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Organocatalytic Asymmetric Cyanosilylation of Nitroalkenes

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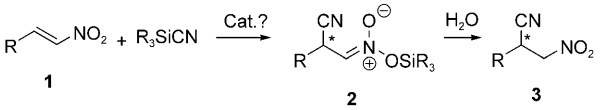
Dedicated to Professor Carmen Nájera on the occasion of her 60th birthday

β-Nitro nitriles are potentially useful intermediates for the synthesis of a variety of bifunctional compounds, including β-amino acids. An intuitive retrosynthetic analysis of these compounds suggests a direct conjugate cyanide addition to nitroalkenes **1** as a straightforward route for such structures. In spite of its apparent simplicity, however, the development of this reaction is restricted by the high tendency of nitroalkenes to polymerize under basic conditions. Consequently, there is only one recent report for use of acetone cyanohydrin as the cyanide source for the conjugate addition to nitroalkenes in its racemic form[1] and a second one for the asymmetric addition, which afforded moderate enantioselectivities and appears to be restricted to (less prone to polymerization) β,β-disubstituted compounds.[2]

Taking into account the relative stability of silyl nitronates, we decided to focus on the use of trialkylsilyl cyanides as reagents to obtain β-cyano silyl nitronates **2** as the primary products of the reaction, thereby avoiding the abovementioned polymerization. Moreover, the rich chemistry of silyl nitronates[3] could be eventually exploited beyond the trivial hydrolysis to β-nitronitriles **3**. Surprisingly, a survey of the literature reveals that this relatively simple reaction remains hitherto unexplored, and that β-cyano silyl nitronates have never been synthesized. We now wish to report on the development of a practical approach for the asymmetric cyanosilylation of nitroalkenes (Scheme 1).



Scheme 1. Cyanosilylation of nitroalkenes.

The reaction of (*E*)-3-methyl-1-nitrobut-1-ene (**1a**) with TMSCN (trimethylsilyl cyanide) was chosen as a model case of study. Several types of catalysts were considered as potential candidates for the activation of the reagent and/or the nitroalkene. Initially, cinchona alkaloids were used for the nucleophilic activation of TMSCN.[4] Unfortunately, the reaction proceeded with low conversions after prolonged reaction times, and partial polymerization of the nitroalkene could not be avoided. Moreover, the selectivity was low in all cases, reaching a maximum of 67:33 enantiomeric ratio (e.r.) for a reaction performed with 5 mol% of quinine in nBu$_2$O (see Supporting Information).

We next explored the behavior of bifunctional thiourea/tertiary amine catalysts for the simultaneous activation of the nitroalkene (by the thiourea as an hydrogen-bond donor moiety) and the reagent (by the amino nitrogen)[5] (Scheme 2). A higher catalytic activity and a better stereochemical control were expected from these catalysts provided by more ordered catalyst–substrate–reagent complexes **I**. Catalysts **4** and **5** were totally inactive, suggesting that a more nucleophilic amine is required. On the other hand, bifunctional catalysts **6** and **7** developed by the groups of Soos[6] and Hiemstra,[7] respectively, afforded he expected product **3a** with higher enantiomeric ratios (75:25 and 79:21 e.r., respectively), but the catalytic activity remained very low (conversions <20% after two days at room temperature; see details in the Supporting Information).

Inspired by recent results by Maruoka et al. on the phase-transfer-catalyzed asymmetric addition of silyl nitronates to nitroalkenes,[8] we decided to explore the suitability of such type of catalysts for the cyanosilylation of nitroalkenes. In preliminary experiments, the model reaction (**1a**+TMSCN) was performed in the presence of several quaternary ammo-

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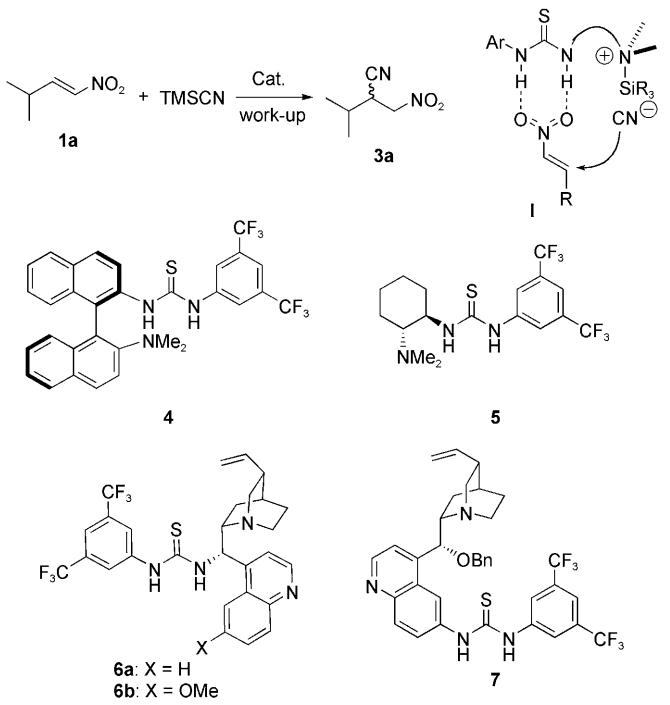
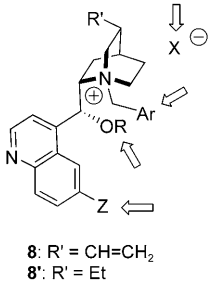


Scheme 2. Bifunctional catalysts for the cyanosilylation of nitroalkenes.

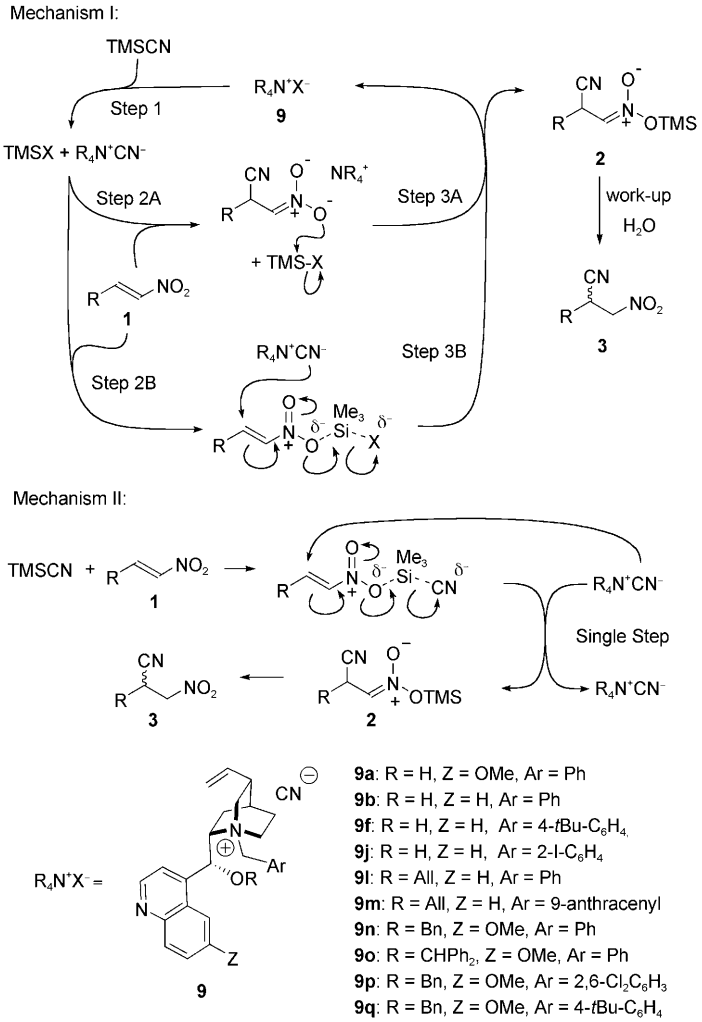
nium salts. We were pleased to observe that TBAI (tetrabutylammonium iodide; 20 mol%) successfully catalyzed the reaction, reaching complete conversions in 32 h at room temperature. A screening of commercially available phase-transfer catalysts (PTCs) led to the identification of cinchona alkaloid derived salts **8** as the most promising candidates



8a: R = H, Z = OMe, Ar = Ph, X = Cl
8b: R = H, Z = H, Ar = Ph, X = Cl
8c: R = H, Z = H, Ar = Ph, X = Br
8d: R = H, Z = H, Ar = Ph, X = I
8e: R = H, Z = H, Ar = 9-anthracenyl, X = Cl
8f: R = H, Z = H, Ar = 4-*t*Bu-C_6H_4, X = Br
8g: R = H, Z = H, Ar = 4-NO_2-C_6H_4, X = Br
8h: R = H, Z = H, Ar = 2,6-$Cl_2C_6H_3$, X = Br
8i: R = H, Z = H, Ar = 2,6-$(OMe)_2C_6H_3$, X = Br
8j: R = H, Z = H, Ar = 2,6-$(NO_2)_2C_6H_3$, X = Br
8k: R = H, Z = H, Ar = 2-I-C_6H_4, X = Cl
8l: R = All, Z = H, Ar = Ph, X = Br
8m: R = All, Z = H, Ar = 9-anthracenyl, X = Br
8n: R = Bn, Z = OMe, Ar = Ph, X = Cl
8o: R = $CHPh_2$, Z = OMe, Ar = Ph, X = Cl
8p: R = Bn, Z = OMe, Ar = 2,6-$Cl_2C_6H_3$, X = Br
8q: R = Bn, Z = OMe, Ar = 4-*t*Bu-C_6H_4, X = Br
8'r: R = 9-phenanthryl, Z = OMe, Ar = Ph, X = Cl
8's: R = 4-methylquinolin-2-yl, Z = OMe, Ar = Ph, X = Cl

for the enantioselective version of the reaction, reaching up to 68:32 e.r. for **8d**; other chiral ammonium derivatives, such as binaphthyl-based structures, exhibited good catalytic activity but very poor selectivity. The modular structure of cinchona alkaloids also allowed the preparation of synthetic derivatives with different substitution patterns at C9, C6′, and the *N*-benzyl group and with different counteranions. Disappointingly, none of the structural modifications tested led to an improvement of the enantioselectivity. Unexpectedly, the nature of the counteranion proved to have a dramatic effect on the catalytic activity. Thus, synthetic cinchonidinium bromides were inactive in the model reaction, while the corresponding chlorides or iodides showed a moderate activity, affording conversions up to 50% in the best cases (see Supporting Information for details).

The catalytic cycle initially proposed to account for the observed results starts with a cyanide exchange of TMSCN with the catalyst's counterion X^- leading to the corresponding quaternary ammonium cyanide (Scheme 3, mechanism I, Step 1). Conjugate addition of this salt to the nitroalkene yields an ammonium nitronate (Step 2A), which is then silylated by the TMSX species formed in the initial step to afford the silyl nitronate and regenerate the catalyst (Step 3A). Alternatively, however, it came into consideration a second possibility that basically differs in the order of the above-mentioned events: after the initial TMSCN/$R_4N^+X^-$ exchange (Step 1), the nitroalkene is activated by



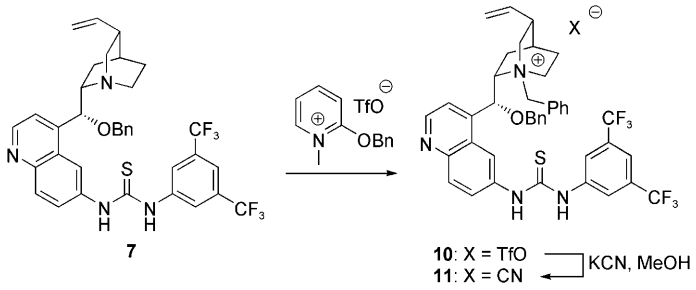
Scheme 3. Proposed mechanisms for tetraalkyl ammonium halides (mechanism I) and cyanides (mechanism II) as catalysts.

the silylating species (TMSX, a Lewis acid; Step 2B) prior to the attack of the cyanide (Step 3B). This second mechanism is in agreement with the observed dependence of the enantioselectivity with the reagent's steric demand: using 10 mol% of catalyst **8k** in nBu$_2$O at 5°C, reactions of **1a** with TMSCN and TBDMSCN afforded product **3a** with 62:38 and 51:49 e.r., respectively.

According to this proposal, the mentioned effect of the counteranion on the catalytic activity could be explained through a rate-limiting anion exchange (Step 1). The use of ammonium cyanides **9** as catalysts was therefore proposed as a strategy to solve the reactivity problem. In this way, the exchange step is eliminated and, assuming that preactivation of the nitroalkene takes place as previously discussed, a single-step mechanism (Scheme 3, mechanism II) can be formulated in which the attacking cyanide proceeding from the catalyst is "regenerated" through silylation of the nitronate by the reagent.

Supporting the above exposed hypothesis, the catalytic activity of the tetraalkylammonium cyanides **9** was clearly higher than that of the corresponding halides, leading in all cases to complete conversions in relatively short reaction times. Although this high catalytic activity makes it possible to perform the reaction at lower temperatures, unfortunately only slight improvements of the enantioselectivities were observed (see Supporting Information).

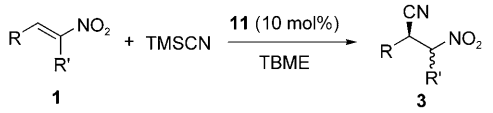
Putting the available information into perspective, it is clear that bifunctional catalysts **6** and **7**, based on a tertiary amine (quinuclidine)/hydrogen-bond donor (thiourea) combination, afford higher levels of stereocontrol, while tetraalkylammonium cyanides **9** are much more active catalysts than the free alkaloids. We therefore decided to synthesize and essay an unprecedented type of catalysts that combine quaternary ammonium cyanides with hzdrogen-bond donor functionality for cooperative binding of the nitroalkene. To this aim, catalyst **11** was synthesized from **7** by alkylation with 2-benzyloxy-1-methyl pyridinium triflate (→**10**)[9] and subsequent anion exchange with KCN (Scheme 4).



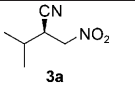
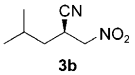
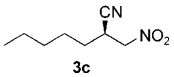
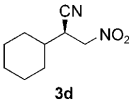
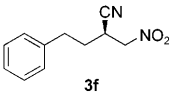
Scheme 4. Synthesis of bifunctional catalyst **11**.

We were pleased to observe that compound **11** efficiently catalyzed the model reaction, affording the desired adduct **3a** in near quantitative yield and improved selectivity. A direct comparison with catalyst **9n** (in which the thiourea moiety is replaced by a methoxy group) highlights the benefits of the bifunctional character of **11**. Thus, reactions carried out in toluene at −20°C with a catalyst loading of 10% yielded product **3a** in 70:30 and 84:16 e.r. for **9n** and **11**, respectively. The high catalytic activity allowed performing the reaction at low temperatures, reaching a 92:8 e.r. in TBME for a reaction carried out at −78°C to room temperature (Table 1, entry 1). Under optimized conditions, the reaction was extended to a variety of aliphatic substrates to afford, in all cases, the desired adducts **3** in high yields and good enantioselectivities (entries 2–6).[10]

Table 1. Catalytic asymmetric cyanosilylation of nitroalkenes.

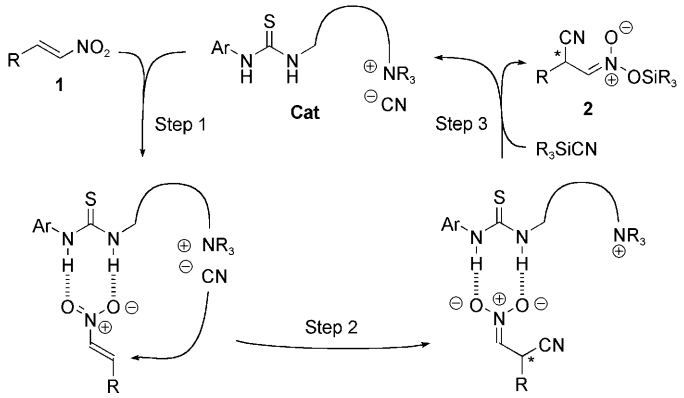


1 3

	Product[a]	T [°C]	t [h]	Yield [%][b]	e.r.[c]
1	 **3a**	−78→−40	48	85	92:8
2	 **3b**	−45	20	98	87:13
3	 **3c**	−78→RT	48	95	80:20
4	 **3d**	−45	96	91	90:10
5	 **3e**	−45	72	56[d,e]	93:7
	 **3e'**	−45	72	19[d,e]	92:8
6	 **3f**	−20	48	88	86:14

[a] The absolute configuration of adduct **3a** was assigned by comparison of its optical rotation with literature data: see reference [11]. The absolute configuration of all other adducts **3** were assigned by analogy assuming a uniform reaction pathway. [b] Isolated yields. [c] Determined by HPLC on chiral stationary phases. [d] A 3:1 *trans*:*cis* ratio was determined by ^{1}H NMR spectroscopy in the reaction crude. [e] Yield of pure diastereomers separated by flash chromatography.

In contrast with the reactions catalyzed by simple phase-transfer catalysts, in this case the steric bulk of the reagent had no effect either on the enantioselectivity or on the reaction rate, now pointing towards an irreversible, rate-limiting, C–C bond formation through a silyl-free intermediate. A proposed mechanism in agreement with these experimental facts is outlined in Scheme 5. Thus, after activation of the nitroalkene by hydrogen bonding (Step 1), conjugate addition of cyanide yields a hydrogen-bonded nitronate intermediate (Step 2), which then reacts with R_3SiCN to afford **2** (Step 3).



Scheme 5. Proposed mode of action and catalytic cycle for bifunctional thiourea/ammonium catalysts.

As for simple tetraalkyl ammonium salts, the bifunctional catalyst incorporates the "active" nucleophile (cyanide), while TMSCN behaves as a silylating agent for the nitronate intermediate and, simultaneously, as a reservoir of cyanide for the regeneration of the catalyst.

Taking into account the experimental work[7] and calculations[12] performed for cinchona-based catalysts with similar topologies in related systems, a model based on a *gauche*-open geometry with the coordinated nitroalkene oriented to the less hindered region is tentatively proposed to explain the observed absolute configuration (Figure 1).

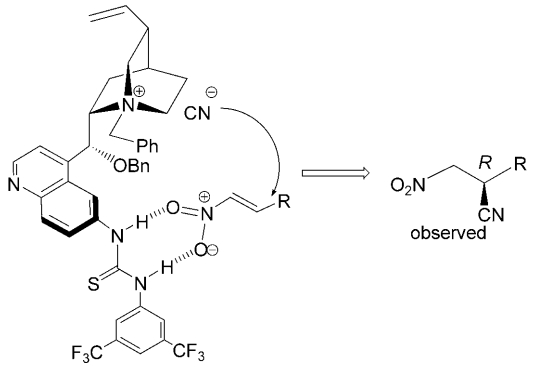


Figure 1. Stereochemical model.

In summary, the unprecedented cyanosilylation of nitroalkenes has been accomplished by using a novel thiourea/tetralkylammonium bifunctional catalyst that binds substrate and reagent through a new mode of activation. Although the applied catalyst **11** already afforded remarkable levels of enantioselectiviy, fine tuning of this scaffold to improve activity and selectivity, as well as its behavior in other related reactions are now under investigation.

Experimental Section

Synthesis of catalyst 11: 2-Benzyloxy-1-methylpyridinium triflate (203 mg, 0.22 mmol) was added to a solution of quinine thiourea derivative **7**[7] (325 mg, 0.49 mmol) in dry THF/CH_2Cl_2 (1:3, 6 mL) under an argon atmosphere. The mixture was stirred at room temperature for 48 h, concentrated, and the resulting residue was purified by flash chromatography (15:1 toluene/MeOH) to afford triflate salt **10** (203 mg; 46%) as a brown solid. $[\alpha]_D^{23}$ −144.6 (c=1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.98 (d, J=4.4 Hz, 1H), 8.31 (s, 2H), 8.09 (s, 2H), 7.65 (d, J=4.4 Hz, 2H), 7.55–7.38 (m, 10H), 7.34 (t, J=8.2 Hz, 3H), 7.05 (s, 1H), 6.12 (s, 1H), 5.55 (ddd, J=17.1, 10.5, 6.6 Hz, 1H), 5.16 (d, J=17.2 Hz, 1H), 5.12–5.02 (m, 2H), 4.95 (d, J=11.9 Hz, 1H), 4.38 (d, J=11.9 Hz, 1H), 4.32 (d, J=12.3 Hz, 1H), 4.19–4.06 (m, 2H), 4.04 (s, 1H), 3.31–3.18 (m, 1H), 3.16–3.02 (m, 1H), 2.56 (s, 1H), 2.23–2.12 (m, 1H), 2.09 (s, 1H), 1.83–1.64 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=179.9, 161.1, 148.9, 148.2, 146.6, 140.9, 138.9, 136.1, 131.3 (q, J=36.5 Hz), 130.8, 130.8, 129.7, 129.7, 129.5, 129.5, 129.4, 129.4, 129.3, 129.3, 129.21, 125.09, 124.69 (q, J=241.9 Hz), 119.53, 118.63, 113.68, 71.77, 67.14, 61.02, 50.75, 37.69, 37.16, 29.76, 26.60 ppm; HRMS (FAB): m/z: calcd for $C_{42}H_{39}F_6N_4OS^+$: 761.2749 [M^+−TfO]; found 761.2759. This material was dissolved in MeOH (5 mL) and KCN (44 mg, 0.67 mmol) was added. The mixture was stirred until total dissolution, concentrated and extracted with methylene chloride to afford **11** (167 mg, 99%). $[\alpha]_D^{23}$ −366.6 (c=1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.81 (d, J=4.4 Hz, 1H), 8.07 (d, J=9.2 Hz, 1H), 7.54 (s, 1H), 7.46 (dd, J=14.7, 7.3 Hz, 2H), 7.33 (ddd, J=21.3, 14.3, 5.8 Hz, 14H), 6.58 (d, J=9.1 Hz, 1H), 5.75–5.64 (m, 1H), 5.08 (s, 1H), 4.91 (d, J=17.1 Hz, 1H), 4.86 (d, J=10.3 Hz, 1H), 4.45–4.28 (m, 2H), 4.02 (s, 2H), 3.33–3.10 (m, 2H), 3.01–2.89 (m, 1H), 2.64–2.43 (m, 2H), 2.26–2.15 (m, 1H), 1.82–1.63 (m, 2H), 1.63–1.49 (m, 1H), 1.47–1.36 (m, 1H), 1.26 ppm (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=180.6, 163.3, 149.2, 146.0, 142.1, 139.7, 138.0, 136.4, 132.2 (q, J=34.9 Hz), 131.3, 129.6, 129.3, 129.3, 128.9, 128.9, 128.5, 128.5, 128.4, 127.9, 127.9, 123.5 (q, J=273.5 Hz), 120.9, 116.5, 114.3, 106.1, 71.3, 67.7, 61.0, 57.1, 40.2, 37.1, 28.0, 27.9 ppm; HRMS (FAB): m/z: calcd for $C_{42}H_{39}F_6N_4OS^+$: 761.2749 [M^+−CN]; found: 761.2730.

Cyanosilylation of nitroalkenes

General procedure: TMSCN (0.3 mmol) was added to a solution of nitroalkene **1** (0.1 mmol) and catalyst **11** (0.01 mmol) in *tert*-butyl methyl ether (1.5 mL) and the mixture was stirred at the desired temperature until TLC monitoring indicated consumption of the starting material. Saturated $NaHCO_3$ solution was added and the mixture was extracted with Et_2O, dried, concentrated and purified by flash chromatography (9:1 cyclohexane/ethyl acetate) to afford pure products **3** (see Supporting Information for characterization).

Acknowledgements

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