Synlett C. K. De et al. Cluster

# Design and Synthesis of Enantiopure Tetrakis(pentafluorophenyl) Borate Analogues for Asymmetric Counteranion Directed Catalysis

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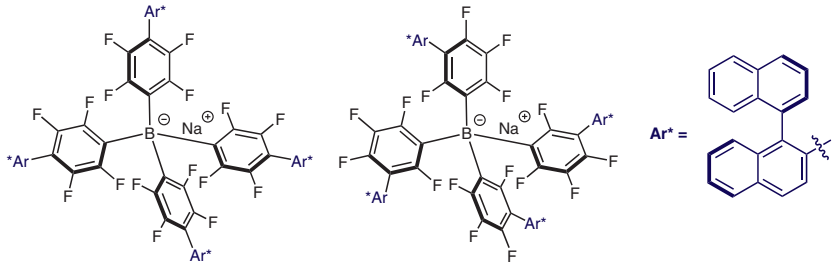
Published as part of the Cluster *Silicon in Synthesis and Catalysis*




Received: 13.06.2017
Accepted after revision: 16.08.2017
Published online: 30.08.2017
DOI: 10.1055/s-0036-1590903; Art ID: st-2017-d0462-c

**Abstract** The design and five-step synthesis of chiral tetrakis(pentafluorophenyl) borate analogues from commercially available enantiopure BINOL is described. The chiral anions have been tested in a catalytic asymmetric Mukaiyama aldol reaction.

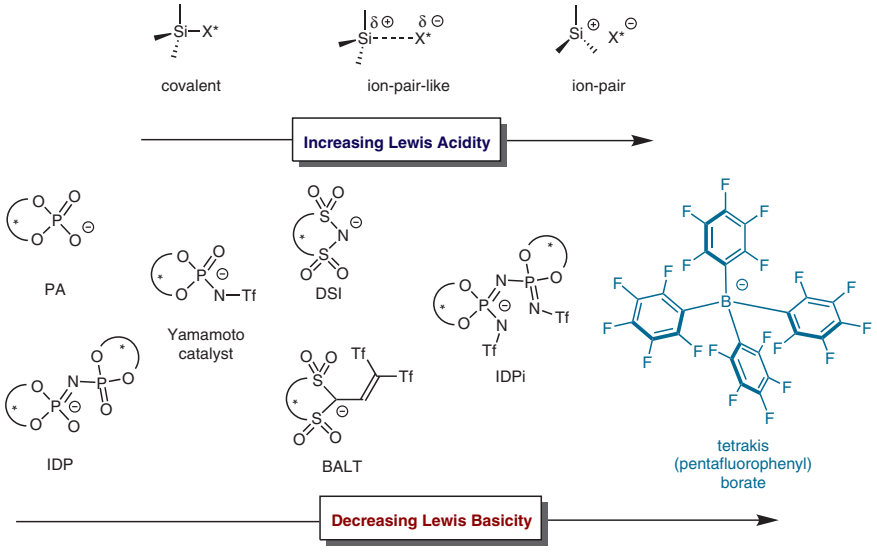
**Key words** asymmetric counteranion-directed catalysis (ACDC), weakly coordinating anion (WCA), chiral $BAr^F$, Mukaiyama aldol reaction

Asymmetric counteranion-directed catalysis (ACDC)[1] has recently been recognized as a broadly applicable approach to asymmetric synthesis. It refers to *'the induction of enantioselectivity in a reaction proceeding through a cationic intermediate by means of ion pairing with a chiral, enantiomerically pure anion provided by the catalyst'*.[1f] Recently, intensive research on pairing catalytically generated cationic intermediates, such as iminium ions, oxocarbenium ions, and cationic organometallic fragments, with enantiopure anions has led to several new asymmetric reactions.[2,3] ACDC with silylium ion equivalents has emerged as a particularly powerful strategy for Lewis acid organocatalysis. As depicted in Scheme 1, the character of the Si–X* bond of the catalyst can be tuned by modifying the counteranion. To increase the Lewis acidity on silicon, the counteranion has to be less basic. We are interested in exploring ever more reactive silylium-ACDC catalysts and therefore in the design of weakly basic (or 'weakly coordinating') chiral anions.[3c] Our studies have led to the advancement of the relatively mildly acidic chiral phosphoric acids to more confined IDP catalysts,[3d] more acidic DSI catalysts,[3c] much more acidic BALT catalysts,[3e] and recently to highly confined *and* highly acidic IDPi catalysts,[3f] which enable powerful silylium-ACDC processes. In the extreme scenario of a super strong silylium Lewis acid catalyst, the Si–X* bond would be completely ionic.[4a] Toward achieving this, non-coordinating chiral anions are required. The fascinating question of whether or not such anions will be capable of inducing asymmetry may appear contradictorily, but is certainly in need of an answer. Here, we report the design and synthesis of chiral enantiopure tetrakis(pentafluorophenyl) borate ($B(C_6F_5)_4^-$) analogues and their exploration in the Mukaiyama aldol reaction.

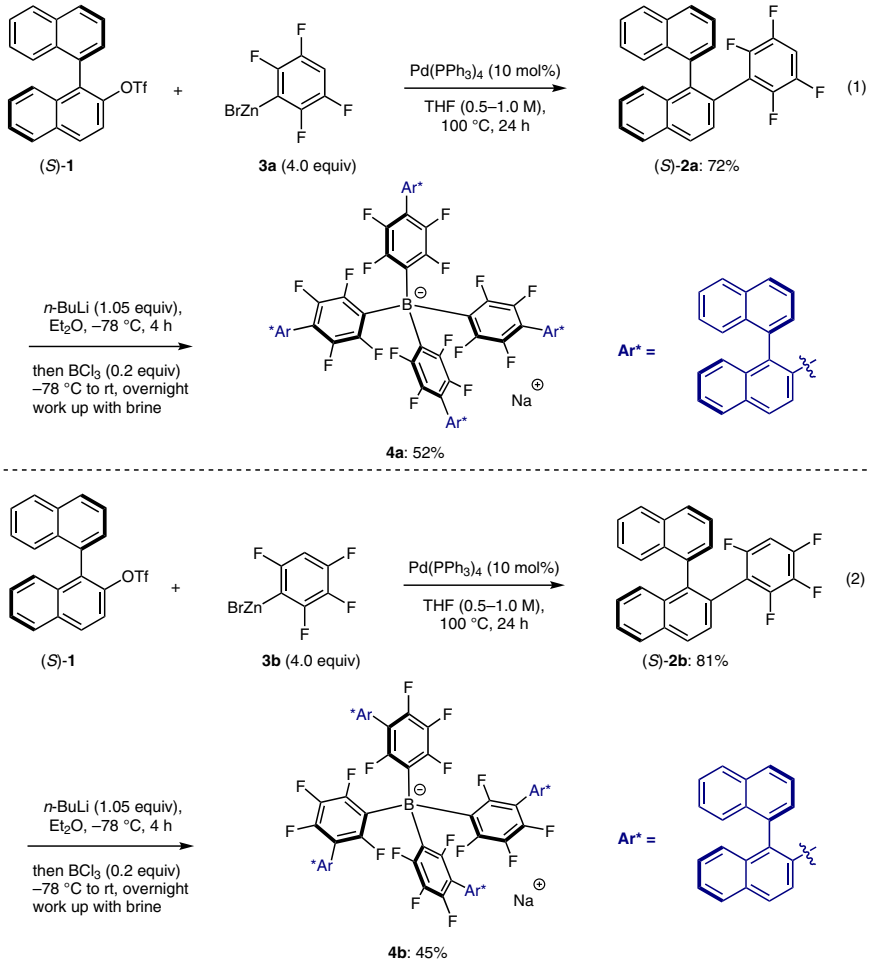
So-called non-coordinating or weakly coordinating anions (WCAs) are becoming increasingly relevant in fundamental and applied chemistry due to their versatile utilities.[4,5] Examples of weakly coordinating anions include $[B(C_6F_5)_4]^-$, $[Sb(OTeF_5)_6]^-$, $[CB_{11}Me_6X_6]^-$ and $[Al(OR^F)_4]^-$. To develop a weakly coordinating anion, its interaction with the cation has to be minimized, which can be achieved by delocalizing the negative charge over a large, non-nucleophilic area. While it remains challenging to design a WCA with essentially no interaction with its countercation, an anion is considered 'non-coordinating' when its coordination towards the cation is weaker than that of surrounding solvent molecules.

We became interested in designing chiral tetrakis(pentafluorophenyl) borate ($B(C_6F_5)_4^-$) analogues. Toward this end, we decided to attach a chiral 1,1′-binaphthalen-2-yl unit onto the perfluorinated aryl groups of the borate anion leading to salts **4a** and **4b** (Scheme 2).

Our synthesis commenced with (*S*)-[1,1′-binaphthalen]-2-yl trifluoromethanesulfonate (**1**), which was prepared from commercially available (*R*)-BINOL in three steps on a gram-scale by following a known procedure.[6] Our initial efforts toward incorporating a tetrafluorophenyl unit onto binaphthyltriflate (*S*)-**1** via Suzuki coupling with the corresponding tetrafluorophenyl boronic acid yielded only trace amounts of product **2a**. An alternative approach for the Suzuki coupling could be reversing the reacting partners; that is, a reaction between [1,1′-binaphthalen]-2-ylboronic

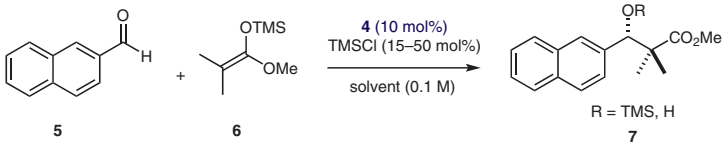



**Scheme 1** Effect of the chiral counteranions on silylium Lewis acidity (Tf = -$SO_2CF_3$)




**Scheme 2** Preparation 2-tetrafluorophenyl-1,1′-binaphthalene **1** and its application to the synthesis of $BAr^F$ **4**

**Table 1** Application of the Na-BAr$^{F*}$ in the Mukaiyama Aldol Reaction




5 6 7

| Entry | Solvent | TMSCl | Catalyst | *T* (°C) | Time (h) | Conv. (%) | er |
|---|---|---|---|---|---|---|---|
| 1 | $Et_2O$ | yes | no | –40 | 20 | <1 | NA |
| 2 | $Et_2O$ | no | **4a** | –40 | 20 | <1 | ND |
| 3 | $Et_2O$ | yes | **4a** | –40 | 20 | 100 | 50:50 |
| 4 | $Et_2O$ | yes | **4b** | –40 | 20 | 100 | 54:46 |
| 5 | PhMe | yes | **4b** | –100 | 72 | 100 | 58:42 |

acid and tetrafluorobromobenzene. However, this would require an additional step to synthesize [1,1′-binaphthalen]-2-ylboronic acid from binaphthyltriflate (*S*)-**1** via Miyaura borylation.

Gratifyingly, we found that when binaphthyltriflate (*S*)-**1** was reacted with 2,3,5,6-tetrafluorophenyl zinc bromide (**3a**) under Negishi cross-coupling conditions, (*S*)-**2a** was obtained in 72% yield (Scheme 2, Eq. 1). Under similar conditions, the reaction between (*S*)-**1** and 2,3,4,6-tetrafluorophenyl zinc bromide (**3b**) provided (*S*)-**2b** in 81% yield (Scheme 2, Eq. 2). Next, we utilized these two (*S*)-tetrafluorophenyl-1,1′-binaphthalenes to synthesize enantiopure chiral borate sodium salts. Accordingly, a one-pot protocol in which a C–H lithiation was followed by reacting the resulting aryl lithium species with boron trichloride furnished sodium borate salts **4a** and **4b** in 52% and 45% isolated yield, respectively (Scheme 2).

Our next goal was to explore these enantiopure counteranions in enantioselective catalysis. Toward this end, the Lewis acid catalyzed Mukaiyama aldol reaction was evaluated using salts **4a** and **4b**.[7] As a model reaction, 2-naphthaldehyde (**5**) was reacted with silyl ketene acetal **6** in the presence of catalytic amounts of both TMSCl and chiral sodium borates **4** (Table 1). We expected these conditions to generate small quantities of the equivalent of a trimethylsilylium borate salt. With catalyst **4a** the desired aldol product **7** was indeed obtained but in racemic form (entry 3). Catalyst **4b** provided aldol product **7** with a small but reproducible 54:46 er (entry 4). Interestingly, when the reaction was performed at –100 °C in toluene an improved er was observed (entry 5). Neither using salt **4** alone nor TMSCl alone led to any product formation under the reaction conditions.

In summary, we have developed a short synthetic route to enantiopure weakly coordinating borates from enantiopure BINOL.[8,9–12] The key step of our synthetic route involved a Negishi cross-coupling reaction with electron-deficient tetrafluorophenyl zinc bromide. The newly designed and synthesized enantiopure borates **4** were evaluated in a Mukaiyama aldol reaction. Clearly, there is a vast potential for weakly coordinating chiral borates in chemistry that can now be explored.

## Funding Information

Funding from the Max-Planck-Society and the European Research Council (Advanced Grant CHAOS) is gratefully acknowledged.

## Acknowledgment

We thank the technicians of our group and the analytical departments of the institute for support of this work. We thank Dr. Sorto and Dr. Alachraf for early contributions.

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(9) **Synthesis of the Zn-reagent:**
A flame-dried 50 mL Schlenk flask was charged with 1,2,3,5-tetrafluorobenzene (4.0 mmol, 1.0 equiv) and a magnetic stirring bar. To this Schlenk flask, anhydrous THF (20 mL) was added under an argon atmosphere. The mixture was stirred at r.t. for 5 min and then cooled to –78 °C. After 30 min at –78 °C, *n*-BuLi (2.5 M in hexane, 1.65 mL, 4.1 mmol, 1.02 equiv) was slowly added through the cold side-wall of the flask under an argon atmosphere (*Note*: direct addition of *n*-BuLi to the cold mixture could lead to an explosive reaction). The reaction mixture was stirred at –78 °C for 1 h and freshly dried $ZnBr_2$ (1.0 M in THF, 4.2 mL, 4.2 mmol, 1.05 equiv) was slowly added to the reaction mixture and stirring was continued for 20 min. The dry-ice bath was removed and the reaction mixture was allowed to warm to r.t. After 20 min at r.t., ca. 15 mL of THF was removed under reduced pressure (Schlenk technique). This Zn-reagent was directly used for the next step.

(10) **General Procedure for Negishi Cross-Coupling:**
A flame-dried 25 mL Schlenk flask was charged with compound (*S*)-**1** (1.0 mmol, 1.0 equiv) and a magnetic stirring bar. To this flask, the freshly prepared Zn-reagent (4.0 mmol, 4.0 equiv) was transferred under an argon atmosphere. The mixture was degassed (three times) and $Pd(PPh_3)_4$ (10 mol%, 0.1 mmol, 0.1 equiv) was added. The reaction mixture was heated to 100 °C for 24 h, then cooled to r.t. and treated with saturated aq. $NH_4Cl$. The crude reaction mixture was extracted with $CH_2Cl_2$ (3 × 10 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. Purification was performed by $SiO_2$ column chromatography using 10% $CH_2Cl_2$/*i*-hexanes.
**(*S*)-2a:** Prepared according to the general procedure as a colorless solid in 72% yield. $^1H$ NMR (500 MHz, $CD_2Cl_2$): δ = 8.11 (d, *J* = 8.5 Hz, 1 H), 8.03 (d, *J* = 8.3 Hz, 1 H), 7.85 (d, *J* = 8.2 Hz, 2 H), 7.60–7.54 (m, 1 H), 7.52 (d, *J* = 8.5 Hz, 1 H), 7.50–7.45 (m, 1 H), 7.44–7.38 (m, 2 H), 7.36–7.29 (m, 1 H), 7.29–7.21 (m, 3 H), 6.88–6.77 (m, 1 H).
**(*S*)-2b:** Prepared according to the general procedure as a colorless solid in 81% yield. Compound (*S*)-**2b** exists as a 1:1 mixture of rotamers. $^1H$ NMR (500 MHz, $CD_2Cl_2$): δ = 8.09 (d, *J* = 8.5 Hz, 2 H), 8.02 (d, *J* = 8.2, Hz, 2 H), 7.88–7.80 (m, 4 H), 7.60–7.53 (m, 2 H), 7.53–7.37 (m, 8 H), 7.34–7.28 (m, 2 H), 7.28–7.18 (m, 6 H), 6.67–6.58 (m, 1 H), 6.52–6.39 (m, 1 H).

(11) **General Procedure for Synthesis of 4:**
A flame-dried 25 mL Schlenk flask was charged with compound (*S*)-**2a** (1.0 mmol, 1.0 equiv) and a magnetic stirring bar. To this flask, anhydrous $Et_2O$ (5 mL) was added under an argon atmosphere. The mixture was stirred at r.t. for 5 min to dissolve the substrate and was then cooled to –78 °C. After 30 min at –78 °C, *n*-BuLi (2.5 M in hexane, 0.42 mL, 1.05 mmol, 1.05 equiv) was slowly added through the cold side-wall of the flask. The reaction mixture was stirred at –78 °C for 4 h. After 4 h, $BCl_3$ (1.0 M in heptane, 0.2 mL, 0.2 mmol, 0.2 equiv) was slowly added to the reaction mixture and warmed to r.t. over 4 h and the stirring was continued for overnight. Then the mixture was cooled and reaction was subsequently quenched with saturated NaCl (aq.). The crude reaction mixture was extracted with $CH_2Cl_2$ (3 × 10 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. Purification was performed by $SiO_2$ column chromatography using 10% MeOH/$CH_2Cl_2$. The purified product was dissolved in $CH_2Cl_2$ and 10 mL saturated NaCl (aq.) solution was added and the reaction mixture was vigorously stirred for 20 min at r.t. It was then extracted with $CH_2Cl_2$ (3 × 10 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure.
**4a:** Prepared according to the general procedure as a white solid in 52% yield. $^{11}B$ NMR (160 MHz, $CD_2Cl_2$): δ = –17.12. HRMS (ESI): *m*/*z* calcd. for $C_{104}H_{52}BF_{16}$ $[M]^-$: 1615.39205; found 1615.39121.
**4b:** Prepared according to the general procedure as a white solid in 41% yield. $^{11}B$ NMR (160 MHz, $CD_2Cl_2$): δ = –17.22. HRMS (ESI): *m*/*z* calcd. for $C_{104}H_{52}BF_{16}$ $[M]^-$: 1615.39205; found 1615.39121.

(12) **General Procedure for Mukaiyama Aldol Reaction:**
An oven-dried 2 mL GC vial was charged with catalyst **4** (4.1 mg, 0.0025 mmol, 0.1 equiv), aldehyde **5** (3.9 mg, 0.025 mmol, 1.0 equiv) and a magnetic stirring bar. To this vial, solvent (0.25 mL) was added and the mixture was stirred at r.t. for 5 min. Then the mixture was cooled to the reaction temperature. Silyl ketene acetal **6** (6.4 µL, 0.031 mmol, 1.25 equiv) was added followed by TMSCl (0.15–0.5 equiv) under an argon atmosphere. After consumption of aldehyde, the reaction was quenched with saturated $NaHCO_3$ (aq.) solution and the crude mixture was directly purified without further work-up on a $SiO_2$ preparative TLC using 5–20% EtOAc/*i*-hexanes (v/v) as eluent.