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Asymmetric Hydrocyanation of Hydrazones Catalyzed by in Situ Formed *O*-Silylated BINOL-Phosphate: A Convenient Access to Versatile α-Hydrazino Acids§

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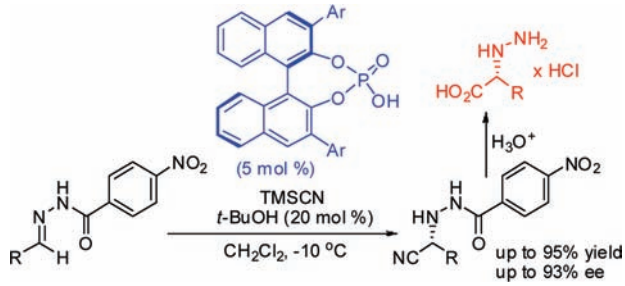
ABSTRACT



A first organocatalytic enantioselective route was developed for the conversion of readily prepared and air stable aliphatic hydrazones to synthetically valuable α-hydrazinonitriles. This BINOL-phosphate catalyzed Strecker-type reaction (see scheme, Ar = *p*-NO_2−Ph) provides a new practical and direct route to α-hydrazino acids of synthetic and biological importance. The actually active catalyst is proposed to be an in situ formed *O*-silylated BINOL-phosphate, thus shifting the nature of catalysis from Brønsted acid to Lewis acid organocatalysis.

Hydrazino acids and their derivates have been identified as inhibitors of several amino acid metabolizing enzymes[1] with potential applications as antibacterial agents[1a,b] or even as anti-HIV therapeutics.[1c] Furthermore, α-hydrazino acids have attracted great interest in recent years, finding applications in the design of novel non-natural peptides.[2]

Routes by which α-hydrazino acids are obtained are still few.[3] In contrast to the hydrocyanation of imines, the Strecker reaction,[4] the hydrazone cyanation, which enables direct access to α-hydrazino acids, is still a rather poorly investigated reaction. The reported few inventions have relied on metal based catalysts.[5,6a] In 2004, the group of Jacobsen reported the first asymmetric variant of the reaction, using

§ This paper is dedicated to Professor Rolf W. Saalfrank on the occasion of his 70th birthday.

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lanthanide-PYBOX complexes.[6a] Recently, the hydrocyanation of chiral oxazolidinone-derived *N*-acylhydrazones has also been demonstrated.[6b] The development of new effective catalytic systems for the asymmetric hydrocyanation of hydrazones with enhanced performance and application potential, especially to aliphatic hydrazones,[6] still remains a challenging task.

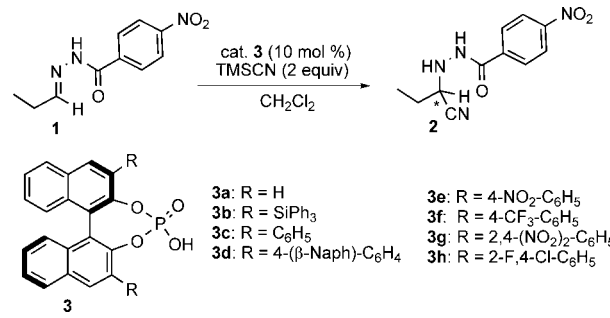
In 2004, the research groups of Akiyama[7a] and Terada[7b] independently developed BINOL-phosphates as organocatalysts for enantioselective C−C bond-forming reactions. Later, several research groups,[8] notably the groups of Rueping,[8a] List,[8b] and Antilla,[8c] reported the application of BINOL-phosphates in the development of various highly enantioselective transformations.

Herein we report, to the best of our knowledge, the first organocatalytic enantioselective hydrocyanation of hydrazones, employing BINOL-phosphate as organocatalyst and which allow the conversion of aliphatic hydrazones with up to 95% yield and 93% ee.

Our studies were commenced with the screening of chiral phosphoric acid catalysts (*R*)-**3a**−**h** (Table 1), easily prepared according to known procedures.[7,8]

Their catalytic efficiency was examined in the hydrocyanation reaction of the aliphatic hydrazone **1**, which is a readily prepared and an air/moisture stable substrate.[9] Easier to handle TMSCN (trimethylsilyl cyanide) was employed instead of HCN. The model reaction was initially carried out at room temperature, using dichloromethane as a solvent and 10 mol % of the catalyst **3** (Table 1, entries 1−8). Notably, catalyst **3a**, without any substituents at the 3,3′-position on the binaphthyl backbone, showed almost no activity (entry 1). We assume that the observed result is due to the poor solubility of the catalyst **3a** in dichloromethane. BINOL-phosphates **3b** and **3c**, bearing 3,3′-$SiPh_3$- and 3,3′-C_6H_5-groups, respectively, both catalyzed the reaction, but with almost no enantioselectivity (Table 1, entries 2 and 3). Variations of the substituents on the 3,3′-C_6H_5-groups were examined next. Introduction of the sterically demanding β-Naph-moiety or the electron-withdrawing NO_2-group into the para-position of the 3,3′-phenyl-moieties of BINOL-phosphate (catalysts **3d** and **3e**, respectively) resulted in a positive effect on the enantioselectivity. That is, catalysts **3d** and **3e** gave the most promising results under the reaction conditions with respect to yields and enantioselectivities (94%, 67% ee and 91%, 64% ee, respectively, entries 4 and 5). Interestingly, introduction of another and/or additional electron-withdrawing group into the 3,3′-phenyl-moieties has not resulted in an improvement of the enantioselectivity, but rather led to its deterioration (Table 1, entries 6−8).

Table 1. Screening of the Catalysts



entry	catalyst	t (°C)	time (h)	yield[a] (%)	ee[b] (%)
1	**3a**	rt	24	traces	6 (*S*)
2	**3b**	rt	24	71	1 (*S*)
3	**3c**	rt	24	99	1 (*S*)
4	**3d**	rt	24	94	67 (*R*)
5	**3e**	rt	24	91	64 (*R*)
6	**3f**	rt	24	95	59 (*R*)
7	**3g**	rt	24	93	8 (*S*)
8	**3h**	rt	24	94	24 (*R*)
9	**3d**	−10	72	37	76 (*R*)
10	**3e**	−10	72	86	90 (*R*)
11	**3e**	−20	72	45	90 (*R*)

[a] Yield of isolated product. [b] Enantioselectivities were determined by chiral-phase HPLC analysis (Daicel Chiralpak IB) in comparison with authentic racemic material.

Further optimization of reaction conditions by changing either solvent or reaction temperature was performed with catalysts **3d** and **3e**. Screening studies demonstrated that the originally chosen dichloromethane was the optimal solvent for the reaction (see the Supporting Information). We noticed a substantial overall improvement of the enantioselectivity upon lowering the reaction temperature (Table 1, entries 9−11). Intriguingly, while a slight improvement of the enantioselectivity and a drastic reduction of the obtained yield (37%, 76% ee, entry 9 vs. entry 4) was observed when lowering the reaction temperature to −10 °C in the presence of catalyst **3d**, an increase in the enantiomeric excess, keeping the accompanying loss of yield minimal, was observed at the same reaction temperature with catalyst **3e** (86%, 90% ee, entry 10 vs. entry 5). Decreasing the temperature further from −10 to −20 °C does not lead to

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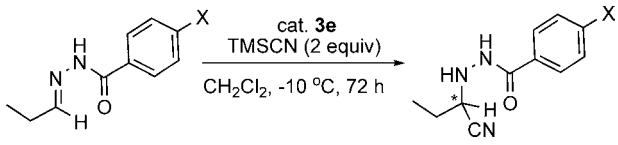
(9) For examples of enantioselective additions to *N*-acylhydrazones as stable and readily prepared substrates, see: (a) Ogawa, C.; Sugiura, M.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 6491. (b) Berger, R.; Duff, K.; Leigton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686. (c) Notte, G. T.; Leigton, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 6676. (d) Yalalov, D. A.; Tsogoeva, S. B.; Shubina, T. E.; Martynova, I. M.; Clark, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 6624. For a review, see: (e) Sugiura, M.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 5176.

further improvement in the enantioselectivity, but rather to the loss of catalytic efficiency (Table 1, entry 11 vs. entry 10).

To further improve the outcome of the reaction, we screened several additives in CH_2Cl_2 at −10 °C and in the presence of catalyst **3e** (Table 2).

Table 2. Optimization of Reaction Conditions



entry	catalyst (mol %)	X	additive (mol %)	yield[a] (%)	ee[b] (%)
1	10	NO_2	MeOH (20)	88	89 (*R*)
2	5	NO_2	MeOH (20)	92	93 (*R*)
3	5	NO_2	*i*-PrOH (20)	76	88 (*R*)
4	5	NO_2	*t*-BuOH (20)	95	93 (*R*)
5	5	NO_2	*t*-BuOH (50)	95	90 (*R*)
6	5	NO_2	*t*-BuOH (200)	76	89 (*R*)
7	5	NO_2	TPM (20)	90	93 (*R*)
8	5	NO_2	HMPA (20)	89	91 (*R*)
9	5	NO_2	DPPO (20)	68	57 (S)
10	5	NO_2	TPPO (20)	35	59 (*R*)
11	5	H	*t*-BuOH (20)	traces	
12	5	Br	*t*-BuOH (20)	16	66 (*R*)

[a] Yield of isolated product. [b] Enantiomeric excess was determined by HPLC methods on a chiral stationary phase (Daicel Chiralpak IB). TPM = triphenylmethanol. HMPA = hexamethylphosphoramide. DPPO = diphenylphosphine oxide. TPPO = triphenylphosphine oxide.

While using MeOH (20 mol %) and carrying out the reaction with 10 and 5 mol % of catalyst **3e**, respectively, we observed that the reduction of catalyst loading has a positive impact, increasing the yield and ee value (Table 2, entry 1 vs. entry 2). Hence, all other additives have been explored in the presence of 5 mol % of **3e**.

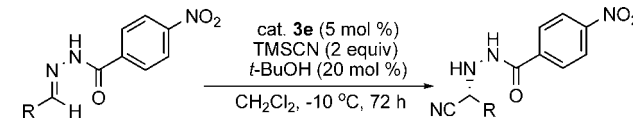
Among the tested alcohols, *t*-BuOH at 20 mol % showed the best performance (95% yield, 93% ee, entry 4). Higher amounts of *t*-BuOH (e.g., 200 mol %) resulted in again decreased yield and selectivity (Table 2, entries 5 and 6). Interestingly, the use of TPM (triphenylmethanol) at 20 mol % provided similarly high enantioselectivity (93% ee), albeit slightly lower yield (90%) with respect to *t*-BuOH at the same loading (Table 2, entry 7 vs. entry 4).

Besides alcohols, we screened also some Lewis bases as additives (Table 2, entries 8−10). Interestingly, using 20 mol % of achiral DPPO additive in combination with **3e** (5 mol %), we observed the enrichment of the opposite enantiomer (*S*) of the isolated product (Table 2, entry 9), a fact that implies that in this case the transition state structure for the product formation might be completely different, as compared to all other reactions from Table 2 (entry 9 vs. entries 1−8, 10). This potentially significant finding is under further investigation in our laboratory and DFT calculations on the mechanism of this catalytic system are currently underway.

The para-substituent at the benzoyl group of the hydrazones apparently plays an important role not only concerning selectivities, but also in enhancing the reactivity of the hydrazone (Table 2, entries 11 and 12 vs. entry 4). When X = H, product was only obtained in traces (entry 11). Intriguingly, while the *p*-Br-substituent at the benzoyl group led to the product formation with only 16% yield and 66% ee (Table 2, entry 12), *N*-*p*-NO_2-benzoyl-protected hydrazone, having encreased electrophilicity of the imino carbon, underwent reaction to give a high yield and enantioselectivity (95%, 93% ee, entry 4).

To illustrate the scope of the reaction, a series of *N*-*p*-NO_2-benzoyl-protected aliphatic hydrazones have been synthesized and subjected to these optimized reaction conditions. To our delight, all reactions investigated can be effected in 71−93% ee, applying the catalyst at only 5 mol % loading (Table 3). When there was a branching at the β-carbon of the hydrazone (e.g., relatively bulky *i*-Bu), the product could be isolated in high enantioselectivity, but the yield eroded (entry 1). Hydrocyanation of hydrazones bearing different alkyl rests (Me, Et, *n*-Pr, *n*-Bu, *n*-Pn) resulted in the formation of the products in good to high yields and enantioselectivities (Table 3, entries 2−6). The chain length in R does not seem to affect significantly the reaction's yield or enantioselectivity (75−95% yields, 86−93% ee, entries 3−6).

Table 3. Scope of Substrates



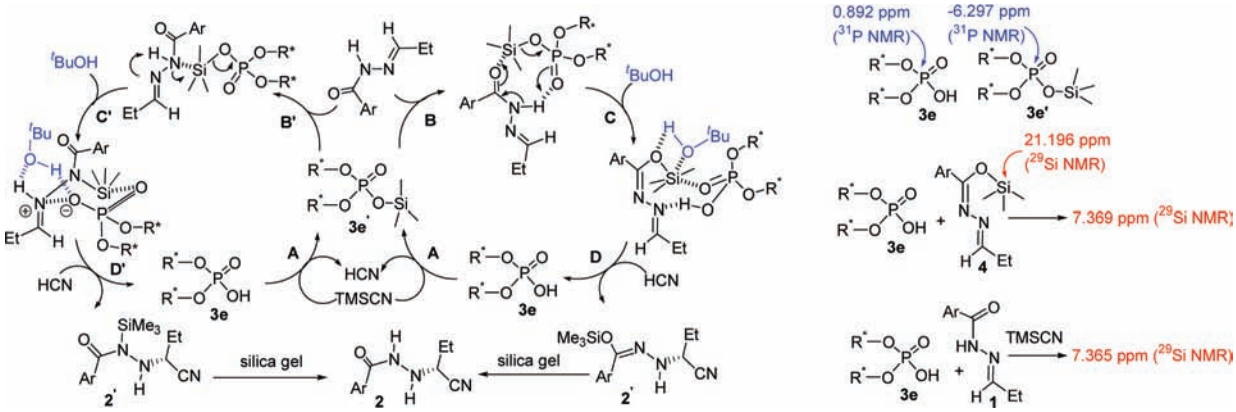
entry	R	yield[a] (%)	ee[b] (%)
1	$(CH_3)_2CHCH_2$	31	90
2	CH_3	54	71
3	CH_3CH_2	95	93
4	$CH_3(CH_2)_2$	75	86
5	$CH_3(CH_2)_3$	86	87
6	$CH_3(CH_2)_4$	86	90
7	$Ph(CH_2)_2$	79	92
8[c]	$PhCH_2$	73	83
9	$CH_3S(CH_2)_2$	26	78

[a] Yield of isolated product. [b] Enantioselectivities were determined by chiral-phase HPLC analysis (Daicel Chiralpak IB) in comparison with authentic racemic material. The stereochemical assignment of entry 8 was made by comparison with literature data,[6a] and all others were made by analogy (see the Supporting Information). [c] The reaction was performed at −5 °C, with 2.5 equiv of TMSCN.

Notably, catalyst **3e** also proved to be well applicable to hydrazones with phenylethyl and benzyl rests (entries 7 and 8). In addition, hydrazone bearing a 1-thioalkyl group provided the desired adduct in good enantioselectivity but with a decrease in the yield of the product (Table 3, entry 9 vs. entry 4).

Regarding the reaction mechanism, we noticed that BINOL-phosphate **3e** reacts easily with TMSCN to give

Scheme 1. Two Plausible Mechanisms for the Strecker-Type Hydrocyanation of Hydrazones by Using BINOL-Phosphate **3e**



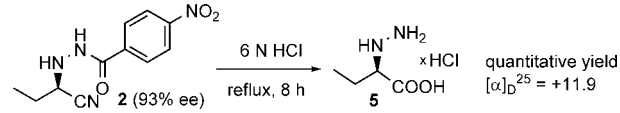
chiral silane **3e′**. New methyl group signals have been observed in ^{1}H NMR spectra (see the SI). We also found that the resulting *O*-silylated BINOL-phosphate **3e′** promoted the hydrocyanation reaction even in the presence of 2,6-di-*tert*-butyl-4-methylpyridine,[10] confirming that the actual catalyst is the in situ generated Lewis acidic **3e′**. Notably, the in situ formation of a TMS-containing compound from BINOL-phosphate has also been reported by Antilla and co-workers in an enantioselective desymmetrization of meso-aziridines with use of TMS-N_3.[8e]

On the basis of thorough ^{29}Si, ^{31}P, and ^{1}H NMR studies (see the SI) we propose the following mechanism for this reaction (Scheme 1): (1) the active catalyst **3e′** forms by displacement of the cyanide (step A); (2) the benzoyl oxygen becomes covalently attached to the catalyst **3e′** (steps B and C); and (3) the resulting species undergoes attack from the cyanide nucleophiles formed in step A, giving the silylated product **2′** (which decomposes on silica gel to form product **2**) and the reformation of **3e**.

Notably, we could not confirm directly the formation of silylhydrazone **4** in the reaction mixture. Furthermore, measuring the ^{29}Si NMR of two mixtures, (1) **3e** + readily prepared **4** and (2) **3e** + **1** + TMSCN, we observed a signal at about 7.36 ppm in both cases (Scheme 1 and the SI). This observation forced us to formulate also an alternative mechanistic pathway involving steps B′, C′, and D′ (Scheme 1). The transition state structures for both mechanistic pathways are supposed to be additionally stabilized by *t*-BuOH additive (Scheme 1).

Conversion of the hydrocyanation products to α-hydrazino acids proved straightforward. Thus, hydrazinonitrile **2** has been smoothly transformed to the corresponding α-hydrazino acid **5** upon refluxing **2** in 6 N HCl (Scheme 2). Notably, both the hydrolysis of the nitrile group and the cleavage of the *N*-benzoyl protecting group took place under these reaction conditions in one step and in quantitative yield.

Scheme 2. Conversion of Protected α-Hydrazinonitrile to α-Hydrazino Acid



In summary, we have successfully developed the first organocatalytic enantioselective hydrocyanation of aliphatic hydrazones, providing a new convenient and direct route to versatile α-hydrazino acids. This organocatalytic transformation provides efficient access to synthetically useful α-hydrazinonitriles in good to high yields and enantioselectivities and demonstrates a rare example of the cyanation of C═N bonds catalyzed by a Lewis acid, generated in situ from a Brønsted acid. Further studies focusing on the full scope of this and related systems, as well as DFT calculations on the mechanism, are currently under investigation and will be reported in due course.

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Supporting Information Available: Experimental procedures and NMR and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) 2,6-Di-*tert*-butyl-4-methylpyridine has been used to differentiate between Lewis acid and Brønsted acid catalyzed pathways: Mathieu, B.; Ghosez, L. *Tetrahedron*, **2002**, *58*, 8219.