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COMMUNICATION

Enantioselective Conjugate Addition of Cyanide to Chalcones Catalyzed by Magnesium-Py-BINMOL Complex

Received 00th January 20xx,
Accepted 00th January 20xx

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DOI: 10.1039/x0xx00000x

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An enantioselective magnesium-catalyzed conjugate addition of trimethylsilyl cyanide to chalcones in the presence of Py-BINMOL with multiple stereogenic centers, through dual activation of substrates, has been successfully developed with moderate to good enantioselectivities and good yields.

Nitriles are undoubtedly important functional compounds in organic chemistry, and it is one of the most useful building blocks for the synthesis of amines, acids or amides, natural products, and pharmaceuticals.¹ Therefore, numerous efforts have been dedicated to the development of enantioselective methods for introducing cyano groups into carbonyl compounds.² Despite the asymmetric 1,2-addition of cyanide to aldehydes or ketones has been established well, the stereoselective synthesis of β -cyano adducts by the 1,4-conjugate addition of cyanide to α,β -unsaturated carbonyl compounds is less well explored and only a limited number has been reported involving enantioselective conjugate hydrocyanation of α,β -unsaturated carbonyl compounds. As a result, the asymmetric 1,4-conjugate cyanation of α,β -unsaturated carbonyl compounds has attracted much attention in from synthetic chemists in the past decade. In 2003, Jacobsen et. al.³ reported the first example of asymmetric catalysis of salen-Al(III)-catalyzed 1,4-conjugate addition with cyanide and α,β -unsaturated imides. Subsequently, a varied of elegant works on enantioselective conjugate hydrocyanation of α,β -unsaturated carbonyl compounds and nitroolefins have been disclosed by several groups,⁴⁻¹¹ generally involving binuclear or bimetallic salen-Al(III) complexes,⁴ gadolinium catalyst,⁵ Sr catalyst derived from Sr(OiPr)₂ and new chiral alcohol ligand,⁶ ruthenium-lithium combined catalysts,⁷ phase-transfer catalysts,⁸ titanium complexes,⁹

BINOL-derived organocatalysts,¹⁰ and chiral ProPhenol-magnesium complexes.¹¹ In this context, we are interested in the development of readily accessible alkaline earth metal-promoted conjugate hydrocyanation of chalcone-type aromatic enones with TMSCN by using of readily available Ar-BINMOL (1,1'-binaphthalene-2- α -arylmethanol-2'-ol) ligands.¹²

We recently reported the synthesis and application of Ar-BINMOL (1,1'-binaphthalene-2- α -arylmethanol-2'-ol) ligands in various organic transformations.¹² Especially, the Ar-BINMOL-derived functional molecule has been recognized as an efficient ligand or catalyst in the enantioselective 1,2-addition of organometallic reagents to aldehydes with high level of enantioselectivity.¹² Notably, the attractive features of the Ar-BINMOLs and its analogues, including their salient structure with axial and sp³ central chirality as well as the easily achieving from commercially available 1,1'-bi-2-naphthol (BINOL), render these ligands very attractive in catalytic asymmetric transformations.¹³ In this regard, Yus and coworkers also reported the privileged role of Ar-BINMOL ligands in the asymmetric catalysis.¹⁴ On the basis of previous work on the successful application of Ar-BINMOLs ligands with multiple stereogenic centers in asymmetric catalysis, we expected that the multifunctional Ar-BINMOLs ligands (**L1-L4**) capable of introduction of alkaline earth metal centers would not only accelerate the catalytic asymmetric conjugate addition of cyanide to chalcones in good stereoselectivity.

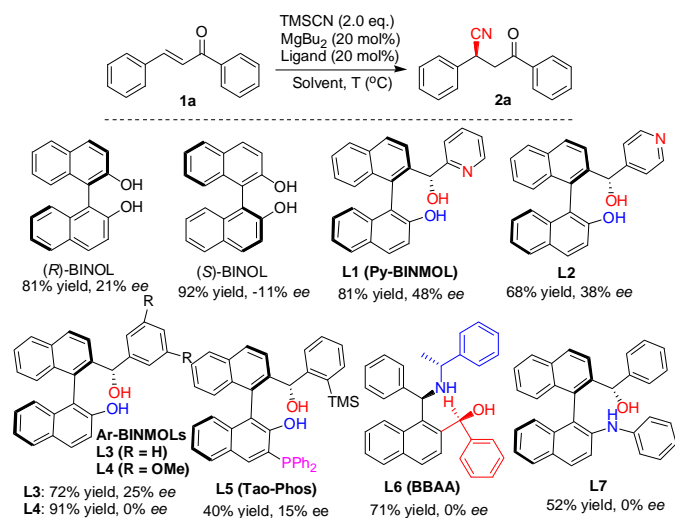
Initially, we hypothesized that the Ar-BINMOLs bearing pyridine moiety would be effective in the enantioselective conjugate addition of cyanide to chalcone **1a** because of its multifunctional *N,O*-groups similarly to the Trost ligand (ProPhenol).^{11,15} In addition, magnesium is not only an environmentally benign and abundant metal but is also inexpensive and readily available. Thus our work commenced with a preliminary survey of the solvent effect using chalcone (**1a**) as the model substrate in the Py-BINMOL (**L1**)^{14d}-promoted magnesium-catalyzed conjugate addition of cyanide. As shown in Table S1 (See Supporting Information), a series of solvent were screened in this reaction. It was found that the diethyl ether was suitable solvent in term of good yield and promising enantioselectivity (48% *ee*), while as the other solvents, such as DCM, toluene, THF, 1,4-dioxane, and toluene, were exhibited to be

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† Footnotes relating to the title and/or authors should appear here. Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

inferior media for both the conversion and enantioselectivity in comparison to that of Et₂O. Next, chiral BINOL and other AR-BINMOL-derived ligands (**L2-L5**, Scheme 1)^{13d-e,14d} with multifunctional diols were exploited in this reaction. These studies indicated that in the presence of chiral BINOL and ligand **L2-L5**, enantioselective conjugate addition of cyanide to chalcone **1a** leads to the formation of β -cyano ketone **2a** with low enantioselectivities (0-38% *ee*). In addition, representative amino alcohols **L6-L7**¹⁶ with multiple stereogenic centers were proved to be no enantioselective induction in this reaction. Thus of the ligands evaluated in this reaction, Py-BINMOL (**L1**) exhibited the best enantioselectivity and yield among these ligands.



Scheme 1. Catalytic asymmetric conjugate hydrocyanation of chalcone with TMSCN

Subsequently, it was found that the enantioselectivity could be improved to 50%*ee* in the presence of phenol (Table 1, entry 1), which suggested the positive activation of phenolic additive in this reaction. As a result, further investigation on the effect of various phenols on the enantioselectivity of catalytic asymmetric conjugate hydrocyanation of chalcone with TMSCN was carried out. As shown in Table 1, the effect of phenolic additives on the enantioselectivity of hydrocyanation reaction is quite obvious, and phenols bearing electron-deficient groups exhibited enhanced enantioselectivity (Entries 8-10). Notably, **L1** promoted the enantioselective Mg-catalyzed conjugate addition of cyanide to chalcone **1a**, giving rise to enantioenriched β -cyano ketone **2a** in good enantioselectivity (Entry 9, 83% yield and 82% *ee*) in the presence of *para*-nitrophenol. However, the use of alcohols, *ortho*-substituted phenols, and methyl-, *tert*-butyl, amino-substituted phenols, as additives, resulted in decreased enantioselectivity in the Py-BINMOL-Mg complex-promoted conjugate hydrocyanation (Entries 2-4, 6, 7, and 22-24). In addition, 20 mol% of phenol additives gave poor enantioselective induction (Entries 11-14). Also interestingly, the use of chiral binaphthol {(*R*)-BINOL or (*S*)-BINOL} as an additive resulted into no enhancement of enantioselectivity in comparison to that of *para*-nitrophenol (Entries 15, 16, and 19). Unexpectedly, the (*S*)-BINOL gave strong negative effect on the catalytic asymmetric conjugate addition of TMSCN to chalcone **1a**, in which the formation of BINOL-involved magnesium complex could be responsible for the change of enantioselectivity. Further

investigation on the effect of temperature in this reaction, summarized in Table 1 (Entries 15-18), establishing the optimized reaction conditions (As depicted in Table 1, entries 11-21). However, the effect of the phenolic additive on enantioselectivity strongly depends on the temperature was unclear. It might be arisen from the stability and activity of multifunctional catalyst system at a reasonable temperature.

Table 1. Further optimization of the reaction conditions by use of additive.

Entry ^a	T (°C)	Additive (R)	Yield (%) ^b	<i>ee</i> (%) ^c
1	0	H	82	50
2	0	2,4- <i>tert</i> -Bu	78	30
3	0	2,6- <i>tert</i> -Bu	75	45
4	0	<i>p</i> - <i>tert</i> -Bu	86	10
5	0	<i>o</i> - <i>tert</i> -Bu	77	62
6	0	<i>m</i> -NH ₂	71	49
7	0	<i>p</i> -Me	83	37
8	0	<i>m</i> -OMe	84	72
9	0	<i>p</i> -NO ₂	83	82
10	0	<i>m</i> -OH	86	77
11	0	<i>o</i> - <i>tert</i> -Bu ^d	76	21
12	0	<i>m</i> -OH ^d	77	16
13	0	<i>p</i> -NO ₂ ^d	77	24
14	0	(<i>R</i>)-BINOL ^d	81	44
15	0	(<i>S</i>)-BINOL ^d	88	34
16	-5	<i>p</i> -NO ₂	89	90
17	-5	(<i>R</i>)-BINOL	88	90
18	-5	(<i>S</i>)-BINOL	91	35
19	-10	<i>p</i> -NO ₂	70	75
20	-10	(<i>R</i>)-BINOL	77	84
21	-10	(<i>S</i>)-BINOL	87	39
22	0	MeOH	88	69
23	0	EtOH	71	62
24	0	CF ₃ CH ₂ OH	56	40

Note: ^a Reaction conditions: 20 mol% of MgBu₂, 20 mol% of ligand (**L1**), chalcone **1a** (0.25 mmol), TMSCN (2 eq.), and additive (1.5 eq.). ^b Isolated yields. ^c The *ee* value or *e.r.* was determined by chiral HPLC. ^d 20 mol% of additive was used in this case.

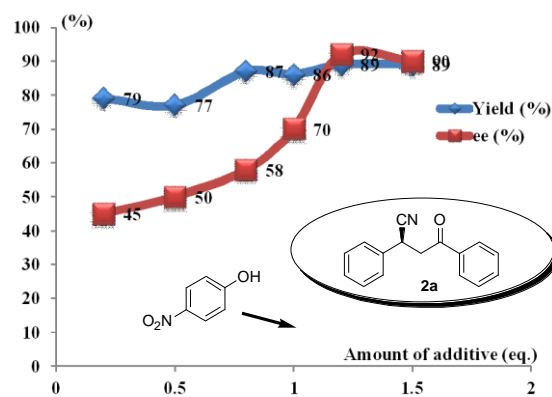
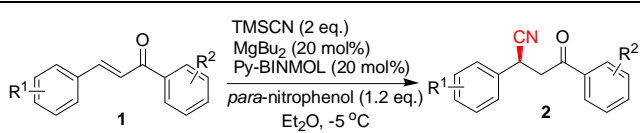


Figure 1. The effect of *para*-nitrophenol (PNP) on the catalytic asymmetric conjugate addition of cyanide to chalcone **1a**.

On the basis of the above findings, we continued to investigate the effect of *para*-nitrophenol (PNP) on the catalytic asymmetric conjugate addition. The experimental results confirmed the use of PNP was the best choice for enantioselective conjugate hydrocyanation in term of yield and enantioselectivity. As shown in Figure 1, it implied that the use of 1.2 equivalents of PNP provided higher enantioselectivity in this reaction (92% *ee*).

Table 2. Substrate scope of the catalytic asymmetric conjugate addition of cyanide to chalcones



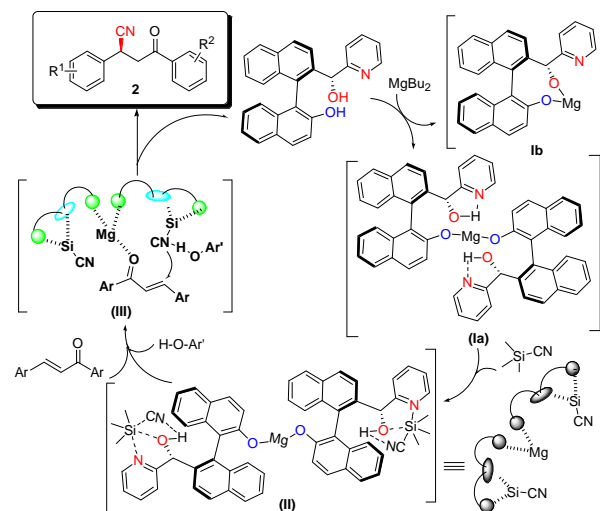
Entry ^a	R ¹	R ²	Yield (%) ^b	<i>ee</i> (%) ^c
1	H	H	2a : 89	92
2	H	4-F	2b : 71	45
3	4-F	4-F	2c : 81	72
4	4-Cl	H	2d : 70	64
5	H	4-Cl	2e : 84	79
6	4-Cl	4-Cl	2f : 72	70
7	4-Br	4-Br	2g : 77	80
8	4-Me	H	2h : 67	51
9	4-CF ₃	H	2i : 90	79
10	4-Ph	H	2j : 71	59
11	2-OMe	H	2k : 76	56
12	3-OMe	H	2l : 85	82
13	4-OMe	H	2m : 72	58
14	4-CF ₃	4-F	2n : 91	79
15	4-F	4-Me	2o : 90	82
16 ^d	4-F	Pyridine ^d	2p : 88	50

Note: ^a Reaction conditions: 20 mol% of MgBu₂, 20 mol% of ligand (**L1**), chalcone **1** (0.25 mmol), TMSCN (2 eq.), and *para*-nitrophenol (1.2 eq.), in diethyl ether, at -5 °C, for 12 h. ^b Isolated yields. ^c The *ee* value was determined by chiral HPLC. ^d The enone is 3-(4-fluoro-phenyl)-1-pyridin-2-yl-propenone.

With the optimized conditions in hand, the substrate scope of the Py-BINMOL-Mg for the synthesis of aromatic β -cyano ketones **2** was investigated. In general, various chalcones bearing electron-rich and electron-deficient substituents exhibited good yields (up to 91% yield) and moderate to good enantioselectivities (up to 92% *ee*). As shown in Table 2, the presence of methyl, halide, methoxyl, trifluoromethyl, and phenyl groups in the chalcones allowed the 1,4-conjugate addition of cyanide to the exclusive formation of aromatic β -cyano ketone **2** in good yields. However, the introduction of nitro-group on chalcones led to significant erosion of yield or no reaction, which revealed the negative effect of nitro group in the bifunctional Py-BINMOL-Mg complex-catalysed conjugate addition of TMSCN to chalcones because of the competing coordination of nitro and carbonyl group of enone during the activation of substrate with catalyst.

On the basis of the experimental results, a plausible catalytic activity for this conjugate addition is depicted in Scheme 2. Similarly to the previous report,¹⁷ we assumed that the chiral ligand, Py-BINMOL, exhibited the strong non-covalent interaction similarly to that of Ar-BINMOLs, leading to the existence of dimeric supramolecular structure. The dimer of Py-BINMOL would act as a

possible supramolecular catalyst with unique functionality. Thus as shown in Scheme 2, Py-BINMOL (**L1**) containing two different type of H-donors might result in dimer with unique functionality due to the intramolecular hydrogen bonding interaction between alcohol and pyridine, which gave the dimeric magnesium complex (**Ia**) in the presence of MgBu₂.



Scheme 2. Proposed mechanism for Py-BINMOL-Mg catalysed hydrocyanation

To gain the support for the characteristics of supramolecular dimers, we made use of electrospray ionization mass spectrometry (ESI-MS).¹⁸ In the cationic ESI-MS spectra of the mixture of Py-BINMOL with MgBu₂, we “fished” the important intermediate signal for the dimeric magnesium complex (Figure S1, see Supporting Information), for intermediate **Ia**, $m/z = 776.6$ (the theoretical molecular weight of Mg-Py-BINMOL, $m/z = 776.2526$). In addition, the experimental result of the nonlinear study¹⁹ by variation of the optical purity of the Py-BINMOL **L1**, graphically depicted in Table S2 and Figure S1 (See ESI) clearly demonstrated that no spectacular NLE was presented. In this case, slight negative nonlinear effect can be exhibited in the presence of Mg-Py-BINMOL system, in which a possible complex with one Mg-center is preferentially involved in the stereochemical rate-determining step of the stereoselective 1,4-conjugate addition reaction.¹⁷ Notably, on the basis of DFT calculation (Figure S5 and Figure S6 of ESI),²⁰ the formation of intermediate **Ia** was more possibly than that of intermediate **Ib**. Therefore, we can conclude that the magnesium complex would be probably generated from two molecules of chiral ligand **L1** and magnesium based on the experimental results. And then the TMSCN could be activated by the *para*-nitrophenol and magnesium complex. The proposed intermediate (**II**) is believed to involve the hypervalent coordination between silicon and functional *N,O*-group,²¹ in which it could be a vital factor in assisting the Si-C bond cleavage (TMS-CN) with aid of *para*-nitrophenol. In fact, we also observed a major peak at $m/z = 920.5$ (Figure S1, see ESI), which could be identified as the silylated magnesium complex came from the cation [2Py-BINOL + Mg + 2TMS]⁺ ($m/z = 920.3$). Although other oligomeric intermediates could still be probably effective in this reaction, we suggested the activated model (**III**) derived from the magnesium complex and substrate (chalcone) might be reasonable. In this case, the dimeric Py-BINMOL-magnesium complex might

provide an asymmetric environment around the substrate to give a promising enantioselectivity.

Conclusions

In summary, the Mg-catalysed conjugate addition of TMSCN to chalcones has been achieved successfully by using multifunctional Py-BINMOL bearing both axial and sp^3 -central chirality¹³ as chiral ligand, in which the corresponding aromatic β -cyano ketones were obtained in moderate to good enantioselectivities (up to 92% *ee*) and good yields (up to 91% yield). In comparison to previous work, a noteworthy feature of the new catalyst system is the dual-mode coordination in the possibly diverse supramolecular structure, which enabled the transition-metal-free hydrocyanation to undergo stereospecific addition by dual action of TMSCN and chalcone respectively. Although the results were not perfect in term of enantioselectivity, the new finding regarded to the multifunctional ligand and main group element as catalyst is very useful for the development of biomimetic catalysis and environmentally benign process with non-toxic catalyst.

Financial support by the NFSC (No. 21173064 and 21472031) and Zhejiang Provincial Natural Science Foundation of China (LR14B030001) is appreciated.

Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

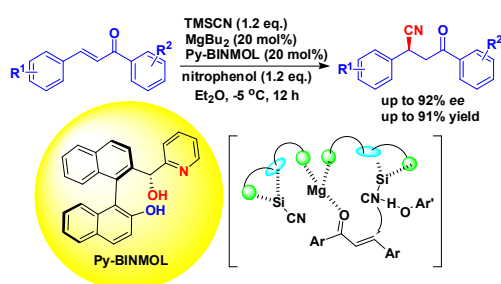
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Graphical Abstract

Enantioselective Conjugate Addition of Cyanide to Chalcones

Catalyzed by Magnesium-Py-BINMOL Complex

Cheng Dong, Tao Song, Xing-Feng Bai, Yu-Ming Cui, Zheng Xu, and Li-Wen Xu*



An efficient asymmetric conjugate addition of trimethylsilyl cyanide (TMSCN) to chalcones, catalyzed by bifunctional Py-BINMOL-Mg complex, with moderate to good enantioselectivities and good yields, has been realized in this work.