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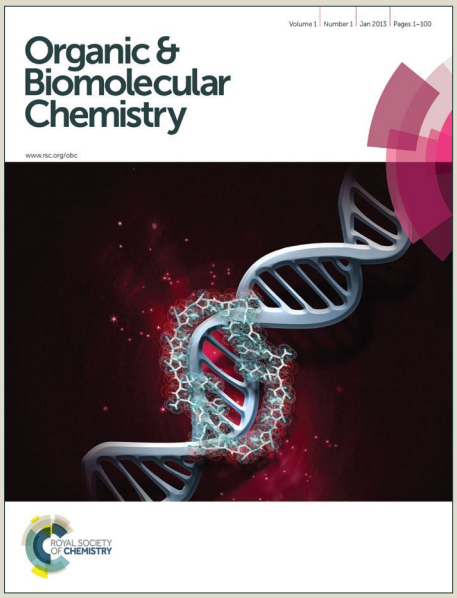

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A Ni-PyBisulidine complex for the asymmetric hydrophosphonylation of aldehydes

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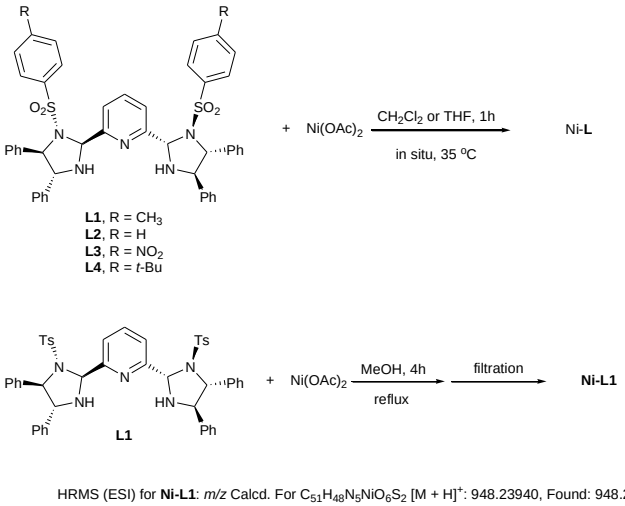
A novel Ni-PyBisulidine complex has been developed for the asymmetric hydrophosphonylation of aldehydes. A variety of aromatic, heteroaromatic, condensed-ring, α,β-unsaturated, and aliphatic aldehydes are found to be suitable substartes for the reaction, and the desired α-hydroxy phosphonates are obtained in up to 99% yield and 97% ee.

Chiral α-hydroxy phosphonates and phosphonic acids usually show potent biological activity.[1] The asymmetric hydrophosphonylation of aldehydes is a powerful and direct reaction for forming α-hydroxy phosphonates.[2] Since the first asymmetric hydrophosphonylation by Shibuya group[3] in 1993 and the first highly enantioselective hydrophosphonylation by Shibasaki group[4] using a BINOL-derived heterometallic complex (BINOL = 1,1'-bi-2-naphthol) in 1996, various types of catalyst systems, containing metal complexes (such as Ti,[5] Al,[6] Yb,[7] Zn,[8] Fe,[9] Cu[10]), and organocatalysts[11] have been studied. Although great progress has been achieved, developing new catalysts for the enantioselective hydrophosphonylation of aldehydes is still challenging and interesting. Recently, a novel sulfonylated pyridine bisimidazolidine (PyBisulidines) ligand was reported and exploited in Fe-catalyzed dehydrogenative α-oxygenation of ethers and selective oxidation of olefins to carbonyls by Xiao group.[12] We hypothesized that this PyBisulidine ligand would afford a high level of chiral induction in the hydrophosphonylation of aldehydes for the bulky, flexible Pyridine bisimidazolidine (PyBidine)[13] skeleton and the electron-withdrawing group. Herein, we present a highly efficient asymmetric hydrophosphonylation of aldehydes catalyzed by Ni-PyBisulidines (Scheme 1). [14]

Initially, PyBisulidine **L1** reacted in situ with various metal acetates to form complexes that catalyze the asymmetric hydrophosphonylation of benzaldehyde (Table 1, entries 1-8). Complex Ni-**L1** catalyzed the reaction smoothly, giving the desired product with 87% *ee* (Table 1, entry 1). Complex Zn-**L1**, Co-**L1** and Mn(II)-**L1** could promoted the conversation with moderate enantioselectivity (Table 1, entries 2, 3 and 8). When Fe(II), Pd(II), Cu(I), Cu(II) were used as the central metal, the low chiral induction was observed (Table 1, entries 4-7). Subsequently, the benzenesulfonyl moiety of the ligands was examined (Table 1, entries 1, 9-11). Different substituent on the benzenesulfonyl provided different reactivity while the substituent hardly affected the enantioselectivity. Considering the reactivity and economy, **L1** was selected for further optimization.

A survey of various solvents revealed that chlorinated hydrocarbons showed a strong solvent effect (Table 2, entries 1-6). Chloroform provided the best enantioselectivity and CH_2ClCH_2Cl gave the best reactivity. CH_2Cl_2 was found to be favourable considering the reactivity and enantioselectivity



HRMS (ESI) for **Ni-L1**: *m/z* Calcd. For $C_{51}H_{48}N_5NiO_6S_2$ [M + H]$^+$: 948.23940, Found: 948.23941

Scheme 1 Syntheses of Ni-PyBisulidine complexes.

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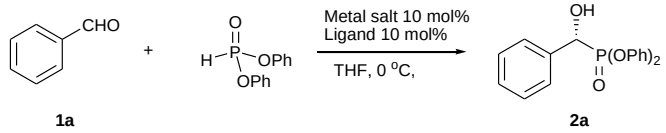
Table 1 The Screening of metals and ligands for the hydrophosphonylation of benzaldehyde[a]

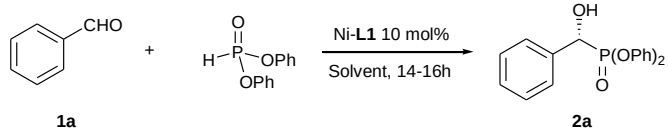


1a **2a**

Entry	Metal salts	Ligand	Time (h)	Yield (%)[b]	ee (%)[c]
1	$Ni(OAc)_2$	**L1**	16	98	87
2	$Zn(OAc)_2$	**L1**	20	43	55
3	$Co(OAc)_2$	**L1**	20	75	50
4	$Fe(OAc)_2$	**L1**	20	52	11
5	$Pd(OAc)_2$	**L1**	20	14	10
6	CuOAc	**L1**	20	22	2
7	$Cu(OAc)_2$	**L1**	20	10	0
8	$Mn(OAc)_2$	**L1**	20	90	50
9	$Ni(OAc)_2$	**L2**	40	94	84
10	$Ni(OAc)_2$	**L3**	14	98	87
11	$Ni(OAc)_2$	**L4**	40	88	88

[a] The reactions were carried out on a 0.2 mmol scale (benzaldehyde) with diphenylphosphite (0.24 mmol) in THF (1.0 mL) in the presence of metal-PyBisulidines prepared in situ. [b] Isolated yield. [c] Enantiomeric excesses were determined by HPLC analysis on a Chiralcel OD-H column; the absolute configuration was established as R by comparison with literature data.[11d,11e]

Table 2 Further optimization of reaction conditions[a]



1a **2a**

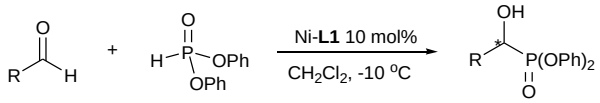
Entry	Solvent	The molar ratio of benzaldehyde and diphenylphosphite	T (°C)	Yield (%)[b]	ee (%)[c]
1	THF	1 : 1.2	0	98	87
2	MeOH	1 : 1.2	0	97	83
3	Toluene	1 : 1.2	0	88	91
4	CH_2Cl_2	1 : 1.2	0	90	93
5	$CHCl_3$	1 : 1.2	0	66	95
6	CH_2ClCH_2Cl	1 : 1.2	0	99	92
7	CH_2Cl_2	1 : 1	0	90	93
8[d]	CH_2Cl_2	1 : 1	0	98	93
9[d]	CH_2Cl_2	1 : 1	-10	92	95
10[d,e]	CH_2Cl_2	1 : 1	-10	92	95

[a] Unless otherwise noted, the reactions were performed with Ni-**L1** complex prepared in situ on a 0.2 mmol (benzaldehyde) in 1.0 mL solvent. [b] isolated yield. [c] Enantiomeric excesses were determined by HPLC analysis. [d] 0.4 mmol benzaldehyde was used. [e] The Ni-**L1** complex was pre-prepared in MeOH by filtration. For details, see supporting information.

(Table 2, entry 4 vs. entries 5 and 6). The molar ratio of benzaldehyde and diphenylphosphite could reduce to 1:1 without any loss of the reactivity and enantioselectivity (Table 2, entry 7 vs. 4). Furthermore, increasing the concentration of the benzaldehyde from 0.2 M to 0.4 M led to higher reactivity and the same enantioselectivity (Table 2, entry 8 vs. 7).[15] The improving enantioselectivity was obtained when reducing the reaction temperature from 0 °C to -10 °C with a slightly decreased reactivity (Table 2, entry 9 vs. entry 8). It should be note that the process is air and moisture tolerant.

In addition, the present Ni-**L1** complex could be pre-prepared in MeOH by filtration (Scheme 1). The complex prepared in situ and the complex pre-prepared provided the same results (Table 2, entry 9 vs. 10). The using of pre-prepared catalyst could greatly facilitate the operation. Substrate scope in Table 3 was investigated using the pre-prepared complex.[16] To gain some insight into the complex, ESI-HRMS analyses of the Ni-**L1** complex was carried out. The spectrum displayed the ion at *m/z* 948.23941, which corresponded to NiOAc/**L1** (Calcd. For $C_{51}H_{48}N_5NiO_6S_2$, $[Ni(OAc)_2 + M_{L1} - HOAc + H]^+$: 948.23940).[17]

Table 3 Substrate scope of the catalytic asymmetric hydrophosphonylation of aldehydes[a]



1 **2**

Entry	R	Product	Time (h)	Yield (%)[b]	ee (%)[c]
1	Ph	**2a**	14	92	95 (*R*)[d]
2	2-MeC_6H_4	**2b**	22	93	96
3	3-MeC_6H_4	**2c**	41	99	95
4	4-MeC6H4	**2d**	33	99	95 (*R*)[d]
5	4-$CF_3C_6H_4$	**2e**	10	95	95
6	4-FC_6H_4	**2f**	48	93	90
7	4-BrC_6H_4	**2g**	39	94	95 (*R*)[d]
8	4-ClC_6H_4	**2h**	37	98	95 (*R*)[d]
9	2-thienyl	**2i**	40	99	95
10	2-furyl	**2j**	41	98	91
11	1-naphthyl	**2k**	41	90	97 (*R*)[d]
12	2-naphthyl	**2l**	44	99	96
13	PhCH=CH	**2m**	40	91	93
14	Cyclohexyl	**2n**	36	99	71 (*S*)[d]
15	$CH_3(CH_2)_2$	**2o**	29	87	79
16	$CH_3(CH_3)_4$	**2p**	36	99	81

[a] The reactions were carried out: aldehyde (0.2 mmol), diphenylphosphite (0.2 mmol), 0.5 mL CH_2Cl_2; the catalyst was pre-pared in MeOH by filtration. [b] Isolated yield. [c] Enantiomeric excesses were determined by HPLC analysis. [d] The absolute configurations were determined by comparison with literature data.[11d,11e]

With the optimized reaction conditions in hand, the substrate scope was explored. The results were summarized in Table 3. No matter aryl aldehydes with an *ortho* substituent or a *meta* substituent or a *para* substituent or an electron-withdrawing substituent as well as heteroaryl aldehyde afforded the corresponding product in excellent yields with excellent enantioselectivities (Table 3, entries 1-10). The bulkier aldehydes, such as 1-naphthaldehyde and 2-naphthaldehyde, also gave excellent results (Table 3, entries 11 and 12). The α,β-unsaturated aldehyde, cinnamaldehyde, gave product **2m** with excellent yield and *ee* (Table 3, entry 13). The aliphatic aldehydes showed reduced enantioselectivity, in which the nonbranched aliphatic aldehydes gave higher ee than branched aliphatic aldehydes (Table 3, entries 14-16).

Although the detailed reaction mechanism remains unclear, the proposed transition state for the reaction using Ni-**L1** as the catalyst is shown in Figure 1.[18] The benzaldehyde coordinated to the chiral Ni(II) catalyst in the equatorial position by avoiding the steric repulsion of PyBisulidine (TS1 vs TS2 and TS3, Figure 1). Coordination of oxygen in phosphite to Ni(II) and the deprotonation of phosphite affords the phosphonates, which attacks to the aldehyde in the coordination sphere of chiral Ni-PyBisulidine salt and leads to chiral addition products.

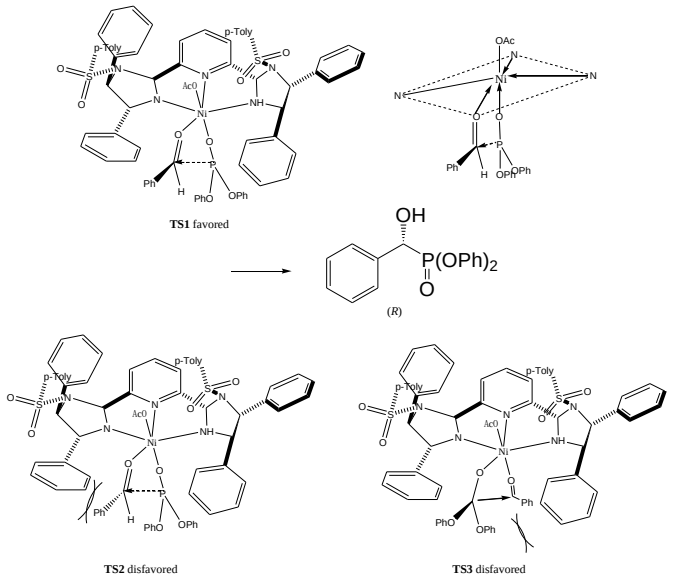


Figure 1 The Proposed mechanistic hypothesis.

Conclusions

We have developed a new chiral Ni-PyBisulidine (sulfonylated pyridine bisimidazolidine) complex for the asymmetric hydrophosphonylation of aldehydes. Various α-hydroxy phosphonates were obtained in good to excellent yields with moderate to excellent enantioselectivities. It is a more environmentally friendly method for the synthesis of α-hydroxy aromatic phosphonates, because of the excellent yields and enantioselectivities of aromatic aldehydes as well as the 1:1 molar ratio of aldehydes and diphenylphosphite. The pathway was air-tolerant and easily manipulated. Further investigations are underway in our laboratory for the detailed mechanism and the application of the desired catalyst to other reactions.

Acknowledgements

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