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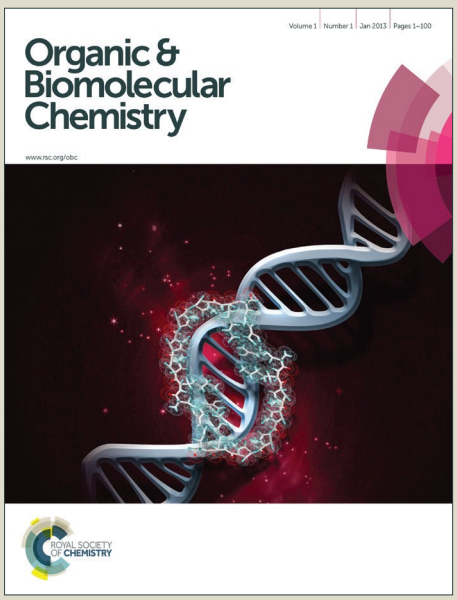

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ARTICLE TYPE

Catalytic enantioselective addition of Isocyanoacetate to 3-methyl-4-nitro-5-styrylisoxazoles under phase transfer catalysis conditions.

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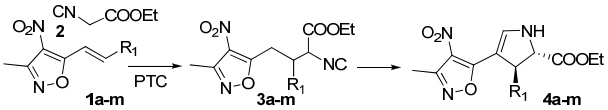
The reaction between 3-methyl-4-nitro-5-styrylisoxazoles and ethyl isocyanoacetate proceeded under phase transfer catalysis to give enantioenriched monoadducts in high enantiomeric excess (up to 99% *ee*). The resulting adducts were subsequently cyclised to give 2,3-dihydropyrroles and substituted pyrrolidines in identical high *ee*s and as a single diastereoisomer.

Herein we report a highly enantioselective (up to 99% *ee*) Michael addition of un-substituted α-isocyanoester **2** to 3-methyl-4-nitro-5-styrylisoxazoles **1a-m** (Scheme 1) that run under phase transfer catalysis. This reaction provided exclusively mono alkylated compounds **3a-m**, whose synthetic relevance was demonstrated by their conversion to 2,3-dihydropyrroles **4a-m** and pyrrolidines **7-9**. *The methodology described in this work allows the mono-addition of un-substituted α-isocyanoacetates to Michael acceptors, which is difficult to control in basic media, by using the soft electrophilic alkene **1***. The reaction reported herein provided enantiomers **3-4** and *ent*-**3-4** in similar high *ee*s.

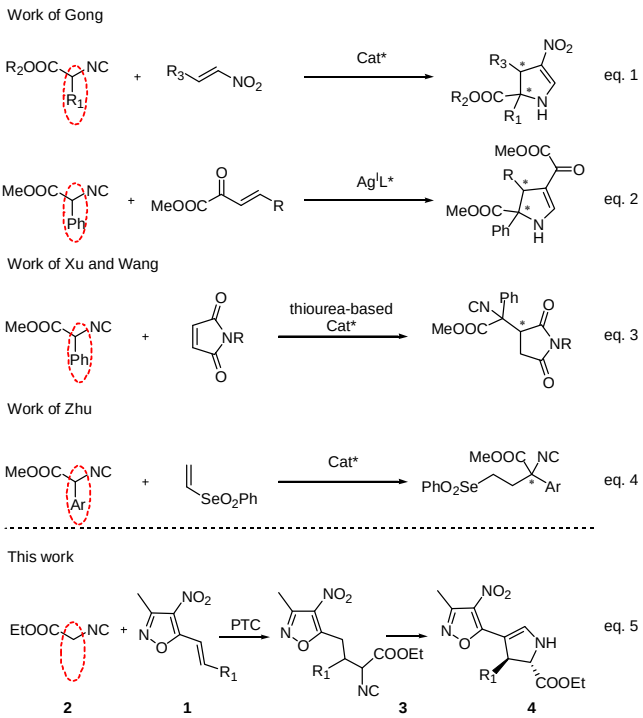
Scheme 1 Addition of α-isocyanoesters **2** to Michael acceptors **1**



Isocyanoacetates are popular reagents and their derivatives have been widely used in organic, inorganic, coordination, polymeric, combinatorial and medicinal chemistry.[1] Products obtained from isocyanoacetates are effective building blocks for the synthesis of biologically active molecules, complex natural products[2] and heterocycles. Formation of carbon-carbon bonds *via* addition of isocyanoacetates to aldehydes,[4] imines,[5] azodicarboxylates,[6] nitroalkenes,[7] α,β-unsaturated ketones,[8] maleimides,[9] carbodiimides,[10] alkynes,[11] and aromatic isocyanides[12] has been previously described. In these reactions, the initially formed Michael adduct undergoes a subsequent intramolecular nucleophilic addition to form oxazoles,[4a, 4c,4e, 4f, 4g] imidazoles,[5h, 5i] isoquinolines [13b] or pyrroles,[11c] effectively *via* a formal [3 +2] cycloaddition.

In contrast to the long history of non-asymmetric variants,[13] the enantioselective catalytic addition of α-isocyanoesters with electron-deficient olefins has only recently been studied (Scheme 2).[14-18] Gong and co-workers reported a *Cinchona* alkaloid catalysed highly enantioselective addition of 2-substituted isocyanoesters to nitroolefins to give 2,3-dihydropyrroles (eq. 1, Scheme 2).[14]

Scheme 2 Comparison between selected existing literature examples and this work.



Recently, the same group reported a highly enantioselective cycloaddition reaction of 2-substituted isocyanoesters and 2-oxobutenoate esters, catalysed by a chiral silver complex (eq. 2, Scheme 2).[15] Xu and Wang developed a diastereoselective and enantioselective Michael addition of 2-substituted isocyanoacetates to *N*-aryl maleimides catalyzed by bifunctional tertiary amine thioureas (eq. 3, Scheme 2).[16] Zhu discovered a catalytic enantioselective *Cinchona* alkaloid catalyzed Michael addition of 2-aryl isocyanoacetates to vinyl phenylselenones, resulting in adducts which are precursors to α-amino acids (eq. 4, Scheme 2).[17] On the contrary, the enantioselective addition of un-substituted **2** to activated alkenes (eq. 5, Scheme 2, this work) is undeveloped and remains a significant challenge, as it involves controlling the stereoselectivity of the Michael addition and suppressing a potential second Michael reaction.

With a view to developing a new organocatalytic synthetic procedure involving reagent **2**, we reasoned that enantioselective mono-addition of **2** to alkenes required an alkene acceptor

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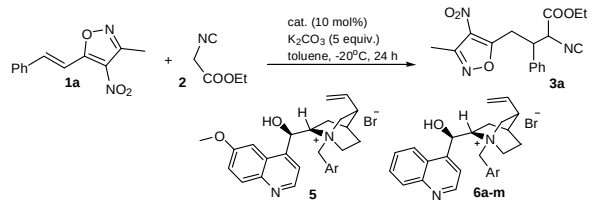
possessing moderate (soft) reactivity. Styrylisoxazoles **1** are cinnamate equivalents that possess high reactivity towards stabilized (soft) nucleophiles.[19,20] Compounds **1** are stable solids that can be obtained in large quantities (10-100 mmol) as single *E*-isomers by reacting commercially available 3,5-dimethyl-4-nitroisoxazole and an aromatic or heteroaromatic aldehyde.[21] The preparation of aliphatic congeners has been recently reported, thus expanding further the application of 4-nitroisoxazoles in synthesis.[22] The synthetic potential of **1** in a catalytic enantioselective system has been recognized by Yuan,[23] Wang[24] and Enders[25] who used **1** under the catalysis of bifuctional aminothioureas. Jorgensen described a formal [4+2] cycloaddition in which **1** reacted with trienamines (generated *in situ*) to provide adducts in high *ee*s and moderate diastereoselectivity.[26] Based on our experience using compounds **1** and *Cinchona* based phase transfer catalysis (PTC),[19] we anticipated these popular catalysts would act as an effective means to control the enantioselection in the formation of compounds **3**.

Initially, we reacted 3-methyl-4-nitro-5-styryl-isoxazole **1a** and ethylisocyanoacetate **2** (3 equiv) in the presence of 10 mol% of *N*-benzylquininium bromide and K_2CO_3 (2 equiv) as the base. This reaction gave desired product **3a** in an encouraging 50% yield. A screening was then carried out involving different bases, solvents and temperatures. This identified solid K_2CO_3, toluene and -20°C as the most suitable conditions, as well as indicating the requirement of 5 equiv of **2** to attain quantitative conversion. With suitable conditions in hand, we screened a number of quaternary ammonium salts derived from *Cinchona* alkaloids as catalysts (Table 1).

Table 1 Representative results from the screening of *Cinchona* derived catalysts **5** and **6**. [a] [d]

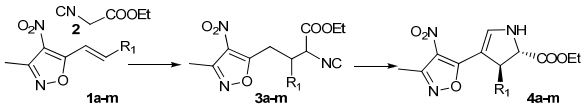


Entry	Cat.	Ar	Conv.[b] [%]	*ee*[c] [%]
1	**5**	C_6H_5	99	50
2	**6a**	C_6H_5	99	71
3	**6b**	2-FC_6H_4	>95	79
4	**6c**	2-$NO_2C_6H_4$	99	62
5	**6d**	2-naphthyl	90	68
6	**6e**	4-$CF_3C_6H_4$	>95	86
7	**6f**	2,3,4-F-C_6H_2	>95	91
8	**6g**	4-$CH_3OC_6H_4$	>95	60
9	**6h**	2-$CF_3C_6H_4$	>95	43
10	**6i**	4-$NO_2C_6H_4$	>95	60
11	**6j**	C_6F_5	>95	68
12	**6k**	2,3-F-C_6H_3	>95	76
13	**6l**	3,5-$(CF_3)_2C_6H_3$	>95	99
14	**6m**	3,5-(^{t}Bu)$_2C_6H_3$	>95	81

[a] Conditions: styrylisoxazole **1a** (0.1 mmol), ethyl isocyanoacetate **2a** (0.50 mmol), cat. **5** or **6a-m** (0.010 mmol), K_2CO_3 (0.50 mmol), toluene (0.5 mL), -20°C, 24 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral stationary phase HPLC run on corresponding cyclised compounds **4a**. [d] Compound **3a** was obtained as a 1 : 1 diastereoisomeric mixture.

Reaction of **1a** and **2** in the presence of quininium catalyst **5** furnished adduct **3a** in low enantiomeric excess (Table 1, entry 1). A major improvement was then achieved by replacement of **5** with *Cinchonidinium* catalysts **6**. A screening of catalysts **6a-m** (Table 1, entries 2-14) identified 3,5-*bis*-(trifluoromethyl)benzyl derivative **6l** as the best. Compound **3a** was efficiently cyclised to compound **4a** by treatment with diisopropylethylamine (DIPEA) at 30°C. Cyclised **4a** was obtained as a single diastereoisomer in 99% *ee*. The absolute stereochemistry of compounds **4** were determined by X-ray crystallographic analysis and assigned to be 2S, 3S.[27] The scope of reaction was shown by reacting styryilisoxazoles **1a-n** with ethyl isocyanoacetate **2** under the catalysis of either **6l** or **6m** (Table 2). The need to adjust the steric bias of the phase transfer catalyst to the substrate to obtain high enantiomeric excesses has been noted by others.[28]

Table 2 Catalytic asymmetric addition of ethyl isocyanoacetate **2** to styrylisoxazoles **1a-n**.



En.	**1**	R_1	**3**[a]	*Yield* [%] [f][g]	**4**[b]	*Yield* [%][f][g]	*Ee* [%][c][g]
1	**1a**	C_6H_5	**3a**	88	**4a**	93	99 [d]
2	**1b**	4-MeC_6H_4	**3b**	91	**4b**	96	93 [d]
3	**1c**	4-ClC_6H_4	**3c**	85	**4c**	92	97 [e]
4	**1d**	2-$MeOC_6H_4$	**3d**	83	**4d**	96(94)	97(92) [g]
5	**1e**	4-FC_6H_4	**3e**	93	**4e**	91	88[e]
6	**1f**	2-furyl	**3f**	91	**4f**	88	90[d]
7	**1g**	4-$MeOC_6H_4$	**3g**	85	**4g**	89	89[e]
8	**1h**	3-MeC_6H_4	**3h**	87	**4h**	84	94[d]
9	**1i**	4-$NO_2C_6H_4$	**3i**	92	**4i**	79	88[d]
10	**1j**	2,3-ClC_6H_3	**3k**	91	**4j**	91	88[e]
11	**1k**	2-Naphthyl	**3l**	86	**4l**	93	86[e]
12	**1l**	4-CNC_6H_4	**3m**	86	**4l**	94	86[e]
13	**1m**	Isobutyl	**3n**	88	**4m**	89	77[d]

a] Conditions: styrylisoxazole **1a** (0.1 mmol), ethyl isocyanoacetate **2** (0.50 mmol), cat. **6l** or **6m** (0.010 mmol), K_2CO_3 (0.50 mmol), toluene (0.5 mL), -20 0 °C. [b] Conditions: **3a** (0.1 mmol), THF (1.0 mL), DIPEA (0.2 mmol), 30°C, 2h; [c] Determined by chiral stationary phase HPLC; [d] obtained using catalyst **6l**; [e] obtained using catalyst **6m**; [f] isolated yields after column chromatography; [g] *Results in brackets refer to the opposite enantiomer* ***ent-4d*** *obtained using* ***6m'*** *as the catalyst.*

The results collected point to the following facts: *i)* compounds containing either electron withdrawing or electron donating groups on the phenyl were equally good substrates (Table 2, entries 2-10); *ii)* the presence of a bulky substituent gave good enantiomeric excess (Table 2, entry 11); *iii) the use of quasi-enantiomeric catalysts* ***6m'****, derived from Cinchonine, allowed the preparation of compound* ***ent-4d*** *with enantioselectivity comparable to the one obtained with catalyst* ***6m*** *(Table 2, entry 4 values in brackets).*

The synthetic potential of compounds **4** was demonstrated in the synthesis of pyrrolidine dicarboxylate **9** (Scheme 3). Hence,

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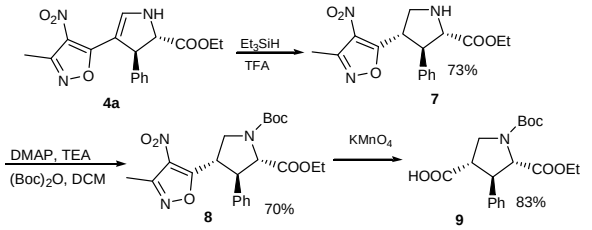
dihydropyrrole **4a** was first reduced to pyrrolidine **7** which was obtained in good isolated yield and as a single diastereoisomer. The stereochemistry of compound **7** was determined to be 2*S*, 3*R*, 4*S* *via* n.O.e. experiments.[29] Significantly, this procedure allowed a chemoselective reduction of the enamine moiety in **4a** whilst leaving the 4-nitroisoxazole nucleus intact. Compound **7** was then transformed to *N*-Boc protected **8** which, finally, was converted to free carboxylic acid **9** by an oxidative procedure.[19c]

Scheme 3. Synthetic elaboration of compound **4a**: preparation of pyrrolidines **7-9**.



In conclusion, we have reported herein a unique procedure to react unsubstituted **2** and alkenes **1a-m** to give monoadducts **3a-m** in high enantioselectivity, which were subsequently converted to 2,3-dihydropyrroles **4a-m** with complete control of diastereoselectivity. This procedure compares well to other related syntheses in terms of yields, diastereoselectivity, enantioselectivity, number of steps and availability of materials required.[30] In addition, it provides 2,3-dihydropyrroles **4** and pyrrolidines **7-9** holding a unique substitution pattern. Therefore this procedure will be of interest to those involved in the preparation of pyrrolidines and their use as bioactive compounds or catalysts.

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Notes and references

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†Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, and spectra of new compounds. This material is available free of charge via the Internet. See DOI: 10.1039/b000000x/

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