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Nickel-catalyzed 1,2-addition of arylboroxines to aromatic aldehydes

Takafumi Arao, Kazuhiro Kondo* and Toyohiko Aoyama*

Graduate School of Pharmaceutical Sciences, Nagoya City University, 3-1 Tanabe-dori, Mizuho-ku, Nagoya 467-8603, Japan

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Abstract—Development of Ni–Et-Duphos-catalyzed 1,2-addition of arylboroxines to aromatic aldehydes is described. The dramatic effect of boron reagent and phosphine ligand is observed. This method with a phosphine ligand allows asymmetric arylation of aromatic aldehydes (up to 78% ee).

The arylation of aromatic aldehydes is one of the most important carbon–carbon bond-forming reactions, because diarylmethanols are important intermediates for the synthesis of biologically active compounds.[1] Among various arylmetal reagents used, arylboron reagents are more desirable due to the recent demand for safe and sustainable organic synthesis, because their reagents are less toxic and air stable. In 1998, Miyaura's group found that Rh(I) complexes catalyze 1,2-addition to aldehyde with arylboronic acid,[2] and later, attention has been focused on the arylation with the combination of the Rh-catalyst and arylboronic acid.[3] Recently, Ohta and Ito,[4a] and we[4b] have reported the use of a cheaper metal than the Rh, Pd catalyst, for the 1,2-addition of aromatic aldehydes with arylboronic acids. From the viewpoint of cost and practical convenience, the use of a much cheaper metal catalyst such as Ni than Rh and Pd is desirable. To date, only one successful example of Ni-catalyzed arylation of aldehydes with arylboron reagents has been reported by Shirakawa and co-workers.[5–7] However, since the use of an alkyne as a ligand is crucial for the arylation and in the presence of a phosphine ligand, the arylation does not proceed at all, the extension for an asymmetric version of Ni-catalyzed arylation seemed to be very difficult. Herein we would like to report a new method for Ni-phosphine ligand-catalyzed arylation of aromatic aldehydes with arylboroxines. In addition, this method with a phosphine ligand allows asymmetric arylation of aromatic aldehydes, although the result is preliminary.

Our initial studies focused on determination of the $Ni(cod)_2$-catalyzed phenylation conditions for 1-naphthaldehyde (**1**) using many phosphine ligands, and phenylboronic acid and phenylboroxine.[8] The selected results are shown in Table 1. The drastic effect of the boron reagent and ligand was observed. When phenylboronic acid as a boron reagent was used, the results for phenylation were not promising at all (entries 1 and 2). So, next, the use of phenylboroxine as a boron reagent was examined. After intensive screening of ligands, as can be seen in entries 3–12, we found that the chemical yield was brought to an acceptable level by using (±)-Et-Duphos (**6b**) (entry 9). Very interestingly, other five-membered chelating ligands such as dppe (**3**), dppben (**5**), and *i*-Pr-Duphos (**6c**), were not good ligands at all. With the promising result using (±)-Et-Duphos (**6b**), further intensive optimization was performed. As the results, the best reaction conditions were determined to be 10 mol % of $Ni(cod)_2$ and (±)-Et-Duphos (**6b**), 2/3 mol equiv of $(PhBO)_3$ and 0.5 mol equiv of NaO*t*-Bu in DME/H_2O (5:1) at 100 °C for 48 h.[9] Other bases such as KO*t*-Bu, LiO*t*-Bu and Et_3N gave less satisfactory results.[9] To our knowledge, this is the first example of Ni-catalyzed arylation of aldehyde with a boron reagent *in the presence of a phosphine ligand*.

The substrate and arylboroxine generality of this reaction under the optimal conditions is shown in Table 2. The electronic effect in the arylboroxines was not

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* Corresponding authors. Tel.: +81 52 836 3442 (K.K.); e-mail addresses: kazuk@phar.nagoya-cu.ac.jp; aoyama@phar.nagoya-cu.ac.jp

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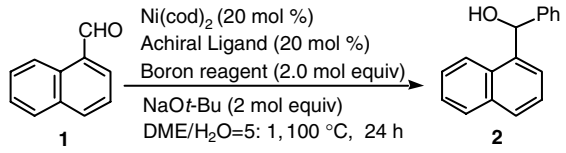
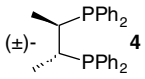
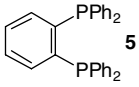
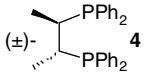
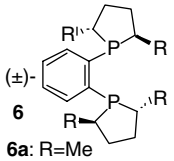
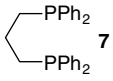
Table 1. Initial optimization of phenylation reaction



Entry	Achiral ligand	Boron reagent	Yield[a] (%)
1	 **3**	$PhB(OH)_2$	Trace
2	(±)-  **4**	$PhB(OH)_2$	7
3	PPh_3	$(PhBO)_3$	Trace
4	PCy_3	$(PhBO)_3$	Trace
5	 **3**	$(PhBO)_3$	Trace
6	 **5**	$(PhBO)_3$	Trace
7	(±)-  **4**	$(PhBO)_3$	65
8	(±)-  **6** **6a**: R=Me	$(PhBO)_3$	68
9	**6b**: R = Et	$(PhBO)_3$	80
10	**6c**: R = *i*-Pr	$(PhBO)_3$	Trace
11	 **7**	$(PhBO)_3$	Trace
12	(±)-BINAP	$(PhBO)_3$	Trace

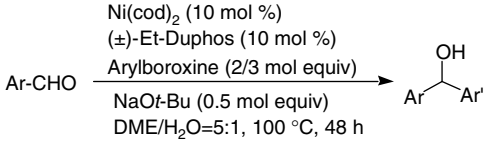
[a] Remainder of the mass balance was the starting 1-naphthaldehyde **1**.

observed (entries 1–3). From a wide range of aromatic aldehydes (entries 4–14), synthetically acceptable chemical yield was generally produced, although reactivity of 4-substituted aromatic aldehydes was a slightly low (entries 9–14 except for entry 11). Interestingly, chloro and bromo groups on the aromatic aldehydes (entries 12 and 13) were tolerated: dehalogented products were not produced in detectable amounts.

We are tempted to assume the mechanism for this arylation as follows (Scheme 1). A Ni(0) complex initially reacts with aromatic aldehyde to generate η^2-coordinated complex[10] **8** and/or its resonance type **9**. Subsequent trans-metalation with arylboroxine and/or its ate complex by the action of OH^- affords intermediate **10** followed by reductive elimination and protonolysis to furnish the diarylmethanol and to regenerate the Ni(0) complex.

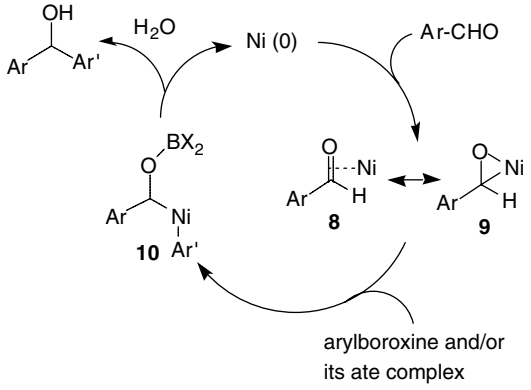
Preliminary attempts to extend this reaction with (*R*,*R*)-Et-Duphos to an asymmetric version[11] were promising

Table 2. Substrate and arylboroxine generality



Entry	Aromatic aldehyde (Ar=)	Arylboroxine (Ar′=)	Yield (%)
1	1-Naphthyl	Ph	93
2	1-Naphthyl	4-*i*-PrO–C_6H_4	94
3	1-Naphthyl	4-Cl–C_6H_4	87
4	2-Me–C_6H_4	Ph	91
5	2-F–C_6H_4	Ph	90
6	2-MeO–C_6H_4	Ph	99
7	3-Me–C_6H_4	Ph	92
8	3-MeO–C_6H_4	Ph	99
9	4-Me–C_6H_4	Ph	87
10	4-*i*-Pr–C_6H_4	Ph	88
11	4-F–C_6H_4	Ph	93
12	4-Cl–C_6H_4	Ph	78[a]
13	4-Br–C_6H_4	Ph	75[a]
14	4-MeO–C_6H_4	Ph	86

[a] Remainder of the mass balance was the starting aromatic aldehyde.

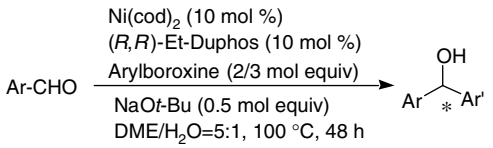


Scheme 1. Plausible reaction mechanism (omitted Et-Duphos for clarity).

(Table 3). 1-Naphthaldehyde and the 2-substituted aromatic aldehydes exhibited acceptable 66–78% enantioselectivity with good chemical yields (entries 1–6). In order to catch up and outrun the successful methods of Shibasaki[12] and Kanai-, and Bolm[13]-asymmetric arylation, we have really focused on tuning Duphos.[14]

*Representative procedure for the Ni(0)-catalyzed asymmetric (achiral) arylation of 1-naphthaldehyde (***1***) with triphenylboroxin (entry 1, Table 2 or entry 1, Table 3)*: To a stirred solution of (*R*,*R*)- or (±)-Et-DUPHOS (8.0 mg, 0.022 mmol) in DME/H_2O (5:1, 0.55 mL) were added $Ni(cod)_2$ (6.1 mg, 0.022 mmol), NaO*t*-Bu (10.6 mg, 0.110 mmol), $(PhBO)_3$ (45.9 mg, 0.147 mmol), and 1-naphthaldehyde (**1**) (30 μL, 34.5 mg, 0.221 mmol). The reaction mixture was stirred for 48 h at 100 °C and allowed to cool. After the usual work-up, purification by silica gel column (hexane–EtOAc = 20/1 to 4/1) affor-

Table 3. Preliminary results of asymmetric version



Entry	Aromatic aldehyde (Ar=)	Arylboroxine (Ar′=)	Yield (%)	ee[a] (%)
1	1-Naphthyl	Ph	93	68 (*R*)
2	1-Naphthyl	4-Cl–C_6H_4	87	66
3	2-Me–C_6H_4	Ph	91	78 (*R*)
4	2-Me–4-MeO–C_6H_4	Ph	86	74
5	2-Me–3-F–C_6H_4	Ph	93	75
6	2-Ph–C_6H_4	Ph	83	72
7	4-F–C_6H_4	Ph	93	55 (*R*)

[a] Determined by HPLC analysis.

ded (1*R*)-(1-naphthyl)phenylmethanol (**2**) (48.1 mg, 93%, 68% ee) as a colorless oil. The spectral data were comparable to those reported.[2a] IR (neat): $\nu = 3381\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta = 2.42$ (s, 1H), 6.48 (s, 1H), 7.21–7.48 (m, 8H), 7.59 (d, $J = 7.1$ Hz, 1H), 7.74–7.86 (m, 2H), 7.98–8.02 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 73.50, 123.86, 124.48, 125.17, 125.44, 125.98, 126.90, 127.48, 128.29, 128.35, 128.60, 130.54, 133.75, 138.63, 142.94. EIMS: $m/z = 234$ (M^+), 217, 157, 129, 128, 105, 77. Anal. Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 86.95; H, 5.99. The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (eluent: hexane/*i*-PrOH, flow: 1.0 mL/min). The absolute configuration was determined by comparison of the reported specific rotation.[2a]

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.025.

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9. For details, see: Tables SI-2 and SI-3 (Supplementary data).
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