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Enantioselective vinylation of aldehydes with the vinyl Grignard reagent catalyzed by magnesium complex of chiral BINOLs

Pei Wang[1] | Guo-Rong Ma[1] | Sheng-Li Yu[2] | Chao-Shan Da[2,3]

[1]School of Basic Medical Sciences, Ningxia Medical University, Yinchuan, China

[2]Institute of Biochemistry and Molecular Biology, School of Life Sciences, Lanzhou University, Lanzhou, China

[3]State Key Laboratory of Organic Chemistry, Lanzhou University, Lanzhou, China

Correspondence
Pei Wang, School of Basic Medical Sciences, Ningxia Medical University, Yinchuan 750004, China.
Email: wangp13@lzu.edu.cn

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Abstract

Enantioselective vinylation of aldehydes via direct catalytic asymmetric Grignard reaction of aldehdyes and the vinyl Grinard reagent is a long-standing challenge. This work demonstrated that the magnesium (*S*)-3,3′-dimethyl BINOLate enantioselectively catalyze the direct vinylation of aldehydes with the deactivated vinylmagnesium bromide by bis(2-[*N*,*N*′-dimethylamino]ethyl) ether (BDMAEE) in the addition of *n*-butylmagnesium chloride. The highest ee of 63% was achieved up to date.

KEYWORDS

asymmetric catalysis, BINOL, deactivation, Grignard reaction, vinylation

1 | INTRODUCTION

Grignard reagents are among the most useful and important organic metal reagents. The addition of Grignard reagents to aldehydes is commonly used cost-effective methodology to construct secondary alcohols via carbon–carbon bond formation. Because of greatly reactive, however, the catalytic asymmetric addition of Grignard reagents to aldehydes is typically challenging.[1-10] Only recently successful strategies were developed in access to highly enantiopure secondary alcohols via catalytic asymmetric Grignard reactions.[11-13] The groups of Harada,[14-16] Xu,[17,18] and Yus[19,20] utilized superstoichiometric Ti (O*i*-Pr)$_4$ to transmetallate RMgX (Br, Cl) to less reactive R-Ti (O*i*-Pr)$_3$, and then R-Ti (O*i*-Pr)$_3$ highly enantioselectively delivered R group to aldehydes catalyzed by chiral diol-Ti (O*i*-Pr)$_2$ complexes. Our group demonstrated that the additive bis([2-[*N*,*N*′-dimethylamino)]thyl) ether (BDMAEE) effectively deactivated the reactivity of Grignard reagents and then similarly transmetallated R functional group of RMgBr to R-Ti (O*i*-Pr)$_3$ by using stoichiometric Ti (O*i*-Pr)$_4$.[21-27] The complex of chiral BINOL-Ti (O*i*-OPr)$_2$ or H$_8$-BINOL-Ti (O*i*-OPr)$_2$ highly catalyzed the enantioselective delivery of R group to aldehydes. Irrespective of the impressive advancement of catalytic alkylation and aromatization of aldehydes with Grignard reagents, the catalytic enantioselective vinylation of aldehydes to produce enaniopure allyl alcohols are far from exploration.

Only two examples were dispersed in the literature. In the first example, stoichiometric chiral BINOL-modified divinylmagnesium was used, and only 12% of enantioselectivity was afforded (Equation 1, Scheme 1).[28] In the second examples, we also investigated deactivated vinylmagnesium bromide with BDMAEE, but low 33% of enantioselectivity was achieved by using substoichiometric chiral catalyst (Equation 2, Scheme 1).[21] The desired and challenging highly enantioselective vinylation of aldehydes hopes novel strategy.

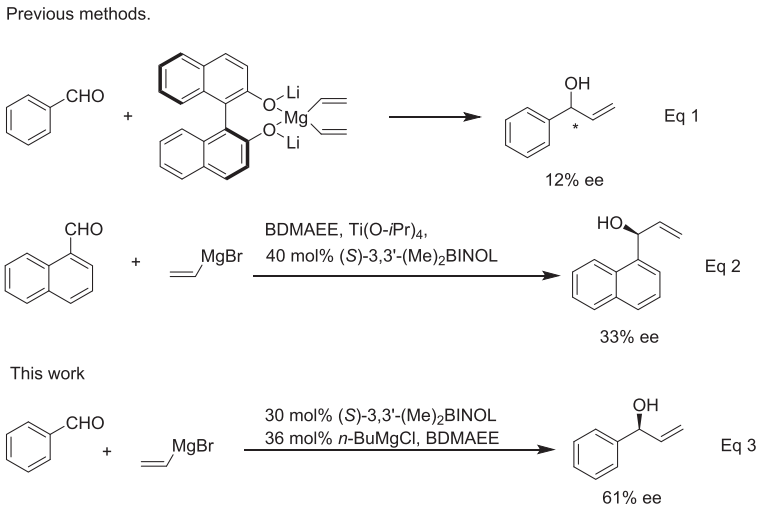
Chiral allylic secondary alcohols are key structural motifs in a considerable number of natural products and pharmaceutically active compounds[29-33] and an important class of indispensable precursors of a wide range of organic transformations.[34-40] These chiral building blocks are typically achieved by enzymatic or nonenzymatic kinetic resolution of the corresponding racemic compounds,[41-44] vinylation of aldehydes with less reactive vinyl metal reagents vinyl zinc,[45-49] silane,[50-52] boron,[53-55] bismuthine,[56] and aluminum[57] and hydroxylation via asymmetric allylic substitution.[58-62] Only Oppolzer and coworker observed the simplest asymmetric vinylation of aldehydes with divinylzinc.[34] And while these methods successfully affording highly enantiopure allylic alcohols, their practicality was significantly hampered by cost-effectiveness. Herein, we firstly reported direct catalytic asymmetric vinylation of aldehydes catalyzed chiral magnesium BINOlate (Equation 3, Scheme 1).

2 | MATERIALS AND METHODS

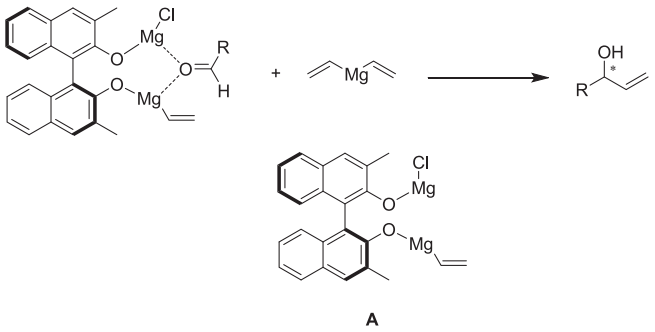
All reactions were performed under an argon atmosphere, and solvents were dried according to established procedures prior to use. All of the reagents were commercial. Reactions were monitored by thin-layer chromatography (TLC); column and preparative TLC purification were carried out using silica gel. Melting points were recorded on an X-4 melting point apparatus and are uncorrected. Optical rotations were recorded on a polarimeter. ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were measured on 200 and 100 MHz spectrometers, respectively, in $CDCl_3$ with TMS as an internal standard; chemical shifts are reported in parts per million. The determination of ee values was carried out using chiral high-performance liquid chromatography (HPLC) with an OD-H, OJ-H, or AS-H column.

2.1 | General procedure for the catalytic asymmetric vinylation of aldehydes

Ligand **L6** (0.15 mmol, 47.1 mg) and 2.0 mL of dry methyl *t*-butyl ether (MTBE) were introduced into a dry 10-mL round bottom flask A equipped with a clean stir bar under an argon atmosphere. *n*-BuMgCl (0.18 mmol, 0.2 mL) was slowly added to the flask A at 0°C, and the mixture was stirred for 1 hour. The vinyl Grignard reagent (2.14 mL, 1.5 mmol) and 7.56 mL of dry MTBE were introduced into another dry 25 mL round bottom flask B equipped with a clean stir bar under an argon atmosphere. Bis(2-[*N,N′*-dimethylamino]ethyl) ether (BDMAEE) (282 μL, 1.5 mmol) was slowly added to flask B at 0°C, and the mixture was stirred 1.5 hours. Benzaldehyde (54 μL, 0.5 mmol) was added to the flask A. After 0.5 hour, the supernatant (6.0 mL, ~1.0 mmol) of flask B was slowly added to the flask A for 30 minutes at −20°C. The mixture was warmed to 0°C and stirred for 5 hours. The reaction was quenched with 1 N HCl at 0°C and extracted with ethyl acetate (5 mL x 3). The



SCHEME 1 The asymmetric vinylation of aldehydes with the vinyl Grignard reagent



SCHEME 2 The possible reaction process

combined organic layer was washed with saturated brine and dried over Na_2SO_4, filtered, and concentrated. The residue followed by flash column chromatography (Petroleum ether: ethyl acetate = 10:1) to give desired products.

2.1.1 | (*S*)-1-phenylprop-2-en-1-ol (3a)[28]

Yield 49.8 mg; 47% yield, 61% ee; $[\alpha]_D^{20} = -3.8$ (c 0.8, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.37 to 7.25 (m, 5H), 6.13 to 5.97 (m, 1H), 5.38 to 5.17 (m, 3H); enantiometric excess was determined by HPLC with a Chiralpak OD-H column 1.0 mL/min, (2-propanol: hexane = 5:95), minor enantiomer t_r = 8.2 minutes, major enantiomer t_r = 9.9 minutes.

2.1.2 | (*S*)-1-(naphthalen-1-yl)prop-2-en-1-ol (3b)[14]

68% yield, 57% ee; $[\alpha]_D^{20} = -14$ (c 1.1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 8.19–8.16 (m, 1H), 7.89 to 7.78 (m, 2H), 7.63 to 7.42 (m, 4H), 6.32 to 6.16 (m, 1H), 5.93 (m, 1H), 5.48 to 5.25 (m, 2H); enantiometric excess was determined by HPLC with a Chiralpak OD-H column 1.0 mL/min, (2-propanol: hexane = 10:90), major enantiomer t_r = 9.4 minutes, minor enantiomer t_r = 15.3 minutes.

2.1.3 | (*S*)-1-(naphthalen-2-yl)prop-2-en-1-ol (3c)[29]

66% yield, 35% ee; $[\alpha]_D^{20} = +2.0$ (c 1.3, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.84 to 7.81 (m, 4H), 7.49 to 7.45 (m, 3H), 6.20 to 6.03 (m, 1H), 5.44 to 5.20 (m, 3H); enantiometric excess was determined by HPLC with a Chiralpak AS-H column 1.0 mL/min, (2-propanol: hexane = 3:97), minor enantiomer t_r = 15.4 minutes, major enantiomer t_r = 17.7 minutes.

2.1.4 | (*S*)-1-(4-chlorophenyl)prop-2-en-1-ol (3d)[29]

49% yield, 42% ee; $[\alpha]_D^{20} = -5.0$ (c 0.4, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.31–7.26 (m, 4H), 6.09 to 5.92 (m, 1H), 5.38 to 5.18 (m, 3H); enantiometric excess was determined by HPLC with a Chiralpak OJ-H column 1.0 mL/min, (2-propanol: hexane = 5:95), major enantiomer t_r = 14.6 minutes, minor enantiomer t_r = 15.9 minutes.

2.1.5 | (*S*)-1-(4-(trifluoromethyl)phenyl) prop-2-en-1-ol (3e)[29]

41% yield, 48% ee; $[\alpha]_D^{20} = -9.4$ (c 0.32, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.64 to 7.26 (m, 4H), 6.10 to 5.93 (m, 1H), 5.42 to 5.22 (m, 3H); enantiometric excess was determined by HPLC with a Chiralpak OJ-H column 1.0 mL/min, (2-propanol: hexane = 5:95), major enantiomer t_r = 14.0 minutes, minor enantiomer t_r = 15.3 minutes.

2.1.6 | (*S*)-1-(p-tolyl)prop-2-en-1-ol (3f)[28]

43% yield, 42% ee; $[\alpha]_D^{20} = -11.8$ (c 0.34, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.28 to 7.14 (m, 4H), 6.12 to 5.96 (m, 1H), 5.38 to 5.15 (m, 3H), 2.34 (s, 3H), 2.03 (s, 1H); enantiometric excess was determined by HPLC with a Chiralpak OJ-H column 1.0 mL/min, (2-propanol: hexane = 5:95), major enantiomer t_r = 16.3 minutes, minor enantiomer t_r = 20.7 minutes.

2.1.7 | (*S*)-1-(m-tolyl)prop-2-en-1-ol (3g)[34]

45% yield, 46% ee; ^1H NMR (200 MHz, $CDCl_3$): δ 7.28 to 7.08 (m, 4H), 6.13 to 5.96 (m, 1H), 5.39 to 5.16 (m, 3H), 2.35 (s, 3H), 2.00 (s, 1H); enantiometric excess was determined by HPLC with a Chiralpak OD-H column 1.0 mL/min, (2-propanol: hexane = 3:97), minor enantiomer t_r = 11.1 minutes, major enantiomer t_r = 15.1 minutes.

2.1.8 | (*S*)-1-(o-tolyl)prop-2-en-1-ol (3h)[28]

46% yield, 30% ee; ^1H NMR (200 MHz, $CDCl_3$): δ 7.46 to 7.43 (m, 1H), 7.23 to 7.17 (m, 3H), 6.12 to 5.95 (m, 1H), 5.42 to 5.18 (m, 3H), 2.36 (s, 1H), 1.92 (s, 1H); enantiometric excess was determined by HPLC with a Chiralpak OD-H column 1.0 mL/min, (2-propanol: hexane = 3:97), minor enantiomer t_r = 12.0 minutes, major enantiomer t_r = 13.6 minutes.

2.1.9 | (*S*)-1-(2-(trifluoromethyl)phenyl) prop-2-en-1-ol (3i)[34]

43% yield, 47% ee; $[\alpha]_D^{20} = -11.8$ (c 0.47, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.75 to 7.26 (m, 4H), 6.12 to 5.95 (m, 1H), 5.66 (m, 1H), 5.43 to 5.19 (m, 2H); enantiometric excess was determined by HPLC with a Chiralpak OD-H column 1.0 mL/min, (2-propanol: hexane = 3:97), minor enantiomer t_r = 9.5 minutes, major enantiomer t_r = 10.3 minutes.

2.1.10 | (*S*)-1-(2-chlorophenyl)prop-2-en-1-ol (3j)[45]

57% yield, 63% ee; $[\alpha]_D^{20} = -6.0$ (c 0.38, $CHCl_3$);^1H NMR (200 MHz, $CDCl_3$): δ 7.55 to 7.18 (m, 4H), 6.12 to 5.95 (m, 1H), 5.64 (m, 1H), 5.43 to 5.20 (m, 2H); enantiometric excess was determined by HPLC with a Chiralpak OD-H column 1.0 mL/min, (2-propanol: hexane = 3:97), minor enantiomer t_r = 11.3 minutes, major enantiomer t_r = 13.8 minutes.

2.1.11 | (*S*)-1-(2-bromophenyl)prop-2-en-1-ol (3k)[29]

51% yield, 47% ee; $[\alpha]_D^{20} = -25.0$ (c 0.42, $CHCl_3$);^1H NMR (200 MHz, $CDCl_3$): δ 7.55 to 7.11 (m, 4 H), 6.11 to 5.95 (m, 1 H), 5.61 (m, 1 H), 5.44 to 5.21 (m, 2 H); enantiometric excess was determined by HPLC with a Chiralpak OD-H column 1.0 mL/min, (2-propanol: hexane = 3:97), minor enantiomer t_r = 12.0 minutes, major enantiomer t_r = 15.8 minutes.

2.1.12 | (*S*)-1-(thiophen-3-yl)prop-2-en-1-ol (3l)[41]

27% yield, 34% ee; $[\alpha]_D^{20} = -19.0$ (c 0.26, $CHCl_3$);^1H NMR (200 MHz, $CDCl_3$): δ 7.33 to 7.06 (m, 3H), 6.17 to 6.00 (m, 1H), 5.61 (m, 1H), 5.40 to 5.19 (m, 3H); enantiometric excess was determined by HPLC with a Chiralpak OD-H column 1.0 mL/min, (2-propanol: hexane = 3:97), major enantiomer t_r = 26.3 minutes, minor enantiomer t_r = 34.4 minutes.

2.1.13 | (*S,E*)-1-phenylpenta-1,4-dien-3-ol (3m)[50]

33% yield, 27% ee; $[\alpha]_D^{20} = -5.6$ (c 0.9, $CHCl_3$);^1H NMR (200 MHz, $CDCl_3$): δ 7.41 to 7.24 (m, 5H), 6.66 to 6.58 (m, 1H), 6.29 to 6.18 (m, 1H), 6.07 to 5.90 (m, 1H), 5.38 to 5.17 (m, 1H), 4.82 to 4.80 (m, 1H); enantiometric excess was determined by HPLC with a Chiralpak AS-H column 1.0 mL/min, (2-propanol: hexane = 3:97), minor enantiomer t_r = 12.6 minutes, major enantiomer t_r = 14.5 minutes.

2.1.14 | (*S*)-5-phenylpent-1-en-3-ol (3n)[53]

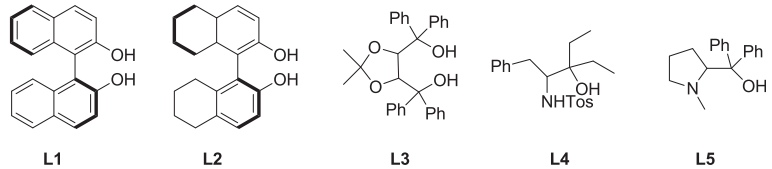
35% yield, 40% ee; $[\alpha]_D^{20} = -5.0$ (c 1.0, $CHCl_3$);^1H NMR (200 MHz, $CDCl_3$): δ 7.32 to 7.18 (m, 5H), 5.99 to 5.82 (m, 1H), 5.28 to 5.11 (m, 2H), 4.14 to 4.11 (m, 1 H), 2.77 to 2.67 (m, 2H), 1.91 to 1.80 (m, 2H); enantiometric excess was determined by HPLC with a Chiralpak OD-H column 1.0 mL/min, (2-propanol: hexane = 3:97), minor enantiomer t_r = 18.2 minutes, major enantiomer t_r = 27.1 minutes.

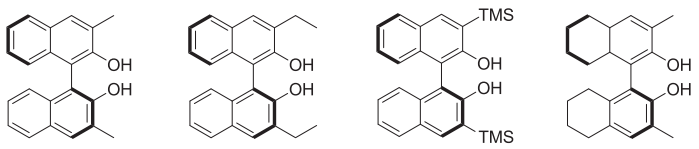
3 | RESULTS AND DISCUSSION

Based upon previous results, BDMAEE was similarly used to deactivate vinylmagnesium bromide (CH_2 = CHMgBr) in this work. A class of chiral Ligands **L2**-**L9** were synthesized except the commercially available (*S*)-BINOL (**L1**). **L1** was initially examined, and BDMAEE was added to deactivate the reactivity of CH_2 = CHMgBr in dichloromethane, and it obtained very low ee of 8% with modest yield (Table 1, entry 1). The smaller dihedral angle H_8-BINOL (**L2**) obtained similar result (entry 2). While TADDOL was used, yield increased accompanying with the slightly reduced ee (entry 3). Unfortunately, chiral amine **L4** and **L5** only obtained racemic allylic alcohol. The 3,3′-bissubstituted BINOLs **L6** and **L7** and (*S*)-3,3′-dimethyl H_8-BINOL **L9** as ligands were observed but the results were still unsatisfactory (entries 6-9), and the highest ee of 13% was afforded with **L6** (entry 6). Another additive was then intended to increase the enantioselectitivty, and a series of metal reagents was examined with **L6** (entries 10-14). Regretfully, only *n*-BuMgCl afforded slightly improved ee of 18% (entry 10). Then, solvents were observed, and THF and methyl *tert*-butyl ether (MTBE) obtained the highest enantioselectivity (28%) and MTBE obtained higher yield than THF (entries 10 and 16–18). Then, the amount of **L6** and *n*-BuMgCl was optimized, and the highest 60% of enantioselectivity was obtained (entries 16-25), indicating a possible chloride Grignard reagent complex **A** (Scheme 2) effectively catalyzing the asymmetric vinylation of aldehydes with the vinyl Grignard reagent.

In order to test the role of the magnesium additive, other magnesium salts were evaluated. When $MgBr_2$ and $MgCl_2$ was respectively added the reaction as additive, the adduct ee dramatically decrease (entries 26-27). Considering Grignard reagent acitivity, *n*-BuMgCl was replaced with *n*-BuMgBr, resulted in noticeable decreases in enantioselectivity (entry 28). Having a small amount chloride anion in reaction system might facilitate halide metathesis in the vinyl Grignard leading to a less reactive vinylmagnesium chloride. To verify this possibility, we

TABLE 1 Optimization of reaction conditions[a, e]





Entry	Ligand (Mol%)	Additive (Mol%)	Solvent	Yield%[b]	ee%[c]
1	**L1** (15)	-	CH_2Cl_2	47	8
2	**L2** (15)	-	CH_2Cl_2	48	6
3	**L3** (15)	-	CH_2Cl_2	64	4
4	**L4** (15)	-	CH_2Cl_2	43	<1
5	**L5** (15)	-	CH_2Cl_2	45	<1
6	**L6** (15)	-	CH_2Cl_2	49	13
7	**L7** (15)	-	CH_2Cl_2	47	9
8	**L8** (15)	-	CH_2Cl_2	48	6
9	**L9** (15)	-	CH_2Cl_2	45	10
10	**L6** (15)	*n*-BuMgCl (30)	CH_2Cl_2	48	18
11	**L6** (15)	Et_2AlCl (30)	CH_2Cl_2	39	<1
12	**L6** (15)	Al $(me)_3$ (30)	CH_2Cl_2	53	<1
13	**L6** (15)	$ZnEt_2$ (30)	CH_2Cl_2	47	<1
14	**L6** (15)	Ti $(Oi\text{-}Pr)_4$ (30)	CH_2Cl_2	-[d]	-[d]
15	**L6** (15)	Al $(Oi\text{-}Pr)_3$ (30)	CH_2Cl_2	49	<1
16	**L6** (15)	*n*-BuMgCl (30)	Toluene	43	22
17	**L6** (15)	*n*-BuMgCl (30)	THF	45	28
18	**L6** (15)	*n*-BuMgCl (30)	MTBE	47	28
19	**L6** (20)	*n*-BuMgCl (40)	MTBE	-[d]	45
20	**L6** (30)	*n*-BuMgCl (60)	MTBE	-[d]	50
21	**L6** (40)	*n*-BuMgCl (80)	MTBE	-[d]	48
22	**L6** (30)	*n*-BuMgCl (48)	MTBE	-[d]	55
23	**L6** (30)	*n*-BuMgCl (42)	MTBE	-[d]	58
24	**L6** (30)	*n*-BuMgCl (36)	MTBE	-[d]	60
25	**L6** (30)	*n*-BuMgCl (30)	MTBE	-[d]	58
26	**L6** (30)	$MgBr_2$ (36)	MTBE	45	14
27	**L6** (30)	$MgCl_2$ (36)	MTBE	46	16
28	**L6** (30)	*n*-BuMgBr (36)	MTBE	61	15

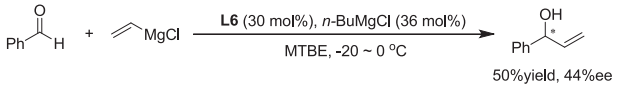
[a]Condition: benzaldehyde (0.5 mmol), vinylmagnesium bromide (1.0 mmol), solvent (5 mL), BDMAEE (1.0 mmol), −20 to 0°C.

[b]Isolated yield.

[c]Determined by chiral HPLC.

[d]Not determined.

[e]The complexing agent was optimized, and see supporting information for the result.

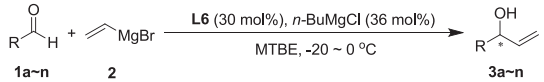


SCHEME 3 The asymmetric vinylation of benzaldehyde with vinylmagnesium chloride

used vinylmagnesium chloride as starting material, but enantioselectivity was not elevated, which was dropped to 44% (Scheme 3). Therefore, halide metathesis is not the main reason for enantioselectivity.

With the optimized reaction conditions, the scope of aldehydes for the Grignard reaction was examined. The results were collected into Table 2. The results show that various aldehydes are well suitable to this process. The electron-withdrawing and electron-donating groups in the benzene ring do not have remarkable effect on enantioselectivity of the reaction. Naphthaldehydes obtained good higher than 60% yield and modest enantioselectivity (Table 2, entries 2-3). 2-Chlorobenzaldehyde obtained the highest 63% enantioselectivity (entry 10). To the best of our knowledge, this is the highest enantioselectivity to date in the catalytic direct enantioselective addition of vinyl Grignard reagent. Heterocyclic aromatic aldehyde was also investigated, and it achieved low eantioselectivity of 34% as well as low 27% of yield (entry 12). The unsaturated aldehyde, ie, cinnamaldehyde, obtained relatively yield and enantioselectivitie (entry 13). Finally, the aliphatic aldehyde afforded yield of 35% and enantioselectivity of 40% (entry 14).

TABLE 2 Catalytic vinylation of aldehydes[a]



Entry	R	Allylic alcohol	Yield%[b]	ee%[c]
1	Ph	**3a**	47	61
2	1-naphthyl	**3b**	68	57
3	2-naphthyl	**3c**	66	35
4	4-cl-C_6H_4	**3d**	49	42
5	4-CF_3-C_6H_4	**3e**	41	48
6	4-me-C_6H_4	**3f**	43	42
7	3-me-C_6H_4	**3g**	45	46
8	2-me-C_6H_4	**3h**	46	30
9	2-CF_3-C_6H_4	**3i**	43	47
10	2-cl-C_6H_4	**3j**	57	63
11	2-Br-C_6H_4	**3k**	51	47
12	3-thiophene	**3l**	27	34
13	(*E*)-PhCH=CH	**3m**	33	27
14	$PhCH_2CH_2$	**3n**	35	40

[a]Condition: aldehyde (0.5 mmol), vinylmagnesium bromide (1.0 mmol), **L6** (0.15 mmol), MTBE (5 mL), *n*-BuMgCl (0.18 mmol), BDMAEE (1.0 mmol), −20 to 0°C for 5 hours.

[b]Isolated yield.

[c]Determined by chiral HPLC.

4 | CONCLUSION

In summary, a new catalytic direct enantioselective vinylation of aldehydes with vinyl Grignard reagent for preparing chiral allylic alcohols was demonstrated. Besides using BDMAEE as effective deactivating reagent, *n*-BuMgCl was found to be an indispensable additive in improving the enantioselectivity of the reaction. MTBE was the ideal solvent and (*S*)-3,3′-dimethyl-BINOL was the optimal ligand. The highest enantioselectivity is up to 63%, and to the best our knowledge, this is the highest enantioselectivity in the catalytic direct asymmetric addition of vinyl Grignard reagents to aldehydes. And this work is the first case to systematically observe the catalytic direct enantioselective vinylation of aldehydes with a vinyl Grignard reagent. This protocol does not need to transform the vinyl Grignard reagent into other less reactive organometal reagent. Therefore, this work demonstrates a cost-effective and operationally convenient method for the synthesis of chiral allylic alcohols.

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ORCID

Pei Wang https://orcid.org/0000-0002-4177-9167
Chao-Shan Da https://orcid.org/0000-0003-1306-4348

REFERENCE

1. Wakefield BJ (Ed). *Organomagnesium Methods in Organic Synthesis*. Academic Press: San Diego. CA; 1995.
2. Franzén RG. Utilization of Grignard reagents in solid-phase synthesis: a review of the literature. *Tetrahedron*. 2000;56(5):685-691.
3. Richey HG (Ed). *New Developments: Grignard Reagents*. Chichester, UK: Wiley; 2000.
4. Seebach D, Behrendt L, Felix D. Titanate-catalyzed enantioselective addition of dialkylzinc compounds-generated in situ from Grignard reagents in ether-to aldehydes. *Angew Chem Int Ed Engl*. 1991;30(8):1008-1009.

5. von dem Bussche-Hüennefeld JL, Seebach D. Enantioselective preparation of sec. Alcohols from aldehydes and dialkyl zinc compounds, generated in situ from Grignard reagents, using substoichiometric amounts of TADDOL-titanates. *Tetrahedron*. 1992;48(27):5719-5730.
6. Kim JG, Walsh PJ. From aryl bromides to enantioenriched benzylic alcohols in a single flask: catalytic asymmetricarylation of aldehydes. *Angew Chem Int Ed*. 2006;45:4175-4178. *Angew. Chem*. 2006; 118: 4281–4284
7. Côté A, Charette AB. General method for the expedient synthesis of salt-free diorganozinc reagents using zinc methoxide. *J Am Chem Soc*. 2008;130(9):2771-2773.
8. Soai K, Kawase Y, Oshio A. Enantioselective phenylation of prochiral aldehydes using a kinetically formed chiral complex between Grignard-zinc halide reagent and *N,N*-dibutylnorephedrine. *J Chem Soc, Perkin Trans*. 1991;1:1613-1615.
9. Hatano M, Mizuno T, Ishihara K. Catalytic enantioselective synthesis of sterically demanding alcohols using di(2°-alkyl) zinc prepared by the refined Charette's method. *Chem Commun*. 2010;46(30):5443-5445.
10. Hatano M, Mizuno T, Ishihara K. A concise synthesis of (*S*)-(+)-Ginnol based on catalytic enantioselective addition of commercially unavailable di(n-alkyl)zinc to aldehydes and ketones. *Synlett*. 2010;13:2024-2028.
11. Luderer MR, Bailey WF, Luderer MR, Fair JD, Dancer RJ, Sommer MB. Asymmetric addition of achiral organomagnesium reagents or organolithiums to achiral aldehydes or ketones: a review. *Tetrahedron: Asymmetry*. 2009;20(9):981-998.
12. Harada T. Development of highly active chiral titanium catalysts for the enantioselective addition of various organometallic reagents to aldehydes. *Chem Rec*. 2016;16(3):1256-1273.
13. Collados JF, Solà R, Harutyunyan SR, Maciá B. Catalytic synthesis of enantiopure chiral alcohols via addition of Grignard reagents to carbonyl compounds. *ACS Catal*. 2016;6(3):1952-1970.
14. Muramatsu Y, Harada T. Catalytic asymmetric alkylation of aldehydes with Grignard reagents. *Angew Chem Int Ed*. 2008;47:1088-1090. *Angew. Chem*. 2008; 120: 1104–1106
15. Muramatsu Y, Harada T. Catalytic asymmetric aryl transfer reactions to aldehydes with Grignard reagents as the aryl source. *Chem A Eur J*. 2008;14(34):10560-10563.
16. Muramatsu Y, Kanehira S, Tanigawa M, Miyawaki Y, Harada T. Catalytic enantioselective alkylation and arylation of aldehydes by using Grignard reagents. *Bull Chem Soc Jpn*. 2010;83(1):19-32.
17. Gao G, Bai XF, Yang HM, Jiang JX, Lai GQ, Xu LW. Ar-BINMOLs with axial and sp^3 central chirality-characterization, chiroptical properties, and application in asymmetric catalysis. *Eur J Org Chem*. 2011;2011(26):5039-5046.
18. Zheng LS, Jiang KZ, Deng Y, et al. Synthesis of Ar-BINMOL ligands by [1,2]-Wittig rearrangement to probe their catalytic activity in 1,2-addition reactions of aldehydes with Grignard reagents. *Eur J Org Chem*. 2013;2013(4):748-755.
19. Fernandez-Mateos E, Maciá B, Ramon DJ, Yus M. Catalytic enantioselective addition of MeMgBr and other Grignard reagents to aldehydes. *Eur J Org Chem*. 2011;2011(34):6851-6855.
20. Fernandez-Mateos E, Maciá B, Yus M. Catalytic enantioselective addition of alkyl Grignard reagents to aliphatic aldehydes. *Adv Synth Catal*. 2013;355(7):1249-1254.
21. Da CS, Wang JR, Yin XG, Fan XY, Liu Y, Yu SL. Highly catalytic asymmetric addition of deactivated alkyl Grignard reagents to aldehydes. *Org Lett*. 2009;11(24):5578-5581.
22. Liu Y, Da CS, Yu SL, et al. Catalytic highly enantioselective alkylation of aldehydes with deactivated Grignard reagents and synthesis of bioactive intermediate secondary arylpropanols. *J Org Chem*. 2010;75(20):6869-6878.
23. Liu XY, Wu X, Chai Z, Wu YY, Zhao G, Zhu SZ. Highly effective and recyclable dendritic ligands for the enantioselective aryl transfer reactions to aldehydes. *J Org Chem*. 2005;70(18):7432-7435.
24. Fan XY, Yang YX, Zhuo FF, et al. Highly enantioselective addition of in situ prepared arylzinc to aldehydes catalyzed by a series of atropisomeric binaphthyl-derived amino alcohols. *Chem A Eur J*. 2010;16(27):7988-7991.
25. Zhang L, Sun L, Li YY, et al. Catalytic asymmetric arylation of enals to enantioenriched linear trisubstituted allylic secondary alcohols by using aryl lithiums generated in situ from aryl bromides. *ChemCatChem*. 2013;5(12):3516-3519.
26. Yang YX, Liu Y, Zhang L, et al. Aryl bromides as inexpensive starting materials in the catalytic enantioselective arylation of aryl aldehydes: the additive TMEDA enhances the enantioselectivity. *J Org Chem*. 2014;79(21):10696-10702.
27. Wang P, Liu Y, Zhang YL, Da CS. The inexpensive additive N-methylmorpholine effectively decreases the equivalents of nucleophiles in the catalytic highly enantioselective arylation of aryl aldehydes. *Chirality*. 2017;29(8):443-450.
28. Noyori R, Suga S, Kawai K, Okada S, Kitamura M. Enantioselective alkylation of carbonyl compounds. From stoichiometric to catalytic asymmetric induction. *Pure Appl Chem*. 1988;60:1597-1606.
29. Radin NS, Muramatsu Y, Harada T. Sphingolipids as coenzymes in anion transfer and tumor death. *Bioorg Med Chem*. 2004;12(23):6029-6037.
30. Liang Y, Jiang X, Yu ZX. Enantioselective total synthesis of (+)-asteriscanolideviaRh(I)-catalyzed [(5+2)+1] reaction. *Chem Commun*. 2011;47(23):6659-6661.
31. Sreedhar E, Venkanna A, Chandramouli N, Babu KS, Rao JM. The first total synthesis of topsentolide B_3. *Eur J Org Chem*. 2011;2011(6):1078-1083.
32. Fujii K, Maki K, Kanai M, Shibasaki M. Formal catalytic asymmetric total synthesis of Fostriecin. *Org Lett*. 2003;5(5):733-736.
33. Legigan T, Clarhaut J, Renoux B, et al. Synthesis and antitumor efficacy of a β-Glucuronidase-responsive albumin-binding prodrug of doxorubicin. *J Med Chem*. 2012;55(9):4516-4520.
34. Lumbroso A, Cooke ML, Breit B. Catalytic asymmetric synthesis of allylic alcohols and derivatives and their applications in organic synthesis. *Angew Chem Int Ed*. 2013;52:1890-1932. *Angew. Chem*. 2013; 125: 1942-1986
35. Tian GQ, Kaiser T, Yang J. Diastereoselective synthesis of syn-1,3-diols by titanium-mediated reductive coupling of propargylic alcohols. *Org Lett*. 2010;12(2):288-290.

36. Adam W, Nestler B. Photooxygenation of chiral allylic alcohols: hydroxy-directed regio- and diastereoselective ene reaction of singlet oxygen. *J Am Chem Soc*. 1992;114(16):6549-6550.
37. Nicolaou KC, Sun YP, Korman H, Sarlah D. Asymmetric total synthesis of cylindrocyclophanes A and F through cyclodimerization and a Ramberg-Bäcklund reaction. *Angew Chem Int Ed*. 2010;49:5875-5878. *Angew. Chem*. 2010; 122: 6011–6014
38. Donohoe TJ, Callens CKA, Lacy AR, Winter C. Tethered aminohydroxylation reaction and its application to Total synthesis. *Eur J Org Chem*. 2012;2012(4):655-663.
39. Berenguer R, Cavero M, Garcia J, MuCoz M. Enantioselective synthesis of α-hydroxy thioesters via oxazaborolidine-mediated reduction of α-phenylthio enones. *Tetrahedron Lett*. 1998;39(15):2183-2186.
40. Breit B, Demel P, Grauer D, Studte C. Stereospecific and stereodivergent construction of tertiary and quaternary carbon centers through switchable directed/nondirected allylic substitution. *Chem Asian J*. 2006;1(4):586-597.
41. Martin VS, Woodard SS, Katsuki T, Yamada Y, Ikeda M, Sharpless KB. Kinetic resolution of racemic allylic alcohols by enantioselective epoxidation. A route to substances of absolute enantiomeric purity? *J Am Chem Soc*. 1981;103(20):6237-6240.
42. Burgess K, Jennings LD. Enantioselective esterifications of unsaturated alcohols mediated by a lipase prepared from Pseudomonas sp. *J Am Chem Soc*. 1991;113(16):6129-6139.
43. Ruble JC, Latham HA, Fu GC. Effective kinetic resolution of secondary alcohols with a planar—chiral analogue of 4-(Dimethylamino)pyridine. Use of the Fe(C5Ph5) group in asymmetric catalysis. *J Am Chem Soc*. 1997;119(6):1492-1493.
44. Vedejs E, MacKay JA. Kinetic resolution of allylic alcohols using a chiral phosphine catalyst. *Org Lett*. 2001;3(4):535-536.
45. Oppolzer W, Nadinov RN. Enantioselective synthesis of sec-allylalcohols by catalytic asymmetric addition of divinylzinc to aldehydes. *Tetrahedron Lett*. 1988;29(44):5645-5648.
46. Soai K, Takahashi K. Asymmetric alkenylation of chiral and prochiral aldehydes catalysed by chiral or achiral amino alcohols: catalytic diastereoselective synthesis of protected erythro-sphingosine and enantioselective synthesis of chiral diallyl alcohols. *J Chem Soc, Perkin Trans*. 1994;1:1257-1258.
47. Shibata T, Nakatsui K, Soai K. Highly enantioselective catalytic isopropenylation of aldehydes using diisopropenylzinc. *Inorg Chim Acta*. 1999;296(1):33-36.
48. Lurain AE, Maestri A, Kelly AR, Carroll PJ, Walsh PJ. Highly enantio- and diastereoselective one-pot synthesis of acyclic epoxy alcohols with three contiguous Stereocenters. *J Am Chem Soc*. 2004;126(42):13608-13609.
49. Li H, Walsh PJ. Catalytic asymmetric vinylation and dienylation of ketones. *J Am Chem Soc*. 2005;127(23):8355-8361.
50. Tomita D, Wada R, Kanai M, Shibasaki M. Enantioselective alkenylation and phenylation catalyzed by a chiral CuF complex. *J Am Chem Soc*. 2005;127(12):4138-4139.
51. Evans DA, Aye Y. Enantioselective scandium-catalyzed vinylsilane additions: a new approach to the synthesis of enantiopure β,γ-unsaturated α-Hydroxy acid derivatives. *J Am Chem Soc*. 2006;128(34):11034-11035.
52. Aikawa K, Hioki Y, Mikami K. Highly enantioselective alkenylation of glyoxylate with vinylsilane catalyzed by chiral dicationic palladium (II) complexes. *J Am Chem Soc*. 2009;131(39):13922-13923.
53. Tomita D, Kanai M, Shibasaki M. Nucleophilic activation of alkenyl and aryl boronates by a chiral cu(I) F complex: catalytic enantioselective alkenylation and arylation of aldehydes. *Chem Asian J*. 2006;1(1-2):161-166.
54. Shintani R, Inoue M, Hayashi T. Rhodium-catalyzed asymmetric addition of aryl- and alkenylboronic acids to isatins. *Angew Chem Int Ed*. 2006;45:3353-3356. *Angew. Chem*. 2006; 118: 3431–3434
55. Shono T, Harada T. Catalytic enantioselective synthesis of secondary allylic alcohols from terminal alkynes and aldehydes via 1-Alkenylboron reagents. *Org Lett*. 2010;12(22):5270-5273.
56. Sato I, Asakura N, Iwashita T. A highly enantioselective synthesis of chiral allylic alcohols by asymmetric addition of novel mixed reagents of trialkenylbismuthines/dialkylzincs to aldehydes. *Tetrahedron: Asymmetry*. 2007;18(22):2638-2642.
57. Biradar DB, Gau HM. Highly enantioselective vinyl additions of vinylaluminum to ketones catalyzed by a titanium (IV) catalyst of (S)-BINOL. *Org Lett*. 2009;11(3):499-502.
58. Kanbayashi N, Onitsuka K. Ruthenium-catalyzed regio- and enantioselective allylic substitution with water: direct synthesis of chiral allylic alcohols. *Angew Chem Int Ed*. 2011;50:5197-5199. *Angew. Chem*. 2011; 123: 5303–5305
59. Lyothier I, Defieber C, Carreira EM. Iridium-catalyzed enantioselective synthesis of allylic alcohols: silanolates as hydroxide equivalents. *Angew Chem Int Ed*. 2006;45:6204-6207. *Angew. Chem*. 2006; 118: 6350–6353
60. Gärtner M, Mader S, Seehafer K, Helmchen G. Enantio- and regioselective iridium-catalyzed allylic hydroxylation. *J Am Chem Soc*. 2011;133(7):2072-2075.
61. Bouziane A, Hélou M, Carboni B, et al. Ruthenium-catalyzed synthesis of allylic alcohols: boronic acid as a hydroxide source. *Chem A Eur J*. 2008;14(18):5630-5637.
62. Miyabe H, Matsumura A, Yoshida K, Takemoto Y. Synthesis of chiral oxime ethers based on regio- and enantioselective allylic substitution catalyzed by iridium–pybox complex. *Tetrahedron*. 2009;65(23):4464-4470.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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