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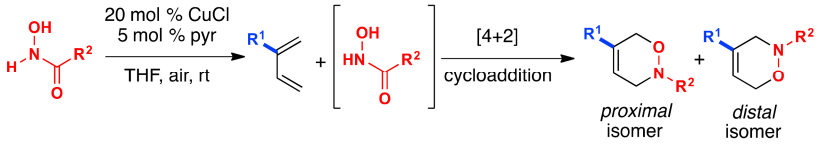

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Nitrosocarbonyl Hetero-Diels–Alder Cycloaddition with 2-Substituted 1,3,-Butadienes

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ABSTRACT

A study of the reactivity of 2-substituted 1,3-butadienes with nitrosocarbonyl compounds in the 4+2 cycloaddion has been carried out showing that the regioselectivity involves a delicate balance of steric and electronic effects. 2-Aryl 1,3-butadienes favor the distal isomer with the magnitude of preference ranging from 4:1 to 15:1 depending on the nature of the nitrosocarbonyl group. However, when bulky 2-substituted dienes are used the proximal isomer is formed preferentially. The results obtained, together with previous theoretical calculations and experimental data, provide further data to aid in synthetic planning.

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Introduction

Transformations that simultaneously construct carbon–nitrogen and carbon–oxygen bonds are essential for streamlining the synthesis of natural products and pharmaceutically relevant agents.[1] In this regard, hetero-Diels–Alder reactions between nitroso compounds and dienes have played an important role in organic chemistry since their discovery in 1947.[2] The oxazine scaffold, which results from the [4+2] cycloaddition, serves as a strategic intermediate for the synthesis of a wide-range of natural products.[3] For example, cleavage of the N–O oxazine bond results in a skeleton with a 1,4-relationship between the alcohol and amine substituents, which are valuable for further elaboration.[1,3,4] However, like many heterocycloadditions, the use of unsymmetrical dienes, such as 2-substituted 1,3-butadiene, necessitates regiocontrol for this transformation to be truly synthetically useful because the nitroso [4+2]-cycloaddition can provide two regioisomers. Figure 1 shows the regiochemical outcome for 2-substituted dienes. When the 2-substituent is close to the oxygen heteroatom of the oxazine adduct it is referred to as the proximal isomer and when the 2-substituent is close to the nitrogen heteroatom of the oxazine adduct it is referred to as the distal isomer.

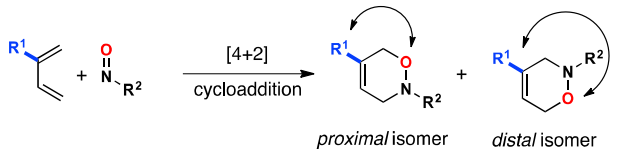
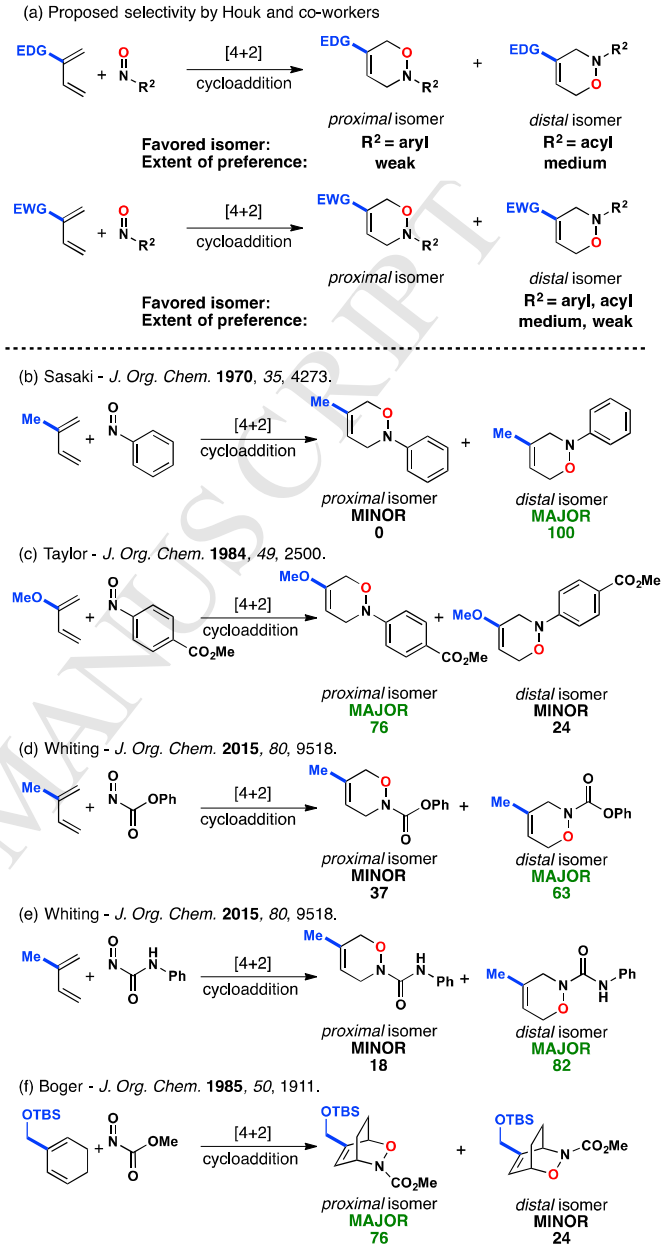


Figure 1. Regioselectivity of nitroso-Diels–Alder reactions with 2-substituted dienes.

Several groups have independently reported on the regiocontrol of the nitroso-Diels–Alder (NDA) reaction using both computational and experimental studies.[5] As can be seen by Scheme 1 the regioselectivity for 2-substituted dienes can depend on a combination of both steric and electronic effects on both the nitroso and the diene partners. Using FMO and DFT calculations, as well as experimental data accumulated from the literature, Houk and co-workers proposed a general rational for regiochemical preference for various monosubsubstituted dienes, including 2-substituted dienes, and nitroso sources (Scheme 1a).[6a,5d,6b] They showed that the principle interaction is between the HOMO(diene) and LUMO(nitroso heterodienophile) and that there is a strong preference for an endo transition state. In general, for 2-substituted dienes the HOMO should have its largest coefficient at the C1-position and hence, the distal isomer is typically expected (Scheme 1b). However, as seen by Scheme 1c using an electron-rich diene in combination with an electron-poor aryl nitroso compound favors the proximal isomer.[5b] Furthermore, Whitting and co-workers recently reported that the magnitude of preference for the proximal vs. distal isomer can also depend on the nature of the nitroso group.[5h] For example, the reaction of nitrosoformate (Scheme 1d) and nitrosoformamide (Scheme 1e), generated in situ through a copper-catalyzed aerobic oxidation, with 2-methyl-1,3-butadiene gave distal and proximal isomers with a preference for the distal form that varied from ~1.7:1 to ~4.6:1 depending on the nature of the nitroso compound. Finally, Boger and co-workers showed that steric effects are also important in governing regioselectivity (Scheme 2f).[5c] Because there is a significant unfavorable interaction between the nitrogen lone pair with the π electrons of the electro-rich diene, the endo transition state is favored.[5d] This exo lone pair effect causes the diene to be in close proximity to the nitrogen substituent and if the steric interaction is large the proximal isomer can be favored. It is clear that the regiochemical preference for the NDA reaction can vary from substrate to substrate and more studies are necessary to help facilitate predictability, specifically for the nitrosocarbonyl Diels–Alder reaction. In the present article, we wish to report our studies with a range of both nitrosocarbonyl compounds and 2-substituted dienes.



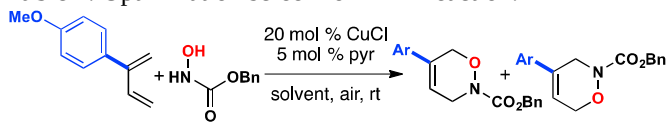
Scheme 1. Literature examples of regiochemical studies for the nitroso-Diels–Alder reaction with 2-substituted dienes.

Results and Discussion

We chose to study 2-aryl-1,3-butadienes initially as they avoid the potentially competing nitrosocarbonyl ene reaction due to their lack of allylic protons.[7] To generate the nitrosocarbonyl compound in situ we employed our previously developed copper-catalyzed aerobic oxidation conditions (20 mol% CuCl, 5 mol% pyridine).[8a,7f,8b-d] Initially a solvent and ligand screen were conducted using 2-aryl-1,3-butadiene **1** and *N*-hydroxycarbamate **2** (Table 1) and in all cases we observed a preference for the distal isomer. The regioselectivity was determined with the aid of HSQC and ^{15}N HMBC. The reaction solvent and ligand for copper showed a modest influence on the overall yield of the NDA reaction, but had little effect on the observed

regioselectivity. This is consistent with previous results and supports a transition state with little polar character.[5c,5d]

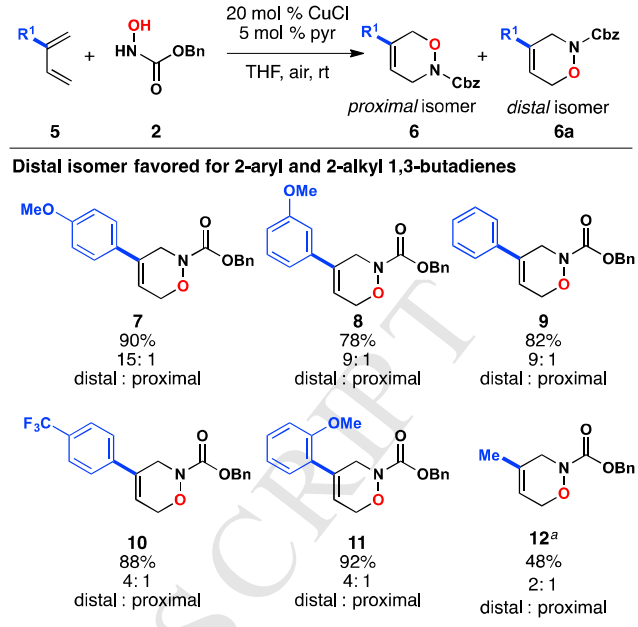
Table 1. Optimization screen for NDA reaction.



Entry	Solvent	Ligand	% Yield	Proximal : Distal
1	toluene	pyridine	61	1 : 14
2	MeOH	pyridine	61	1 : 15
3	2-Me THF	pyridine	71	1 : 15
4	THF	pyridine	85	1 : 15
5	THF	ethyl oxazoline	78	1 : 15
6	THF	ethyl nicotinate	58	1 : 14
7	THF	bipyridyl	60	1 : 15

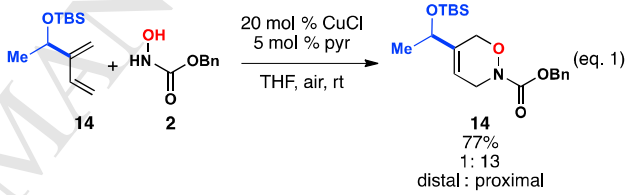
We next evaluated the electronic effects of the 2-substituent of the 1,3-butadiene on regioselectivity using *N*-hydroxycarbamate **2** as the nitroso precursor (Table 2, only major regioisomer shown). Based on Houk's model one would predict that the distal isomer would be preferred as the group at the 2-position increases in electron density because the interaction between the HOMO(diene) and LUMO(nitroso heterodienophile) is maximized.[5d] This trend was observed in our experimental results. Electron donating aryl groups give the highest preference for the distal regioisomer with selectivities up to 15:1, while electron withdrawing aryl groups show a lower preference for the distal regioisomer with selectivities dropping to 4:1. Interestingly, the *o*-methoxy aryl group (**11**) resulted in a modest 4:1 selectivity despite being electronically similar to the *p*-methoxy aryl group (**7**). Presumably, the reduced selectivity results from allyic strain that causes the aryl ring to rotate out of conjugation with the diene in the reactive *s*-cis conformation thus reducing electron density on the alkene and minimizing the electronic preference for the distal isomer. Consistent with the literature, 2-methyl-1,3-butadiene gave only a slight preference for the distal isomer (2:1, distal:proximal) and nitrosocarbonyl ene adduct was also observed in 38% yield.[5h] However, in the case of a bulky 2-substituent the proximal isomer was formed preferentially (eq. 1). Of note, no nitrosocarbonyl ene reaction was observed for this example. This highlights that sterics can override the electronic preference for the distal isomer. Presumably, the reversal in selectivity is due to unfavorable interactions between the bulky group of the diene and the nitrosocarbonyl in the preferred endo transition state. While the exo transition state would lead to the distal isomer, this is unlikely due to the exo lone pair effect and hence the proximal isomer is favored in this case.

Table 2. Scope of nitrosoformate hetero-Diels–Alder reaction with a range of 2-substituted 1,3-butadienes.



[a] When 2-methyl 1,3-butadiene was used a 38% yield of the nitrosocarbonyl ene product was also isolated.

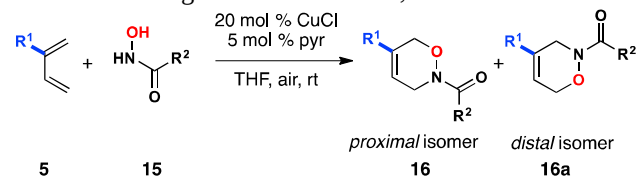
Proximal isomer favored for bulky 2-alkyl 1,3-butadienes



To further study the regiochemical outcome of the NDA reaction, we next evaluated the effects of the N-substituent of the nitrosocarbonyl compound on the reaction (Table 3). Initially, using neutral 2-phenyl-1,3-butadiene, which gave average regioselectivity for the distal isomer (9:1), we evaluated three different formate groups (Cbz, Troc, and Boc) on the nitrogen substituent of the nitrosocarbonyl (Table 3, **10**, **19**, and **20**). While N-Troc protected hydroxylamine gave comparable degrees of regioselectivity to N-Cbz (8:1 and 9:1, respectively), switching to the bulky N-Boc group caused a significant drop in selectivity from 9:1 to 3:1. These results show that steric effects of the nitrosocarbonyl compound influence the regioselectivity and should be considered at the design stage. In this case, we speculate that the drop in selectivity is due to unfavorable interactions of the O-*tert*-butyl group of the nitrosocarbonyl and the phenyl substituent of the diene in the preferred endo transition state. Next, we investigated the use of nitrosoformamide derivatives, which provided the highest selectivity for Whiting and co-workers with 2-methyl-1,3-butadiene (Scheme 1e vs. Scheme 1d).[5h] In the presence of electron rich *p*-methoxy aryl group, mixed results were observed with the preference for the distal isomer varying from 20:1 (**19**), which was an improvement compared to Cbz-nitrosoformate (**7**, 15:1), to 9:1 (**20**). Switching the methoxy group on the aryl ring to the *meta*-position decreased the selectivity from 9:1 to as low as 4:1 compared to the analogous nitrosoformate (**8** vs. **21**–**23**). However, with electron deficient *p*-CF_3-aryl group a notable increase in selectivity was observed with the formation of **24**, while adduct **25** was isolated in with a similar distal preference as the corresponding N-Cbz adduct **10**. When 2-methyl 1,3-

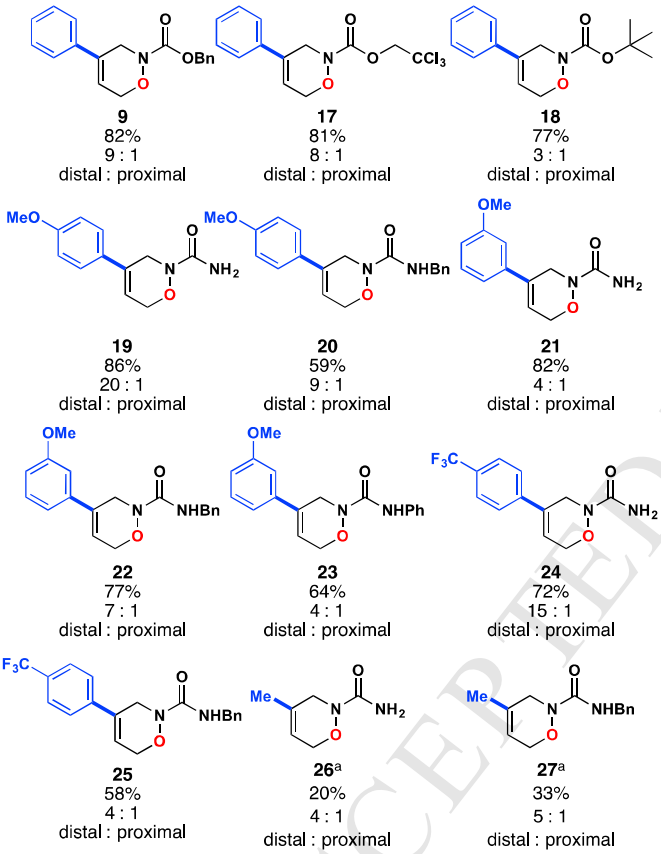
butadiene was employed improved regioselectivity was observed (**26** and **27**), which is consistent with Whiting and co-workers results. Finally, the use of bulky 2-substituted 1,3-dienes were studied with Cbz, Troc, and Boc nitrogen protected nitrosocarbonyl compounds (**14**, **28**, and **29**). Similar to our previous results, these reactions were highly selective for the proximal isomer with selectivities up to 1:17. However, unlike the 2-aryl substituted dienes, the selectivity was improved when bulky N-Boc group was used.

Table 3. Scope of nitrosocarbonyl hetero-Diels–Alder reaction with a range of 2-substituted 1,3-butadienes.



5 15 16 16a

Distal isomer favored for 2-aryl and 2-alkyl 1,3-butadienes



9 82% 9 : 1 distal : proximal

17 81% 8 : 1 distal : proximal

18 77% 3 : 1 distal : proximal

19 86% 20 : 1 distal : proximal

20 59% 9 : 1 distal : proximal

21 82% 4 : 1 distal : proximal

22 77% 7 : 1 distal : proximal

23 64% 4 : 1 distal : proximal

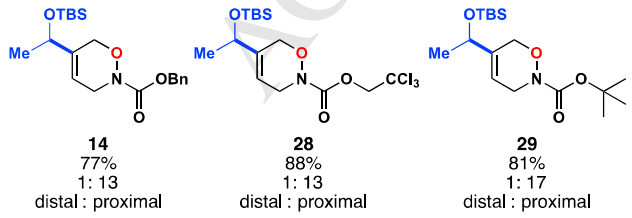
24 72% 15 : 1 distal : proximal

25 58% 4 : 1 distal : proximal

26[a] 20% 4 : 1 distal : proximal

27[a] 33% 5 : 1 distal : proximal

Proximal isomer favored for bulky 2-alkyl 1,3-butadienes



14 77% 1: 13 distal : proximal

28 88% 1: 13 distal : proximal

29 81% 1: 17 distal : proximal

[a] When 2-methyl 1,3-butadiene was used the ene adduct was also isolated (**26** = 10% and **27** = 12%, respectively).

Conclusion

In conclusion, this study revealed that the hetero-Diels–Alder cycloaddition of nitrosocarbonyl compounds and 2-substituted 1,3-butadienes can afford either the distal or proximal isomer preferentially. The factors governing the regioselectivity depend on the both the steric and electronic effects of both the diene and nitroso reagent. With aryl groups at the 2-position, the distal isomer is always favored but the ratio can vary depending on the sterics of the formate group appended to the nitrosocarbonyl. In this case, N-Boc gave the lowest selectivity. While nitrosoformamides consistently afforded oxazine adducts with a preference for the distal isomer, the factors governing the selectivity was less predictable. This work also showed that the proximal isomer is favored when a bulky 2-substituted 1,3-butadiene is used. In general, the results can be rationalized using Houk's model where there is a strong preference for the endo path and the regioselectivities of 2-substituted dienes involves the delicate balance of stereoelectronic effects. The results presented will help aid in synthetic planning and provide further examples to strengthen the predicted outcome of the nitrosocarbonyl hetero-Diels–Alder reaction.

Experimental section

General Procedure: To a stirred solution of hydroxamic acid (1 equiv) and 2-substituted-1,3-butadiene (1.2 equiv) in THF (0.1 M) was added 20 mol % CuCl and 5 mol % pyridine. The reaction was stirred at room temperature open to the air until complete by TLC. Upon completion, the reaction was quenched with EDTA (0.5 M, pH 7.0), diluted with ethyl acetate and stirred until color no longer persisted in organic layer (approx. 30 min). The reaction was extracted with ethyl acetate three times and the combined organic layers were dried over MgSO4. The product was filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford the corresponding oxazine product.

Benzyl 4-(4-methoxyphenyl)-3,6-dihydro-2H-1,2-oxazine-2-carboxylate (**7**):

According to the general procedure, oxazine products **7** and **7a** were isolated as a mixture (28 mg, 90%, 15:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 – 7.25 (m, 7H), 6.91 – 6.84 (m, 2H), 6.09 – 6.04 (m, 1H), 5.24 (s, 2H), 4.61 – 4.56 (m, 2H), 4.51 – 4.46 (m, 2H), 3.80 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.6, 155.6, 135.9, 132.3, 129.5, 128.5, 128.3, 128.2, 126.0, 118.1, 114.0, 68.8, 67.8, 55.3, 46.3; IR (thin film) 3041, 2933, 1706, 1608, 1515, 1455, 1346, 1283, 1246, 1182, 1095, 1032 cm^{-1}; MS (ESI) *m/z* 348.13 (348.12 calculated for $C_{19}H_{19}NO_4Na$ $[M+Na]^+$).

Benzyl 4-(3-methoxyphenyl)-3,6-dihydro-2H-1,2-oxazine-2-carboxylate (**8**): According to the general procedure, oxazine products **8** and **8a** were isolated as a mixture (24 mg, 78%, 9:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.22 (m, 6H), 6.96 – 6.91 (m, 1H), 6.89 – 6.82 (m, 2H), 6.19 – 6.11 (m, 1H), 5.24 (s, 2H), 4.62 – 4.57 (m, 2H), 4.52 – 4.48 (m, 2H), 3.80 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.8, 155.6, 138.4, 135.9, 132.9, 129.7, 128.6, 128.3, 128.2, 120.2, 117.3, 113.4, 110.9, 68.7, 67.8, 55.2, 46.3; IR (thin film) 3064, 2941, 2839, 1706, 1600, 1580, 1430, 1346, 1289, 1211, 1171, 1098, 1050 cm-1; HRMS (ESI) *m/z* 348.1248 (348.1212 calculated for $C_{19}H_{19}NO_4Na$ $[M+Na]^+$).

Benzyl 4-phenyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate (**9**): According to the general procedure, oxazine products 9 and 9a were isolated as a mixture (25 mg, 82%, 9:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.25 (m, 10H), 6.23 – 6.18 (m, 1H), 5.27 (s, 2H), 4.65 – 4.60 (m, 2H), 4.57 – 4.52 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.6, 136.9, 135.9, 133.0, 128.7, 128.6, 128.3, 128.2, 128.2, 124.9, 119.9, 68.8, 67.9, 46.3; IR (thin film) 3033, 2906, 2849, 1704, 1497, 1408, 1347, 1221, 1096 cm^{-1}; MS (ESI) *m/z* 318.12 (318.11 calculated for $C_{18}H_{17}NO_3Na$ $[M+Na]_+$).

Benzyl 4-(4-(trifluoromethyl)phenyl)-3,6-dihydro-2H-1,2-oxazine-2-carboxylate (**10**): According to the general procedure, oxazine products **10** and **10a** were isolated as a mixture (30 mg, 88%, 4:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.42 – 7.30 (m, 5H), 6.30 – 6.26 (m, 1H), 5.25 (s, 2H), 4.64 – 4.60 (m, 2H), 4.54 – 4.50 (m, 2H); Mixture ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.5, 155.5, 140.3, 139.9, 135.8, 133.8, 132.1, 130.1 (q, *J* = 32.7 Hz), 128.6, 128.4, 128.2, 128.2, 125.6 (q, *J* = 3.7 Hz), 125.1, 123.9 (q, *J* = 272.2 Hz), 122.2, 120.5, 69.6, 68.6, 68.0, 68.0, 46.1, 45.1; IR (thin film) 3035, 2922, 2850, 1708, 1616, 1414, 1327, 1167, 1117, 1071 cm^{-1}; HRMS (ESI) *m/z* 386.1095 (100%), 387.1143 (21%), 388.1161 (3%) (386.0980, 387.1014, 388.1047 calculated for $C_{19}H_{16}F_3NO_3Na$ $[M+Na]^+$).

Benzyl 4-(2-methoxyphenyl)-3,6-dihydro-2H-1,2-oxazine-2-carboxylate (**11**): According to the general procedure, oxazine products **11** and **11a** were isolated as a mixture (29 mg, 92%, 4:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.25 (m, 6H), 7.19 – 7.14 (m, 1H), 6.96 – 6.84 (m, 2H), 5.95 – 5.91 (m, 1H), 5.23 (s, 2H), 4.63 – 4.58 (m, 2H), 4.55 – 4.51 (m, 2H), 3.77 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.9, 155.6, 136.1, 133.8, 129.5, 129.4, 128.6, 128.3, 128.2, 121.9, 120.9, 110.9, 77.2, 68.8, 67.7, 55.4, 47.5; IR (thin film) 3064, 3033, 2943, 2838, 1727, 1706, 1597, 1490, 1455, 1343, 1215, 1094 cm^{-1}; HRMS (ESI) *m/z* 348.1326 (348.1212 calculated for $C_{19}H_{19}NO_4Na$ $[M+Na]^+$).

Benzyl 4-methyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate (**12**) and benzyl hydroxy(2-methylenebut-3-en-1-yl)carbamate (**S-6**): According to the general procedure, oxazine products **12** and **12a** were isolated as a mixture (62 mg, 48%, 2:1) separate from carbamate product **S-6** (49 mg, 38%). **(12):** ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 5.54 – 5.47 (m, 1H), 5.20 (s, 2H), 4.40 – 4.34 (m, 2H), 4.02 – 3.98 (m, 2H), 1.72 (s, 3H); **(12a):** ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 5.54 – 5.47 (m, 1H), 5.20 (s, 2H), 4.28 – 4.24 (m, 2H), 4.12 – 4.06 (m, 2H), 1.64 (s, 3H); Mixture: ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.6, 155.5, 136.0, 136.0, 131.5, 130.1, 128.5, 128.5, 128.2, 128.1, 128.1, 118.0, 116.2, 71.6, 68.5, 67.7, 67.7, 48.5, 44.7, 19.7, 18.3.

Benzyl 4-(1-((*tert*-butyldimethylsilyl)oxy)ethyl)-3,6-dihydro-2H-1,2-oxazine-2-carboxylate (**14**): According to the general procedure, oxazine products **14** and **14a** were isolated as a mixture (95 mg, 77%, 1:13). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 5.67 – 5.62 (m, 1H), 5.20 (s, 2H), 4.46 – 4.39 (m, 2H), 4.25 (q, *J* = 6.6 Hz, 1H), 4.14 – 4.10 (m, 2H), 1.19 (d, *J* = 6.5 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.5, 139.8, 136.0, 128.5, 128.2, 128.1, 115.0, 69.3, 68.4, 67.7, 44.6, 25.7, 23.2, 18.1, -4.8, -4.9; IR (thin film) 3066, 2955, 2856, 1712, 1343, 1214, 1088 cm^{-1}; MS (ESI) *m/z* 400.21 (400.19 calculated for $C_{20}H_{31}NO_4SiNa$ $[M+Na]^+$).

2,2,2-Trichloroethyl 4-phenyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate (**17**): According to the general procedure, oxazine products 17 and 17a were isolated as a mixture (94 mg, 81%, 8:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 5H), 6.22 – 6.18 (m, 1H), 4.84 (s, 2H), 4.69 – 4.65 (m, 2H), 4.61 – 4.57 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.6, 136.7, 132.8, 128.8, 128.3, 124.9, 119.7, 95.1, 75.1, 68.9, 46.2; IR (thin film) 3059, 2955, 2851, 1745, 1720, 1496, 1436, 1347, 1229, 1114 cm^{-1}; MS (ESI) *m/z* 357.99 (100%), 359.99 (95%), 361.98 (33%) (357.98, 359.98, 361.97 calculated for $C_{13}H_{12}C_{l3}NO_3Na$ $[M+Na]_+$).

tert-Butyl 4-phenyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate (**18**): According to the general procedure, oxazine products 18 and 18a were isolated as a mixture (70 mg, 77%, 3:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.23 (m, 5H), 6.19 – 6.15 (m, 1H), 4.60 – 4.55 (m, 2H), 4.46 – 4.42 (m, 2H), 1.51 (s, 9H); Mixture ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.0, 155.0, 137.2, 136.6, 134.6, 133.2, 128.7, 128.6, 128.0, 124.8, 124.8, 120.1, 118.5, 81.8, 81.8, 69.3, 68.2, 46.4, 45.2, 28.3, 28.3, 27.6; IR (thin film) 3058, 2978, 2849, 1702, 1496, 1367, 1235, 1164, 1099 cm^{-1}; MS (ESI) *m/z* 284.13 (284.13 calculated for $C_{15}H_{19}NO_3Na$ $[M+Na]^+$).

4-(4-Methoxyphenyl)-3,6-dihydro-2H-1,2-oxazine-2-carboxamide (**19**): According to the general procedure, oxazine products **19** and **19a** were isolated as a mixture (25 mg, 86%, 20:1). ^{1}H NMR (600 MHz, CD_3OD) δ 7.39 – 7.33 (m, 2H), 6.93 – 6.87 (m, 2H), 6.19 – 6.14 (m, 1H), 4.60 – 4.55 (m, 2H), 4.37 – 4.33 (m, 2H), 3.78 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 161.8, 161.1, 133.8, 131.0, 127.0, 119.3, 115.1, 70.1, 55.7, 46.1; IR (thin film) 3453, 3221, 2905, 1677, 1607, 1518, 1446, 1281, 1241, 1031 cm^{-1}; HRMS (ESI) *m/z* 257.0966 (257.0902 calculated for $C_{12}H_{14}N_2O_3Na$ $[M+Na]^+$).

4-(3-Methoxyphenyl)-3,6-dihydro-2H-1,2-oxazine-2-carboxamide (**21**): According to the general procedure, oxazine products **21** and **21a** were isolated as a mixture (24 mg, 82%, 4:1). ^{1}H NMR (600 MHz, CD_3OD) δ 7.25 (t, *J* = 8.0 Hz, 1H), 7.01 – 6.82 (m, 3H), 6.29 – 6.26 (m, 1H), 4.61 – 4.56 (m, 2H), 4.38 – 4.34 (m, 2H), 3.79 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 160.3, 160.0, 138.6, 132.9, 129.3, 120.1, 116.8, 113.1, 110.2, 68.6, 54.2, 44.7; IR (thin film) 3469, 3331, 2924, 1676, 1580, 1430, 1288, 1210, 1050 cm^{-1}; HRMS (ESI) *m/z* 257.0966 (257.0902 calculated for $C_{12}H_{14}N_2O_3Na$ $[M+Na]^+$).

N-Benzyl-4-(3-methoxyphenyl)-3,6-dihydro-2H-1,2-oxazine-2-carboxamide (**22**): According to the general procedure, oxazine products **22** and **22a** were isolated as a mixture (31 mg, 77%, 7:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.23 (m, 6H), 7.03 – 6.82 (m, 3H), 6.19 – 6.15 (m, 1H), 4.59 – 4.56 (m, 2H), 4.49 (d, *J* = 5.8 Hz, 2H), 4.47 – 4.44 (m, 2H), 3.81 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.8, 158.6, 138.7, 138.7, 133.8, 129.6, 128.7, 127.7, 127.4, 119.9, 117.5, 113.5, 110.8, 69.3, 55.3, 46.3, 44.0; IR (thin film) 3341, 3033, 2933, 2837, 1670, 1523, 1431, 1288, 1209, 1049 cm^{-1}; HRMS (ESI) *m/z* 347.1475 (347.1372 calculated for $C_{19}H_{20}N_2O_3Na$ $[M+Na]^+$).

4-(3-Methoxyphenyl)-N-phenyl-3,6-dihydro-2H-1,2-oxazine-2-carboxamide (**23**): According to the general procedure, oxazine products **23** and **23a** were isolated as a mixture (25 mg, 64%, 4:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.55 – 7.26 (m, 5H), 7.11 – 6.81 (m, 4H), 6.22 – 6.19 (m, 1H), 4.72 – 4.67 (m, 2H), 4.53 – 4.49 (m, 2H), 3.82 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.0, 155.7, 138.7, 138.0, 133.9, 129.9, 129.8, 129.2, 123.7, 119.8, 119.5, 117.7, 113.8, 111.0, 77.2, 69.9, 55.5, 45.9; IR (thin film) 3321, 3063, 2920, 2837, 1675, 1531, 1446, 1288, 1208, 1050 cm^{-1}; HRMS (ESI) *m/z* 333.1364 (333.1215 calculated for $C_{18}H_{18}N_2O_3Na$ $[M+Na]^+$).

4-(4-(Trifluoromethyl)phenyl)-3,6-dihydro-2H-1,2-oxazine-2-carboxamide (**24**): According to the general procedure, oxazine products 24 and 24a were isolated as a mixture (109 mg, 72%, 15:1). 1H NMR (600 MHz, CD3OD) δ 7.67 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H), 6.50 – 6.46 (m, 1H), 4.67 – 4.62 (m, 2H), 4.46 – 4.41 (m, 2H); 13C NMR (150 MHz, CD3OD) δ 160.3, 140.9, 131.9, 129.45 (q, J = 32.3 Hz), 125.20 (q, J = 3.8 Hz), 125.0, 122.6, 121.0, 68.6, 44.5; IR (thin film) 3420, 3192, 2959, 2846, 1638, 1592, 1326, 1171, 1128, 1070 cm-1; MS (ESI) m/z 295.06 (100%), 296.07 (25%), 297.07 (6%) (295.07, 296.07, 297.08 calculated for $C_{12}H_{11}F_3N_2O_2Na$ $[M+Na]^+$).

N-Benzyl-4-(4-(trifluoromethyl)phenyl)-3,6-dihydro-2H-1,2-oxazine-2-carboxamide (25): According to the general procedure, oxazine products **25** and **25a** were isolated as a mixture (118 mg, 58%, 4:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.40 – 7.25 (m, 5H),

6.28 – 6.24 (m, 1H), 6.18 – 6.13 (br, 1H), 4.62 – 4.56 (m, 2H), 4.51 – 4.48 (m, 2H), 4.47 – 4.44 (m, 2H); ^{13}C NMR (150 MHz, CD_3OD) δ 159.4, 140.9, 139.4, 131.9, 129.34 (q, *J* = 32.2 Hz), 128.0, 126.9, 126.7, 125.19 (q, *J* = 3.7 Hz), 125.0, 122.6, 68.7, 45.3, 43.0; IR (thin film) 3435, 3342, 3032, 2891, 2844, 1674, 1525, 1326, 1166, 1116, 1071 cm^{-1}; MS (ESI) *m/z* 386.11 (100%), 387.12 (24%), 388.12 (7%) (385.11, 386.12, 387.12 calculated for $C_{19}H_{17}F_3N_2O_2Na$ $[M+Na]^+$).

4-Methyl-3,6-dihydro-2H-1,2-oxazine-2-carboxamide (**26**) and 1-hydroxy-1-(2-methylenebut-3-en-1-yl)urea (**S-12**): According to the general procedure, oxazine products **26** and **26a** were isolated as a mixture (34 mg, 20%, 4:1) separate from urea product **S-12** (20 mg, 10%). ^{1}H NMR (600 MHz, CD_3OD) δ 5.60 – 5.53 (m, 1H), 4.39 – 4.33 (m, 2H), 3.89 – 3.85 (m, 2H), 1.74 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 160.2, 130.2, 117.7, 68.2, 46.8, 18.4; IR (thin film) 3335, 2853, 1668, 1584, 1440, 1102 cm^{-1}; MS (ESI) *m/z* 165.06 (165.06 calculated for $C_6H_{10}N_2O_2Na$ $[M+Na]^+$).

N-Benzyl-4-methyl-3,6-dihydro-2H-1,2-oxazine-2-carboxamide (**27**) and 3-benzyl-1-hydroxy-1-(2-methylenebut-3-en-1-yl)urea (**S-13**): According to the general procedure, oxazine products 27 and 27a were isolated as a mixture (46 mg, 33%, 5:1) separate from urea product S-13 (16 mg, 12%). (27): ^{1}H NMR (600 MHz, CD_3OD) δ 7.61 – 7.56 (br, 1H), 7.31 – 7.24 (m, 5H), 5.58 – 5.52 (m, 1H), 4.35 (s, 2H), 4.35 – 4.33 (m, 2H), 3.89 – 3.85 (m, 2H), 1.73 (s, 3H); (27a): ^{1}H NMR (600 MHz, CD_3OD) δ 7.61 – 7.56 (m, 1H), 7.24 – 7.16 (m, 5H), 5.58 – 5.52 (m, 1H), 4.36 (s, 2H), 4.30 – 4.23 (m, 2H), 3.95 – 3.90 (m, 2H), 1.65 (s, 3H); Mixture: ^{13}C NMR (150 MHz, CD_3OD) δ 159.4, 159.3, 139.6, 139.5, 131.6, 130.3, 128.0, 126.8, 126.8, 126.6, 126.6, 117.8, 116.3, 71.5, 68.3, 47.6, 43.9, 43.0, 42.9, 18.5, 16.8; IR (thin film) 3444, 3030, 2914, 1658, 1524, 1496, 1452, 1206, 1105, 1059, 1027 cm^{-1}; MS (ESI) *m/z* 255.11 (255.11 calculated for $C_{13}H_{16}N_2O_2Na$ $[M+Na]^+$).

2,2,2-Trichloroethyl 4-(1-((*tert*-butyldimethylsilyl)oxy)ethyl)-3,6-dihydro-2H-1,2-oxazine-2-carboxylate (**28**): According to the general procedure, oxazine products **28** and **28a** were isolated as a mixture (69 mg, 88%, 1:13). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.71 – 5.66 (m, 1H), 4.81 (d, *J* = 3.3 Hz, 2H), 4.52 – 4.50 (m, 2H), 4.28 (q, *J* = 6.4 Hz, 1H), 4.23 – 4.18 (m, 2H), 1.22 (d, *J* = 6.4 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.5, 139.8, 120.5, 114.6, 75.0, 69.3, 68.6, 25.7, 23.2, 18.1, -4.8, -4.9; IR (thin film) 2956, 2857, 1724, 1440, 1213, 1112 cm^{-1}; MS (ESI) *m/z* 440.07 (99%), 442.07 (100%), 444.07 (36%) (440.06, 442.06, 444.05 calculated for $C_{15}H_{26}Cl_3NO_4SiNa$ $[M+Na]^+$).

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Supplementary Material

Experimental procedures and characterization data for all compounds (PDF) is available.