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Catalytic Enantioselective Synthesis of 3,4,5-Trisubstituted Isoxazoline *N*-oxides and Regioselective Synthesis of 3,4,5-Trisubstituted Isoxazoles

Subas Chandra Sahoo and Subhas Chandra Pan*[a]

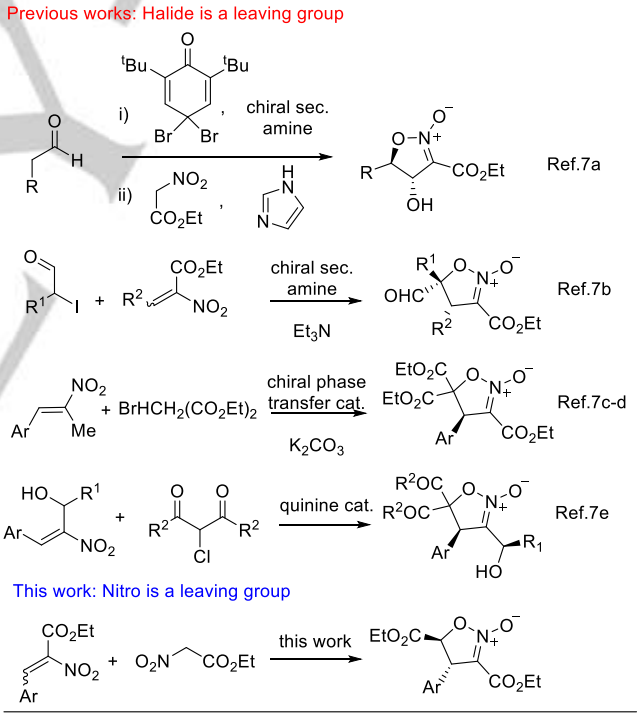
Dedication ((optional))

Abstract: An efficient catalytic asymmetric synthesis of 3,4,5-trisubstituted isoxazoline *N*-oxides and regioselective synthesis of 3,4,5-trisubstituted isoxazoles has been described. *α*-Nitrocinnamates and *α*-nitrobenzophenones were utilized as Michael acceptors respectively. Hydroquinine derived thiourea in combination with cesium carbonate was effective for the synthesis of isoxazoline *N*-oxides whereas stoichiometric *di*-isopropylethylamine (DIPEA) was the best choice for isoxazole synthesis. In both cases a range of aryl and heteroaromatic groups was tolerated.

Introduction

Isoxazoline *N*-oxides, important five-membered heterocycles, are familiar precursors for the synthesis of highly functionalized *γ*-hydroxy-*α*-amino acids or *γ*-amino-*α*-hydroxy acids,[1,2] natural products,[1c,3] and biologically active compounds.[4] Owing to their versatile use in organic synthesis, a range of synthetic approaches for the preparation of isoxazoline *N*-oxides have been documented.[3,5] In the past, the synthesis of chiral isoxazoline *N*-oxides relied on the use of optically pure starting materials[5] and on stoichiometric quantities of chiral reagents[6]. Recently a few catalytic asymmetric strategies have been reported in the literature (Scheme 1).[7] Jørgensen and co-workers reported a one pot synthesis of functionalized chiral isoxazoline *N*-oxides through *α*-bromination, Henry reaction and cyclization sequence.[7a] Zhong and co-workers reported secondary amine catalysed [4+1] annulation between *α*-iodo aldehydes and (*E*/*Z*)-nitrocinnamates.[7b] Maruoka group developed a phase transfer catalysed conjugate addition of bromomalonates to nitroolefins followed by cyclization for the synthesis of isoxazoline *N*-oxides.[7c-d] Zhu group utilized quinine as a catalyst for the cyclization reaction between Morita Baylis Hillman adducts and chloro-1,3-diketones.[7e] However, halogen free synthesis of chiral isoxazoline *N*-oxides was not reported.

Similarly, isoxazoles are often found in natural products and biologically active compounds as well as used as building blocks in organic synthesis.[8,9] In particular 3,4,5-trisubstituted oxazoles[10] have drawn attention in view of their biological antagonism,[11] antibacterial and antifugal activities[12] and inhibition of casein kinase. [13] These bioactivities have prompted the development for the synthesis of a variety of trisubstituted isoxazoles.[14] Although the reported methods have been demonstrated effective in the preparation of isoxazoline and isoxazoline *N*-oxides with specific structures, there is still requirement for the exploration of new and efficient synthetic methods for structurally diverse isoxazoline *N*-oxides and isoxazolines. Here in, we report a direct synthesis of chiral isoxazoline *N*-oxides from ethyl α-nitrocinnamates and ethyl nitroacetate and also regioselective synthesis of isoxazolines from α-nitrochalcones and nitroketones.



Scheme 1: Catalytic asymmetric synthesis of isoxazoline N-oxides

Results and Discussion

We began our investigation by reacting *α*-nitrocinnamate **1a** and ethyl nitroacetate **2a** with Takemoto catalyst (**I**) in the presence of sodium carbonate in chloroform and little amount of water at room temperature (Table 1). Delightfully, after stirring for 7 days, the desired isoxazoline *N*-oxide **3a** was formed in 30% yield and >20:1 diastereomeric ratio but the enantioselectivity was poor (Table 1, entry 1). To improve the enantioselectivity, hydroquinine derived thiourea catalyst **II** was employed but only little enhancement was observed (Table 1, entry 2). Squaramide

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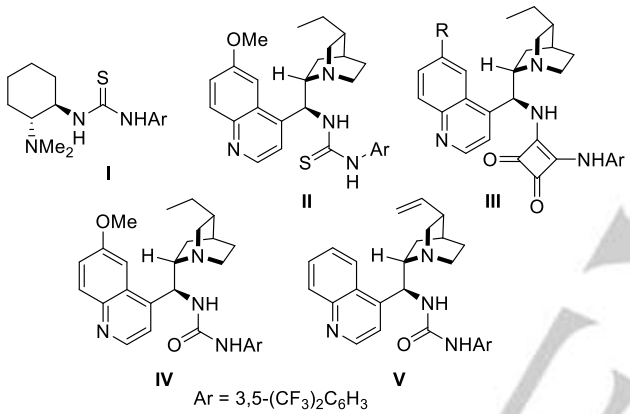
catalyst **III** was also found to be not efficient for this reaction. Then we prepared hydroquinine derived urea catalyst **IV** and better yield as well as enantioselectivity (82:18 er) was detected (Table 1, entry 4). Cinchonidine derived urea catalyst **V** was also screened and provided the product **3a** in lesser yield and enantioselectivity. Thus catalyst **IV** was used for further optimization. Consequently we turned our attention on the screening of different bases and it proved to be fruitful. Though potassium carbonate could not improve the enantioselectivity, a higher enantioselectivity (86:14 er) was obtained with cesium carbonate (Table 1, entries 6-7). Then we decided to change the equivalents of cesium carbonate in the reaction. Infact the best result (93:7 er) was achieved with 4 equivalents of cesium carbonate (Table 1, entries 8-9). Other solvents were also screened (see supporting information for details) but inferior results were obtained.

Table 1. Catalyst screening and optimization of the reaction conditions for the synthesis of isoxazoline *N*-oxide **3a**

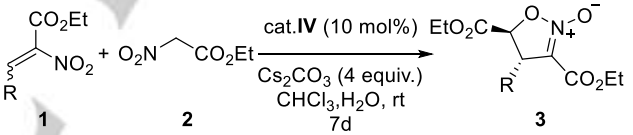


Entry[a]	Catalyst	Base	Yield[b]	er[c]
1	**I**	Na_2CO_3	30	45:55
2	**II**	Na_2CO_3	40	57:43
3	**III**	Na_2CO_3	42	55:45
4	**IV**	Na_2CO_3	72	82:18
5	**V**	Na_2CO_3	65	73:27
6	**IV**	K_2CO_3	72	73:27
7	**IV**	Cs_2CO_3	78	86:14
8[d]	**IV**	Cs_2CO_3	75	89:11
9[e]	**IV**	Cs_2CO_3	70	93:7

[a] Reaction condition: Unless otherwise mentioned, 0.05 mmol of **1a** and 0.05 mmol of **2** with 1 eq. base in 0.5 mL chloroform and 100 μL water using 10 mol% catalyst and a single diastereomer was detected. [b] Isolated yield after silica gel column chromatography.[c] Determined by chiral HPLC. [d] Two equivalents of Cs_2CO_3. [e] Four equivalents of Cs_2CO_3.

After the optimized conditions got established, the scope of ethyl *α*-nitrocinnamates in the reaction was investigated. As displayed in Table 2, a wide range of aryl group containing nitrocinnamates could be employed in the reaction and moderate to good results were achieved. Also, pleasingly, in all of the cases, only a single diastereomer formation was observed. Initially, different *ortho*-substituted aryl groups were tested and delightfully good results were obtained. For example, *o*-tolyl containing nitrocinnamate **1b** delivered product **3b** in 65% yield with 95:5 er. Nitrocinnamate **2c** having 2-anisyl substituent also participated in the reaction with acceptable yield and slight lower enantioselectivity was detected. Halo substitutions were also tolerated and products **3d** and **3e** were isolated in good yields. It is interesting that the enantioselectivity of **3e** was higher than **3d**. Then *m*-substituted nitrocinnamates **1f** and **1g** were screened in the reactions and moderate enantioselectivities were achieved for products **3f** and **3g**. Our methodology was also found to be suitable for *o*-substiuted nitrocinnamates and good results were observed. In particular, product **3j** having 4-fluoro substituent was isolated in 78% yield with 90:10 er. 1-Naphthyl substituted nitrocinnamate **1l** also took part in the reaction to deliver product **3l** in moderate enantioselectivty. Finally furyl substituted nitrocinnamate **1m** was employed in the reaction and similar result was observed.

Table 2. Scope of nitrocinnamates in the synthesis of isoxazoline *N*-oxides



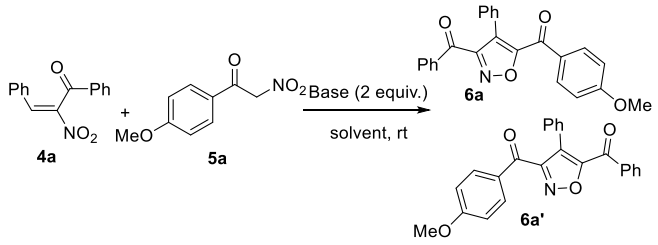
1 2 3

Entry[a]	R	3	Yield[b](%)	dr[c]	er[d]
1	Ph	**3a**	70	>20:1	93:7
2	2-MeC_6H_4	**3b**	65	>20:1	95:5
3	2-$OMeC_6H_4$	**3c**	70	>20:1	86:14
4	2-FC_6H_4	**3d**	80	>20:1	85:15
5	2-ClC_6H_4	**3e**	78	>20:1	92:8
6	3-MeC_6H_4	**3f**	72	>20:1	86:14
7	3-ClC_6H_4	**3g**	75	>20:1	84:16
8	4-MeC_6H_4	**3h**	78	>20:1	75:25
9	4-$OMeC_6H_4$	**3i**	75	>20:1	80:20
10	4-FC_6H_4	**3j**	78	>20:1	90:10
11	4-ClC_6H_4	**3k**	74	>20:1	82:18
12	1-naphthyl	**3l**	78	>20:1	77:23
13	2-furyl	**3m**	35	>20:1	78:22

[a] Reaction conditions: 0.1 mmol of **1** and 0.1 mmol of **2** with 4 eq. Cs_2CO_3 in 1 mL chloroform and 200 µL water using 10 mol% catalyst **IV**. [b] Isolated yield after silica gel column chromatography. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC.

Then we screened organic base mediated reaction between *α*-nitrobenzophenone **4a** and nitroketone **5a** and interestingly using DBU as base, an isoxazole product **6a** was isolated in 3:1 ratio along with the regioisomer **6a'** (Table 3, entry 1).[15] The yield as well as regioselectivity got improved with *di*-isopropylethylamine (Table 3, entry 2). Then we turned our attention on the solvent optimization. Interestingly, the yield got decreased in toluene and also DMSO was not at all a good solvent only providing 5% yield (Table 3, entries 3-4). Gratifyingly a decent yield of 72% with a high regioselectivity was achieved in acetonitrile (Table 3, entry 5).

Table 3. Optimization of the reaction conditions for the synthesis of isoxazole

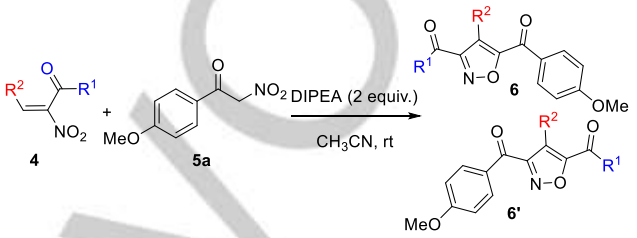


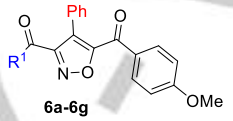
Entry[a]	base	solvent	time (h)	Yield[b](%)	**6a**/**6a'**[c]
1	DBU	$CHCl_3$	24	68	3:1
2	DIPEA	$CHCl_3$	36	71	3.5:1
3	DIPEA	toluene	36	55	2:1
4	DIPEA	DMSO	36	5	-
5	DIPEA	CH_3CN	36	72	5:1

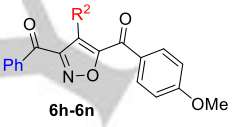
[a] Reaction conditions: 0.05 mmol of **4a** and 0.05 mmol of **5a** in 0.5 mL solvent using 2 eq. base at room temperature. [b]Isolated yield after silica gel column chromatography. [c]Determined by ^{1}H NMR.

After the best reaction conditions got established, the scope and generality of the reaction **6** was ventured. Initially the keto-functionality of *α*-nitrobenzophenone was varied and the results are shown in Table 4. At the beginning, different *para*-substitutions were tested and the products **6b**-**6d** were obtained in good yields and high to excellent regioselectivities. In particular, product **6d** having 4-chloro substitution was isolated as single regioisomer in 80% yield. Then benzophenone **4e** having 2,4-dimethylphenyl group was employed and delightfully here also the product **6e** was attained as a single regioisomer. Smooth conversion was also seen with thiphenyl enone **4f** but in this case the opposite regioisomer **6f'** was formed as major product because of more electron density of thiophene ring. Moreover an alphatic enone **4g** was also tolerated in the reaction, albeit slight lower yield was observed. Then we turned our attention to check different groups of the olefin functionality in enone **4** (Table 4). Thus enones **4h**-**4k** having electron donating and withdrawing group at *para*-position were engaged in the reaction. Delightfully, the products **6h**-**6k** were isolated in acceptable yields and good regioisomeric ratios. For example, products **6i** and **6j** having 4-methoxy and 4-chloro substituents respectively, were obtained with 5.6:1 and 5.1:1 regioisomeric ratios. Also, high regioselectivity and acceptable yield was observed for product **6k** having 4-nitroaryl group. The regioselectivity got enhanced when *meta*-substituted enone **4l** was employed in the reaction. Our methodology also worked with *ortho*-substituted enone **4m** *albeit* slight lower yield was observed for product **6m**. A heteroaromatic furyl group was also screend and the regioisomeric product **6n** was obtained as 4.6:1 mixture.

Table 4. Scope of enones in the synthesis of isoxazoles [a],[b]





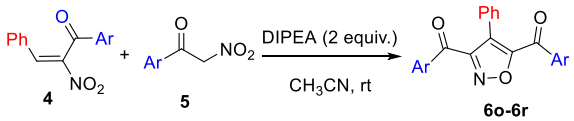


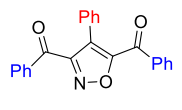
R^1 = Ph, **6a/6a'**, 72%, 5:1, 36h
R^1 = 4-^{i}PrC$_6$H$_4$, **6b/6b'**, 69%, 2.4:1, 36h
R^1 = 4-FC$_6$H$_4$,**6c/6c'**, 78%, 6:1, 36h
R^1 = 4-ClC$_6$H$_4$,**6d/6d'** , 80%, >20:1, 36h
R^1 = 2,4-Me$_2$C$_6$H$_3$,**6e/6e'** , 60%, >20:1, 36h
R^1 = 2-thienyl, **6f/6f'**, 71%,1:3.1, 30h
R^1 = isovaleryl,**6g/6g'**, 42%, >20:1, 36h
R^2 = 4-MeC$_6$H$_4$, **6h/6h'**, 70%, 4:1, 36h
R^2 = 4-OMeC$_6$H$_4$, **6i/6i'**, 72%, 5.6:1, 30h
R^2 = 4-ClC$_6$H$_4$, **6j/6j'**, 68%, 5.1:1, 36h
R^2 = 4-NO$_2$C$_6$H$_4$,**6k/6k'**, 69%, 7.3:1, 36h
R^2 = 3-ClC$_6$H$_4$,**6l/6l'** , 70%, 8:1, 30h
R^2 = 2-ClC$_6$H$_3$,**6m/6m'** , 35%, 4:1, 72h
R^2 = 2-furyl, **6n/6n'**, 52%, 4.6:1, 36h

[a] Reaction conditions: 0.1 mmol of **4** with 0.1 mmol of **5a** in 1 ml CH_3CN. [b]Yields correspond to isolated yields after silica gel column chromatography and regioselectivity was determined by ^{1}H NMR.

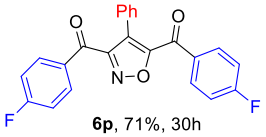
The generality of the reaction was further established by by preparing isoxazoles with same ketofunctionalities (Table 5). Thus the reaction of enone **1a** with phenyl nitroketone **2b** provided the product **6o** in 66% yield. Similarly other products **6p**-**6r** were isolated in good yields. In these cases, the cyclization happened through a symmetrical intermediate.

Table 5. Synthesis of isoxazoles with same keto functionalities [a],[b]

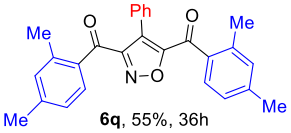




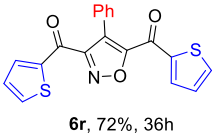
6o, 66%, 24h



6p, 71%, 30h



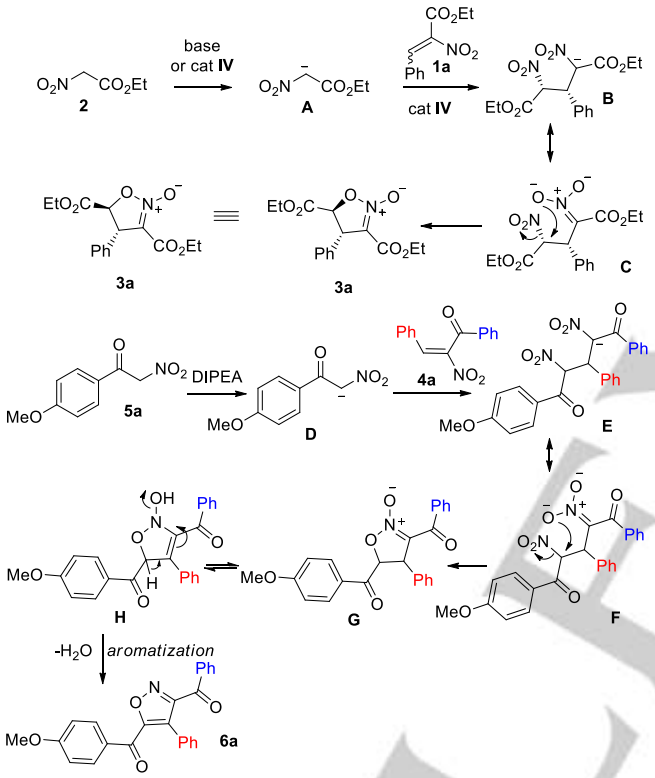
6q, 55%, 36h



6r, 72%, 36h

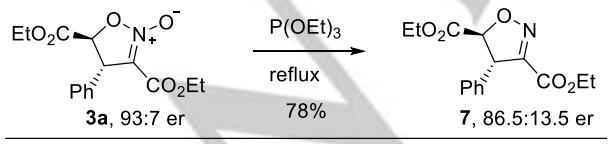
[a] Reaction conditions: 0.1 mmol of **4** with 0.1 mmol of **5** in 1 ml CH_3CN. [b] Yields correspond to isolated yields after silica gel column chromatography.

Plausible mechanism has been shown in Scheme 2 to explain the formation of products **3a** and **6a**. Initially ethyl *α*-nitrocinnamate **2** gets deprotonated either by catalyst or base to generate active nucleophile **A** which then reacts with *α*-nitrocinnamate **2a** to provide **B**. Intramolecular substitution reaction in the resonance form **C** with nitro as the leaving group delivers product **3a**. Similarly, for the formation of isoxazole **6a**, nitroketone **5a** first gets deprotonated by DIPEA to form **D** which undergoes conjugate addition reaction to α-nitrobenzophenone **4a** to form intermediate **E**. Intramolecular cyclization of **F** then delivers **G** which tautomerizes to **H**. Finally product **6a** is formed after water elimination and aromatization.



Scheme 2. Proposed mechanism for the formation of **3a** and **6a**.

To show a synthetic application, product **3a** was converted to isoxazoline **7** *via* triethylphosphite mediated deoxygenation reaction, however a decrease in enantioselectivity was observed (Scheme 3).



Scheme 3. Deoxygenation reaction of **3a**.

Conclusion

In summary, we have developed an efficient catalytic asymmetric synthesis of 3,4,5-trisubstituted isoxazoline *N*-oxides and regioselective synthesis of 3,4,5-trisubstituted isoxazoles. Easily available starting materials *α*-nitrocinnamates, *α*-nitrobenzophenones, nitroacetate and *α*- nitroketones were employed in this method. The products 3,4,5-trisubstituted isoxazoline *N*-oxides and isoxazoles could be useful in the development of new pharmaceuticals.

Experimental procedures

General procedure for the synthesis of Isoxazoline *N*-oxides 3:

Cs_2CO_3 (130 mg, 0.4 mmol) and hydroquinine derived thiourea catalyst **IV** (5.9 mg, 0.01 mmol) were added to solution of **1** (0.1 mmol) and **2** (0.1 mmol) in Chlororom (1 mL). Then water (200 *μ*L) water was added to it. After stirring for 7 days at RT, 3 mL of water was added. The resulting mixture was extracted with DCM (3 X 2 mL). The combined organic phase was dried with Na_2SO_4, evaporated in vacuum and purified by column chromatography (15%-20% EtOAc in Hexane) to give compound **3**.

General procedure for the synthesis of Isoxazole 6:

DIPEA (34 *μ*L, 0.2 mmol) was added to a stirred solution of **4** (0.1 mmol) and **5** (0.1 mmol) in CH_3CN (1 mL) and stirring was maintained at room temperature. After consumption of starting materials, 3 mL of water was added. The resulting mixture was extracted with EtOAc (3 X 2 mL). The combined organic phase was dried with Na_2SO_4, evaporated in vacuum and purified by column chromatography (4%-8% EtOAc in hexane) to provide compound **6**.

Acknowledgements

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Keywords: Isoxazoline *N*-oxides; *α*-Nitrocinnamates; Organocatalysis; Regioselective; Isoxazoles

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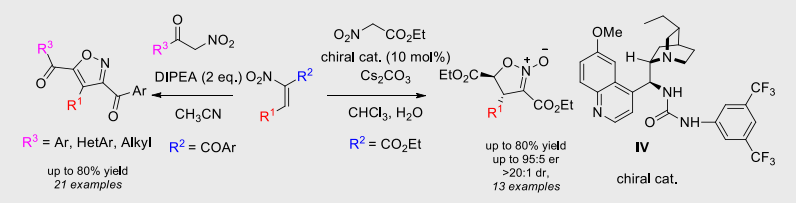

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Catalytic Enantioselective Synthesis of 3,4,5-Trisubstituted Isoxazoline *N*-oxides and Regioselective Synthesis of 3,4,5-Trisubstituted Isoxazoles

A convenient catalytic asymmetric synthesis of 3,4,5-trisubstituted isoxazoline *N*-oxides and regioselective synthesis of 3,4,5-trisubstituted isoxazoles has been developed.