Received: 16 February 2017 | Revised: 8 April 2017 | Accepted: 10 April 2017

DOI: 10.1002/chir.22709

REGULAR ARTICLE

WILEY

The inexpensive additive *N*-methylmorpholine effectively decreases the equivalents of nucleophiles in the catalytic highly enantioselective arylation of aryl aldehydes

Pei Wang[1] | Yue Liu[1] | Ya-Lun Zhang[1] | Chao-Shan Da[1,2]

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

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

Correspondence
Chao-Shan Da, Institute of Biochemistry and Molecular Biology, School of Life Sciences, Lanzhou University, Lanzhou 730000, China.
Email: dachaoshan@lzu.edu.cn

Funding information
National Natural Science Foundation of China, Grant/Award Number: 21072087

Abstract

Highly enantioselective arylation of aryl aldehydes catalyzed by (*S*)-H_8-BINOL-Ti(O*i*-Pr)$_2$ complex in the presence of *N*-methylmorpholine (NMM) as an effective and inexpensive additive is described for the first time. We found high enantioselectivity and yield but successfully reduced the equivalents of nucleophiles triarylaluminums by 50% compared with our previous report. The practicability of the process was thereby greatly increased.

KEYWORDS

aryl aldehydes, arylation, asymmetric catalysis, NMM, triarylaluminum

1 | INTRODUCTION

Enantiopure diarylmethanols are important structural scaffolds in the synthesis of pharmaceuticals and bioactive compounds.[1-8] Accordingly, the catalytic asymmetric addition of arylmetal reagents and aryl boronic acids to aldehydes has attracted considerable attention over the past decades.[9-17] Since Fu and coworkers seminally reported the asymmetric addition with Ph_2Zn,[18] arylzinc reagents from various aryl sources such as arylboronic acids have been commonly explored for the enantioselective synthesis of diarylmethanols.[19-30] Meanwhile, other active aryl metals such as arylaluminum, arylmagnesium, and aryllithium have transferred aryl to less active aryl titanium intermediates ArTi(Oi-Pr)$_3$ as nucleophiles for enantiopure diarylmethanols because of their higher reactivity.[31-40] But the enantioselectivity is still not very satisfied using only the less active ArTi(Oi-Pr)$_3$ in situ-generated from aryl metals and Ti(Oi-Pr)$_4$ to arylate aldehydes in the presence of chiral catalysts. The reason is that Lewis acids simultaneously generate in the transmetallation process and then promote the unwanted racemic background reactions and thus lead to low enantioselectivity.[41,42] To solve this problem, Weber and Seebach removed the Lewis acid by centrifugation to obtain salt-free ArTi(Oi-Pr)$_3$ reagents.[42] Harada and coworkers chose to introduce excessive ArTi(Oi-Pr)$_3$ reagents derived in situ from aryllithium reagents or Grignard reagents with Ti(Oi-Pr)$_4$ for a very long period of time, or to change the solvent during the reaction process.[31,32,43] While all these measures have produced significant effects on achieving high enantioselectivities, their practicalities are greatly hampered by the great operational inconvenience and lower cost-effectiveness. Another alternative strategy is to use an appropriate additive to inhibit the racemic background reactions, demonstrated by the groups of Bolm,[44] Chan,[45] and Walsh,[46,47] respectively. In their works, however, excessive aryl metals to aldehydes are unavoidably used and the additives are expensive.

Our group has successfully demonstrated that bis2-(*N*, *N*-dimethylamino)ethylether (BDMAEE) and tetramethylethylenediamine (TMEDA) as the additives can suppress the background reaction in the catalytic enantioselective arylation of aldehydes.[34,48,49] The

limitation is that excessive aryl metals are similarly used and the two additives are still not inexpensive enough, although the highly enantiopure diarylmethanols have been achieved in high yield. To reduce the loading of starting materials and to use more inexpensive additives is challenging and will generate general interest to society for its practicability and environmental friendliness. Therefore, we determined to explore more inexpensive additives to replace the expensive ones and effectively reduce the used equivalents of nucleophiles to greatly increase the practicability of the process. After a series of experiments, we found that more inexpensive *N*-methylmorpholine (NMM) can satisfactorily replace BDMAEE and TMEDA to afford high enantioselectivity of the process and loading of the nucleophilic triarylaluminums have become equimolar to aldehydes for the first time, reducing by 50% compared with the previous report.[48] Herein we report such findings.

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 NMR and ^{13}C NMR spectra were measured on 400 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 enantiomeric excess (*ee*) values was carried out using chiral high-performance liquid chromatography (HPLC) with an OD-H, OB-H, OJ-H, or AD-H column.

2.1 | General procedure for the catalytic asymmetric arylation of aldehydes

Freshly distilled bromobenzene (1.0 mmol, 0.105 mL) and 1.0 mL of dry tetrahydrofuran (THF) were introduced into a dry 10 mL round-bottom flask equipped with a clean stir bar under an argon atmosphere. The flask was placed into a cold bath at −78 °C, and *n*-BuLi (1.8 M, 1.2 mmol, 0.67 mL) was added dropwise. After 1 h, the mixture was warmed to 0 °C, and a solution of $AlCl_3$ (33.5 mg, 0.25 mmol) in 1.0 mL of dry THF was added dropwise into the flask. Then it was warmed to room temperature and kept stirring for about 12 h and NMM (1.0 mmol, 110 μL) was added. After 30 min of stirring, a mixture of (*S*)-H_8-BINOL (7.4 mg, 0.025 mmol) and Ti(O*i*-Pr)$_4$ (0.425 mmol, 125.9 μL), which had previously been mixed and stirred for about 15 min in 1.0 mL of dry THF, was introduced, and the resulting mixture was stirred for further 60 min. Then 1-naphthaldehyde (39.0 mg, 0.25 mmol) was added to the flask at room temperature, and the flask was placed into an oil bath at 40 °C and kept stirring for about 8 h (checking with TLC until the reaction was complete). Two drops of ice water were added to the mixture to quench the reaction with a pipette, followed by 3.0 mL of 5% HCl. The resulting mixture was extracted with ethyl acetate (8.0 mL × 3), and the organic layers were combined, washed with 2.0 mL of brine, dried with anhydrous Na_2SO_4, and condensed under reduced pressure to give an oily residue. The residue was then purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 8:1) to furnish the pure diarylmethanol.

2.1.1 | (*S*)-(2-Methoxyphenyl)(phenyl)methanol (1)[50]

Yield 49.8 mg, 93%; colorless oil; $[\alpha]_D^{25}$ = −27 (*c* 1.0, $CHCl_3$); HPLC (OD-H, hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ 227.9 nm) t_r (major) = 20.8 min, t_r (minor) = 23.3 min, *ee* = 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.15 (s, 1H), 3.80 (s, 3H), 6.05 (s, 1H), 6.89–6.94 (m, 2H), 7.22–7.38 (m, 7H).

2.1.2 | (*S*)-(3-Methoxyphenyl)(phenyl)methanol (2)[48]

Yield 50.1 mg, 94%; colorless oil; $[\alpha]_D^{25}$ = +9 (*c* 1.0, $CHCl_3$); HPLC (OD-H, hexane/*i*-PrOH = 75/25, flow rate 1.0 mL/min, λ 261.5 nm) t_r (major) = 7.4 min, t_r (minor) = 10.1 min, *ee* = 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 1H), 3.76 (s, 3H), 5.78 (s, 1H), 6.78–6.80 (d, *J* = 8.0 Hz, 1H), 6.92–6.94 (m, 2H), 7.23–7.37 (m, 6H).

2.1.3 | (*S*)-(4-Methoxyphenyl)(phenyl)methanol (3)[48]

Yield 51.4 mg, 96%; light yellow oil; $[\alpha]_D^{25}$ = −19 (*c* 1.0, $CHCl_3$); HPLC (OJ-H, hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ 235.8 nm) t_r (major) = 40.0 min, t_r (minor) = 35.3 min, *ee* = 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 5.80 (s, 1H), 6.85–6.87 (d, *J* = 8.0 Hz, 2H), 7.26–7.35 (m, 7H).

2.1.4 | (*S*)-phenyl(o-tolyl)methanol (4)[51]

Yield 45.1 mg, 91%; white solid, mp 89–90 °C; $[\alpha]_D^{25}$ = +5 (*c* 1.0, $CHCl_3$); HPLC (OD-H, hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ 222.9 nm) t_r (major) = 27.4 min, t_r

(minor) = 25.7 min, *ee* = 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 5.98 (s, 1H), 7.12–7.32 (m, 8H), 7.50–7.52 (d, *J* = 8.0 Hz, 1H).

2.1.5 | (*S*)-phenyl(p-tolyl)methanol (5)[48]

Yield 47.5 mg, 96%; white solid, mp 57–58 °C; $[\alpha]_D^{25} = -6$ (*c* 1.0, $CHCl_3$); HPLC (OB-H, hexane/*i*-PrOH = 90/10, flow rate 0.4 mL/min, λ 227.9 nm) t_r (major) = 19.0 min, t_r (minor) = 16.5 min, *ee* = 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.40 (s, 1H), 5.81 (s, 1H), 7.13–7.36 (m, 9H).

2.1.6 | (*S*)-(4-Bromophenyl)(phenyl)methanol (6)[48]

Yield 61.7 mg, 94%; white solid, mp 74–75 °C; $[\alpha]_D^{25} = +19$ (*c* 1.0, $CHCl_3$); HPLC (OB-H, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ 236.9 nm) t_r (major) = 10.7 min, t_r (minor) = 8.8 min, *ee* = 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 1H), 5.76 (s, 1H), 7.23–7.45 (m, 9H).

2.1.7 | (*S*)-(4-Fluorophenyl)(phenyl)methanol (7)[48]

Yield 45.7 mg, 90%; light yellow oil; $[\alpha]_D^{25} = +9$ (*c* 1.0, $CHCl_3$),; HPLC (OB-H, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ 220.4 nm) t_r (major) = 17.8 min, t_r (minor) = 15.3 min, *ee* = 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (s, 1H), 6.99–7.03 (m, 2H), 7.25–7.35 (m, 7H).

2.1.8 | (*S*)-phenyl(4-(trifluoromethyl)phenyl) methanol (8)[48]

Yield 59.9 mg, 95%; white solid, mp 79–80 °C; $[\alpha]_D^{25} = +28$ (*c* 1.0, $CHCl_3$); HPLC (OB-H, hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ 229.1 nm) t_r (major) = 9.4 min, t_r (minor) = 7.2 min, *ee* = 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (s, 1H), 5.87 (s, 1H), 7.25–7.35 (m, 5H), 7.49–7.51 (d, *J* = 12.0 Hz, 2H), 7.57–7.60 (d, *J* = 12.0 Hz, 2H).

2.1.9 | (*S*)-phenyl(thiophen-2-yl)methanol (9)[48]

Yield 44.7 mg, 94%; white solid, mp 49–51 °C; $[\alpha]_D^{25} = +25$ (*c* 1.0, $CHCl_3$); HPLC (OD-H, hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ 238.4 nm) t_r (major) = 17.5 min, t_r (minor) = 19.6 min, *ee* = 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (s, 1H), 6.02 (s, 1H), 6.86–6.92 (m, 2H), 7.24–7.42 (m, 6H).

2.1.10 | (*S*)-furan-2-yl(phenyl)methanol (10)[48]

Yield 42.3 mg, 97%; light yellow oil; $[\alpha]_D^{25} = -8$ (*c* 1.0, $CHCl_3$); HPLC (OD-H, hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ 233.0 nm) t_r (major) = 15.4 min, t_r (minor) = 19.0 min, *ee* = 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (s, 1H), 5.81 (s, 1H), 6.10–6.11 (m, 1H), 6.30–6.31 (m, 1H), 7.33–7.43 (m, 6H).

2.1.11 | (*S*)-Naphthalen-1-yl(phenyl)methanol (11)[48]

Yield 52.7 mg, 90%; colorless oil; $[\alpha]_D^{25} = -45$ (*c* 1.0, $CHCl_3$); HPLC (OD-H, hexane/*i*-PrOH = 75/25, flow rate 1.0 mL/min, λ 257.3 nm) t_r (major) = 7.6 min, t_r (minor) = 15.6 min, *ee* = 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (s, 1H), 6.51 (s, 1H), 7.23–7.49 (m, 8H), 7.61–7.63 (d, *J* = 8.0 Hz, 1H), 7.79–7.86 (m, 2H), 8.00–8.02 (d, *J* = 8.0 Hz, 1H).

2.1.12 | (*S*)-Naphthalen-2-yl(phenyl)methanol (12)[48]

Yield 54.5 mg, 93%; white solid, mp 44–46 °C; $[\alpha]_D^{25} = +7$ (*c* 1.0, $CHCl_3$); HPLC (OD-H, hexane/*i*-PrOH = 92/8, flow rate 1.0 mL/min, λ 235.7 nm) t_r (major) = 18.3 min, t_r (minor) = 22.3 min, *ee* = 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.72 (s, 1H), 6.00 (s, 1H), 7.26–7.47 (m, 8H), 7.77–7.89 (m, 4H).

2.1.13 | (*R*)-Cyclohexyl(phenyl)methanol (13)[48]

Yield 32.3 mg, 68%; white solid, mp 64–65 °C; $[\alpha]_D^{25} = +26$ (*c* 1.0, $CHCl_3$); HPLC (OD-H, hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ 218.4 nm) t_r (major) = 13.2 min, t_r (minor) = 11.8 min, *ee* = 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87–1.28 (m, 7H), 1.61–1.64 (m, 3H), 1.75–1.78 (d, *J* = 12.0 Hz, 1H), 1.97–2.01 (d, *J* = 16.0 Hz, 1H), 4.36–4.38 (d, *J* = 8.0 Hz, 1H), 7.27–7.34 (m, 5H).

2.1.14 | (*R*)-1-Phenyldecan-1-ol (14)[48]

Yield 41.6 mg, 71%; colorless oil; $[\alpha]_D^{25} = +20$ (*c* 1.0, $CHCl_3$); HPLC (OD-H, hexane/*i*-PrOH = 98/2, flow rate 0.7 mL/min, λ 220.5 nm) t_r (major) = 12.4 min, t_r (minor) = 14.1 min, *ee* = 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85–0.89 (t, *J* = 8.0 Hz, 3H), 1.24–1.43 (m, 14H), 1.68–1.80 (m, 2H), 1.93 (s, 1H), 4.63–4.67 (t, *J* = 8.0 Hz, 1H), 7.25–7.34 (m, 5H).

2.1.15 | (*R*)-(4-Fluorophenyl)(phenyl)methanol (15)[48]

Yield 49.0 mg, 97%; light yellow oil; $[\alpha]_D^{25} = -11$ (*c* 1.0, $CHCl_3$); HPLC (OB-H, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ 220.7 nm) t_r (major) = 14.7 min, t_r (minor) = 19.2 min, *ee* = 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 1H), 5.82 (s, 1H), 6.99–7.03 (m, 2H), 7.25–7.35 (m, 7H).

2.1.16 | (*S*)-(4-Fluorophenyl)(naphthalen-2-yl)methanol (16)[48]

Yield 56.3 mg, 89%; light yellow oil; $[\alpha]_D^{25} = -44$ (*c* 1.0, $CHCl_3$); HPLC (OD-H, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ 282.3 nm) t_r (major) = 8.5 min, t_r (minor) = 9.8 min, *ee* = 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 1H), 5.99 (s, 1H), 7.00–7.04 (t, *J* = 8.0 Hz, 2H), 7.36–7.51 (m, 5H), 7.79–7.87 (m, 4H).

2.1.17 | (*S*)-(4-Fluorophenyl)(naphthalen-1-yl)methanol (17)[48]

Yield 58.9 mg, 93%; white solid, mp 54–56 °C; $[\alpha]_D^{25} = +5$ (*c* 1.0, $CHCl_3$); HPLC (OD-H, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ 230.5 nm) t_r (major) = 8.0 min, t_r (minor) = 19.1 min, *ee* = 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 1H), 6.51 (s, 1H), 6.98–7.02 (t, *J* = 8.0 Hz, 2H), 7.35–7.51 (m, 5H), 7.61–7.63 (d, *J* = 8.0 Hz, 1H), 7.82–7.88(m, 2H),7.97–7.99(d, *J* = 8.0 Hz, 1H).

2.1.18 | (*R*)-phenyl(p-tolyl)methanol (18)[48]

Yield 46.4 mg, 94%; white solid, mp 55–57 °C; $[\alpha]_D^{25} = +21$ (*c* 1.0, $CHCl_3$); HPLC (OB-H, hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ 223.8 nm) t_r (major) = 10.3 min, t_r (minor) = 12.4 min, *ee* = 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 1H), 2.32 (s, 3H), 5.79 (s, 1H), 7.12–7.37 (m, 9H).

2.1.19 | (*S*)-Naphthalen-1-yl(p-tolyl)methanol (19)[48]

Yield 60.8 mg, 98%; light yellow oil; $[\alpha]_D^{25} = -31$ (*c* 1.0, $CHCl_3$); HPLC (OD-H, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ 293.5 nm) t_r (major) = 7.5 min, t_r (minor) = 15.4 min, *ee* = 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 4H), 6.51 (s, 1H), 7.12–7.14 (d, *J* = 8.0 Hz, 2H), 7.25–7.30 (m, 2H), 7.40–7.51 (m, 3H), 7.65–7.67 (d, *J* = 8.0 Hz, 1H), 7.80–7.87 (m, 2H), 8.00–8.02 (d, *J* = 8.0 Hz, 1H).

2.1.20 | (*S*)-Thiophen-2-yl(p-tolyl)methanol (20)[48]

Yield 47.9 mg, 94%; light yellow solid, mp 64–65 °C; $[\alpha]_D^{25} = +12$ (*c* 1.0, $CHCl_3$); HPLC (AD-H, hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ 253.7 nm) t_r (major) = 13.1 min, t_r (minor) = 15.0 min, *ee* = 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 4H), 6.04 (s, 1H), 6.88–6.95 (m, 2H), 7.17–7.35 (m, 5H).

2.2 | Typical procedure for the synthesis of (*S*)-H_8-BINOL from (*S*)-BINOL[52]

(*S*)-BINOL (1.43 g, 5 mmol) and 5% Pd/C (1.5 g, 50% wet) were added to 50 mL of EtOH in a 100 mL high-pressure vessel. The reaction mixture was stirred under 10 MPa H_2 at 70 °C for about 7 h until no more H_2 consumption could be detected. The vessel was cooled to room temperature, after which Pd/C was filtered off and the vessel was washed with CH_2Cl_2 (3 × 50 mL). The organic layers were combined and condensed to dryness under reduced pressure to give a white solid. The solid was recrystallized with *n*-heptane to furnish (*S*)-H_8-BINOL as white crystals. Yield 1.40 g, 95%; mp 160–161 °C; $[\alpha]_D^{25} = -72$ (c 1.0, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ 1.64–1.77 (m, 8H), 2.12–2.33 (m, 4H), 2.73–2.76 (m, 4H), 4.57 (s, 2H), 6.82–6.84 (d, *J* = 8.0 Hz, 2H), 7.05–7.07 (d, *J* = 8.0 Hz, 2H).

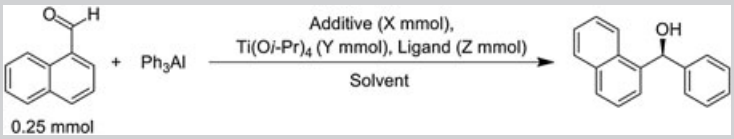
3 | RESULTS AND DISCUSSION

We performed our exploration with the typical reaction of catalytic enantioselective phenylation of 1-naphthaldehyde catalyzed by chiral BINOL and H_8-BINOL titanium complexes with the amine additive to inhibit the unwanted racemic background phenylation (Table 1). Triphenylaluminum was in situ prepared from benzene bromide, butyllithium (dissolved in hexane), and anhydrous $AlCl_3$ in THF according to the well-established method.[46] The chiral catalyst (*S*)-BINOL-Ti(O*i*-Pr)$_2$ was similarly in situ generated from (*S*)-BINOL and its equivalent titanium tetrapropoxide in THF. We wanted to find some less-expensive amine additive than the previously used TMEDA while using 1.6 equivalent triphenylaluminum to the aldehyde at room temperature. We delightedly found that NMM can be an ideal additive, more inexpensive than TMEDA, to achieve excellent 90% enantioselectivity in the catalysis of (*S*)-BINOL-Ti(O*i*-Pr)$_2$ complex (Table 1, entry 1). Replacing (*S*)-BINOL with (*S*)-H_8-BINOL, the enantioselectivity was further increased to 95% (entry 2). When diisopropylethylamine (DIPEA) and trimethylamine (Et_3N) were used as amine additives to inhibit the background racemic reaction, the enantioselectivity dropped to lower than 90% (entries 3–4).

A decrease of the catalyst (*S*)-H_8-BINOL-Ti(O*i*-Pr)$_2$ loading only slightly reduced the enantioselectivity to 94% from 95%, but it greatly lengthened the reaction time (entries 2 and 5). An increase of the catalyst loading did not further raise the enantioselectivity (entries 2 and 6). The decrease and increase of titanium tetrapropoxide both slightly reduced enantioselectivity to 94% and 93%, respectively (entries 2, 7, 8). For the loading of NMM, 1.6 mmol NMM was ideal in view of the 95% *ee* (entries 2, 9, 10). As the temperature rose from room temperature to 40 °C, the enantioselectivity did not change but the reaction time was greatly shortened to 8 h (entry 12). Then we tried to reduce the loading of Ph_3Al, and the amount of NMM was proportionally changed according to the optimized load (entry 2). The results clearly indicated that the reduced 0.25 mmol Ph_3Al was ideal for the high enantioselectivity (96%) in high conversion (entry 14). Compared with the previous reported loading of two equivalents of triarylaluminums to aldehydes, the loading of nucleophilic starting aryl metals is largely reduced by 50%. And the loading of nucleophilic triarylaluminums in the catalytic enantioselective arylation of aldehydes is first reduced to the equimolar to aldehydes, greatly increasing the practicability of the process. Experiments on solvents finally confirmed that mixed THF/hexane was the preferred solvent (entries 15–17). Therefore, the optimal reaction conditions were determined (entry 13).

With the optimized reaction conditions, we then started to extend the scope of aldehydes for phenylation and examined other two triarylaluminums for arylation of aldehydes (Table 2). The results show that various aldehydes are well suited for this arylation process. Benzaldehydes with electron-withdrawing and electron-donating groups in the benzene rings all achieved excellent enantioselectivity in high yields (Table 2, entries 1–8). Two heterocyclic aromatic aldehydes also achieved up to 94% enantioselectivity as well as high yields (entries 9, 10). 1-Naphthaldehyde obtained the

TABLE 1 Optimization of reaction conditions of the asymmetric phenylation of the α-naphthaldehyde



Entry	$AlPh_3$ (mmol)[a]	X	Ligand[b] (Y mmol)	Additive[c] (Z mmol)	Solvent	°C (time)	Conv. (%)[d]	*ee* (%)[e]
1	0.4	0.425	L_1(0.025)	NMM (1.6)	THF/hex	rt (24 h)	98	90
2	0.4	0.425	L_2(0.025)	NMM (1.6)	THF/hex	rt (24 h)	99	95
3	0.4	0.425	L_2(0.025)	DIPEA (1.6)	THF/hex	rt (30 h)	72	76
4	0.4	0.425	L_2(0.025)	Tea (1.6)	THF/hex	rt (24 h)	94	85
5	0.4	0.4125	L_2(0.0125)	NMM (1.6)	THF/hex	rt (50 h)	99	94
6	0.4	0.4325	L_2(0.0325)	NMM (1.6)	THF/hex	rt (24 h)	99	95
7	0.4	0.345	L_2(0.025)	NMM (1.6)	THF/hex	rt (50 h)	95	94
8	0.4	0.505	L_2(0.025)	NMM(1.6)	THF/hex	rt (50 h)	94	93
9	0.4	0.425	L_2(0.025)	NMM (2.0)	THF/hex	rt (24 h)	99	95
10	0.4	0.425	L_2(0.025)	NMM (1.2)	THF/hex	rt (50 h)	99	94
11	0.4	0.425	L_2(0.025)	NMM(1.6)	THF/hex	30 (12 h)	99	95
12	0.4	0.425	L_2(0.025)	NMM (1.6)	THF/hex	40 (8 h)	99	95
13	0.25	0.425	L_2(0.025)	NMM (1.0)	THF/hex	40 (8 h)	99	96
14	0.15	0.425	L_2(0.025)	NMM (0.6)	THF/hex	40 (22 h)	92	96
15	0.1	0.425	L_2(0.025)	NMM (0.4)	THF/hex	40 (22 h)	90	96
16	0.25	0.425	L_2(0.025)	NMM (1.0)	DIPE/THF = 1:1	40 (31 h)	74	93
17	0.25	0.425	L_2(0.025)	NMM (1.0)	MTBE[f]	40 (31 h)	73	n.d

[a]PhBr: *n*-BuLi: $AlCl_3$ = 4:4.8:1 were used in preparation for triphenylaluminum.

[b]$\mathbf{L_1}$ is (*S*)-BINOL; $\mathbf{L_2}$ is (*S*)-H_8-BINOL.

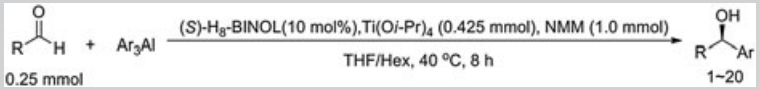
[c]The coordinative additive. DIPEA = *N,N*-Diisopropylethylamine, TEA = triethylamine.

[d]The conversion was determined with HPLC using diphenyl as an inner standard.

[e]Determined by HPLC analysis.

[f]MTBE = methyl *tert*-butyl ether.

TABLE 2 Catalytic asymmetric arylation of aryl aldehydes[a]



Entry	Ar	R	Product	Yield (%)[b]	*ee* (%)[c]
1	Ph	2-$MeOC_6H_4$	1	93	84
2	Ph	3-$MeOC_6H_4$	2	94	92
3	Ph	4-$MeOC_6H_4$	3	96	89
4	Ph	2-MeC_6H_4	4	91	89
5	Ph	4-MeC_6H_4	5	96	92
6	Ph	4-BrC_6H_4	6	94	88
7	Ph	4-FC_6H_4	7	90	89
8	Ph	4-$F_3CC_6H_4$	8	95	87
9	Ph	Thienyl	9	94	94
10	Ph	Furyl	10	97	87
11	Ph	1-naphth	11	90	96
12	Ph	2-naphth	12	93	90
13	Ph	*c*-hexane	13	68	88
14	Ph	$CH_3(CH_2)_8$-	14	71	84
15	4-FC_6H_4	C_6H_5	15	97	94
16	4-FC_6H_4	2-naphth	16	89	92
17	4-FC_6H_4	1-naphth	17	93	95
18	4-MeC_6H_4	C_6H_5	18	94	91
19	4-MeC_6H_4	1-naphth	19	98	90
20	4-MeC_6H_4	Thienyl	20	94	94

[a]0.25 mmol Ar_3Al was prepared in situ from 1.0 mmol aryl bromine, 1.2 mmol *n*-BuLi, and 0.25 mmol $AlCl_3$.

[b]Isolated yields.

[c]Determined with chiral HPLC.

highest enantioselectivity of 96% (entry 11). For both the [α]-branched and linear alkyl aldehydes, good yields and high enantioselectivities were similarly obtained (entries 13, 14). While the two different nucleophilic triarylaluminums, with electron-withdrawing and electron-donating groups in benzene rings, were utilized to replace triphenylaluminum, all investigated aromatic aldehydes obtained high yields and excellent enantioselectivities (entries 15–20). The highest enantioselectivity was up to 95% (entry 17). Even the heterocyclic 2-thienylaldehyde similarly resulted in an excellent *ee* of 94% (entry 20). Therefore, NMM is an ideal and cost-effective additive in view of enantioselectivity and yield in this transformation.

4 | CONCLUSION

In summary, we first report the highly enantioselective arylation of aryl aldehydes catalyzed by (*S*)-H_8-BINOL-$Ti(Oi\text{-}Pr)_2$ complex in the presence of NMM as an inexpensive additive. Compared with the previous report, the nucleophilic triarylaluminums were largely reduced by 50% from two equivalents to equimolar with respect to aldehydes for the synthesis of series of enantiopure diarylmethanols with no reduction of yield and enantioselectivity. Therefore, this process is apparently practical for preparation of highly enantiopure diarylmethanols.

ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China for its financial support (No. 21072087).

REFERENCES

1. Wu PY, Wu HL, Uang BJ. Asymmetric synthesis of functionalized diarylmethanols catalyzed by a new gamma-amino thiol. *J Org Chem*. 2006;71:833-835.

2. Casy AF, Drake AF, Ganellin CR, Mercer AD, Upton C. Stereochemical studies of chiral h-1 antagonists of histamine: The resolution, chiral analysis, and biological evaluation of four antipodal pairs. *Chirality.* 1992;4:356-366.
3. Meguro K, Aizawa M, Sohda T, Kawamatsu Y, Nagaoka A. New 1,4-dihydropyridine derivatives with potent and long-lasting hypotensive effect. *Chem Pharm Bull*. 1985;33:3787-3797.
4. Stanchev S, Rakovska R, Berova N, Snatzke G. Synthesis, absolute configuration and circular dichroism of some diarylmethane derivatives. *Tetrahedron Asymmetry.* 1995;6:183-198.
5. Radin NS. Sphingolipids as coenzymes in anion transfer and tumor death. *Bioorgan Med Chem*. 2004;12:6029-6037.
6. Bolshan Y, Chen CY, Chilenski JR, et al. Nucleophilic displacement at benzhydryl centers: Asymmetric synthesis of 1,1-diarylalkyl derivatives. *Org Lett*. 2004;6:111-114.
7. Schmidt F, Stemmler RT, Rudolphand J, Bolm C. Catalytic asymmetric approaches towards enantiomerically enriched diarylmethanols and diarylmethylamines. *Chem Soc Rev.* 2006;35:454-470.
8. Paixão MW, Braga AL, Lüdtke DS. Catalytic enantioselective arylations: Boron to zinc exchange as a powerful tool for the generation of transferable aryl groups. *J Braz Chem Soc*. 2008;19:813-830.
9. 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;20:981-998.
10. Zhang R, Xu Q, Zhang XC, Zhang T, Shi M. Axially chiral C_2-symmetric N-heterocyclic carbene (NHC) palladium complexes-catalyzed asymmetric arylation of aldehydes with arylboronic acids. *Tetrahedron Asymmetry.* 2010;21:1928-1935.
11. Ji JX, Wu J, Xu L, Yip CW, Lam KH, Chan ASC. Catalytic asymmetric addition reactions leading to carbon-carbon bond formation: Phenyl and alkenyl transfer to aldehydes and alkynylation of alpha-imino esters. *Pure Appl Chem*. 2006;78:267-274.
12. Denizaltı S, Türkmen H, Çetinkaya B. Chelating alkoxy NHC–Rh(I) complexes and their applications in the arylation of aldehydes. *Tetrahedron Lett*. 2014;55:4129-4132.
13. Martins BS, Lüdtke DS. Boron/zinc exchange reaction in the diastereoselective arylation of N-protected L-prolinal. *Eur J Org Chem*. 2014;5364-5369.
14. Duan WZ, Ma YD, Qu B, Zhao L, Chen JQ, Song C. Synthesis of new alkoxy/sulfonate-substituted carbene precursors derived from [2.2] paracyclophane and their application in the asymmetric arylation of aldehydes. *Tetrahedron Asymmetry.* 2012;23:1369-1375.
15. Wouters AD, Diogo S, Lüdtke DS. Diastereoselective addition of arylzinc reagents to sugar aldehydes. *Org Lett*. 2012;14:3962-3965.
16. Wouters AD, Bessa AB, Sachini M, Wessjohann LA, Lüdtke DS. Boron–zinc exchange in the diastereoselective arylation of sugar-based aldehydes: Stereoselective synthesis of (+)-7-epi-goniofufurone and analogues. *Synthesis*. 2013;45:2222-2233.
17. Magnus NA, Anzeveno PB, Coffey DS, et al. Optimized catalytic enantioselective aryl transfer process gives access to mGlu2 receptor potentiators. *Org Proc Res Dev.* 2007;11:560-567.
18. Dosa PI, Ruble JC, Fu GC. Planar-chiral heterocycles as ligands in metal-catalyzed processes: Enantioselective addition of organozinc reagents to aldehydes. *J Org Chem*. 1997;62:444-445.
19. Ito K, Tomita Y, Katsuki T. Enantioselective phenyl transfer to aldehydes using 1,1′-bi-2-naphthol-3,3′-dicarboxamide as chiral auxiliary. *Tetrahedron Lett*. 2005;46:6083-6086.
20. Huang WS, Pu L. The first highly enantioselective catalytic diphenylzinc additions to aldehydes: Synthesis of chiral diarylcarbinols by asymmetric catalysis. *J Org Chem*. 1999;64:4222-4223.
21. Carlos AMM, Contreira ME, Martins BS, Immich MF, Moro AV, Lüdtke DS. Catalytic asymmetric arylation of aliphatic aldehydes using a B/Zn exchange reaction. *Tetrahedron*. 2015;71:1202-1206.
22. Moro AV, Tiekink ERT, Zukerman-Schpector J, Lüdtke DS, Correia CRD. Chiral triphenylprolinol ligands for the efficient catalytic asymmetric arylation of aldehydes. *Eur J Org Chem*. 2010;3696-3703.
23. Braga AL, Lüdtke DS, Vargas F, Paixão MW. Catalytic enantioselective arylation of aldehydes: Boronic acids as a suitable source of transferable aryl groups. *Chem Commun*. 2005;2512-2514.
24. Dahmen S, Lormann M. Triarylborane ammonia complexes as ideal precursors for arylzinc reagents in asymmetric catalysis. *Org Lett*. 2005;7:4597-4600.
25. 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;70:7432-7435.
26. Lu G, Kwong FY, Ruan JW, Li YM, Chan ASC. Highly enantioselective addition of in situ prepared arylzinc to aldehydes catalyzed by a series of atropisomeric binaphthyl-derived amino alcohols. *Chem A Eur J*. 2006;12:4115-4120.
27. Wu X, Liu X, Zhao G. Catalyzed asymmetric aryl transfer reactions to aldehydes with boroxines as aryl source. *Tetrahedron Asymmetry.* 2005;16:2299-2305.
28. Ji JX, Wu J, Au-Yeung TTL, Yip CW, Haynes RK, Chan ASC. Highly enantioselective phenyl transfer to aryl aldehydes catalyzed by easily accessible chiral tertiary aminonaphthol. *J Org Chem*. 2005;70:1093-1095.
29. Schwab RS, Soares LC, Dornelles L, et al. Chiral chalcogen peptides as ligands for the catalytic enantioselective aryl transfer reaction to aldehydes. *Eur J Org Chem.* 2010;3574-3578.
30. Berardinis AM, Turlington M, Pu L. Activation of functional arylzincs prepared from aryl iodides and highly enantioselective addition to aldehydes. *Org Lett*. 2008;10:2709-2712.
31. Nakagawa Y, Muramatsu Y, Harada T. Catalytic enantioselective synthesis of diarylmethanols from aryl bromides and aldehydes by using organolithium reagents. *Eur J Org Chem.* 2010;6535-6538.
32. Uenishi U, Nakagawa Y, Osumi H, Harada T. Practical enantioselective arylation and heteroarylation of aldehydes with in situ prepared organotitanium reagents catalyzed by 3-aryl-H_8-BINOL-derived titanium complexes. *Chem A Eur J.* 2013;19:4896-4905.
33. Muramatsu Y, Harada T. Catalytic asymmetric aryl transfer reactions to aldehydes with Grignard reagents as the aryl source. *Chem A Eur J*. 2008;14:10560-10563.

34. Fan XY, Yang YX, Zhuo FF, et al. $AlCl_3$ and BDMAEE: A pair of potent reactive regulators of aryl Grignard reagents and highly catalytic asymmetric arylation of aldehydes. *Chem A Eur J*. 2010;16:7988-7991.

35. Fernández-Mateos E, Maciá B, Ramón DJ, Yus M. Catalytic enantioselective addition of MeMgBr and other Grignard reagents to aldehydes. *Eur J Org Chem.* 2011;6851-6855.

36. 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;748-755.

37. Wu KH, Gau HM. Remarkably efficient enantioselective titanium(IV)-(*R*)-H_8-BINOLate catalyst for arylations to aldehydes by triaryl(tetrahydrofuran)aluminum reagents. *J Am Chem Soc*. 2006;128:14808-14809.

38. Wu KH, Zhou S, Chen CA, et al. Instantaneous room-temperature and highly enantioselective $ArTi(O\text{-}i\text{-}Pr)_3$ additions to aldehydes. *Chem Commun*. 2011;47:11668-11670.

39. Mateos EF, Maciá B, Yus M. Catalytic enantioselective addition of organoaluminum reagents to aldehydes. *Tetrahedron Asymmetry.* 2012;23:789-794.

40. 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;748-755.

41. Rudolph J, Hermanns N, Bolm C. The MPEG effect: Improving asymmetric processes by simple additives. *J Org Chem*. 2004;69:3997-4000.

42. Weber B, Seebach D. Ti-TADDOLate-catalyzed, highly enantioselective addition of alkyl- and aryl-titanum derivatives to aldehydes. *Tetrahedron*. 1994;50:7473-7484.

43. Muramatsu Y, Harada T. Catalytic asymmetric aryl transfer reactions to aldehydes with Grignard reagents as the aryl source. *Chem A Eur J*. 2008;14:10560-10563.

44. Bolm C, Rudolph J. Catalyzed asymmetric aryl transfer reactions to aldehydes with boronic acids as aryl source. *J Am Chem Soc*. 2002;124:14850-14851.

45. Ji JX, Wu J, Au-Yeung TTL, Yip CW, Haynes RK, Chan A. Highly enantioselective phenyl transfer to aryl aldehydes catalyzed by easily accessible chiral tertiary aminonaphthol. *J Org Chem*. 2005;70:1093-1095.

46. Kim JG, Walsh PJ. From aryl bromides to enantioenriched benzylic alcohols in a single flask: Catalytic asymmetric arylation of aldehydes. *Angew Chem Int Ed*. 2006;45:4175-4178. Angew Chem 2006;118:4281–4284

47. Salvi L, Kim JG, Walsh PJ. Practical catalytic asymmetric synthesis of diaryl-, aryl heteroaryl-, and diheteroarylmethanols. *J Am Chem Soc*. 2009;131:12483-12493.

48. 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;79:10696-10702.

49. 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;5:3516-3519.

50. Yamamoto Y, Kurihara K, Miyaura N. Me-bipam for enantioselective ruthenium (II)-catalyzed arylation of aldehydes with arylboronic acids. *Angew Chem Int Ed*. 2009;48:4414-4416. Angew Chem 2009;121:4478–4480

51. Umeda R, Studer A. Ag-catalyzed stereoselective cyclohexadienyl transfer: A novel entry into arylphenylmethanols. *Org Lett*. 2008;10:993-996.

52. Korostylev A, Tararov VI, Fischer C, Monsees A, Borner A. Convenient and efficient reduction of 1,1′-binaphthyls to H_8-1,1′-binaphthyl derivatives with Pd and Ru catalysts on solid support. *J Org Chem*. 2004;69:3220-3221.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Wang P, Liu Y, Zhang Y-L, Da C-S. The inexpensive additive *N*-methylmorpholine effectively decreases the equivalents of nucleophiles in the catalytic highly enantioselective arylation of aryl aldehydes. *Chirality.* 2017. https://doi.org/10.1002/chir.22709