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Intriguing Behavior of Cinchona Alkaloids in the Enantioselective Organocatalytic Hydroxyamination of α-Substituted-α-cyanoacetates

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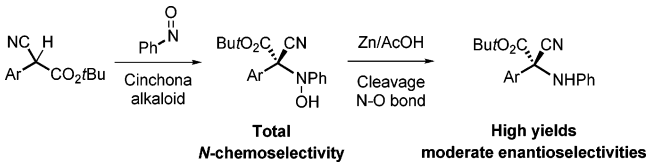

The cinchona alkaloid quinine promotes the enantioselective nitroso-aldol reaction between α-aryl-α-cyanoacetates and nitrosobenzene to give the hydroxyamination products with total chemoselectivity. Treatment of the reaction mixture with Zn/AcOH affords the corresponding amines in high yield and moderate enantioselectivity. An unusual effect on the enantioselectivity was observed with the catalyst loading and solvent. A reductive protocol allows the construction of an optically active 1,2-diamine moiety bearing a quaternary center.

Nitroso compounds are interesting reagents used in synthetic organic chemistry mainly due to their application in nitroso-aldol and Diels−Alder reactions.[1] Different strategies based on not only metal[2] but also organocatalytic[3−6] approaches have been developed to control the chemo- and enantioselectivity of the nitroso-aldol reaction. For example, aminoxylation (nucleophile attacks to the oxygen atom of the nitroso derivative) or hydroxyamination (nucleophile attacks to the nitrogen atom of the nitroso derivative) products can be obtained chemoselectively in the reaction between nitrosobenzene and enolates or enamines depending on the metal catalyst employed.[2] A number of studies of the reaction between nitrosobenzene and simple aldehydes or ketones employing L-proline, its derivatives, or other secondary amines as enantioselective organocatalysts have also been carried out.[3−6] These chiral catalysts simultaneously activate both reaction partners: the carbonyl compound through enamine formation, and the nitrosobenzene by coordination to an acid[3,4] or alcohol[5,6] group. This determines the *O*- versus *N*-selectivity. In 2005, Yamamoto and co-workers reported the reaction between preformed enamines and nitrosobenzene using either a chiral acid or a chiral alcohol, obtaining the *aminoxylation* or the *hydroxyamination* product, respectively.[4] In short, all the examples reported so far for the enantioselective organocatalytic version of this reaction employ an enamine intermediate and *O*-selectivity is obtained in the majority of the examples.

Cinchona alkaloids have been successfully applied in various organocatalytic transformations,[7,8] acting as nucleophilic,[9] phase-transfer,[10] and chiral-base catalysts.[11] However, this concept has not yet been applied to the nitroso-aldol reaction, despite the potential for the formation of highly functionalized products that would contain attractive structural features.

In the last several years, we have reported different organocatalyzed asymmetric reactions using α-substituted-α-cyanoacetates as nucleophiles.[11c,f] Herein, we report the development of a new approach to the direct nitroso-aldol reaction between

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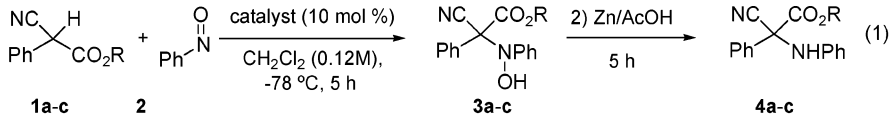
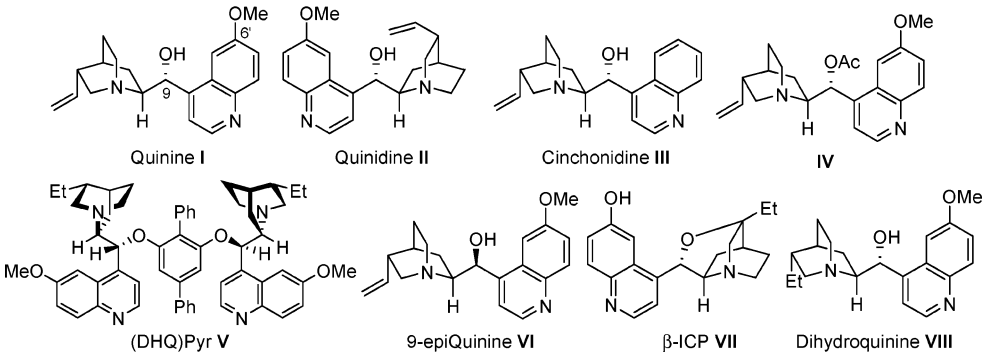
TABLE 1. Nitroso-Aldol Reaction Catalyzed by Various Chiral Bases[a]





entry	ester (R)	catalyst	product	conv[b] (%)	ee[c] (%)
1	**1a**, Me	**I**	**4a**	95	32
2	**1b**, Bn	**I**	**4b**	90	40
3	**1c**, *t*-Bu	**I**	**4c**	80	(+)-59[d]
4	**1c**, *t*-Bu	**II**	**4c**	85	(−)-42
5	**1c**, *t*-Bu	**III**	**4c**	84	(−)-15
6	**1c**, *t*-Bu	**IV**	**4c**	20	(+)-8
7	**1c**, *t*-Bu	**V**	**4c**	46	(−)-30
8	**1c**, *t*-Bu	**VI**	**4c**	33	(+)-8
9	**1c**, *t*-Bu	**VII**	**4c**	78	0
10	**1c**, *t*-Bu	**VIII**	**4c**	82	(+)-50
11	**1c**, *t*-Bu	Et_3N	**4c**	79	

[a] Reaction performed at a 0.1 mmol scale (**1**) with 1.1 equiv of **2** and 10 mol % of catalyst in CH_2Cl_2 at 0.12 M. [b] Estimated by ^1H NMR of the crude mixture. [c] Ee determined by HPLC. [d] The absolute configuration is (*S*), see the Supporting Information for details.

nitrosobenzene (**2**) and α-substituted-α-cyanoacetates (**1**), which affords highly functionalized products with a quaternary stereocenter.

The reaction between nitrosobenzene and **1** in the presence of cinchona alkaloids (**I**−**VIII**) displayed total chemoselectivity, affording exclusively the hydroxyamination product. However, the hydroxylamine derivative **3** obtained was found to be chemically and configurationally unstable. Therefore, the N−O bond was cleaved employing Zn/AcOH as reducing reagent, resulting in the amine products **4** in a one-pot process (eq 1). Various catalysts and different ester groups were tested during the screening for the optimal conditions (Table 1).

When methyl ester **1a** and nitrosobenzene were dissolved in CH_2Cl_2 at −78 °C and treated with quinine (10 mol %), the aminated product **4a** was obtained in excellent conversion after two steps and with moderate enantioselectivity (Table 1, entry 1). Higher enantioselectivity was obtained by increasing the size of the ester group with small erosion of the conversion (compare entries 1−3). The quasienantiomer quinidine **II** gave the opposite enantiomer with lower enantioselectivity (entry 4). Cinchonidine **III**, which differs from quinine **I** only in the absence of a methoxy group at C6′, showed lower and opposite enantioselectivity (entry 5). When the hydroxyl group at the C9-position is not free (entries 6 and 7), low conversion and enantioselectivities were obtained. The 9-epiquinine catalyst **VI**, having inverted configuration at the C9-position, gave low reactivity, and almost no enantioselectivity was obtained (entry 8). The role of the position of the hydroxyl group was tested by using catalyst **VII**, which provides excellent conversion, but no enantioselection at all (entry 9). Dihydroquinine **VIII** gave similar conversion and the enantioselectivity of **4c** was found to be 50% ee (entry 10). The racemic compounds **4**, necessary to measure the enantiomeric excess, were prepared by using Et_3N as the catalyst and also gave good conversion and total *N*-chemoselectivity (entry 11).

These experiments indicate that both the presence and position of a free hydroxyl group are important structural features for achieving good conversion and reasonable enantioselectivities when this reaction is catalyzed by cinchona alkaloids (compare entries 3, 6, 7, and 9). This could probably be due to activation of the electrophile by the free hydroxyl group, as has been proposed in other reactions.[12] Moreover, the methoxy group at C6′ apparently plays an important role in the transition state of the reaction, as its absence inverts the enantioselectivity (compare entries 3 and 5). This fact is unusual in asymmetric catalysis, although Prelog and Wilhelm[13] and Kagan[14] observed the same effects in hydrocyanation and Diels−Alder reactions catalyzed by cinchona alkaloids, respectively.

During the solvent screening for the standard reaction (Table 1, entry 3), we could observe an inversion in enantioselectivity when coordinating solvents were used (eq 2, Table 2). While toluene and C_6H_5Cl showed the same trend of stereoselection as CH_2Cl_2 (entries 2 and 3), THF, Et_2O, DMF, and acetone gave the opposite enantiomer (entries 4−7) accompanied by a significant decrease in reactivity. A possible explanation for

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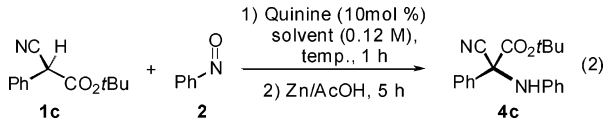
TABLE 2. Solvent Screening for the Reaction of *tert*-Butyl α-Phenyl-α-cyanoacetate 1c with Nitrosobenzene (2) in the Presence of Quinine and Reduction with Zn/AcOH[a]



entry	solvent	temp (°C)	conv[b] (%)	ee[c] (%)
1	CH_2Cl_2	−78	89	(+)-59
2	C_6H_5Cl	−50	94	(+)-30
3	toluene	−78	55	(+)-28
4	THF	−78	43	(−)-41
5	DMF	−50	35	(−)-30
6	Et_2O	−78	30	(−)-24
7	$(CH_3)_2CO$	−78	25	(−)-32
8	MeOH	−78	93	(−)-14

[a] Reaction performed at a 0.1 mmol scale (**1c**) with 1.1 equiv of **2**, using 10 mol % of quinine **I** in the indicated solvent at 0.12 M. [b] Estimated by ^{1}H NMR. [c] Ee determined by HPLC.

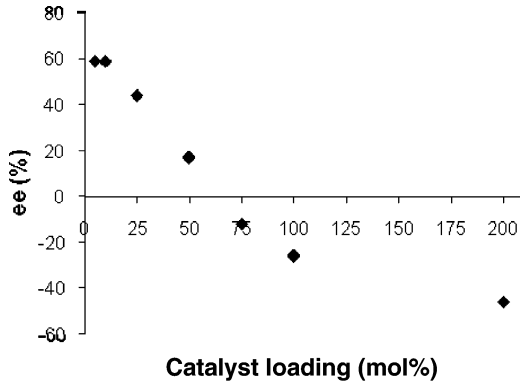


FIGURE 1. Enantiomeric excess (ee) vs catalyst loading for the reaction of **1c** and **2** in CH_2Cl_2 (0.12 M) at −78 °C and quinine **I** as the catalyst.

these findings could be that coordinating solvents block the hydroxyl group making it unavailable for the electrophile activation and as a consequence completely change the transition state geometry to now favor formation of the opposite enantiomer of product **4c**. Although it is known that cinchona alkaloids adopt different conformations depending on the solvent,[15] to our knowledge such effects on the enantioselectivity are very rare. In the case of MeOH, a combination of the effects mentioned above may explain the high reactivity, but low enantioselectivity was observed (entry 8).

The effect of the catalyst loading on the enantioselectivity obtained in the standard reaction (Table 1, entry 3) at −78 °C has also been evaluated and the results are shown in Figure 1. It was observed that the enantiomeric excess of **4c** decreased when the catalyst loading was increased and it was even inverted when 1 or 2 equiv were used.[16] It is worth mentioning that Evans et al. also found an inversion in the asymmetric induction by increasing the catalyst loading in the enantioselective Friedel−Crafts alkylations of α,β-unsaturated 2-acyl imidazoles catalyzed by bis(oxazolinyl)pyridine−$Sc(OTf)_3$ complexes.[17] To explain this result, the authors propose the formation of a 1:1:1 substrate:product:catalyst complex that is favored at lower catalyst loadings and is more enantioselective than the corresponding 1:1 substrate:catalyst complex that would be favored at higher catalyst loadings. At the present stage of investigations, we speculate that related effects might explain our observed stereochemical inversion.

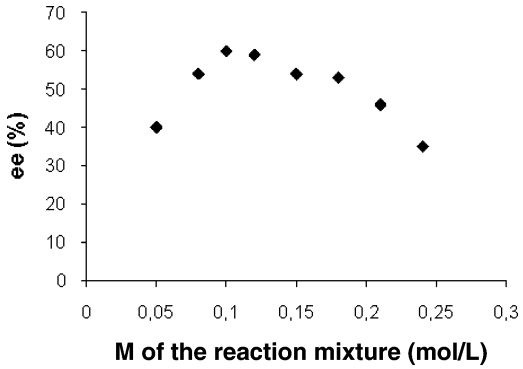


FIGURE 2. Ee vs reaction molarity for the reaction of **1c** and **2** in CH_2Cl_2 at −78 °C and quinine **I** as the catalyst (10 mol %).

The few examples found in the literature where quinine is used in stoichiometric amount show an increase of the enantioselectivity compared with lower catalyst loadings.[18] In fact, this is the tendency observed when the influence of the catalyst loading on the enantioselectivity of the reaction of **1c** and nitrosobenzene was studied in CH_2Cl_2 at −78 °C, either with catalysts, without a free hydroxyl group such as **IV** ($ee_{10mol\%}$ = 8% compare to $ee_{100mol\%}$ = 7%) and **V** ($ee_{10mol\%}$ = −30% compare to $ee_{100mol\%}$ = −46%), or with quinine **I** in THF as solvent at −78 °C ($ee_{10mol\%}$ = −41%; $ee_{100mol\%}$ = −48%).

On the basis of these data, it was obvious that only catalysts with the OH-group free displayed peculiar behavior, and we then turned our attention to the effect of both substrate and catalyst concentration on the enantioselectivity of the reaction. The enantioselectivity of the reaction as a function of the reaction molarity is represented in Figure 2, showing a significant variation with the maximum between 0.10 and 0.12 M of **1c**. On the other hand, when 1 equiv of quinine **I** is used, the enantioselectivity showed no variation with the concentration, e.g., 0.12 M (ee = −26%) and 0.012 M (ee = −24%).[19]

Intrigued by the behavior of quinine in this reaction we decided to investigate if we were observing autocatalysis, kinetic resolution, or autoinduction.[20] Toward this end, we have observed that no reaction occur when a mixture of compounds **1c** and **2** was treated with 10% of product **3c** under the same

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(16) To a smaller extent, a drop in the enantioselectivity has also been observed in the reaction of compound **1d** in the presence of 1 equiv of quinine **I** ($ee_{10mol\%}$ = 59%; $ee_{100mol\%}$ = 29%).

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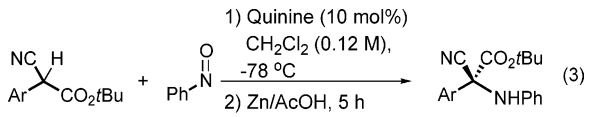
TABLE 3. Reaction Scope of *tert*-butyl α-Aryl-α-cyanoacetates (1c−h) with Nitrosobenzene[a]



1c-h **2** **4c-h**

entry	Ar	time (h)	conv[b] (%)	yield[c] (%)	ee[d] (%)
1	**1c**, C_6H_5	5	**4c**, 80	76	59
2	**1d**, 4-Cl-C_6H_4	5	**4d**, 97	85	59
3	**1e**, 3-Me-C_6H_4	5	**4e**, 80	71	52
4	**1f**, 4-MeO-C_6H_4	5	**4f**, 85	80	22
5	**1g**, 4-CN-C_6H_4	3	**4g**, 85	78	49
6	**1h**, 2-naphthyl	4	**4h**, 79	73	52

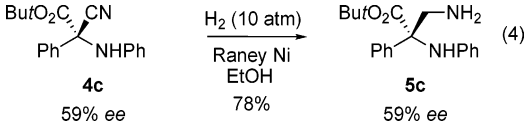
[a] Reactions performed at a 0.2 mmol scale (**1**) with 1.1 equiv of **2**, using 10 mol % of quinine **I** in CH_2Cl_2 at 0.12 M. [b] Estimated by ^{1}H NMR analysis. [c] Isolated yield after FC. [d] Determined by HPLC analysis.

conditions shown in Table 1, and that no significant variation of the enantiomeric excess of **4c** could be observed when it was measured after different reaction times (for data, see Supporting Information).

The optimized conditions were used to evaluate the scope of the nitroso-aldol reaction. A series of *tert*-butyl α-aryl-α-cyanoacetates **1d**−**h** were combined with nitrosobenzene catalyzed by quinine (10 mol %) (eq 3, Table 3). Substituents present in the meta- and para-position were tolerated (entries 2 and 3) providing the amine derivatives in high yields and with analogous enantioselectivities, whereas ortho derivatives were not able to react under the same reaction conditions. An electron-deficient substrate (entry 5) underwent the reaction with yield and enantioselectivity comparable to those of the standard reaction, but an electron-rich substrate (entry 4) led to diminished selectivity. The 2-naphthyl derivative **1h** also reacts with the nitrosobenzene to give product **4h** in 73% yield after two steps with 52% ee (entry 6).

The absolute configuration of the main enantiomer was established to be (*S*) by X-ray crystallographic analysis. Compound **4c** was prepared under the standard conditions described above. Recrystallization from a mixture *i*-PrOH: hexane (1:1) gave **4c** as a single enantiomer (confirmed by HPLC, see the Supporting Information for details).

1,2-Diamines are remarkable structural motifs, not only because of their occurrence in biologically active compounds, including natural products, but also as valuable building blocks, chiral auxiliaries, and ligands.[21] Thus, compound **4c** was transformed into the 1,2-diamine **5c** in 78% yield without affecting the optical purity by treatment with H_2/Raney-Ni in EtOH (eq 4).



4c 59% *ee* **5c** 59% *ee*

In conclusion, we have developed the organocatalytic asymmetric addition of α-aryl-α-cyanoacetates to nitrosobenzene. The process is catalyzed by quinine and shows *N*-chemoselectivity, giving the corresponding (*S*)-α-arylamine after in situ reduction of the hydroxylamine precursors in high yields and moderate enantioselectivities. An unusual effect of the solvent and the catalyst loading on the enantioselectivitity has been found. A useful transformation underlines the utility of the methodology.

Experimental Section

Representative Procedure for the Enantioselective Nitroso-Aldol Reaction of Cyanoesters 1c−h to Nitrosobenzene 2, Using Quinine I as Catalyst and Reduction with Zn/AcOH. To a vial equipped with a magnetic stirring bar were sequentially added the α-aryl α-cyano esters **1** (0.2 mmol), nitrosobenzene **2** (0.22 mmol), and CH_2Cl_2 (1.7 mL, M = 0.12 mmol/mL). The vial was placed at −78 °C and then quinine **I** (10 mol %) was added. No precautions were taken to exclude moisture or air. The reaction was followed by TLC and when finished, 1 mL of AcOH was added and the bath removed, and once the mixture was defrosted, 80 mg of Zn was added. After vigorous stirring during 5 h, the mixture was filtered through a short pad of silica gel and washed with CH_2Cl_2. The crude was purified by FC, using hexane/CH_2Cl_2 mixtures (from 7:1 to 2:1).

(*S*)-*tert*-Butyl 2-Cyano-2-phenyl-2-(phenylamino)acetate (4c). 4c was obtained as a white solid according to the general procedure after 5 h for the first step (76% yield). ^{1}H NMR δ 7.70 (dd, J 8.0, 2.2 Hz, 2H), 7.41 (m, 3H), 7.14 (t, J = 7.6 Hz, 2H), 6.80 (t, J = 7.4 Hz, 1H), 6.59 (d, J = 7.7 Hz, 2H), 5.27 (br s, 1H), 1.40 (s, 9H). ^{13}C NMR δ 164.7, 142.1, 134.7, 129.4, 129.1 (2C), 126.2, 119.6, 116.7, 115.1, 86.1, 63.5, 27.3. HRMS calcd for $C_{19}H_{20}NaN_2O_2$ 331.1417, found 331.1427. The ee was determined by HPLC with a Chiralpak AD column [hexane/*i*PrOH = 95:5]; flow rate 1.0 mL/min; τ_{major} = 11.2 min, τ_{minor} = 8.2 min (59% ee). $[\alpha]^{20}_D$ +41 (*c* 1.0, CH_2Cl_2).

(*S*)-*tert*-Butyl 2-(4-Chlorophenyl)-2-cyano-2-(phenylamino)-acetate (4d). 4d was obtained as a white solid according to the general procedure after 5 h for the first step (85% yield). ^{1}H NMR δ 7.63 (d, J = 8.7 = Hz, 2H), 7.39 (d, J = 8.7 Hz, 2H), 7.14 (t, J = 7.6 Hz, 2H), 6.80 (t, J = 7.5 Hz, 1H), 6.56 (d, J = 7.7 Hz, 2H), 5.28 (br s, 1H), 1.41 (s, 9H). ^{13}C NMR δ 164.3, 141.7, 135.5, 133.4, 129.3, 129.2, 127.6, 119.9, 115.2, 116.3, 86.6, 62.9, 27.4. HRMS calcd for $C_{19}H_{19}ClNaN_2O_2$ 365.1027, found 365.1029. The ee was determined by HPLC with a Chiralpak AD column [hexane/*i*PrOH = 95:5]; flow rate 1.0 mL/min; τ_{major} = 13.7 min, τ_{minor} = 8.8 min (59% ee). $[\alpha]^{20}_D$ +33 (*c* 0.9, CH_2Cl_2).

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) In this sense, Blackmond et al. showed that an autoinductive process is working on the nitroso-aldol reactions between aldehydes and nitrosobenzene promoted by L-proline: Mathew, S. P.; Iwamura, H.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3317.

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