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Chiral Bicyclo[2.2.2]octa-2,5-dienyltrifluoroborate Derivative as a Useful and Stable Precursor of C_1-Symmetric Chiral Dienes

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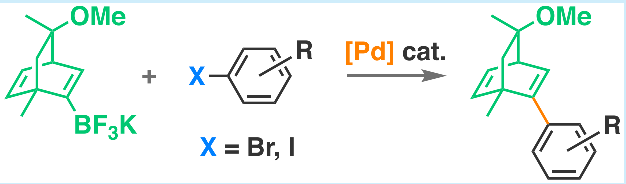
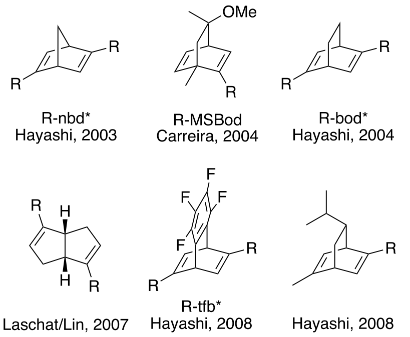
Supporting Information

ABSTRACT: A new approach has been developed to prepare monosubstituted C_1-symmetric chiral dienes Ar-MSBod from easily accessible chiral bicyclo[2.2.2]octa-2,5-dienyltrifluoroborate derivative. This alkenyl trifluoroborate was synthesized in five steps from inexpensive (−)-carvone. This approach allows the construction of large libraries of diversely substituted chiral dienes via cross-coupling reactions with inexpensive and widely available aryl halides.



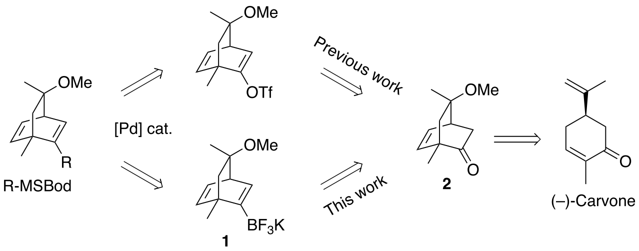
Over the two past decades, the transition metal/chiral diene catalytic systems have proved to be very powerful for the formation of C−C bonds, thanks to their unique reactivity and selectivity due to the strong π-accepting ability of diene ligands.[1] In 2003, Hayashi and co-workers described the first use of chiral dienes for the Rh-catalyzed asymmetric 1,4-addition on α,β-unsaturated ketones using disubstituted bicyclo[2.2.1]heptadiene (nbd*) ligand (Scheme 1).[2] Almost concomitantly, Carreira's group developed another family of chiral dienes, the C_1-symmetric monosubstituted bicyclo[2.2.2]octa-2,5-diene-type ligands (Ar-MSBod), in Ir-catalyzed allylic substitution.[3] Since then, other chiral dienes have been developed bearing different structural backbones, mainly C_2-symmetric bicyclo[2.2.2]octadiene type ligands, like bod*,[4] tfb*,[5] and another[6] developed by Hayashi's group or a disubstituted diene, derived from carvone, described by Carreira and co-workers.[7] Laschat and Lin also reported the development of C_2-symmetric bicyclo[3.3.0]octadienes and their use in asymmetric catalytic reactions.[8]

Scheme 1. Some Representative Chiral Dienes



All of those chiral dienes have been shown to be useful in asymmetric transition-metal-catalyzed reactions, particularly in rhodium-catalyzed asymmetric transformations.[1,9] Among these chiral dienes, the C_1-symmetric Ar-MSBod ligands are attractive not only because they have been shown to be efficient in many rhodium-catalyzed reactions[10] but also because of their ease of synthesis starting from the cheap and commercially available (+)- or (−)-carvone (Scheme 2).

Scheme 2. New Synthetic Route for the Preparation of R-MSBod



In 2004, Carreira's group reported the first synthesis of Ar-MSBod ligands using a Negishi-type coupling with the triflate derived from ketone **2**[11] and arylzinc reagents (Scheme 2).[3] Inspired by this work, we described a more general preparation of Ar-MSBod by introducing the aryl substituent through a palladium-catalyzed Suzuki−Miyaura cross-coupling reaction with readily available arylboron reagents.[12] However, this approach presented some drawbacks such as the cost of the triflating reagents, the use of large excess of aryl derivative reagents, and sometimes low yields, particularly for introducing bulky aryl substituents and a moderate availability of commercial organoboron compounds.

We envisioned a reverse approach for the synthesis of Ar-MSBod ligands, involving the cross-coupling of potassium

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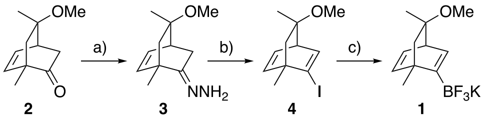
alkenyl trifluoroborate **1** with aryl halides (Scheme 2). Interest in potassium organotrifluoroborates lies in their high stability, easy purification, and good reactivity in palladium-catalyzed cross-coupling reactions.[13] Another advantage of this reverse approach comes from the great diversity and availability of aryl halides, allowing a fast access to larger libraries of monosubstituted dienes.

We report herein a facile and readily scalable synthesis of enantiomerically pure Ar-MSBod relying on the alkenyl trifluoroborate key derivative **1** as coupling partner with aryl halide reagents through the Suzuki–Miyaura reaction.

We envisioned the formation of potassium alkenyl trifluoroborate **1** via lithium–halogen exchange from the corresponding vinyl iodine **4** (Scheme 3), which could be prepared from readily available ketone **2**. Among the few approaches described for transforming a ketone to vinyl iodide, the Barton iodination reaction[14] is predominantly used, although it requires the prior conversion of the ketone to hydrazone. In the presence of iodine and a strong non-nucleophilic base, the hydrazone is generally converted to vinyl iodide with good yields.[15]

Scheme 3. Preparation of Potassium Alkenyltrifluoroborate 1[a]



[a]Key: (a) $NH_2NH_2 \cdot H_2O$ (2.5 equiv), AcOH cat., EtOH, rt, 91%; (b) I_2 (2 equiv), DABCO (5 equiv), Et_2O, rt, 63%; (c) *n*-BuLi (1.1 equiv), $B(OMe)_3$ (1.5 equiv), THF, −78 °C to rt, then aq KHF_2 (8 equiv), 75%.

To avoid the reduction of the double bond, mild conditions were used to convert ketone **2** to hydrazone **3**, that is, hydrazine monohydrate, in the presence of a catalytic amount of acetic acid, which provided the expected hydrazone **3** in 72% yield after recrystallization. Hydrazone **3** was converted to the vinyl iodide **4** by oxidation using iodine and DABCO at room temperature in 63% yield. Vinyl iodide **4**, which provides a cheap alternative to the corresponding triflate derivative, was successfully cross-coupled with arylboronic acids to prepare Ar-MSBod via Suzuki–Miyaura cross-coupling.[16] However, vinyl iodide **4** proved to be quite unstable at room temperature. which motivated the formation of potassium organotrifluoroborate **1**, affording an attractive alternative for the formation of Ar-MSBod ligands. The potassium trifluoroborate derivative **1** was obtained from the vinyl iodide **4** in 75% yield via lithium–halogen exchange, transmetalation, and fluorination. To the best of our knowledge, this is the first example of formation of a chiral diene–BF_3K. Starting from (+)-carvone, it is possible to synthesize the other enantiomer of this chiral alkenyl trifluoroborate.

At this stage, no single crystals suitable for X-ray analysis could be obtained from alkenyl trifluoroborate **1**, but the structure of the corresponding boronic acid **7**, obtained by defluorination of **1** over wet silica gel,[17] was unambiguously confirmed (Scheme 4).

Formation of Ar-MSBod via Suzuki–Miyaura reaction was then studied using the Pd-catalyzed cross-coupling between the alkenyl trifluoroborate **1** and 4-bromoanisole (**5a**) as model substrates (Table 1).

Scheme 4. Preparation of Alkenylboronic Acid 7 and X-ray Crystal Structure of 7·H_2O

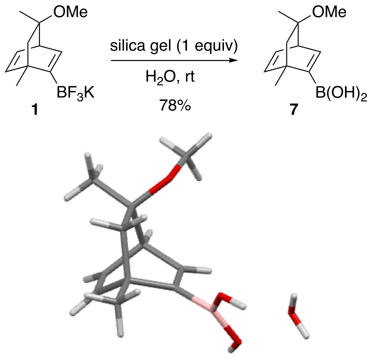
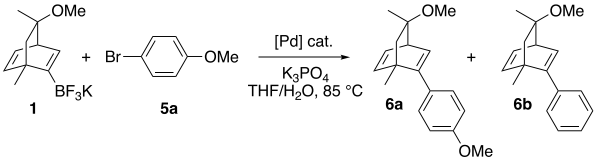


Table 1. Optimization of the Suzuki–Miyaura Reaction with 1[a]



entry	[Pd] cat.	ligand	conv of **5a**[b] (%)	**6a**/**6b** ratio[b]
1	$PdCl_2$	PPh_3	48	50:50
2	$Pd(OAc)_2$	PPh_3	32	78:22
3	Pd_2dba_3	PPh_3	52	67:33
4[c]	Pd_2dba_3	dppf	48	86:14
5[c]	Pd_2dba_3	RuPhos	30	100:0
6[c]	Pd_2dba_3	$HPCy_3BF_4$	43	100:0
7	RuPhos Pd G4		25	100:0
8[c]	$Pd(OAc)_2$	$HPCy_3BF_4$	17	100:0
9	PCy_3 Pd G4		16	100:0
10[d]	Pd_2dba_3	$HPCy_3BF_4$	100	100:0

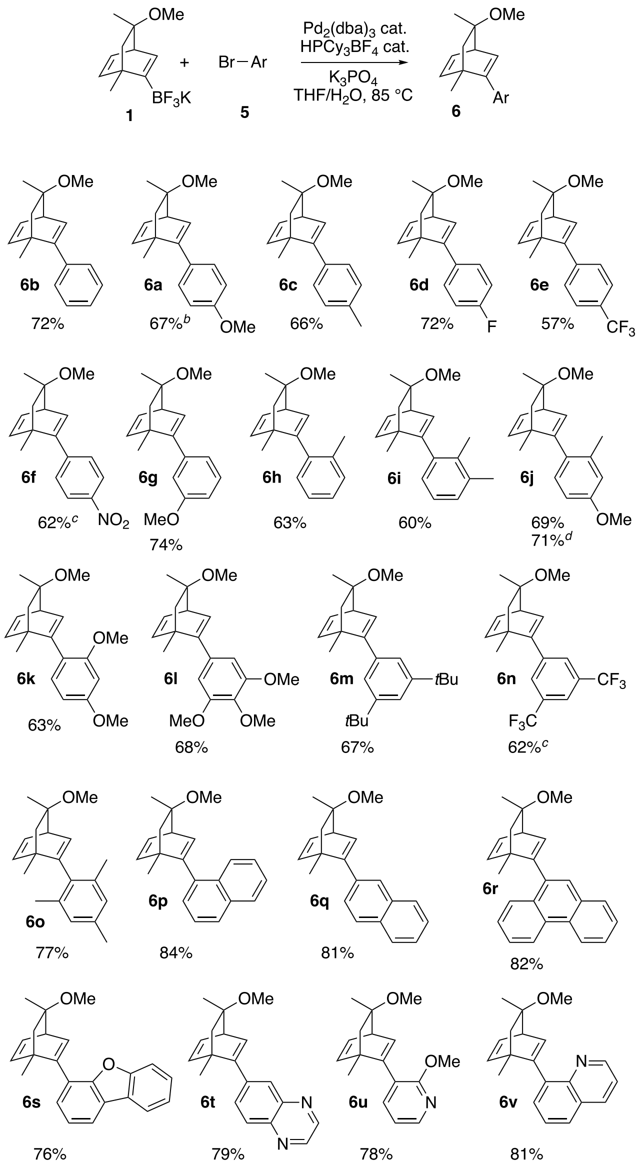
[a]The reaction was conducted with **1** (0.3 mmol), **5a** (0.25 mmol), [Pd] cat. (4 mol % Pd), ligand (12 mol %) and K_3PO_4 (0.9 mmol) in degassed THF/H_2O 10:1 at 85 °C. [b]Determined by GC using naphthalene as internal standard. [c]8 mol % of ligand. [d]Pd_2dba_3 (8 mol % Pd) and $HPCy_3BF_4$ (16 mol %).

Inspired by the work of Molander's group[18] dealing with the Suzuki–Miyaura reaction of alkenyl trifluoroborates and aryl halides, catalytic systems, using Pd(II) sources and PPh_3 as ligand, were tried (Table 1, entries 1 and 2), using THF/water as solvent mixture and K_3PO_4 as a base. However, these conditions showed low conversions of 4-bromoanisole. More surprisingly, a side product **6b** was observed which resulted from the exchange of one of the phenyl group of PPh_3, indicating that the reduction elimination is the rate-determining step.[19] The use of a Pd(0) precursor, Pd_2dba_3, offered a better reactivity than $PdCl_2$ favoring the formation of the desired diene **6a** (Table 1, entries 3 and 4). To avoid aryl scrambling on the palladium center, some nonphenyl-containing phosphine ligands were evaluated in the presence of Pd_2dba_3 (Table 1, entries 5 and 6). Despite lower activity compared to [Pd/PPh_3] catalytic systems, the formation of side product **6b** was totally suppressed. Other sources of Pd(II), such as $Pd(OAc)_2$ and Buchwald's precatalysts, known for their readily activation in mild conditions,[20] did not offer better reactivity (Table 1, entries 7–9). It seems that the in situ reduction of Pd(II) to Pd(0) is a limiting process which, in this case, forces the use of Pd(0) directly. Finally, a full conversion of 4-bromoanisole had been obtained by increasing the catalyst loading to 8 mol % Pd in the presence of $HPCy_3BF_4$ as ligand (Table 1, entry 10). These reaction conditions allowed us to isolate the desired diene **6a** in 67% yield, without any formation of other side products.

These conditions proved to be quite general, and the reaction of diversely substituted aryl bromide reagents **5** with **1** afforded the expected Ar-MSBod **6** with moderate to good yields (Scheme 5).

These optimized conditions are also adapted for the coupling of aryl iodides as the reaction of 4-iodoanisole, under identical conditions, furnished the chiral diene **6a** in 71% yield. Chiral dienes **6f** and **6n** were also obtained from the corresponding aryl iodide with good yields. However, cross-coupling reaction with more interesting aryl chlorides failed. Moreover, cross-coupling reaction with 2- and 3-substituted electron-rich aryl bromides does afford the expected chiral Ar-MSBod with equally good yields, while the cross-coupling of the corresponding diene triflate with the corresponding boronic acids was generally low yielding.[3,10e−g,12] Indeed, the yields were increased by 10 to 30% in the formation of chiral dienes **6a**, **6g**, and **6j−m**, and compound **6o** was produced with 77% yield, while the coupling of the corresponding diene triflate was low yielding (11%). This represents an interesting feature of this approach as those 2- and 3-substituted chiral diene are generally the most effective in asymmetric rhodium-catalyzed reactions.[10] Diversely substituted heteroaryl bromides were also successfully cross-coupled with **1** to afford chiral dienes bearing dibenzo[*b*,*d*]furan (**6s**), quinoxaline (**6t**), pyridine (**6u**), or quinoline (**6v**) substituents with good yields. The efficiency of this approach to monosubstituted chiral dienes was supported by a scale-up experiment. Under standard conditions, a gram-scale reaction of **1** with 1-bromo-4-methoxy-2-methylbenzene delivered the desired diene **6j** in 71% yield.

Scheme 5. Chiral Ar-MSBod from Potassium Alkenyltrifluoroborate 1[a]



[a]The reaction was conducted with **1** (0.3 mmol), aryl bromide **5** (0.25 mmol), K_3PO_4 (0.9 mmol), Pd_2dba_3 (4 mol %), and $HPCy_3BF_4$ (16 mol %) in degassed THF/H_2O 10:1 at 85 °C. Isolated yields are indicated. [b]71% yield using 4-iodoanisole instead of 4-bromoanisole and no reaction observed using 4-chloroanisole instead of 4-bromoanisole. [c]Reaction from the corresponding aryl iodide. [d]Reaction conducted with 4 mmol of **1**.

In conclusion, we have developed an efficient and easily scalable method for the synthesis of Ar-MSBod chiral diene ligands using the Suzuki−Miyaura cross-coupling reaction of stable potassium bicyclo[2.2.2]octa-2,5-dienyltrifluoroborate derivative **1** as key intermediate and inexpensive and widely available aryl halides. This synthetic approach allows the formation of a large variety of Ar-MSBod, notably the ones substituted in the *ortho* positions, which could further lead to better activity and selectivity in transition-metal/chiral diene catalytic systems.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01609.

Experimental procedures, description of the compounds, and X-ray diffraction of 7 (PDF)

Accession Codes

CCDC 1903322 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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