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Amine nucleophilic addition to nitroalkene as a new practical approach for the synthesis of fully substituted isoxazoline-*N*-oxide

Cheng Zhong, Lekh Nath S. Gautam, Dawei Wang, Novruz G. Akhmedov, Jeffrey L. Petersen, Xiaodong Shi *

C. Eugene Bennett Department of Chemistry, West Virginia University, Morgantown, WV 26506, USA

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ABSTRACT

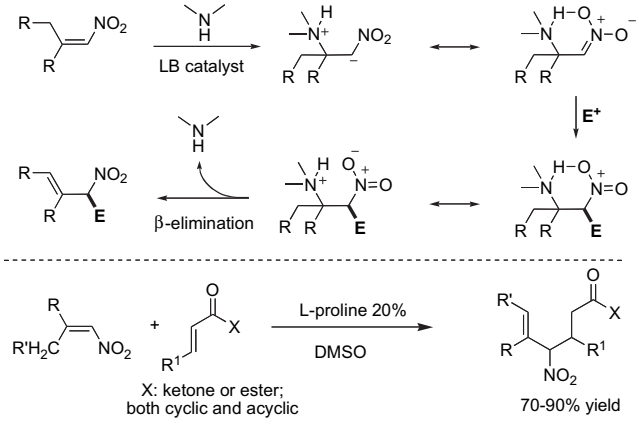
The secondary amine nucleophilic addition to the nitroalkene was used to generate the active nitronate intermediate, followed by the sequential addition to aldehyde and ylide, giving the fully substituted isoxazoline-*N*-oxide in one-pot fashion. Mechanistic studies revealed the equilibrium nature of the diene intermediates, which provide the foundation for the asymmetric synthesis of this interesting heterocycles.

1. Introduction

In the last 3 years, our group reported the application of the secondary amines as nucleophilic catalysts for the activation of nitroalkene as a new reaction mode in promoting multiple-component cascade reactions (Scheme 1).[1] Two key features of this strategy were (A) Lewis base activation allowed the nitroalkene, a popular electrophile in literature, to serve as the nucleophile for the sequential addition; and (B) the introduction of the β-hydrogen elimination provided irreversible step for the effective catalyst turnover. With this method, the first intermolecular cross conjugate additions between two different Michael receptors were achieved.

Recently, we further extended the cascade by reacting the amine-activated nitroalkene with aldehyde to form highly reactive nitroalkene intermediate. Further reaction with the third component gave substituted heterocyclic compounds, such as 1,2,3-triazoles[1b,2] and dihydrofuran,[3] in one-pot (Scheme 2). These transformations were efficient and provided the functional group enriched products from simple starting materials.

It is clear that this type of multiple-component condensation can be very useful in complex molecule synthesis. Given the complicate nature of these reactions, to further extend this strategy, especially for potential asymmetric catalysis, it is important to understand how different substrates interact with each other and which is the rate determination step in the overall transformation. In this study, we report the investigation of amine catalyzed nitroalkene–aldehyde-ylide condensation in the synthesis of fully substituted isoxazoline-*N*-oxide, which provided us some mechanistic insight regarding the amine catalyzed nitroalkene activation.



Scheme 1. Intermolecular catalytic cascade reaction promoted by secondary amine nucleophilic addition to nitroalkene.

* Corresponding author. E-mail address: xiaodong.shi@mail.wvu.edu (X. Shi).

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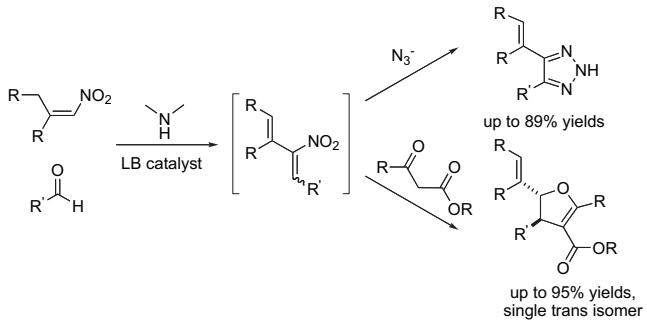
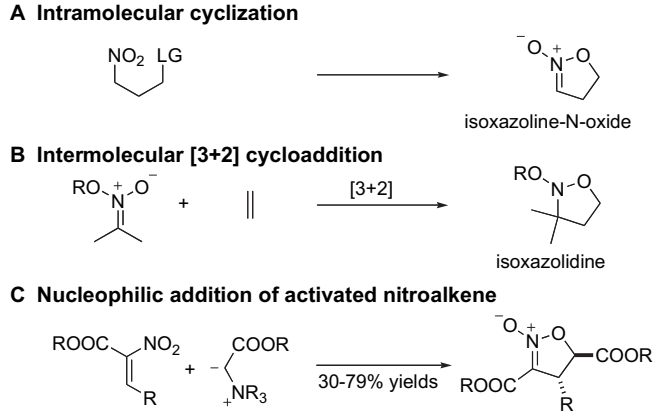


Scheme 2. Intermolecular catalytic cascade reaction promoted by secondary amine nucleophilic addition to nitroalkene.

The isoxazoline-*N*-oxide and its derivatives[4] are one particularly interesting class of heterocyclics,[5] which play a predominant role in chembiology research and medicinal chemistry research, due to their structural uniqueness and the significant biological properties.[6] Despite of the potential in pharmaceutical industry,[7] the isoxazoline-*N*-oxide and its derivatives have also been widely used as practical synthetic building blocks, which could be readily converted into useful intermediates for stereoselective preparation of complex molecules[8] and natural product total synthesis.[9] Some representative syntheses of this heterocycles are summarized in Scheme 3.

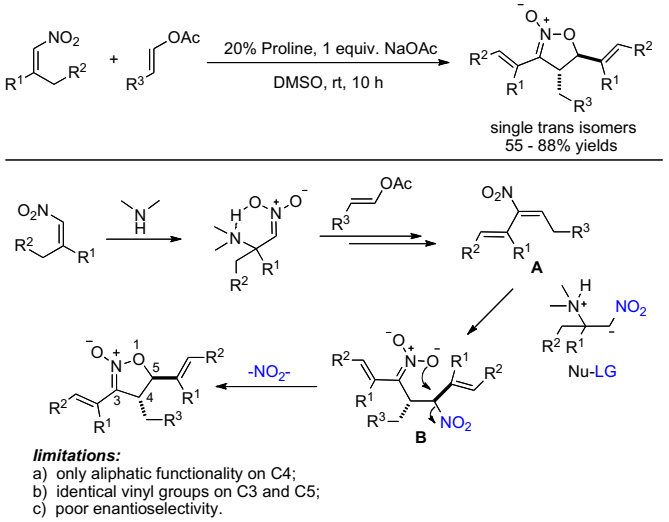


Scheme 3. Literature reported synthesis.

As reported in literature, the conventional strategy for the preparation of isoxazoline frameworks was from the intramolecular *5-exo-tet* cyclization of aliphatic nitro compounds (Scheme 3A).[10] But the lack of practical preparation the specific nitro group containing starting materials compromised the generic application of this method, which also tended to give low overall yields and limited substrate scope. Further efforts were made in developing intermolecular [3+2] cycloaddition as an alternative approach (Scheme 3B).[11] However, most of these studies focused on the preparation of nitronate[12], which made the overall strategy less practical. Recent research of Tang and co-workers revealed a successful ylide addition to carbonyl-activated nitroalkene, giving the isoxazoline-*N*-oxides with decent yields and excellent diastereoselectivity (Scheme 3C).[13] Although with high efficiency and mild reaction conditions, the requirement of specific nitroalkenes could limit the substrate scope for further application. Thus, up-to-date, practical synthesis of isoxazoline-*N*-oxides is still considered as one big challenge and new efficient methodologies are highly desirable.[14]

Based on the amine-catalyzed nitroalkene developed in our lab, we recently discovered an interesting method using nitroalkene and vinyl ester for the synthesis of isoxazoline *N*-oxides in a one-pot fashion.[15]

As shown in Scheme 4, reactions between *b*-alkyl nitroalkene and vinyl ester gave the diene intermediate **A** in the presence of proline catalyst. Sequential conjugate addition by the *second nitro carbanion* led to the di-nitro intermediate **B** and intramolecular cyclization gave the substituted isoxazoline-*N*-oxide as single trans isomer.



Scheme 4. Cascade isoxazoline-*N*-oxide synthesis through Lewis base and its limitations.

This cascade approach provided a new strategy to produce active diene intermediate **A** in situ, which allowed the preparation of isoxazoline *N*-oxide without going through the challenging nitronate intermediate synthesis. However, despite the high efficiency, this process suffered from some obvious limitations: (a) the C-4 substitution was limited to aliphatic groups; (b) two identical vinyl groups on C-3 and C-5 positions, and; (c) poor enantioselectivity (<15% ee was observed). Considering the unique mechanism and high efficiency, it is expected that successful strategies in overcoming the above-mentioned limitations will lead to the discovery of concise synthesis of the isoxazoline motifs. Moreover, investigation of how each component involved in the process will lead to the needed mechanistic insight, which is critical for further extension of this attractive multiple-component process. Herein, we report the investigation of this reaction with the focuses on the role of Lewis base catalyst, effective reaction intermediates and factors that controlled the reaction chemo- and stereo-selectivity.

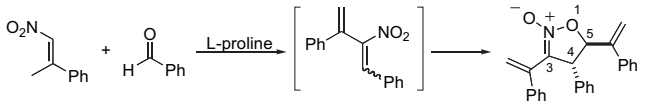
2. Results and discussions

2.1. Synthesis of isoxazoline-*N*-oxides through one-pot condensation of nitroalkenes and aldehydes

The key step for the isoxazoline-*N*-oxide synthesis was the formation of diene intermediate **A**. Besides the previously reported nitroalkene-vinyl ester condensation approach,[17a] the diene could also be prepared through the Lewis based mediated Henry process between nitroalkene **1** and aldehyde **2**. Thus, the desired homo-isoxazoline-*N*-oxide **3a** would be prepared through a more general method with good variety on the C-4 position. The reactions between **1a** and benzaldehyde **2a** were then investigated. As expected, isoxazoline-*N*-oxide **3a** was obtained as a single diastereomer. The reaction condition optimization is summarized in Table 1.

Similar to the previous reported cases, the reaction did not go well when only proline or only weak base NaOAc was applied (entries 1–2). The major side reaction was the polymerization of **1a**.

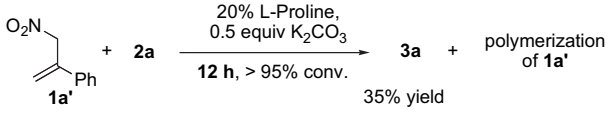
Table 1
One-pot synthesis of homo-isoxazoline-*N*-oxide by Lewis base activated nitroalkene–aldehyde condensation[a]



	SOL	LB (20%)	Additive	*t* (h)	Conv.[b] (%)	Yield[c] (%)
1	DMSO	Proline	—	12	46	11
2	DMSO	—	NaOAc (1.0 equiv)	12	79	<5
3	DMSO	Proline	NaOAc (1.0 equiv)	3	>95	87[d]
4	DMSO	Proline	K_2CO_3 (0.5 equiv)	3	>95	92[d]
5	DMSO	Proline	NaO^{t}Bu (1.0 equiv)	3	84	70[d]
6	DMSO	Proline	Et_3N (1.0 equiv)	12	89	65[d]
7	DMSO	Others[e]	K_2CO_3 (0.5 equiv)	3	>95	<50
8	THF	Proline	K_2CO_3 (0.5 equiv)	12	23	19
9	THF	Proline	BF_3–THF (1.0 equiv)	12	35	Trace
10	Others[f]	Proline	K_2CO_3 (0.5 equiv)	3–12	45–90	13–49
11	MeOH	Proline	K_2CO_3 (0.5 equiv)	12	>95	43
12	DMSO	Pyrrolidine	K_2CO_3 (0.5 equiv)	3	>95	88

[a] General reaction condition: **1a** (2.2 equiv), **2a** (1.0 equiv, 0.1 M) and catalysts were mixed in solvents. The reactions were monitored by TLC.
[b] Based on the consumption of **2a**.
[c] NMR yield with 1,3,5-trimethoxybenzene as internal standard.
[d] Isolated yield.
[e] Other Lewis bases include DMAP, DABCO, NMI, Ph_3P.
[f] Other solvents include EtOAc, DCM, Toluene, MeCN, *i*PrOH.

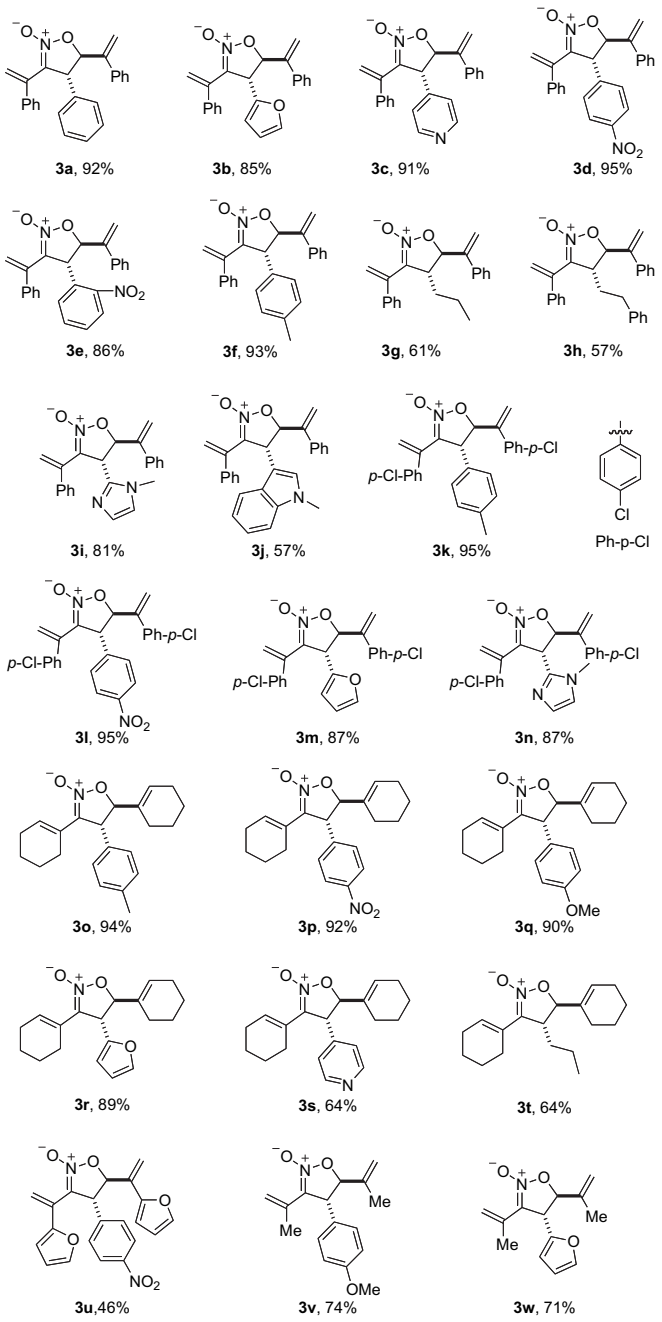
The desired product **3a** was received in good yield when both proline and NaOAc were used and reaction finished within 3 h (entry 3), which provided another strong support for our proposed proline nucleophilic addition to nitroalkene mechanism. Strong base, such as NaO^{t}Bu, caused significant polymerization of **1a** and 0.5 equiv of K_2CO_3 was identified as the optimal choice with minimum polymerization (entries 4–6). To investigate the reaction mechanism, the allylic nitro compound **1a**′ was prepared separately and applied into the optimal reaction conditions. As shown in Scheme 5, a slower reaction was observed (took 12 h for starting materials consumption) with much lower yield (32% yield while >95% starting material was consumed). This significant difference between **1a** and **1a**′ as the starting materials provided strong evidence for the proposed amine nucleophilic addition to nitroalkene other than the alternative Brønsted base deprotonation path (formation of nitro carbanion).



Scheme 5. Reactivity difference between **1a** and allylic nitro **1a**′.

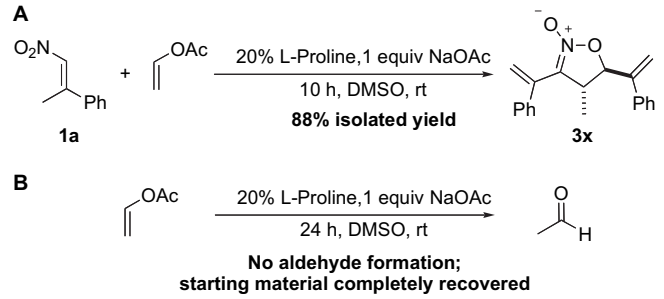
Other general nucleophilic catalysts, such as DMAP, DABCO, NMI, etc. have also been tested, giving uncompetitive results (entry 7). These results highlighted the unique reaction nature of proline nucleophilic addition to nitroalkenes: the problematic nitroalkene polymerization associated with the Lewis base catalyzed mechanism was successfully avoided by forming a rather stable H-bond intermediate (Scheme 1). The pyrrolidine was also effective LB catalyst for this transformation (entry 12, 88% yield) and proline was selected in this study because of the practical nature (in-expensive and easy to handle). Solvent screening revealed DMSO as the optimal solvent (entry 10). Various isoxazoline-*N*-oxides were prepared under the optimal conditions, with different substitution on C-4 position from corresponding aldehydes as shown in Table 2.

Table 2
Substrate scope of one-pot homo isoxazoline-*N*-oxide synthesis[a,b]



[a] Reaction condition: **1a** (2.2 equiv), **2** (1.0 equiv, 0.15 M) and ylide 4 (1.1 equiv) were mixed DMSO. The reactions were monitored by TLC.
[b] Isolated yield.

Among all these substrates, excellent diastereoselectivity was achieved and only trans isomers were obtained. The aromatic aldehydes generally gave good to excellent yields, while slightly lower yields were observed with aliphatic aldehydes (**3g**, **3h**, **3t**). This was likely caused by the side reactions resulting from the formation of enamines. These results generated skeptical thought that whether our previously reported nitroalkene–vinyl ester condensation went through the hydration of vinyl ester, forming the aliphatic aldehyde in situ, followed by the similar Henry reaction to yield the corresponding isoxazoline (Scheme 6A). To verify this concern, the vinyl ester was treated with the proline under identical conditions without addition of nitroalkene **1a**. Interestingly, based on the NMR



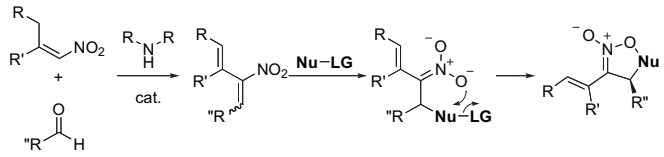
Scheme 6. Vinyl ester condensation as alternative strategy for aliphatic aldehyde.

study, no hydration product observed based on the NMR, which supported our previously proposed [3+2] mechanism between Lewis based activated nitroalkene and vinyl ester (Scheme 6B). This study was important since it revealed the possibility for thermal [3+2] process with the amine-activated nitroalkene, which would likely lead to possible new cascade reactions through the Lewis based catalyzed nitroalkene activation (currently under investigation in our lab). Moreover, considering the modest yields with the aliphatic aldehydes, the vinyl ester condensation is likely a better alternative route for the synthesis of the isoxazoline-*N*-oxide derivatives with alkyl group on the C-4 position.

2.2. Three-component condensation to introduce different substitute groups on C-3 and C-5 positions

As demonstrated by our previous work, the diene **A** was the key intermediate for this cascade process. We postulated that an alternative path involved the third component with the featured functionality as Nu–LG (with nucleophile and leaving group on the same molecule) could be the potential solution to introduce three different components at the C-3, C-4, and C-5 positions (Scheme 7).

Based on this hypothesis, several ylides were prepared to react with nitroalkene **1a** and aldehyde **2a**. The results are summarized in Table 3.

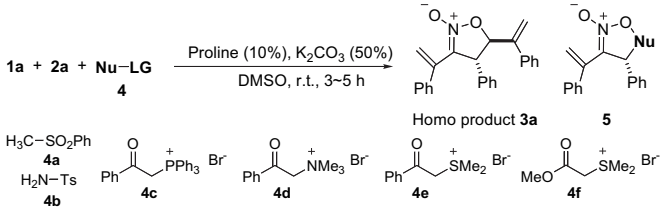


Scheme 7. Proposed alternative reaction path to introduce the third component in the synthesis of isoxazoline-*N*-oxide.

As shown in Table 3, application of **4a** and **4b**, under the previously developed optimal condition, produced only the homo-isoxazoline-*N*-oxide **3a**, which was probably due to the low reactivity of the sulfonate nucleophiles (entries 1 and 2). The phosphine ylide **4c** and amine ylide **4d** did generate the desired product **5**. However, the reaction suffered from the significant competition of homo-condensation (entries 3 and 4). Interestingly, application of sulfur ylides **4e** and **4f** gave compound **5** as the dominant product in excellent yields (entries 5 and 6) with only trace amount **3a** observed.

Notably, it was well known that the reaction between aldehyde **2a** and sulfur ylide **4e** could produce the corresponding epoxides in good yields.[16] However, under the reported reaction condition, no significant formation of epoxide was observed. This result further highlighted the significance of the reported cascade

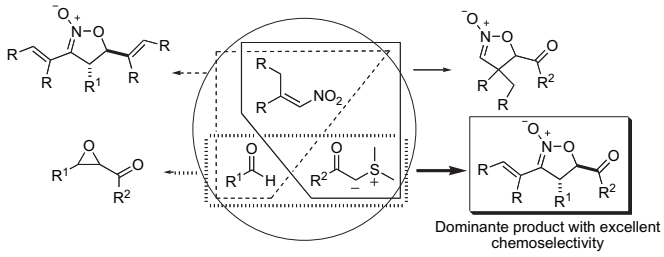
Table 3
Substrate screening for three-component condensation in the synthesis of isoxazoline-*N*-oxide[a]



Entry	Nu–LG	Product	
		3a (%)	**5** (%)
1	**4a**	76[b]	<5
2	**4b**	85[b]	<5
3	**4c**	58[b]	35[b]
4	**4d**	74[b]	18[b]
5	**4e**	<5[b]	91[c]
6	**4f**	<5[b]	92[c]

[a] Reaction condition: **1a** (1.0 equiv), **2a** (1.0 equiv, 0.75 M), and catalysts were mixed in solvents. The reactions were monitored by TLC.
[b] NMR yields with 1,3,5-trimethoxybenzene as internal standard.
[c] Isolated yield.

process: with the presence of alternative reaction paths (formation of homo-condensation product **3a** and aldehyde epoxidation), well-designed cascade process could direct the reaction pathway to products that would not be achieved from the stepwise approach (Scheme 8).



Scheme 8. Achieving excellent chemoselectivity.

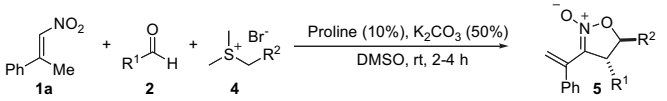
With the optimal three-component conditions revealed, some representative isoxazoline-*N*-oxides were prepared as shown in Table 4.

2.3. Characterization of diene intermediate and cross cyclizations

As discussed earlier, the nitro-diene **A** was the key intermediate that accounted for the formation of the desired product. Interestingly, previous study had informed us that conducting the reaction with the presence of D_2O revealed effective deuterium exchange on various positions, except the C-4 proton (Scheme 9).[16]

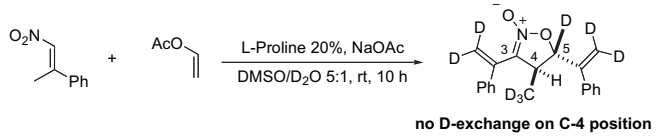
This result suggested that the C-4 stereogenic center was not epimerizable under the reaction condition. Therefore, the absolute stereochemistry of the products would be determined by the second nucleophilic addition to the diene. This result raised the concern for the asymmetric synthesis of the isoxazoline since the diene intermediate was likely formed as *Z*/*E* isomer mixtures without good stereochemistry control. To verify this concern, efforts were the put in obtaining the diene intermediate. As show in Scheme 10, diene **A′** was successfully isolated as mixtures of isomers (*Z*/*E*=1:1.5, conformations were determined by 2D NMR).

Table 4
Representative isoxazoline-*N*-oxides from three-component condensation[a]

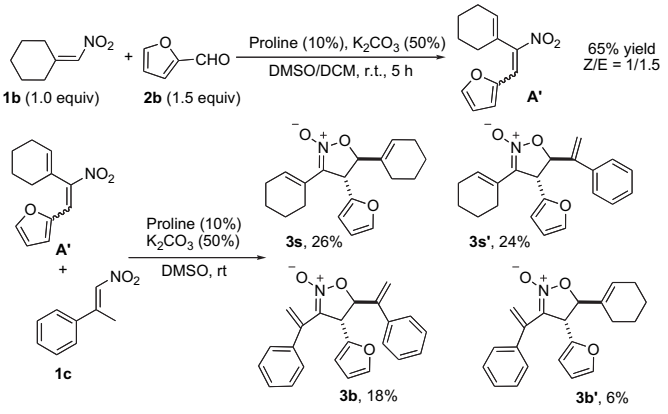


Entry	R^1	R^2		Yield[b] (%)
1	C_6H_5	$-C(O)C_6H_5$	**5a**	91
2	*p*-$CH_3-C_6H_4$		**5b**	92
3	2-Furyl		**5c**	73
4	*n*-C_3H_7		**5d**	62
5	*i*-C_3H_7		**5e**	52
6	*p*-$NO_2-C_6H_4$		**5f**	92
7	2-Nap	$-CO_2Et$	**5g**	88
8	*p*-$NO_2-C_6H_4$		**5h**	92
9	*p*-$CH_3-C_6H_4$	$-C(O)$-*p*-$Br-C_6H_4$	**5i**	91
10	*p*-$NO_2-C_6H_4$		**5j**	73
11	*p*-$OCH_3-C_6H_4$		**5k**	92
12	*p*-Pyridinyl		**5l**	92

[a] Reaction condition: **1a** (1.1 equiv), **2** (1.0 equiv, 0.15 M) and ylide 4 (1.1 equiv) were mixed DMSO. The reactions were monitored by TLC.
[b] Isolated yield.



Scheme 9. Deuterium exchange experiment.



Scheme 10. Cross condensation with nitro-diene.

The formation of *Z*/*E* isomer mixture made the asymmetric synthesis very challenging since it was hard to achieve good enantioselectivity with two diastereomeric intermediates (*Z*/*E* isomers) present in a similar ratio. The enantioselective synthesis of the desired isoxazoline-*N*-oxides then relied on the different reactivity of the two isomers, under the assumption that these two isomers could inter-convert into each other (dynamic kinetic resolution).[17] To investigate the diene's reactivity, the cross-condensation between diene **A**′ and nitroalkene **1c** was performed. Interestingly, mixtures of four different isoxazoline-*N*-oxides were obtained in the crude NMR (Scheme 5), which indicated that the equilibrium between nitroalkene **A**′ and starting materials (nitroalkene **1** and aldehyde **2**). Therefore, it is feasible to control the C-4 stereogenic center with proper nucleophile with dynamic kinetic resolution.

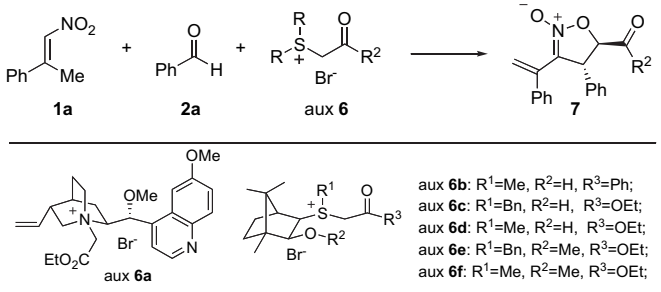
2.4. Asymmetric synthesis with chiral auxiliary

Enantioselective synthesis of isoxazoline derivatives is considered as one challenging task and few asymmetric syntheses of this compound have been reported in literature.[10,11] As shown in previous sections, the Lewis base catalyzed cascade approach gave excellent diastereoselectivity, where only trans isomers were observed in all cases. However, based on the reaction mechanism, the chiral Lewis base was unlikely a feasible solution in pursuing asymmetric synthesis due to the poor involvement of Lewis base catalysts in the stereochemistry determining step (formation of the C-4 stereogenic center). This was consistent with the observed low ee (<15%) for all tested chiral secondary amines.[18]

In previous section, one valid approach in achieving asymmetric synthesis of fully substituted isoxazoline-*N*-oxides had been discussed, that is, to develop stereoselective nucleophilic addition of chiral ylides to diene intermediates through dynamic kinetic resolution. Several readily available chiral ylides were then applied to evaluate the stereoselectivity of these auxiliaries in this cascade process. Detailed reaction condition screening is shown in Table 5.

The amine-based ylide **6a** did not promote the hetero coupling reaction (entry 1) very well, giving the homo coupling product **3a** (>85% yield) as the major product. Similar result was observed with ketone ylide **6b** (entry 2), which was likely caused by the reduced nucleophilicity associated with more hindered chiral ylide (comparing with the simple ketone ylide **4**, which gave the desired hetero coupling product in excellent yields). The ester modified ylide **6c** did give the hetero coupling product **7** though with poor yield (entry 3). Solvent screening indicated that MeOH was the optimal solvent (entries 4–6). Further modification on the ylides revealed **6d** (R^1=Me and R^2=H) as the optimal auxiliary (entry 7) and Cs_2CO_3 as preferred choice of base (entry 10), producing the desired product **7a** in excellent yield. In addition, to our great

Table 5
Reaction condition screening of different auxiliaries for asymmetric isoxazoline-*N*-oxide synthesis[a]



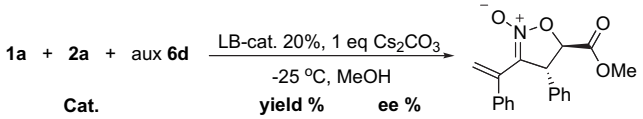
	Sol	LB (20%)	Base (1.0 equiv)	aux	Temp (°C)	Time (h)	Yield %[b] (ee %)[c]
1	DMSO	L-Proline	K_2CO_3	aux **6a**	rt	12	<5 (n.d.)[d]
2	DMSO	L-Proline	K_2CO_3	aux **6b**	rt	12	<5 (n.d.)[d]
3	DMSO	L-Proline	K_2CO_3	aux **6c**	rt	6	19 (n.d.)
4	Acetone	L-Proline	K_2CO_3	aux **6c**	rt	6	16 (n.d.)
5	THF	L-Proline	K_2CO_3	aux **6c**	rt	24	13 (n.d.)
6	MeOH	L-Proline	K_2CO_3	aux **6c**	rt	6	60[e] (36)
7	MeOH	L-Proline	K_2CO_3	aux **6d**	rt	6	81[e] (75)
8	MeOH	L-Proline	K_2CO_3	aux **6e**	rt	6	23 (40)
9	MeOH	L-Proline	K_2CO_3	aux **6f**	rt	6	43 (59)
10	MeOH	L-Proline	Cs_2CO_3	aux **6d**	rt	6	54 (76)
11	MeOH	L-Proline	Cs_2CO_3	aux **6d**	−25	48	87[e] (82)
12	MeOH	L-Proline	Cs_2CO_3	aux **6d**	−40	60	62[e] (82)

[a] General reaction condition: **1a** (1.2 equiv), **2a** (1.0 equiv, 0.15 M) and auxiliary **6** (1.1 equiv). Fast ester exchange happened under mild basic condition in MeOH, only methyl ester was detected.
[b] NMR yields with 1,3,5-trimethoxybenzene as internal standard.
[c] Determined by chiral HPLC.
[d] Major products were homo-isoxazoline **3a** and the epoxide.
[e] Isolated yield.

please, good enantioselectivity was also received (75% ee). Considering that diene intermediate gave low *Z*/*E* selectivity, the success in obtaining good enantioselectivity supported the hypothesis that chiral ylide nucleophile reacted with the diene intermediate with good stereochemistry control and the asymmetric synthesis achieved through dynamic kinetic resolution (DKR).

2.5. Influence of amine catalysts in stereoselectivity

Although the proline was simply identified as the secondary amine Lewis base catalyst in the nitroalkene activation, it was indeed a chiral catalyst. One concern was whether the stereochemistry of amine catalysts influenced the reaction stereoselectivity. Investigations of different chiral amines gave interesting results, where D-proline and achiral pyrrolidine gave improved enantioselectivity (Scheme 11).



Cat.	yield %	ee %
L-Proline	87	82
D-Proline	90	85
pyrrolidine	86	91
N-methyl-Glycine	51	89

Scheme 11. Influence from amine catalysts.

The influence from the amine on the product stereochemistry, though was subtle, provided interesting information regarding how amine interact with nitroalkene. The amine Lewis base could remain contact with the nitroalkene, either through H-bond or as ion pair (by protonation). The exact mechanism remained uncertain at this moment. However, the application of chiral amines in prompting similar cross conjugated addition was recently reported, which suggested the critical role of amine Lewis base in stereoselective cascade process. The asymmetric isoxazoline-*N*-oxide synthesis along with the stereoselective total synthesis of Clausenamide have been recently reported by our group, which were based on this full investigation.

3. Conclusion

The one-pot condensation of nitroalkene–aldehyde–ylide condensation was developed for the synthesis of fully substituted isoxazoline-*N*-oxides. Broad substrates were tested, giving series new isoxazoline-*N*-oxides with full characterization. Equilibrium between the nitroalkene intermediate to the nitroalkene and aldehyde starting materials was confirmed through the cross conjugate addition. Combined with the observed enantioselective synthesis through chiral auxiliary, the dynamic kinetic resolution mechanism was confirmed. The influence from chiral Lewis base on the product stereochemistry revealed the important role of chiral amine. Overall, these studies provided strong mechanistic information for the further extension of this highly efficient amine-mediated nitroalkene activation cascade process for the synthesis of complex organic molecules.

4. Experimental procedures

4.1. General procedure for preparation of homo-isoxazoline-*N*-oxide (3)

The nitroalkene (1.1 mmol, 2.2 equiv) was added to a DMSO solution of aldehyde (0.5 mmol, 1.0 equiv), L-Proline (25 mg, 0.22 mmol, 0.2 equiv), and K_2CO_3 (35 mg, 0.25 mmol, 0.5 equiv), with a concentration of 0.1 M aldehyde. The resulting reaction mixture was stirred at room temperature for 2–5 h monitored by TLC. Upon the aldehyde was all consumed, the mixture was diluted with EtOAc (100 mL). The organic phase was washed by HCl solution (1.0 M), saturated $NaHCO_3$ (aq) and brine, and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a residue. Flash silica gel chromatography was then applied to give the product.

*4.1.1. 4-Phenyl-3,5-bis (1-phenylvinyl) isoxazoline-N-oxide (**3a**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 92%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.37–7.34 (m, 5H), 7.22–7.17 (m, 4H), 7.15–7.12 (m, 2H), 6.85–6.81 (m, 4H), 6.17 (s, 1H), 5.67 (s, 1H), 5.53 (d, *J*=7.8 Hz, 2H), 5.31 (d, *J*=4.2 Hz, 1H), 4.15 (d, *J*=5.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=144.8, 138.7, 138.0, 137.1, 135.9, 128.9, 128.7, 128.4, 128.0, 127.9, 127.8, 127.5, 127.1, 127.0, 121.8, 116.2, 115.0, 82.9, 56.7; HRMS Calculated for $[C_{25}H_{21}NO_2+H]^+$: 368.16450, found: 368.16474.

*4.1.2. 4-Furyl-3,5-bis (1-phenylvinyl) isoxazoline-N-oxide (**3b**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 85%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.41–7.33 (m, 5H), 7.30–7.29 (s, 1H), 7.23–7.17 (m, 3H), 6.93–6.91 (m, 2H), 6.19 (s, 1H), 6.16 (s, 1H), 5.82 (d, *J*=3.0 Hz, 1H), 5.67 (s, 1H), 5.60 (s, 1H), 5.57 (s, 1H), 5.57–5.47 (m, 1H), 4.35 (d, *J*=4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=149.9, 144.2, 142.7, 137.9, 136.9, 135.8, 128.7, 128.4, 128.1, 127.9, 127.3, 127.0, 121.6, 115.7, 113.6, 110.5, 108.0, 80.2, 50.3; HRMS calculated for $[C_{23}H_{19}NO_3+H]^+$: 358.14377, found: 358.14397.

*4.1.3. 4-Pyridin-4-yl-3,5-bis (1-phenylvinyl) isoxazoline-N-oxide (**3c**).* Purified by flash chromatography (hexane–EtOAc) as yellowish solid (yield: 91%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=8.42–8.41 (dd, *J*=4.8, 3.6 Hz, 2H), 7.39–7.36 (m, 3H), 7.33–7.32 (m, 2H), 7.21–7.18 (m, 1H), 7.15–7.12 (m, 2H), 6.80–6.78 (dd, *J*=7.2, 1.8 Hz, 2H), 6.73–6.72 (dd, *J*=4.2, 3.0 Hz, 2H), 6.30 (s, 1H), 5.68 (s, 1H), 5.58 (s, 1H), 5.56 (s, 1H), 5.27–5.26 (d, *J*=4.2 Hz, 1H), 4.13–4.12 (d, *J*=3.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=150.31, 147.42, 144.28, 137.8, 136.8, 135.4, 128.8, 128.6, 128.1, 128.0, 127.6, 127.0, 122.0, 115.5, 115.0, 82.0, 55.93; HRMS calculated for $[C_{24}H_{20}N_2O_2+Na]^+$: 391.14170, found: 391.14190.

*4.1.4. 4-p-Nitro-phenyl-3,5-bis-(1-phenylvinyl) isoxazoline-N-oxide (**3d**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 95%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=8.03–8.01 (d, *J*=9.0 Hz, 2H), 7.38–7.37 (m, 3H), 7.32–7.31 (m, 2H), 7.21–7.18 (t, *J*=7.8 Hz, 1H), 7.14–7.11 (t, *J*=7.8 Hz, 2H), 6.93–6.92 (d, *J*=8.4 Hz, 2H), 6.78–6.76 (d, *J*=7.2 Hz, 2H), 6.34 (s, 1H), 5.69 (s, 1H), 5.59 (s, 1H), 5.56 (s, 1H), 5.28–5.27 (d, *J*=3.6 Hz, 1H), 4.26–4.25 (d, *J*=4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=147.5, 145.8, 144.2, 137.9, 136.9, 135.3, 128.9, 128.7, 128.2, 128.1, 127.6, 127.0, 124.1, 122.1, 115.6, 115.3, 82.2, 56.3; HRMS calculated for $[C_{25}H_{20}N_2O_4+H]^+$: 413.14958, found: 413.14967.

*4.1.5. 4-o-Nitro-3,5-bis (1-phenylvinyl) isoxazoline-N-oxide (**3e**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 86%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.68–7.67 (d, *J*=8.4 Hz, 1H), 7.62–7.60 (t, *J*=7.8 Hz, 1H), 7.47–7.36 (m, 7H), 7.16–7.13 (t, *J*=7.2 Hz, 1H), 7.05–7.02 (t, *J*=7.2 Hz, 2H), 6.47–6.46 (d, *J*=7.8 Hz, 2H), 6.36 (s, 1H), 5.53 (s, 1H), 5.48 (s, 1H), 5.45 (s, 1H), 5.18 (d, *J*=3.6 Hz, 1H), 5.00 (d, *J*=3.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=147.9, 145.2, 137.8, 137.5, 135.4, 133.9, 133.7, 129.5, 128.8, 128.6, 128.4, 128.1, 128.0, 127.8, 127.3, 124.8, 121.8, 118.5, 115.9, 84.0, 50.6; HRMS calculated $[C_{25}H_{20}N_2O_4+H]^+$: 413.14958, found: 413.14967.

*4.1.6. p-Toulyl-3,5-bis (1-phenylvinyl) isoxazoline-N-oxide (**3f**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 93%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.36–7.33 (m, 5H),

7.21–7.18 (t, J=7.2 Hz, 1H), 7.16–7.13 (m, 2H), 7.01 (d, J=7.8 Hz, 2H), 6.85–6.83 (m, 2H), 6.76–6.75 (d, J=8.4 Hz, 2H), 6.11 (s, 1H), 5.66 (s, 1H), 5.54–5.52 (d, J=11.8 Hz, 2H), 5.29–5.28 (dd, J=3.6, 3.0 Hz, 1H), 4.11 (d, J=3.6 Hz, 1H), 2.29(s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=144.88, 138.0, 137.7, 137.1, 135.9, 135.7, 129.6, 128.7, 128.3, 127.9, 127.7, 127.5, 127.0, 121.7, 116.2, 114.8, 83.0, 56.4, 21.0; HRMS calculated for $[C_{26}H_{23}NO_2+H]^+$: 382.18016, found: 382.18161.

*4.1.7. 4-Propyl-3,5-bis (1-phenylvinyl) isoxazoline-N-oxide (**3g**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 61%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.38–7.34 (m, 5H), 7.25–7.22 (m, 3H), 6.99–6.89 (dd, J=6.0, 6.0 Hz, 2H), 6.27 (s, 1H), 5.71 (s, 1H), 5.63 (s, 1H), 5.43 (s, 1H), 5.09 (d, J=2.4 Hz, 1H), 3.06–3.04 (m, 1H), 1.47–1.41 (m, 1H), 1.31–1.25 (m, 1H), 1.22–1.16 (m, 1H), 1.09–1.02 (m, 1H), 0.58–0.55 (t, J=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=145.81, 138.29, 137.88, 135.87, 128.68, 128.28, 128.0, 127.4, 127.2, 121.4, 116.4, 115.1, 80.3, 49.5, 33.85, 18.68, 13.2; HRMS calculated for $[C_{22}H_{23}NO_2+H]^+$: 334.18016, found: 334.18031.

*4.1.8. 4-Phenyl-ethyl-3,5-bis (1-phenylvinyl) isoxazoline-N-oxide (**3h**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 57%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.39–7.33 (m, 5H), 7.25–7.22 (m, 1H), 7.20–7.17 (m, 2H), 7.12–7.09 (m, 3H), 6.92–6.90 (m, 2H), 6.73–6.71 (dd, J=8.4, 6.0 Hz, 2H), 6.24 (s, 1H), 5.68 (d, J=1.2 Hz, 1H), 5.62 (t, J=1.2 Hz, 1H), 5.41 (s, 1H), 5.16 (d, J=2.4 Hz, 1H), 3.09–3.07 (m, 1H), 2.51–2.46 (m, 1H), 2.35–2.30 (m, 1H), 1.80–1.74 (m, 1H), 1.69–1.63 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=145.7, 139.9, 138.1, 137.8, 135.7, 128.7, 128.36, 128.34, 128.1, 127.9, 127.4, 127.3, 125.9, 121.6, 116.1, 115.6, 80.4, 49.3, 33.1, 31.6; HRMS calculated for $[C_{27}H_{25}NO_2+H]^+$: 396.19581, found: 396.19613.

*4.1.9. 4-Methyl-imidazole-3,5-bis (1-phenylvinyl) isoxazoline-N-oxide (**3i**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 81%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.28–7.25 (m, 3H), 7.22–7.20 (m, 2H), 7.17–7.12 (m, 3H), 6.96 (d, J=1.2 Hz, 1H), 6.81–6.79 (m, 2H), 6.47 (s, 1H), 6.36 (d, J=1.2 Hz, 1H), 5.67 (s, 1H), 5.64–5.64 (d, J=6.6 Hz, 1H), 5.55 (s, 1H), 5.49 (s, 1H), 4.28–4.26 (d, J=7.2 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=144.0, 143.5, 138.8, 137.1, 135.2, 128.7, 128.6, 128.4, 128.1, 127.7, 127.4, 126.9, 121.9, 120.5, 115.4, 114.8, 81.1, 84.2, 30.9; HRMS calculated for $[C_{23}H_{21}N_3O_2+H]^+$: 372.17065, found: 372.17094.

*4.1.10. 4-N-Methyl-indole-3,5-bis (1-phenylvinyl) isoxazoline-N-oxide (**3j**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 53%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.41–7.39 (m, 2H), 7.38–7.35 (m, 4H), 7.22–7.17 (m, 3H), 7.13–7.10 (t, J=7.8 Hz, 2H), 7.04–7.02 (t, J=7.8 Hz, 1H), 6.83–6.81 (m, 2H), 6.49 (s, 1H), 6.14 (d, J=1.2 Hz, 1H), 5.70 (s, 1H), 5.56 (s, 1H), 5.50 (d, J=1.2 Hz, 1H), 5.42 (d, J=3.0 Hz, 1H), 5.45 (d, J=3.6 Hz, 1H), 3.64 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=145.2, 138.2, 137.4, 137.1, 136.0, 128.9, 128.7, 128.3, 127.9, 127.6, 127.5, 127.19, 127.12, 125.7, 122.0, 121.6, 119.6, 118.8, 115.7, 114.6, 111.5, 109.3, 82.29, 48.9, 32.6; HRMS calculated for $[C_{28}H_{24}N_2O_2+H]^+$:421.19105, found: 421.19143.

*4.1.11. 4-p-Toulyl-3,5-bis (p-chloribenzylvinyl) isoxazoline-N-oxide (**3k**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 95%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.35–7.33 (m, 2H), 7.30–7.28 (m, 2H), 7.15–7.13 (dt, J=8.4, 4.8 Hz, 2H), 7.06–7.05 (d, J=7.8 Hz, 2H), 6.81–6.79 (d, J=7.8 Hz, 2H), 6.78–6.75 (dt, J=8.4, 4.2 Hz, 2H), 6.04 (s, 1H), 5.64 (s, 1H), 5,53 (s, 1H), 5.49 (s, 1H), 5.25 (d, J=4.2 Hz, 1H), 4.06 (d, J=4.2 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=143.6, 138.1, 136.2, 135.48, 135.42, 134.9, 134.5, 133.9, 129.8, 129.0, 128.8, 128.3, 128.2, 127.0, 122.3, 115.8, 115.7, 83.0, 56.5, 21.0; HRMS calculated for $[C_{26}H_{21}NO_2Cl_2+H]^+$: 450.10221, found: 450.10252.

*4.1.12. 4-p-Nitro-phenyl-3,5-bis (p-chloribenzylvinyl) isoxazoline-N-oxide (**3l**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 95%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=8.10–8.09 (m, 2H), 7.38–7.36 (m, 2H), 7.29–7.26 (m, 2H), 7.15–7.13 (m, 2H), 7.04–7.03 (m, 2H), 6.73–6.71 (m, 2H), 6.21 (s, 1H), 5.68 (s, 1H), 5.56 (s, 2H), 5.25 (d, J=4.2 Hz, 1H), 4.20 (d, J=4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=147.8, 145.4, 143.0, 136.0, 135.1, 134.9, 134.4, 134.3, 129.2, 128.8, 128.5, 128.3, 128.1, 124.3, 122.7, 116.7, 114.7,82.3, 56.3; HRMS calculated for $[C_{25}H_{18}Cl_2N_2O_4+H]^+$: 481.07164, found: 481.07172.

*4.1.13. 4-Furyl-3,5-bis (p-chloribenzylvinyl) isoxazoline-N-oxide (**3m**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 87%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.36–7.32 (m, 5H), 7.19–7.17 (m, 2H), 6.87–6.85 (m, 2H), 6.23 (q, J=3.0 Hz, 1H), 6.07 (s, 1H), 5.89 (d, J=3.0 Hz, 1H), 5.66 (s, 1H), 5.56 (s, 1H), 5.55 (s, 1H), 5.44 (d, J=4.8 Hz, 1H), 4.31 (d, J=4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=149.5, 143.0, 142.9, 136.0, 135.2, 134.8, 134.6, 134.0, 129.0, 128.6, 128.4, 128.3, 122.0, 116.5, 113.2, 110.7, 108.3, 80.2, 50.3; HRMS calculated for $[C_{24}H_{20}NO_3Cl_2+H]^+$: 406.12048, found: 406.12060.

*4.1.14. 4-2′-Methyl-imidazole-3,5-bis (p-chloribenzylvinyl) isoxazoline-N-oxide (**3n**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 87%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.27–7.25 (m, 3H), 7.17–7.13 (m, 4H), 6.96 (d, J=1.2 Hz, 1H), 6.77–6.76 (m, 2H), 6.47 (d, J=1.2 Hz, 1H), 6.32 (s, 1H), 5.65 (s, 1H), 5.63–5.62 (d, J=7.8 Hz, 1H), 5.52 (s, 1H), 4.29 (d, J=7.2 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=143.1, 142.7, 136.7, 135.2, 134.6, 134.3, 133.9, 128.9, 128.79, 128.73, 128.3, 128.2, 122.2, 120.9, 116.5, 114.4, 81.2, 48.3, 31.3; HRMS calculated for $[C_{23}H_{19}N_3O_2Cl_2+H]^+$: 440.09271, found: 440.09301.

*4.1.15. 4-Toulyl-3,5-bis (cyclohexenyl) isoxazoline-N-oxide (**3o**).* Purified by flash chromatography (hexane–EtOAc) as a white solid (yield: 94%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.16–7.15 (d, J=7.8 Hz, 2H), 7.10–7.09 (m, 2H), 6.58 (t, J=1.8 Hz, 2H), 4.51 (d, J=4.2 Hz, 1H), 4.24 (d, J=4.8 Hz, 1H), 2.34 (s, 3H), 2.25–1.95 (m, 8H), 1.80–1.41 (m, 8H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=137.5, 137.2, 134.3, 132.4, 129.8, 126.9, 126.1, 124.8, 118.3, 86.4, 55.0, 25.8, 24.8,22.8, 22.2, 22.19, 22.15, 21.3, 21.0; HRMS calculated for $[C_{22}H_{27}NO_2+H]^+$: 338.21146, found: 338.21159.

*4.1.16. 4-p-Nitrophenyl-3,5-bis (cyclohexenyl) isoxazoline-N-oxide (**3p**).* Purified by flash chromatography (hexane–EtOAc) as a yellow solid (yield: 92%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=8.25–8.23 (m, 2H), 7.42–7.40 (m, 2H), 6.47–6.45 (p, J=4.2 Hz, 1H), 5.76 (s, 1H), 4.51 (d, J=4.2 Hz, 1H), 4.41 (d, J=4.2 Hz, 1H), 2.30–1.92 (m, 8H), 1.78–1.40 (m, 8H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=147.6, 147.4, 133.7, 133.1, 128.0, 127.3, 124.56, 124.53, 117.3, 85.7, 55.0, 25.8, 24.8, 22.7, 22.1, 22.09, 22.04, 21.2; HRMS calculated for $[C_{21}H_{24}N_2O_4+H]^+$: 369.18088, found: 369.18118.

*4.1.17. 4-p-Anisyl-3,5-bis (cyclohexenyl) isoxazoline-N-oxide (**3q**).* Purified by flash chromatography (hexane–EtOAc) as a white solid (yield: 90%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.26–7.11 (m, 2H), 6.89–6.87 (m, 2H), 6.59–6.58 (m, 1H), 5.73 (s, 1H), 4.51 (d, J=4.8 Hz, 1H), 4.23 (d, J=4.2 Hz, 1H), 3.80 (s, 3H), 2.22–1.94 (m, 8H), 1.73–1.44 (m, 8H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=159.1, 134.3, 132.5, 132.2, 128.1, 126.2, 124.8, 118.4, 114.5, 86.6, 55.2, 54.7, 25.8, 24.8, 22.8, 22.2, 22.1, 21.3; HRMS calculated for $[C_{22}H_{27}NO_3+H]^+$: 354.20637, found: 354.20658.

*4.1.18. 4-Furyl-3,5-bis (cyclohexenyl) isoxazoline-N-oxide (**3r**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil

(yield: 89%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.38 (s, 1H), 6.60–6.58 (m, 1H), 6.34 (m, 1H), 6.19 (d, J=3.6 Hz, 1H), 5.81 (s, 1H), 4.72 (d, J=4.2 Hz, 1H), 4.43 (d, J=4.2 Hz, 1H), 2.24–2.23 (t, J=4.2 Hz, 2H), 2.17–2.12 (m, 3H), 2.06–2.04 (m, 2H), 1.98–1.92 (m, 1H), 1.76–1.48 (m, 8H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=151.7, 142.4, 133.8, 132.2, 126.5, 124.8, 115.8, 110.7, 107.3, 83.2, 48.8, 25.9, 25.5, 24.8, 22.8, 22.3, 22.1, 22.0, 21.3; HRMS calculated for $[C_{19}H_{23}NO_3+H]^+$: 314.17507, found: 314.117533.

*4.1.19. 4-Pyridin-4-yl-3,5-bis (cyclohexenyl) isoxazoline-N-oxide (**3s**).* Purified by flash chromatography (hexane–EtOAc) as an orange solid (yield: 92%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=8.61 (dd, J=4.8, 3.6 Hz, 2H), 7.17–7.16 (dd, J=4.8, 3.0 Hz, 2H), 6.47 (m, 1H), 5.76 (s, 1H), 4.51 (d, J=3.6 Hz, 1H), 4.28 (d, J=4.2 Hz, 1H), 2.30–1.92 (m, 8H), 1.78–1.40 (m, 8H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=150.6, 148.9, 133.7, 132.9, 127.0, 124.5, 122.0, 117.0, 85.4, 54.5, 25.8, 25.7, 24.8, 22.7, 22.1, 22.05, 22.0, 21.2; HRMS calculated for $[C_{20}H_{24}N_2O_2+H]^+$: 325.19105, found: 325.19129.

*4.1.20. 4-n-Propyl-3,5-bis (cyclohexenyl) isoxazoline-N-oxide (**3t**).* Purified by flash chromatography (hexane–EtOAc) as a white solid (yield: 64%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=6.45–6.43 (m, 1H), 4.47 (d, J=2.4 Hz, 1H), 3.13–3.11 (m, 1H), 2.52–2.48 (m, 1H), 2.29–1.88 (m, 6H), 1.89–1.80 (m, 1H), 1.78–1.30 (m, 13H), 0.95 (t, J=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=135.3, 131.6, 125.1, 124.9, 119.0, 82.9, 48.5, 34.1, 25.9, 25.5, 24.7, 22.8, 22.3, 22.16, 22.13, 21.4, 19.3, 13.9; HRMS calculated for $[C_{18}H_{27}NO_2+H]^+$: 390.21146, found: 290.21173.

*4.1.21. 4-p-Nitro-phenyl-3,5-bis (1-furylvinyl)isoxazoline-N-oxide (**3u**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 46%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=8.14–8.12 (m, 2H), 7.39 (d, J=1.8 Hz, 1H), 7.11–7.09 (m, 2H), 6.76 (d, J=1.8 Hz, 1H), 6.47 (q, J=2.4 Hz, 1H), 6.39 (q, J=2.4 Hz, 1H), 6.17–6.16 (d, J=3.0 Hz, 1H), 5.96–5.65 (t, J=3.6 Hz, 1H), 5.77 (s, 1H), 5.64 (d, J=1.2 Hz, 1H), 5.61–5.60 (q, J=3.6 Hz, 1H), 5.59 (s, 1H), 5.17 (dd, J=2.4, 1.2 Hz, 1H), 4.28 (d, J=3.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=150.2, 147.7, 146.2, 142.8, 134.5, 129.3, 128.2, 126.4, 124.7, 124.0, 120.9, 116.0, 111.4, 110.2, 109.7, 107.6, 107.1, 79.6, 57.6, 46.2, 33.1, 29.6; HRMS calculated for $[C_{21}H_{16}N_2O_6+H]^+$: 393.10811, found: 393.08662.

*4.1.22. 4-p-Anisyl-3,5-bis (methylvinyl) isoxazoline-N-oxide (**3v**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 74%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.16–7.13 (m, 2H), 6.90–6.88 (m, 2H), 5.67 (s, 1H), 5.23 (t, J=1.8 Hz, 1H), 5.07 (s, 1H), 4.97 (s, 1H), 4.64 (d, J=4.8 Hz, 1H), 4.26 (d, J=4.8 Hz, 1H), 3.80 (s, 3H), 1.92 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=159.4, 141.0, 131.6, 130.6, 128.2, 119.7, 117.8, 114.7, 113.8, 85.3, 55.2, 20.8, 16.9; HRMS calculated for $[C_{16}H_{19}NO_2+H]^+$: 258.14886, found: 258.14896.

*4.1.23. 4-2′-Furyl-3,5-bis (methylvinyl) isoxazoline-N-oxide (**3w**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 71%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.40–7.39 (m, 1H), 6.36–6.35 (dd, J=3.0, 1.8 Hz, 1H), 6.23 (d, J=3.0 Hz, 1H), 5.68 (s, 1H), 5.26 (s, 1H), 5.14 (s, 1H), 5.01 (s, 1H), 4.84 (d, J=4.8 Hz, 1H), 4.47 (d, J=4.8 Hz, 1H), 1.97 (s, 3H), 1.85–1.84 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=159.4, 141.0, 131.6, 130.6, 128.2, 119.7, 117.8, 114.7, 113.8, 85.3, 55.2, 20.8, 16.9; HRMS calculated for $[C_{13}H_{15}NO_3+H]^+$: 234.11247, found: 234.11261.

4.2. General procedure for preparation of three-component isoxazoline-*N*-oxide (5)

The nitroalkene (0.6 mmol, 1.2 equiv) was added to a solution of the corresponding sulfur ylide (0.55 mmol, 1.1 equiv) DMSO (0.2 M for nitroalkene) solution, till the ylide is all dissolved. Proline (12 mg, 0.1 mmol, 0.2 equiv) and K_2CO_3 (35 mg, 0.25 mmol, 0.5 equiv) were then added in and stir for 5 min. The aldehyde (0.5 mmol, 1.0 equiv) and DMSO solution (0.2 M) were added drop wise through 5 min. The resulting reaction mixture was stirred at room temperature for 1–5 h monitored by TLC. Upon the aldehyde was all consumed, the mixture was diluted with EtOAc (100 mL). The organic phase was washed by HCl solution (1.0 M), saturated $NaHCO_3$ (aq) and brine, and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a residue. Flash silica gel chromatography was then applied to give the product.

*4.2.1. 4-Phenyl-3-(1-phenylvinyl)-5-(phenylketone)-isoxazoline-N-oxide (**5a**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 91%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.97–7.95 (m, 2H), 7.62–7.59 (tt, J=7.2 Hz, 1H), 7.48–7.46 (t, J=7.8 Hz, 2H), 7.26–7.21 (m, 6H), 7.06–7.02 (m, 4H), 6.29 (s, 1H), 5.60 (s, 1H), 5.55 (d, J=3.6 Hz, 1H), 5.07 (d, J=3.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=192.4, 138.1, 137.9, 135.6, 134.3, 133.7, 129.4, 129.1, 128.9, 128.2, 128.1, 127.9, 127.8, 127.5, 122.3, 115.6, 81.0, 52.4; HRMS calculated for $[C_{22}H_{27}NO_3+H]^+$: 370.14377, found: 370.14390.

*4.2.2. 4-p-Toulyl-3-(1-phenylvinyl)-5-(phenylketone)-isoxazoline-N-oxide (**5b**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 92%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.97–7.95 (m, 2H), 7.62–7.60 (tt, J=6.0 Hz, 1H), 7.49–7.46 (t, J=5.4 Hz, 2H), 7.26–7.23 (m, 3H), 7.08–7.05 (m, 4H), 6.93–6.92 (d, J=7.8 Hz, 2H), 6.24 (s, 1H), 5.60 (s, 1H), 5.53 (d, J=3.6 Hz, 1H), 5.01 (d, J=3.6 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=192.5, 138.1, 137.9, 135.6, 135.1, 134.3, 133.7, 129.8, 129.3, 128.9, 128.1, 127.9, 127.7, 127.3, 122.2, 115.6, 81.2, 52.2, 21.0; HRMS calculated for $[C_{25}H_{21}NO_3+H]^+$: 384.15942, found: 384.15955.

*4.2.3. 4-Furyl-3-(1-phenylvinyl)-5-(phenylketone)-isoxazoline-N-oxide (**5c**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 73%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=8.03–8.01 (m, 2H), 7.65–7.62 (tt, J=6.0, 2.4 Hz, 1H), 7.52–7.49 (t, J=7.8 Hz, 2H), 7.34 (m, 1H), 7.31–7.25 (m, 3H), 7.18–7.16 (m, 2H), 6.28 (s, 1H), 6.23–6.22 (q, J=3.6 Hz, 1H), 5.92 (d, J=3.0 Hz, 1H), 5.70 (d, J=4.2 Hz, 1H), 5.67 (s, 1H), 5.35 (d, J=4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=191.8, 186.8, 149.2, 143.0, 137.8, 135.5, 134.4, 133.7, 129.5, 128.9, 128.2, 128.1, 127.6, 122.1, 110.7, 108.6, 78.1, 46.0; HRMS calculated for $[C_{22}H_{17}NO_4+Na]^+$: 382.10498, found: 382.10522.

*4.2.4. 4-Propyl-3-(1-phenylvinyl)-5-(phenylketone)-isoxazoline-N-oxide (**5d**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 62%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=8.03–8.01 (m, 2H), 7.64–7.61 (tt, J=6.0, 2.4 Hz, 1H), 7.52–7.50 (t, J=7.8 Hz, 2H), 7.39–7.29 (m, 5H), 6.37 (s, 1H), 5.78 (s, 1H), 5.32 (d, J=3.0 Hz, 1H), 4.06–4.04 (m, 1H), 1.56–1.50 (m, 1H), 1.47–1.41 (m, 1H), 1.31–1.30 (m, 2H), 0.75 (t, J=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=193.6, 138.1, 135.6, 134.17, 134.12, 129.3, 128.8, 128.5, 128.2, 127.6, 122.0, 115.8, 78.6, 45.8, 33.3, 18.9, 13.4; HRMS calculated for $[C_{21}H_{21}NO_3+H]^+$: 336.15942, found: 336.16080.

*4.2.5. 4-i-Propyl-3 (1-phenylvinyl) 5-(phenylketone) isoxazoline-N-oxide (**5e**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 52%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=8.05–8.04 (m, 2H), 7.65–7.62 (m, 1H), 7.53–7.51 (m, 2H), 7.39–7.25 (m, 5H), 7.36 (s, 1H), 5.83 (s, 1H), 5.38 (d, J=2.4 Hz, 1H), 4.02–4.01 (dd, J=4.2, 1.2 Hz, 1H), 1.86–1.80 (m, 1H), 0.95–0.89 (m, 3H), 0.82 (d, J=6.6 Hz, 3H), 0.74 (t, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=194.0, 138.2, 135.9, 134.2, 134.1, 129.4, 128.8, 128.5, 128.3, 127.6, 122.2, 115.0, 75.4, 51.6, 29.3, 19.4, 17.5; HRMS calculated for $[C_{21}H_{21}NO_3+H]^+$: 336.15942, found: 358.15967.

*4.2.6. 4-p-Nitrophenyl-3-(1-phenylvinyl)-5-(phenylketone) isoxazoline-N-oxide (**5f**).* Purified by flash chromatography (hexane–EtOAc)

as a colorless oil (yield: 92%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=8.08–8.06 (d, J=7.2 Hz, 2H), 8.00–7.99 (d, J=8.4 Hz, 2H), 7.66–7.63 (t, J=8.4 Hz, 1H), 7.52–7.50 (t, J=7.8 Hz, 2H), 7.28–7.24 (m, 3H), 7.17–7.15 (m, 2H), 7.04–7.03 (d, J=7.8 Hz, 2H), 6.46 (s, 1H), 5.67 (s, 1H), 5.48 (d, J=4.2 Hz, 1H), 5.34 (d, J=4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=191.7, 147.6, 145.2, 138.0, 135.0, 134.7, 133.6, 129.5, 129.0, 128.6, 128.4, 128.3, 127.9, 124.2, 122.7, 114.9, 80.4, 51.5; HRMS calculated for $[C_{24}H_{18}N_2O_5+H]^+$: 415.12885, found: 415.21173.

*4.2.7. 4-Napthyl-3-(1-phenylvinyl)-5-(ethyl ester)-isoxazoline-N-oxide (**5g**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 88%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.85–7.79 (m, 3H), 7.49–7.35 (m, 4H), 7.14–7.12 (m, 3H), 7.03 (d, J=3.0, 2H), 6.33 (s, 1H), 5.62 (s, 1H), 4.81 (d, J=3.0 Hz, 1H), 4.64 (d, J=3.0 Hz, 1H), 4.37–4.33 (m, 2H), 1.37–1.35 (t, J=7.2, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=169.3, 137.9, 135.5, 134.0, 133.0, 132.8, 130.3, 129.1, 129.0, 128.1, 127.9, 127.6, 126.9, 126.0, 125.4, 122.4, 122.1, 78.1, 62.6, 49.1, 14.6; HRMS calculated for $[C_{20}H_{19}NO_4+H]^+$: 388.15433, found: 388.15453.

*4.2.8. 4-p-Nitrophenyl-3-(1-phenylvinyl)-5-(ethyl ester) isoxazoline-N-oxide (**5h**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 92%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=8.10–8.07 (m, 2H), 7.30–7.23 (m, 3H), 7.14–7.12 (m, 2H), 6.99–6.98 (m, 2H), 6.43 (s, 1H), 5.66 (s, 1H), 4.82–4.80 (dd, J=10.2, 6.6 Hz, 2H), 4.39–4.35 (m, 2H), 1.39–1.36 (t, J=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=168.2, 147.7, 144.7, 137.8, 134.8, 128.4, 128.3, 128.1, 127.7, 124.2, 122.5, 113.9, 62.7, 54.1, 14.0; HRMS calculated for $[C_{20}H_{18}N_2O_6+H]^+$: 383.12376, found: 383.12396.

*4.2.9. 4-p-Toulyl-3-(1-phenylvinyl)-5-(p-bromophenyl ketone) isoxazoline-N-oxide (**5i**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 91%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.84–7.82 (m, 2H), 7.64–7.62 (m, 2H), 7.27–7.23 (m, 3H), 7.06–7.05 (m, 4H), 6.92–6.90 (d, J=8.4 Hz, 2H), 6.25 (s, 1H), 5.60 (s, 1H), 5.45 (d, J=4.2 Hz, 1H), 5.02 (d, J=3.6 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=191.7, 138.2, 137.8, 135.5, 134.9, 132.5, 132.2, 130.8, 129.8, 128.1, 127.9, 127.7, 127.3, 122.4, 115.5, 81.1, 52.0, 21.0; HRMS calculated for $[C_{25}H_{20}NO_3Br+H]^+$: 462.06993, found: 462.07183.

*4.2.10. 4-p-Nitrophenyl-3-(1-phenylvinyl)-5-(p-bromophenylketone)-isoxazoline-N-oxide (**5j**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 73%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=8.09–8.06 (m, 2H), 8.00–7.99 (d, J=7.2 Hz, 2H), 7.66–7.63 (tt, J=6.0, 2.4 Hz, 1H), 7.52–7.50 (t, J=6.6 Hz, 2H), 7.30–7.24 (m, 2H), 7.17–7.15 (m, 2H), 7.04–7.03 (d, J=4.8 Hz, 2H), 6.46 (s, 1H), 5.67 (s, 1H), 5.49 (d, J=4.2 Hz, 1H), 5.35 (d, J=4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=191.7, 147.6, 145.2, 138.0, 135.0, 134.7, 133.6, 129.5, 129.0, 128.6, 128.4, 128.3, 127.9, 124.2, 122.7, 114.9, 80.5, 51.5; HRMS calculated for $[C_{25}H_{20}BrNO_4+H]^+$: 478.06485, found: 478.06495.

*4.2.11. 4-p-Anisyl-3 (1-phenylvinyl) 5- (p-bromophenyl ketone) isoxazoline-N-oxide (**5k**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 92%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.84–7.82 (d, J=8.4 Hz, 2H), 7.64–7.62 (d, J=9.0 Hz, 2H), 7.27–7.23 (m, 3H), 7.05–7.04 (m, 2H), 6.93–6.91 (d, J=8.4 Hz, 2H), 6.77–6.76 (d, J=6.6 Hz, 2H), 6.28 (s, 1H), 5.61 (s, 1H), 5.44 (d, J=3.6 Hz, 1H), 5.01 (d, J=3.6 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=191.8, 159.5, 138.0, 135.5, 132.5, 132.2, 130.8, 129.8, 128.6, 128.1, 128.0, 127.7, 122.4, 115.6, 114.5, 81.2, 55.2, 51.7; HRMS calculated for $[C_{25}H_{20}BrNO_4+H]^+$: 478.06485, found: 478.06498.

*4.2.12. 4-Pyridin-4-yl-3-(1-phenylvinyl)-5-(p-bromophenyl ketone) isoxazoline-N-oxide (**5l**).* Purified by flash chromatography (hexane–EtOAc) as a colorless oil (yield: 92%); ^{1}H NMR (600 MHz, $CDCl_3$): δ=8.41–8.40 (dd, J=4.8, 3.0 Hz, 2H), 8.05–8.04 (dd, J=7.2, 5.4 Hz, 2H), 7.66–7.63 (t, J=8.4 Hz, 1H), 7.52–7.50 (t, J=8.4 Hz, 2H), 7.26–7.20 (m, 6H), 7.14–7.13 (dd, J=4.2, 3.0 Hz, 2H), 5.91 (s, 1H), 5.69 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=182.5, 162.8, 162.4, 149.5, 146.9, 137.0, 136.6, 136.3, 135.7, 135.4, 134.5, 130.2, 128.7, 128.6, 128.4, 126.7, 124.0, 121.8, 121.2; HRMS calculated for $[C_{23}H_{17}N_2O_3Br+H]^+$: 449.04953, found: 449.04984.

4.3. Procedure for diene intermediate A′ and the cross condensation. (Scheme 10)

The nitroalkene **1b** (141 mg, 1.0 mmol, 1.0 equiv, 0.1 M) and DMSO solution were added to a DCM solution of aldehyde (1.5 mmol, 1.5 equiv, 0.15 M), L-proline (11 mg, 0.1 mmol, 0.1 equiv), and K_2CO_3 (35 mg, 0.25 mmol, 0.5 equiv) mixture. Add the nitroalkene drop wise to the reaction mixtures in 5 min. The resulting mixture was stirred at room temperature for 2 h. Upon the nitroalkene was all consumed, the mixture was diluted with EtOAc (100 mL). The organic phase was washed by brine and then dried over anhydrous Na_2SO_4. Flash silica gel chromatography was then applied to give the *Z*/*E* isomers **A′** as a mixture (143 mg, 65% yield), *Z*/*E*=1/1.5. ^{1}H NMR (600 MHz, $CDCl_3$): *set* 1, δ=7.81 (s, 1H), 7.57 (d, J=3.2 Hz, 1H) 6.85–6.86 (d, 1H), 6.52–6.53 (dd, J=3.6 Hz, 1H), 5.95–5.96 (m, 1H), 2.17–2.24 (m, 4H), 1.72–1.83 (m, 3H), 1.62–1.65 (m, 1H); *set* 2, δ=7.43 (d, 1H), 6.49–6.50 (d, 1H), 6.41–6.42 (dd, J=3.6, 1.8 Hz, 1H), 6.15 (s, 1H), 5.86–5.88 (t, J=7.2 Hz, 1H), 2.17–2.24 (m, 4H), 1.72–1.83 (m, 3H), 1.62–1.65 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): *set* 1, δ=148.0, 146.1, 144.3, 133.8, 120.8, 117.1, 112.9, 112.0, 26.8, 25.5, 22.5, 21.5; *set* 2 δ=149.0, 148.5, 147.2, 129.1, 128.0, 112.8, 104.9, 29.7, 25.7, 24.5, 22.1; HRMS calculated for $[C_{12}H_{13}NO_3+H]^+$: 220.09682, found: 220.09697.

The diene **A′** (132 mg, 0.6 mmol, 1.0 equiv) was then mixed with nitroalkene **1a** (106 mg, 0.65 mmol, 1.1 equiv) in DMSO, with **A′** as 0.1 M. Proline (14 mg, 0.12 mmol, 0.2 equiv) and K_2CO_3 (41 mg, 0.30 mmol, 0.5 equiv) were added in the solution. 2 h later, the nitroalkene was all consumed, the mixture was diluted with EtOAc (100 mL). The organic phase was washed brine and then dried over anhydrous Na_2SO_4. Flash silica gel chromatography was then applied to give the crude product **3b** (18%), **3b′** (6%), **3s** (26%), **3s′** (24%). These four compounds could not be separated by chromatography.

4.4. General procedure for preparation of three-component isoxazoline-*N*-oxide (optical sample for Table 5)

The nitroalkene **1a** (114 mg, 0.7 mmol, 1.4 equiv) was added to a solution of the sulfur ylide **4d** (219 mg, 0.6 mmol, 1.2 equiv) in MeOH (0.4 M for nitroalkene), till the ylide is all dissolved. The mixture was cooled down to −25 °C. Pyrrolidine (7 mg, 0.1 mmol, 0.2 equiv) and K_2CO_3 (35 mg, 0.25 mmol, 0.5 equiv) were then added in and stir for 30 min. The aldehyde **2a** (0.5 mmol, 1.0 equiv) MeOH solution (0.4 M) was added drop wise through 10 min. The resulting reaction mixture was stirred at −25 °C for 48 h. The mixture was then diluted with EtOAc (20 mL) and the water phase was extracted with EtOAc (20 mL×3). The organic phase was washed by HCl solution (1.0 M), saturated $NaHCO_3$ (aq) and brine, and then dried over anhydrous Na_2SO_4. Flash silica gel chromatography was then applied to give the product **7a** (144 mg, 89%) as clear oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ=7.27–7.22 (m, 6H), 7.01–6.98 (m, 4H), 6.29 (s, 1H), 5.61 (s, 1H), 4.83 (d, J=3.0 Hz, 1H), 4.65 (d, J=3.0 Hz, 1H), 3.89(s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): 169.4, 137.9, 137.7, 135.4, 129.1, 129.10, 128.7, 128.3, 128.1, 128.0, 127.7, 127.0, 122.3, 114.7, 78.2, 54.8, 53.1; HRMS calculated for $[C_{19}H_{17}NO_4+H]^+$: 324.12303, found: 324.12316. $[\alpha]_D^{26}$ 104.5° (*c* 1.0 $CHCl_3$). Enantiomeric excess was determined by HPLC with a Chiralcel OD-H

column; λ=254 nm; eluent: hexane–isopropanol=90/10; flow rate: 1.0 mL/min; t_{minor}=10.352 min, t_{major}=12.964 min; ee%=91%.

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References and notes

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18. The interaction between chiral secondary amine LB and the nitroalkene or the intermediate is currently under investigation.