 Hz), 143.5, 135.5, 130.1 (d, *J* = 33.0 Hz), 129.5 (d, *J* = 32.5 Hz), 129.3, 127.7, 123.0 (d, *J* = 11.0 Hz), 122.3 (d, *J* = 11.0 Hz), 114.4 (d, *J* = 14.5 Hz), 114.2 (d, *J*= 10.0 Hz), 113.6 (d, *J* = 48.0 Hz), 113.4 (d, *J* = 46.5 Hz), 61.4, 45.8, 41.5, 40.1, 31.6, 21.5; HRMS (ESI) Calcd for $C_{24}H_{24}F_2NO_2S$[M+H]: 428.1490, found 428.1490.

Synthesis of **2,4-bis(3-bromophenyl)-1-tosylpiperidine (5j)** was followed general procedure and percentage yield of reaction between DTD and 3-bromostyrene was 26% with 72:28 dr ratio . ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 7.22 – 7.20 (m, 4H), 7.14 (t, *J* = 7.8 Hz, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 7.7 Hz, 1H), 4.18 (dd, *J* = 11.3, 4.3 Hz, 1H), 4.08 (dt, *J* = 12.9, 5.1 Hz, 1H), 3.22 (ddd, *J* = 13.2, 9.3, 4.3 Hz, 1H), 2.57 – 2.52 (m, 1H), 2.43 (s, 3H), 2.13 – 2.10 (m, 1H), 2.03 – 1.99 (m, 1H), 1.89 (dd, *J* = 19.9, 8.2 Hz, 1H) 1.84 –1.79 (m, 1H). **13**C NMR (125 MHz, $CDCl_3$) δ 146.6, 143.5, 143.2, 135.9, 130.7, 130.6, 130.2, 129.8, 129.8, 129.6, 129.4, 127.6, 126.5, 125.3, 122.7, 122.0, 61.6, 46.0, 41.4, 40.4, 31.8, 21.6. HRMS (ESI) Calcd for $C_{24}H_{24}Br_2NO_2S$[M+H]: 547.9889, found 546.9888.

Synthesis of **2,4-bis(4-bromo-2-fluorophenyl)-1-tosylpiperidine (5k)** was followed general procedure and percentage yield of reaction between DTD and 4-bromo-2-fluorostyrene was 31% with 71:29 dr ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.25 – 7.22 (m, 3H), 7.21 – 7.17 (m, 3H), 7.16 – 7.14 (m, 1H), 7.04 – 7.01 (m, 2H), 4.40 (dd, *J* = 11.5, 4.1 Hz, 1H), 4.14 – 4.09 (m, 2H), 3.16 (ddd, *J* = 13.5, 9.3, 4.2 Hz, 1H), 2.84 – 2.81 (m, 1H), 2.44 (s, 3H), 2.06 – 2.01 (m, 1H), 1.96 – 1.92 (m, 1H), 1.59 – 1.50 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.2 (d, *J* = 249.0 Hz), 159.5 (d, *J* = 250.0 Hz), 143.6, 137.6, 135.0, 130.8 (d, *J* = 4.6 Hz), 130.2, 130.1, 129.8, 129.4, 128.7 (d, *J* = 5.4 Hz), 127.6, 127.4, 127.2 (d, *J* = 3.5 Hz), 127.0, 121.6 (d, *J* = 9.6 Hz), 120.3 (d, *J* = 9.8 Hz), 119.2 (d, *J* = 25.9 Hz), 118.9 (d, *J* = 25.4 Hz), 55.8, 46.4, 37.7, 33.8, 30.4, 21.5; HRMS (ESI) Calcd for $C_{24}H_{22}Br_2F_2NO_2S$[M+H]: 583.9700, found 583.9692.

Synthesis of **2,4-bis(dinaphthalene-2-ly)-1-tosylpiperidine (5l)** was followed general procedure and percentage yield of reaction DTD and 2-vinylnaphthalene was 50% with 86: 14 dr ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 – 7.84 (m, 4H), 7.80 – 7.72 (m, 5H), 7.54 (dd, J = 8.5, 1.5 Hz, 1H), 7.51 – 7.49 (m, 2H), 7.48 – 7.42 (m, 3H), 7.37 (d, J = 8.0 Hz, 2H), 7.12 (dd, *J* = 8.5, 1.5 Hz, 1H), 5.67 (d, *J* = 4.5 Hz, 1H), 4.17 – 4.12 (m, 1H), 3.31 – 3.25 (m, 1H), 2.94 – 2.88 (m, 1H), 2.63 (d, *J* = 14.5 Hz, 1H), 2.49 (s, 3H), 2.08 – 2.02 (m, 1H), 1.71 – 1.60 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 142.5, 138.6, 135.9, 133.4, 133.3, 132.3, 132.3, 129.9, 128.7, 128.2, 128.0, 127.6, 127.5, 127.5, 127.2, 126.2, 126.2, 126.1, 125.8, 125.6, 125.4, 124.8, 124.7, 55.6, 42.0, 36.6, 34.3, 31.8, 21.6. HRMS (ESI) Calcd for $C_{32}H_{30}NO_2S$ [M+H]: 492.1991, found 492.1991.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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Biosketches

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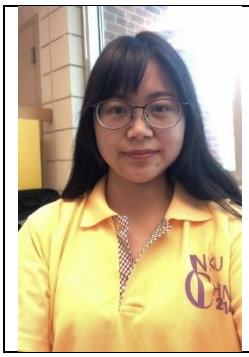
Jacob Istre received his B.S. in Chemistry from Mississippi State University in 2019. He has worked as an undergraduate research associate in Prof. Xin Cui's laboratory, where he studied the development of new cycloaddition methodologies to construct nitrogen-containing heterocycles from alkenes. He is now a Ph.D. student in the research group of Prof. Bradley Merner at Auburn University.



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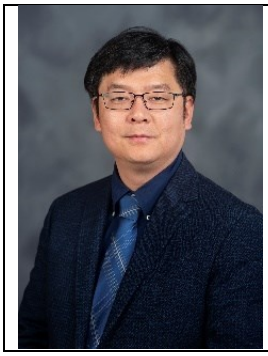

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