Tetrahedron Letters 50 (2009) 6001–6003

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Et-duphos-nickel-catalyzed asymmetric arylation of benzaldehyde derivatives bearing an *ortho*-Me_2PhSi group with potassium aryltriolborates

Fumie Sakurai, Kazuhiro Kondo *, Toyohiko Aoyama *

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

ARTICLE INFO

Article history:
Received 27 July 2009
Revised 10 August 2009
Accepted 11 August 2009
Available online 14 August 2009

ABSTRACT

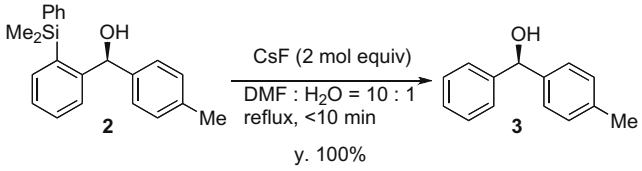
The Ni-catalyzed asymmetric arylation of benzaldehydes bearing an *ortho*-masked H group with potassium aryltriolborates has been developed. The keys to success were (i) steric tuning of benzaldehyde derivatives with an *ortho*-Me_2PhSi group, and (ii) the use of potassium aryltriolborates as aryl sources.

Control of the stereochemistry in the formation of chiral diarylmethanols has attracted considerable interest over the past 15 years, because they are important intermediates in the synthesis of biologically active compounds, and precursors of diarylmethylamines and 1,1-diarylalkyl units.[1] Catalytic asymmetric arylation of aromatic aldehydes with arylating reagents is one of the most useful reactions used to synthesize chiral diarylmethanols. From the viewpoint of modern organic synthesis, the use of catalysts and reagents, which are composed of elements of a high Clarke number, is desirable. To date, the only one successful example of catalytic asymmetric arylation that satisfies these requirements, has been reported by Shibasaki.[2] As an alternative protocol,[3–6] we have reported Ni-catalyzed arylation of aromatic aldehyde with arylboroxines and potassium aryltrifluoroborates.[7] However, our method requires the presence of *ortho*-alkyl or aryl-substituents on the benzene ring of aromatic aldehydes, in order to achieve 75–81% enantioselectivities. Herein, we report our efforts for improving the enantioselectivity. The keys to success were (i) steric tuning of benzaldehyde derivatives with an *ortho*-Me_2PhSi group,[8] and (ii) the use of potassium 1-aryl-4-methyl-2,6,7-trioxa-1-boranuidabicyclo[2.2.2]octanes (aryltriolborates)[9] as aryl sources.

Our initial studies focused on the determination of an arylboron reagent for Et-duphos-nickel catalyzed arylation with the benzaldehyde **1a** bearing an *ortho*-TMS group (Table 1, entries 1–8).[10,11] As shown in entries 1–4 of Table 1, *p*-tolylboronic acid and K(*p*-tolyl)BF_3 gave disappointing results. The use of (*p*-tolylBO)$_3$ gave 87–89% enantioselectivities, but the chemical yields were low (entries 5 and 6). Since we surmised that the low yields in entries 5 and 6 might be due to be the solvolysis of (*p*-tolylBO)$_3$, we next tested the water-stable *p*-tolyltriolborate (entries 7 and 8).[12] The use of *p*-tolyltriolborate led to a 94% enantioselectivity, but the chemical yield was not satisfactory: compared with the Cs aryltriolborate, the K aryltriolborate led to a better yield. For further improvement in yield, we then screened *ortho*-silyl groups of benzaldehyde (entries 9–12). Among the silyl groups employed, the Me_2PhSi group gave the desired product with the best chemical yield (81%, entry 10). From the viewpoint of both chemical yield and enantioselectivity, we chose the Me_2PhSi group as an *ortho*-substituent. The protodesilylation of the diarylmethanol **2** bearing a Me_2PhSi group was examined. The Me_2PhSi group was smoothly deprotected with 2 mol equiv. of CsF within 10 min, affording **3** in quantitative yield (cf. in the case of **2** bearing a TMS group, the protodesilylation was required for 15 h with 40 mol equiv of CsF to complete the reaction, affording **3** in 88% yield) (Scheme 1).

Encouraged by the results of the above arylation and protodesilylation, we tested the generality of this reaction (Table 2). The arylation of the combination of several aryltriolborates and *o*-dimethylphenylsilylaldehydes, gave **2** with good enantioselectivity up to 99% ee. To our knowledge, this is the first successful example of asymmetric Ni-catalyzed arylation of aldehyde with a boron reagent. Then, the entire amount of **2** was smoothly protodesilylated, affording the corresponding diarylmethanols **3** in high yields, as shown in Scheme 2.

We assume the mechanism for the arylation as shown in Scheme 3. The duphos-Ni complex initially reacts enantiodiscriminatively with aldehyde to generate η^2-coordinated complex[13] **4** and/or its resonance type **5**. Subsequent *trans*-metalation with

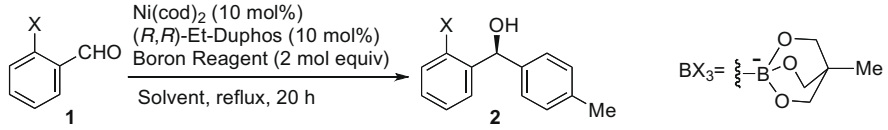


Scheme 1. Protodesilylation.

* Corresponding authors.
E-mail addresses: kazu@gakushikai.jp (K. Kondo), aoyama@phar.nagoya-cu.ac.jp (T. Aoyama).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.08.019

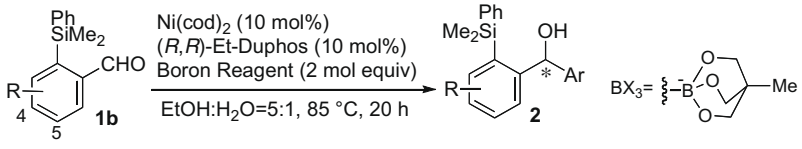
Table 1
Effects of Boron reagents and solvents



Entry	Aldehyde	Boron reagent	Solvent	Yield (%)	ee[a] (%)
1[b]	**1a**: X = TMS	*p*-tolylB(OH)$_2$	Dioxane/H$_2$O = 5:1	Trace[c]	—
2[b]	**1a**	*p*-tolylB(OH)$_2$	EtOH/H$_2$O = 5:1	Trace[c]	—
3	**1a**	K(*p*-Tolyl)BF$_3$	Dioxane/H$_2$O = 5:1	Trace[c]	—
4	**1a**	K(*p*-Tolyl)BF$_3$	EtOH/H$_2$O = 5:1	Trace[c]	—
5[d]	**1a**	(*p*-TolylBO)$_3$	dioxane/H$_2$O = 5:1	22[c]	89 (*S*)
6[d]	**1a**	(*p*-TolylBO)$_3$	EtOH/H$_2$O = 5:1	40[c]	87 (*S*)
7	**1a**	Cs(*p*-Tolyl)BX$_3$	EtOH/H$_2$O = 5:1	32[c]	94 (*S*)
8	**1a**	K(*p*-Tolyl)BX$_3$	EtOH/H$_2$O = 5:1	58[c]	94 (*S*)
9	**1b**: X = Me$_2$PhSi	Cs(*p*-Tolyl)BX$_3$	EtOH/H$_2$O = 5:1	64[c]	90 (*S*)
10	**1b**	K(*p*-Tolyl)BX$_3$	EtOH/H$_2$O = 5:1	81	90 (*S*)
11	**1c**: X = Me$_2$HSi	K(*p*-Tolyl)BX$_3$	EtOH/H$_2$O = 5:1	Trace	—
12	**1d**: X = Ph$_3$Si	K(*p*-Tolyl)BX$_3$	EtOH/H$_2$O = 5:1	Trace	—

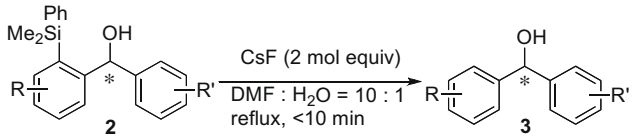
[a] Determined by HPLC analysis after desilylation. The absolute configuration of the desilylated product was determined by comparison of its retention time (HPLC) to a sample known configuration.
[b] 1.5 mol equiv of NaO*t*-Bu was used.
[c] TLC showed the major remainder to be the starting aldehyde.
[d] 0.5 mol equiv of NaO*t*-Bu and 2/3 mol equiv of boroxine were used.

Table 2
Generality



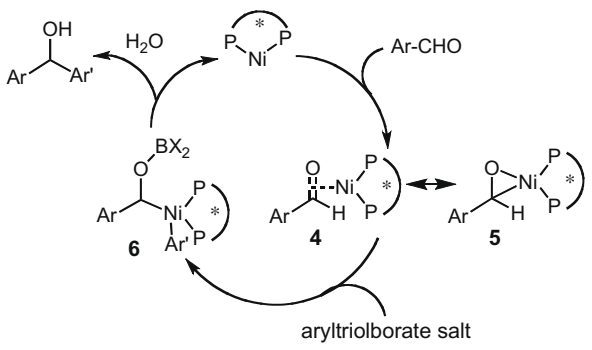
Entry	Aldehyde **1b** (R =)	Boron reagent	Yield (%)	ee[a] (%)
1	H	K(*p*-F–C$_6$H$_4$)BX$_3$	90	>99 (*S*)
2	H	K(*p*-*i*-Pr–C$_6$H$_4$)BX$_3$	73[c]	93
3	H	K(*m*-tolyl)BX$_3$	94	93 (*S*)
4	H	K(3,5-di-Me–C$_6$H$_3$)BX$_3$	92	>99
5	H	K(*m*-MeO–C$_6$H$_4$)BX$_3$	81[c]	92 (*S*)
6[b]	H	K(*p*-MeO–C$_6$H$_4$)BX$_3$	90	89 (*S*)
7	4-Me	KPhBX$_3$	70[c]	91 (*R*)
8	5-F	K(*p*-tolyl)BX$_3$	84[c]	91 (*R*)
9[d]	5-F	K(*p*-MeO–C$_6$H$_4$)BX$_3$	72[c]	90
10	5-MeO	K(*p*-tolyl)BX$_3$	98	93

[a] Determined by HPLC analysis after desilylation. The absolute configuration of the desilylated product was determined by comparison of its retention time (HPLC) to a sample known configuration.
[b] Performed in EtOH/H$_2$O = 19:1 at 70 °C.
[c] TLC showed the major remainder to be the starting aldehyde.
[d] Performed at 70 °C.



Scheme 2. Protodesilylation of **2** shown in Table 2. Reagents and conditions: R = H, R′ = *p*-F (y. 100%); *p*-*i*-Pr (100%); *m*-Me (y. 99%); 3,5-di-Me (y. 100%); *m*-MeO (y. 96%); *p*-MeO (y. 99%). R = 4-Me, R′ = H (y. 100%); R = 4-Me, R′ = H (y. 99%); R = 5-F, R′ = *p*-Me (y. 100%); R = 5-F, R′ = *p*-MeO (y. 94%); R = 5-MeO, R′ = *p*-Me (y. 98%).

the arylborate affords **6**. Since, in this step, enantiodiscrimination of **4** and/or **5** would be kept, this arylation would give good enantioselectivity. Reductive elimination and protonolysis furnish the chiral diarylmethanol and regenerate the duphos-Ni complex.



Scheme 3. Plausible reaction mechanism.

In summary, in the Et-duphos-Ni-catalyzed asymmetric arylation, we utilized a Me_2PhSi group as an *ortho*-substituent, which led to good enantioselectivity (up to 99% ee). To our knowledge, this is the first successful example of asymmetric Ni-catalyzed arylation of aldehyde with a boron reagent. In the near future, we hope that our developed method will be one of the candidates for the synthesis of chiral diarylmethanols in addition to Shibasaki's method.[14]

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.019.

References and notes

1. Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454–471.
2. (a) Tomita, D.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4138–4139; (b) Tomita, D.; Kanai, M.; Shibasaki, M. *Chem. Asian J.* **2006**, *1–2*, 161–166.
3. Iminoalcohol-catalyed asymmetric arylation with the combination of arylboronic acid and 7.2 equiv of Et_2Zn: Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850–14851.
4. Miyaura's group first reported that Rh(I) complexes catalyze the asymmetric 1,2-addition to 1-naphthaldehyde with phenylboronic acid, giving the corresponding products in 41% ee: Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 3279–3281; Quite recent successful example of Ru-catalyzed asymmetric arylation with arylboronic acids: Yamamoto, Y.; Kurihara, K.; Miyaura, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4414–4416.
5. For other Rh-catalyzed asymmetric arylations of aldehydes and activated ketones with arylboron reagents, see: (a) Moreau, C.; Hague, C.; Weller, A. S.; Frost, C. G. *Tetrahedron Lett.* **2001**, *42*, 6957–6960; (b) Focken, T.; Rudolph, J.; Bolm, C. *Synthesis* **2005**, 429–436; (c) Suzuki, K.; Ishii, S.; Kondo, K.; Aoyama, T. *Synlett* **2006**, 648–650; (d) Suzuki, K.; Kondo, K.; Aoyama, T. *Synthesis* **2006**, 1360–1364; (e) Arao, T.; Sato, K.; Kondo, K.; Aoyama, T. *Chem. Pharm. Bull.* **2006**, *54*, 1576–1581; (f) Arao, T.; Suzuki, K.; Kondo, K.; Aoyama, T. *Synthesis* **2006**, 3809–3814; (g) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353–3356; (h) Duan, H.-F.; Xie, J.-H.; Shi, W.-J.; Zhang, Q.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 1479–1481; (i) Jagt, R. B. C.; Toullec, P. Y.; Schudde, E. P.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *J. Comb. Chem.* **2007**, *9*, 407–414; (j) Toullec, P. Y.; Jagt, R. B. C.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Org. Lett.* **2006**, *8*, 2715–2718; (k) Duan, H.-F.; Xie, J.-H.; Qiao, X.-C.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4351–4353; For Pd-catalyzed asymmetric intramolecular arylations of ketones with arylboron substrate: (l) Liu, G.; Lu, X. *J. Am. Chem. Soc.* **2006**, *128*, 16504–16505.
6. For recent contributions of Ni-catalyzed addition to aldehydes, see: (a) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698–3699; (b) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442–3443; (c) Saito, N.; Yamazaki, T.; Sato, Y. *Tetrahedron Lett.* **2008**, *49*, 5073–5076; (d) Sato, Y.; Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 1624–1634.
7. (a) Arao, T.; Kondo, K.; Aoyama, T. *Tetrahedron Lett.* **2007**, *48*, 4115–4117; (b) Yamamoto, K.; Tsurumi, K.; Sakurai, F.; Kondo, K.; Aoyama, T. *Synthesis* **2008**, 3585–3590; (c) Sakurai, F.; Kondo, K.; Aoyama, T. *Chem. Pharm. Bull.* **2009**, *57*, 511–512.
8. For recent successful examples of synthesis of chiral diarylmethanol or diarylmethylamine with an *ortho*-substituted substrate, see: *ortho*-various substituents: (a) Ohkuma, T.; Koizumi, M.; Ikehira, H.; Yokozawa, T.; Noyori, R. *Org. Lett.* **2000**, *2*, 659–662; *ortho*-TMS group: (b) Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128–8129; *orhto*-Cl, Br, and TMS groups: (c) Lee, C.-T.; Lipshutz, B. H. *Org. Lett.* **2008**, *10*, 4187–4190.
9. Yamamoto, Y.; Takizawa, M.; Yu, X.-Q.; Miyaura, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 928–931.
10. Many ligands such as BINAP, Segphos, DIPAMP, DIOP, BPPM, and DPPFA derivatives resulted in no reaction.
11. The use of 95%EtOH, DMF, DMSO, MeCN, toluene, 2-propanol or 1-butanol as a solvent gave less satisfactory results.
12. The use of Na and Rb salts as an aryltriolborate gave less satisfactory results.
13. η^2-Coordinated nickel complexes with aldehydes have been reported: (a) Ogoshi, S.; Oka, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2004**, *126*, 11802–11803; (b) Ogoshi, S.; Kamada, H.; Kurosawa, H. *Tetrahedron* **2006**, *62*, 7583–7588.
14. Other spectral data were shown in Supplementary data except for the below. Potassium 1-aryl-4-methyl-2,6,7-trioxa-1-boranuidabicyclo[2.2.2]octanes were prepared according to the same procedure reported.[9]
Preparation of ortho-dimethylphenylsilylbenzaldehyde (**1b**): To a stirred solution of *ortho*-bromobenzaldehyde (3.0 mL 25.0 mmol) in EtOH (54 mL) was added $TsOH{\cdot}H_2O$ (905 mg 4.71 mmol) at rt. The reaction mixture was stirred for 21 h under reflux, allowed to cool, quenched by the addition of $NaHCO_3$ aq at 0 °C, and directly evaporated. The residue was diluted with H_2O and extracted with EtOAc. The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. These crude products (6.68 g) were used for the next step without purification. To a stirred solution of the crude products (6.68 g) in Et_2O (20 mL) was gradually added BuLi (19.0 mL, 31.4 mmol 1.65 M in hexane) at −78 °C. The reaction mixture was stirred for 1 h at −78 °C. To this solution was gradually added $Me_2PhSiCl$ (5.2 mL 30.6 mmol), and then the whole mixture was stirred for 0.5 h at −78 °C and additionally for 3 h at rt, quenched by the addition of water, and extracted with EtOAc. The organic extracts were washed with saturated NH_4Cl aq and brine, dried (Na_2SO_4), and concentrated. These crude products were used for the next step without purification. The solution of the crude products and $TsOH{\cdot}H_2O$ (991 mg 5.26 mmol) in acetone (100 mL) was stirred for 1 h at rt, quenched by the addition of saturated $NaHCO_3$ aq at 0 °C, and directly evaporated. The residue was diluted with water and extracted with EtOAc. The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification by SiO_2 column (hexane/EtOAc = 30:1) afforded *ortho*-dimethylphenylsilylbenzaldehyde (4.93 g, overall 82 %) as a colorless oil. IR (neat): 1713 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.63 (s, 6H), 7.30–7.35 (m, 3H), 7.48–7.65 (m, 5H), 7.89–7.92 (m, 1H), 10.04 (s, 1H). ^{13}C NMR($CDCl_3$): δ = −1.09, 127.70, 128.86, 129.60, 131.80, 132.87, 133.82, 136.58, 138.59, 140.62, 141.04, 192.74. FABMS: m/z = 241 (M^++1). Anal. Calcd for $C_{15}H_{16}OSi$: C, 74.95; H, 6.71; found: C, 74.55; H, 6.81.
Representative procedure for the asymmetric Ni-catalyzed arylation (Table 2, entry 4): To a stirred solution of (*R*,*R*)-Et-duphos (11.1 mg, 0.0300 mmol) in EtOH (0.6 mL) were added potassium 1-(3,5-dimethylphenyl)-4-methyl-2,6,7-trioxa-1-boranuidabicyclo[2.2.2]octane (163 mg, 0.600 mmol), *ortho*-dimethylphenylsilylbenzaldehyde (**1b**) (72.2 mg, 0.300 mmol), $Ni(cod)_2$ (8.3 mg, 0.0300 mmol), and H_2O (0.12 mL). The reaction mixture was stirred for 20 h at 85 °C (oil bath temperature) and allowed to cool. After usual work-up, purification by silica gel column (hexane/EtOAc = 20:1) afforded 3,5-dimethylphenyl-2-dimethylphenylsilylphenylmethanol (95.9 mg, 92%) as a colorless oil. IR (neat): ν = 3383 cm^{-1}. ^1H NMR($CDCl_3$): δ = 0.63 (s, 3H), 0.67 (s, 3H), 1.74 (br s, 1H), 2.19 (s, 3H×2), 5.86 (s, 1H), 6.65 (s, 2H), 6.80 (s, 1H), 7.18–7.34 (m, 6H), 7.51–7.63 (m, 3H). ^{13}C NMR ($CDCl_3$): δ = −0.59, −0.49, 21.53, 74.45, 124.02, 127.13, 128.20, 128.50, 128.57, 129.35, 130.34, 133.99, 135.19, 136.59, 137.49, 139.37, 143.25, 149.92. EIMS: m/z = 329 (M^+−OH), 269 (M^+−Ph), 253 (bp), 211 (M^+−$SiMe_2Ph$). HRMS (M^+−Ph): calcd for $C_{17}H_{21}OSi$: 269.12966; found: 269.13618. *Protodesilylation*: The reaction mixture of 3,5-dimethylphenyl-2-dimethylphenylsilylphenylmethanol (28.3 mg, 0.0820 mmol) and CsF (24.8 mg, 0.163 mmol) in DMF/H_2O (10:1, 0.55 mL) was stirred for 10 min under reflux and allowed to cool. After usual work-up, purification by silica gel column (hexane/EtOAc = 10:1) afforded 3,5-dimethylphenyl-phenylmethanol (17.4 mg, 100%, >99% ee) as a colorless oil. The ee was determined by HPLC analysis using Daicel chiralpak IA. IR (neat): ν = 3354 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.17 (br d, 1H, J = 2.6 Hz), 2.29 (s, 3H×2), 5.76 (s, 1H), 6.90 (s, 1H), 6.98 (s, 1H), 7.22–7.40 (m, 6H). ^{13}C NMR ($CDCl_3$): δ = 21.43, 76.32, 124.21, 126.37, 127.34, 128.34, 129.16, 137.97, 143.65, 143.79. EIMS: m/z = 212 (M^+), 107 (bp). HRMS (M^+): calcd for $C_{15}H_{16}O$: 212.12012; found: 212.11923.