Selenium-catalyzed Regioselective Intermolecular Diamination of Dienes and Dienolate Derivatives

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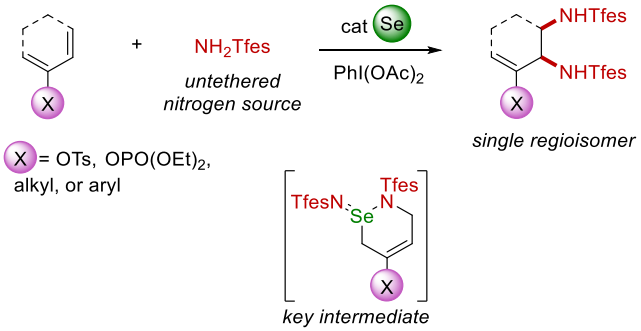
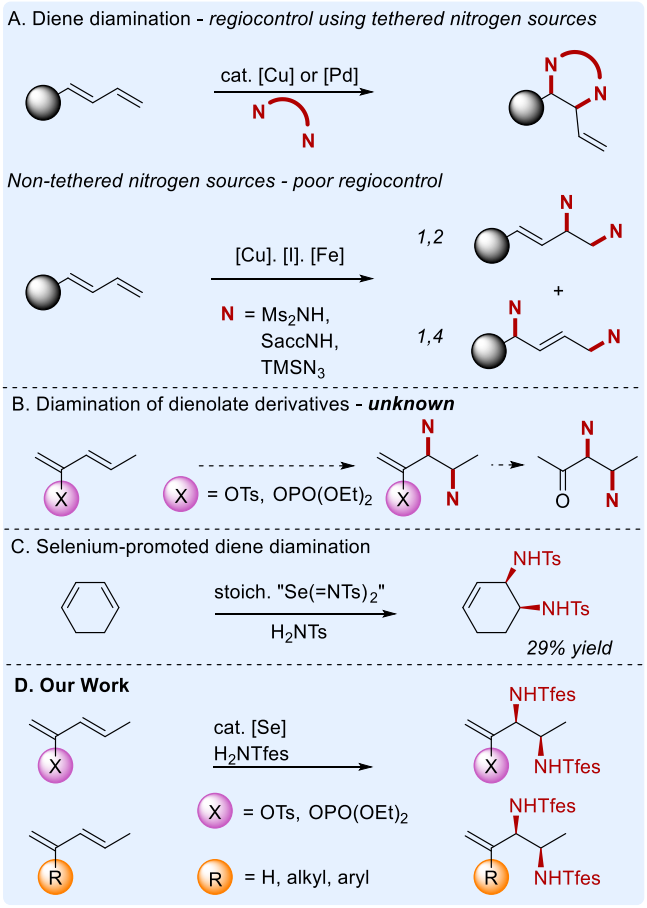


ABSTRACT: We report a selenium-catalyzed diamination of dienes using sulfamates as a convenient nitrogen source. This reaction proceeds regioselectively for 1,2-addition at the less substituted alkene, without need for a tethered diamine. We also report the first diamination of dienyl phosphates and tosylates, affording synthetically useful α,β-diaminoketone derivatives in high *syn* diastereoselectivity. DFT calculations support a mechanism proceeding via [4+2] cycloaddition of the diene with a selenium bis(imide), followed by ring-opening aminolysis and [2,3]-sigmatropic rearrangement.

Vicinal diamines are a recurring structural motif in biologically relevant compounds and serve as important building blocks and synthetic intermediates.[1] The generation of vicinal diamine functionality by direct diamination of alkenes has long been an appealing approach to the synthesis of these compounds.[2] In particular, 1,3-dienes are an attractive carbon feedstock for diamination reactions because they offer increased reactivity relative to alkenes while generating products retaining a C=C bond for further derivatization. On the other hand, the presence of two reactive C=C moieties poses a significant challenge in controlling the regioselectivity of addition, since three distinct regioisomeric products can be formed (1,2- and 1,4-addition). The most common solution to this problem is tethering the two nitrogen groups together, thereby strongly favoring either 1,2-addition[3-6] or 1,4-addition[7]. Successful diaminations employing this approach include the Pd and Cu catalyzed systems reported by Booker-Milburn and Shi and the cycloaddition strategy of Jeffery, affording cyclic urea products in a variety of regioselectivities (Scheme 1A). While these methods offer controllable regioselectivity, subsequent removal of this urea tether is often challenging and requires harsh conditions.

Diamination reactions that incorporate two untethered nitrogen sources are much rarer and are more limited in substrate scope. Regioselectivity is most often controlled by introduction of a conjugating group at the 1-position, thereby introducing a strong thermodynamic preference for terminal 1,2-addition.[8-12] In the absence of this conjugating substituent, selectivity for 1,2- vs. 1,4-addition is poor.[12,13]



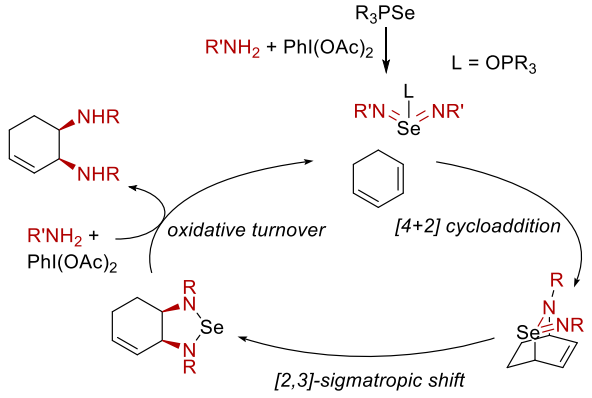
Scheme 1. Challenges in Diene Diamination Reactions.

We also noted that diamination reactions of dienes bearing potentially functionalizable heteroatomic substituents such as sulfonates and phosphates have not yet been reported (Scheme 1B). These novel dienes are readily prepared from α,β-unsaturated ketones. Development of a diamination of these substrates would allow access to a much broader range of products by taking advantage of the powerful reactivity of the resulting vinyl sulfonate/phosphate.[14]

Based on stoichiometric [4+2] reactions of dienes with sulfur bis(imides) by Weinreb,[15] Sharpless reported a regioselective diamination of a few 1,3-dienes using stoichiometric Se, anhydrous chloramine-T, and $TsNH_2$ to generate a putative selenium bis(imide).[16] Exclusive 1,2-addition was observed, but yields were poor (Scheme 1C).

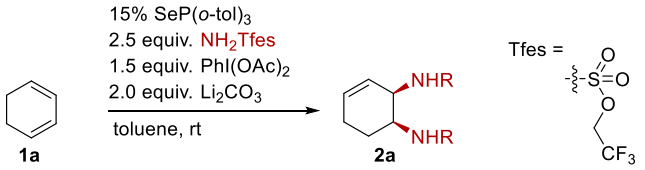
There has recently been renewed interest in selenium catalysis for alkene functionalization.[17-19] We recently developed a Se-catalyzed allylic amination that allows mild catalytic turnover of the key selenium bis(imide) intermediate, giving allylic sulfonamides in high yields for a wide range of substrates.[21] We imagined that phosphine selenides could be used to catalyze a highly regioselective diamination of dienes, where the unique [4+2]-cycloaddition/[2,3]-sigmatropic rearrangement mechanism would enforce exclusive 1,2-addition without the need for a hard-to-remove tether (Scheme 2). Furthermore, the unusual tolerance for reactive heteroatom-substituted alkenes these metal-free catalysts have previously displayed[22] hinted that we might be able to perform similar diamination reactions for previously unknown dienes bearing sulfonates and phosphates, which could serve as convenient handles for further functionalization. Here, we report the development of a Se-catalyzed diamination of dienes and dienyl phosphates and tosylates that proceeds in high regioselectivity using a simple untethered sulfamate (Scheme 1D).

Scheme 2: Proposed Se-Catalyzed Diamination Mechanism.



For initial investigations, we chose 1,3-cyclohexadiene as our test substrate, as few diaminations have been reported using this diene. Our typical allylic amination conditions gave full consumption of diene, but only low yield of the expected diamination product, comparable to Sharpless' initial stoichiometric result (Table 1). Switching from $NsNH_2$ to electron poor sulfamates such as $TcesNH_2$ and $TfesNH_2$ gave substantially improved yields. A screening of catalysts found that phosphine selenides with bulky aryl substituents, such as SeP(*o*-tolyl)$_3$ and SeP(1-naphthyl)$_3$ gave higher yields than trialkyl phosphines or sterically unhindered triarylphosphines. The addition of inorganic bases such as MgO and Li_2CO_3 further increased the observed yield, presumably by neutralizing small quantities of in situ generated acid, as we have seen previously.[22] Dichloromethane and toluene were suitable solvents, with toluene generally giving the highest yields.

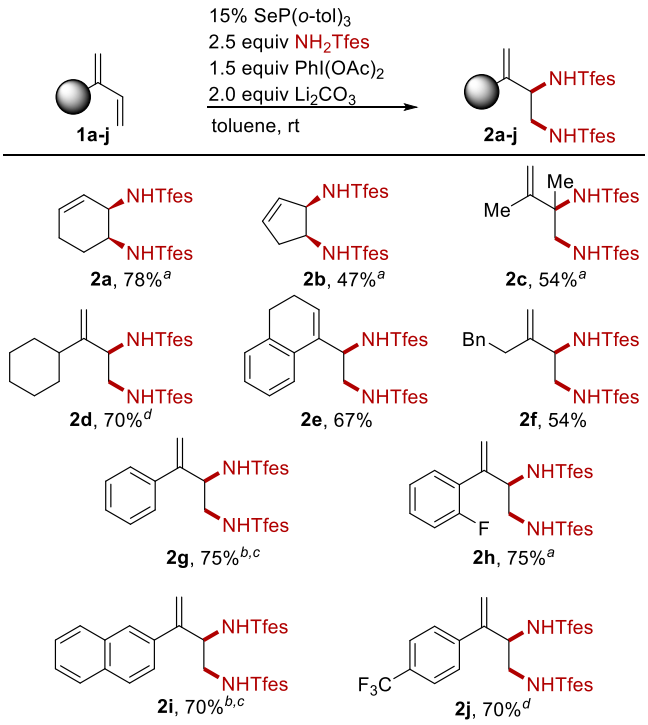
Table 1. Optimized Conditions for Diene Diamination.



Deviation from Conditions	yield
none	78%
$NsNH_2$ instead of $TfesNH_2$, no base	20%
$TfesNH_2$, no base	68%
$SePCy_3$ instead of SeP(*o*-tol)$_3$, no base	35%
SeP(1-Np)$_3$ instead of SeP(*o*-tol)$_3$, no base	50%
SeIMe instead of SeP(*o*-tol)$_3$, no base	16%
MgO instead of Li_2CO_3	76%

With these optimized conditions, we set out to examine the scope of dienes compatible with this reaction (Scheme 3). 5- and 6-membered ring systems were successfully functionalized, both giving exclusively the *cis* diastereomer. Several 2-aryl and 2-alkyl substituted 1,3-butadienes reacted to give a single regioisomer of the vicinal diamines in good yields. Additionally, 1,2- and 2,3- disubstituted butadienes were also selectively functionalized under these reaction conditions. In all cases, diamination took place at the less substituted alkene, as expected from consideration of the electronics of the [4+2] reaction (see Scheme 5). Simple 1-substituted dienes were fully consumed under these reaction conditions, but gave a mixture of unidentified products.

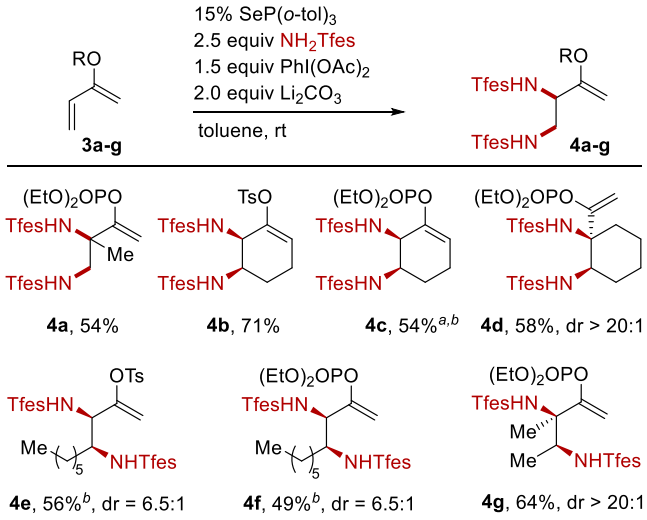
Scheme 3. Substrate Scope for Diene Diamination.



[a]CH_2Cl_2 as solvent [b]$SeP(1\text{-}Np)_3$ as catalyst [c]MgO as base [d]5 mol% DMAP as base

At this stage, we considered dienyl phosphates and tosylates as potential diamination substrates. We hypothesized that the electron-withdrawing ability of the phosphate and sulfonate substituents could attenuate the reactivity of the diene and thereby reduce its side reactivity and improve the yield of diamination. At the same time, resonance donation from oxygen would direct the [4+2] regioselectivity. Additionally, these dienyl phosphates could be further transformed via cross-coupling or hydrolysis to other vicinal diamine derivatives.

Scheme 4. Substrate Scope for Dienyl Phosphate and Tosylate Diamination.



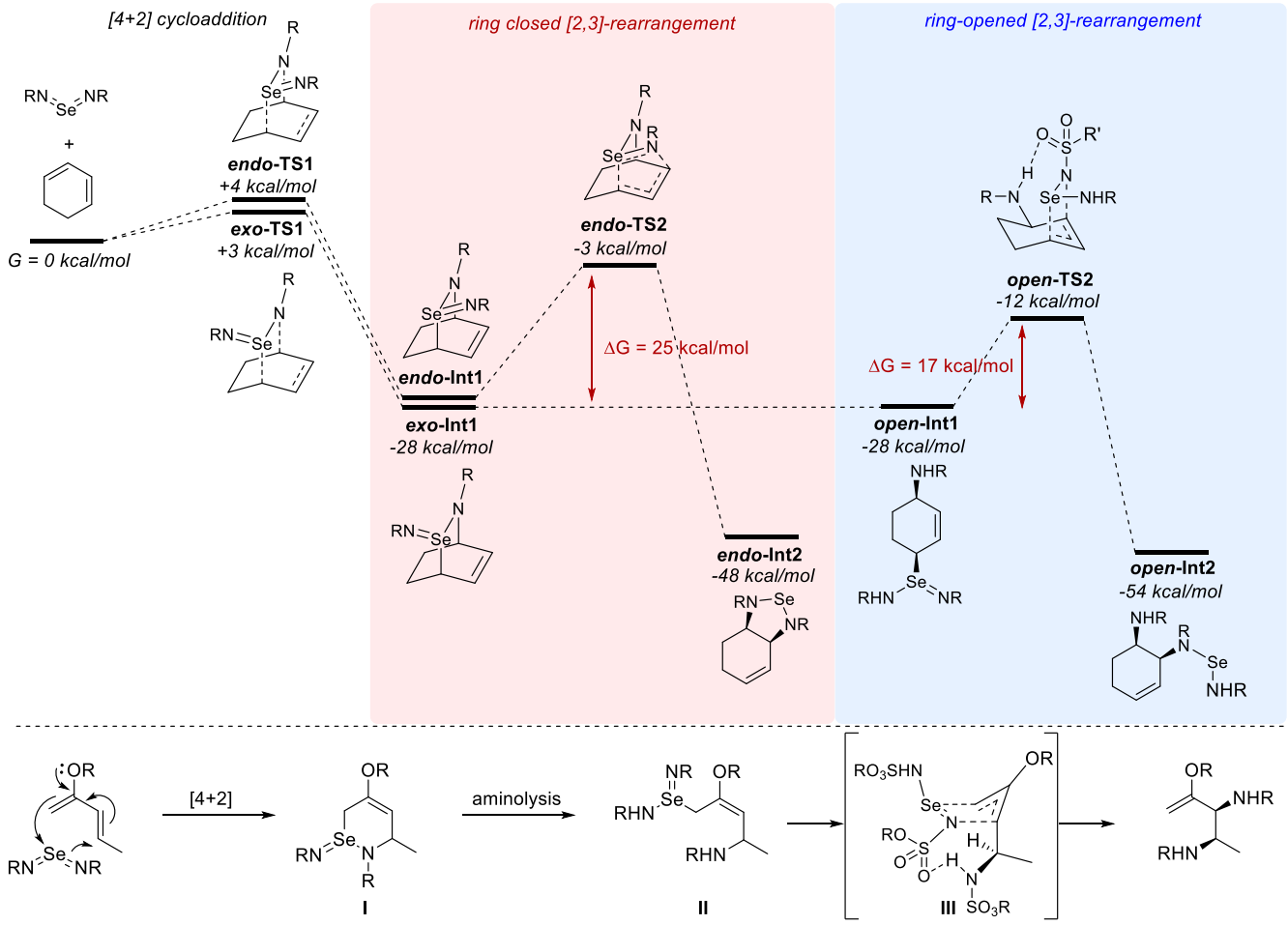
[a]$SeP(1\text{-}Np)_3$ as catalyst [b]MgO as base.

Gratifyingly, dienyl phosphates and tosylates were smoothly functionalized under our conditions to furnish diamines in good yields (Scheme 4). An unusually wide range of substitution patterns were tolerated, including 2,3-, 1,2,4-, 1,3-, and 1,2,3-substituted dienes, allowing the formation of primary, secondary, and tertiary alkyl amines. In all cases, a single regioisomer was formed, always arising from diamination of the non-oxygenated alkene, leaving the vinyl phosphate/tosylate group intact in the products. In all cases, good to excellent diastereoselectivity was observed favoring syn addition to the alkene (see SI).

To better understand the mechanism and the origin of the *syn* addition selectivity, we performed DFT calculations on the proposed [4+2]-cycloaddition/[2,3]-sigmatropic shift mechanism (Scheme 5).[23] The initial cycloaddition can proceed with either *endo* or *exo* selectivity via transition states ***endo*-TS1** or ***exo*-TS1**. Calculations find that there is almost no difference in energy between *endo* and *exo* cycloaddition transition states or products, indicating that a mixture of ***endo*-Int1** and ***exo*-Int1** isomers is likely to be formed in the first step. The cycloaddition is highly exergonic (ΔG = -28 kcal/mol), and thus unlikely to be reversible. This is consistent with Weinreb's observation of a 1:1 mixture of *endo* and *exo* products in stoichiometric [4+2]-cycloadditions of sulfur bis(imide)s.[15]

Based on these calculations, an irreversible cycloaddition should produce substantial amounts of the *exo* cycloadduct

Scheme 5. DFT Calculations and Stereochemical Model.



which is incapable of [2,3]-rearrangement or cycloreversion, and thus, this catalytic system should not be feasible. As an alternative, we considered the possibility that the bicyclic ring system of the [4+2] cycloadducts could be opened by aminolysis of the Se-N bond. Calculations indicate that this transformation is nearly ergoneutral. This ring-opened product (***open*-Int1**) can now undergo a [2,3]-rearrangement with a significantly lower activation barrier ($\Delta G^{\ddagger}$ = 17 kcal/mol). This set of calculations allows the ring strain for each selenium-containing ring to be estimated. The 6-membered ring [4+2] adducts suffer from substantially less ring strain ($\Delta H_{aminolysis}$ = -9 kcal/mol) than the 5-membered ring [2,3]-rearrangement product (***endo*-Int2**) (ΔH = -15 kcal/mol), and the transition state ***endo*-TS2** has the highest ring strain of all (ΔH = -19 kcal/mol), explaining the abnormally high activation barrier. The aminolysis pathway avoids this developing strain and allows conversion of both *endo* and *exo* cycloadducts to the final rearrangement product.

In all cases, the regioselectivity of diamination can be predicted by considering the electronics of the initial [4+2] cycloaddition. Electron-releasing substituents at the 2-position result in C-1 attack on selenium, leading to selective formation of cycladduct **I**, and eventually to amination of the less nucleophilic alkene. The phosphate and tosylate groups exert overriding control over the regioselectivity of the diamination reaction, suggesting that significant resonance donation from oxygen is a strong controlling factor in the [4+2] transition state.

Since the stereochemistry at selenium is destroyed in the aminolysis mechanism, the *syn* selectivity is exclusively controlled by the [2,3]-sigmatropic rearrangement step from cis-alkene intermediate **II**. Here, avoidance of $A_{1,3}$-strain results in preferred conformation **III**, and approach of the Se=N group in the envelope transition state occurs preferentially from the same face as the sulfamate nitrogen, driven by a hydrogen bond between the sulfamate N-H and the imide sulfonyl group.

In conclusion, we have developed a Se-catalyzed diamination of dienes that gives excellent regioselectivity while still employing a simple untethered sulfamate as the nitrogen source. This metal-free catalytic system allows dienyl phosphates and dienyl tosylates to be diaminated in good yield, regioselectivity, and syn diastereoselectivity in both cyclic and acyclic systems. Calculations reveal that ring-opening aminolysis of the initial [4+2] cycloadducts reduces the strain in the [2,3]-sigmatropic rearrangement, and allows a mixture of [4+2] cycloadducts to converge to a single diastereomeric product.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedure and additional data (PDF)
Spectral characterization of materials (PDF)
DFT calculations (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Lucet, D.; Le Gall. T.; Mioskowski. C. The Chemistry of Vicinal Diamines. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580-2627.

(2) Cardona, F.; Goti, A. Metal-catalysed 1,2-diamination reactions. *Nat. Chem*. **2009**, *1*, 269-275.

(3) a) Zhu, Y.; Cornwall, R. G.; Du, H.; Zhao, B.; Shi Y. Catalytic Diamination of Olefins via N-N Bond Activation. *Acc. Chem. Res.* **2014**, *47*, 3665–3678; b) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. Catalytic Asymmetric Diamination of Conjugated Dienes and Triene. *J. Am. Chem. Soc.* **2007**, *129*, 762–763.

(4) Bar, G. L. J.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. Pd(II)-Catalyzed Intermolecular 1,2-Diamination of Conjugated Dienes. *J. Am. Chem. Soc.* **2005**, *127*, 7308–7309.

(5) Wu, M. -S.; Fan, T.; Chen, S. -S.; Han, Z. -Y.; Gong, L. -Z. Pd(II)-Catalyzed Asymmetric Oxidative 1,2-Diamination of Conjugated Dienes with Ureas. *Org. Lett*. **2018**, *20*, 2485–2489.

(6) a) Wu, Z.; Wen, K.; Zhang, J.; Zhang, W. Pd(II)-Catalyzed Aerobic Intermolecular 1,2-Diamination of Conjugated Dienes: A Regio- and Chemoselective [4+2] Annulation for the Synthesis of Tetrahydroquinoxalines. *Org. Lett.* **2017**, *19*, 2813-2816. b) Liu, H.; Li, Y.; Yang, Z.; Ge, Q.; Wu, Z.; Zhang, W. Pd-Catalyzed Aerobic Intermolecular 1,2-Diamination of Conjugated Dienes: Regio- and Chemoselective Synthesis of Piperazines and 2-Piperazinones. *Chem. Eur. J.* **2022**, *28*, e202201808.

(7) a) Jeffrey, C. S.; Anumandla, D.; Carson, C. R. 1,4-Diamination of Cyclic Dienes via a (4 + 3) Cycloaddition of Diaza-Allyl Cationic Intermediates. *Org. Lett.* **2012**, *14*, 5764–5767. b) D. Anumandla, D.; Littlefield, R.; Jeffrey, C. S. Oxidative 1,4-Diamination of Dienes Using Simple Urea Derivatives. *Org. Lett*. **2014**, *16*, 5112–5115.

(8) Zhou, H.; Jian, W.; Qian, Bo.; Ye, C.; Li, D.; Zhour, J.; Bao, H. Copper-Catalyzed Ligand-Free Diazidation of Olefins with $TMSN_3$ in CH_3CN or in H_2O. *Org. Lett*. **2017**, *19*, 6120-6123.

(9) Shen S. -J.; Zhu, C. -L.; Lu, D. -F.; Xu, Hao. X. Iron-Catalyzed Direct Olefin Diazidation via Peroxyester Activation Promoted by Nitrogen-Based Ligands. *ACS Catal*, **2018**, *8*, 4473-4482.

(10) a) Forster, D.; Guo, W.; Wang, Q.; Zhu, J. Photoredox Catalytic Three-Component Amidoazidation of 1,3-Dienes. *ACS Catal*. **2021**, *11*, 10871-10877. b) Guo, W.; Wang, Q.; Zhu, J.; Selective 1,2-Aminoisothiocyanation of 1,3-Dienes Under Visible-Light Photoredox Catalysis. *Angew. Chem. Int. Ed*. **2021**, *60*, 4085-4089.

(11) Dai, Z. -Y.; Guzei, I. A.; Schomaker, J. M. Iron-Catalyzed Site- and Regioselective 1,2- Azidoamidations of 1,3-Dienes. *Org. Lett*. **2024**, *26*, 269-273.

(12) Lishchynskyi, A.; Muñiz, K. An Approach to the Regioselective Diamination of Conjugated Di- and Trienes. *Chem. Eur. J.* **2012**, *18*, 2212–2216.

(13) Martínez, C.; Martínez, L.; Kirsch, J.; Escudero-Adán, E. C.; Martin, E.; Muñiz, K. Copper-Mediated 1,4-Diamination of 1,3-Butadienes. *Eur. J. Org. Chem*. **2014**, *2014*, 2017–2021.

(14) Sellars, J. D.; Steel, P. G. Transition metal-catalysed cross-coupling reactions of P-activated enols. *Chem. Soc. Rev*. **2011**, *40*, 5170-5180.

(15) a) Weinreb, S. M. Synthetic methodology based upon N-sulfinyl dienophile [4+2]- cycloaddition reactions. *Acc. Chem. Res*. **1988**, *21*, 313-318. b) Natsugari, H.; Whittle, R. R.; Weinreb, S. M. Stereocontrolled synthesis of unsaturated vicinal diamines from Diels-Alder adducts of sulfur dioxide bis(imides). *J. Am. Chem. Soc*. **1984**, *106*, 7867-7872.

(16) a) Sharpless, K. B.; Singer, S. P. 1,2-Diamination of 1,3-Dienes by Imido Selenium Compounds. *J. Org. Chem.* **1976**, *41*, 2504–2506. b) Bruncko, M.; Khuong, T.-V. V.; Sharpless, K. B. Allylic Amination and 1,2-Diamintion with a Modified Diimidoselenium Reagent. *Angew. Chem. Int. Ed*. **1996**, *35*, 454-456.

(17) a) Trenner, J.; Depken, C.; Weber, T.; Breder, A. Direct Oxidative Allylic and Vinylic Amination of Alkenes Through Selenium Catalysis. *Angew. Chem. Int. Ed.* **2013**, *52*, 8952-8956. b) Ortgies, S.; Breder, A. Oxidative Alkene Functionalizations via Selenium-π-Acid Catalysis *ACS Catal*. **2017**, *7*, 5828-5840.

(18) Shao, L.; Li, Yiming.; Lu, J.; Jiang, X. Recent progress in selenium-catalyzed organic reactions. *Org. Chem. Front*. **2019**, *6*, 2999-3041.

(19) Singh, F. V.; Wirth, T. Selenium reagents as catalysts. *Catal. Sci. Technol*. **2019**, *9*, 1073-1091.

(20) Tao, Z.; Gilbert, B. B.; Denmark, S. E. Catalytic, Enantioselective syn-Diamination of Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 19161-19170.

(21) a) Teh, W. P.; Obenschain, D. C.; Black, B. M.; Michael, F. E. Catalytic Metal-free Allylic C-H Amination of Terpenoids. *J. Am. Chem. Soc*. **2020**, *142*, 16716-16722. b) Maloney, T. P.; Dohoda, A. F.; Zhu, A. C.; Michael, F. E.; Stereoretentive and regioselective selenium-catalyzed intermolecular propargylic C–H amination of alkynes. *Chem. Sci.* **2022**, *13*, 2121-2127.

(22) Maloney, T. P.; Berman, J. L.; Michael, F. E. Metal-Free Allylic C-H Amination of Vinylsilanes and Vinylboronates using Silicon or Boron as a Regioselectivity Switch. *Angew. Chem. Int. Ed*. **2022**, *61*, e202210109.

(23) Gaussian 16, Revision C.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.;

Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2016.