Organocatalysis

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Catalytic Asymmetric Conjugate Addition of Nitroalkanes to 4-Nitro-5-styrylisoxazoles**

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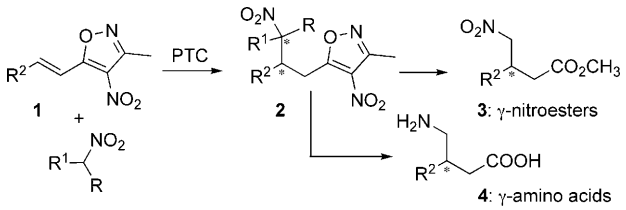
Herein, we describe the development of an organocatalytic enantioselective conjugate addition (Michael reaction) of nitroalkanes to 3-methyl-4-nitro-5-styrylisoxazoles **1** and the use of the resulting adducts **2** for the preparation of enantiomerically enriched compounds of pharmaceutical interest, such as γ-nitroesters **3** and γ-amino acids **4** (Scheme 1).



Scheme 1. Catalytic asymmetric conjugate addition of nitroalkanes to 4-nitro-5-styrylisoxazoles **1** and synthetic applications of Michael adducts **2**.

The conjugate addition of nitroalkanes to activated alkenes is a useful reaction[1] that involves the formation of a new C–C bond and the installation of an aliphatic nitro group: a precursor of an amine, a ketone, or a carboxylate.[2] Several catalytic asymmetric variants of this transformation have been reported for alkenes that act as soft electrophiles.[1a] However, reported methods are not suitable for α,β-unsaturated esters or acids, such as cinnamates, which are poor substrates in catalytic enantioselective Michael reactions.[1b–d] This experimental finding is justified by the electrophilic nature of cinnamates, which is not well-matched with soft nitroalkane nucleophiles. Additionally, since the carbonyl group of cinnamates does not establish well-defined interactions with commonly used catalysts (e.g. amines or chiral Lewis acid complexes), an efficient transfer of chirality from the catalyst to the substrate is problematic. To overcome these problems, various α,β-unsaturated carbonyl compounds have been used in catalytic enantioselective Michael reactions[3–7] to give products in which the desired carboxylates could be unveiled in a subsequent step. Notable examples of such compounds include chalcones,[3] enals,[4] α′-hydroxyenones,[5] alkylidene malonates,[6] and alkenoyl pyrazoles and pyrroles.[7]

We have developed styrylisoxazoles **1** as cinnamate equivalents that show high reactivity towards stabilized (soft) nucleophiles. Compounds **1** are stable solids that can be obtained in large quantities (10–100 mmol) as single *E* isomers through the reaction of commercially available 3,5-dimethyl-4-nitroisoxazole with an aromatic or heteroaromatic aldehyde.[8] We previously described efficient Michael addition reactions of compounds **1** with soft nucleophiles, such as enolates,[9] nitroalkanes,[10] and indoles.[11] The 4-nitroisoxazol-5-yl core present in adducts **2** (Scheme 1) could be opened to display a carboxylic acid by a reaction described by Sarti-Fantoni and co-workers: an operationally simple procedure involving the treatment of 4-nitroisoxazoles with excess aqueous NaOH.[12]

Therefore, compounds **1** constitute a valuable synthetic alternative to cinnamic esters in procedures that require tuning of the acceptor electrophilicity. We now report the use of compounds **1** in catalytic asymmetric settings in combination with phase-transfer catalysis (PTC)[13] and the use of the resulting adducts **2** for the preparation of γ-nitroesters **3** and γ-amino acids **4**. The high enantioselectivity observed when the reactions were carried out at room temperature with a low catalyst loading (2–5 mol%), the compatibility of nitromethane as well as secondary and tertiary nitroalkanes with the reaction conditions, and the unusual diastereocontrol when secondary nitroalkanes were used, are advantages of this process over many other procedures in which α,β-unsaturated carboxylic acid analogues are used.[3–7] As the substrate and catalyst could be prepared in one step from inexpensive starting materials, the procedure is also practical to execute.

We initially treated the styrylisoxazole **1a** with nitromethane (5 equiv) in the presence of various inorganic bases in suitable organic solvents. This study identified solid K_2CO_3 and toluene as the most suitable combination of a base and a solvent. Having identified suitable reaction conditions, we tested a range of quaternary ammonium salts derived from cinchona alkaloids as catalysts (Table 1).[14] Use of the

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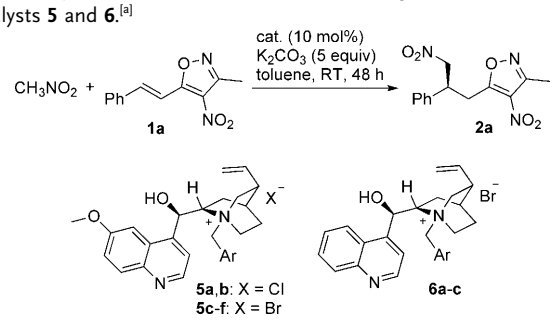
commercially available quininium chloride **5a** led to 89% conversion of **1a** into **2a** with promising enantioselectivity (78% *ee*; Table 1, entry 1). The reaction of **1a** and nitromethane in the presence of other quinine-based catalysts **5b–f** furnished adduct **2a** in variable yields and with *ee* values ranging from 69% for catalyst **5d** to 83% for catalyst **5e** (Table 1, entries 2–6). A major improvement was observed upon the replacement of the quinine catalysts **5** with cinchonidine catalysts **6**. The reaction of **1a** and nitromethane in the presence of catalyst **6a** gave **2a** with 90% *ee* (Table 1, entry 7). On the basis of results collected for the quinine series, we carried out a focused screening of cinchonidine catalysts **6** (Table 1, entries 8 and 9). This study quickly identified the 3,5-bis(trifluoromethyl)benzyl derivative **6c**[15] as the best catalyst. Catalyst **6c** ensured complete conversion of **1a** and gave **2a** with 97% *ee*. Importantly, the catalytic loading of **6c** could be limited to 5.0 mol% without a decrease in the conversion and yield (Table 1, entry 10).[16]

Table 1: Representative results of the screening of cinchona-derived catalysts **5** and **6**.[a]

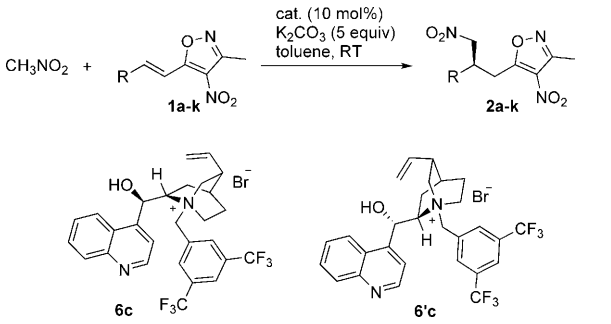


Entry	Catalyst	Ar	Conversion[b] [%]	*ee*[c] [%]
1	**5a**	C_6H_5	89	78
2	**5b**	2-$MeOC_6H_4$	>95	76
3	**5c**	2-FC_6H_4	57	78
4	**5d**	4-$MeOC_6H_4$	91	69
5	**5e**	4-$CF_3C_6H_4$	78	83
6	**5f**	2-naphthyl	78	81
7	**6a**	C_6H_5	>95	90
8	**6b**	4-$CF_3C_6H_4$	>95	93
9	**6c**	3,5-$(CF_3)_2C_6H_3$	>95	97
10	**6c**[d]	3,5-$(CF_3)_2C_6H_3$	>95	97

[a] Reaction conditions: **1a** (0.10 mmol), nitromethane (0.50 mmol), **5** or **6** (0.010 mmol), K_2CO_3 (0.50 mmol), toluene (1.0 mL), room temperature, 48 h. [b] Conversion was determined by ^{1}H NMR spectroscopy. [c] The *ee* value was determined by HPLC on a chiral stationary phase. [d] Catalyst: 0.0050 mmol (5.0 mol%).

We explored the scope of the reaction by treating styrylisoxazoles **1b–k** with nitromethane under the catalysis of **6c** (Table 2). We found that compounds containing electron-withdrawing or electron-donating groups were equally good substrates, with the exception of the sterically demanding 2,6-dichloro derivative **1d** (Table 2, entries 2–7). Importantly, we verified that at least compounds **2a** and **2c** could be obtained on a preparative scale (Table 2, entries 1 and 3) without a decrease in yield or enantioselectivity. Styrylisoxazole **1h**, which contains an extended aromatic pyranyl system, was converted efficiently into **2h** with 98% *ee*. Compounds **1i–k** containing aromatic heterocycles were also excellent substrates; the products **2i–k** were formed with high enantioselectivity, although in the case of **2i** and **2j** a prolonged reaction time was required (Table 2, entries 9–11). The quasienantiomeric catalyst **6′c** derived from cinchonine enabled the preparation of compounds *ent*-**2** with comparable high enantioselectivity (Table 2, entries 1, 3, and 7, values in brackets).

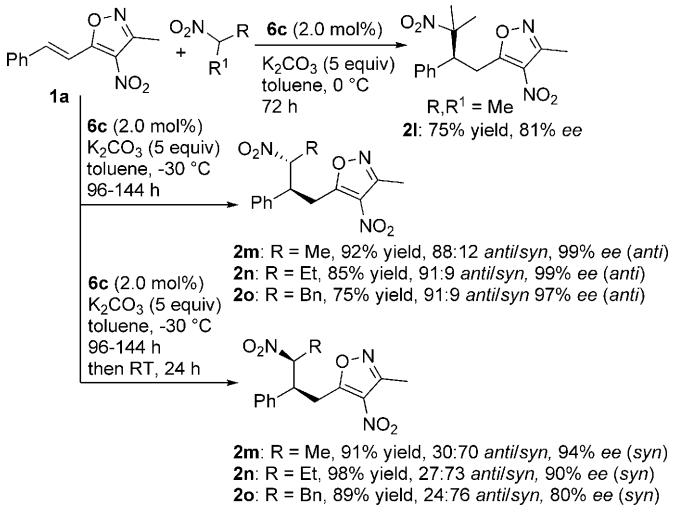
Table 2: Catalytic asymmetric addition of nitromethane to styrylisoxazoles **1a–k**.[a]



Entry	**1**	R	*t* [h]	**2**	Yield[b] [%]	*ee*[c] [%]
1[d]	**1a**	C_6H_5	48	**2a**	80 (78)	97[f] (90)
2	**1b**	3-ClC_6H_4	48	**2b**	75	94
3[e]	**1c**	4-ClC_6H_4	48	**2c**	74 (62)	91[f] (89)
4	**1d**	2,6-$Cl_2C_6H_3$	48	**2d**	50	77
5	**1e**	3,5-$Cl_2C_6H_3$	48	**2e**	70	93
6	**1f**	2,4-$Cl_2C_6H_3$	48	**2f**	75	87
7	**1g**	4-$MeOC_6H_4$	48	**2g**	88 (75)	96 (90)
8	**1h**	1-pyranyl	160	**2h**	80	98
9	**1i**	3-indolyl	240	**2i**	55	88
10	**1j**	2-furyl	120	**2j**	65	97
11	**1k**	2-pyridyl	48	**2k**	82	96

[a] Reaction conditions: **1** (0.25 mmol), nitromethane (1.25 mmol), **6c** (0.0125 mmol), K_2CO_3 (1.25 mmol), toluene (2.5 mL), room temperature. Results in brackets refer to the synthesis of the opposite enantiomer through the use of **6′c** as the catalyst. [b] Yield of the isolated product after chromatography on silica gel. [c] The *ee* value was determined by HPLC on a chiral stationary phase. [d] The reaction was performed on a 1.0 mmol scale. [e] The reaction was performed on a 1.50 mmol scale. [f] The absolute configuration was determined to be *S* by chemical correlation (see the Supporting Information).

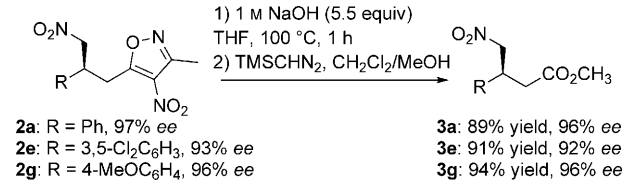
Having established a highly enantioselective procedure for the conjugate addition of nitromethane to styrylisoxazoles **1a–k**, we tested other nitroalkanes as nucleophiles. The reaction of styrylisoxazole **1a** with 2-nitropropane proceeded at 0°C to give the expected adduct **2l** in 75% yield with 81% *ee* (Scheme 2, top). A decrease in the catalyst loading to 2.0 mol% for this reaction was not detrimental to the yield or enantioselectivity. Similarly, **1a** reacted with nitroethane, 1-nitropropane, and 2-phenylnitroethane to give products **2m–o** in high yield with high diastereo- and enantioselectivity (Scheme 2, middle). In these experiments, which were carried out at −30°C, the kinetic product *anti*-**2m–o** prevailed. This result could be rationalized on the basis of an acyclic, extended transition state.[17] Importantly, the more thermodynamically stable isomers *syn*-**2m–o** were obtained preferentially by simply stirring the reaction mixture at room temperature for 24 h after the catalytic Michael addition was



Scheme 2. Catalytic asymmetric addition of secondary and tertiary nitroalkanes to 5-styrylisoxazole **1a**. Bn = benzyl.

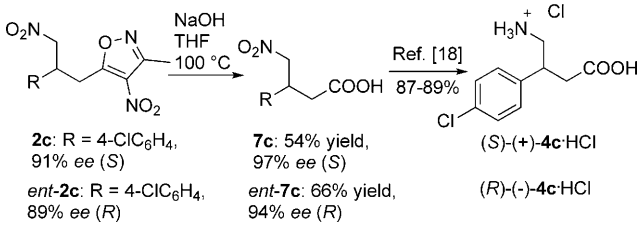
complete. The basic conditions and the higher temperature enabled thermodynamic equilibration, which gave *syn*-**2m–o** with moderate diastereoselectivity (Scheme 2, bottom).

The carboxylic acid functionality was then unveiled in Michael adducts **2a**, **2e**, and **2g**, which were converted efficiently into the corresponding γ-nitroesters **3a**, **3e**, and **3g** by treatment with 1M aqueous NaOH in THF and subsequent formation of the methyl ester to facilitate their isolation by chromatography on silica gel (Scheme 3). The *ee* values of γ-nitroesters **3a**, **3e**, and **3g** reflected those observed for the starting materials **2**, which demonstrated the configurational stability of these compounds under the conditions used.



Scheme 3. Preparation of enantiomerically enriched γ-nitroesters **3**. TMS = trimethylsilyl.

The transformation of Michael adducts **2** into γ-nitro carboxylic acids was also possible, as exemplified by the reactions of **2c** and *ent*-**2c** (Scheme 4). A previously described



Scheme 4. Preparation of the (*S*)-(+)-baclofen and (*R*)-(−)-baclofen hydrochlorides **4c**·HCl.

Raney Ni catalyzed reduction of the resulting γ-nitro acids **7c** and *ent*-**7c** gave the (*S*)- and (*R*)-baclofen hydrochlorides (+)-**4c**·HCl and (−)-**4c**·HCl, respectively.[18]

Baclofen, a $GABA_B$-receptor agonist used in the treatment of spasticity, is currently commercialized as a racemate (Lioresal, Baclon) although only the *R* enantiomer is active.[19] γ-Amino butyric acid (GABA) is the most abundant neurotransmitter in the mammalian brain. Several disorders are linked to the metabolism of GABA, and the study of such disorders necessarily relies on straightforward, and possibly enantioselective, syntheses of γ-amino acid derivatives.[20]

In conclusion, we have described a highly enantioselective addition of nitroalkanes to 5-styrylisoxazoles **1** under mild PTC catalysis. This study has provided a family of novel Michael acceptors to be used in asymmetric synthesis as well as a procedure for the preparation of versatile enantiomerically pure adducts **2**.

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