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Direct Catalytic Asymmetric Addition of Acetonitrile to Aldimines

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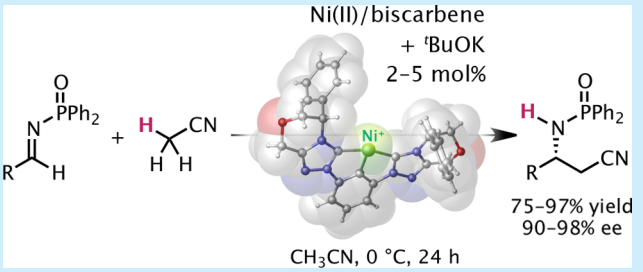
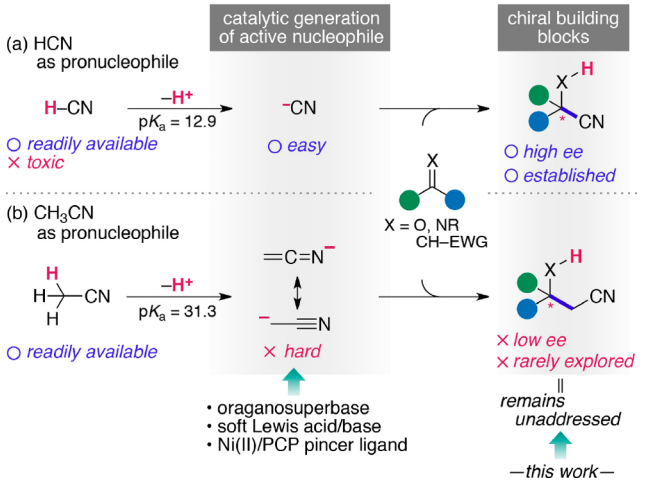
Supporting Information

ABSTRACT: Despite significant advances in catalytic asymmetric reactions with decent stereocontrol, those using acetonitrile as a pronucleophile are often disregarded due to their low reactivity and insufficient enantioselectivity. Herein we report the resurgence of this reaction in the chemical toolbox with high enantioselectivity (avg. > 95% ee). The combined use of a Ni(II) complex ligated with a chiral biscarbene and ^{t}BuOK engages acetonitrile in the catalytic generation of an α-cyanocarbanion and subsequent highly enantioselective addition to aldimines.



Cyano functionality plays a pivotal role as masked amines and carboxylic acid derivatives in synthetic organic chemistry.[1] Hydrogen cyanide and its derivatives are established as readily available and viable C1 pronucleophiles capable of introducing a cyano group into a wide variety of electrophiles in a highly enantioselective manner (Scheme 1a).[2] Given the acute toxicity of cyanide, the application of readily available acetonitrile as an alternative pronucleophile has long been desired as a safer option for gaining access to cyano-containing chiral building blocks (Scheme 1b).[3] The significant difference in the pK_a between hydrogen cyanide (12.9 in DMSO) and acetonitrile (31.3 in DMSO), however, hampers the catalytic generation of a nucleophilically active α-cyanocarbanion from acetonitrile.[4] Hence, anion-taming α-substituents are generally harnessed to facilitate deprotonative activation and decorated nitrile-pronucleophiles have been successfully utilized in C−C bond-forming asymmetric catalysis.[5−9] On the other hand, the significantly less reactive parent acetonitrile has been largely neglected as a potential pronucleophile and generally regarded as a chemically inert solvent.[10]

Scheme 1. Disparity of Hydrogen Cyanide and Acetonitrile in Catalytic Asymmetric C−C Bond-Forming Reactions



In this context, the proazaphosphatrane organosuperbase found its particular utility in catalytic deprotonation of acetonitrile and subsequent addition to carbonyl compounds,[11] eliminating the necessity for using stoichiometric amounts of strong bases. Strategic use of soft Lewis acids to activate the inherently soft Lewis basic cyano functionality allowed for direct catalytic addition of acetonitrile under milder basic conditions.[12] The Ni(II) complex of a PCP-type pincer ligand displayed the highest catalytic turnover to date, although the enantioselective entry was not reported.[13] In contrast to steady advances in the catalytic generation of the α-cyanocarbanion from acetonitrile, there remains considerable room for stereochemical control in the addition to electrophiles. A survey of precedent enantioselective examples in this reaction manifold revealed surprisingly insufficient enantioselectivity (avg. < 62% ee)[14−16]—significantly lower than that observed for the analogous nucleophilic addition of α-substituted nitriles or enolates. This prominent anomaly of acetonitrile is presumably due to the linear topology of the corresponding α-cyanocarbanion, which fails to pose an adequate steric bias to manifest a practical level of enantioselection. Herein we report the highly enantioselective direct catalytic addition of acetonitrile to aldimines promoted by a chiral Ni(II)/biscarbene complex. Divergent conversion of the cyano group of the product into a carboxylic acid and an amino group highlights the synthetic utility of the present catalysis as a viable C2 homologation reaction complementary to the C1 counterpart via the cyanide addition.

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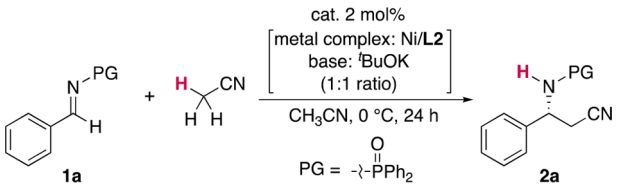
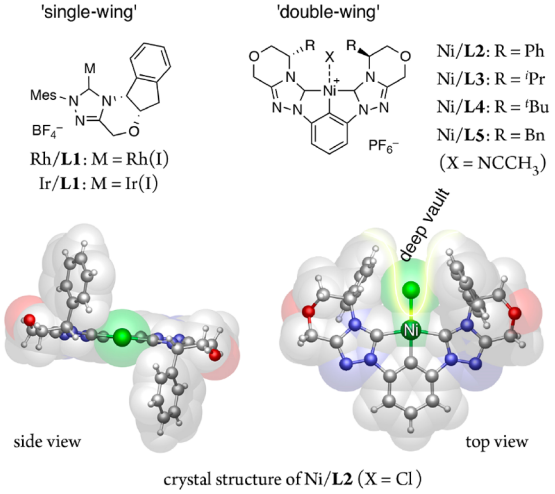
Through our previous attempts to exploit acetonitrile as a pronucleophile, we found that Rh(I) and Ir (I) complexes ligated with electron-rich chiral carbenes promote the direct addition of acetonitrile to C═O and C═N electrophiles in the presence of a mild Brønsted base.[14d,e] Despite systematic structural modifications of the monocarbene ligands, however, the enantioselectivity remained low to moderate. We reasoned that the insufficient stereoselection originated from the size-mismatch of the small α-cyanocarbanion and a "single-wing" monocarbene ligand **L1** (Table 1, entries 8, 9).[17]

Table 1. Optimization of Reaction Conditions[a]



entry	change from standard conditions	yield (%)	ee (%)
0	—	>99	97
1	cat. 5 mol%	>99	97
2	cat. 5 mol%, rt, 1 h	99	93
3	cat. 5 mol%, complex Ni/**L3**, rt, 1 h[b]	99	45
4	cat. 5 mol%, complex Ni/**L4**, rt, 2 h[b]	>99	51
5	cat. 5 mol%, complex Ni/**L5**, rt, 1 h[b]	>99	58
6	cat. 5 mol%, PG = Boc, rt, 2 h	99	85
7	cat. 5 mol%, PG = Ts, rt	78	86
8	cat. 5 mol%, complex Rh/**L1**, rt	0	—
9	cat. 5 mol%, complex Ir/**L1**, rt	65	20



[a]**1a**: 0.1 mmol, 0.1 M. [b]Ni-acetonitrile complex was prepared from the corresponding Ni–Cl complex (X = Cl) with $AgPF_6$ and directly used.

This assumption led us to investigate "double-wing" type pincer biscarbene ligands **L2–5**, which furnished rigid cationic metal complexes with the metal cation located at the bottom of the deep vault.[18,19] In an attempted reaction of *N*-diphenylphosphinoyl(*N*-Dpp)imine **1a** and acetonitrile,[20] the combined use of biscarbene pincer complex Ni(II)/**L2** and ^{t}BuOK emerged as a competent catalyst (2 mol%) to complete the reaction at 0 °C in 24 h (entry 0). Notably, this reaction was highly enantioselective, outperforming precedents of direct addition reactions of acetonitrile. Comparable enantioselectivity was observed by running the reaction at room temperature (entry 2), and reactions with ligands bearing different substituents under otherwise identical conditions demonstrated the superiority of the chiral environment of **L2** (entries 3–5). Attachments on the imine nitrogen partly dictated the enantioselectivity, and crystalline *N*-Dpp imine **1a** was optimal with respect to reactivity and enantioselectivity (entries 6, 7).

High enantioselectivity was generally observed in the reactions with a range of *N*-Dpp imines **1** (Figure 1). The

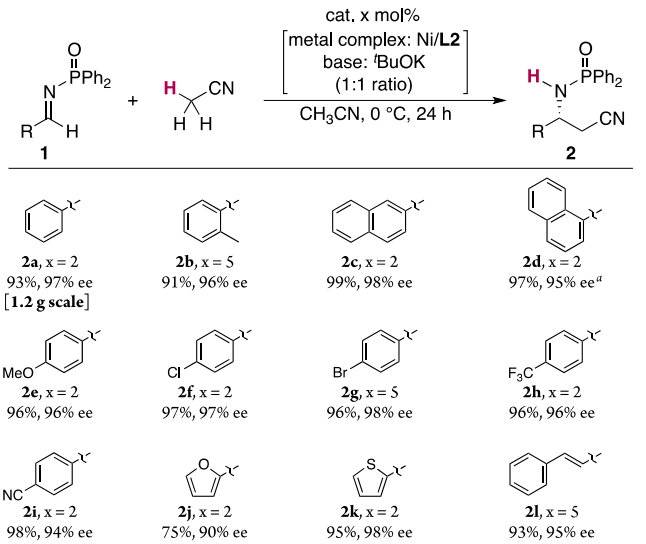


Figure 1. Substrate generality (0.1 mmol, 0.1 M). [a]Mixed solvent CH_3CN/THF = 9/1 was used for homogeneity.

steric bias of the *o*-Me substituent, as well as the α- and β-naphthyl units, was well accommodated to achieve high yield and enantioselectivity (**2b–d**). Studies of the electronic effects of the reaction using imines bearing electron-donating *p*-OMe and electron-withdrawing *p*-halogen/*p*-CF_3/*p*-CN underscored the tolerance of the present reaction toward electronic effects (**2e–i**). The Ni(II) pincer complex was redox inactive under the optimized conditions, and the Ar–Br bond remained intact (**2g**). Heteroaromatic imines barely interfered with the catalysis to provide the desired cyanomethylated products (**2j,k**), albeit with a marginal decrease in the yield and enantioselectivity for 2-furyl imine (**2j**). An imine bearing an (*E*)-cinnamyl unit proved to be a suitable substrate to expand the generality (**2l**). This operationally simple reaction was readily scaled up, and the attempted gram-scale reaction exhibited no detrimental effects (**2a**). The inspection of the initial rate of separate reactions in CH_3CN/THF and CD_3CN/THF revealed the positive kinetic isotope effect of k_H/k_D = 3.0.[21] This result is consistent with the finding that the reaction rate was generally not related to the sterics and electronics of the imines, and suggests that the catalyst turnover step (deprotonation of acetonitrile) is rate-determining. As such, less reactive propionitrile failed to induce the reaction under the optimized conditions.

Nitrile functionality can be regarded as a masked amine and carboxylic acid derivative (Scheme 2). The Dpp group was readily removed by treating **2a** with 2 N HCl/MeOH at room temperature to give free amine **3** with the nitrile moiety intact. Basic hydrolysis of **2a** in refluxing 2 N NaOH aq. afforded *N*-protected carboxylic acid **4**. Sequential hydride reduction unmasked the cyano group to furnish primary amine **5**.

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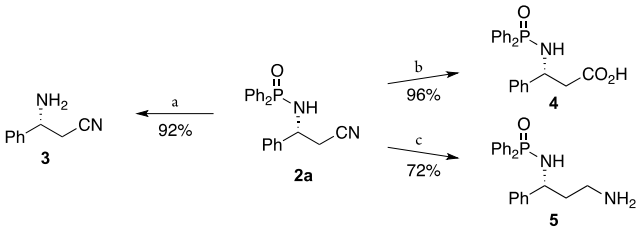
Scheme 2. Transformation of the Product[a]



[a]Reagents and conditions: (a) 2 N HCl/MeOH, rt, 4 h, 92%. (b) 2 N NaOH aq., EtOH, reflux, 16 h, 96%. (c) DIBAL, THF, −78 °C, 2 h; $NaBH_4$, −78 °C to rt, 16 h, 72%.

Direct catalytic asymmetric addition of acetonitrile has long been burdened by insufficient enantioselectivity, which was addressed herein via strategic use of a unique asymmetric environment provided by a deep-vaulted biscarbene ligand. The corresponding α-cyanocarbanion was catalytically generated by the Ni(II)/biscarbene ligand/^{t}BuOK catalytic system, and subsequent addition to *N*-Dpp imines proceeded with decent stereocontrol. Extrapolation of the present catalysis to carbonyl-type electrophiles will significantly expand the utility of alkylnitriles as versatile pronucleophiles, and is currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02821.

Experimental procedures, spectroscopic data for new compounds, and NMR spectra (PDF)

Accession Codes

CCDC 1922993 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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