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A new and effective method for providing optically active monosubstituted malononitriles: selective reduction of α,β-unsaturated dinitriles catalyzed by copper hydride complexes

Yunlai Ren, Xianlun Xu,* Kunpeng Sun and Jian Xu

State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences and Graduate School of the Chinese Academy of Sciences, 342 Tianshui Road, Lanzhou 730000, China

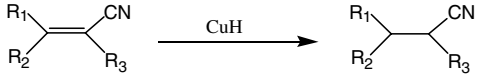
Received 20 September 2005; revised 6 November 2005; accepted 10 November 2005

Abstract—A copper hydride complex, which was generated in situ from CuO*t*-Bu, BINAP, and $PhSiH_3$, was found to be a highly effective catalyst for the reduction of the C=C of α,β-unsaturated dinitriles. In addition to CuO*t*-Bu, some air and moisture stable Cu salts were also effective as catalyst precursors in this reduction. Herein, we have developed an effective method for providing optically active monosubstituted malononitriles.

1. Introduction

The selective reduction of the C=C units conjugated with electron-withdrawing groups is an important multi-step transformation in synthetic organic chemistry.[1] Amongst these types of reactions, selective reduction of a C=C conjugated with a cyano group has long been a difficult synthetic problem, because it often proceeds with concomitant decyanation, reduction of the nitrile moiety, hydrodimerization, and polymerization.[2] Recently, some excellent reducing reagents such as 1,4-dihydropyridine ester,[3] 2-phenylbenzimidazoline,[1,4] indium metal,[5] 2-phenylbenzothiazoline,[6] and indium hydride,[7,8] have been found. However, the number of examples of the catalytic reduction of the C=C of α,β-unsaturated dinitriles is still scant. To the best of our knowledge, there is only one example of an asymmetric reduction of the carbon–carbon double bond of α,β-unsaturated dinitriles.[9] In this example, a chiral diamine–ruthenium complex was used as catalyst with the obtained enantioselectivities being unsatisfactory.

Recently, copper hydride complexes have been found to be highly effective catalysts for the conjugate reduction of α,β-unsaturated carbonyl complexes[10–20] and nitroalkenes.[21–23] In addition, copper hydride complexes have been also found to be effective reducing reagents in the reduction of C=C bonds conjugated with a cyano group (Scheme 1). However, the use of copper hydride complexes was not in a catalytic amount.[24] Inspired by these results, we attempted to use a catalytic amount of copper hydride complexes to finish this reaction, and were pleased to find that the copper hydride complexes displayed high catalytic activity in the reduction of α,β-unsaturated dinitriles. In order to optimize the procedure for asymmetric reduction of the carbon–carbon double bonds of α,β-unsaturated dinitriles, we first used (±)-BINAP as the ligand for the catalyst. Then, by applying the optimized procedure, we investigated the asymmetric reduction of the carbon–carbon double bonds of α,β-unsaturated dinitriles (Scheme 2).



Scheme 1. Paquette's method for the reduction of C=C bonds conjugated with a cyano group.

2. Results and discussion

In order to search for an optimized procedure for the asymmetric reduction of the carbon–carbon double bonds of α,β-unsaturated dinitriles, we first used

* Corresponding author. Tel.: +86 931 4968537; fax: +86 931 8274069; e-mail: xlxu@ns.lzb.ac.cn

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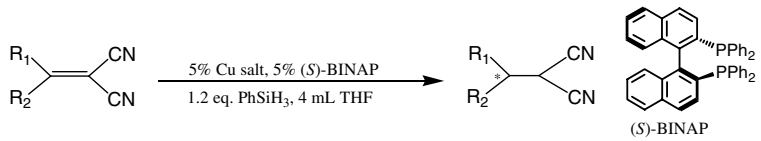
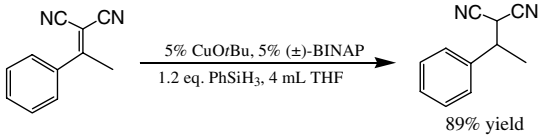
doi:10.1016/j.tetasy.2005.11.013



Scheme 2. Our method for the reduction of C=C conjugated with cyano group.

(±)-BINAP as a ligand for the catalyst. The catalyst was generated in situ from CuCl, NaO*t*-Bu, (±)-BINAP, and $PhSiH_3$. The desired product was obtained in very low yield (8%) after 24 h. The low yield possibly resulted from the concomitant product (NaCl), which could possibly inhibit catalytic activity. A similar problem was also reported by Carreira in the catalytic conjugate reduction of disubstituted nitroalkenes.[21–23] As a result, we used isolated CuO*t*-Bu to enhance the reaction yield; a yield of 89% was obtained after 24 h (Scheme 3). It is unfortunate, however, that CuO*t*-Bu is an extremely air- and moisture-sensitive complex, which is a drawback to the broad application of this process. These questions prompted us to search for other air stable copper sources to replace the air and moisture sensitive CuO*t*-Bu.



Scheme 3.

Fortunately, some copper carboxylates and other copper salts were also effective as catalyst precursors (Table 1, entries 2–13). For example, with the $Cu(OAc)_2$ system, the product was obtained in high yield after 24 h. Air and moisture stable $Cu(OAc)_2{\cdot}H_2O$ was also as effective as $Cu(OAc)_2$ in the reaction. However, it was not satisfactory that the above reactions required a long reaction time.

Table 1. Catalytic reduction of C=C in α-methylbenzylidenemalononitrile with copper hydride complexes generated in situ from Cu salts, (±)-BINAP and $PhSiH_3$[a]

Entry	Cu precursor	Alcohol	Time (h)	Yield (%)[b]
1	CuO*t*-Bu	—	24	89
2	CuOAc	—	24	91
3	$Cu(OAc)_2$	—	24	82
4	$Cu(OAc)_2{\cdot}H_2O$	—	24	86
5	$Cu(OAc)_2{\cdot}H_2O$	*t*-BuOH	6	90
6	$Cu(OAc)_2{\cdot}H_2O$	*t*-AmOH	8	79
7	$Cu(OAc)_2{\cdot}H_2O$	*i*-PrOH	6	81
8	$Cu(OAc)_2{\cdot}H_2O$	EtOH	8	56
9	Cu(acac) $\cdot 1/2H_2O$	*t*-BuOH	6	79
10	$Cu(CF_3COO)_2{\cdot}H_2O$	*t*-BuOH	6	83
11	$Cu(NO_3)_2{\cdot}3H_2O$	*t*-BuOH	12	21
12	$Cu(SO_4)_2{\cdot}5H_2O$	*t*-BuOH	12	15
13	CuF_2	*t*-BuOH	6	85

[a] Reaction conditions and analytical procedures are shown in Section 4.
[b] Isolated yield.

Recently, it was observed by Buchwald that the addition of some alcohols could result in the rate acceleration of the conjugate reduction of unsaturated esters.[18] As a result, we also added some alcohols to optimize our reaction system (Table 1, entries 5–13). When three equivalents of *t*-BuOH were added to the reaction mixture, a yield of 90% was obtained after 6 h (Table 1, entry 5). Other alcohols, such as EtOH, *t*-AmOH, and *i*-PrOH, also enhanced the reaction rate. However, with three equivalents of MeOH, rapid gas (H_2) evolution was observed, and no reduction was observed even after 10 h.

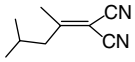
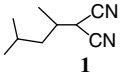
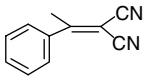
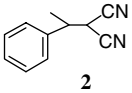
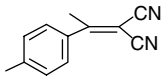
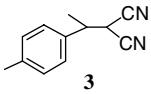
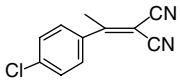
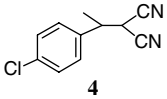
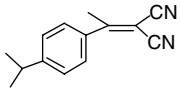
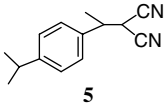
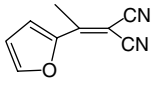
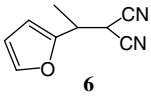
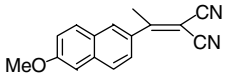
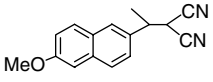
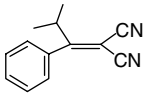
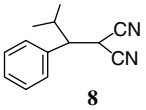
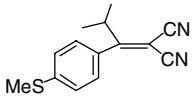
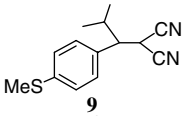
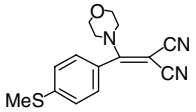
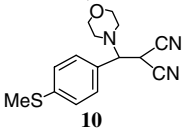
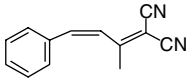
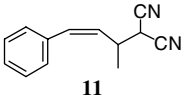
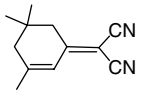
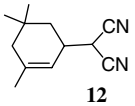
Among the screened catalyst precursors, CuF_2 and some copper carboxylates turned out to be highly effective in this reaction (Table 1). However, when $Cu(NO_3)_2{\cdot}3H_2O$ and $Cu(SO_4)_2{\cdot}5H_2O$ were used, low yields were obtained after 12 h (Table 1, entries 11 and 12). As reported in the previous literature,[25] an oxygen acceleration effect was observed in hydrosilylation of ketones catalyzed by copper fluoride–phosphine complexes. This finding prompted us to examine exposure of our system to air (CuF_2 was used as copper source); however, it was unfortunate that the presence of air led to significant inhibition of the reduction.

The above optimization studies revealed that the best results were obtained when 5 mol % of $Cu(OAc)_2{\cdot}H_2O$, 5 mol % of (±)-BINAP and 3 equiv of *t*-BuOH were used. Applying this optimized procedure [instead of (±)-BINAP, (S)-BINAP was used], we investigated the asymmetric reduction of the carbon–carbon double bonds of α,β-unsaturated dinitriles, and up to 93% ee was obtained (Table 2). When both the substituted groups of 1,1-dicyanoalkene were alkyl groups, a good yield was obtained, although the observed ee was low (Table 2, entry 1). When one of the two substituted groups was a benzene derivative, most of the obtained yields and enantioselectivities were satisfying (Table 2, entries 2–10). In addition, the electronic properties of the substrates had a remarkable effect on the enantioselectivity of this reaction. α-Methyl-*p*-chlorobenzylidenemalononitrile gave only 68% ee (Table 2, entry 4), whereas α-methylbenzylidenemalononitrile gave 80% ee (Table 2, entry 2).

3. Conclusion

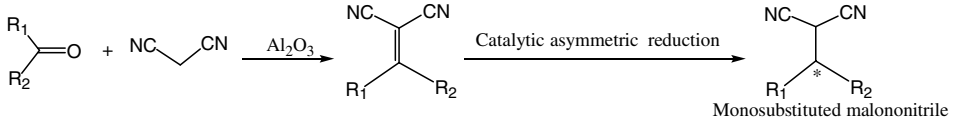
In conclusion, some copper hydride complexes were found to be highly effective catalysts in the reduction of the C=C of α,β-unsaturated dinitriles (high yields were obtained after 6 h). Moreover, the asymmetric reduction of the carbon–carbon double bonds of α,β-unsaturated dinitriles was also investigated. Herein, it

Table 2. Catalytic asymmetric reduction of the C=C in α,β-unsaturated dinitriles with copper hydride complexes generated in situ from $Cu(OAc)_2 \cdot H_2O$, (*S*)-BINAP and $PhSiH_3$[a]

Entry	Substrate	Product	Time (h)	Yield (%)[b]	ee (%)[c]
1		 **1**	6	87	22
2		 **2**	6	90	80[d]
3		 **3**	6	87	83
4		 **4**	10	72	68
5		 **5**	12	79	87
6		 **6**	10	85	76
7		 **7**	8	80	91
8		 **8**	10	65	90
9		 **9**	10	59	90
10		 **10**	12	47	93
11		 **11**	9	65	83
12		 **12**	12	18	39

[a] Reaction conditions and analytical procedures are shown in Section 4.
[b] Isolated yield.
[c] The ee was determined by HPLC analysis using a chiral OD column.
[d] The absolute configuration was *R* as determined by comparison of the specific rotation.[28]

is important that we have developed a new and effective method for providing optically active monosubstituted malononitriles from ketones and malononitrile (Scheme 4).[26] Although the obtained enantioselectivities



Scheme 4.

were moderate (up to 93% ee), we believe that excellent enantioselectivities can be obtained by searching for other chiral ligands. This search is currently underway in our laboratory.

4. Experimental

4.1. Reagents and materials

α,β-Unsaturated dinitriles were readily obtained in one step standard procedures as described in previous literatures.[26] THF was freshly distilled from sodium benzophenone ketyl under argon before use. *i*-PrOH, *t*-BuOH, and *t*-AmOH (*tert*-amyl alcohol) were freshly distilled from CaH_2 under argon before use. CuCl was prepared from $CuCl_2$ and Cu.[27] NaO*t*-Bu was purchased from Aldrich and used as received. BINAP was purchased from Alfa Aesar and used as received. $NaBH_4$ and other Cu(I) and Cu(II) salts were purchased from Chinese Tianjin Chemical Reagent Co. and used as received. ^{1}H NMR spectra were recorded as $CDCl_3$ or DMSO-d_6 solutions using 400 MHz spectrometer; peak positions are reported as δ (ppm) downfield from internal Me_4Si; peaks are reported as singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m). ^{13}C NMR were recorded as $CDCl_3$ solutions at 400 MHz; peak positions are reported as δ (ppm). HPLC analyses were performed on a Shimadzu VP liquid chromatograph equipped with a chiral OD column. Optical rotations were measured on a Perkin–Elmer 341 polarimeter.

4.2. Representative procedure for the catalytic reduction of the carbon–carbon double bonds of α,β-unsaturated dinitriles with copper hydride complexes

Copper salt (0.05 mmol) and BINAP (0.05 mmol) were added into a flame-dried 10 ml round-bottomed flask (RBF). Then, the mixture was stirred in THF (2 ml) at room temperature for 30 min to give a solution. A flame-dried 5 ml pear-bottomed flask (PBF) was cooled under argon and charged with THF (2 ml), and then 1,1-dicyanoalkene (1 mmol) was added at room temperature. The RBF was then charged with $PhSiH_3$ (1.2 mmol) at room temperature to give a solution, which was then cooled to −30 °C. The contents of the PBF were then added to the RBF via cannula. Over the course of the reaction, the corresponding alcohol (3 mmol) and water (0.2 mmol) were continuously added in 3 h. Upon completion, the reaction mixture was quenched with H_2O (5 ml) and stirred for 3 h. Purification of the mixture by column chromatography provided the desired product. The product was determined by ^{1}H NMR and ^{13}C NMR spectra. The ee was determined by HPLC analysis using a chiral OD column. The absolute configuration was determined by the comparison with the specific rotation in the literature report.[28]

The products of the reduction are simple and familiar.[1–9,28,29] As a result, only ^{1}H NMR, ^{13}C NMR spectra or elemental analysis data for the products in Table 2 are shown as follows:

1,1-Dicyano-2,4-dimethylpentane **1**: ^{1}H NMR (DMSO-d_6): $\delta = 3.64$ (d, $J = 5.2$ Hz, 1H, CN*CH*CN), 2.18–2.25 (m, 1H), 1.61–1.67 (m, 1H), 1.31–1.39 (m, 2H), 1.19 (d, $J = 6.8$ Hz, 3H), 0.92 (d, $J = 6.4$ Hz, 3H), 0.88 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (DMSO-d_6): $\delta = 112.3$, 111.8, 42.5, 33.3, 29.4, 24.9, 22.9, 21.4, 16.7.

1,1-Dicyano-2-phenylpropane **2**: ^{1}H NMR ($CDCl_3$): $\delta = 7.31$–7.42 (m, 5H, Ph), 3.86 (d, $J = 6.4$ Hz, 1H, CN*CH*CN), 3.42–3.45 (m, 1H, Ph*CH*), 1.62 (d, $J = 6.8$ Hz, 3H, *CH*$_3$); ^{13}C NMR ($CDCl_3$): $\delta = 138.1$, 129.1, 128.7, 127.2, 112.0, 111.9, 40.9, 31.0, 17.6.

1,1-Dicyano-2-(4-methylphenyl)propane **3**: ^{1}H NMR ($CDCl_3$): $\delta = 7.14$–7.34 (m, 4H, Ph), 3.86 (d, $J = 6.0$ Hz, 1H, CN*CH*CN), 3.42–3.45 (m, 1H, Ph*CH*), 2.38 (s, 3H, Ph*CH*$_3$), 1.63 (d, 3H, $J = 6.8$ Hz, *CH*$_3$); ^{13}C NMR ($CDCl_3$): $\delta = 138.4$, 135.1, 129.7, 127.0, 112.1, 111.8, 40.5, 31.1, 20.9, 17.6.

1,1-Dicyano-2-(4-chlorophenyl)propane **4**: ^{1}H NMR ($CDCl_3$): $\delta = 7.16$–7.38 (m, 4H, Ph), 3.85 (d, $J = 6.4$ Hz, 1H, CN*CH*CN), 3.41–3.46 (m, 1H, Ph*CH*), 1.61 (d, 3H, $J = 7.2$ Hz, *CH*$_3$); ^{13}C NMR ($CDCl_3$): $\delta = 136.5$, 134.7, 129.3, 128.6, 111.7, 111.5, 40.4, 31.0, 20.8.

1,1-Dicyano-2-(4-isopropylphenyl)propane **5**: ^{1}H NMR ($CDCl_3$): $\delta = 7.17$–7.22 (m, 4H, Ph), 4.19 (d, $J = 6.0$ Hz, 1H, CN*CH*CN), 2.44 (s, 3H), 1.73 (m, 1H), 1.07–1.09 (m, 1H), 0.83 (d, $J = 6.4$ Hz, 3H), 0.72 (d, $J = 6.4$ Hz, 3H). Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N,13.20. Found: C, 79.28; H, 7.64; N, 13.08.

1,1-Dicyano-2-(2-furyl)propane **6**: ^{1}H NMR ($CDCl_3$): $\delta = 6.01$–7.52 (m, 3H, Ph), 4.05 (d, $J = 7.2$ Hz, 1H, CN*CH*CN), 3.87–4.11 (m, 1H, Ph*CH*), 1.83 (d, $J = 6.4$ Hz, 3H, *CH*$_3$); ^{13}C NMR ($CDCl_3$): $\delta = 150.2$, 138.0, 110.6, 106.2, 103.9, 39.4, 36.3, 16.6.

1,1-Dicyano-2-(6-methoxynaphthyl)propane **7**: ^{1}H NMR ($CDCl_3$): $\delta = 7.10$–7.76 (m, 6H), 3.90 (s, 3H), 3.88 (d, $J = 2.8$ Hz, 1H, CN*CH*CN), 3.53–3.56 (m, 1H), 1.69 (d, 3H, $J = 7.2$ Hz). Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.65; H, 5.57; N, 11.13.

1,1-Dicyano-2-phenyl-3-methylbutane **8**: ^{1}H NMR ($CDCl_3$): $\delta = 7.28$–7.45 (m, 5H), 3.73 (d, $J = 6.4$ Hz, 1H), 3.61–3.69 (m, 1H), 2.15–2.20 (m, 1H), 0.81–0.89 (m, 6H). Anal. Calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.81; H, 7.14; N, 14.02.

1,1-Dicyano-2-(4-methylthiophenyl)-3-methylbutane **9**: ^{1}H NMR ($CDCl_3$): $\delta = 7.06$–7.31 (m, 4H), 3.58 (d, $J = 6.4$ Hz, 1H), 3.55–3.59 (m, 1H), 2.57 (s, 3H), 1.76–1.83 (m, 1H), 0.83–0.86 (m, 6H). Anal. Calcd for $C_{14}H_{16}N_2S$: C, 68.81; H, 6.60; N, 11.46. Found: C, 68.72; H, 6.64; N, 11.53.

1,1-Dicyano-2-(4-methylthiophenyl)-2-morpholinoethane **10**: ^{1}H NMR (DMSO-d_6): $\delta = 7.16$–7.31 (m, 4H), 3.91 (d, $J = 6.0$ Hz, 1H), 3.56 (s, 3H), 3.34 (d, $J = 6.4$ Hz,

1H), 2.43–2.57 (m, 4H), 1.21–1.30 (m, 4H). Anal. Calcd for $C_{15}H_{17}N_3OS$: C, 62.69; H, 5.96; N, 14.62. Found: C, 62.53; H, 5.88; N, 14.69.

1-Phenyl-3-methyl-4,4-dicyano-1-butene **11**: ^{1}H NMR ($CDCl_3$): $\delta = 7.34$–7.40 (m, 5H), 6.58–6.68 (m, 1H), 6.07–6.11 (m, 1H), 3.74 (d, $J = 5.2$ Hz, 1H), 3.03–3.05 (m, 1H), 1.45 (d, $J = 6.8$ Hz, 3H). Anal. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27. Found: C, 79.38; H, 6.19; N, 14.34.

Monosubstituted malononitrile **12**: ^{1}H NMR ($CDCl_3$): $\delta = 5.82$ (s, 1H), 3.66–3.73 (m, 1H), 2.41–2.49 (m, 1H), 2.31 (d, $J = 4.8$ Hz, 2H), 2.13 (d, $J = 9.2$ Hz, 2H), 1.91 (s, 3H), 0.98 (s, 6H). Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.63; H, 8.61; N, 14.75.

Acknowledgements

The authors wish to thank National Nature Science Foundation of China (No. 29933042) for financial support.

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