Exploration of New Reactivities of Azetidinols and Alkynylborates

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2014

Preface

The studies presented in this thesis have been carried out under the direction of Professor Masahiro Murakami at Kyoto University during 2008-2014. The studies concerned with the development of the new synthetic reactions using azetidinols and alkynyl borates.

The author would like to express his sincerest gratitude to Professor Masahiro Murakami for his kind guidance, powerful encouragement, stimulating discussions throughout this study. The author learned a lot of things from Professor Murakami. They are not only chemistry but also important things to live.

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General Introduction

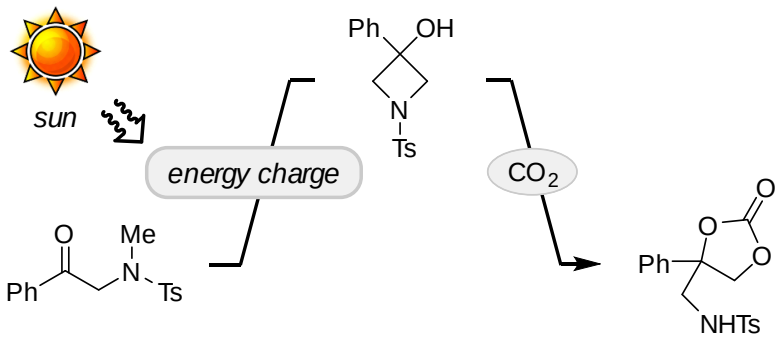
Organic synthesis has contributed to our lives. For example, various chemical industries, pharmaceutical chemistry, material chemistry, and others make our lives more comfortable and convenient.

In this thesis, the author would like to describe new synthetic reactions which are directed towards following issues.

(1) Solar-driven incorporation of carbon dioxides into α-amino ketones
(2) 1,5-Rhodium shift in rearrangement of *N*-arenesulfonylazetidinols into benzo-sultams
(3) Palladium catalyzed reaction of alkynylborates with aryl halides

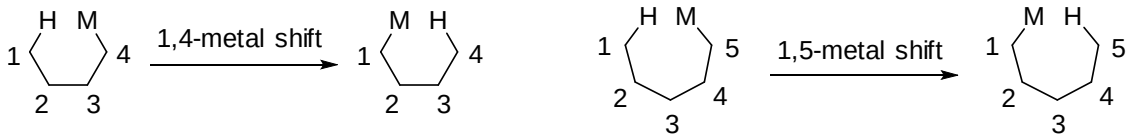
(1) Solar-driven incorporation of carbon dioxides into α-amino ketones

The utilization of solar energy is an attractive subject in organic synthesis because solar energy is one of the most sustainable energy in the world.[1] On the other hand, the utilization of carbon dioxides as the C1 source is still significant challenge because of its stability.[2] In chapter 1, the author describs solar-driven incorporation of carbon dioxide into α-amino ketones. In first step, photoreaction promoted by solar light produces azetidinols.[3] This transformation is endergonic, thus harvesting the solar energy as the chemical energy in the form of structural strain. In second step, carbon dioxides is incorporated into the azetidinls to afford cyclic carbonates. The relief of the structural strain serves as driving force for the CO_2 incorporation reaction. This two phase reaction system demonstrates a simple model of chemical utilization of solar energy for CO_2 incorporation.

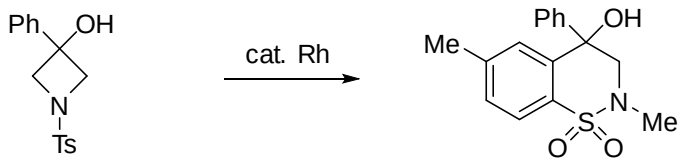


(2) 1,5-Rhodium shift in rearrangement of *N*-arenesulfonylazetidinols into benzosultams

1,n-metal shift is an attractive process which enables unique metal catalyzed reactions. Therefore, many reactions have been developed via a 1,n-metal shift. Especially, a lot of rhodium, and palladium catalyzed reactions involving 1,4-metal shift have been developed.[4,5,6] However, there are much less examples of 1,5-metal shift than 1,4-metal shift.[7]



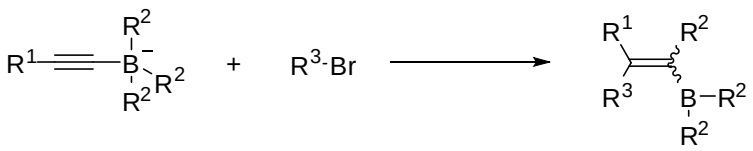
In chapter 2, the author describes rhodium catalyzed rearrangement of *N*-arenesulfonylazetidinols into benzosultams via 1,5-rhodium shift. Various benzosultams were obtained in quantitative yield. In addition, chiral azetidinols, which are easily available by modified Seebach's procedure[8], afford the enatio- and diastereopure benzosultams quantitatively.



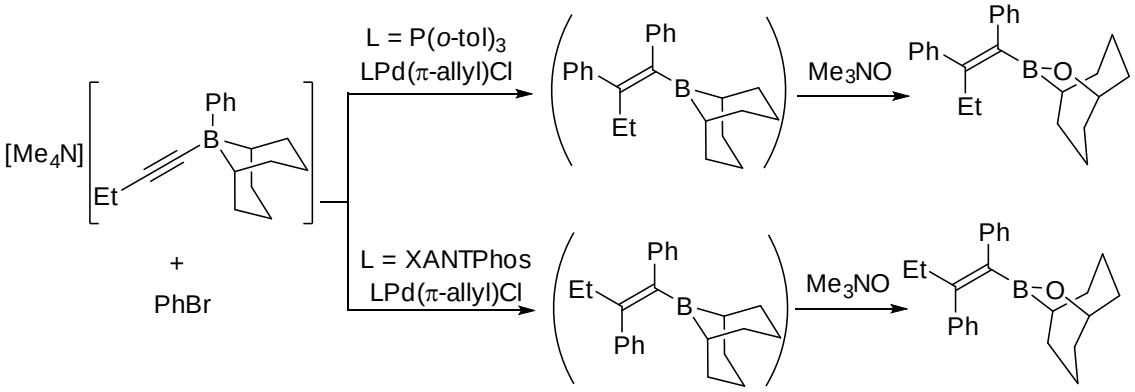
(3) Palladium catalyzed reaction of alkynylborates with aryl halide

Organoboron compounds are versatile synthetic reagents for carbon-carbon bond formation reactions, because they are easily handled and have the well known reactivities[9]. In addition, their utilizations are increasing in the field of pharmaceutical chemistry[10], and material science[11]. Therefore, it is the important for organic chemists to develop the new efficient methods to synthesis the organoboron compounds precisely.

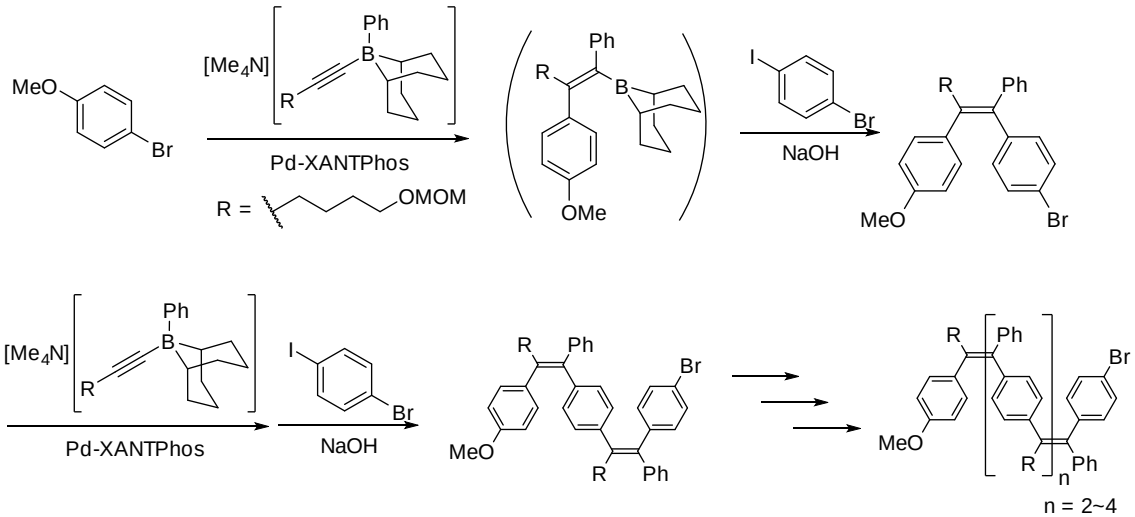
Alkynylborates react with electrophiles on the β-position of boron to afford the alkenylboranes which are difficult to synthesize by other conventional methods[12]. We have focused such reactivities and developed a palladium catalyzed reaction of alkynylborates[13].



In chapter 3, the author describes the palladium catalyzed reaction of alkynylborates with aryl halides, which provids the trisubstituted alkenylboranes regio- and stereoselectively. The stereochemistry of the alkenylboranes is dependent upon the ligand employed. Using Xantphos as the ligand, (*Z*)-alkenylboranes were obtained stereoselectively. On the other hand, in the case of (*o*-tol)$_3$P, (*E*)-alkenylboranes were obtained.

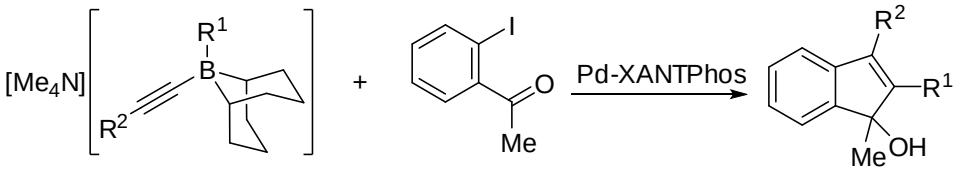


Oligo(arylenevinylene)s are important compounds in the field of material science[14]. Though a wide variety of oligo(arylenevinylene)s have been synthesized, oligo(arylenevinylene)s with tetrasubstituted olefin units have not been synthesized. In chapter 4, the author describes an iterative approach to this class of molecules. Various oligo(arylenevinylene)s are synthesized stereoselectively starting from bromo (iodo) benzenes and alkynylborates.



Indene skeleton is an important substructure in the field of pharmaceutical chemistry and material science. An annulation reaction of *o*-halobenzoyl compounds with alkyne provides an efficient way to synthesize indenols, however, it is difficult to control the regioselectivity. In chapter 5, the author describs a palladuium-catalyzed reaction of

alkynylborates with *o*-iodophenyl ketones, which provides 2,3-disubstituted indenols regioselectively.



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Chapter 1

Solar-Driven Incorporation of Carbon Dioxide into α-Amino Ketones

Abstract

α-Amino ketones react with carbon dioxides to give cyclic carbonates via photocyclization promoted by solar light. This reaction demonstrates a model of chemical utilization of solar energy for CO_2 incorporation.

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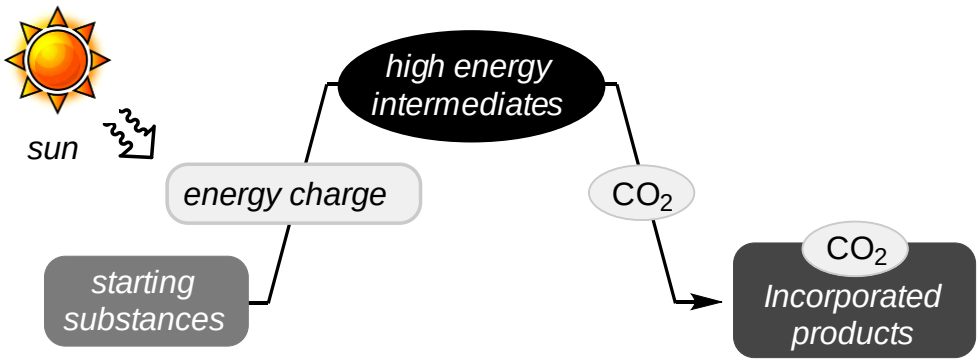
Introduction

The recent manifestation of the potential risk inherent to nuclear technologies has incited a strong demand for exploration of innovative means to exploit energy from natural sources, thus increasing the need for research on sustainable energy in many scientific fields. Chemists can contribute by developing chemical systems to utilize solar light, which is undoubtedly the best source of sustainable energy available on the planet.[1] Another imperative issue is the establishment of carbon-neutral systems.[2] One synthetic approach to this issue is the incorporation of CO_2 into organic compounds as a chemical feedstock.[3] High-energy compounds suit energetically low CO_2 as the reaction partner. Under these circumstances, it presents a significant challenge to simultaneously tackle the two issues mentioned above. Thus, we tried to develop a reaction that is promoted by solar light and utilizes CO_2 as a chemical feedstock (Figure 1).

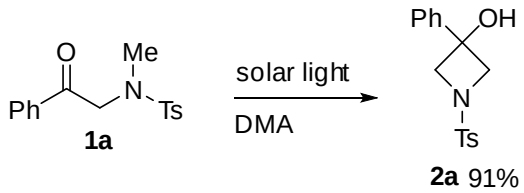
Figure 1. Solar Driven Incorporation of Carbon Dioxide



Results and Discussion

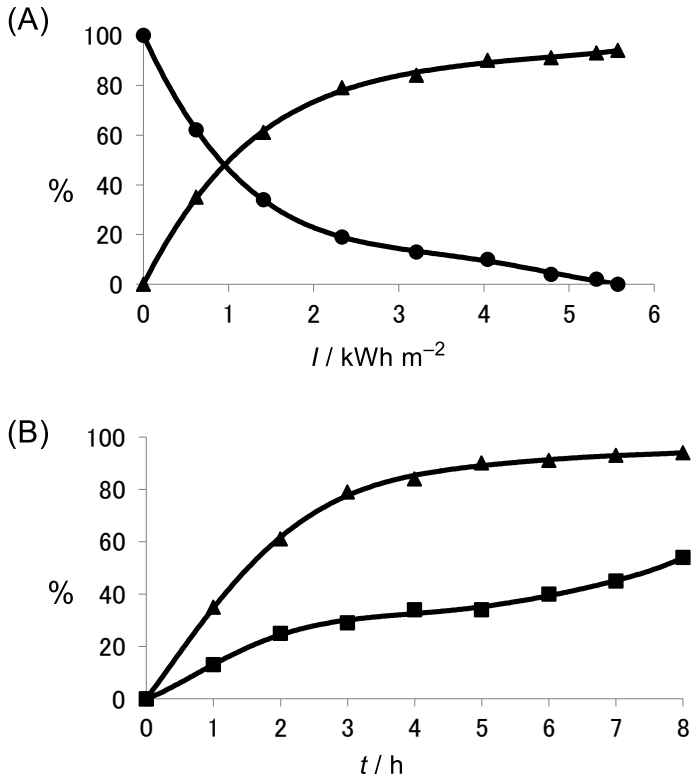
We report herein a solar-driven process that incorporates CO_2 into α-methylamino ketones. The resulting aminosubstituted cyclic carbonates are expected to be useful building blocks of pharmaceuticals and fuel additives.[4] Our attention was initially directed to a photochemical cyclization reaction observed with a-methylamino ketones.[5] Of note was that this photoreaction proceeded in an energetically uphill direction. A high-energy four-membered ring[6] was constructed through the insertion of a photo-excited carbonyl group into the carbon-hydrogen bond of a pendant methyl group on a nitrogen atom. In a formal sense, the intrinsically inert carbon-hydrogen bond was cleaved[7] and added across the carbon-oxygen double bond in a 4-exo-trig mode.[8] Although the reaction was originally reported to require irradiation with a mercury lamp, which used electricity,[5b] we discovered that natural solar light successfully effected this energetically uphill reaction; α-amino ketone **1a** cyclized at a reasonable rate upon exposure to solar light (Scheme 1).

Scheme 1. Solar Light Promoted Cyclization of 1a



Furthermore, ordinary Pyrex glass, not quartz was suitable for the reaction vessel; light of wavelengths below 400 nm was required for the photoreaction, and Pyrex glass transmitted a sufficient amount of operative light even on a cloudy day. Thus, simply setting a Pyrex tube containing a solution of **1a** in *N,N*-dimethylacetamide (DMA) on a balcony or rooftop brought about the cyclization. The conversion was dependent upon the amount of solar radiation. We defined it as "sunny" when an hourly solar radiation over 0.4 kWm^{-2} was observed, and as "cloudy" when it ranged from 0.1 to 0.4 kWm^{-2}. Typically, the total amount of solar radiation amounted to 5.5 $kWhm^{-2}$ in eight hours on a sunny day to cause full conversion of **1a** on a 0.1 mmol scale (0.10 $mmolL^{-1}$; Figure 2A). The reaction mixture was subsequently applied to conventional column chromatography on silica gel and analytically pure azetidinol **2a** was isolated in 91% yield. In contrast, an analogous experiment on a cloudy day produced **2a** in 54%yield after eight hours (Figure 2B), when the total amount of solar radiation reached 0.9 $kWhm^{-2}$. Thus, it turned out to be possible to transfer 1a into the product[9] by using solar energy even on a cloudy day.

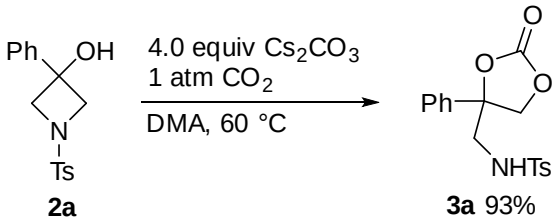
Figure 2. Solar-Light Promoted Cyclization of 1a



(A) Residual ratio of **1a** (●) and yield of **2a** (▲) during solar radiation, (B) Yield of **2a** over time on sunny (▲) and cloudy day (■)

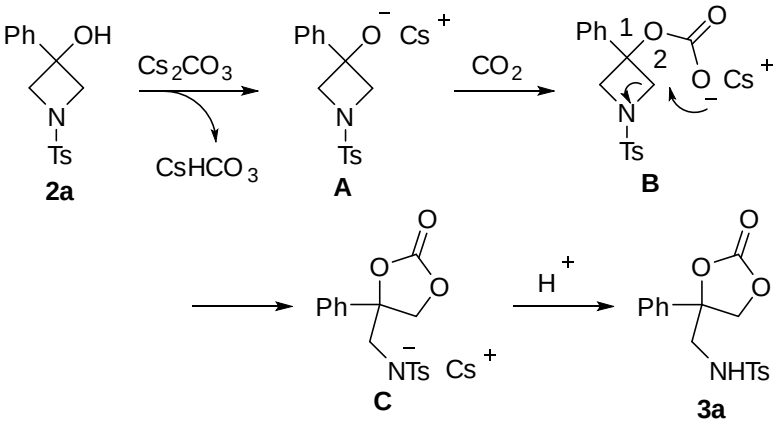
We next attempted to incorporate CO_2 into azetidinol **2a**, in which energy has been stored, by reacting it with CO_2, and a remarkably simple way was found; CO_2 was successfully incorporated upon exposure of a solution of **2a** in DMA to gaseous CO_2 in the presence of a base. For example, stirring a heterogeneous mixture of **2a** and Cs_2CO_3 (4.0 equiv) in DMA under an atmosphere of CO_2 (1 atm) at 60°C for ten hours led to the quantitative production of the cyclic carbonate **3a**, which was isolated in 93% yield after purification by chromatography (Scheme 2). Organic bases, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), also afforded 3a, albeit in a lower yield (56%).

Scheme 2. Incorporation of Carbon Dioxide

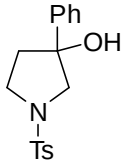


The formation of **3a** is explained by assuming the pathway depicted in Scheme 3.[4] Azetidinol **2a** is initially deprotonated by Cs_2CO_3 to produce alkoxide anion **A**, which subsequently adds to CO_2 to afford carbonate anion **B**. The following nucleophilic attack of the anionic oxygen onto the 2-carbon atom prompts displacement of the tosylamide anion through a 5-exo-tet process.[8] Thus, the four-membered ring is opened, thereby releasing the energy originating from sun. Finally, protonation of **C** affords **3a**.

Scheme 3. Plausible Mechanism



For comparison, pyrrolidinol **4** was subjected to the identical reaction conditions. Unlike the four-membered counterpart **2a**, the five-membered compound **4** failed to react and was recovered unchanged. The contrasting results observed with **2a** and **4** lend support to the explanation that the major driving force for the CO_2-capturing reaction is the release of the energy stored in the form of the strained four-membered ring.



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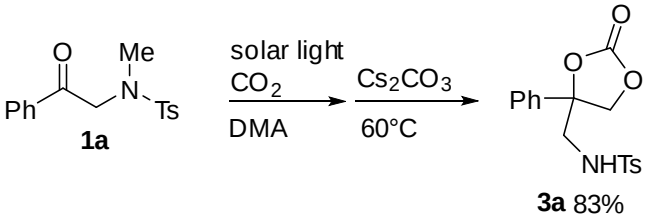
The experimental procedures for both the photochemical cyclization reaction and the CO_2-capturing reaction are so simple that it is possible to carry them out in a single flask (Scheme 4). Initially, a DMA solution of **1a** in an atmosphere of CO_2 (1 atm) was irradiated with solar light outside. After completion of the photoreaction, Cs_2CO_3 was simply added to the reaction mixture, which was then heated at 60°C for ten hours in a

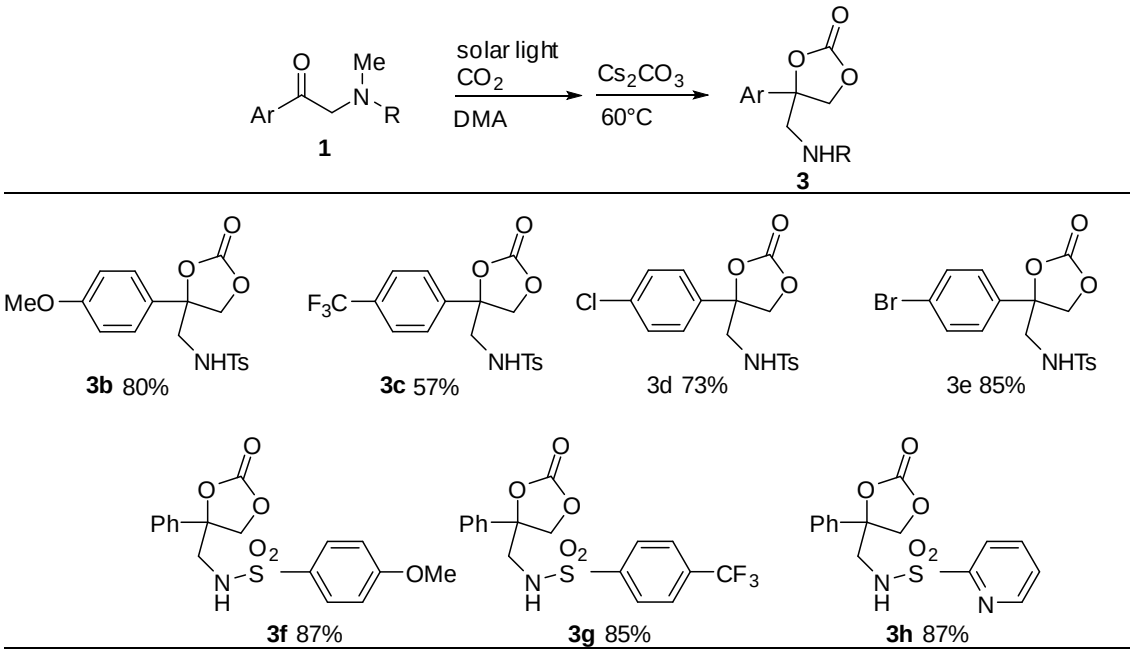
fume hood. Isolation by chromatography afforded the analytically pure cyclic carbonate **3a** in 83% yield based on **1a**.

Scheme 4. Solar Driven Incorporation of Carbon Dioxide into α-Amino Ketone 1a



The broad generality of this consecutive process was verified by application to various acetophenone derivatives (Scheme 5). Both an electron-donating methoxy group and an electron-withdrawing trifluoromethyl group were allowed at the para-position of the benzoyl group, and the corresponding products **3b** and **3c** were isolated in reasonable total yields. The presence of possibly photoactive bromo and chloro groups[10] had essentially no effect on the reaction (**3d** and **3e**). Sulfonyl groups other than a p-toluenesulfonyl group were also suitable as the substituent on the nitrogen atom (**3f–h**).

Table 1. Scope of Solar Driven CO_2 Incorporation into α-Amino Ketone



Overall yields of isolated products are given. Reactions were conducted on a 0.2 mmol scale with the following reagents and conditions: 1 (0.20 mmol), DMA (1.0 mL), solar light, ambient temperature, CO_2 (1 atm); then Cs_2CO_3 (0.80 mmol), 60 °C.

Conclusions

In summary, we have developed the unique solar-driven transformation of α-amino ketones. CO_2 is incorporated to afford amino-substituted cyclic carbonates, which are potentially useful ingredients in industry.

Although photosynthesis is a complex assembly of a number of elementary reactions, it can be divided into two major reactions; the light reaction and the dark reaction. In the former reaction, solar energy is captured to promote an energetically uphill process with production of high-energy molecules (adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide phosphate (NADPH). The dark reaction is an energetically downhill process that does not require light. ATP and NADPH, which have chemically stored solar energy during the former reaction, assist in the fixation of CO_2, which is intrinsically low in energy. Photosynthesis as a whole reduces CO_2 into carbohydrates. Although the present consecutive process does not involve CO_2 reduction, its mechanistic profile of energy resembles that of photosynthesis and presents a simple model of the chemical utilization of solar energy for CO_2 incorporation.

Experimental Section

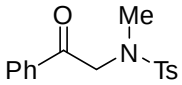
General. All reactions were carried out with standard Schlenk techniques. IR measurements were performed on a FTIR SHIMADZU DR-8000 spectrometer fitted with a Pike Technologies MIRacle Single Reflection ATR adapter. 1H and 13C NMR spectra were recorded on a Varian Mercury-vx400 (1H at 400.44 MHz and 13C at 100.69 MHz) spectrometer. NMR data were obtained in CDCl3. Proton chemical shifts were referenced to the residual proton signal of CHCl3 at 7.26 ppm. Carbon chemical shifts were referenced to the carbon signal of CDCl3 at 77.0 ppm. High-resolution mass spectra were recorded on a Thermo Scientific Exactive (ESI) spectrometer. Flash column chromatography was performed with silica gel 60N (Kanto). Preparative thin-layer chromatography (PTLC) was performed on silica gel plates with PF254 indicator (Merck).

Materials. Unless otherwise noted, all chemicals and anhydrous solvents were obtained from commercial suppliers. (2-Pyridyl)sulfonyl chloride1 was prepared according to the reported procedure.

Preparation of α-Amino Ketone 1a: A Typical Procedure for the Preparation of α-Amino Ketone 1a-1h

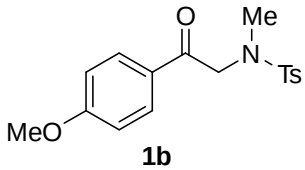
To an Et_2O solution (40 mL) of *p*-toluenesulfonyl chloride (3.8 g, 20 mmol) was added an aqueous solution of methylamine (40 wt%, 4.0 mL). After being stirred for 6 h at room temperature, water was added to the reaction mixture. The organic layer was separated and the remaining aqueous layer was extracted with AcOEt (3 times). The combined organic layer was washed with brine (once), dried over $MgSO_4$ and concentrated. The residue was subsequently dissolved in acetonitrile. 2-Bromoacetophenone (4.0 g, 20 mmol) and potassium carbonate (2.8 g, 20 mmol) were added therein. After being stirred overnight, water was added to the reaction mixture. The aqueous layer was extracted with AcOEt (3 times), washed with brine (once), dried over $MgSO_4$ and concentrated. The residue was purified by Flash column chromatography on silica gel (hexane/ethyl acetate = 5/1) to afford the α-amino ketone

1a (5.1 g, 17 mmol, 84% yield).



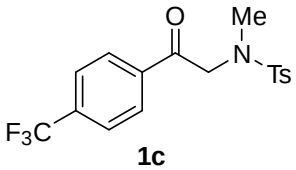
1a

^{1}H NMR: δ = 2.44 (s, 3H), 2.83 (s, 3H), 4.57 (s, 2H), 7.33 (dd, *J* = 8.8, 0.4 Hz, 2H), 7.45-7.51 (m, 2H), 7.60 (tt, *J* = 7.6, 1.2 Hz, 1H), 7.71-7.75 (m, 2H), 7.95-7.99 (m, 2H); ^{13}C NMR: δ = 21.5, 35.6, 56.0, 127.5, 128.2, 128.8, 129.7, 133.8, 134.7, 134.8, 143.6, 193.7; HRMS (ESI^{+}): Calcd for $C_{16}H_{18}NO_3S$, M+H^{+} 304.1002, Found m/z 304.0994; IR (ATR): 1693, 1339, 1227, 1157, 743 cm^{-1}.



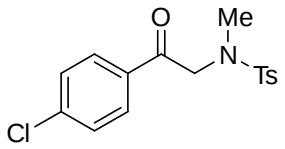
1b

^{1}H NMR: δ = 2.44 (s, 3H), 2.80 (s, 3H), 3.88 (s, 3H), 4.47 (s, 2H), 6.93-6.97 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.70-7.74 (m, 2H), 7.96-8.02 (m, 2H); ^{13}C NMR: δ = 21.5, 35.5, 55.5, 55.8, 113.9, 127.5, 127.7, 129.6, 130.7, 134.6, 143.6, 164.0, 192.1; HRMS (ESI^{+}): Calcd for $C_{17}H_{20}NO_4S$, M+H^{+} 334.1108, Found m/z 334.1101; IR (ATR): 1688, 1601, 1329, 1180, 1159 cm^{-1}.



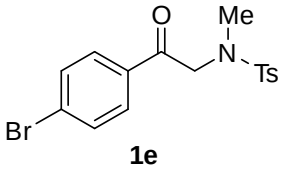
1c

^{1}H NMR: δ = 2.45 (s, 3H), 2.80 (s, 3H), 4.53 (s, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 8.12 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR: δ = 21.5, 35.7, 56.4, 123.4, (q, $J_{C\text{-}F}$ = 271.1 Hz), 125.9 (q, $J_{C\text{-}F}$ = 3.7 Hz), 127.6, 128.8, 129.8, 134.4, 135.0 (q, $J_{C\text{-}F}$ = 32.7 Hz), 137.3, 143.9, 193.2; HRMS (ESI^{+}): Calcd for $C_{17}H_{17}F_3NO_3S$, M+H^{+} 372.0876, Found m/z 372.0865; IR (ATR): 1697, 1325, 1161, 1121, 1109 cm^{-1}.



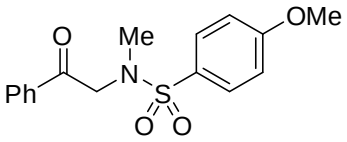
1d

^{1}H NMR: δ = 2.45 (s, 3H), 2.79 (s, 3H), 4.48 (s, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.44-7.48 (m, 2H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.92-7.96 (m, 2H); ^{13}C NMR: δ = 21.6, 35.6, 56.1, 127.6, 129.2, 129.7, 129.8, 133.0, 134.4, 140.4, 143.8, 192.8; HRMS (ESI^{+}): Calcd for $C_{16}H_{17}ClNO_3S$, M+H^{+} 338.0612, Found m/z 338.0600; IR (ATR): 1692, 1339, 1225, 1159, 1088 cm^{-1}.



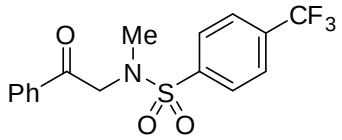
1e

^{1}H NMR: δ = 2.44 (s, 3H), 2.79 (s, 3H), 4.47 (s, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR: δ = 21.5, 35.6, 56.1, 127.5, 129.1, 129.7, 129.8, 132.1, 133.4, 134.4, 143.8, 193.0; HRMS (ESI^{+}): Calcd for $C_{16}H_{17}BrNO_3S$, M+H^{+} 382.0107, Found m/z 382.0094; IR (ATR): 1697, 1325, 1223, 1155, 810cm^{-1}.



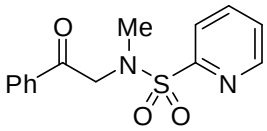
1f

^{1}H NMR: δ = 2.82 (s, 3H), 3.89 (s, 3H), 4.56 (s, 2H), 6.98-7.03 (m, 2H), 7.46-7.51 (m, 2H), 7.61 (tt, *J* = 7.2, 1.2 Hz, 1H),7.76-7.81 (m, 2H), 7.96-8.00 (m, 2H); ^{13}C NMR: δ = 35.6, 55.6, 56.1, 114.2, 128.3, 128.8, 129.4, 129.7, 133.8, 134.8, 163.0, 193.8; HRMS (ESI^{+}): Calcd for $C_{16}H_{18}NO_4S$, M+H^{+} 320.0951, Found m/z 320.0943; IR (ATR): 1692, 1342, 1259, 1155, 741 cm^{-1}



1g

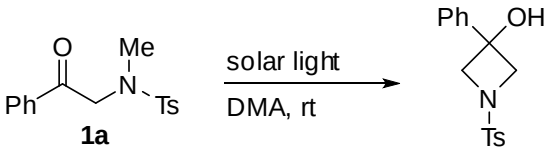
^{1}H NMR: δ = 2.94 (s, 3H), 4.74 (s, 2H), 7.47-7.52 (m, 2H), 7.62 (tt, *J* = 7.6, 1.2 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.90-7.94 (m, 2H), 7.98 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR: δ = 35.6, 55.8, 123.3 (q, $J_{C\text{-}F}$ = 271.1 Hz), 126.1 (q, $J_{C\text{-}F}$ = 3.6 Hz), 127.96, 127.99, 128.9, 134.0, 134.3 (q, $J_{C\text{-}F}$ = 32.7 Hz), 134.5, 142.1, 193.1; HRMS (ESI$^+$): Calcd for $C_{16}H_{15}F_3NO_3S$, M+H$^+$ 358.0719, Found m/z 358.0707; IR (ATR): 1699, 1319, 1128, 1059, 748 cm^{-1}.



1h

^{1}H NMR: δ = 3.02 (s, 3H), 4.86 (s, 2H), 7.44-7.53 (m, 3H), 7.57-7.62 (m, 1H), 7.88-7.98 (m, 4H), 8.70 (ddd, *J* = 4.8, 1.6, 0.8 Hz, 1H);^{13}C NMR: δ = 36.3, 56.9, 122.4, 126.6, 128.1, 128.8, 133.8, 134.7, 137.9, 149.9, 157.0, 193.6; HRMS (ESI$^+$): Calcd for $C_{14}H_{15}N_2O_3S$, M+H$^+$ 291.0798, Found m/z 291.0785; IR (ATR): 1695, 1337, 1175, 945, 752 cm^{-1}.

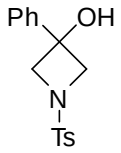
Photoreaction of α-Amino Ketone 1a upon Irradiation with Solar Light



1a **2a**

α-Amino ketone **1a** (30.3 mg, 0.10 mmol) was placed in a Pyrex flask, which was subsequently filled with an atmospheric pressure of CO_2 by vacuum-refill cycles. The flask was added *N*,*N*-dimethylacetamide (1.0 mL) and exposed to solar light outside. After 10 h, water was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (3 times), washed with water (3 times), brine (once), dried over $MgSO_4$ and concentrated. The residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 2/1) to afford the azetidinol **2a**

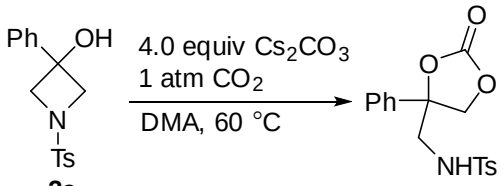
(25.3 mg, 0.091 mmol, 91% yield).



2a

^{1}H NMR: δ = 2.29 (s, 1H), 2.48 (s, 3H), 3.97 (d, *J* = 9.6 Hz, 2H), 4.15 (d, *J* = 9.6 Hz, 2H), 7.28-7.37 (m, 5H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR: δ = 21.6, 65.2, 70.3, 124.4, 128.1, 128.4, 128.6, 129.9, 131.2, 142.0, 144.4; HRMS (ESI^{+}): Calcd for $C_{16}H_{18}NO_3S$, M+H^{+} 304.1002, Found m/z 304.0995. Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62; O, 15.82; S, 10.57. Found: C, 63.17; H, 5.55; N, 4.58; O, 15.55; S, 10.58; IR (ATR): 3477, 1333, 1184, 1148, 671 cm^{-1}.

Reaction of Azetidinol 2a with Carbon Dioxide

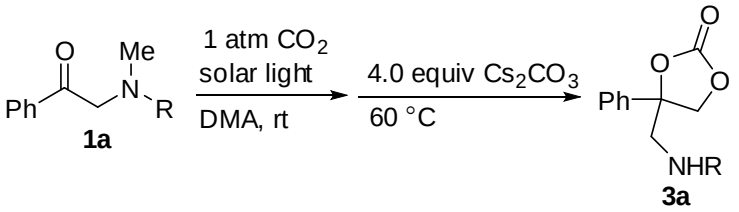


2a **3a**

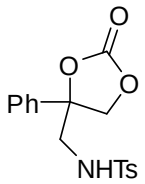
Under an atmospheric pressure of CO_2, an *N*,*N*-dimethylacetamide solution (1.0 mL) containing azetidinol **2a** (30.3 mg, 0.10 mmol) and cesium carbonate (130 mg, 0.40 mmol) were stirred at 60 °C for 10 h. The reaction mixture then treated with HCl aq (2.0 M), and the aqueous layer was extracted with Et_2O (3 times). The combined organic layer was washed with water (3 times), brine (once), dried over $MgSO_4$ and concentrated. The residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 3/1) to afford the cyclic carbonate **3a** (32.2 mg, 0.093 mmol, 93% yield).

One-Pot Reaction of α-Amino Ketone 1a with Carbon Dioxide.

A Typical Procedure for the CO_2-Capturing Reaction of α-Amino Ketones.

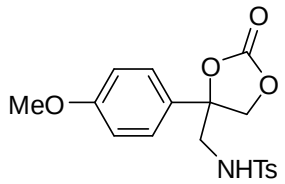


α-Amino ketone **1a** (30.3 mg, 0.10 mmol) was placed in a Pyrex flask, which was subsequently filled with an atmospheric pressure of CO_2 by vacuum-refill cycles. The flask was added *N*,*N*-dimethylacetamide (1.0 mL) and exposed to solar light outside. After completion of the photochemical reaction, Cs_2CO_3 (130 mg, 0.40 mmol) was added to the reaction mixture, which was then stirred at 60 °C for 10 h in a room. The reaction mixture was treated with HCl aq. (2.0 M) and the aqueous layer was extracted with Et_2O (3 times). The combined organic layer was washed with water (3 times), brine (once), dried over $MgSO_4$ and concentrated. The residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 3/1) to afford the cyclic carbonate **3a** (28.8 mg, 0.083 mmol, 83% yield).



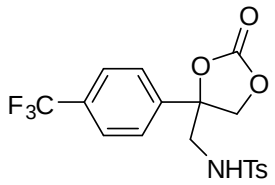
3a

^{1}H NMR: δ = 2.40 (s, 3H), 3.30 (dd, *J* = 14.4, 5.6 Hz, 1H), 3.40 (dd, *J* = 14.4, 8.8 Hz, 1H), 4.54 (d, *J* = 8.4 Hz, 1H), 5.08 (d, *J* = 8.4 Hz, 1H), 5.70 (dd, *J* = 8.4 Hz, 5.6 Hz, 1H), 7.26-7.32 (m, 4H), 7.34-7.43 (m, 3H), 7.69-7.73 (m, 2H); ^{13}C NMR: δ = 21.5, 50.3, 72.4, 85.0, 124.2, 126.9, 129.2, 129.9, 136.5, 138.1, 143.9, 154.2; HRMS (ESI$^+$): Calcd for $C_{17}H_{18}NO_5S$, M+H$^+$ 348.0900, Found m/z 348.0892; Anal. Calcd for $C_{17}H_{18}NO_5S$: C, 58.78; H, 4.93; N, 4.03; O, 23.03; S, 9.23. Found: C, 58.71; H, 4.96; N, 3.89; O, 22.84; S, 9.32; IR (ATR): 3261, 1773, 1435, 1319, 1045 cm^{-1}.



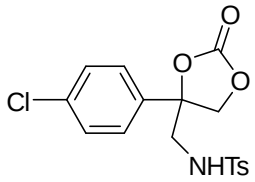
3b

^{1}H NMR: δ = 2.40 (s, 3H), 3.27 (dd, *J* = 14.4, 5.6 Hz, 1H), 3.35 (dd, *J* = 14.4, 8.8 Hz, 1H), 3.80 (s, 3H), 4.52 (d, *J* = 8.4 Hz, 1H), 5.04 (d, *J* = 8.8 Hz, 1H), 5.64 (dd, *J* = 8.4, 5.6 Hz, 1H), 6.88-6.93 (m, 2H), 7.19-7.24 (m, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR: δ = 21.5, 50.3, 55.4, 72.4, 84.8, 114.5, 125.6, 126.9, 129.8, 129.9, 136.5, 144.0, 154.1, 160.1; HRMS (ESI^{+}): Calcd for $C_{18}H_{20}NO_6S$, M+H^{+} 378.1006, Found m/z 378.0996; IR (ATR): 3238, 1794, 1518, 1329, 1057, 723 cm^{-1}.



3c

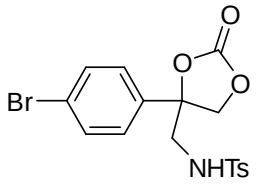
^{1}H NMR: δ = 2.40 (s, 3H), 3.31 (dd, *J* = 14.4, 5.6 Hz, 1H), 3.42 (dd, *J* = 14.8, 8.4 Hz, 1H), 4.53 (d, *J* = 8.8 Hz, 1H), 5.13 (d, *J* = 8.4 Hz, 1H), 5.65 (dd, *J* = 8.4, 6.0 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.65-7.71 (m, 4H); ^{13}C NMR: δ = 21.5, 50.1, 72.2, 84.6, 123.5 (q, $J_{C\text{-}F}$ = 270.4 Hz), 124.9, 126.3 (q, $J_{C\text{-}F}$ = 3.7 Hz), 126.8, 130.0, 131.5 (q, $J_{C\text{-}F}$ = 32.7 Hz), 136.3, 141.8, 144.2, 153.7; HRMS (EI): Calcd for $C_{18}H_{16}F_3NO_5S$, M 415.0701, Found m/z 415.0701; IR (ATR): 3244, 1801, 1323, 1157, 1067 cm^{-1}.



3d

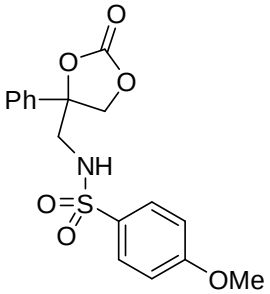
^{1}H NMR: δ = 2.40 (s, 3H), 3.28 (dd, *J* = 14.4, 6.0 Hz, 1H), 3.37 (dd, *J* = 14.4, 8.4 Hz, 1H), 4.50 (d, *J* = 8.4 Hz, 1H), 5.07 (d, *J* = 8.8 Hz, 1H), 5.72 (dd, *J* = 8.4, 6.0 Hz, 1H), 7.22-7.27 (m, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.35-7.39 (m, 2H), 7.69 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR: δ = 21.5, 50.2, 72.3, 84.7, 125.7, 126.8, 129.4, 130.0, 135.3, 136.4, 136.5, 144.1, 153.9; HRMS (ESI^{+}): Calcd for $C_{17}H_{17}ClNO_5S$, M+H^{+} 382.0510, Found m/z

382.0506; IR (ATR): 3250, 1800, 1325, 1155, 1069 cm^{-1}.



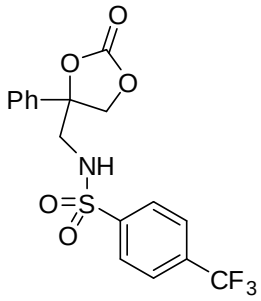
3e

^{1}H NMR: δ = 2.41 (s, 3H), 3.28 (dd, *J* = 14.4, 5.6 Hz, 1H), 3.37 (dd, *J* = 14.4, 8.4 Hz, 1H), 4.49 (d, *J* = 8.4 Hz, 1H), 5.06 (d, *J* = 8.4 Hz, 1H), 5.74 (dd, *J* = 8.4, 6.0 Hz, 1H), 7.16-7.20 (m, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.50-7.55 (m, 2H), 7.66-7.70 (m, 2H); ^{13}C NMR: δ = 21.5, 50.1, 72.3, 84.7, 123.5, 126.0, 126.8, 130.0, 132.3, 136.4, 137.0, 144.1, 153.8; HRMS (ESI^{+}): Calcd for $C_{17}H_{17}BrNO_5S$, $M+H^{+}$ 426.0005, Found m/z 426.0003; IR (ATR): 3252, 1800, 1331, 1175, 1057 cm^{-1}.



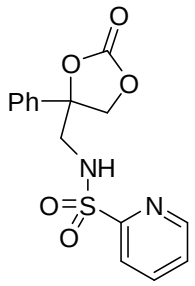
3f

^{1}H NMR: δ = 3.30 (dd, *J* = 14.4, 6.0 Hz, 1H), 3.39 (dd, *J* = 14.4, 8.8 Hz, 1H), 3.84 (s, 3H), 4.54 (d, *J* = 8.4 Hz, 1H), 5.06 (d, *J* = 8.4 Hz, 1H), 5.55 (dd, *J* = 8.8, 6.0 Hz, 1H), 6.93-6.98 (m, 2H), 7.27-7.32 (m, 2H), 7.34-7.44 (m, 3H), 7.73-7.78 (m, 2H); ^{13}C NMR: δ = 50.3, 55.6, 72.4, 84.9, 114.5, 124.2, 129.1, 129.2, 131.0, 138.1, 154.1, 163.2; HRMS (ESI^{+}): Calcd for $C_{17}H_{18}NO_6S$, $M+H^{+}$ 364.0849, Found m/z 364.0836; IR (ATR): 3246, 1801, 1325, 1155, 1067 cm^{-1}.



3g

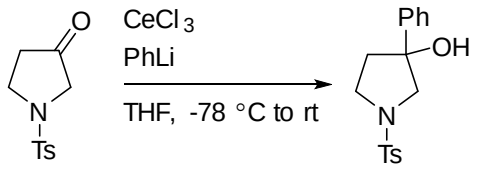
^{1}H NMR: δ = 3.36 (dd, *J* = 14.4, 5.2 Hz, 1H), 3.47 (dd, *J* = 14.4, 8.8 Hz, 1H), 4.59 (d, *J* = 8.4 Hz, 1H), 5.10 (d, *J* = 8.4 Hz, 1H), 6.28 (dd, *J* = 8.4, 5.2 Hz, 1H), 7.27-7.31 (m, 2H), 7.35-7.44 (m, 3H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.96 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR: δ = 50.5, 72.5, 85.1, 123.1 (q, $J_{C\text{-}F}$ = 271.1 Hz), 124.1, 126.5 (q, $J_{C\text{-}F}$ = 3.7 Hz), 127.4, 129.3, 129.4, 134.7 (q, $J_{C\text{-}F}$ = 33.7 Hz), 137.7, 143.2, 154.2; HRMS (ESI^{+}): Calcd for $C_{17}H_{15}F_3NO_5S$, M+H^{+} 402.0618, Found m/z 402.0609; IR (ATR): 3335, 1784, 1337, 1161, 1105 cm^{-1}.



3h

^{1}H NMR: δ = 3.57 (dd, *J* = 14.8, 6.0 Hz, 1H), 3.65 (dd, *J* = 14.8, 8.4 Hz, 1H), 4.56 (d, *J* = 8.4 Hz, 1H), 5.14 (d, *J* = 8.4 Hz, 1H), 5.97 (dd, *J* = 8.0, 6.0 Hz, 1H), 7.29-7.34 (m, 2H), 7.35-7.45 (m, 3H), 7.51 (ddd, *J* = 7.2, 4.8, 1.2 Hz, 1H), 7.92 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.98 (d, *J* = 7.6 Hz, 1H), 8.66 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR: δ = 51.0, 72.3, 84.9, 121.9, 124.2, 127.1, 129.2, 138.0, 138.3, 150.1, 153.9, 157.2; HRMS (ESI^{+}): Calcd for $C_{15}H_{15}N_2O_5S$, M+H^{+} 335.0696, Found m/z 335.0686; IR (ATR): 3258, 1801, 1337, 1175, 1063 cm^{-1}.

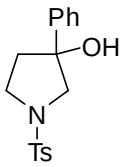
Synthesis of *N*-Tosyl-3-phenyl-3-pyrrolidinol 4 from *N*-Tosyl-3-pyrrolidinone



4

$CeCl_3$ (570 mg, 1.5 mmol) was dried under vacuum at 140 °C for 5 h. After cooling the flask to ambient temperature, the vessel was filled with argon. THF (5.0 mL) was added therein. The resulting suspension was cooled to -78 °C and PhLi (1.0 M in Et_2O, 1.5 ml, 1.5 mmol) was added. After being stirred for 30 min, *N*-tosyl-3-pyrrolidinone (240 mg, 1.0 mmol) was added. The cooling bath was removed to allow the mixture to reach

room temperature. The reaction was quenched by adding NH_4Cl aq. and the aqueous layer was extracted with AcOEt (3 times). The combined organic layer was washed with brine (once), dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 3/1) to afford the *N*-tosyl-3-phenyl-3-pyrrolidinol **4** (270 mg, 0.85 mmol, 85% yield)



4

^{1}H NMR: δ = 1.99 (br s, 1H), 2.09-2.15 (m, 1H), 2.18-2.27 (m, 1H), 2.43 (s, 3H), 3.51-3.64 (m, 4H), 7.26-7.38 (m, 7H), 7.73-7.77 (m, 2H); ^{13}C NMR: δ = 21.5, 39.6, 46.9, 60.8, 80.4, 125.0, 127.6, 128.0, 128.6, 129.7, 133.9, 141.8, 143.5; HRMS (ESI$^+$): Calcd for $C_{17}H_{23}N_2O_3S$, M+NH_4^+ 335.1424, Found m/z 335.1412; IR (ATR): 3491, 1325, 1159, 1101, 770 cm^{-1}.

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Chapter 2

1,5-Rhodium Shift in Rearrangement of *N*-Arenesulfonylazetidin-3-ols into Benzosultams

Abstract

Benzosultams are synthesized in an enantiopure form starting from α-amino acids through a rhodium-catalyzed rearrangement reaction of *N*-arenesulfonylazetidin-3-ols. Mechanistically, it involves C-C bond cleavage by β-carbon elimination and C-H bond cleavage by 1,5-rhodium shift.

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Introduction

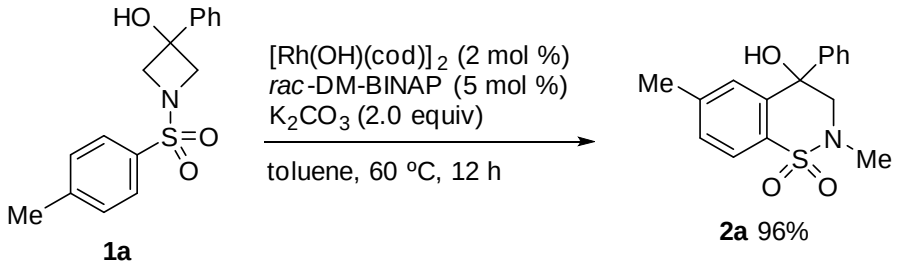
Carbon–carbon (C–C) and carbon–hydrogen (C–H) bonds constitute the major frameworks of organic molecules. Such nonpolar σ-bonds are kinetically inert and thermodynamically stable in general, and therefore, remain intact under most conventional reaction conditions. The past few decades, however, have seen the rise of methods to selectively transform such intrinsically unreactive bonds with the use of transition metal catalysts.[1,2]

A 1,4-metal shift is defined as an intramolecular metal-hydrogen exchange process occurring between 1- and 4-positions. This process provides a convenient way to activate a specific C–H bond, and a number of unique reactions involving a 1,4-metal shift have been reported.[3-6] For example, Catellani and coworkers have reported a palladium-catalyzed reaction of bromobenzenes with norbornenes, in which multiple C–C bonds are introduced on the benzene ring through a 1,4-palladium shift.[4a] A 1,4-rhodium shift has been also successfully exploited.[5] Phenylboronic acid is multiply alkylated with norbornene through repetition of a 1,4-rhodium shift.[5a] Indanones are synthesized through rearrangement of 1-arylpropargyl alcohols.[5c,d] A rearrangement reaction of cyclobutanols affords indanols in an enantio- and diastereoselective way.[5h,i] On the other hand, there are significantly less precedents reported for a 1,5-metal shift.[7] Herein, we report a rearrangement reaction of *N*-arenesulfonylazetidin-3-ols into benzosultams[8] which involves a 1,5-rhodium shift as the key mechanistic element. It provides a stereoselective synthetic pathway starting from natural α-amino acids leading to enantiopure benzosultams, which are substructures of potent pharmaceuticals like Piroxicam and Meloxicam.[9]

Results and Discussion

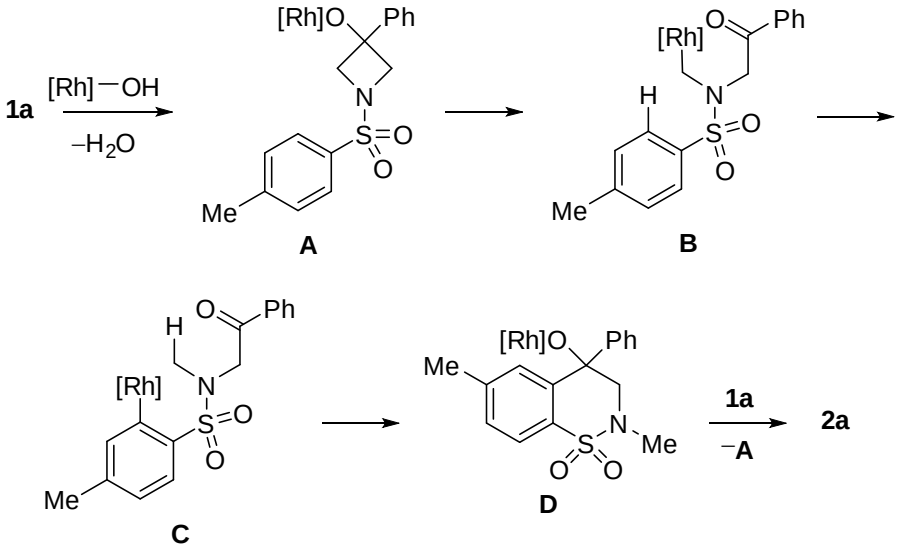
Initially, *N*-*p*-toluenesulfonylazetidinol **1a** was prepared from commercially available azetidin-3-ol in 3 steps.[10] Then, the reaction of **1a** was examined in the presence of $[Rh(OH)(cod)]_2$ (2 mol %) and various phosphine ligands (Rh : P = 1 : 2.5).[10] Whereas almost no reaction occurred when ligands like PPh_3, DPPB, DPPF were employed, the use of *rac*-BINAP prompted a rearrangement reaction to give **2a** in 46% yield. *Rac*-DM-BINAP, which possessed 3,5-xylyl groups in place of phenyl groups on phosphorus, exhibited a considerably higher activity to promote quantitative transfor mation of **1a**. Simple elution of the reaction mixture through a pad of silica gel afforded **2a** in 96% isolated yield (Scheme 1).

Scheme 1. Rhodium-Catalyzed Rearrangement of 1a to 2a



A stepwise mechanism involving a 1,5-rhodium shift from C(sp^3) to C(sp^2) is proposed to explain the formation of **2a** from **1a** (Scheme 2). Initially, the hydroxy group of **1a** is exchanged onto the rhodium hydroxide to generate rhodium alkoxide **A**. Subsequently, β-carbon elimination follows to cleave the carbon–carbon bond of the symmetrical azetidine ring, thereby relieving the ring strain.[11] The generated alkylrhodium **B** then undergoes a 1,5-rhodium shift to furnish arylrhodium species **C**. An intramolecular 6-*exo* addition to the carbonyl group[12] occurs with **C** to reconstruct the six-membered ring structure of a benzosultam skeleton. Finally, the rhodium alkoxide **D** is exchanged with the hydroxy group of another azetidinol **1a** to release the benzosultam **2a** with regeneration of intermediate **A**.

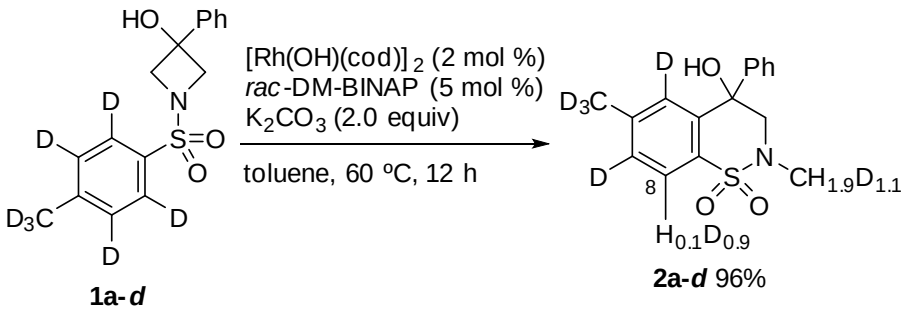
Scheme 2. Proposed Mechanism for the Rearrangement of 1a to 2a



We next carried out the reaction of **1a-*d***, whose *p*-tolyl group was fully deuterated (Scheme 3). One of the deuterium atoms on the ortho positions of the *p*-tolyl moiety was transferred onto the *N*-methyl group of **2a-*d***, being consistent with the proposed

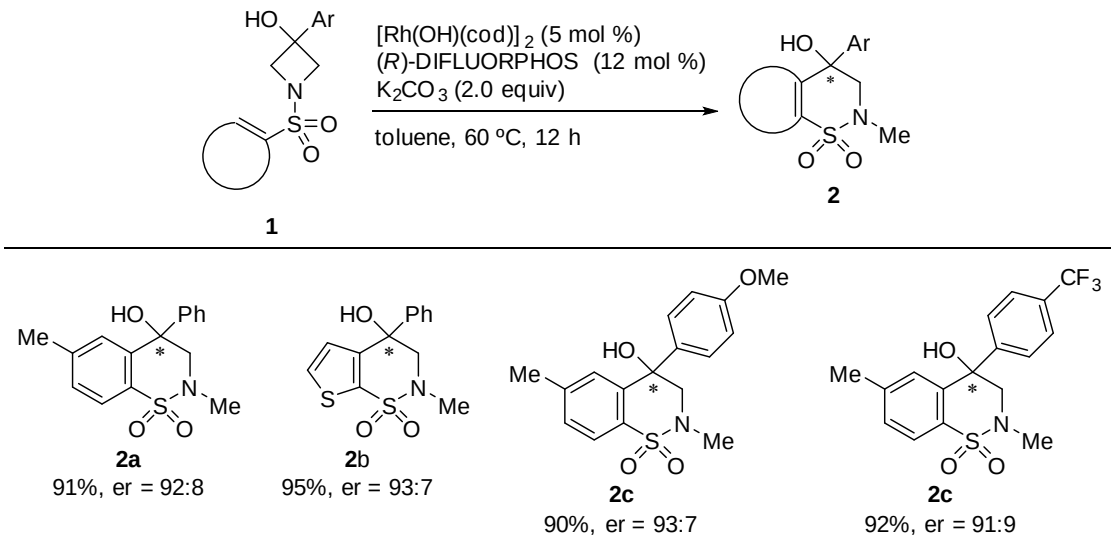
mechanism. The H/D ratio of the *N*-methyl group and the 8-position were 1.9/1.1 and 0.1/0.9, respectively. The slightly lower and higher H/D ratios at the *N*-methyl and 8-positions, respectively, than expected may suggest the microscopic reversibility between the intermediary arylrhodium **C** and the alkylrhodium **B**.

Scheme 3. Rhodium-Catalyzed Reaction of 1a-*d* to 2a-*d*



Next, optically active diphosphine ligands were examined to induce enantioselectivity at the step of intramolecular carbonyl addition, *i.e.* from **C** leading to **D**.[12] Although (*R*)-DM-BINAP exhibited the best reactivity among the chiral ligands examined to give **2a** in 94% yield, the enantiomeric ratio (er) was low (62:38). (*R*)-DIFLUORPHOS afforded the best selectivity of 92:8 er (91% yield).[10] Application of this reaction conditions to various azetidinols **1** furnished benzosultams **2** in the range of 91:9 to 93:7 er (Table 1).

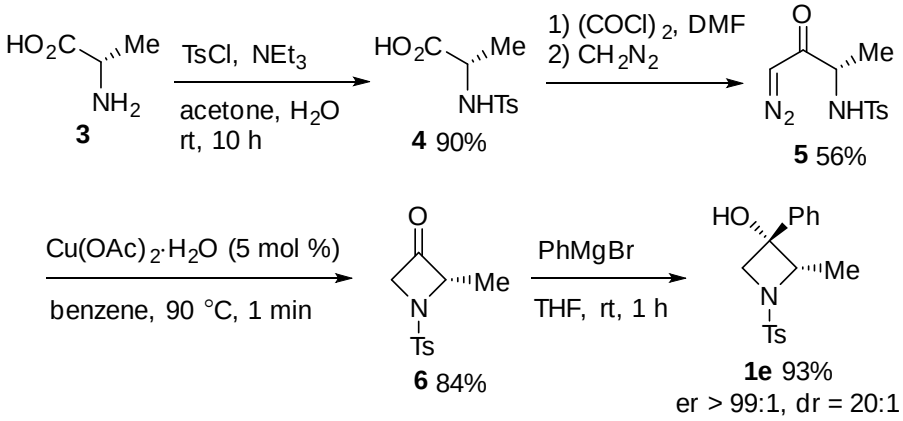
Table 1. Enantioselective Rearrangement of 1 to 2[a,b]



[a] Reaction conditions: $[Rh(OH)(cod)]_2$ (5 mol %), (R)-DIFLUORPHOS (12 mol %), toluene, 60 °C, 12 h. [b] Isolated yield.

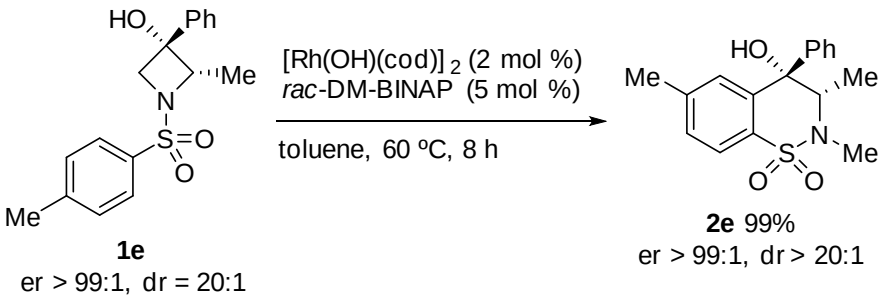
Asymmetrical azetidinol **1e** was prepared in an enantiopure form from (*L*)-alanine according to the modified Seebach's method (Scheme 4).[13] Initially, (*L*)-alanine (**3**) was treated with *p*-toluenesulfonyl chloride to afford *N*-tosylate **4**. Subsequent treatment with oxalyl chloride followed by coupling with diazomethane gave diazo ketone **5**. Copper-catalyzed denitrogenative cyclization of **5** afforded azetidinone **6**. Addition of phenylmagnesium bromide to **6** occurred selectively from the face opposite to the methyl group to furnish azetidinol **1e** in an enantiopure form.

Scheme 4. Synthesis of Enantiopure Azetidinol 1e



The azetidinol **1e** was heated at 60 °C in toluene for 8 h in the presence of $[Rh(OH)(cod)]_2$ (2 mol %) and *rac*-DM-BINAP (5 mol %) (Scheme 5). The rearrangement reaction proceeded efficiently to furnish the benzosultam **2e** in a quantitative yield stereoselectively with the enantiopurity retained. The stereochemistry was confirmed by X-ray crystallography.[10]

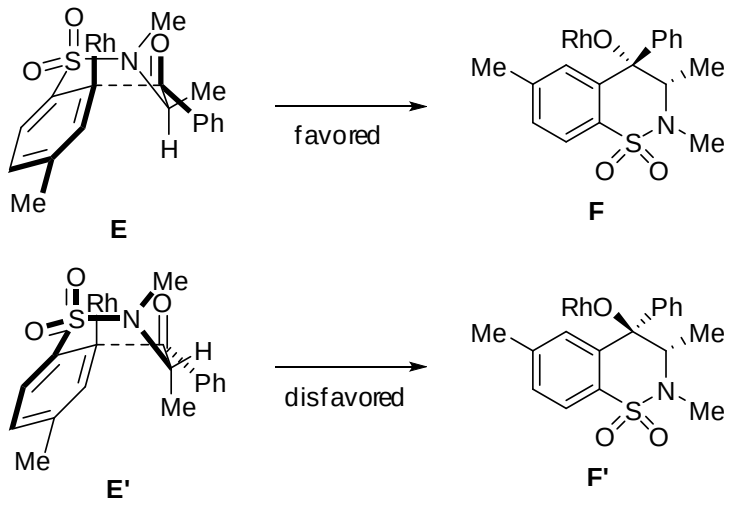
Scheme 5. Rearrangement of 1e to 2e



The exclusive formation of **2e** demonstrates that the β-carbon elimination occurs site-selectively at the methylene side rather than at the methyne side, probably due to

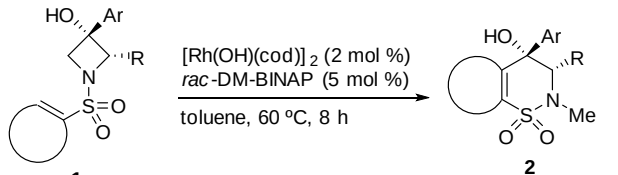
steric reasons. In addition, intramolecular carbonyl addition takes place in a diastereoselective fashion. We assume that the six-membered ring transition state takes a boat-like conformation, in which the C–Rh linkage can align with the C=O bond for the maximum orbital interaction as shown in Scheme 8. With the conformer **E**, the methyl group at the α-position takes a pseudoequatorial position, whereas the α-methyl group of the conformer **E'** takes a pseudoaxial position. Thus, the conformer **E** is favored over the conformer **E'** to produce the adduct **F** diastereoselectively.

Scheme 6. Models for Diastereoselective *6-exo-dig* Cyclization



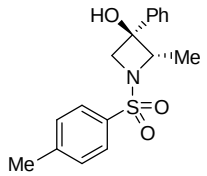
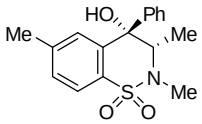
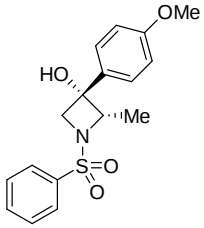
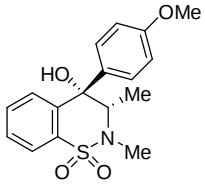
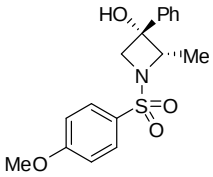
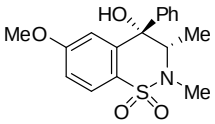
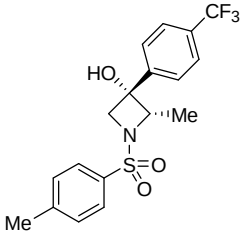
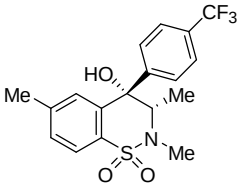
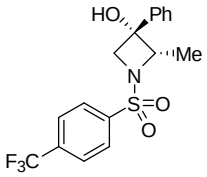
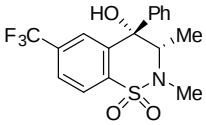
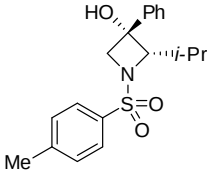
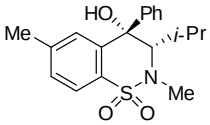
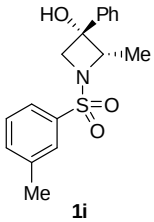
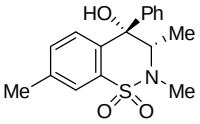
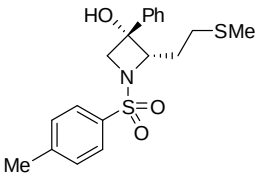
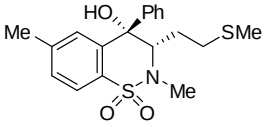
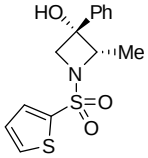
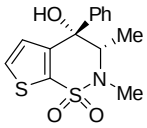
Various benzosultams were synthesized in an enantio- and diasteropure form (Table 2). The reaction of *N*-*p*-toluenesulfonylazetidinol **1f**, the diastereomer of **1e**, also furnished the same stereoisomer **2e** exclusively, being consistent with the proposed mechanism; the stereochemistry of the alcohol moiety once disappears upon β-carbon elimination to produce the same intermediate **C**. Azetidinols **1g-1j** having various aryl groups on the sulfonyl moiety gave the corresponding products **2g-2j** (entries 2-5). The reaction of *N*-*m*-toluenesulfonylazetidinol **1i** gave product **2i** with complete regioselectivity (entry 4), suggesting that rhodium preferred the sterically less hindered position as the destination of its 1,5-shift. Substituted aryl groups were allowed at the C3-position (entries 6, 7).[14] Benzosultam **2m** was obtained from azetidinol **1m**, which was prepared from valine (entry 8). The reaction of methionine-derived **1n** successfully furnished **2n**, demonstrating the compatibility of a sulfide functionality (entry 9).

Table 2. Rhodium-Catalyzed Rearrangement of 1 to 2[a]



1
er > 99:1, dr > 20:1

2
er > 99:1, dr > 20:1

entry	1	2[b]	entry	1	2[b]
1	 **1f**	 **2e** 99%	6	 **1k**	 **2k** 97%
2	 **1g**	 **2g** 98%	7	 **1l**	 **2l** 97%
3	 **1h**	 **2h** 99%	8	 **1m**	 **2m** 97%
4	 **1i**	 **2i** 99%	9		 **2n** 97%
5	 **1j**	 **2j** 99%			

[a] Reaction conditions: $[Rh(OH)(cod)]_2$ (2 mol %), *rac*-DM-BINAP (5 mol %), toluene, 60 °C, 8 h. [b] Isolated yield.

Conclusions

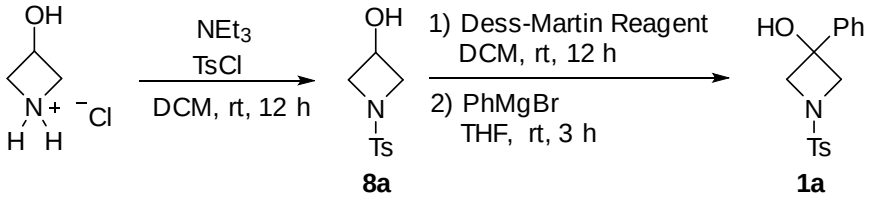
In summary, we have described the rhodium-catalyzed rearrangement reaction of *N*-arenesulfonylazetidinols into benzosultams. The unique transformation mechanistically involves reorganization of nonpolar σ-bonds via 1,5-rhodium shift, and provides a method to synthesize enantio- and diastereopure benzosultams starting from natural α-amino acids.

Experimental Section

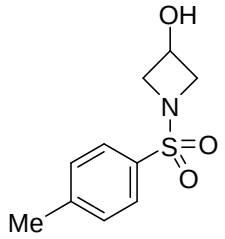
General. All reactions were carried out with standard Schlenk techniques. IR measurements were performed on a FTIR SHIMADZU DR-8000 spectrometer fitted with a Pike Technologies MIRacle Single Reflection ATR adapter. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury-vx400 (^{1}H at 400.44 MHz and ^{13}C at 100.69 MHz) and JEOL JNM-ECA600 (^{1}H at 600.17 MHz) spectrometer. NMR data were obtained in $CDCl_3$ and C_6D_6. Proton chemical shifts were referenced to the residual proton signal of the solvent at 7.26 ppm ($CHCl_3$) and 7.16 ppm (C_6D_6). Carbon chemical shifts were referenced to the carbon signal of the solvent at 77.0 ppm ($CDCl_3$). High-resolution mass spectra were recorded on a Thermo Scientific Exactive (ESI) spectrometer. Flash column chromatography was performed with silica gel 60N (Kanto). Preparative thin-layer chromatography (PTLC) was performed on silica gel plates with PF254 indicator (Merck).

Materials. Unless otherwise noted, all chemicals and anhydrous solvents were obtained from commercial suppliers.

Preparation of *N*-Toluenesulfonylazetidinol 1a and 1a-*d*

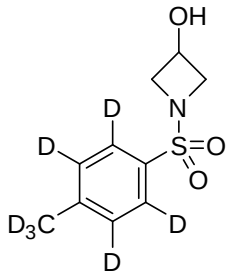


To a dichloromethane solution (20 mL) of 3-hydroxyazetidine hydrochloride (1.2 g, 11 mmol) and triethylamine (3.1 mL, 22 mmol) was added *p*-toluenesulfonyl chloride (1.9 g, 10 mmol). After being stirred at room temperature for 12 h, HCl aq. (2N) was added to the reaction mixture. The organic layer was separated and the remaining aqueous layer was extracted with dichloromethane (3 times). The combined organic layer was washed with brine (once), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by Flash column chromatography on silica gel (hexane/ethyl acetate = 1/1) to afford the *N*-toluenesulfonylazetidinol **8a** (1.5 g, 6.6 mmol, 66% yield).



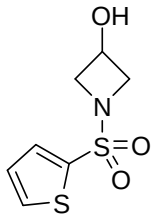
8a

^{1}H NMR: δ = 2.13 (bs, 1H), 2.45 (s, 3H), 3.50-3.61 (m, 2H), 3.94-4.04 (m, 2H), 4.42-4.52 (m, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR: δ = 21.6, 60.2, 60.5, 128.4, 129.8, 131.3, 144.3; HRMS (ESI^{+}): Calcd for $C_{10}H_{14}NO_3S$, M+H^{+} 228.0689, Found m/z 228.0686; IR (ATR): 3501, 1331, 1144, 1049, 665 cm^{-1}.



8a-*d*

^{1}H NMR: δ = 2.83 (bs, 1H), 3.49-3.55 (m, 2H), 3.89-3.96 (m, 2H), 4.35-4.44 (m, 1H); ^{13}C NMR: δ = 19.5-20.2 (m), 60.1, 60.2, 127.9 (t, $J_{C\text{-}D}$ = 24.7 Hz), 129.4 (t, *J* = 24.7 Hz), 130.8, 144.1; HRMS (ESI^{+}): Calcd for $C_{10}H_7D_7NO_3S$, M+H^{+} 235.1128, Found m/z 235.1125; IR (ATR): 3503, 1333, 1142, 1059, 638 cm^{-1}.

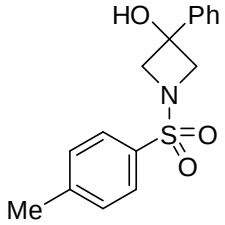


8b

^{1}H NMR: δ = 2.77 (bs, 1H), 3.57-3.64 (m, 2H), 4.00-4.07 (m, 2H), 4.41-4.50 (m, 1H), 7.21 (dd, *J* = 4.8, 4.0 Hz, 1H), 7.62 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.71 (dd, *J* = 5.2, 1.2 Hz, 1H); ^{13}C NMR: δ = 60.0, 60.6, 127.9, 133.2, 133.5, 133.8; HRMS (ESI^{+}): Calcd for $C_7H_{10}D_7NO_3S_2$, M+H^{+} 220.0097, Found m/z 220.0094; IR (ATR): 3476, 1325, 1148, 1038, 737 cm^{-1}.

To a dichloromethane solution (20 mL) of *N*-toluenesulfonylazetidinol **8** (780 mg, 3.4 mmol) was added Dess-Martin reagent (1.5 g, 3.5 mmol). After being stirred for 12 h at room temperature, saturated Na_2CO_3 aq. was added to the reaction mixture. The organic layer was separated and the remaining aqueous layer was extracted with dichloromethane (3 times). The combined organic layer was washed with brine (once), dried over $MgSO_4$ and concentrated.

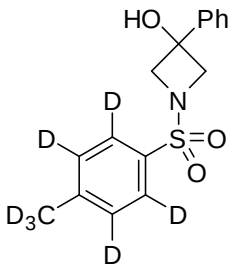
The residue was dissolved in THF (20 mL). PhMgBr (1.0 M in THF, 5 mL, 5 mmol) was added therein at -78 °C and the reaction mixture was then allowed to be at room temperature. After being stirred for 3 h, HCl (2N) was added to the reaction mixture at 0 °C. The aqueous layer was extracted with AcOEt (3 times), washed with brine (once), dried over $MgSO_4$ and concentrated. The residue was purified by Flash column chromatography on silica gel (hexane/ethyl acetate = 3/1) to afford the *N*-toluenesulfonylazetidinol **1a** (600 mg, 2.0 mmol, 59 % yield).



1a

^{1}H NMR: δ = 1.62 (s, 1H), 2.47 (s, 3H), 3.97 (d, *J* = 9.2 Hz, 2H), 4.13 (d, *J* = 9.2 Hz, 2H), 7.28-7.37 (m, 5H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR: δ = 21.6, 65.2, 70.3, 124.4, 128.1, 128.4, 128.6, 129.9, 131.2, 142.0, 144.4; HRMS (ESI$^+$): Calcd for $C_{16}H_{18}NO_3S$, M+H$^+$ 304.1002, Found m/z 304.0995; IR (ATR): 3477, 1333, 1184, 1148, 671 cm^{-1}.

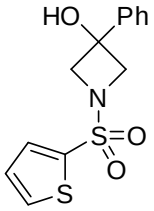
The spectral characteristics of **1a** were in agreement with the previously reported data.[15]



1a-*d*

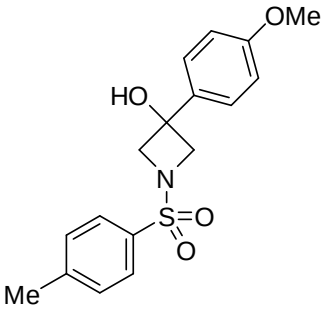
^{1}H NMR: δ = 2.50 (bs, 1H), 3.97 (d, *J* = 9.2 Hz, 2H), 4.13 (d, *J* = 9.2 Hz, 2H), 7.27-7.36 (m, 5H); ^{13}C NMR: δ = 20.3-21.1 (m), 65.2, 70.3, 124.4, 128.1 (t, $J_{C\text{-}D}$ = 24.7 Hz), 128.1, 128.6, 129.4 (t, $J_{C\text{-}D}$ = 24.7 Hz), 131.1, 142.0, 144.1; HRMS (ESI$^+$): Calcd for

$C_{16}H_{11}D_7NO_3S$, M+H$^+$ 311.1441, Found m/z 311.1434; IR (ATR): 3481, 1335, 1142, 702, 648 cm^{-1}.



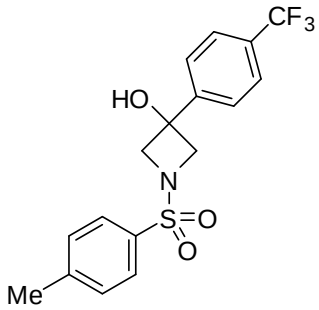
1b

^{1}H NMR: δ = 2.32 (bs, 1H), 4.00-4.08 (m, 2H), 4.16-4.24 (m, 2H), 7.24 (dd, *J* = 4.8, 3.6 Hz, 1H), 7.30-7.37 (m, 5H), 7.68 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.73 (dd, *J* = 4.8, 1.2 Hz, 1H); ^{13}C NMR: δ = 65.6, 70.2, 124.4, 128.0, 128.3, 128.8, 133.1, 133.87, 133.92, 141.7; HRMS (ESI$^+$): Calcd for $C_{13}H_{14}NO_3S_2$, M+H$^+$ 296.0410, Found m/z 296.0404; IR (ATR): 3524, 1333, 1161, 1148, 748 cm^{-1}.



1c

^{1}H NMR: δ = 2.46 (s, 3H), 2.57 (bs, 1H), 3.79 (s, 3H), 3.93 (d, *J* = 8.4 Hz, 2H), 4.08 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR: δ =21.6, 55.3, 65.2, 70.2, 113.9, 125.9, 128.5, 129.8, 131.2, 134.0, 144.3, 159.3; HRMS (ESI$^+$): Calcd for $C_{17}H_{20}NO_4S$, M+H$^+$ 334.1108, Found m/z 334.1097; IR (ATR): 3460, 1518, 1331, 1250, 1146 cm^{-1}.

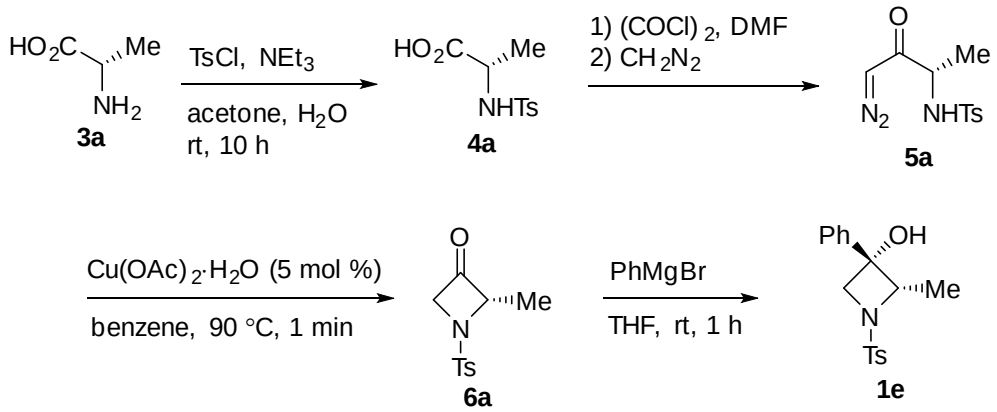


1d

^{1}H NMR: δ = 2.47 (s, 3H), 3.18 (bs, 1H), 3.96-4.10 (m, 4H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR: δ

=21.6, 65.4, 69.7, 123.9 (q, $J_{C\text{-}F}$ = 270.4 Hz), 124.9, 125.5 (q, $J_{C\text{-}F}$ = 3.7 Hz), 128.4, 130.0, 130.2 (q, $J_{C\text{-}F}$ = 32.0 Hz), 131.0, 144.8, 146.0; HRMS (ESI^+): Calcd for $C_{17}H_{17}F_3NO_3S$, $M+H^+$ 372.0876, Found m/z 372.0866; IR (ATR): 3450, 1329, 1151, 1109, 1076 cm^{-1}.

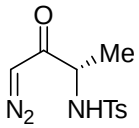
Preparation of *N*-Toluenesulfonylazetidinol 1e: A Typical Procedure of 1e, and 1l-1n



Preparation of α-Diazo Ketone 5a: A Typical Procedure for Preparation of 5a-5c

N-toluenesulfonylalanine **4a** (2.4 g, 10 mmol) was prepared according to the reported procedure.[16] The resulting **4a** was dissolved in dichloromethane (50 mL). The mixture was cooled to 0 °C under argon atmosphere, and oxalyl chloride (1.3 mL, 15 mmol) and one-drop of *N*,*N*-dimethylformamide were added. After being stirred at room temperature for 12 h, solvent was removed under reduced pressure.

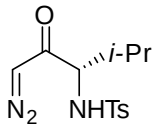
The residue was dissolved in THF under argon atmosphere. Diazomethane (which was freshly prepared by diazald and KOH, 25 mmol) in Et_2O was added to the solution at 0 °C. After being stirred for 3 h at room temperature, water was added to the reaction mixture. The organic layer was separated and the remaining aqueous layer was extracted with ethyl acetate (3 times). The combined organic layer was washed with brine (once), dried over $MgSO_4$ and concentrated. The residue was purified by Flash column chromatography on silica gel (hexane/ethyl acetate = 2/1 to 1/1) to afford the α-diazo ketone **5a** (1.5 g, 5.6 mmol, 56 % yield).



5a

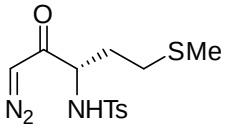
^{1}H NMR: δ = 1.26 (d, *J* = 7.2 Hz, 3H), 2.42 (s, 3H), 3.78-3.90 (m, 1H), 5.37-5.52 (m,

2H), 7.30 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H); ^{13}C NMR: δ = 19.4, 21.5, 53.9, 55.4, 127.1, 129.7, 136.8, 143.8, 192.8; HRMS (ESI$^+$): Calcd for $C_{11}H_{14}N_3O_3S$, M+H$^+$ 268.0750, Found m/z 268.0747; IR (ATR): 2112, 1639, 1337, 1319, 1161 cm^{-1}
$[\alpha]^{27}_D$ = -118.4 (c = 0.79, in $CHCl_3$)
The spectral characteristics of **5a** were in agreement with the previously reported data.[17]



5b

^{1}H NMR: δ = 0.81 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H), 1.90-2.02 (m, 1H), 2.40 (s, 3H), 3.52-3.68 (m, 1H), 5.27 (s, 1H), 5.51 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H); ^{13}C NMR: δ =16.9, 19.3, 21.5, 31.5, 54.8, 64.7, 127.3, 129.6, 136.7, 143.6, 192.2; HRMS (ESI$^+$): Calcd for $C_{13}H_{18}N_3O_3S$, M+H$^+$ 296.1063, Found m/z 296.1060; IR (ATR): 2129, 1622, 1362, 1329, 1161 cm^{-1}
$[\alpha]^{28}_D$ = -73.0 (c = 0.71, in $CHCl_3$)

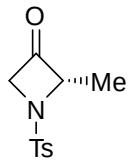


5c

^{1}H NMR: δ = 1.74-1.96 (m, 2H), 2.04 (s, 3H), 2.42 (s, 3H), 2.44-2.52 (m, 2H), 3.90-4.00 (m, 1H), 5.41 (s, 1H), 5.60-5.72 (m, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H); ^{13}C NMR: δ = 15.3, 21.5, 29.7, 32.3, 54.5, 58.5, 127.2, 129.7, 136.6, 143.9, 191.8; HRMS (ESI$^+$): Calcd for $C_{13}H_{18}N_3O_3S_2$, M+H$^+$ 328.0784, Found m/z 328.0779; IR (ATR): 2129, 1618, 1375, 1339, 1163 cm^{-1}
$[\alpha]^{29}_D$ = -50.6 (c = 0.63, in $CHCl_3$)
The spectral characteristics of **5c** were in agreement with the previously reported data.[17]

Preparation of *N*-Toluenesulfonylazetidinone 6a: A Typical Procedure for Preparation of 6a-6c

$Cu(OAc)_2 \cdot H_2O$ (80 mg, 0.4 mmol) was added to a benzene solution (70 mL) of α-diazo ketone **5a** (1.2 g, 4.5 mmol) at 90 °C. After being stirred for 1 min, the reaction mixture was allowed to be at room temperature. Solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (Hexane/AcOEt = 3/1) to afford *N*-toluenesulfonylazetidinone **6a** (0.90 g, 3.8 mmol, 84% yield).

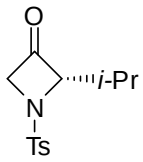


6a

^{1}H NMR: δ = 1.45 (d, *J* = 6.8 Hz, 3H), 2.46 (s, 3H), 4.43-4.54 (m, 2H), 4.73-4.80 (m, 1H), 7.36-7.42 (m, 2H), 7.76-7.81 (m, 2H); ^{13}C NMR: δ = 15.7, 21.6, 69.6, 81.0, 128.4, 130.0, 131.5, 145.0, 196.7; HRMS (ESI^{+}): Calcd for $C_{11}H_{14}NO_3S$, M+H^{+} 240.0689, Found m/z 240.0688; IR (ATR): 1825, 1339, 1155, 669 cm^{-1}

$[\alpha]^{28}_{D}$ = 61.4 (c = 0.81, in $CHCl_3$)

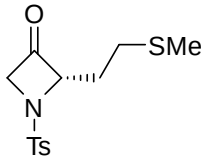
The spectral characteristics of **6a** were in agreement with the previously reported data.[17]



6b

^{1}H NMR: δ = 0.99-1.11 (m, 6H), 2.06-2.18 (m, 1H), 2.46 (s, 3H), 4.41 (dd, *J* = 16.4, 3.6 Hz, 1H), 4.50 (d, *J* = 16.4 Hz, 1H), 4.61 (dd, *J* = 5.2, 3.6 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR: δ = 17.4, 18.1, 21.6, 30.4, 70.3, 90.3, 128.4, 130.0, 132.0, 144.9, 197.3; HRMS (ESI^{+}): Calcd for $C_{13}H_{18}NO_3S$, M+H^{+} 268.1002, Found m/z 268.0998; IR (ATR): 1815, 1340, 1155, 1007, 671 cm^{-1}

$[\alpha]^{29}_{D}$ = 56.7 (c = 0.95, in $CHCl_3$)



6c

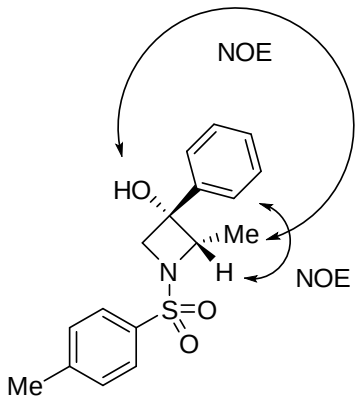
^{1}H NMR: δ = 2.04 (s, 3H), 2.09-2.18 (m, 2H), 2.47 (s, 3H), 2.65-2.79 (m, 2H), 4.46 (d, *J* = 15.6 Hz, 1H), 4.60 (dd, *J* = 15.6, 3.6 Hz, 1H), 4.82-4.88 (m, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR: δ = 14.7, 21.6, 29.1, 29.3, 70.5, 83.2, 128.6, 130.1, 131.1, 145.1, 196.3; HRMS (ESI^{+}): Calcd for $C_{13}H_{18}NO_3S_2$, M+H^{+} 300.0723, Found m/z 300.0718; IR (ATR): 1813, 1342, 1308, 1157, 667 cm^{-1}

$[\alpha]^{29}_{D}$ = 118.3 (c = 0.36, in $CHCl_3$)

The spectral characteristics of **6c** were in agreement with the previously reported data.[17]

Preparation of *N*-Toluenesulfonylazetidinol 1e: A Typical Procedure for Preparation of 1e, and 1l-1n

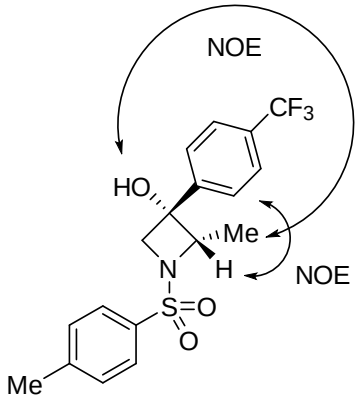
To a THF solution (20 mL) of *N*-toluenesulfonylazetidinone **6a** (1.2 g, 5.0 mmol) at -78 °C was added PhMgBr (1.0 M in THF, 5.5 mL, 5.5 mmol). The reaction mixture was then allowed to be at room temperature. After being stirred for 3 h, HCl aq (2N) was added to the reaction mixture at 0 °C. The aqueous layer was extracted with AcOEt (3 times), washed with brine (once), dried over $MgSO_4$ and concentrated. The residue was purified by Flash column chromatography on silica gel (hexane/ethyl acetate = 3/1) to afford the N-toluenesulfonylazetidinol **1e** (1.5 mg, 4.7 mmol, 93% yield).



1e

^{1}H NMR: δ =1.42 (d, *J* = 6.8 Hz, 3H), 1.62 (bs, 1H), 2.48 (s, 3H), 3.88 (dd, *J* = 9.2, 0.8 Hz, 1H), 3.99 (d, *J* = 9.2 Hz, 1H), 4.19 (q, *J* = 6.4 Hz, 1H), 6.94-6.98 (m, 2H), 7.20-7.22 (m, 3H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR: δ = 14.4, 21.6, 62.8, 70.2, 73.1, 124.7, 127.9, 128.4, 128.5, 129.8, 131.9, 141.5, 144.3; HRMS (ESI$^+$): Calcd for $C_{17}H_{20}NO_3S$, M+H$^+$ 318.1158, Found m/z 318.1154; IR (ATR): 3470, 1335, 1155, 1092, 667 cm^{-1}.

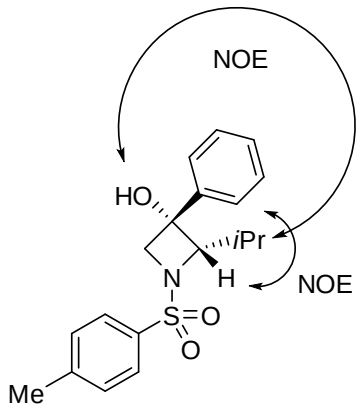
$[\alpha]^{25}_D$ = 36.4 (c = 1.06, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC, hexane/*i*-PrOH = 70/30, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 25.1 min (minor), t_2 = 28.7 min (major), er > 99:1.



1l

^{1}H NMR: δ = 1.42 (d, *J* = 6.4 Hz, 3H), 2.51 (s, 3H), 2.95 (bs, 1H), 3.92 (d, *J* = 9.2 Hz, 1H), 3.98 (d, *J* = 9.6 Hz, 1H), 4.16, (q, *J* = 6.4 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.39-7.47 (m, 4H), 7.77 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR: δ = 14.3, 21.6, 63.0, 70.6, 72.7, 123.8 ($J_{C\text{-}F}$ = 270.4 Hz), 125.3, 125.4 ($J_{C\text{-}F}$ = 3.6 Hz), 128.5, 129.9, 130.1 ($J_{C\text{-}F}$ = 32.4 Hz), 131.6, 144.6, 145.4; HRMS (ESI$^+$): Calcd for $C_{18}H_{19}F_3NO_3S$, M+H$^+$ 386.1032, Found m/z 386.1025; IR (ATR): 3422, 1327, 1151, 1109, 839 cm^{-1}.

$[\alpha]^{28}_D$ = 40.4 (c = 0.89, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC, hexane/*i*-PrOH = 70/30, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 11.1 min (minor), t_2 = 12.3 min (major), er > 99:1.

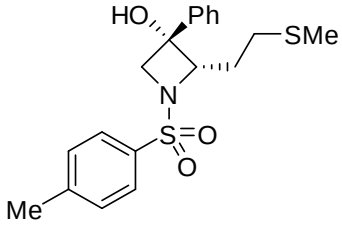


1m

^{1}H NMR: δ = 0.87 (d, *J* = 6.8 Hz, 3H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.61 (bs, 1H), 2.26-2.40 (m, 1H), 2.45 (s, 3H), 3.86 (d, *J* = 9.2 Hz, 1H), 3.93 (dd, *J* = 9.6, 0.8 Hz, 1H), 4.10 (d, *J* = 10.0 Hz, 1H), 6.90-6.96 (m, 2H), 7.12-7.20 (m, 3H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR: δ = 19.0, 19.3, 21.5, 29.1, 64.1, 72.9, 80.1, 124.7, 127.5, 128.4, 128.5, 129.7, 132.4, 142.8, 144.1; HRMS (ESI$^+$): Calcd for $C_{19}H_{24}NO_3S$, M+H$^+$ 346.1471, Found m/z 346.1466; IR (ATR): 3454, 1331, 1163, 739, 669 cm^{-1}.

$[\alpha]^{27}_D$ = 61.1 (c = 1.18, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC, hexane/*i*-PrOH = 90/10, flow rate = 0.6 mL/min, λ = 260 nm): t_1

= 38.7 min (minor), t_2 = 40.9 min (major), er > 99:1.

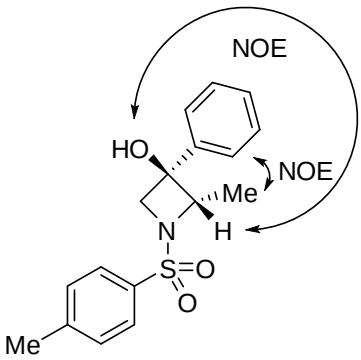


1n

^{1}H NMR: δ = 2.02 (s, 3H), 2.18-2.58 (m, 8H), 3.88-3.94 (m, 2H), 4.27 (dd, *J* = 8.4, 4.8 Hz, 1H), 6.88-6.93 (m, 2H), 7.14-7.21 (m, 3H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR: δ = 15.4, 21.6, 29.0, 29.7, 63.4, 72.5, 73.3, 124.6, 127.7, 128.4, 128.6, 129.9, 131.8, 142.4, 144.3; HRMS (ESI$^+$): Calcd for $C_{19}H_{24}NO_3S_2$, M+H$^+$ 378.1192, Found m/z 378.1188; IR (ATR): 3481, 1339, 1157, 702, 669 cm^{-1}.
$[\alpha]^{28}_D$ = 71.9 (c = 0.90, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IB, hexane/*i*-PrOH = 90/10, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 18.2 min (minor), t_2 = 19.3 min (major), er > 99:1.

Preparation of *N*-Toluenesulfonylazetidinol 1f

A mixture containing *N*-toluenesulfonylazetidinol **1e** (31.7 mg, 0.10 mmol), $[Rh(OH)(cod)]_2$ (0.9 mg, 2 μmol, 2 mol %), and (S)-DM-BINAP (3.7 mg, 5 μmol, 5 mol %) in toluene (1.0 mL) was heated at 60 °C. After being stirred for 1 h, the reaction mixture was passed through a pad of florisil. The solvent was removed under reduced pressure. The crude residue was purified by preparative thin-layer chromatography on silica gel (dichloromethane/ethyl acetate = 5/1) and GPC to afford the *N*-toluenesulfonylazetidinol **1f** (6.2 mg, 0.020 mmol, 20% yield).

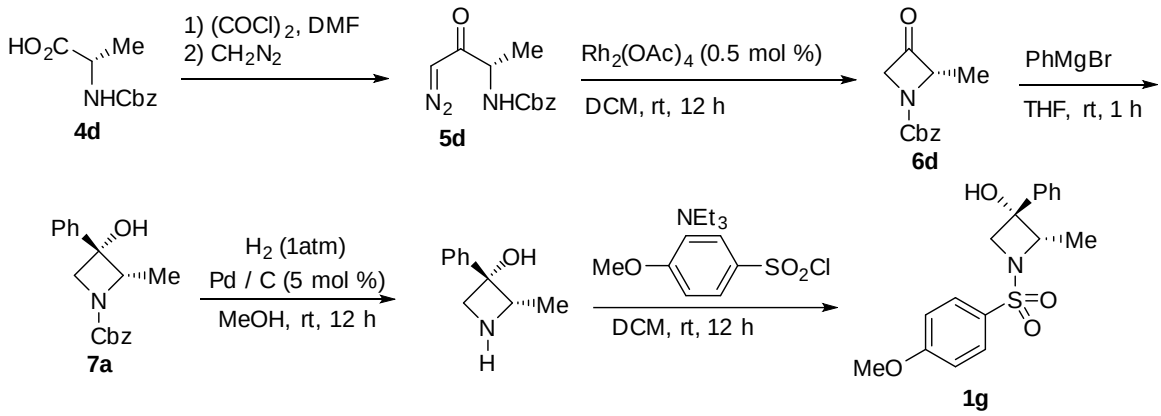


1f

^{1}H NMR: δ = 0.89 (d, *J* = 6.4 Hz, 3H), 2.24 (bs, 1H), 2.47 (s, 3H), 3.66 (d, *J* = 8.4 Hz, 1H), 3.98 (q, *J* = 6.4 Hz, 1H), 4.24 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.32-7.44 (m, 5H), 7.50-7.55 (m, 2H), 7.74-7.78 (m, 2H); ^{13}C NMR: δ = 16.5, 21.6, 62.7, 71.8, 73.9, 125.7,

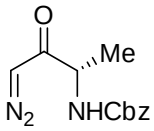
128.2, 128.5, 128.6, 129.8, 131.0, 139.0, 144.3; HRMS (ESI$^+$): Calcd for $C_{17}H_{20}NO_3S$, M+H$^+$ 318.1158, Found m/z 318.1154; IR (ATR): 3425, 1325, 1175, 1146, 694 cm^{-1}.
$[\alpha]^{25}_D$ = 6.8 (c = 0.30, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC, hexane/*i*-PrOH = 70/30, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 12.8 min (minor), t_2 = 15.3 min (major), er > 99:1.

Preparation of *N*-Toluenesulfonylazetidinol 1g: A Typical Procedure for Preparation of 1g-1k



Preparation of α-Diazo Ketone 5d

The *N*-benzyloxycarbonylalanine **4d** (6.7 g, 30 mmol) was dissolved in THF (150 mL). Triethylamine (6 mL) and ethyl chlorocarbonate were added therein at –15 °C. Diazomethane in Et_2O (which was freshly prepared by diazald and KOH, 70 mmol) was added. The mixture was stirred at room temperature for 3 h, and then, water was added. The mixture was extracted with AcOEt, washed with water and brine, dried over $MgSO_4$ and concentrated. The residue was washed with Et_2O to afford the α-diazo ketone (5.9 g, 24 mmol, 80 % yield).

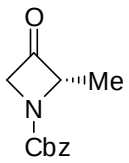


5d

^{1}H NMR: δ = 1.34 (d, *J* = 6.8 Hz, 3H), 4.20-4.36 (m, 1H), 5.04-5.16 (m, 2H), 5.34-5.64 (m, 2H), 7.28-7.36 (m, 5H); ^{13}C NMR: δ = 18.4, 53.5 (2C), 66.9, 128.0, 128.2, 128.5, 136.1, 155.6, 193.8; HRMS (ESI$^+$): Calcd for $C_{12}H_{14}N_3O_3$, M+H$^+$ 248.1030, Found m/z 248.1028; IR (ATR): 2116, 1717, 1636, 1533, 1252 cm^{-1}.
$[\alpha]^{28}_D$ = -43.4 (c = 0.85, in $CHCl_3$).
The spectral characteristics of **5d** were in agreement with the previously reported data.[18]

Preparation of *N*-Benzyloxycarbonylazetidinone 6d

To a dichloromethane solution (50 mL) of α-diazo ketone **5d** (2.5 g, 10 mmol) at 0 °C was added $Rh_2(OAc)_4$ (20 mg, 0.05 mmol, 0.5 mol %). The reaction mixture was then warmed to room temperature. After being stirred for 12 h, solvent was removed under reduced pressure. The residue was purified by GPC to afford *N*-benzyloxycarbonylazetidinone **6d** (1.2 g, 5.6 mmol, 56% yield).



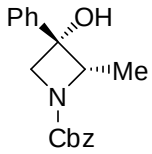
6d

^{1}H NMR: δ = 1.49 (d, *J* = 7.2 Hz, 3H), 4.66 (dd, *J* = 16.4, 4.0 Hz, 1H), 4.77 (d, *J* = 16.4 Hz, 1H), 4.98-5.05 (m, 1H), 5.13-5.21 (m, 2H), 7.31-7.39 (m, 5H); ^{13}C NMR: δ = 15.3, 67.4, 68.7, 79.0, 128.1, 128.3, 128.6, 136.1, 156.3, 199.8; HRMS (ESI$^+$): Calcd for $C_{12}H_{14}NO_3$, M+H$^+$ 220.0968, Found m/z 220.0966; IR (ATR): 1811, 1690, 1410, 1342, 696 cm^{-1}.

$[\alpha]^{29}_D$ = 39.0 (c = 0.68, in $CHCl_3$).

Preparation of *N*-Benzyloxycarbonylazetidinol 7a and 7b

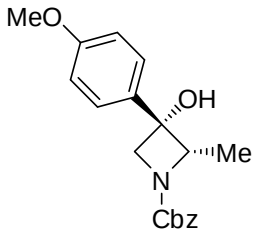
To a THF solution (20 mL) of *N*-benzyloxycarbonylazetidinone **6d** (1.1 g, 5.0 mmol) at -78 °C was added PhMgBr (1.0 M in THF, 5.5 mL, 5.5 mmol). The reaction mixture was then warmed to room temperature. After being stirred for 3 h, HCl aq (2N) was added at 0 °C. The mixture was separated and the aqueous layer was extracted with AcOEt (3 times). The combined organic phase was washed with brine (once), dried over $MgSO_4$ and concentrated. The residue was purified by Flash column chromatography on silica gel (hexane/ethyl acetate = 1/1) to afford the *N*-benzyloxycarbonyl azetidinol **7a** (1.4 g, 4.8 mmol, 96% yield).



7a

^{1}H NMR: δ = 1.50 (d, *J* = 6.4 Hz, 3H), 2.51 (bs, 1H), 4.11 (d, *J* = 9.6 Hz, 1H), 4.34 (d, *J* = 9.6 Hz, 1H), 4.58 (q, *J* = 6.4 Hz, 1H), 5.07-5.18 (m, 2H), 7.29-7.46 (m, 10H); ^{13}C NMR: δ = 14.2, 62.3, 66.7, 68.9, 73.0, 124.6, 127.8, 127.9, 128.0, 128.5, 128.7, 136.6,

143.4, 156.5; HRMS (ESI$^+$): Calcd for $C_{18}H_{20}NO_3$, M+H$^+$ 298.1438, Found m/z 298.1433; IR (ATR): 1670, 1423, 1248, 1016, 702 cm^{-1}.
$[\alpha]^{29}_D$ = 4.6 (c = 0.89, in $CHCl_3$).



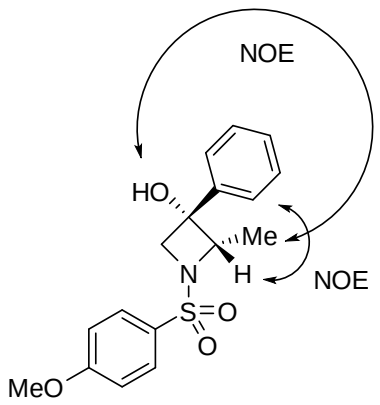
7b

^{1}H NMR: δ = 1.49 (d, *J* = 6.4 Hz, 3H), 2.26 (bs, 1H), 3.81 (s, 3H), 4.09 (d, *J* = 9.6 Hz, 1H), 4.32 (d, *J* = 9.6 Hz, 1H), 4.52-4.61 (m, 1H), 5.06-5.18 (m, 2H), 6.87-6.94 (m, 2H), 7.26-7.39 (m, 7H); ^{13}C NMR: δ = 14.3, 55.3, 62.2, 66.6, 68.7, 72.9, 114.0, 126.0, 127.8, 128.0, 128.5, 135.5, 136.6, 156.6, 159.3; HRMS (ESI$^+$): Calcd for $C_{19}H_{22}NO_4$, M+H$^+$ 328.1543, Found m/z 328.1539; IR (ATR): 1682, 1418, 1352, 1024, 696 cm^{-1}.
$[\alpha]^{29}_D$ = 0.2 (c = 0.85, in $CHCl_3$).

Preparation of *N*-Toluenesulfonylazetidinol 1g: A Typical procedure for Preparation of 1g-1k

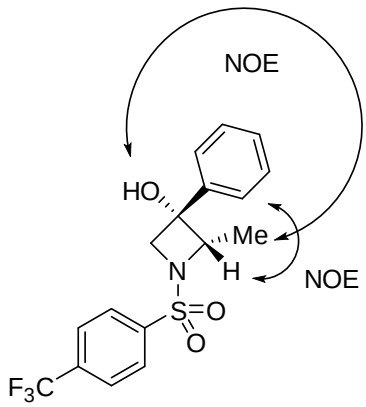
Pd/C (100 mg) was placed in a flask. A methanol (20 mL) solution of *N*-benzyloxycarbonylazetidinol **7a** (5 mmol, 1.5 mmol) was added therein and the flask was purged with hydrogen. After being stirred at room temperature for 12 h, the reaction mixture was passed through a pad of celite®. The solvent was removed under reduced pressure.

The residue was dissolved in dichloromethane (20 mL), and *p*-methoxyphenylsulfonyl chloride (1.0 g, 5.0 mmol) and NEt_3 (700 mL, 5 mmol) were added. The reaction mixture was stirred for 12 h and then water was added. The aqueous layer was extracted with dichloromethane (3 times), washed with brine (once), dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 3/1) to afford the *p*-methoxyphenylazetidinol **1g** (960 mg, 2.9 mmol, 58% yield).



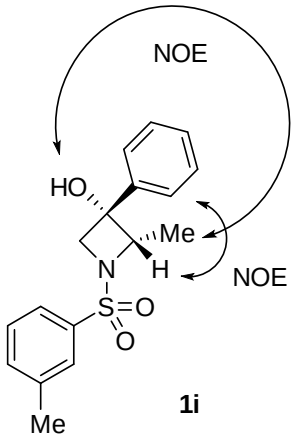
1g

^{1}H NMR: δ = 1.41 (d, *J* = 6.4 Hz, 3H), 2.59 (bs, 1H), 3.87 (dd, *J* = 9.2, 0.8 Hz, 1H), 3.90 (s, 3H), 3.99 (d, *J* = 9.2 Hz, 1H), 4.19 (q, *J* = 6.0 Hz, 1H), 6.98-7.07 (m, 4H), 7.20-7.27 (m, 3H), 7.79-7.85 (m, 2H); ^{13}C NMR: δ = 14.3, 55.7, 62.7, 70.1, 73.1, 114.4, 124.7, 126.5, 128.0, 128.5, 130.6, 141.6, 163.5; HRMS (ESI^{+}): Calcd for $C_{17}H_{20}NO_4S$, M+H^{+} 334.1108, Found m/z 334.1102; IR (ATR): 3470, 1595, 1333, 1153, 671 cm^{-1}.
$[\alpha]^{28}_{D}$ = 38.4 (c = 0.89, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC, hexane/*i*-PrOH = 70/30, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 30.9 min (minor), t_2 = 35.9 min (major), er > 99:1.



1h

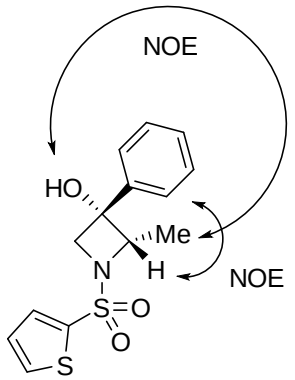
^{1}H NMR: δ = 1.47 (d, *J* = 6.4 Hz, 3H), 2.55 (bs, 1H), 3.95 (dd, *J* = 8.8, 0.8 Hz, 1H), 4.06, (d, *J* = 9.2 Hz, 1H), 4.30 (qd, *J* = 6.4, 0.8 Hz, 1H), 6.94-6.99 (m, 2H), 7.21-7.27 (m, 3H), 7.84 (d, *J* = 8.0 Hz, 2H), 8.01 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR: δ = 14.5, 62.9, 70.6, 72.9, 123.2 ($J_{C\text{-}F}$ = 271.1 Hz), 124.5, 126.3 ($J_{C\text{-}F}$ = 3.7 Hz), 128.3, 128.68, 128.71, 135.0 ($J_{C\text{-}F}$ = 32.7 Hz), 139.2, 141.4; HRMS (ESI^{+}): Calcd for $C_{17}H_{17}F_3NO_3S$, M+H^{+} 372.0876, Found m/z 372.0870; IR (ATR): 3503, 1348, 1323, 1165, 646 cm^{-1}.
$[\alpha]^{28}_{D}$ = 34.0 (c = 0.77, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC, hexane/*i*-PrOH = 70/30, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 12.0 min (minor), t_2 = 13.0 min (major), er > 99:1.



1i

^{1}H NMR: δ = 1.44 (d, *J* = 6.4 Hz, 3H), 2.17 (bs, 1H), 2.45 (s, 3H), 3.89 (d, *J* = 9.2 Hz, 1H), 4.01 (d, *J* = 8.8 Hz, 1H), 4.22 (q, *J* = 6.4 Hz, 1H), 6.94-6.98 (m, 2H), 7.20-7.24 (m, 3H), 7.46-7.50 (m, 2H), 7.67-7.72 (m, 2H); ^{13}C NMR: δ = 14.4, 21.4, 63.0, 70.4, 73.0, 124.7, 125.6, 127.9, 128.5, 128.6, 129.1, 134.1, 134.7, 139.5, 141.6; HRMS (ESI^{+}): Calcd for $C_{17}H_{20}NO_3S$, M+H^{+} 318.1158, Found m/z 318.1154; IR (ATR): 3487, 1325, 1151, 714, 700 cm^{-1}.

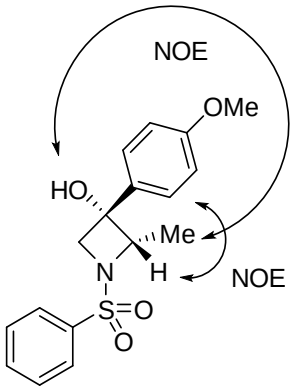
$[\alpha]^{29}_{D}$ = 38.0 (c = 1.05, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC, hexane/*i*-PrOH = 70/30, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 20.4 min (minor), t_2 = 21.8 min (major), er > 99:1.



1j

^{1}H NMR: δ = 1.48 (d, *J* = 6.4 Hz, 3H), 2.59 (bs, 1H), 3.96-4.01 (m, 1H), 4.06 (d, *J* = 9.2 Hz, 1H), 4.25 (q, *J* = 6.4 Hz, 1H), 6.96-7.01 (m, 2H), 7.20-7.28 (m, 4H), 7.64-7.67 (m, 1H), 7.69-7.72 (m, 1H); ^{13}C NMR: δ = 14.4, 63.2, 70.9, 73.0, 124.6, 127.9, 128.1, 128.6, 132.9, 133.7, 134.6, 141.4; HRMS (ESI^{+}): Calcd for $C_{14}H_{16}NO_3S_2$, M+H^{+} 310.0566, Found m/z 310.0559; IR (ATR): 3508, 1340, 1151, 756, 669 cm^{-1}.

$[\alpha]^{29}_{D}$ = 34.2 (c = 1.00, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC, hexane/*i*-PrOH = 70/30, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 18.3 min (minor), t_2 = 22.0 min (major), er > 99:1.



1k

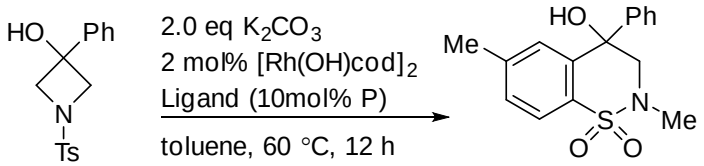
^{1}H NMR: δ = 1.42 (d, *J* = 6.4 Hz, 3H), 2.61 (bs, 1H), 3.75 (s, 3H), 3.87 (d, *J* = 9.2 Hz, 1H), 3.94 (d, *J* = 8.8 Hz, 1H), 4.16, (q, *J* = 6.4 Hz, 1H), 6.70-6.75 (m, 2H), 6.84-6.89 (m, 2H), 7.56-7.62 (m, 2H), 7.65-7.70 (m, 1H), 7.86-7.90 (m, 2H); ^{13}C NMR: δ = 14.3, 55.3, 63.0, 70.4, 72.9, 113.8, 125.9, 128.3, 129.2, 133.2, 133.7, 134.8, 159.2; HRMS (ESI^{+}): Calcd for $C_{17}H_{20}NO_4S$, M+H^{+} 334.1108, Found m/z 334.1102; IR (ATR): 3466, 1508, 1327, 1155, 606 cm^{-1}.

$[\alpha]^{29}_{D}$ = 36.0 (c = 1.13, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC, hexane/*i*-PrOH = 70/30, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 41.7 min (minor), t_2 = 49.9 min (major), er > 99:1.

Rhodium-Catalyzed Reaction of Azetidinol 1a: A Typical Procedure for Ligand Screening

A mixture containing *N*-toluenesulfonylazetidinol **1a** (30.3 mg, 0.10 mmol), K_2CO_3 (27.6 mg, 0.20 mmol), $[Rh(OH)(cod)]_2$ (0.9 mg, 2 μmol, 2 mol %), and *rac*-DM-BINAP (3.7 mg, 5 μmol, 5 mol %) in toluene (1.0 mL) was heated at 60 °C. After being stirred for 12 h, the reaction mixture was passed through a pad of florisil. The solvent was removed and the residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 3/1) to afford the benzosultam **2a** (29.1 mg, 0.093 mmol, 93% yield).

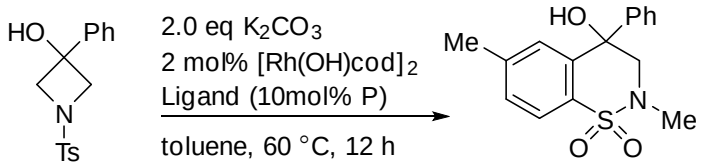
Table S1: Screening of Achiral Ligands



1a **2a**

entry	Ligand	yield / %
1	none	n.d
2	PPh_3	n.d
3	PCy_3	n.d
4	dppe	n.d
5	dppb	trace
6	dppf	trace
7	*rac*-BINAP	46
8	*rac*-DM-BINAP	93

Table S2: Screening of Chiral Ligands

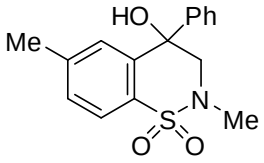


1a **2a**

entry	Ligand	yield / %	er
1	(R)-BINAP	48	31:69
2	(R)-DM-BINAP	94	38:62
3	(R)-SEGPHOS	43	12:88
4	(R)-DM-SEGPHOS	91	14:86
5	(R)-DTBM-SEGPHOS	trace	-
6	(R)-DIFLUORPHOS	46	8:92
7	(R)-MeO-BIPHEP	64	24:76
8	(R)-MeO-DM-BIPHEP	91	25:75

Rhodium-Catalyzed Reaction of Azetidinol 1a: A Typical Procedure for Reactions of Azetidinols 1a-1d

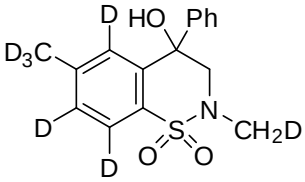
A mixture containing *N*-toluenesulfonylazetidinol **1a** (30.3 mg, 0.10 mmol), K_2CO_3 (27.6 mg, 0.20 mmol), $[Rh(OH)(cod)]_2$ (2.3 mg, 5 μmol, 5 mol %), and (R)-DIFLUORPHOS (8.2 mg, 12 μmol, 12 mol %) in toluene (1.0 mL) was heated at 60 °C. After being stirred for 12 h, the reaction mixture was passed through a pad of florisil. The solvent was removed and the residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 3/1) to afford the benzosultam **2a** (27.5 mg, 0.091 mmol, 91% yield).



2a

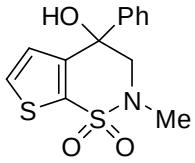
^{1}H NMR: δ = 2.28 (s, 3H), 2.77 (bs, 1H), 3.04 (s, 3H), 3.47 (d, *J* = 14.8 Hz, 1H), 4.29 (d, *J* = 14.8 Hz, 1H), 6.83 (s, 1H), 7.27-7.44 (m, 6H), 7.81 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR: δ = 21.6, 36.1, 62.6, 73.2, 123.8, 126.3, 128.0, 128.4, 129.9, 130.1, 133.0, 141.2, 143.1, 143.8; HRMS (ESI$^+$): Calcd for $C_{16}H_{18}NO_3S$, M+H$^+$ 304.1002, Found m/z 304.0998; IR (ATR): 3472, 1325, 1161, 1142, 735 cm^{-1}.

$[\alpha]^{29}_D$ = 33.9 (c = 0.28, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IB, hexane/*i*-PrOH = 90/10, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 17.5 min (minor), t_2 = 19.4 min (major), er = 92:8.



2a-*d*

^{1}H NMR: δ = 2.93 (bs, 1H), 3.00 (t, *J* = 2.0 Hz, 3H), 3.47 (d, *J* = 14.8 Hz, 1H), 4.26 (d, *J* = 14.8 Hz, 1H), 7.28-7.43 (m, 5H); ^{13}C NMR: δ = 20.1-21.0 (m), 35.8 (t, $J_{C\text{-}D}$ = 21.2 Hz), 62.5, 73.1, 123.4 (t, $J_{C\text{-}D}$ = 24.9 Hz), 126.2, 127.9, 128.3, 129.1-130.0 (m, 2C), 132.7, 141.1, 143,2, 143.4; HRMS (ESI$^+$): Calcd for $C_{16}H_{11}D_7NO_3S$, M+H$^+$ 311.1441, Found m/z 311.1436; IR (ATR): 3524, 1318, 1290, 1150, 721 cm^{-1}.

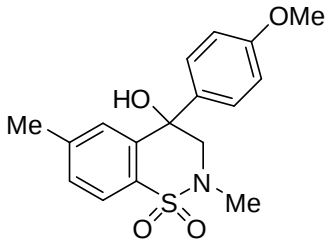


2b

^{1}H NMR: δ = 2.63 (bs, 1H), 3.10 (s, 3H), 3.59 (d, *J* = 15.2 Hz, 1H), 4.28 (d, *J* = 15.6 Hz, 1H), 6.68 (d, *J* = 5.2 z, 1H), 7.30-7.38 (m, 5H), 7.50 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR: δ = 37.8, 63.0, 72.2, 125.7, 126.4, 128.2, 128.6, 129.9, 133.8, 142.7, 146.7; HRMS (ESI$^+$): Calcd for $C_{13}H_{14}NO_3S_2$, M+H$^+$ 296.0410, Found m/z 296.0403; IR (ATR): 3437, 1323, 1150, 1063, 748 cm^{-1}.

$[\alpha]^{29}_D$ = 31.3 (c = 1.00, in $CHCl_3$); Enantiomeric excess was determined by HPLC with

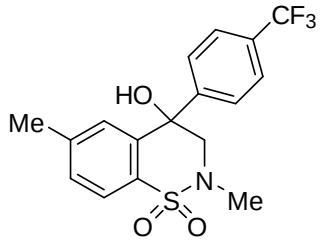
a Daicel Chiralpak IB, hexane/*i*-PrOH = 90/10, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 26.6 min (major), t_2 = 30.6 min (minor), er = 93:7.



2c

^{1}H NMR: δ = 2.27 (s, 3H), 2.90-3.26 (m, 4H), 3.45 (d, *J* = 14.8 Hz, 1H), 3.81 (s, 3H), 4.22 (d, *J* = 14.8 Hz, 1H), 6.84-6.90 (m, 3H), 7.24-7.33 (m, 3H), 7.74-7.79 (m, 1H); ^{13}C NMR: δ = 21.6, 36.0, 55.3, 62.6, 72.9, 113.7, 123.7, 127.5, 129.9, 123.0, 132.8, 135.1, 141.3, 143.7, 159.2; HRMS (ESI$^+$): Calcd for $C_{17}H_{20}NO_4S$, M+H$^+$ 334.1108, Found m/z 334.1098; IR (ATR): 3441, 1508, 1250, 1144, 735 cm^{-1}.

$[\alpha]^{29}_D$ = 16.6 (c = 0.33, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IB, hexane/*i*-PrOH = 90/10, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 24.4 min (minor), t_2 = 26.1 min (major), er = 93:7.



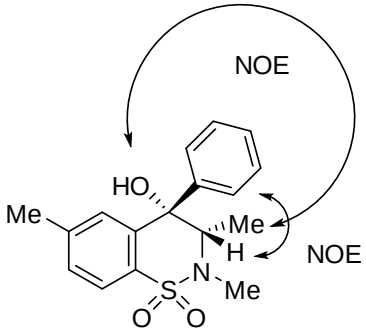
2d

^{1}H NMR: δ = 2.29 (s, 3H), 3.04 (s, 3H), 3.47 (d, *J* = 14.8 Hz, 1H), 4.25 (d, *J* = 14.8 Hz, 1H), 6.77 (s, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR: δ = 21.6, 36.0, 62.5, 73.1, 123.92 (q, $J_{C\text{-}F}$ = 270.8), 123.95, 125.4, (q, $J_{C\text{-}F}$ = 3.6 Hz), 126.8, 129.8, 130.3 (q, $J_{C\text{-}F}$ = 35.2), 132.9, 140.4, 144.1, 147.1; HRMS (ESI$^+$): Calcd for $C_{17}H_{17}F_3NO_3S$, M+H$^+$ 372.0876, Found m/z 372.0869; IR (ATR): 3481, 1323, 1121, 1067, 733 cm^{-1}.

$[\alpha]^{29}_D$ = 16.2 (c = 0.26, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IB, hexane/*i*-PrOH = 90/10, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 16.7 min (minor), t_2 = 19.2 min (major), er = 91:9.

Rhodium-Catalyzed Reaction of Azetidinol 1e: A Typical Procedure for Reactions of Azetidinols 1e-1n

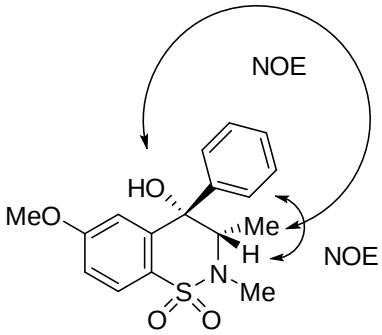
A mixture containing *N*-toluenesulfonylazetidinol **1e** (31.7 mg, 0.10 mmol), $[Rh(OH)(cod)]_2$ (0.9 mg, 2 μmol, 2 mol %), and *rac*-DM-BINAP (3.7 mg, 5 μmol, 5 mol %) in toluene (1.0 mL) was heated at 60 °C. After being stirred for 12 h, the reaction mixture was passed through a pad of florisil. The solvent was removed under reduced pressure. The crude residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 3/1) to afford the benzosultam **2e** (31.3 mg, 0.099 mmol, 99% yield).



2e

^{1}H NMR: δ = 1.20 (d, *J* = 6.4 Hz, 3H), 2.24 (s, 3H), 2.26 (s, 1H), 2.97 (s, 3H), 4.68 (q, *J* = 6.8 Hz, 1H), 6.75 (s, 1H), 7.23-7.38 (m, 6H), 7.77 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR: δ = 11.9, 21.5, 31.4, 60.8, 75.0, 124.2, 126.2, 127.5, 128.2, 129.8, 130.1, 131.6, 142.7, 143.6, 144.0; HRMS (ESI$^+$): Calcd for $C_{17}H_{20}NO_3S$, M+H$^+$ 318.1158, Found m/z 318.1155; IR (ATR): 3481, 1315, 1163, 1146, 683 cm^{-1}.

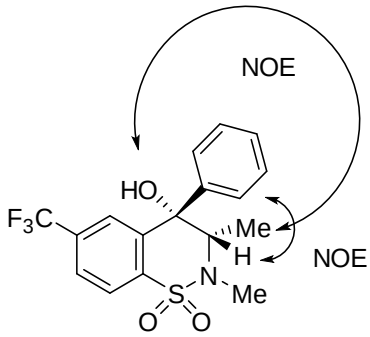
$[\alpha]^{28}_D$ = -64.0 (c = 0.93, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC, hexane/*i*-PrOH = 90/10, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 32.4 min (minor), t_2 = 38.5 min (major), er > 99:1.



2g

^{1}H NMR: δ = 1.19 (d, *J* = 6.8 Hz, 3H), 2.39 (s, 1H), 2.96 (s, 3H), 3.67 (s, 3H), 4.67 (q, *J* = 6.8 Hz, 1H), 6.41 (d, *J* = 2.4 Hz, 1H), 6.94 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.24-7.36 (m, 5H), 7.82 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR: δ = 12.0, 31.4, 55.5, 60.9, 75.2, 114.4, 115.1, 126.1, 126.2, 126.8, 127.6, 128.2, 143.9, 145.0, 162.6; HRMS (ESI^{+}): Calcd for $C_{17}H_{20}NO_4S$, M+H^{+} 334.1108, Found m/z 334.1103; IR (ATR): 3487, 1327, 1161, 1142, 735 cm^{-1}.

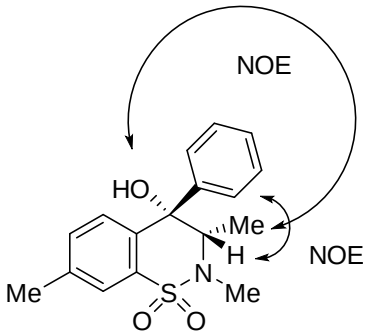
$[\alpha]^{29}_{D}$ = -37.3 (c = 0.60, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC, hexane/*i*-PrOH = 70/30, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 17.6 min (minor), t_2 = 19.6 min (major), er > 99:1.



2h

^{1}H NMR: δ = 1.24 (d, *J* = 6.8 Hz, 3H), 2.53 (bs, 1H), 3.00 (s, 3H), 4.73 (q, *J* = 6.8 Hz, 1H), 7.24 (s, 1H), 7.30-7.40 (m, 5H), 7.70 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR: δ = 11.8, 31.4, 60.8, 75.0, 122.8 (q, $J_{C\text{-}F}$ = 271.1 Hz), 125.1, 125.8 (q, $J_{C\text{-}F}$ = 3.7 Hz), 126.0, 127.4 (q, $J_{C\text{-}F}$ = 3.7 Hz), 128.1, 128.6, 134.6 (q, $J_{C\text{-}F}$ = 32.7 Hz), 137.7, 142.8, 143.7; HRMS (ESI^{+}): Calcd for $C_{17}H_{17}F_3NO_3S$, M+H^{+} 372.0876, Found m/z 372.0872; IR (ATR): 3461, 1325, 1161, 1142, 739 cm^{-1}.

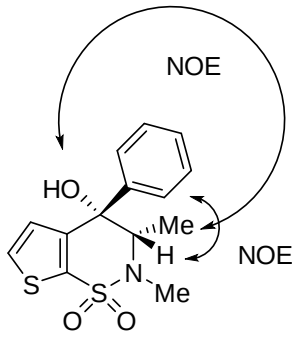
$[\alpha]^{29}_{D}$ = -64.0 (c = 0.63, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC, hexane/*i*-PrOH = 90/10, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 13.2 min (minor), t_2 = 14.3 min (major), er > 99:1.



2i

^{1}H NMR: δ = 1.21 (d, *J* = 6.8 Hz, 3H), 2.18 (bs, 1H), 2.38 (s, 3H), 3.00 (s, 3H), 4.68 (q, *J* = 6.8 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 7.18-7.36 (m, 6H), 7.70 (s, 1H); ^{13}C NMR: δ =11.9, 21.1, 31.4, 60.7, 74.8, 124.2, 126.2, 127.5, 128.2, 129.9, 133.8, 134.1, 139.5, 139.9, 144.1; HRMS (ESI^{+}): Calcd for $C_{17}H_{20}NO_3S$, M+H^{+} 318.1158, Found m/z 318.1155; IR (ATR): 3489, 1448, 1319, 1148, 735 cm^{-1}.

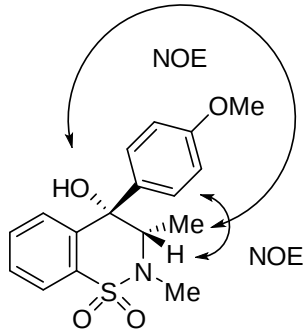
$[\alpha]^{29}_{D}$ = -96.2 (c = 0.62, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC, hexane/*i*-PrOH = 70/30, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 12.4 min (minor), t_2 = 14.1 min (major), er > 99:1.



2j

^{1}H NMR: δ = 1.24 (d, *J* = 6.8 Hz, 3H), 2.24 (bs, 1H), 3.01 (s, 3H), 4.61 (q, *J* = 6.8 Hz, 1H), 6.56 (d, *J* = 5.2 Hz, 1H), 7.26-7.36 (m, 5H), 7.43 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR: δ = 11.4, 31.9, 61.9, 74.2, 125.6, 126.6, 127.8, 128.4, 129.7, 133.4, 142.9, 148.0; HRMS (ESI^{+}): Calcd for $C_{14}H_{16}NO_3S_2$, M+H^{+} 310.0566, Found m/z 310.0561; IR (ATR): 3524, 1329, 1151, 1020, 729 cm^{-1}.

$[\alpha]^{29}_{D}$ = -80.3 (c = 0.53, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC, hexane/*i*-PrOH = 90/10, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 25.3 min (major), t_2 = 27.3 min (minor), er > 99:1.

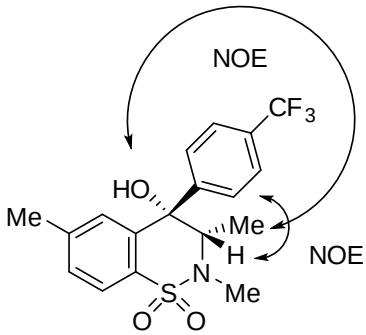


2k

^{1}H NMR: δ = 1.21 (d, *J* = 6.8 Hz, 3H), 2.26 (bs, 1H), 2.98 (s, 3H), 3.79 (s, 3H), 4.66 (q, *J* = 6.8 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.98-7.03 (m, 1H), 7.22-7.30 (m, 2H), 7.38-7.48 (m, 2H), 7.85-7.90 (m, 1H); ^{13}C NMR: δ = 11.9, 31.4, 55.3, 60.8, 74.7, 113.6,

124.1, 127.4, 128.9, 130.0, 132.8, 134.4, 135.9, 142.9, 158.9; HRMS (ESI$^+$): Calcd for $C_{17}H_{20}NO_4S$, M+H$^+$ 334.1108, Found m/z 334.1101; IR (ATR): 3479, 1508, 1313, 1157, 760 cm^{-1}.

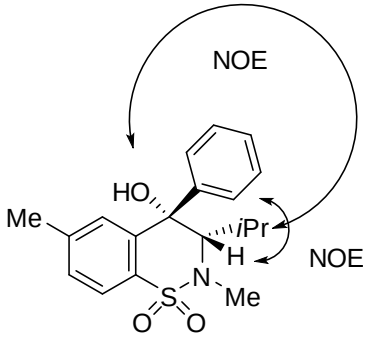
$[\alpha]^{26}_D$ = -100.7 (c = 0.87, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC, hexane/*i*-PrOH = 70/30, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 11.2 min (minor), t_2 = 12.5 min (major), er > 99:1.



2l

^{1}H NMR: δ = 1.20 (d, *J* = 6.8 Hz, 3H), 2.26 (s, 3H), 2.35 (s, 1H), 2.96 (s, 3H), 4.65 (q, *J* = 6.8 Hz, 1H), 6.70 (s, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR: δ = 11.9, 21.5, 31.3, 60.7, 74.9, 123.9 ($J_{C\text{-}F}$ = 270.4 Hz), 124.4, 125.2, ($J_{C\text{-}F}$ = 4.3 Hz), 126.8, 129.9 ($J_{C\text{-}F}$ = 31.6 Hz), 130.0, 130.3, 131.6, 141.9, 143.9, 148.2; HRMS (ESI$^+$): Calcd for $C_{18}H_{19}F_3NO_3S$, M+H$^+$ 386.1032, Found m/z 386.1026; IR (ATR): 3481, 1323, 1159, 1118, 731 cm^{-1}.

$[\alpha]^{26}_D$ = -51.7 (c = 0.60, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC, hexane/*i*-PrOH = 90/10, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 16.9 min (minor), t_2 = 19.5 min (major), er > 99:1.

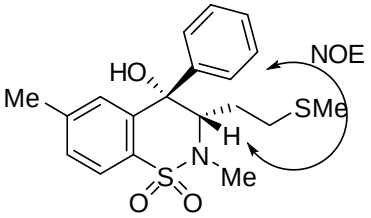


2m

^{1}H NMR: δ = 0.56 (d, *J* = 6.8 Hz, 3H), 1.10 (d, *J* = 6.4 Hz, 3H), 2.22 (s, 3H), 2.30-2.41 (m, 1H), 2.64 (s, 1H), 2.85 (s, 3H), 4.41 (d, *J* = 10.0 Hz, 1H), 6.85 (s, 1H), 7.14-7.35 (m, 4H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR: δ = 21.1, 21.4, 21.7, 27.8, 33.0, 71.8, 74.2, 124.4, 125.6, 127.0, 128.3, 129.2, 129.5, 130.0, 143.5, 144.2, 146.4; HRMS (ESI$^+$): Calcd for $C_{19}H_{24}NO_3S$, M+H$^+$ 346.1471, Found m/z 346.1466; IR

(ATR): 3412, 1315, 1165, 1146, 683 cm^{-1}.

$[\alpha]^{29}_{D}$ = -152.8 (c = 0.59, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC, hexane/*i*-PrOH = 70/30, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 12.7 min (major), t_2 = 13.9 min (minor), er > 99:1.



2n

^{1}H NMR: δ = 1.60-1.70 (m, 1H), 1.84 (s, 3H), 2.12-2.26 (m, 4H), 2.30-2.42 (m, 2H), 2.54-2.63 (m, 1H), 2.94 (s, 3H), 4.71 (dd, *J* = 10.8, 2.8 Hz, 1H), 6.75 (s, 1H), 7.22-7.38 (m, 6H), 7.76 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR: δ = 15.0, 21.5, 24.2, 30.1, 32.1, 64.3, 74.8, 124.5, 126.2, 127.6, 128.3, 129.86, 129.93, 131.2, 1429, 143.7, 144.1; HRMS (ESI^+): Calcd for $C_{19}H_{24}NO_3S_2$, $M+H^+$ 378.1192, Found m/z 378.1186; IR (ATR): 3483, 1319, 1165, 1134, 748 cm^{-1}.

$[\alpha]^{28}_{D}$ = -124.0 (c = 0.47, in $CHCl_3$); Enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC, hexane/*i*-PrOH = 70/30, flow rate = 0.6 mL/min, λ = 260 nm): t_1 = 16.6 min (minor), t_2 = 23.0 min (major), er > 99:1.

Details for X-ray Crystallography

Single crystal of **2e** was obtained from hexane/dichloromethane solution and mounted on a grass capillary. The data was collected on a Rigaku R-AXIS imaging plate area detector with graphite-monochromated Mo $K\alpha$ radiation operating at 50 kV and 40 mA at −173 °C. All the following procedure for analysis, Yadokari-XG[19] was used as a graphical interface. The structure was solved by direct methods with SIR-97[20] and refined by full-matrix least-squares techniques against F^2 (SHELXL-97).[21] All non-hydrogen atoms were refined anisotropically. The positions of hydrogen atoms were calculated, and their contributions in structural factor calculations were included.

Figure S1. ORTEP diagram of **2e**

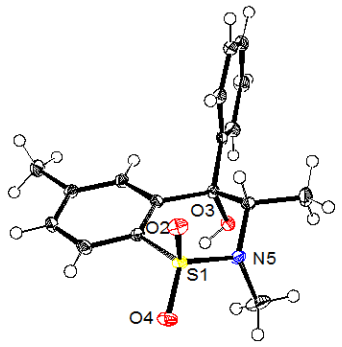


Table S3. Crystallographic data and structure refinement details for **2e**

	2e
formula	$C_{17}H_{19}NO_3S$
fw	317.39
T (K)	100(2)
cryst syst	monoclinic
space group	*P21/c*
a, (Å)	10.5967(5)
b, (Å)	13.4725(7)
c, (Å)	11.0152(5)
α, (°)	90.00
β, (°)	104.7740(15)
γ, (°)	90.00
V, (Å^3)	1520.58(13)
Z	4
D_{calc}, (g/cm^3)	1.386
μ (mm^{-1})	0.225
F(000)	672
cryst size (mm)	1.20×0.60×0.30
radiation λ (Å)	0.71075
reflns collected	14659
indep reflns/R_{int}	3485/0.0135
params	203
GOF on F^2	1.069
R_1, wR_2 [I>2σ(I)]	0.0322, 0.0868
R_1, wR_2 (all data)	0.0335, 0.0878

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Chapter 3

Stereoselective Synthesis of (*E*)-(Trisubstituted alkenyl)borinic Esters: Stereochemistry Reversed by Ligand in the Palladium-Catalyzed Reaction of Alkynylborates with Aryl Halides

Abstract

The palladium-catalyzed reaction of alkynylborates with aryl halides stereoselectively gave (*E*)-(trisubstituted alkenyl)-9-BBNs, in which two different aryl groups were installed *trans* to each other.

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Introduction

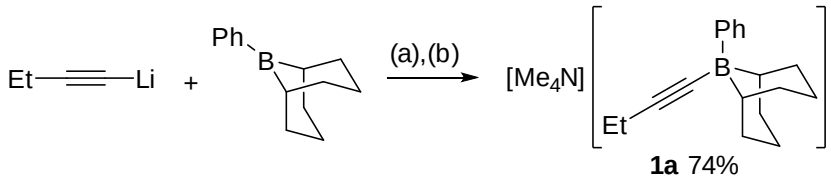
Organoboron compounds are stable and easily handled organometallics with well understood reactivities, rendering them indispensable synthetic reagents for carbon–carbon bond formation.[1] In addition, organoboron compounds have found increasing applications in the fields of pharmaceutical chemistry[2] and materials science.[3] Therefore, the development of efficient methods to prepare them is of even higher demand than ever.

Well established preparative methods exist for the synthesis of (monosubstituted alkenyl)(diorganyl)boranes such that these compounds have been widely applied for the synthesis of unsaturated organic compounds like allylic alcohols.[4] However the selective preparation of both stereoisomers of (trisubstituted alkenyl)(diorganyl)boranes remains a significant challenge.[5,6] We have reported that alkynyl(triaryl)borates (aryl = Ar^1) react with aryl halides (Ar^2–X) in the presence of a palladium catalyst to afford a (trisubstituted alkenyl)(diaryl)boranes, in which the two aryl groups (Ar^1 and Ar^2) are incorporated *cis* to each other across the resulting carbon–carbon double bond.[7] Considering the potential utility of these compounds, we embarked on the development of a complementary synthetic method for the (*E*)-isomers. In this communication, we describe the stereoselective synthesis of (*E*)-(trisubstituted alkenyl)-9-BBNs by a palladium-catalyzed reaction of alkynylborates with aryl halides, in which the two different aryl groups are installed *trans* to each other.

Results and Discussion

Alkynylborate **1a** was readily prepared by the reaction of Ph-9-BBN with but-1-ynyllithium in THF,[8] and subsequent cation exchange with tetramethylammonium chloride in methanol (Scheme 1). Borate **1a** obtained is a white precipitate of high purity, stable to air and moisture, and therefore, storable without any decomposition for several months.

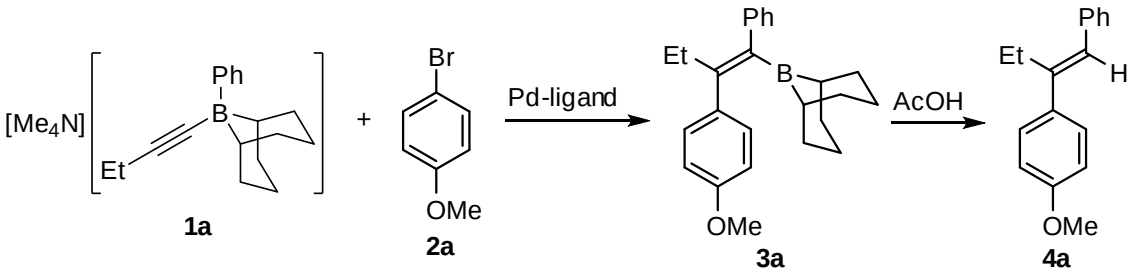
Scheme 1. Preparation of Alkynyl Borate 1a[a]



[a] Reagents and conditions: (a) THF, - 78 °C to rt, 1 h. (b) Me_4NCl, MeOH, rt, 5 min

Alkynylborate **1a** thus derived from Ph-9-BBN is preferred over the corresponding alkynyl*triaryl*borate as the starting substance from a synthetic point of view. It was subjected to the palladium-catalyzed reaction with 4-bromoanisole in the presence of various phosphine ligands (Table 1). When tri(*o*-tolyl)phosphine was employed as the ligand, the phenyl group on boron underwent 1,3-migration onto the palladium in preference to the bridgehead sp^3 carbons of the 9-BBN moiety, and the (*Z*)-isomer was stereoselectively formed, as with the case of the corresponding triphenylborate.[7a] Although we attempted to isolate the produced triorganoborane **3a**, it failed because **3a** was prone to decompose in air. Instead, **3a** was immediately hydrolyzed with acetic acid[9] to give the alkene (*Z*)-**4a** (*E*/*Z* = 3/97, entry 1). The *E*/*Z* ratio changed in favor of the (*E*)-isomer as the steric bulkiness of the monodentate phosphine increased (entries 2-4). Surprisingly, the stereochemical preference was reversed for the (*E*)-isomer (*E*/*Z* = 92/8) when bidentate ligand DPEPhos having a large bite angle was used (entry 5). Finally, it was found that XANTPhos, possessing an even larger bite angle exclusively gave (*E*)-**4a** in 73% yield (entry 6).

Table 1. Ligand Screening[a]



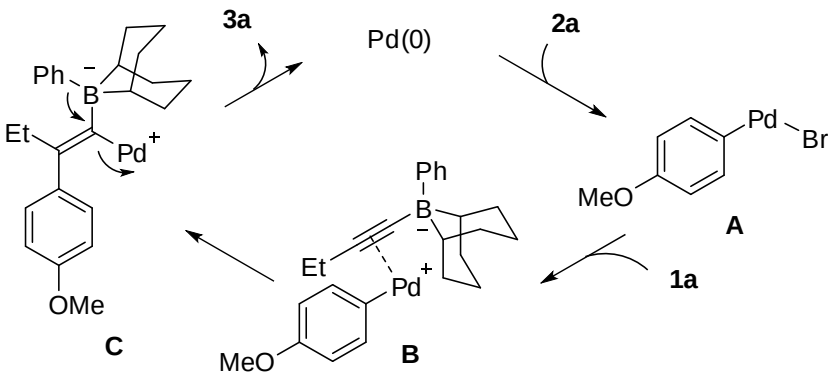
entry	ligand	yield of **4a**/ %[b]	*E*/*Z* of **4a**[b]
1	P(*o*-tol)$_3$	69	3/97
2	P(*t*-Bu)$_3$	47	17/83
3	1-[(*t*-Bu)$_2$P](biphenyl)	18	28/72
4	2-[(*t*-Bu)$_2$P](1,1'-binaphthyl)	21	67/33
5	DPEPhos	24	92/8
6	XANTPhos	73	>1/99

[a] reaction conditions: 1.0 equiv of **1a,** 1.05 equiv of **2a**, 2.5 mol % of [Pd(π-allyl)Cl]$_2$, 6 mol % of Ligand, toluene, 70 °C, 30 min; then AcOH, rt, 3 h. [b] Dtermined by GC analysis

Thus, the stereochemistry of the product depended strongly on the phosphine ligand employed. A proposed mechanism for the *trans*-addition reaction is shown in Scheme 2;

(i) oxidative addition of 4-bromoanisole (**2a**) to palladium(0) gives arylpalladium bromide **A**, (ii) arylpalladium species **A** is coordinated by alkynylborate **1a** to form intermediate **B**, (iii) carbopalladation across the carbon–carbon triple bond occurs in a *cis* fashion to provide alkenylpalladium **C**, (iv) a phenyl group on boron migrates to the α-carbon with inversion of stereochemistry,[10,11] resulting in the formation of *trans*-addition product **3a** with regeneration of the palladium(0).[12]

Scheme 2. Proposed Mechanism



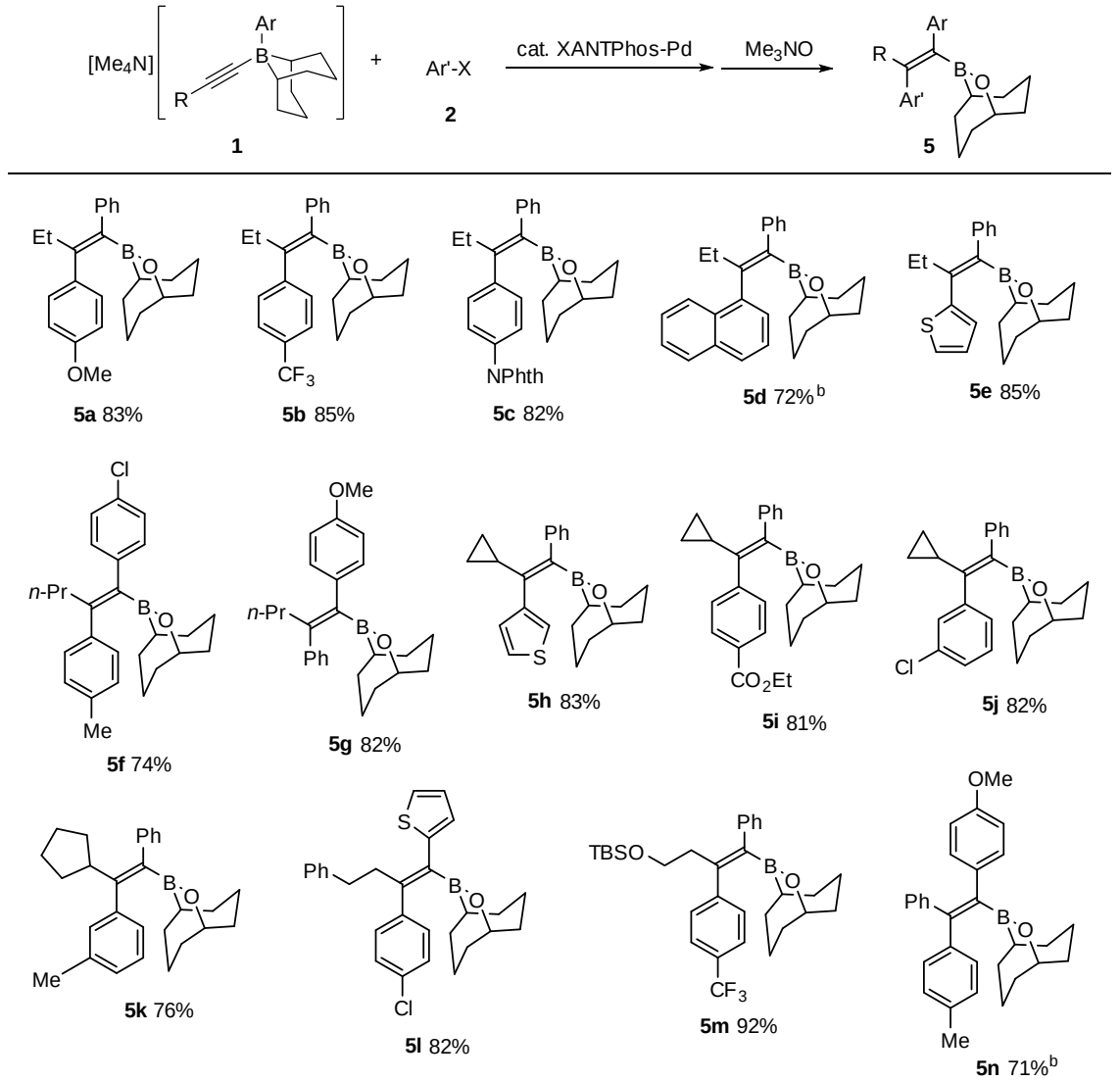
The ligand-dependent reaction pathway of the phenyl migration is explained as follows. Tri(*o*-tolyl)phosphine is relatively less stereo-demanding and, when located around the palladium center, provides enough space for the phenyl group on boron to undergo 1,3-migration to palladium (Scheme 4). On the other hand, a bulky bidentate ligand XANTPhos likely disfavors the 1,3-phenyl migration from boron to palladium. Instead, the direct 1,2-migration of the phenyl group from boron onto the α-carbon dominates,[10] giving *trans*-addition product. Tri(*t*-butyl)phosphine and Buchwald type ligands, which are intermediates between tri(*o*-tolyl)phosphine and XANTPhos in sterics, may permit both of these pathways, resulting in a mixture of *E*/*Z* isomers.

Next, we tried to isolate the addition product in a form of an alkenylborane which was applicable to subsequent synthetic transformations rather than loosing a carbon–boron linkage by hydrolysis. When the reaction mixture was directly subjected to a migrative oxidation reaction with trimethylamine-*N*-oxide, (trisubstituted alkenyl)borinic ester **5a** in which the bridgehead sp^3 carbon migrated onto oxygen was obtained stereoselectively.[13] The resulting borinic ester (*E*)-**5a** was stable enough to be isolated by column chromatography on silica gel and could be stored without any decomposition for a longer period of time than 1 month. Most importantly, this reagent could be employed for subsequent carbon–carbon bond forming reactions (vide infra).

A wide variety of borinic esters were synthesized using the palladium/XANTPhos system followed by migrative oxidation with trimethylamine-*N*-oxide (Scheme 3). Aryl

halides having either an electron-donating or an electron-withdrawing substituent gave the corresponding borinic esters in good yields (**5a** and **5b**). Phthalimide (**5c**), chloro (**5f**, **5j**, and **5l**), and ester (**5i**) groups remained intact under the reaction conditions. A sterically demanding aryl iodide was also reactive (**5d**). In addition to the substituted phenyl groups, 2- and 3-bromothiophene afforded the desired product in good yield (**5e** and **5h**). Primary alkyl (**5a** to **5g**, **5l**, and **5m**), secondary alkyl (**5h** to **5k**), and aryl (**5n**) groups can be used as the substituent of the alkynyl moiety. The scope of the aryl group on boron was also broad; electron-rich (**5g** and **5n**) and -deficient (**5f**) phenyl and thienyl (**5l**) groups successfully participated in the migration reaction.

Table 2. Synthesis of Borinic Esters

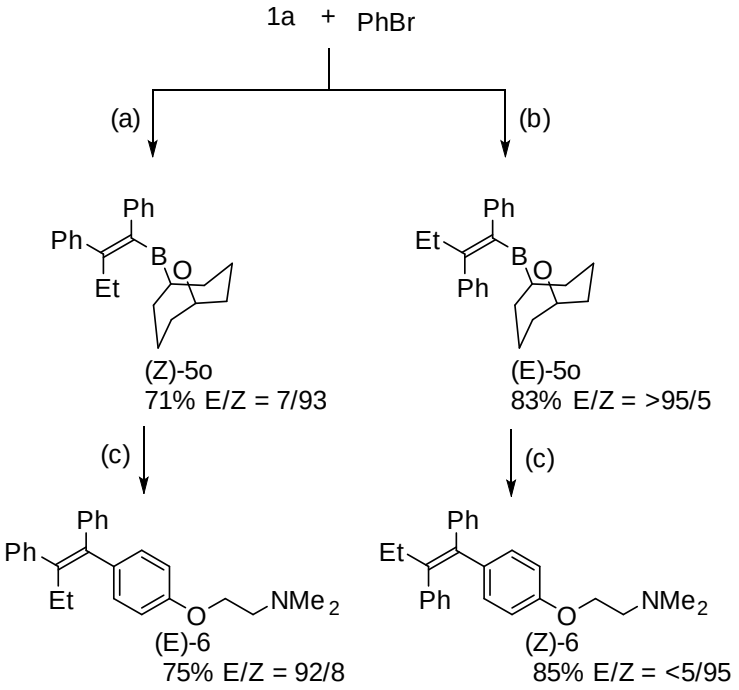


[a] Reaction conditions: 1.0 equiv of alkynylborate **1**, 1.05 equiv of aryl halide **2**, 1 mol % of (xantphos)PdCl(π-allyl), toluene, 70 °C, 30 min; then 1.5 equiv of Me_3NO, DCM, rt, 2 h. Isolated yields were shown. The major isomers shown in the table were observed >95/5 ratio by NMR analysis. [b] Aryl iodide was used

Finally, we applied this reaction to the synthesis of both isomers of Tamoxifen (Scheme 5), which has been in clinical use for cancer treatment.[14,15] The reaction of **1a** with bromobenzene with the palladium/tri(*o*-tolyl)phospine catalyst followed by oxidation with trimethylamine-*N*-oxide gave borinic ester (*Z*)-**5o** (71% yield, *E*/*Z* = 7/93). On the other hand, the corresponding (*E*)-isomer was stereoselectively obtained in 83% yield (*E*/*Z* = >95/5) when the reaction of **1a** with bromobenzene was carried out with the palladium/XANTPhos calatyst, the loading of which could be decreased even

to 0.1 mol%. The Suzuki-Miyaura coupling reaction of each stereoisomer of **5o** with 1-bromo-4-[2-(*N*,*N*-dimethylamino)ethoxy]benzene (**2b)** afforded Tamoxifen (**6**) with retention of the each stereochemistry. Thus, the present study made it possible to synthesize either stereoisomer of tetrasubstituted olefins[16] starting from the same substances by choice of the appropriate ligand.

Scheme 3. Synthesis of Tamoxifens[a]



[a] Reagents and conditions: (a) 1 mol % of (*o*-tol)$_3$PPdCl(π-allyl), toluene, 70 °C, 30 min; then 1.5 equiv of Me_3NO, DCM, rt, 2 h. (b) 0.1 mol % of (xantphos)PdCl(π-allyl), toluene, 70 °C, 30 min; then 1.5 equiv of Me_3NO, DCM, rt, 2 h. (c) 1.05 equiv of 4-$BrC_6H_4[O(CH_2)_2NMe_2]$ (**2b**), 2.5 mol % of $Pd(OAc)_2$, 5 mol % of SPhos, K_3PO_4, THF, 60 °C, 12 h for (*E*)-**5o**, 24 h for (*Z*)-**5o**

Conclusions

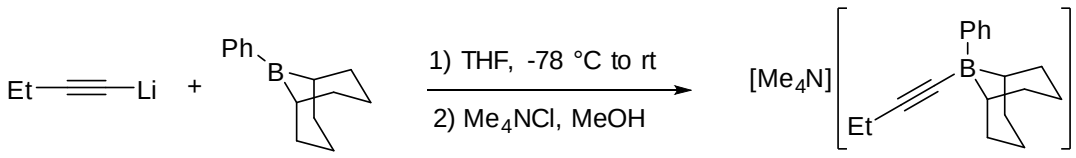
In summary, we have developed a new catalyst system for the palladium-catalyzed reaction of alkynylborates with aryl halides, which produces (*E*)-(trisubstituted alkenyl)boranes stereoselectively. With both stereoisomers being available, the reinforced palladium-catalyzed reaction of alkynylborates serves as an authentic method for the synthesis of (trisubstituted alkenyl)boron compounds.

Experimental Section

General. NMR spectra were recorded on a Varian Gemini 2000 (^{1}H at 300 MHz and ^{13}C at 75 MHz) or Varian Mercury-400 (^{1}H at 400 MHz and ^{11}B at 128 MHz) spectrometers. Unless otherwise noted, $CDCl_3$ was used as a solvent. Chemical Shifts are recorded in δ ppm referenced to a residual $CDCl_3$ (δ = 7.26 for ^{1}H, δ 77.0 for ^{13}C), CD_3CN (δ = 1.94 for ^{1}H, δ =1.32 for ^{13}C), and $BF_3 \cdot OEt_2$ (δ = 0.00 for ^{11}B). High-resolution mass spectra were recorded on JEOL JMS-SX102A spectrometer. Infrared spectra were recorded on SHIMADZU FT-IR 8100. Column chromatography was performed with silica gel 60 N (Kanto). Preparative thin-layer chromatography was performed with Silica gel 60 PF_{254} (Merck).

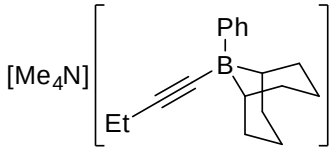
Materials. Unless otherwise noted, all chemicals and anhydrous solvents were obtained from commercial suppliers and used as received. Toluene was dried over Na-benzophenone ketyl. AcOH was degassed by N_2 bubbling. (XANTPhos)Pd(π-allyl)Cl[17] and Ph-9-BBN[18] were prepared according to the reported procedures.

Preparation of alkynylborates 1a.



1a

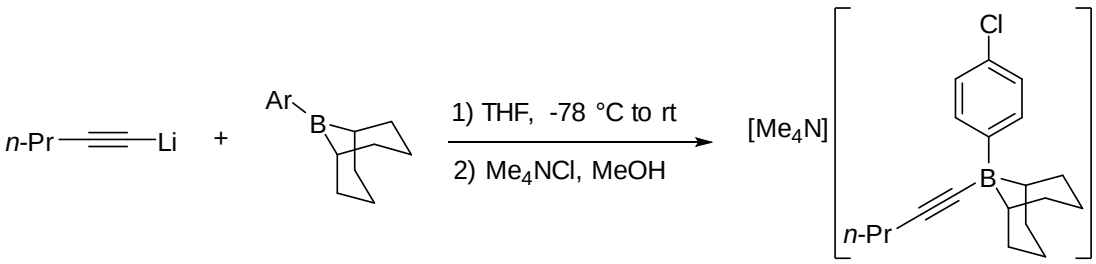
To a stirred solution of 1-butyne (1 ml) in THF (8.0 ml) at -78 ˚C was added *n*-BuLi (1.6 M in hexane, 3.4 ml, 5.5 mmol). After 30 minutes at this temperature, Ph-9-BBN (990 mg, 5.0 mmol) was added and the cooling bath was then removed. After being stirred for 1 h at room temperature, the reaction was quenched by adding a small amount of methanol. Then, volatile materials were removed under reduced pressure. The residue was dissolved in methanol and tetramethylammonium chloride (600 mg, 5.5 mmol) was added with stirring at -78 ˚C, resulting in white solid. It was collected by filtration and washed with cold methanol to give alkynylborate **1a** (1.2 g, 3.7 mmol, 74% yield).



1a

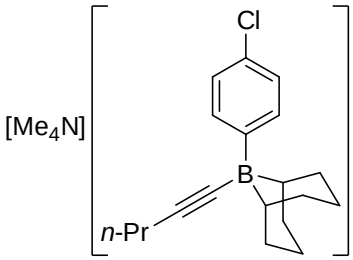
^{1}H NMR (CD_3CN): δ = 0.92 (bs, 2H), 0.97 (t, *J* = 7.8 Hz, 3H), 1.11-1.20 (m, 1H), 1.36-2.07 (m, 11H), 2.36-2.50 (m, 2H), 3.03 (s, 12 H), 6.79-6.86 (m, 1H), 7.00-7.07 (m, 2H), 7.35 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (CD_3CN): δ = 14.9, 16.6, 26.6 (q, $J_{C\text{-}B}$ = 37.9 Hz), 27.1, 27.5, 32.4, 34.9, 56.1, 94.8, 122.1, 126.9, 133.9; ^{11}B NMR: δ = -13.3; HRMS (FAB) Calcd for $C_{18}H_{24}B$ [M-(NMe_4)] 251.1971. Found 251.1975.

Preparation of alkynylborates 1b: A typical procedure for the preparation of alkynylborates 1b-1h.



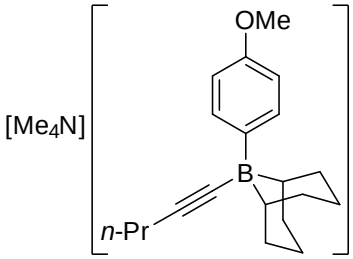
1b

To a stirred solution of 1-pentyne (375 mg, 5.5 mmol) in THF (8.0 ml) at -78 ˚C was added *n*-BuLi (1.6 M in hexane, 3.4 ml, 5.5 mmol). After 30 minutes at this temperature, 4-ClC_6H_4-9-BBN (1.16 g, 5.0 mmol) was added and the cooling bath was removed. After being stirred for 1 h at room temperature, the reaction was quenched by adding a small amount of methanol. Then, volatile materials were removed under reduced pressure. The residue was dissolved in methanol and tetramethylammonium chloride (600 mg, 5.5 mmol) was added with stirring at -78 ˚C, resulting in white solid. It was collected by filtration and was washed with cold methanol to give alkynylborate **1b** (1.05g, 2.8 mmol, 56% yield).



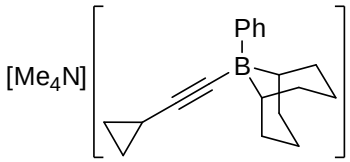
1b

^{1}H NMR (CD_3CN): δ = 0.84-0.96 (m, 5H), 1.11-1.21 (m, 1H), 1.26-2.00 (m, 13H), 2.35-2.50 (m, 2H), 3.04 (s, 12H), 7.00-7.05 (m, 2H), 7.33 (d, J = 8.4 Hz, 2H); ^{13}C NMR (CD_3CN): δ = 13.9, 23.4, 24.9, 26.6 (q, $J_{C\text{-}B}$ = 39.3 Hz), 27.0, 27.3, 32.3, 34.8, 56.1, 93.3, 126.5, 127.2, 135.5; ^{11}B NMR: δ = -13.3; HRMS (FAB) Calcd for $C_{19}H_{25}BCl$ [M-(NMe_4)] 299.1738. Found 299.1730.



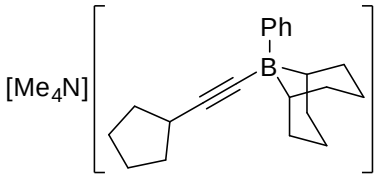
1c

^{1}H NMR (CD_3CN): δ = 0.87 (bs, 2H), 0.93 (t, J = 7.2 Hz, 3H), 1.10-1.20 (m, 1H), 1.28-2.01 (m, 13H), 2.37-2.52 (m, 2H), 3.03 (s, 12H), 3.71 (s, 3H), 6.63-6.68 (m, 2H), 7.23 (d, J = 8.1 Hz, 2H); ^{13}C NMR (CD_3CN): δ = 14.0, 23.5, 25.0, 26.8 (q, $J_{C\text{-}B}$ = 39.3 Hz), 27.2, 27.5, 32.4, 34.9, 55.4, 56.1, 92.9, 112.8, 134.4, 156.1; ^{11}B NMR: δ = -13.5; HRMS (FAB) Calcd for $C_{20}H_{28}BO$ [M-(NMe_4)] 295.2233. Found 295.2231.



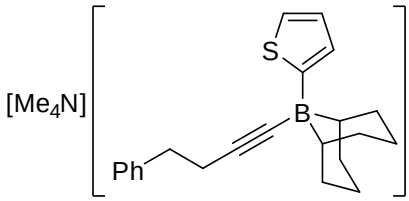
1d

^{1}H NMR (CD_3CN): δ = 0.20-0.28 (m, 2H), 0.45-0.53 (m, 2H), 0.89 (bs, 2H), 0.98-1.19 (m, 2H), 1.34-1.96 (m, 9H), 2.30-2.44 (m, 2H), 3.04 (s, 12H), 6.79-6.86 (m, 1H), 6.99-7.06 (m, 2H), 7.33 (d, J = 7.2 Hz, 2H); ^{13}C NMR (CD_3CN): δ =2.3, 8.7, 26.6 (q, $J_{C\text{-}B}$ = 39.3 Hz), 27.1, 27.4, 32.3, 34.9, 56.2, 122.2, 126.9, 133.8; ^{11}B NMR: δ = -13.4; HRMS (FAB) Calcd for $C_{19}H_{24}B$ [M-(NMe_4)] 263.1971. Found 263.1976.



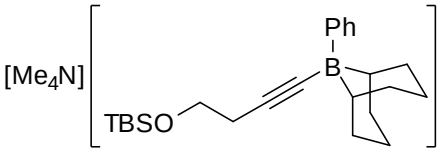
1e

^{1}H NMR (CD_3CN): δ = 0.90 (bs, 2H), 1.10-1.20 (m, 1H), 1.30-1.96 (m, 17H), 2.36-2.54 (m, 3H), 3.02 (s, 12H), 6.79-6.86 (m, 1H), 6.99-7.06 (m, 2H), 7.34 (d, J = 6.6 Hz, 2H) ; ^{13}C NMR (CD_3CN): δ = 25.3, 26.8 (q, $J_{C\text{-}B}$ = 37.9 Hz), 27.1, 27.5, 32.4, 33.3, 34.9, 36.1, 56.1, 98.0, 122.1, 126.9, 133.9; ^{11}B NMR: δ = -13.3; HRMS (FAB) Calcd for $C_{21}H_{28}B$ [M-(NMe_4)] 291.2284. Found 291.2278.



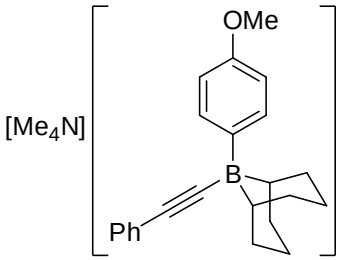
1f

^{1}H NMR (CD_3CN): δ = 0.77 (bs, 2H), 1.17-1.28 (m, 1H), 1.38-1.60 (m, 5H), 1.68- 1.97 (m, 4H), 2.31 (t, J = 7.5 Hz, 2H), 2.34-2.37 (m, 2H), 2.68 (t, J = 7.5 Hz, 2H), 3.01 (s, 12H), 6.73 (dd, J = 3.0, 0.6 Hz, 1H), 6.89 (dd, J = 4.8, 3.0 Hz, 1H), 7.07 (dd, J = 4.5, 0.9 Hz, 1H), 7.12-7.30 (m, 5H); ^{13}C NMR (CD_3CN): δ = 24.0, 26.8-29.0 (m), 32.5, 34.7, 38.0, 56.2, 92.8, 122.5, 126.1, 126.5, 127.1, 128.9, 129.7, 143.4; ^{11}B NMR: δ = -13.5; HRMS (FAB) Calcd for $C_{22}H_{26}BS$ [M-(NMe_4)] 333.1848. Found 333.1852.



1g

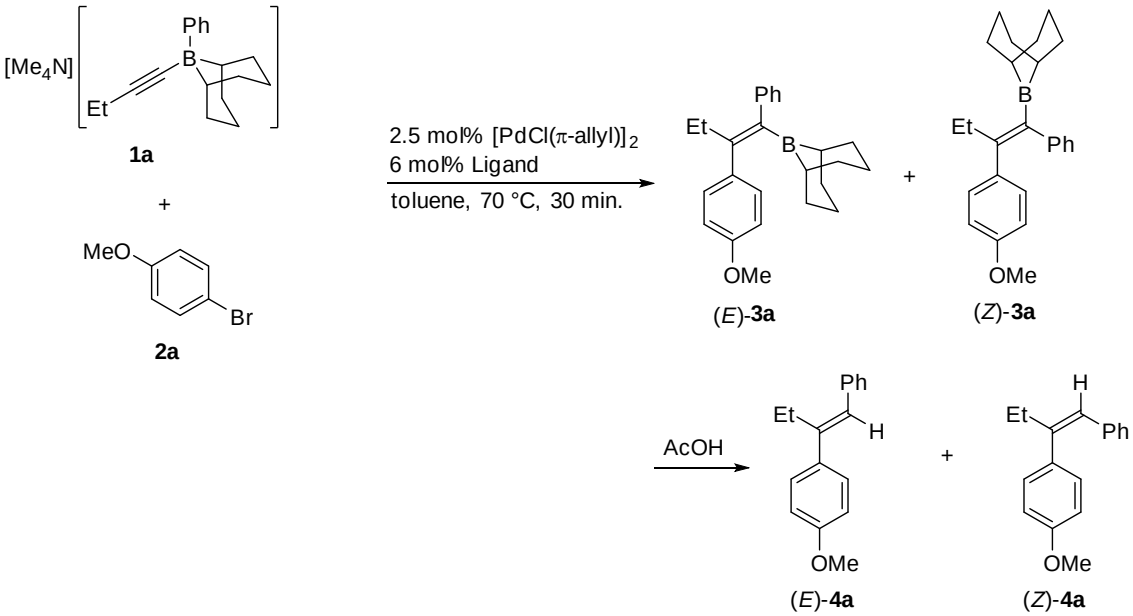
^{1}H NMR (CD_3CN): δ = 0.05 (s, 6H), 0.84-0.96 (m, 11H), 1.10-1.20 (m, 1H), 1.34-1.97 (m, 9H), 2.16-2.33 (t, J = 7.2 Hz, 2H), 2.35-2.50 (m, 2H), 3.01 (s, 12H), 3.56 (t, J = 7.8 Hz, 2H), 6.80-6.87 (m, 1H), 7.00-7.08 (m, 2H), 7.35 (d, J = 6.6 Hz, 2H); ^{13}C NMR (CD_3CN): δ = -5.0, 18.9, 25.4-27.7 (m), 32.3, 34.8, 56.1, 64.9, 88.9, 122.2, 126.9, 133.9; ^{11}B NMR: δ = -13.3; HRMS (FAB) Calcd for $C_{24}H_{38}BOSi$ [M-(NMe_4)] 381.2785. Found 381.2789.



1h

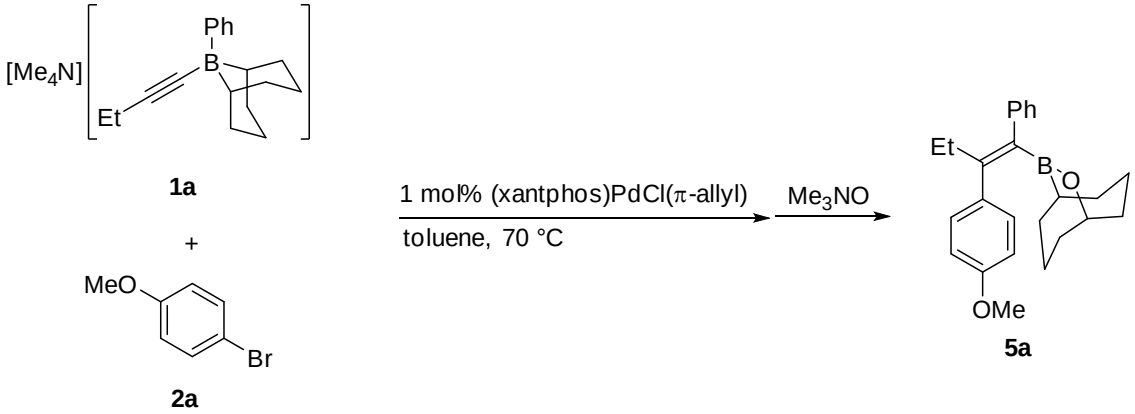
^{1}H NMR (CD_3CN): δ = 1.04 (bs, 2H), 1.16-1.26 (m, 1H), 1.40-2.03 (m, 9H), 2.40-2.54 (m, 2H), 2.98 (s, 12H), 3.73 (s, 3H), 6.68-6.74 (m, 2H), 7.01-7.18 (m, 5H), 7.32 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (CD_3CN): δ = 25.5-27.7 (m) 32.2, 35.0, 55.4, 56.1, 96.1, 112.9, 125.1, 128.7, 130.2, 131.2, 134.5, 156.4; ^{11}B NMR: δ = -13.1; HRMS (FAB) Calcd for $C_{23}H_{26}BO$ [M-(NMe_4)] 329.2077. Found 329.2081.

Palladium-Catalyzed Reaction of Alkynylborate 1a with 4-Bromoanisole. Typical Procedure for the Ligand Screening.

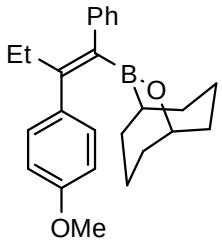


Under an argon atmosphere, a toluene solution (1.0 ml) of alkynylborate **1a** (65.1 mg, 0.20 mmol), [Pd(π-allyl)Cl]$_2$ (1.8 mg, 5 μmol), P(*o*-tol)$_3$ (3.7 mg, 12 μmol) and 4-bromoanisole **2a** (39.3 mg, 0.21 mmol) was stirred for 30 minutes at 70 ˚C. To the reaction mixture was added AcOH at room temperature. After being stirred for 3 h, the resulting mixture was neutralized with saturated Na_2CO_3 solution. The aqueous layer was extracted with AcOEt (3 times), washed with water (once), brine (once), dried over $MgSO_4$ and concentrated. A portion of the sample was taken in a GC tube and diluted with Et_2O to determine the GC yields.

Palladium/XANTPhos-Catalyzed Reaction of Alkynylborate 1a with 4-Bromoanisole. A Typical Procedure for the Palladium/XANTPhos-Catalyzed Reaction of Alkynylborates with Arylhalides.

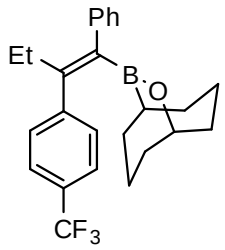


Under an argon atmosphere, a toluene solution (1.0 ml) of alkynylborate **1a** (65.1 mg, 0.20 mmol), (XANTPhos)Pd(π-allyl)Cl (1.5 mg, 2.0 μmol), and 4-bromoanisole **2a** (39.3 mg, 0.21 mmol) was stirred for 30 minutes at 70 ˚C. To the reaction mixture were added Me_3NO (22.5 mg, 0.30 mmol) and CH_2Cl_2 (1.0 ml) at room temperature. After being stirred for 2 h, the resulting mixture was passed through a pad of Florisil and eluted with ethyl acetate. The residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 50/1) to afford the (trisubstituted alkenyl)borinic ester **5a** (61.9 mg, 0.17 mmol, 83% yield, *E/Z* = >95/5).



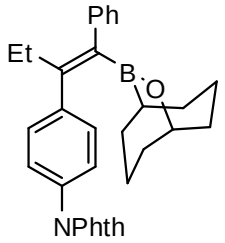
5a

^{1}H NMR: δ = 0.80 (t, *J* = 7.8 Hz, 3H), 1.02-1.71 (m, 13H), 2.27 (q, *J* = 7.8 Hz, 2H), 3.83 (s, 3H), 4.38-4.44 (m, 1H), 6.85-6.91 (m, 2H), 7.14-7.36 (m, 7H); ^{13}C NMR: δ = 13.8, 22.1, 26.7, 27.3 (br), 27.7, 31.2, 55.3, 73.6, 113.2, 125.1, 127.8, 128.3, 129.8, 136.6, 143.6, 149.4, 158.6; ^{11}B NMR: δ = 50.0; HRMS (EI) Calcd for $C_{25}H_{31}BO_2$ (M^+) 374.2417 Found 374.2410.



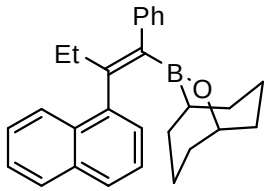
5b

^{1}H NMR: δ = 0.81 (t, *J* = 7.5 Hz, 3H), 0.97-1.70 (m, 13H), 2.31 (q, *J* = 7.5 Hz, 2H), 4.37-4.43 (m, 1H), 7.18-7.26 (m, 3H), 7.34-7.39 (m, 2H), 7.45-7.48 (m, 2H), 7.60-7.63 (m, 2H); ^{13}C NMR: δ = 13.5, 22.0, 26.6, 27.1 (br), 27.6, 31.2, 73.8, 124.29 (q, $J_{C\text{-}F}$ = 270.1 Hz), 124.7 (q, $J_{C\text{-}F}$ = 3.6 Hz), 128.0, 128.1, 128.9 (q, $J_{C\text{-}F}$ = 32.0 Hz), 129.1, 142.5, 147.6, 148.0; ^{11}B NMR: δ = 50.5; HRMS (EI) Calcd for $C_{25}H_{28}BF_3O$ (M^+) 412.2185. Found 412.2186.



5c

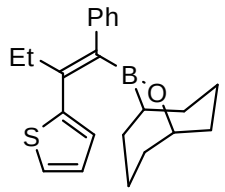
^{1}H NMR: δ = 0.88 (t, *J* = 7.8 Hz, 3H), 1.05-1.76 (m, 13H), 2.34 (q, *J* = 7.5 Hz, 2H), 4.40-4.50 (m, 1H), 7.20-7.27 (m, 3H), 7.34-7.39 (m, 2H), 7.43-7.51 (m, 4H), 7.77-7.83 (m, 2H), 7.94-8.00 (m, 2H); ^{13}C NMR: δ = 13.7, 22.1, 26.6, 27.4 (br), 27.5, 31.2, 73.8, 123.5, 125.4, 125.8, 127.9, 128.2, 129.4, 130.4, 131.7, 134.2, 142.9, 144.0, 148.2, 167.1; ^{11}B NMR: δ = 50.2; IR (KBr) = 2928, 1742, 1509, 1381, 714 cm^{-1}; HRMS (EI) Calcd for $C_{32}H_{32}BNO_3$ (M^+) 489.2475. Found 489.2473.



5d

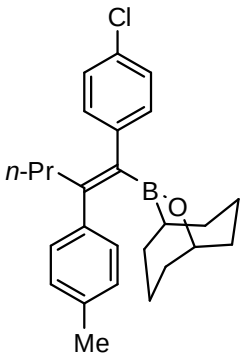
^{1}H NMR: δ = 0.21-0.34 (m, 1H), 0.68-1.00 (m, 8H), 1.20-1.50 (m, 7H), 2.24-2.38 (m, 1H), 2.44-2.58 (m, 1H), 4.24-4.31 (m, 1H), 7.22-7.54 (m, 9H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.83-7.88 (m, 1H), 8.09-8.16 (m, 1H); ^{13}C NMR: δ = 13.7, 21.6, 21.9, 25.9, 26.2, 26.4 (br), 28.2, 30.9, 31.4, 73.4, 124.9, 125.37, 125.39, 125.5, 126.4, 127.0, 127.3, 127.95,

127.99, 128.3, 132.1, 133.5, 141.3, 142.7, 146.7; ^{11}B NMR: δ = 49.7; HRMS (EI) Calcd for $C_{28}H_{31}BO$ (M^+) 394.2468. Found 394.2476.



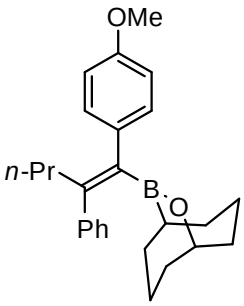
5e

^{1}H NMR: δ = 0.92 (t, *J* = 7.8 Hz, 3H), 1.18-1.82 (m, 13H), 2.28 (q, *J* = 7.8 Hz, 2H), 4.48-4.56 (m, 1H), 7.02 (dd, *J* = 5.1, 3.6 Hz, 1H), 7.08 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.15-7.30 (m, 4H), 7.32-7.38 (m, 2H); ^{13}C NMR: δ =14.1, 22.1, 27.1, 28.9, 31.2, 73.9, 125.0, 125.5, 126.6, 126.9, 127.9, 128.1, 141.6, 142.7, 146.8; ^{11}B NMR: δ = 49.6; HRMS (EI) Calcd for $C_{22}H_{27}BOS$ (M^+) 350.1876. Found 350.1880.



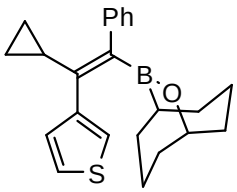
5f

^{1}H NMR: δ = 0.70 (t, *J* = 7.5 Hz, 3H), 0.96-1.33 (m, 9H), 1.42-1.72 (m, 6H), 2.20-2.28 (m, 2H), 2.37 (s, 3H), 4.39-4.46 (m, 1H), 7.08-7.35 (m, 8H); ^{13}C NMR: δ = 14.0, 21.2, 21.9, 22.1, 26.7, 27.4 (br), 31.3, 36.3, 73.7, 127.9, 128.46, 128.55, 129.8, 130.9, 136.5, 141.1, 142.0, 148.8; ^{11}B NMR: δ = 50.6; HRMS (EI) Calcd for $C_{26}H_{32}BClO$ (M^+) 406.2235. Found 406.2237.



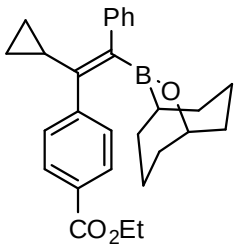
5g

^{1}H NMR: δ = 0.73 (t, *J* = 7.2 Hz, 3H), 0.95-1.70 (m, 15H), 2.29 (t, *J* = 7.8 Hz, 2H), 3.84 (s, 3H), 4.35-4.50 (m, 1H), 6.90 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 7.20-7.40 (m, 5H); ^{13}C NMR: δ = 14.0, 21.9, 22.1, 26.7, 27.4 (br), 31.2, 36.2, 55.1, 73.6, 113.3, 126.7, 127.8, 128.7, 129.4, 135.4, 144.6, 147.5, 157.3; ^{11}B NMR: δ = 50.7; HRMS (EI) Calcd for $C_{26}H_{33}BO_2$ (M^+) 388.2754. Found 388.2572. The stereochemistry was assigned by NOE analysis.



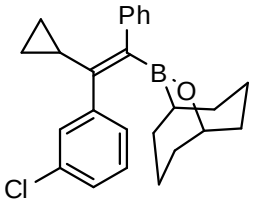
5h

^{1}H NMR: δ = 0.27-0.32 (m, 2H), 0.46-0.52 (m, 2H), 0.98-1.30 (m, 6H), 1.40-1.70 (m, 8H), 4.30-4.45 (m, 1H), 6.96-7.00 (m, 1H), 7.04-7.07 (m, 1H), 7.15-7.26 (m, 2H), 7.29-7.38 (m, 4H); ^{13}C NMR: δ = 6.0, 15.0, 22.2, 26.3, 27.2 (br), 31.3, 73.6, 124.1, 124.3, 125.3, 127.8, 129.0, 129.5, 141.0, 142.5, 143.1; ^{11}B NMR: δ = 49.8; HRMS (EI) Calcd for $C_{23}H_{27}BOS$ (M^+) 362.1876. Found 362.1881.



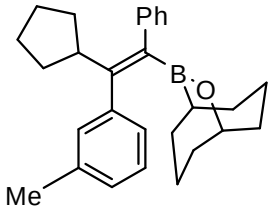
5i

^{1}H NMR: δ = 0.17-0.23 (m, 2H), 0.45-0.53 (m, 2H), 0.90-1.19 (m, 6H), 1.32-1.73 (m, 11H), 4.27-4.33 (m, 1H), 4.38 (q, *J* = 7.5 Hz, 2H), 7.18-7.38, (m, 7H), 7.98 (dt, *J* = 7.8, 1.5 Hz, 2H); ^{13}C NMR: δ = 5.6, 14.4, 15.1, 22.0, 26.3, 26.9 (br), 31.2, 60.9, 73.5, 125.5, 127.9, 128.4, 128.7, 128.9, 130.3, 142.3, 145.3, 146.9, 166.5; ^{11}B NMR: δ = 49.6; IR (KBr) = 2928, 1717, 1287, 1100 cm^{-1}; HRMS (EI) Calcd for $C_{28}H_{33}BO_3$ (M^+) 428.2523. Found 428.2526.



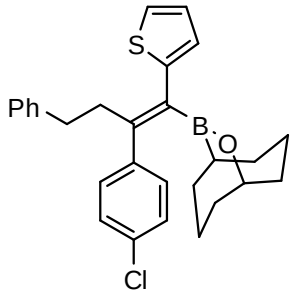
5j

^{1}H NMR: δ = 0.23-0.29 (m, 2H), 0.48-0.55 (m, 2H), 0.94-1.23 (m, 6H), 1.34-1.71 (m, 8H), 4.32-4.39 (m, 1H), 7.06-7.14 (m, 1H), 7.18-7.26 (m, 4H), 7.28-7.38 (m, 4H); ^{13}C NMR: δ = 5.7, 15.0, 22.0, 26.3, 27.1 (br), 31.2, 73.6, 125.5, 126.7, 127.9, 128.3, 128.4, 128.9, 130.4, 133.2, 142.3, 142.4, 146.1; ^{11}B NMR: δ = 49.6; HRMS (EI) Calcd for $C_{25}H_{28}BClO$ (M^+) 390.1922. Found 390.1923.



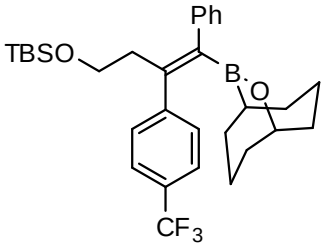
5k

^{1}H NMR: δ = 0.82-1.13 (m, 6H), 1.26-1.64 (m, 15H), 2.37 (s, 3H), 2.68-2.80 (m, 1H), 4.34-4.41 (m, 1H), 7.04-7.09 (m, 3H), 7.17-7.25 (m, 4H), 7.30-7.37 (m, 2H); ^{13}C NMR: δ = 21.5, 21.9, 24.8, 26.3, 27.3 (br), 31.2, 31.5, 43.3, 73.5, 125.2, 126.89, 126.93, 127.5, 127.8, 128.3, 131.6, 136.5, 141.8, 142.4, 148.1; ^{11}B NMR: δ = 49.8; HRMS (EI) Calcd for $C_{28}H_{35}BO$ (M^+) 398.2781. Found 398.2780.



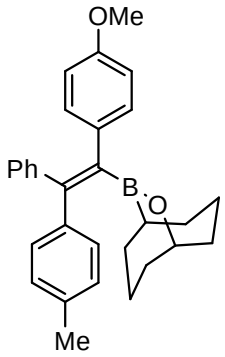
5l

^{1}H NMR: δ = 1.06-1.76 (m, 13H), 2.50-2.60 (m, 2H), 2.72-2.80 (m, 2H), 4.41-4.49 (m, 1H), 6.74 (dd, *J* = 3.3, 1.2 Hz, 1H), 6.97-7.03 (m, 3H), 7.09-7.38 (m, 8H); ^{13}C NMR(C_6D_6): δ =22.5, 27.2, 27.7 (br), 31.5, 35.8, 37.5, 73.9, 124.7, 125.3, 126.1, 127.2, 128.5, 128.56, 128.61, 130.6, 133.5, 141.9, 142.7, 143.7, 149.1; ^{11}B NMR: δ = 49.5; HRMS (EI) Calcd for $C_{28}H_{30}BClOS$ (M^+) 460.1799. Found 460.1797.



5m

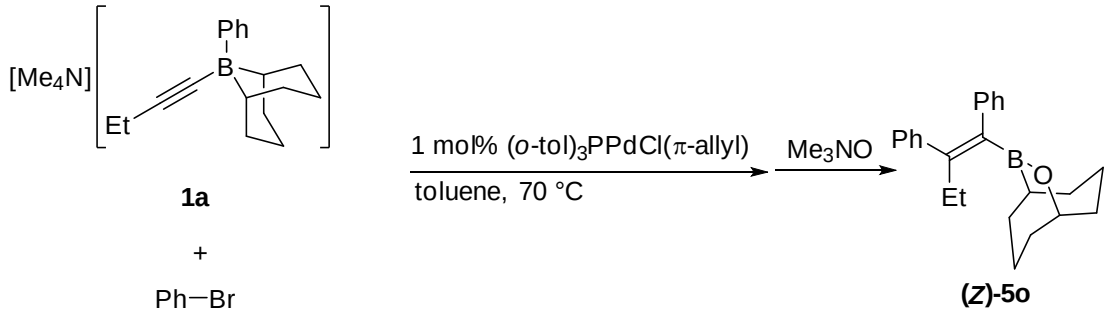
^{1}H NMR: δ = -0.14 (s, 6H), 0.79 (s, 9H), 0.95-1.36 (m, 6H), 1.42-1.68 (m, 7H), 2.55 (t, *J* = 7.2 Hz, 2H), 3.43 (t, *J* = 7.2 Hz, 2H), 4.35-4.42 (m, 1H), 7.18-7.26 (m, 3H), 7.31-7.37 (m, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.59 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR: δ = -5.4, 18.3, 22.0, 25.9, 26.6, 27.1 (br), 31.1, 37.7, 61.6, 73.9, 124.2 (q, $J_{C\text{-}F}$ = 269.4 Hz), 124.7 (q, $J_{C\text{-}F}$ = 3.6 Hz), 125.8, 128.0, 128.2, 129.0 (q, $J_{C\text{-}F}$ = 32.0 Hz), 129.1, 142.1, 142.2, 148.0; ^{11}B NMR: δ = 50.5; HRMS (FAB) Calcd for $C_{31}H_{42}BF_3O_2Si$ (M^+) 542.2999. Found 542.2992. The stereochemistry was assigned by NOE analysis.



5n

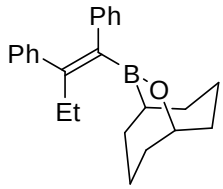
^{1}H NMR: δ = 1.22-1.30 (m, 4H), 1.38-1.62 (m, 5H), 1.68-1.86 (m, 4H), 2.37 (s, 3H), 3.75 (s, 3H), 4.43-4.50 (m, 1H), 6.70 (dt, *J* = 9.0, 2.1 Hz, 2H), 6.90-6.97 (m, 4H), 7.02-7.08 (m, 3H), 7.10-7.20 (m, 4H); ^{13}C NMR: δ = 21.3, 22.2, 26.9, 31.2, 55.0, 73.8, 113.2, 126.0, 127.2, 128.5, 130.1, 130.7, 131.0, 136.2, 136.9, 142.3, 142.9, 148.3, 157.1; ^{11}B NMR: δ = 51.0; HRMS (EI) Calcd for $C_{30}H_{33}BO_2$ (M^+) 436.2574. Found 436.2561.

Palladium/Tri(*o*-tolyl)phosphine-Catalyzed Reaction of Alkynylborate 1a with 4-Bromobenzene.



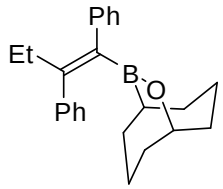
Under an argon atmosphere, a toluene solution (2.0 ml) of alkynylborate **1a** (195.2 mg, 0.60 mmol), (*o*-tol)$_3$PPd(π-allyl)Cl (3.0 mg, 6.0 μmol), and 4-bromobenzene (98.9 mg, 0.63 mmol) was stirred for 30 minutes at 70 ˚C. To the reaction mixture were added

Me_3NO (67.8 mg, 0.90 mmol) and CH_2Cl_2 (2.0 ml) at room temperature. After being stirred for 2 h, the resulting mixture was passed through a pad of Florisil and eluted with ethyl acetate. The residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 50/1) to afford the (trisubstituted alkenyl)borinic ester (*Z*)-**5b** (146.9 mg, 0.43 mmol, 71% yield, *E*/*Z* = 7/93).



(*Z*)-5o

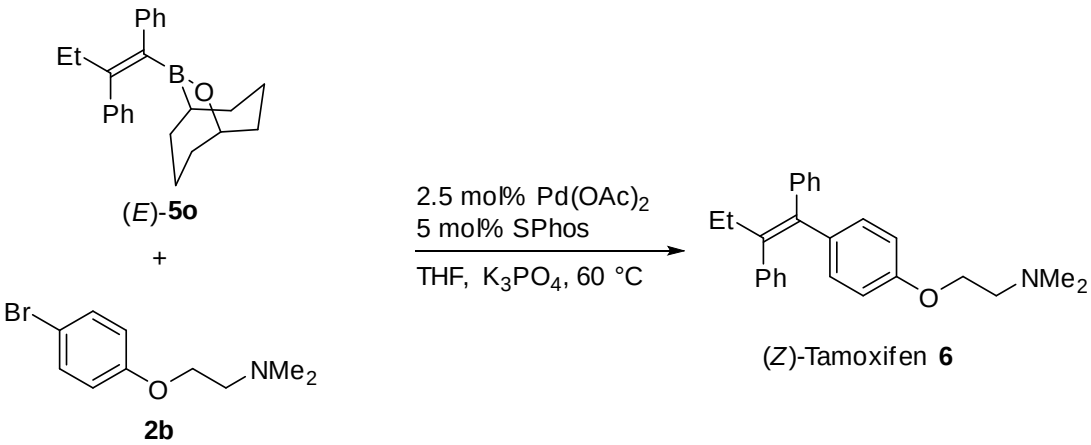
^{1}H NMR: δ = 1.01 (t, *J* = 7.2 H, 3H), 1.39-2.00 (m, 13H), 2.67 (q, *J* = 7.2 Hz, 2H), 4.70-4.75 (m, 1H), 6.85-7.10 (m, 10H); ^{13}C NMR: δ = 13.9, 22.4, 26.7, 31.3, 31.7, 74.0, 124.8, 125.7, 127.2, 127.4,129.38, 129.41, 142.1, 142.5, 127.5; ^{11}B NMR: δ = 51.2; HRMS (EI) Calcd for $C_{24}H_{29}BO$ (M^+) 344.2311. Found 344. 2310.



(*E*)-5o

^{1}H NMR: δ = 0.81 (t, *J* = 7.2 Hz, 3H), 1.00-1.69 (m, 13H), 2.30 (q, *J* = 7.2 Hz, 2H), 4.38-4.43 (m, 1H), 7.18-7.37 (m, 10H); ^{13}C NMR: δ = 13.7, 22.1, 26.6, 27.4 (br), 27.7, 31.2, 73.7, 125.3, 126.8, 127.8, 127.9, 128.3, 128.8, 143.3, 144.2, 149.4; ^{11}B NMR: δ = 50.4; HRMS (EI) Calcd for $C_{24}H_{29}BO$ (M^+) 344.2311. Found 344.2313.

Typical Procedure for Palladium-Catalyzed Reaction of Borinic Ester 5o with Aryl Bromide 2b.



Under an argon atmosphere, borinic ester (*E*)-**5o** (68.9 mg, 0.20 mmol), $Pd(OAc)_2$ (1.1 mg, 5.0 μmol), SPhos (4.1 mg, 1.0 μmol), and **2b** (51.2 mg, 0.21 mmol) in THF (1.0 ml) was stirred for 12 h at 60 ˚C. After cooling the reaction mixture to room temperature, water was added. The organic layer was separated and extracted with CH_2Cl_2 (3 times), and washed with water (once), brine (once), dried over Na_2SO_4 and concentrated. The residue was purified by preparative thin-layer chromatography on silica gel ($CHCl_3$/ EtOH/NEt_3 = 100/5/1) to afford the (*Z*)-Tamoxifen **6** (63.3 mg, 0.17 mmol, 85 %, *E*/*Z* = >5/95). The spectral data was identical to that reported.[19]

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Chapter 4

Iterative Approach to Oligo(arylenevinylene)s Containing Tetrasubstituted Vinylene Units

Abstract

Monodispersed oligo(arylenevinylene)s containing tetrasubstituted vinylene units were stereoselectively synthesized in an efficient manner by iteration of two different kinds of palladium-catalyzed reactions.

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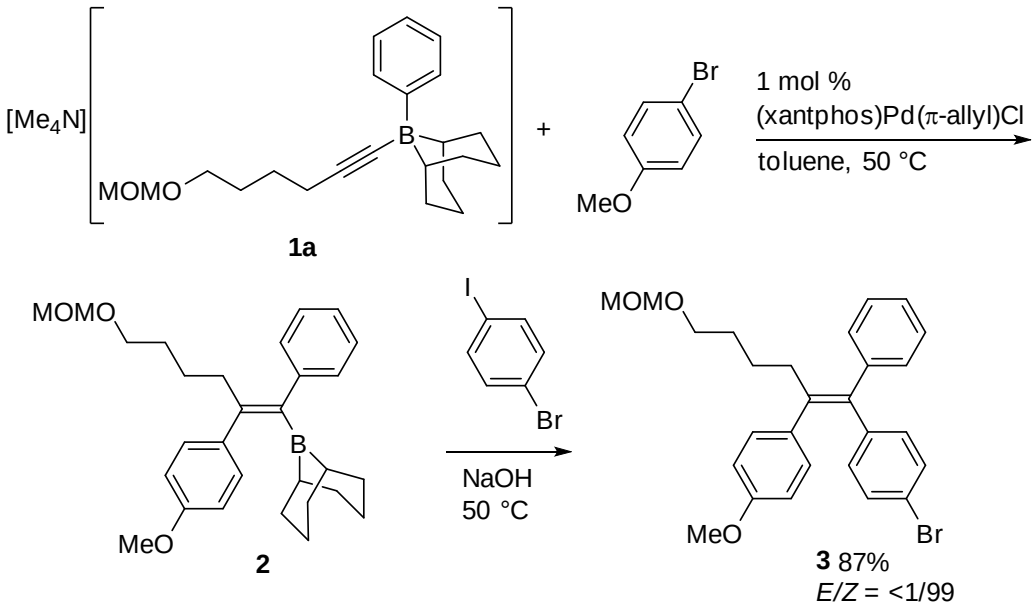
Introduction

It is one of current topics in organic synthesis to prepare structurally well-defined oligomeric compounds of higher molecular weight. Among various oligomers, oligo(phenylenevinylene)s (OPVs) are of significant interest and have been extensively studied in the field of organic electronics.[1] A wide variety of substituted OPVs have been synthesized and applied to optoelectronic devices such as organic light-emitting diodes[2] and organic solar cells.[3] However, it is still a formidable task to synthesize oligo(arylenevinylene)s containing tetrasubstituted vinylene units due to the difficulty of constructing sterically congested vinylene units in a stereoselective manner.[4] In this paper, we report an efficient and high yielding method to synthesize such oligo(arylenevinylene)s of single molecular weight.

Results and Discussion

Initially, 4-bromoanisole was treated with 1.0 equiv of alkynylborate **1a** in the presence of (xantphos)Pd(π-allyl)Cl (1 mol %), and (trisubstituted alkenyl)-9-BBN **2** was formed in a stereoselective manner, as we previously reported (Scheme 1).[5] Although the product **2** contained an alkenylborane moiety, it did not couple with 4-bromoanisole in the absence of a base. After completion of the initial reaction with alkynylborate **1a**, 1.0 equiv of 4-bromoiodobenzene and 3 equiv of NaOH were directly added to the reaction mixture. The Suzuki-Miyaura coupling reaction took place chemoselectively at the iodo site to give tetrasubstituted olefin **3** in 87% yield with excellent stereoselectivity (*E*/*Z* = <1/99). The bromoaryl moiety was retained in the coupling product **3** due to the reactivity difference between the iodo and bromo groups.[6] Thus, the Pd/XANTPHOS catalyst was proved to be active enough to promote the two different kinds of carbon–carbon bond forming reactions in one-pot without the need for any additional catalyst or ligand. Through this sequential one-pot procedure, the initial aryl bromide (*i.e.* 4-bromoanisole) grew into the second-generation aryl bromide **3**, which is expected to be directly used in the reaction with the borate **1a** again without intervention of any activation or deprotection step.

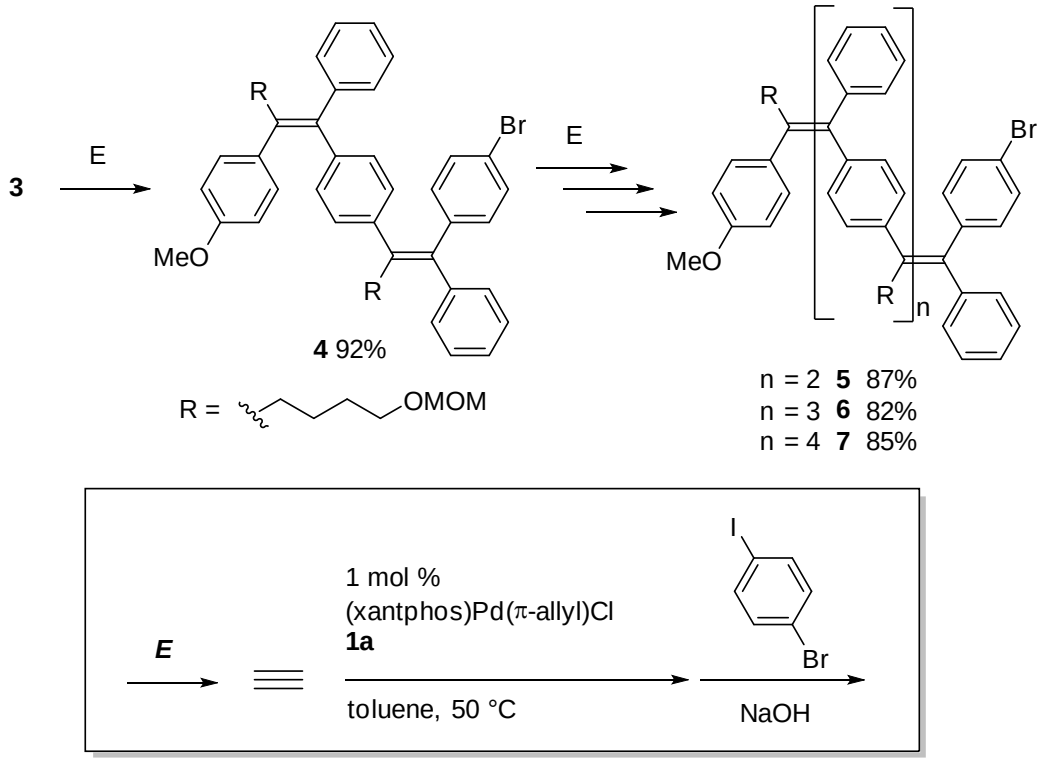
Scheme 1. One-Pot Synthesis of Tetrasubstituted Olefin



Next, aryl bromide **3** was subjected to the second-round sequential one-pot procedure. Treatment of **3** with alkynylborate **1a** (1.1 equiv) followed by direct addition of 4-bromoiodobenzene (1.1 equiv) and NaOH to the reaction mixture afforded the third-generation aryl bromide **4** in 92% yield (Scheme 2). Further application of the third-round sequential procedure to **4** furnished the fourth-generation aryl bromide **5** in 87% yield. The sequential procedure was repeated on **5** once to give the fifth-generation **6** in 82% yield, and twice to give the sixth-generation **7** in 85% yield. These oligomers were readily soluble in common organic solvents like toluene, THF, AcOEt and chloroform, and therefore, were isolated with high purity by column chromatography on silica gel, and identified by ^{1}H and ^{13}C NMR and mass spectroscopy. Importantly, the yield of each round did not decrease as the molecular size increased, suggesting that further elongation by the iterative method would be possible. Thus, one (tetrasubstituted vinylene)phenylene unit could be added to the chain in a stepwise manner with high efficiency and stereoselectivity by repetition of the sequential one-pot procedure.

Monodispersed oligomers can be divergently synthesized by repeating an iterative procedure which generally consists of an extension step and an activation step.[1,7] An extending unit possessing a dormant coupling site is initially added to a main chain (an extension step). The dormant site is then activated to be subsequently coupled with another extending unit (an activation step). On the contrary, the present method to synthesize OPVs dispenses with the need for activation.[8] One cycle adding a vinylene-phenylene unit consists of two different extension steps, one extending a tetrasubstituted vinylene unit and the other extending a phenylene unit. Both extension steps can be executed by the same catalyst system in one-pot. Thus, this simple method makes it practical to synthesize a structurally well-defined oligomer of single molecular weight in an efficient way.

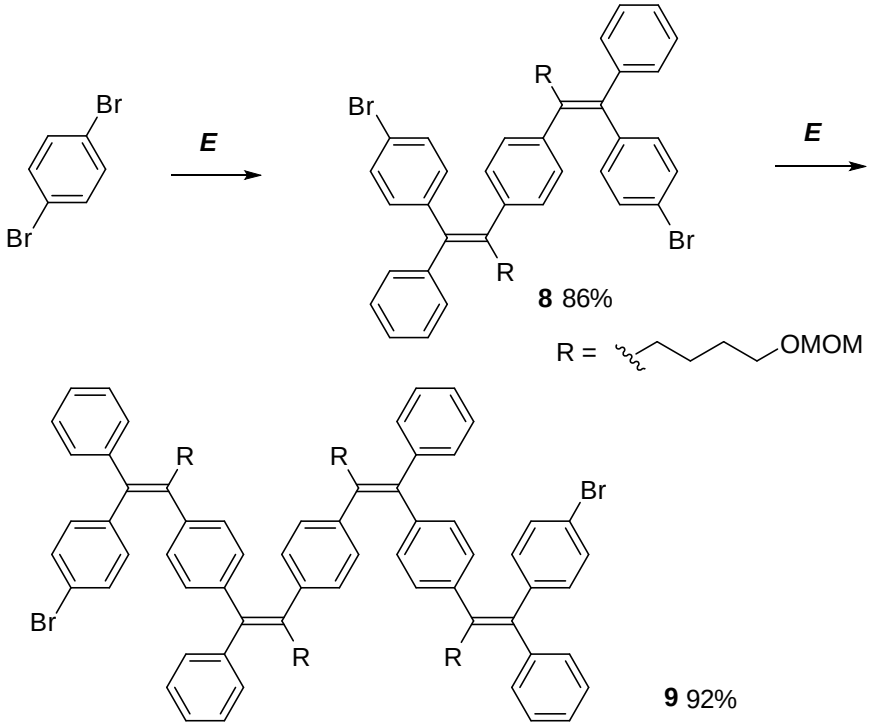
Scheme 2. Repetition of the Sequential Procedure



A phenylenevinylene chain could be extended into two directions by using 1,4-dibromobenzene as the starting aryl bromide (Scheme 3). 1,4-Dibromobenzene was reacted with the alkynylborates **1a** (2.1 equiv) under the standard conditions, and the subsequent double cross-coupling reaction with 4-bromoiodobenzene (2.2 equiv) furnished the dibromide **8** in 86% yield. The dibromide **8** was then reacted with the alkynylborate **1a** (3.0 equiv) to afford diborylated phenylenevinylene intermediate, which was treated with 4-bromoiodobenzene (4.0 equiv) and NaOH, resulting in the

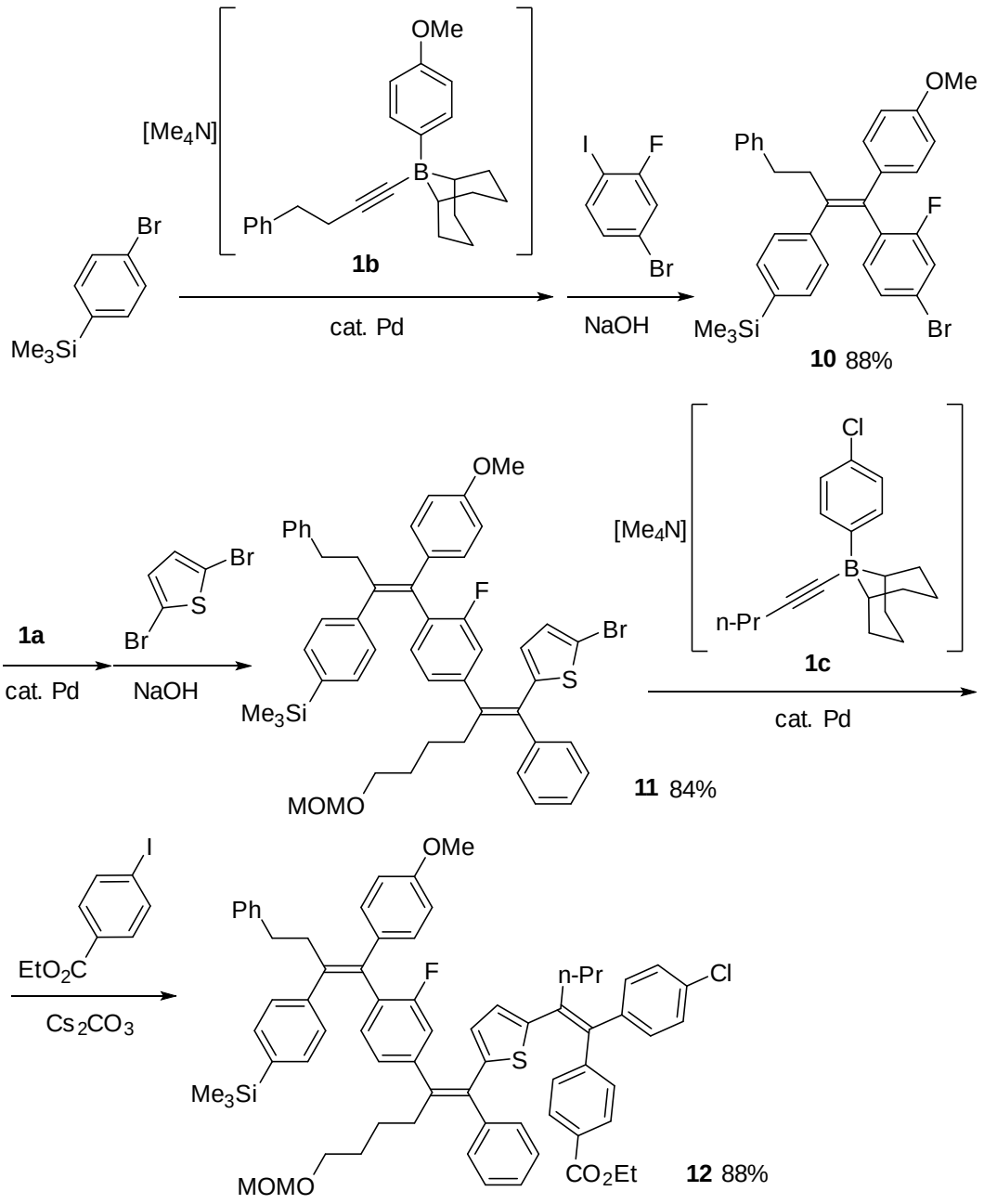
formation of OPV **9** in 92% yield. Interestingly, OPV **9** exhibited visible blue fluorescence in solution, whereas OPVs **4-7** did not. Thus, even a small structural change of the OPVs may cause a significant influence on their photophysical properties.

Scheme 3. Extention into Two Directions



Finally, the functional group compatibility of the palladium-catalyzed sequential procedure was exploited to synthesize the structurally diversified oligo(arylenevinylene) **12** (Scheme 4). 4-Bromotrimethylsilylbenzene was reacted with 1.0 equiv of the alkynylborate **1b** having a 4-methoxyphenyl group on boron, and the reaction mixture was then treated with 1.0 equiv of 4-bromo-2-fluoroiodobenzene to give **10** in 88% yield. The second-round extension was carried out using the alkynylborate **1a** (1.1 equiv) and then 2,5-dibromothiophene (3.0 equiv) and NaOH. The bi(arylenevinylene) **11** possesing five different aryl groups and two alkyl groups was obtained in 84% yield. Furthermore, **11** was subjected to the third-round extension using 1.1 equiv of the alkynylborate **1c** with a 4-chlorophenyl group on boron and then 1.1 equiv of 4-(ethoxycarbonyl)iodobenzene to give the ter(arylenevinylene) **12** in 88% yield. The structure of **12** is highly diversified, consisting of seven different aryl groups and three alkyl groups. Thus, a wide variety of structural modification could be installed at desired positions by changing arylene and vinylene modules.

Scheme 4. Synthesis of Oligo(arylenevinylene) 12



Conclusions

In conclusion, we have developed an efficient iterative method for the synthesis of oligo(arylenevinylene)s containing tetrasubstituted vinylene units. Of note is that an aryl bromide grew into the next generation aryl bromide in one-pot through two different kinds of extending steps. The method dispenses with the need of activation steps, and thus, rapidly increases the molecular complexity. Synthesis of new OPVs, and studies on structural features and photophysical properties are now in progress.

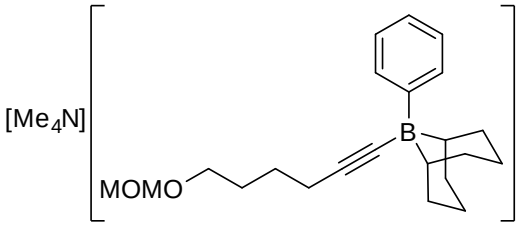
Experimental Section

General. NMR spectra were recorded on a Varian Gemini 2000 (^{1}H at 300 MHz and ^{13}C at 75 MHz), JEOL JNM-A500 (^{1}H at 500 MHz and ^{13}C at 150 MHz), or Varian 400-MR Auto Tune X5 (^{11}B at 128 MHz) spectrometers. Unless otherwise noted, $CDCl_3$ was used as a solvent. Chemical Shifts are recorded in δ ppm referenced to a residual $CDCl_3$ (δ = 7.26 for ^{1}H, δ 77.0 for ^{13}C), CD_3CN (δ = 1.94 for ^{1}H, δ =1.32 for ^{13}C), and $BF_3 \cdot OEt_2$ (δ = 0.00 for ^{11}B). High-resolution mass spectra were recorded on Applied Biosystems Voyager Elite or JEOL JMS-HX110A spectrometer. Infrared spectra were recorded on a SHIMADZU FT-IR 8100. Column chromatography was performed with silica gel 60 N (Kanto). Preparative thin-layer chromatography was performed with Silica gel 60 PF_{254} (Merck). Gel permeation chromatography (GPC) was carried out with Japan Analytical Industry LC-908 or LC-9204.

Materials. Unless otherwise noted, all chemicals and anhydrous solvents were obtained from commercial suppliers. Toluene was dried over Na-benzophenone ketyl. (XANTPhos)Pd(π-allyl)Cl,[9] Ar-9-BBN,[10] and 5-Hexyn-1-yl(methoxymethyl)ether[11] were prepared according to the reported procedure.

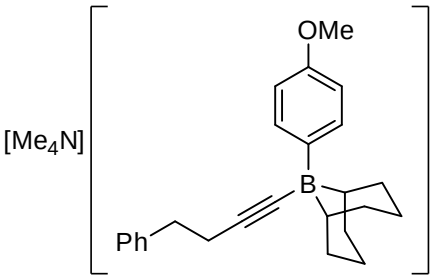
Preparation of Alkynylborates 1a: A Typical Procedure for the Preparation of Alkynylborates 1a, 1b

To a stirred solution of 5-hexyn-1-yl(methoxymethyl)ether (2.04 g, 14.4 mmol) in THF (20.0 ml) at -78 ˚C was added *n*-BuLi (1.6 M in hexane, 9.0 ml, 14.4 mmol). After 30 minnutes at this temperature, phenyl-9-BBN (2.60 g, 13.0 mmol) was added and the cooling bath was removed. After being stirred for 1 h at room temperature, the reaction was quenched by adding a small amount of methanol. Then, volatile materials were removed under reduced pressure. The residue was dissolved in methanol and tetramethylammonium chloride (1.60 g, 14.6 mmol) was added with stirring at -78 ˚C, resulting in white solid. It was collected by filtration and was washed with cold methanol to give alkynylborate **1a** (3.20 g, 7.7 mmol, 60% yield).



1a

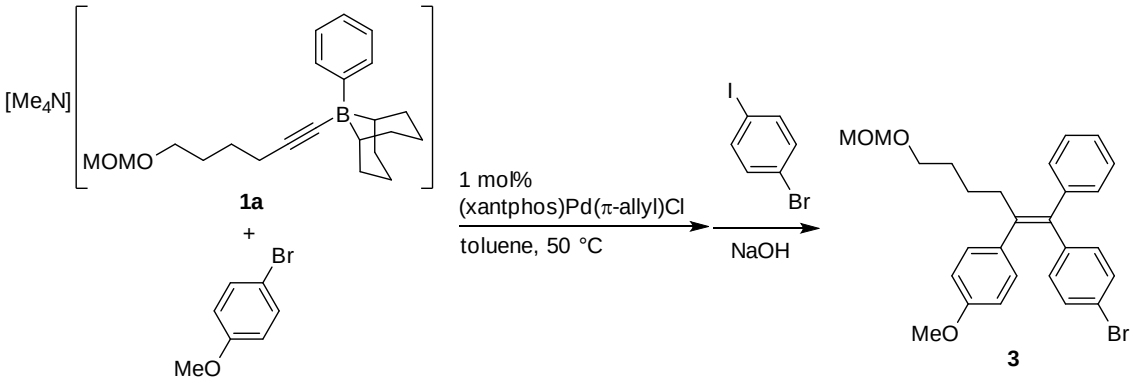
^{1}H NMR (CD_3CN, 300 MHz): δ = 0.91 (bs, 2H), 1.10-1.19 (m, 1H), 1.32-1.96 (m, 15H), 2.02 (t, *J* = 6.6 Hz, 2H), 2.36-2.51 (m, 2H), 3.04 (s, 12H), 3.28 (s, 3H), 3.46 (t, *J* = 6.9 Hz, 2H), 4.54 (s, 2H), 6.78-6.85 (m, 1H), 6.98-7.05 (m, 2H), 7.34 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (CD_3CN, 75 MHz): δ = 21.0, 26.7 (br), 27.1, 27.5, 28.2, 29.7, 32.4, 34.9, 55.1, 56.1, 68.1, 92.8, 96.8, 122.1, 126.9, 133.8; ^{11}B NMR (128 MHz): δ = -18.0; HRMS (FAB) Calcd for $C_{22}H_{32}BO_2$ $[M-(NMe_4)]^-$ 339.2495. Found 339.2493.



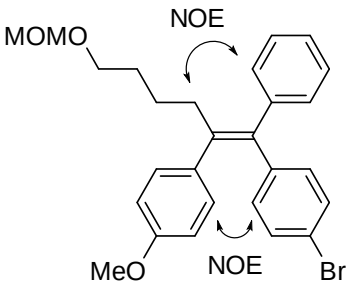
1b

^{1}H NMR (CD_3CN, 300 MHz): δ = 0.88 (bs, 2H), 1.10-1.20 (m, 1H), 1.34-1.96 (m, 9H), 2.25 (t, *J* = 7.2 Hz, 2H), 2.34-2.49 (m, 2H), 2.63 (t, *J* = 7.2 Hz, 2H), 3.03 (s, 12H), 3.72 (s, 3H), 6.63-6.69 (m, 2H), 7.11-7.28 (m, 7H); ^{13}C NMR (CD_3CN, 100 MHz) δ = 24.2, 27.2, 27.5, 32.4, 34.9, 38.1, 55.4, 56.0, 112.9, 126.6, 128.9, 129.8, 134.6, 143.4, 156.3; ^{11}B NMR (128 MHz): δ = -18.2; HRMS (FAB) Calcd for $C_{25}H_{30}BO$ $[M-(NMe_4)]^-$ 357.2390. Found 357.2383.

One-Pot Synthesis of Tetrasubstituted Olefin 3. A Typical Procedure for the Synthesis of Tetrasubstituted Oligo(arylenevinylene)s 3-12.



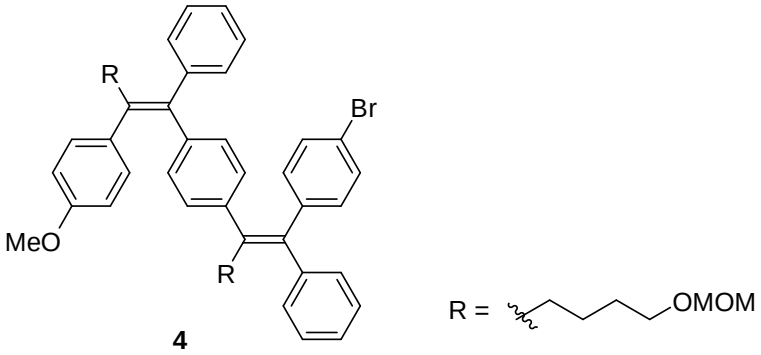
Under an argon atmosphere, a mixture of alkynylborate **1**, (XANTPhos)Pd(π-allyl)Cl (X mg, Y mmol), and aryl halide **A** in toluene was stirred for time $\mathbf{t_1}$ at 50 ˚C. Then, aryl halide **B** and base **C** were added to the reaction mixture, which was stirred for time $\mathbf{t_2}$ and water was added. After addition of water, the aqueous layer was extracted with AcOEt (3 times), washed with water (once), brine (once), dried over Na_2SO_4 and concentrated. The residue was purified by GPC to afford the tetrasubstituted oligo(arylenevinylene)s



3

alkynylborate **1**: **1a** (827 mg, 2.0 mmol), (XANTPhos)Pd(π-allyl)Cl (15 mg, 20 μmol), aryl halide **A**: 4-bromoanisole (393 mg, 2.1 mmol), aryl halide **B**: 4-bromoiodobenzene (566 mg, 2.0 mmol), base **C**: NaOH (240 mg, 6.0 mmol), $\mathbf{t_1}$: 0.5 h, $\mathbf{t_2}$: 6 h

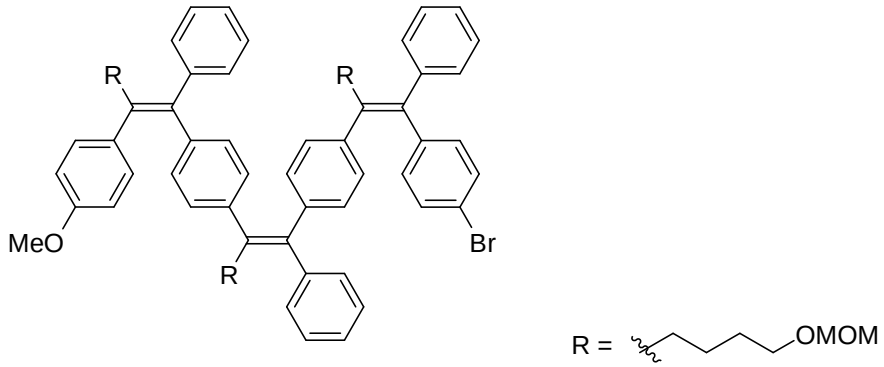
^{1}H NMR (300 MHz): δ = 1.30-1.58 (m, 4H), 2.41 (t, *J* = 7.8 Hz, 2H), 3.27 (s, 3H), 3.37 (t, *J* = 6.6 Hz, 2H), 3.76 (s, 3H), 4.52 (s, 2H), 6.67-6.75 (m, 4H), 6.97-7.02 (m, 2H), 7.09-7.36 (m, 7H); ^{13}C NMR (75 MHz): δ = 25.5, 29.8, 35.6, 55.10, 55.14, 67.6, 96.4, 113.4, 119.6, 126.7, 128.2, 129.4, 130.46, 130.49, 132.3, 133.9, 137.6, 140.8, 142.0, 143.0, 158.0; HRMS (MALDI-TOF-MS (DCTB) calcd for $C_{27}H_{29}BrO_3$ $[M]^+$ 480.1300. Found 480.1269. The (*Z*)-stereochemistry was determined by the 2D NOESY spectroscopy.



4

alkynylborate **1**: **1a** (863 mg, 2.1 mmol), (XANTPhos)Pd(π-allyl)Cl (15 mg, 20 μmol), aryl halide **A**: **3** (963 mg, 2.0 mmol), aryl halide **B**: 4-bromoiodobenzene (622 mg, 2.2 mmol), base **C**: NaOH (240 mg, 6.0 mmol), $\mathbf{t_1}$: 0.5 h, $\mathbf{t_2}$: 6 h

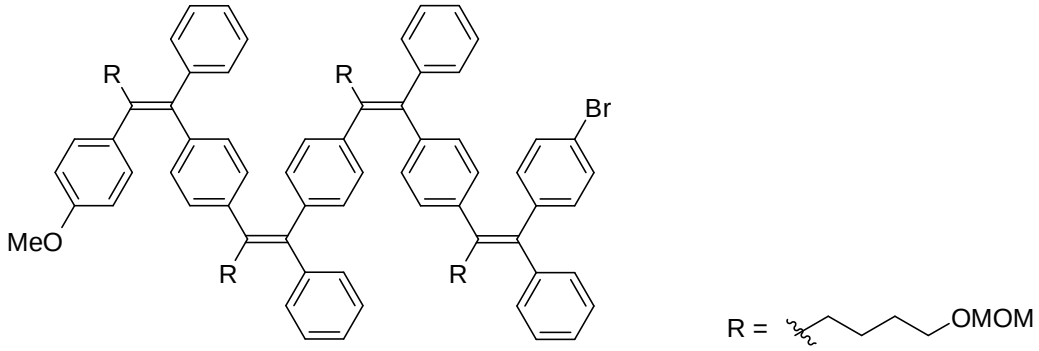
^{1}H NMR (300 MHz): δ = 1.24-1.54 (m, 8H), 2.33 (t, *J* = 7.8 Hz, 2H), 2.42 (t, *J* = 7.5 Hz, 2H), 3.25 (s, 3H), 3.29 (s, 3H), 3.31-3.41 (m, 4H), 3.80 (s, 3H), 4.51 (s, 2H), 4.53 (s, 2H), 6.62-6.78 (m, 8H), 6.97-7.03 (m, 2H), 7.06-7.38 (m, 12H); ^{13}C NMR (150 MHz): δ = 25.2, 25.4, 29.5, 29.6, 35.3, 35.4, 55.02, 55.04, 55.2, 67.5, 67.6, 96.29, 96.32, 113.1, 119.6, 126.5, 126.7, 128.1, 128.2, 128.5, 129.41, 129.42, 130.3, 130.4, 130.6, 132.4, 134.3, 137.7, 138.5, 139.0, 140.0, 141.3, 141.4, 141.8, 142.9, 143.5, 157.9; HRMS (MALDI-TOF-MS (DIT)) calcd for $C_{47}H_{51}BrO_5Na$ $[M+Na]^+$ 797.2818. Found 797.2849.



5

alkynylborate **1**: **1a** (434 mg, 1.05 mmol), (XANTPhos)Pd(π-allyl)Cl (7.6 mg, 10 μmol), aryl halide **A**: **4** (775 mg, 1.0 mmol), aryl halide **B** : 4-bromoiodobenzene (310 mg, 1.1 mmol), base **C**: NaOH (120 mg, 3.0 mmol), $\mathbf{t_1}$: 1 h, $\mathbf{t_2}$: 12 h

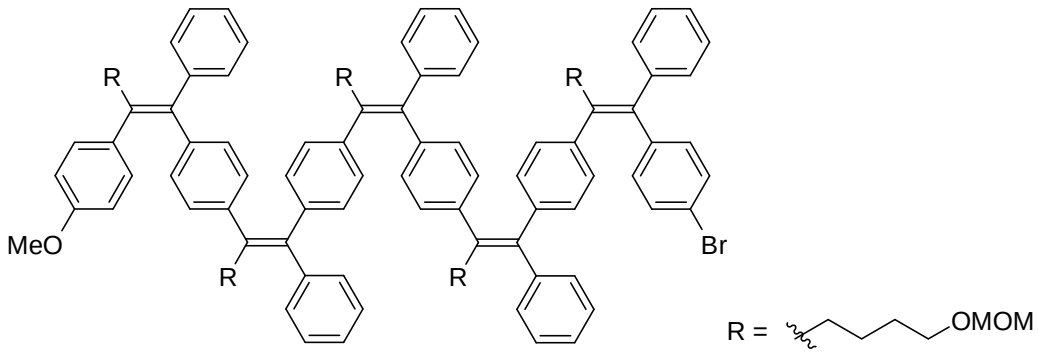
^{1}H NMR (300 MHz): δ = 1.22-1.55 (m,12 H), 2.28-2.39 (m,4H), 2.46 (t, *J* = 7.5, 2H), 3.25 (s, 3H), 3.27 (s, 3H), 3.28 (s, 3H), 3.30-3.42 (m, 6H), 3.74 (s, 3H), 4.50 (s, 2H), 4.52 (s, 2H), 4.54 (s, 2H), 6.54-6.62 (m, 4H), 6.66-6.78 (m, 8H), 6.96-7.04 (m, 4H), 7.12-7.37 (m, 15H) ; ^{13}C NMR (75 MHz): δ = 25.4, 25.6, 29.6, 29.7, 29.8, 35.26, 35.34, 35.5, 55.1, 67.5, 67.6, 96.3, 113.0, 119.6, 126.4, 126.7, 128.0, 128.1, 128.6, 129.4, 130.1, 130.2, 130.4, 130.6, 132.4, 134.4, 137.7, 138.4, 138.7, 139.2, 139.3, 139.8, 140.2, 140.9, 141.4, 141.5, 141.7, 142.8, 143.3, 143.5, 157.7; HRMS (MALDI-TOF-MS (DIT)) calcd for $C_{67}H_{73}BrO_7Na$ $[M+Na]^+$ 1091.4437. Found 1091.4482.



6

alkynylborate **1**: **1a** (434 mg, 1.05 mmol), (XANTPhos)Pd(π-allyl)Cl (7.6 mg, 10 µmol), aryl halide **A**: **5** (1.07 mg, 1.0 mmol), aryl halide **B**: 4-bromoiodobenzene (310 mg, 1.1 mmol), base **C**: NaOH (120 mg, 3.0 mmol), $\mathbf{t_1}$: 1.5 h, $\mathbf{t_2}$: 12 h

^{1}H NMR (300 MHz): δ = 1.20-1.56 (m, 16H), 2.26-2.48 (m, 8H), 3.22-3.28 (m, 12H), 3.30-3.41 (m, 8H), 3.71 (s, 3H), 4.48-4.54 (m, 8H), 6.48-6.75 (m, 16H), 6.95-7.03 (m, 4H), 7.14-7.37 (m, 20H); ^{13}C NMR (75 MHz): δ = 25.3, 25.4, 25.6, 25.7, 29.69, 29.74, 29.8, 35.0, 35.4, 35.6, 55.0, 55.1, 67.5, 67.6, 96.3, 113.1, 119.6, 126.4, 126.7, 127.9, 128.0, 128.1, 128.3, 128.8, 129.3, 129.4, 130.0, 130.1, 130.2, 130.5, 130.6, 132.3, 134.2, 137.7, 138.5, 138.7, 138.9, 139.1, 139.4, 139.6, 139.7, 140.1, 140.5, 140.9, 141.1, 141.3, 141.4, 141.7, 142.7, 143.2, 143.3, 143.5, 157.7; HRMS (MALDI-TOF-MS (DIT)) calcd for $C_{87}H_{95}BrO_9Na$ $[M+Na]^+$ 1385.6057. Found 1385.6062.

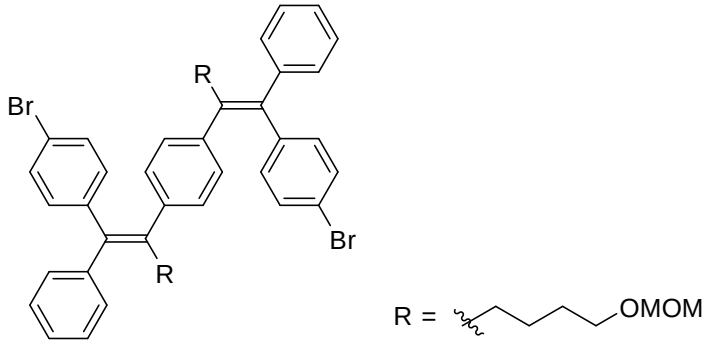


7

alkynylborate **1**: **1a** (227 mg, 0.55 mmol), (XANTPhos)Pd(π-allyl)Cl (3.8 mg, 5.0 µmol), aryl halide **A**: **6** (682 mg, 0.50 mmol), aryl halide **B** : 4-bromoiodobenzene (170 mg, 0.60 mmol), base **C**: NaOH (60 mg, 1.5 mmol), $\mathbf{t_1}$: 1.5 h, $\mathbf{t_2}$: 12 h

^{1}H NMR (300 MHz): δ = 1.18-1.55 (m, 20H), 2.24-2.48 (m, 10H), 3.22-3.40 (m, 25H), 3.74 (s, 3H), 4.47-4.52 (m, 10 H), 6.49-6.79 (m, 20 H), 6.90-6.95 (m, 2H), 7.01-7.06 (m, 2H), 7.10-7.36 (m, 25H); ^{13}C NMR (75 MHz): δ = 25.29, 25.35, 25.6, 25.7, 29.68,

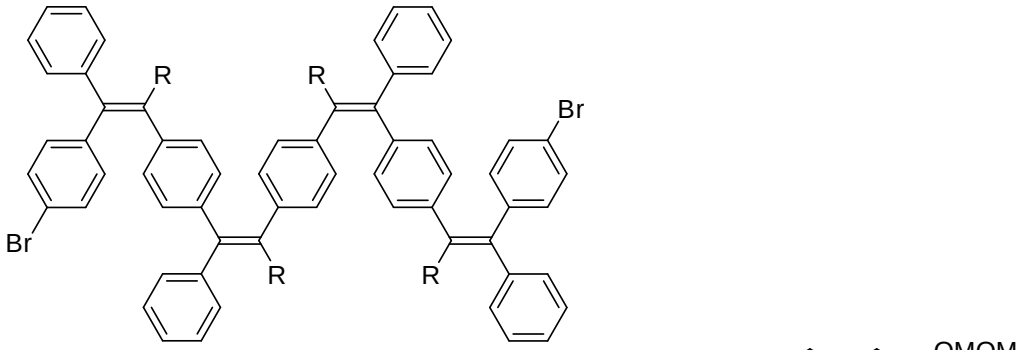
29.71, 29.8, 35.1, 35.4, 35.5, 35.6, 55.0, 67.46, 67.55, 67.6, 96.3, 113.1, 119.5, 126.4, 126.7, 127.95, 128.0, 128.1, 128.3, 128.5, 128.7, 129.3, 129.37, 129.44, 130.1, 130.2, 130.4, 130.6, 132.2, 134.3, 137.7, 138.4, 138.7, 138.9, 139.0, 139.1, 139.4, 139.76, 139.79, 140.1, 140.4, 140.8, 140.9, 141.2, 141.3, 141.6, 142.7, 143.18, 143.21, 143.4, 143.5, 157.8; HRMS (MALDI-TOF-MS (DIT)) calcd for $C_{107}H_{117}BrO_{11}Na$ $[M+Na]^+$ 1679.7677. Found 1679.7694.



8

alkynylborate **1**: **1a** (868 mg, 2.1 mmol), (XANTPhos)Pd(π-allyl)Cl (7.6 mg, 10 μmol), aryl halide **A**: 1,4-dibromobenzene (236 mg, 1.0 mmol), aryl halide **B**: 4-bromoiodobenzene (622 mg, 2.2 mmol), base **C**: NaOH (240 mg, 6.0 mmol), $\mathbf{t_1}$: 1.0 h, $\mathbf{t_2}$: 24 h

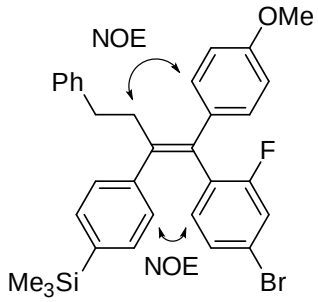
^{1}H NMR (300 MHz): δ = 1.28-1.54 (m, 8H), 2.40 (t, *J* = 7.8 Hz, 4H), 3.30 (s, 6H), 3.39 (t, *J* = 6.6 Hz, 4H), 4.56 (s, 4H), 6.68-6.73 (m, 4H), 6.91 (s, 4H), 7.10-7.21 (m, 8H), 7.22-7.37 (m, 6H); ^{13}C NMR (75 MHz): δ = 25.4, 29.7, 35.4, 55.1, 67.6, 96.3, 119.8, 126.8, 128.2, 129.1, 129.3, 130.3, 132.3, 138.0, 140.0, 141.1, 141.7, 142.7; HRMS (MALDI-TOF-MS (DCTB)) calcd for $C_{46}H_{48}Br_2O_4Na$ $[M+Na]^+$ 822.1919. Found 822.1905.



9

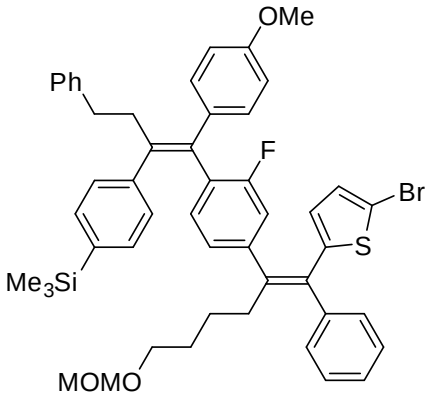
alkynylborate **1**: **1a** (62.0 mg, 0.15 mmol), (XANTPhos)Pd(π-allyl)Cl (0.80 mg, 1.0 μmol), aryl halide **A**: **8** (41.2 mg, 0.050 mmol), aryl halide **B**: 4-bromoiodobenzene

(56.6 mg, 0.20 mmol), base **C**: NaOH (18.0 mg, 4.5 mmol), $\mathbf{t_1}$: 2.0 h, $\mathbf{t_2}$: 24 h
^{1}H NMR (300 MHz): δ = 1.22-1.54 (m, 16H), 2.29-2.45 (m, 8H), 3.22 (s, 6H), 3.29 (s, 6H), 3.30-3.40 (m, 8H), 4.46 (s, 4H), 4.53 (s, 4H), 6.56-6.72 (m, 12H), 6.88 (s, 4H), 7.04-7.10 (m, 4H), 7.14-7.18 (m, 4H), 7.22-7.40 (m, 16H); ^{13}C NMR (150 MHz): δ = 25.4, 29.62, 29.63, 35.6, 35.7, 55.01, 55.03, 67.4, 67.6, 96.29, 96.31, 119.7, 126.6, 126.8, 128.1, 128.18, 128.22, 129.0, 129.5, 129.6, 130.4, 130.8, 132.4, 137.9, 138.5, 139.4, 140.3, 140.5, 140.9, 141.6, 141.7, 142.7, 143.4; HRMS (MALDI-TOF-MS (DIT)) calcd for $C_{86}H_{92}Br_2O_8Na$ $[M+Na]^+$ 1433.5057. Found 1433.5040.



10

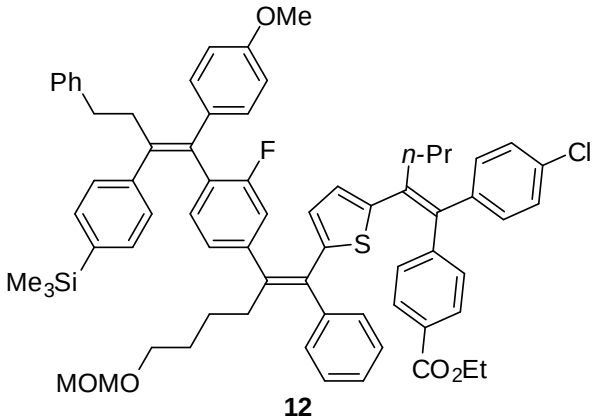
alkynylborate **1**: **1b** (432 mg, 1.0 mmol), (XANTPhos)Pd(π-allyl)Cl (7.6 mg, 10 μmol), aryl halide **A**: 4-bromotrimethylsilylbenzene (241 mg, 1.05 mmol), aryl halide **B**: 4-bromo-2-fluoroiodobenzene (301 mg, 1.0 mmol), base **C**: NaOH (120 mg, 3.0 mmol), $\mathbf{t_1}$: 0.5 h, $\mathbf{t_2}$: 12 h
^{1}H NMR (300 MHz): δ = 0.24 (s, 9H), 2.60-2.67 (m, 2H), 2.76-2.83 (m, 2H), 3.80 (s, 3H), 6.76-6.86 (m, 3H), 6.94-7.07 (m, 6H), 7.09-7.28 (m, 5H), 7.34 (d, J = 8.4 Hz, 2H); ^{13}C NMR (150 MHz): δ = -1.1, 34.9, 37.2, 55.2, 113.5, 118.9 (d, $J_{C\text{-}F}$ = 25.5 Hz),120.2 (d, $J_{C\text{-}F}$ = 9.2 Hz), 125.8, 126.8 (d, $J_{C\text{-}F}$ = 3.5 Hz), 128.0, 128.3, 128.4, 130.0, 130.4 (d, $J_{C\text{-}F}$ = 15.9 Hz), 132.6, 132.9, 133.2 (d, $J_{C\text{-}F}$ = 4.5 Hz), 133.9, 138.7, 141.7, 141.8, 143.0, 158.5, 159.6 (d, $J_{C\text{-}F}$ = 249.3 Hz); HRMS (MALDI-TOF-MS (DCTB)) calcd for $C_{32}H_{32}BrFOSi$ $[M]^+$ 558.1390. Found 558.1392. The (*Z*)-stereochemistry was determined by the 2D NOESY spectroscopy.



11

alkynylborate **1**: **1a** (219 mg, 0.53 mmol), (XANTPhos)Pd(π-allyl)Cl (3.8 mg, 5.0 µmol), aryl halide **A**: **10** (279 mg, 0.50 mmol), aryl halide **B**: 2,5-dibromothiophene (406 mg, 1.5 mmol), base **C**: NaOH (60 mg, 1.5 mmol), $\mathbf{t_1}$: 0.5 h, $\mathbf{t_2}$: 12 h

^{1}H NMR (300 MHz): δ = 0.24 (s, 9H), 1.16-1.26 (m, 2H), 1.30-1.42 (m, 2H), 2.11 (t, *J* = 7.8, 2H), 2.64-2.72 (m, 2H), 2.82-2.89 (m, 2H), 3.25 (s, 3H), 3,28 (t, *J* = 6.6 Hz, 2H), 3.82 (s 3H), 4.48 (s, 2H), 5.87 (d, *J* = 3.9 Hz, 1H), 6.60 (d, *J* = 3.9 Hz, 1H), 6.69-6.76 (m, 2H), 6.84-6.96 (m, 3H), 7.05-7.42 (m, 16H); ^{13}C NMR (150 MHz): δ = -1.0, 24.4, 29.3, 35.1, 36.2, 37.2, 55.0, 55.2, 67.3, 96.3, 112.7, 113.5, 116.1 (d, $J_{C\text{-}F}$ = 22.5 Hz), 124.4 (d, $J_{C\text{-}F}$ = 3.2 Hz), 125.8, 127.4, 128.27, 128.31, 128.37, 128.40, 128.56, 128.61, 129.5, 130.2, 130.7 (d, $J_{C\text{-}F}$ = 15.5 Hz), 132.4, 132.9, 133.0 (d, $J_{C\text{-}F}$ = 4.5 Hz), 133.3, 134.5, 138.5, 139.5 (d, $J_{C\text{-}F}$ = 1.2 Hz), 141.2, 141.6 (d, $J_{C\text{-}F}$ = 8.0 Hz), 141.9, 142.2, 142.3, 146.2, 158.4, 160.2 (d, $J_{C\text{-}F}$ = 246.5 Hz); HRMS (MALDI-TOF-MS (DCTB)) calcd for $C_{50}H_{52}BrFO_3SSiNa$ $[M+Na]^+$ 858.2574. Found 858.2600.



12

alkynylborate **1**: **1c** (39.3 mg, 0.105 mmol), (XANTPhos)Pd(π-allyl)Cl (0.80 mg, 1.0 µmol), aryl halide **A**: **11** (86.0 mg, 0.10 mmol), aryl halide **B**: 4-(ethoxycarbonyl)iodobenzene (30.4 mg, 0.11 mmol), base **C**: Cs_2CO_3 (97.7 mg, 0.30 mmol), $\mathbf{t_1}$: 1.0 h, $\mathbf{t_2}$: 12 h

^{1}H NMR (300 MHz): δ = 0.21 (s, 9H), 0.77 (t, *J* = 7.2 Hz, 3H), 1.12-1.43 (m, 9H) 2.10-2.24 (m, 4H), 2.64-2.72 (m, 2H), 2.79-2.87 (m, 2H), 3.23-3.33 (m, 5H), 3,73 (s, 3H), 4.34 (q, *J* = 6.9 Hz, 2H), 4.51 (s, 2H), 5.80 (d, *J* = 3.6 Hz, 1H), 6.13 (d, *J* = 3.9 Hz, 1H), 6.66-6.72 (m, 2H), 6.79-6.94 (m, 5H), 7.03-7.37 (m, 20H), 7.73 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (150 MHz): δ = -1.1, 14.1, 14.3, 22.5, 24.4, 29.3, 35.0, 35.9, 37.0, 38.5, 55.0, 55.1, 60.7, 67.4, 96.3, 113.4, 115.9 (d, $J_{C\text{-}F}$ = 22.4 Hz), 124.3 (d, $J_{C\text{-}F}$ = 2.9 Hz), 125.8, 126.9, 127.1, 128.08, 128.11, 128.15, 128.20, 128.23, 128.38, 128.44, 129.0, 129.3, 130.0, 130.1 (d, $J_{C\text{-}F}$ = 15.8 Hz), 130.2, 130.7, 132.3 (d, $J_{C\text{-}F}$ = 4.7 Hz), 132.58, 132.61, 132.8, 133.6, 134.4, 135.6, 137.9, 138.2, 139.0 (d, $J_{C\text{-}F}$ = 1.2 Hz), 140.9, 141.90, 141.91, 142.16 (d, $J_{C\text{-}F}$ = 8.0 Hz), 142.19, 142.22, 143.8, 144.6, 147.6, 158.3, 160.0 (d, $J_{C\text{-}F}$ = 244.8 Hz), 166.4; IR (KBr) = 2955, 1717, 1509, 1273, 1248, 1111, 837 cm^{-1}; HRMS (MALDI-TOF-MS (DIT)) calcd for $C_{70}H_{72}ClFO_5SSiNa$ $[M+Na]^+$ 1129.4440. Found 1129.4465.

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(1) For reviews, see: (a) Tour, J. M. *Chem. Rev.* **1996**, *96*, 537. (b) Martin, R. E.; Diederich, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 1350. (c) Scherf, U. *Top. Curr. Chem.* **1999**, *201*, 163.

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Chapter 5

Regioselective Construction of Indene Skeletons by Palladium-Catalyzed Annulation of Alkynylborates with *o*-Iodophenyl Ketones

Abstract

A palladium-catalyzed annulation reaction of alkynylborates with *o*-iodophenyl ketones to form indenes is described. Highly substituted indene skeletons are efficiently constructed with site-specific installation of substituents.

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Introduction

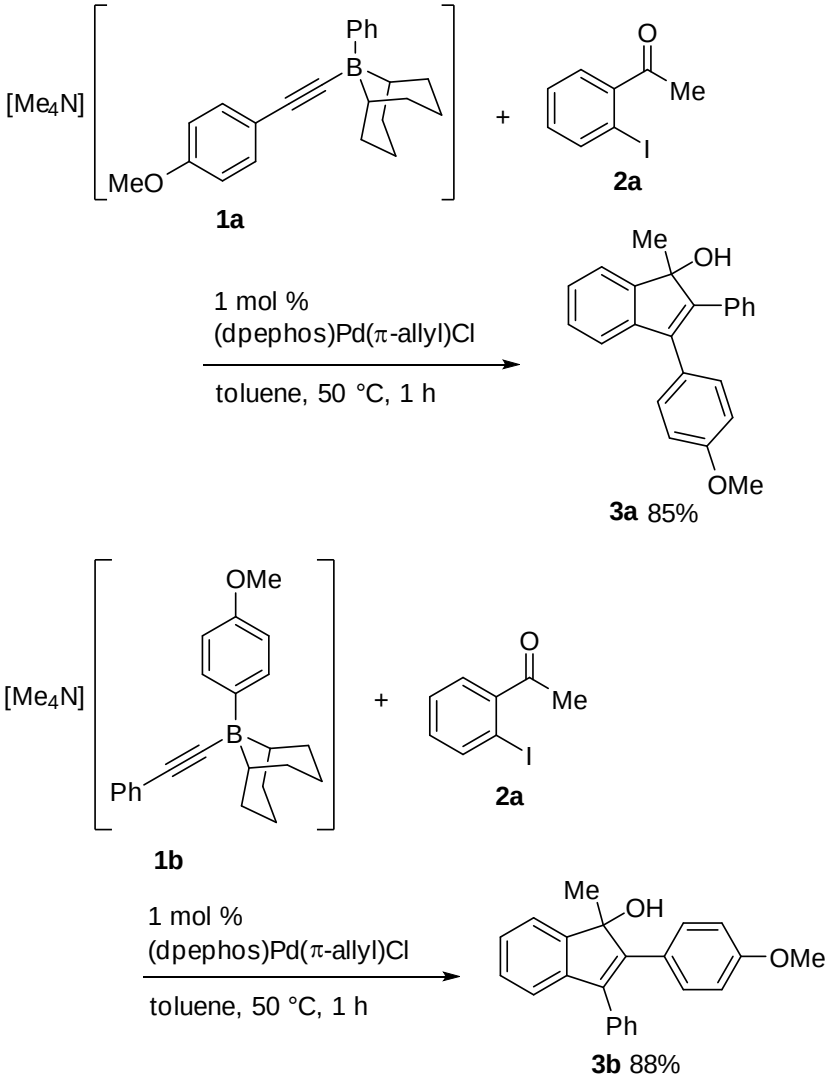
Indenes are important structural motif found in a number of biologically active compounds.[1] For example, an indene framework with an *exo*-alkylidene moiety is imbedded in sulindac, which is a non-steroidal anti-inflammatory drug.[1a] Dimethindene, an oral antihistamine agent, has an indene core tethered to an amine moiety.[1b] In addition to these commercial medicines, indene derivatives have also been exploited as materials for optoelectronics[2] and ligands for transition metal complexes.[3] Consequently, development of a new method to construct indene skeletons has been an attractive subject in organic synthesis.[4]

Alkynylboron compounds have been utilized as useful intermediates in organic synthesis.[5] We have previously developed the palladium-catalyzed reaction of alkynylborates with aryl halides.[6] (Trisubstituted alkenyl)boranes, which are otherwise difficult to synthesize, are readily obtained in a regio- and stereoselective fashion. Now, the palladium-catalyzed reaction is extended to the construction of indene skeletons. Alkynylborates react with *o*-iodophenyl ketones to afford 2,3-disubstituted indenols with specific installation of 2- and 3-substituents.

Results and Discussion

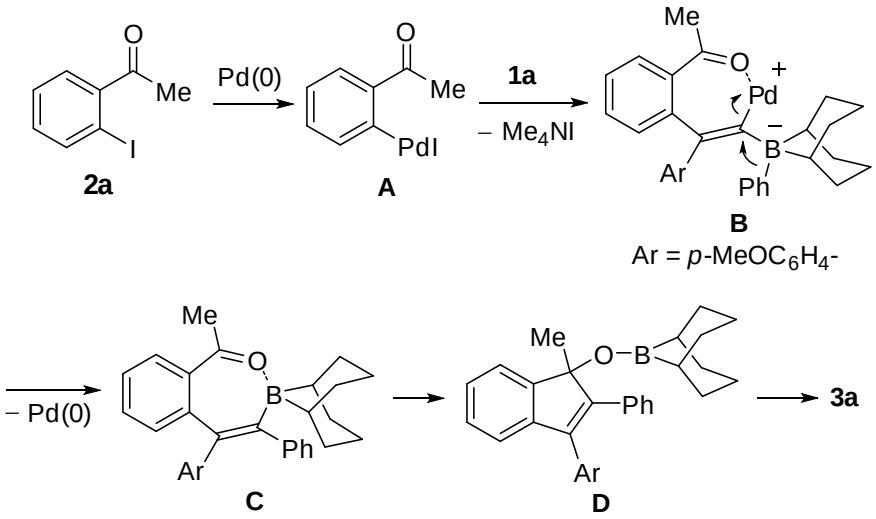
Alkynylborate **1a** and its constitutional isomer **1b** were prepared from the corresponding *B*-aryl-9-borabicyclo[3.3.1]nonane (Ar-9-BBN) and terminal alkyne according to the reported method.[6c] The borate **1a** (1.0 equiv) was treated with *o*-iodoacetophenone (**2a**, 1.05 equiv) in the presence of (dpephos)Pd(p-allyl)Cl (1 mol %) at 50 ℃ for 1 h (Scheme 1). The reaction mixture was then treated with hydrogen peroxide to oxidize the organoboron residue. Purification by column chromatography on silica gel afforded 2,3-diarylindenol **3a** in 85% yield. In sharp contrast, the reaction of the borate **1b** with **2a** selectively provided the regioisomeric indenol **3b** in 88% yield. Thus, the present palladium-catalyzed reaction makes possible selective production of both regioisomers of 2,3-diarylindenols, which is difficult to perform using the conventional annulation reaction of *o*-halophenyl ketones with 1,2-diarylalkynes.[4b]

Scheme 1. Reactions of Alkynylborates 1 and *o*-Iodoacetophenone 2a



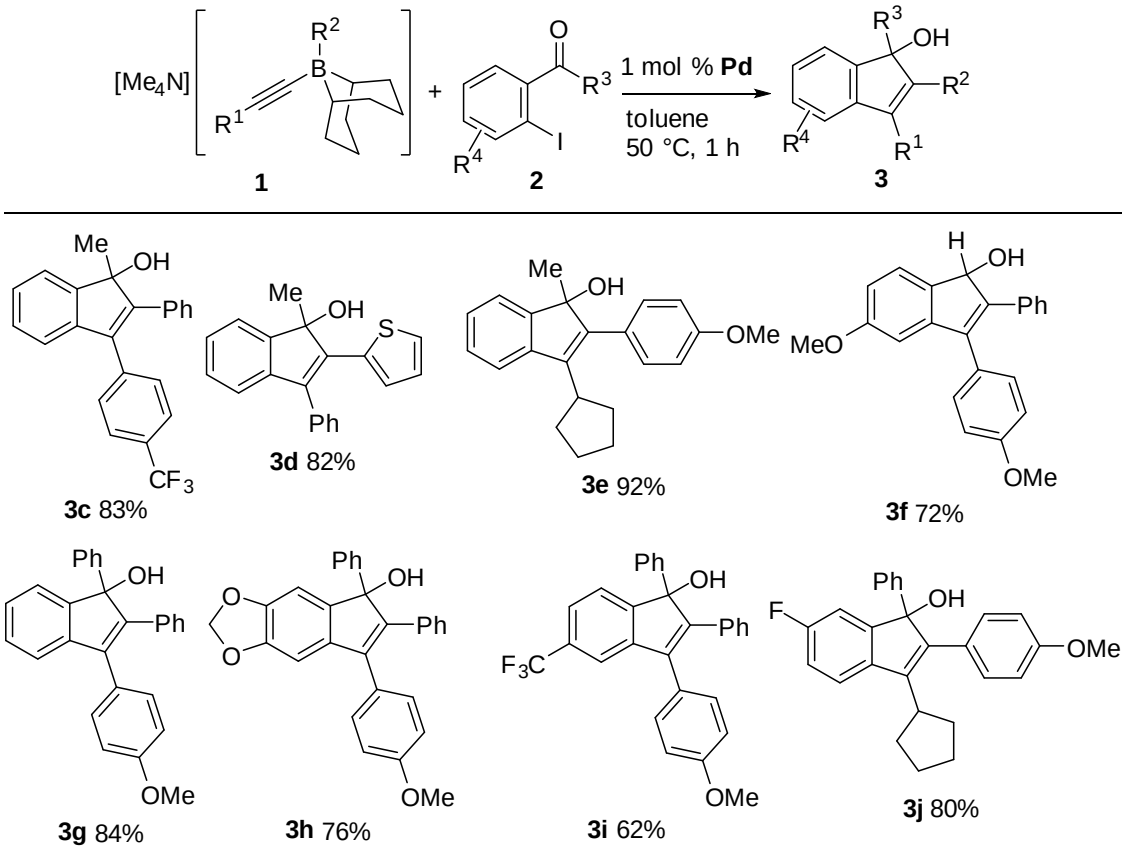
The selective formation of **3a** from **1a** and **2a** can be explained by the mechanism shown in scheme 2, which is based on the proposed mechanism of the palladium-catalyzed reaction of alkynylborates with simple aryl halides.[6c] Oxidative addition of **2a** to palladium(0) forms arylpalladium **A**. Regioselective *cis*-carbopalladation across the carbon–carbon triple bond of **1a** gives alkenylpalladium **B**, so that the phenyl group on the anionic boron migrates onto the a-carbon. The carbon–palladium bond is substituted with inversion of the stereochemistry to afford alkenylborane **C**.[7] The ketone moiety remains intact during the course of the palladium-catalyzed reaction. The generated *B*-alkenyl-9-BBN moiety undergoes intramolecular addition to the carbonyl group[8] to form the boron indenolate **B**. Upon the following oxidative work-up with $NaOH/H_2O_2$, **B** is hydrolyzed to the indenol **3a**.

Scheme 2. Mechanism Proposed for the Formation of 3a



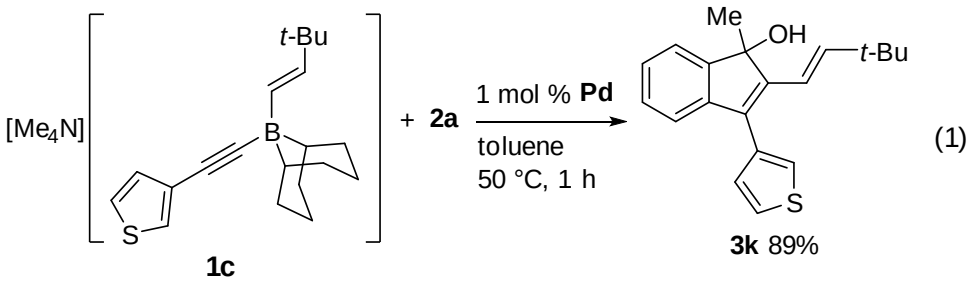
The present reaction successfully furnished a wide variety of highly-substituted indenols (Table 1). For example, thiophene-substituted **3d** and alkyl-substituted **3e** were obtained in 82% and 92% yield, respectively. The use of *o*-iodobenzaldehyde and *o*-iodobenzophenone gave the corresponding indenols **3f** and **3g**. The indenols equipped with alkoxy, trifluoromethyl, and fluorine groups on the aromatic ring (**3h-i**) could also be synthesized.

Table 1. Synthesis of Indenols 3[a]

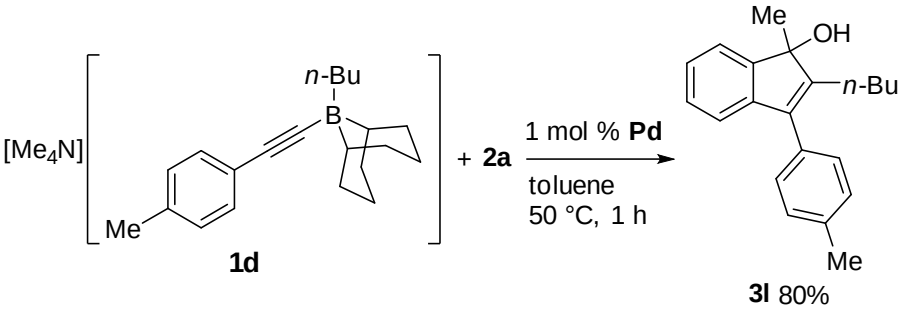


[a] Reagents and conditions: 1.0 equiv. of alkynylborates **1**, 1.05 equiv. of *o*-iodophenyl ketone **2**, 1 mol % of [(dpephos)PdCl(π-allyl)], toluene, 50 °C, 1 h; then aq. H_2O_2, aq. NaOH, MeOH, room temp., 2 h. Isolated yields are shown.

Alkenyl-substituted **3k** and alkyl-substituted **3l** were also synthesized from *B*-alkenyl-9-BBN **1c** and *B*-alkyl-9-BBN **1d**, respectively [Eqs. (1) and (2)]. The formation of **3l** is noteworthy from the mechanistic point of view; the *n*-butyl group on the anionic boron migrates onto the a-carbon in preference to the bridgehead sp^3 carbon of the 9-BBN framework.[9] This selectivity stands in sharp contrast to that observed in the reaction with iodine.[10]



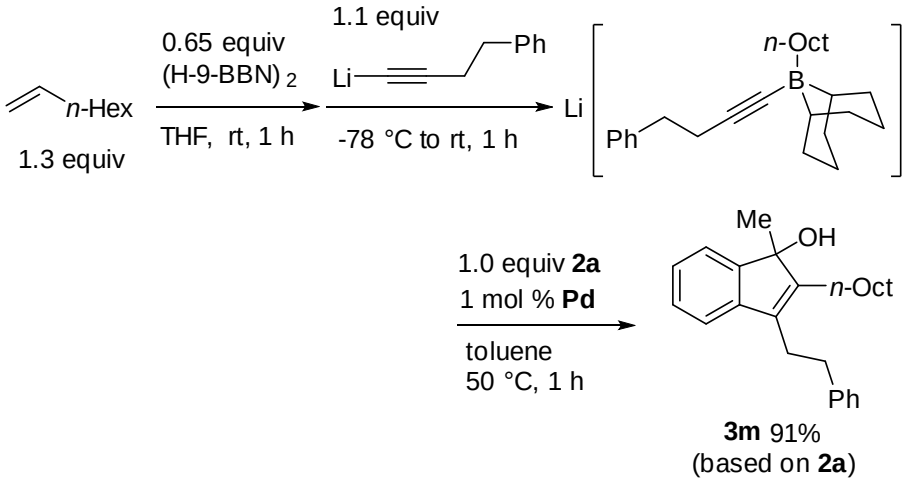
(1)



(2)

It was possible to directly synthesize 2,3-dialkylindenol **3m** in one-pot starting from 1-octene, 4-phenylbut-1-yne and *o*-iodoacetophenone **2a** without isolation of the intermediates (Scheme 3). Hydroboration of 1-octene with H-9-BBN in THF afforded *B*-*n*-octyl-9-BBN, which was then treated with 4-phenylbut-1-ynyllithium to form the corresponding lithium alkynylborate. A toluene solution containing *o*-iodoacetophenone (**2a**) and (dpephos)Pd(p-allyl)Cl was added to the reaction mixture, which was heated at 50 ℃ for 1 h. Oxidative work-up and purification by column chromatography furnished **3m** in 91% isolated yield based on **2a**.

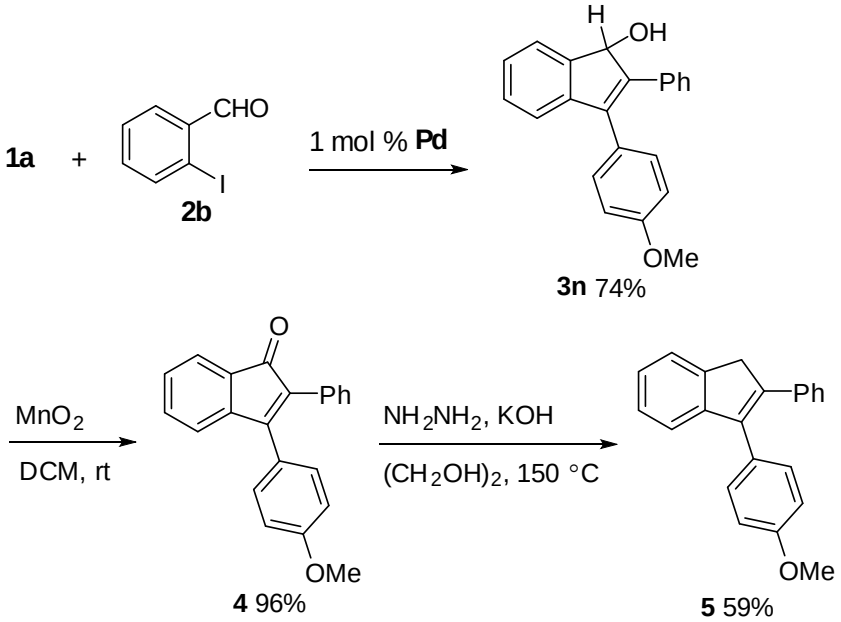
Scheme 3. Synthesis of indenol 3m from 1-octene



The palladium-catalyzed annulation of **1a** with **2b** gave indenol **3n** in 74% yield, which was subjected to further derivatization (Scheme 4). Oxidation of **3n** with manganese(IV) oxide furnished the indenone **4**. The following Wolff-Kishner reaction

reduced the carbonyl group without isomerization of the double bond to give indene **5** in 59% yield.[11]

Scheme 4. Synthesis of Indenone 4 and Indene 5



Conclusions

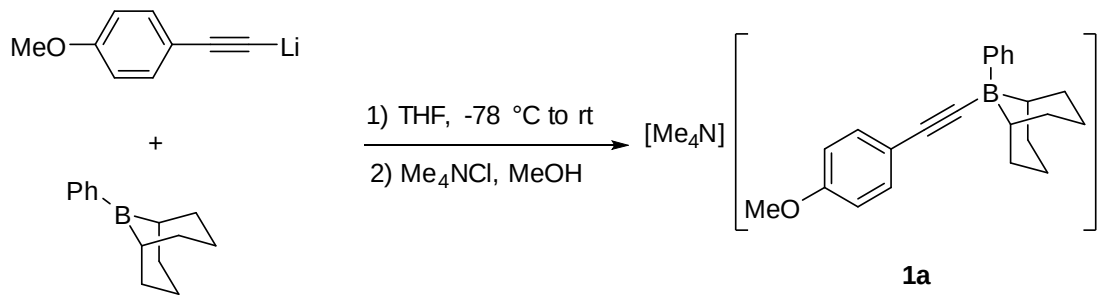
We have described the palladium-catalyzed annulation reaction of alkynylborates with *o*-iodophenyl ketones. A wide variety of highly-substituted indenols are regiospecifically synthesized by this method.

Experimental Section

General. NMR spectra were recorded by a Varian Mercury-vx400 (^{1}H at 400.44 MHz and ^{13}C at 100.69 MHz), or Varian 400-MR Auto Tune X5 (^{11}B at 128 MHz) spectrometers. Unless otherwise noted, $CDCl_3$ was used as a solvent. Chemical Shifts were recorded in δ ppm referenced to a residual $CDCl_3$ (δ = 7.26 for ^{1}H , δ = 77.0 for ^{13}C), CD_3CN (δ = 1.94 for ^{1}H, δ = 1.32 for ^{13}C), and $BF_3 \cdot OEt_2$ (δ = 0.00 for ^{11}B). IR measurements were performed by a FTIR SHIMADZU DR-8000 spectrometer fitted with a Pike Technologies MIRacle Single Reflection ATR adapter. High-resolution mass spectra were recorded by a Thermo Scientific Exactive (ESI) spectrometer. Column chromatography was performed with silica gel 60N (Kanto). Preparative thin-layer chromatography (PTLC) was performed on silica gel plates with PF_{254} indicator (Merck).

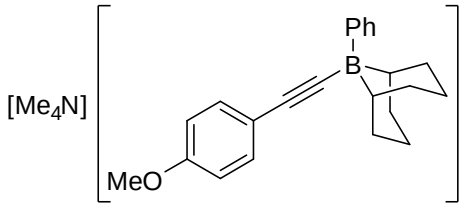
Materials. Unless otherwise noted, all chemicals and anhydrous solvents were obtained from commercial suppliers and used as received. Toluene was dried over Na-benzophenone ketyl. Ar-9-BBN[12], (DPEPhos)[Pd(π-allyl)Cl][13], and alkynylborate[14] were prepared by according to literature procedure.

Preparation of Alkynylborates 1a: A Typical Procedure for the Preparation of Alkynylborates 1a,1b,1d-1f



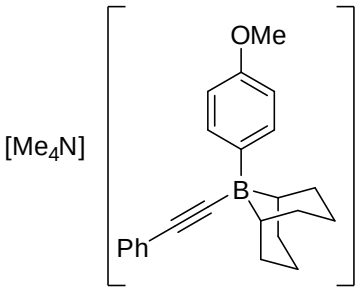
1a

To a stirred solution of *p*-ethynylanisole (1.45 g, 11.0 mmol) in THF (20.0 mL) at -78 ℃ was added *n*-BuLi (1.6 M in hexane, 6.9 mL, 11.0 mmol). After 30 minutes at this temperature, Ph-9-BBN (1.98 g, 10.0 mmol) was added and the cooling bath was removed. After being stirred for 1 h at room temperature, the reaction was quenched by adding a small amount of methanol. Then, volatile materials were removed under reduced pressure. The residue was dissolved in methanol and tetramethylammonium chloride (1.21 g, 11.0 mmol) was added with stirring at room temperature, resulting in white precipitates. It was collected by filtration and washed with cold methanol to give alkynylborate **1a** (2.7 g, 6.7 mmol, 67% yield).



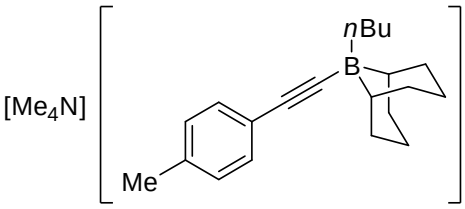
1a

^{1}H NMR (CD_3CN): δ = 1.06 (bs, 2H), 1.16-1.24 (m, 1H), 1.41-2.02 (m, 9H), 2.41-2.54 (m, 2H), 2.96 (s, 12H), 3.72 (s, 3H), 6.68-6.75 (m, 2H), 6.85-6.91 (m, 1H), 7.00-7.12 (m, 4H), 7.43 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (CD_3CN): δ = 25.6-27.2 (m), 27.0, 27.4, 32.2, 35.0, 55.7, 56.0, 95.5, 114.5, 122.7 (2C), 127.3, 132.4, 134.1, 157.8. The boron-bound sp^2 and sp carbons were not detected due to quadrupolar relaxation; ^{11}B NMR (CD_3CN): δ = -17.7; HRMS (FAB-) Calcd for $C_{23}H_{26}BO$ [M-(NMe_4)] 329.2082. Found 329.2079.



1b

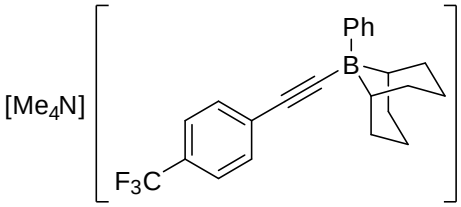
^{1}H NMR (CD_3CN): δ = 1.04 (bs, 2H), 1.14-1.26 (m, 1H), 1.40-2.02 (m, 9H), 2.40-2.53 (m, 2H), 2.95 (s, 12H), 3.74 (s, 3H), 6.66-6.75 (m, 2H), 7.02-7.18 (m, 5H), 7.33 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (CD_3CN): δ = 25.4-27.4 (m), 27.0, 27.3, 32.1, 35.0, 55.4, 56.0, 96.2, 113.0, 125.3, 128.9, 130.2, 131.3, 134.6, 156.5. The boron-bound sp^2 and sp carbons were not detected due to quadrupolar relaxation; ^{11}B NMR (CD_3CN): δ = -18.0: HRMS (ESI-) Calcd for $C_{23}H_{26}BO$ [M-(NMe_4)]$^-$ 329.2082. Found 329.2088.



1d

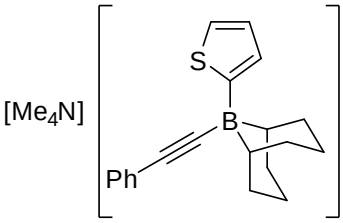
^{1}H NMR (CD_3CN): δ = 0.22 (bs, 2H), 0.36 (bs, 2H), 0.89 (t, *J* = 7.2 Hz, 3H), 1.22-1.34 (m, 4H), 1.36-1.57 (m, 6H), 1.70-1.96 (m, 4H), 2.20-2.34 (m, 5H), 3.04 (s, 12H), 6.97-7.01 (m, 2H), 7.04-7.09 (m, 2H); ^{13}C NMR (CD_3CN); δ = 15.2, 21.2, 27.0, 27.1-29.0 (m), 28.2, 28.8, 31.8, 32.4, 35.7, 56.1, 127.9, 129.6, 131.4, 134.4. The

alkyne carbons and boron-bound sp^3 carbon of *n*-Bu group were not detected due to quadrupolar relaxation; ^{11}B NMR (CD_3CN): δ = -17.8; HRMS (ESI-) Calcd for $C_{21}H_{30}B$ $[M-(NMe_4)]^-$ 293.2446. Found 293.2454.



1e

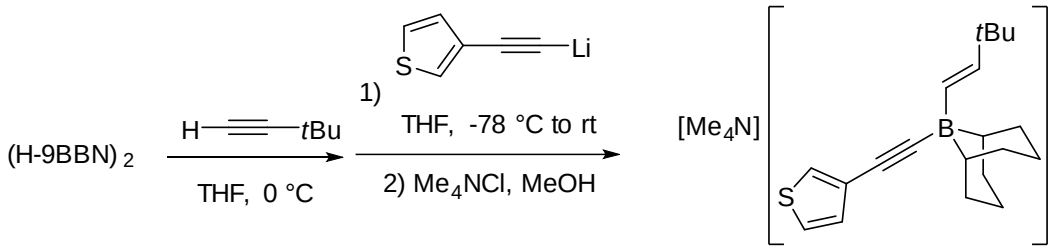
^1H NMR (CD_3CN); δ = 1.15 (bs 2H), 1.21-1.30 (m, 1H), 1.48-2.07 (m, 9H), 2.43-2.55 (m, 2H), 2.92 (s, 12H), 6.90-6.96 (m, 1H), 7.10-7.18 (m, 2H), 7.28 (dd, *J* = 8.8, 0.8 Hz, 2H), 7.44-7.52 (m, 4H); ^{13}C NMR (CD_3CN): δ = 25.2-27.0 (m), 26.9, 27.3, 32.1, 35.1, 56.0, 95.8, 123.0, 125.6 (q, $J_{C\text{-}F}$ = 268.7 Hz), 125.8 (q, $J_{C\text{-}F}$ = 3.7 Hz), 126.2 (q, $J_{C\text{-}F}$ = 31.5 Hz), 127.5, 131.7, 134.2, 134.3. The boron-bound sp^2 and sp carbons were not detected due to quadrupolar relaxation; ^{11}B NMR (CD_3CN): δ = -17.6; HRMS (FAB-) Calcd for $C_{23}H_{23}BF_3$ $[M-(NMe_4)]^-$ 367.1850. Found 367.1849.



1f

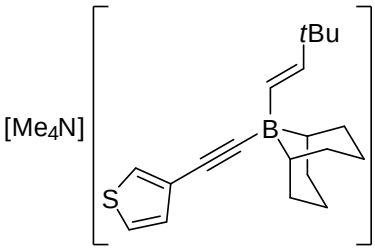
^1H NMR (CD_3CN): δ = 0.90 (bs, 2H), 1.20-1.30 (m, 1H), 1.43-1.67 (m, 4H), 1.73-1.98 (m, 5H), 2.38-2.50 (m, 2H), 3.04 (s, 12H), 6.79 (dd, *J* = 8.8, 0.8 Hz, 1H), 6.91 (dd, *J* = 4.8, 3.2 Hz, 1H), 7.03-7.19 (m, 6H); ^{13}C NMR (CD_3CN): δ = 26.6, 27.2, 27.0-28.6 (m), 32.3, 34.8, 56.0, 96.2, 123.1, 125.6, 126.6, 127.4, 129.0, 130.0, 131.4. The boron-bound sp^2 and sp^3 carbons were not detected due to quadrupolar relaxation; ^{11}B NMR (CD_3CN): δ = -18.1; HRMS (ESI^-) Calcd for $C_{20}H_{22}BS$ $[M-(NMe_4)]^-$ 305.1541. Found 305.1541.

Preparation of Alkynylborates 1c.



1c

Under an argon atmosphere, a solution of 3,3-dimethyl-1-butyne (0.84 g, 10 mmol) in THF (15 mL) was added to $(H\text{-}9\text{-}BBN)_2$ (1.22 g, 5.0 mmol), and then the mixture was stirred for 1 h at room temperature. In another flask, *n*BuLi (1.56 M in hexane, 7.3 mL, 11.4 mmol) was added dropwise to a solution of 4-phenylbut-1-yne (1.30 g, 10.0 mmol) in THF (15 mL) at -78 ℃. After stirred for 30 minutes at this temperature, the two solutions were combined and then the cooling bath was removed. After being stirred for 1 h at room temperature, the reaction was quenched by adding a small amount of methanol. Then, volatile materials were removed under reduced pressure. The residue was dissolved in methanol and tetramethylammonium chloride (1.21 g, 11.0 mmol) was added with stirring at room temperature. After being concentrated under reduced pressure, the residue was dissolved in methanol again and stirred at -78℃, resulting in white precipitates. It was collected by filtration and washed with cold methanol to give alkynylborate **1c** (760 mg, 2.0 mmol, 20 % yield).

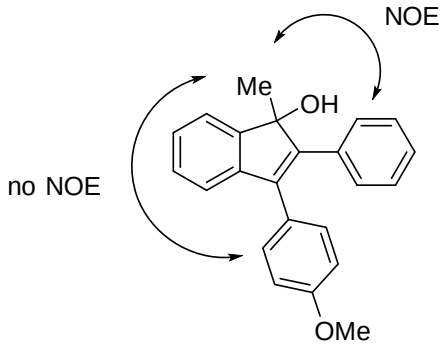


1c

^{1}H NMR (CD_3CN): δ= 0.38 (bs, 2H), 0.96 (s, 9H), 1.36-1.56 (m, 6H), 1.73-2.04 (m, 4H), 2.22-2.35 (m, 2H), 3.06 (s, 12H), 5.52 (d, *J* = 17.2 Hz, 1H), 5.91 (d, *J* = 17.6 Hz, 1H), 6.91 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.98 (dd, *J* = 2.8, 1.2 Hz, 1H), 7.22 (dd, *J* = 2.8, 5.0 Hz, 1H); ^{13}C NMR (CD_3CN): δ = 27.3, 27.6, 27.8-29.6 (m), 31.1, 32.7, 34.1, 35.2, 56.1, 90.8, 122.8, 125.1, 129.8, 131.4, 141.1. The boron-bound sp^2 and sp carbons were not detected due to quadrupolar relaxation; ^{11}B NMR (CD_3CN): δ= -18.1; HRMS (ESI$^-$) Calcd for $C_{20}H_{28}BS$ $[M\text{-}(NMe_4)]^-$ 311.2010. Found 311.2016.

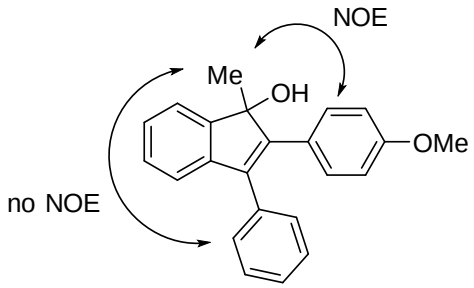
Palladium/DPEPhos-Catalyzed Reaction of Alkynylborate 1a with *o*-Iodoacetophenone (2a)

Under an argon atmosphere, a toluene solution (1.0 mL) of alkynylborate **1a** (80.68 mg, 0.20 mmol), dpephos)PdCl(π-allyl) (1.44 mg, 0.002 mmol), and *o*-iodoacetophenone (**2a**) was stirred for 1 h at 50 ℃. To the reaction mixture were added aqueous H_2O_2 (0.5 mL, 30 wt%), aqueous NaOH (0.5 mL, 20 wt%), and MeOH (0.5 mL) at 0 ℃. After being stirred for 2 h at room temperature, the resulting mixture was diluted with water and extracted with ethyl acetate (3×15 mL). The combined organic layers were washed by brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 5/1) to afford the indenol **3a** (55.9 mg, 0.17 mmol, 85% yield).



3a

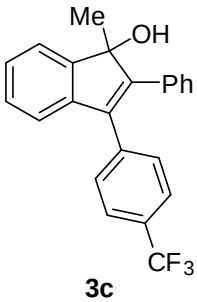
IR (ATR): 3315, 1508, 1248, 752, 694 cm^{-1}; ^1H NMR: δ = 1.59 (s, 3H), 2.04 (bs, 1H), 3.82 (s, 3H), 6.84-6.90 (m, 2H), 7.21-7.30 (m, 8H), 7.42-7.48 (m, 2H), 7.51-7.55 (m, 1H); ^{13}C NMR: δ = 23.9, 55.2, 83.2, 113.9, 120.8, 121.8, 126.5, 126.8, 127.2, 128.0, 128.4, 129.4, 130.5, 135.0, 138.2, 142.3, 146.2, 149.6, 158.9; HRMS (ESI^+) Calcd for $C_{23}H_{21}O_2$ $[M+H]^+$ 329.1536. Found 329.1556.



3b

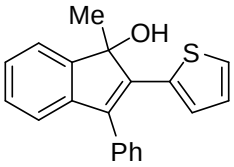
IR (ATR): 3319, 1508, 1248, 760, 702 cm^{-1}; ^1H NMR: δ = 1.60 (s, 3H), 2.08 (s, 1H), 3.78 (s, 3H), 6.74-6.80 (m, 2H), 7.18-7.23(m, 1H), 7.24-7.44 (m, 9H), 7.50-7.55 (m, 1H); ^{13}C NMR: δ = 24.1, 55.1, 83.3, 113.4, 120.5, 121.8, 126.3, 127.0, 127.4, 128.4, 128.6, 129.3, 130.6, 135.0, 137.6, 142.3, 146.4, 149.5, 158.7; HRMS (ESI^-) Calcd for

$C_{23}H_{20}O_2Cl$ $[M+Cl]^-$ 363.1146. Found 363.1148.



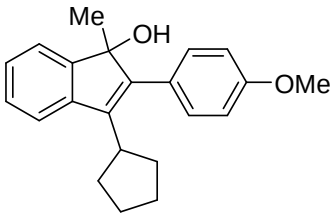
3c

IR (ATR); 3298, 1319, 1121, 750, 696 cm^{-1}; ^1H NMR: δ = 1.60 (s, 3H), 2.10 (bs, 1H), 7.16-7.22 (m, 1H), 7.23-7.32 (m, 5H), 7.37-7.47 (m, 4H), 7.52-7.64 (m, 3H); ^{13}C NMR: δ = 24.0, 83.3, 120.5, 122.1, 124.1 (q, J_{C-F} = 270.1 Hz), 125.5 (q, J_{C-F} = 3.7 Hz), 126.9, 127.7, 128.2, 128.6, 129.3, 129.5 (q, J_{C-F} = 32.2 Hz), 129.6, 134.1, 137.3, 138.5, 141.4, 148.5, 149.3; HRMS ($APCI^-$) Calcd for $C_{23}H_{16}F_3O$ $[M-H]^-$ 365.1159. Found 365.1159.



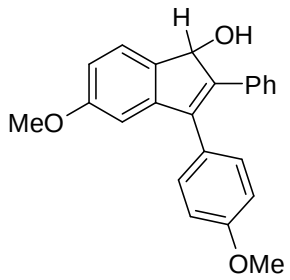
3d

IR (ATR): 3319, 1350, 1088, 752, 694 cm^{-1}; ^1H NMR: δ = 1.77 (s, 3H), 2.09 (bs, 1H), 6.96-7.02 (m, 2H), 7.18 (dd, *J* = 5.2 Hz, 1.2Hz, 1H), 7.23-7.30 (m, 2H), 7.35-7.40 (m, 3H), 7.42-7.52 (m, 3H), 7.53-7.58 (m, 1H); ^{13}C NMR: δ = 25.4, 83.3, 120.7, 121.6, 125.9, 126.5, 126.6, 127.5, 128.2, 128.7, 129.0, 129.4, 134.7, 136.0, 137.4, 141.0, 142.6, 149.3; HRMS (ESI^+) Calcd for $C_{20}H_{17}OS$ $[M+H]^+$ 305.0995. Found 305.0992.



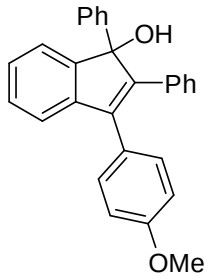
3e

IR (ATR): 3310, 1508, 1244, 1034, 758 cm^{-1}; ^1H NMR: δ = 1.44 (s, 3H), 1.58-2.02 (m, 9H), 3.07 (quintet, *J* = 8.8 Hz, 1H), 3.85 (s, 3H), 6.96 (d, *J* = 8.8 Hz, 2H), 7.18-7.38 (m, 5H), 7.47 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR: δ = 23.8, 26.6, 26.7, 30.5, 31.1, 38.2, 55.2, 82.2, 113.6, 121.1, 121.9, 125.7, 127.89, 127.93, 130.4, 140.6, 140.9, 146.7, 149.9, 158.8; HRMS (ESI^+) Calcd for $C_{22}H_{28}O_2N$ $[M+NH_4]^+$ 338.2115. Found 338.2104.



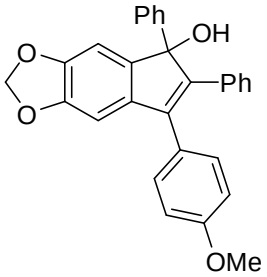
3f

IR (ATR): 3472, 1601, 1508, 1244, 704 cm^{-1}; ^{1}H NMR: δ = 1.74 (d, *J* = 8.8 Hz, 1H), 3.79 (s, 3H), 3.86 (s, 3H), 5.63 (d, *J* = 8.4 Hz, 1H), 6.74 (d, *J* = 2.4 Hz, 1H), 6.79 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H), 6.92-6.97 (m, 2H), 7.18-7.30 (m, 5H), 7.32-7.36 (m, 2H), 7.53 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR: δ = 55.2, 55.5, 76.6, 107.2, 110.9, 114.3, 124.4, 126.7, 127.2, 128.3, 129.2, 130.3, 134.2, 136.3, 139.0, 144.5, 145.7, 159.2, 160.6; HRMS (ESI^{+}) Calcd for $C_{23}H_{21}O_3$ $[M+H]^{+}$ 345.1485. Found 345.1484.



3g

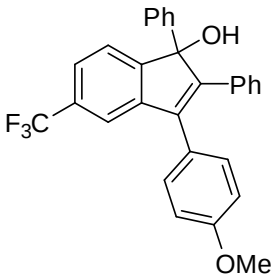
IR (ATR): 3422, 1508, 1244, 1028, 746, 698 cm^{-1}; ^{1}H NMR: δ = 2.48 (s, 1H), 3.85 (s, 3H), 6.95 (d, *J* = 8.8 Hz, 2H), 7.04-7.14 (m, 5H), 7.15-7.32 (m, 7H), 7.36-7.40 (m, 2H) 7.55 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR: δ = 55.2, 86.8, 114.1, 121.0, 123.1, 125.0, 126.8, 126.98, 127.02, 127.1, 127.8, 128.36, 128.44, 129.4, 130.4, 134.0, 140.2, 141.7, 142.7, 146.6, 150.8, 159.1; HRMS (ESI^{+}) Calcd for $C_{28}H_{23}O_2$ $[M+H]^{+}$ 391.1693. Found 391.1718.



3h

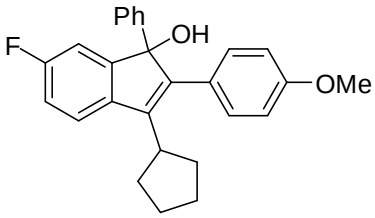
IR (ATR): 3362, 1470, 1244, 1034, 696 cm^{-1}; ^{1}H NMR: δ = 2.39 (s, 1H), 3.85 (s, 3H), 5.91 (dd, *J* = 16.4, 1.6 Hz, 2H), 6.73 (d, *J* = 4.4 Hz, 2H), 6.90-6.96 (m, 2H), 7.02-7.08 (m, 5H), 7.20-7.36 (m, 5H), 7.49-7.54 (m, 2H); ^{13}C NMR: δ = 55.2, 86.3, 101.2, 102.4,

104.9, 114.2, 124.9, 126.90, 126.92, 127.0, 127.8, 128.5, 129.2, 130.4, 134.0, 136.7, 139.8, 142.0, 145.0, 145.8, 146.9, 147.8, 159.2; HRMS (EI^+) Calcd for $C_{29}H_{22}O_4$ $[M]^+$ 434.1518. Found 434.1505.



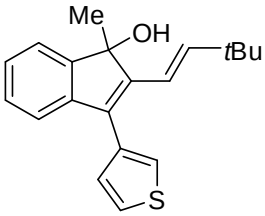
3i

IR (ATR): 3545, 1508, 1321, 1115, 696 cm^{-1}; ^1H NMR: δ = 2.49 (s, 1H), 3.87 (s, 3H), 6.94-7.00 (m, 2H), 7.04-7.15 (m, 5H), 7.23-7.38 (m, 6H), 7.42-7.55 (m, 4H); ^{13}C NMR: δ = 55.3, 86.6, 114.5, 117.7 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.3, 124.1 (q, $J_{C\text{-}F}$ = 3.6 Hz), 124.2 (q, $J_{C\text{-}F}$ = 270.2 Hz), 124.9, 126.0, 127.5, 127.6, 128.0, 128.7, 129.5, 130.4, 130.8 (q, $J_{C\text{-}F}$ = 32.3 Hz), 133.4, 139.3, 140.7, 143.7, 148.1, 154.2, 159.5; HRMS ($APCI^-$) Calcd for $C_{29}H_{21}F_3O_2Cl$ $[M+Cl]^-$ 493.1177. Found 493.1192.



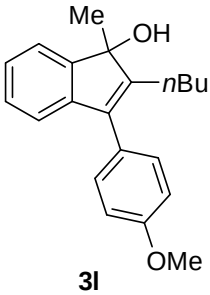
3j

IR (ATR): 3356, 1242, 1028, 741, 696 cm^{-1}; ^1H NMR: δ = 1.64-1.78 (m, 2H), 1.83-2.08 (m, 7H), 3.16 (quintet, J = 8.4 Hz, 1H), 3.76 (s, 3H), 6.75-6.80 (m, 2H), 6.86-6.98 (m, 4H), 7.19-7.37 (m, 6H); ^{13}C NMR: δ = 26.75, 26.81, 30.8, 31.0, 38.3, 55.1, 86.2, 111.4 (d, $J_{C\text{-}F}$ = 23.3 Hz), 113.6, 114.3 (d, $J_{C\text{-}F}$ = 21.8 Hz), 122.0 (d, $J_{C\text{-}F}$ = 8.0 Hz), 125.2, 126.8, 127.1, 128.3, 130.3, 137.1 (d, $J_{C\text{-}F}$ = 2.9 Hz), 141.0, 141.8 (d, $J_{C\text{-}F}$ = 1.5 Hz), 147.4 (d, $J_{C\text{-}F}$ = 4.3 Hz), 153.8 (d, $J_{C\text{-}F}$ = 7.3 Hz), 158.9, 161.9 (d, $J_{C\text{-}F}$ = 244.3 Hz); HRMS (EI^+) Calcd for $C_{27}H_{25}OF_2$ $[M]^+$ 400.1839. Found 400.1835.



3k

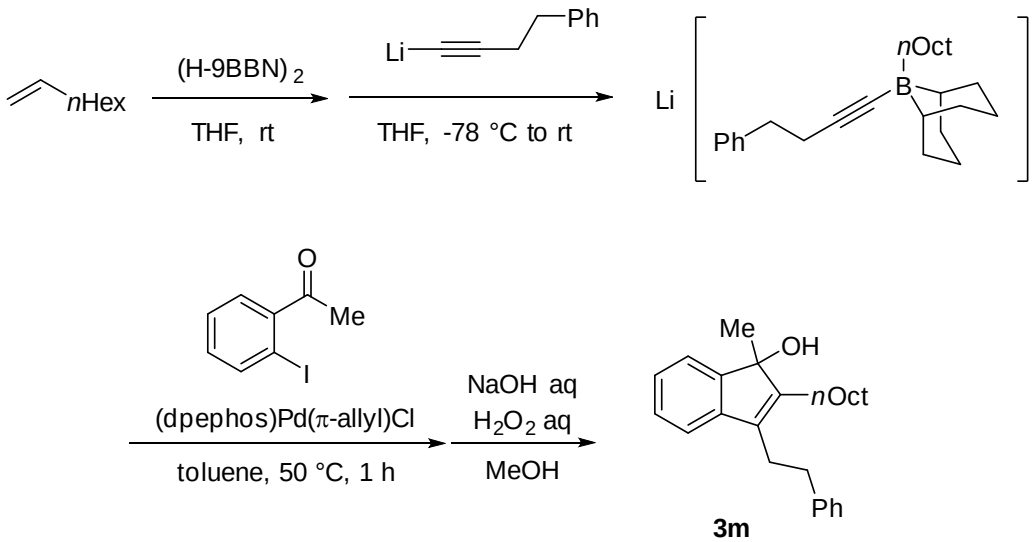
IR (ATR): 3298, 1358, 1078, 756, 689 cm^{-1}; ^{1}H NMR: δ = 1.11 (s, 9H), 1.68 (s, 3H), 1.88 (s, 1H), 6.40 (d, *J* = 16.4 Hz, 1H), 6.56 (d, *J* = 16.4 Hz, 1H), 7.18-7.30 (m, 4H), 7.39-7.51 (m, 3H); ^{13}C NMR: δ = 25.7, 29.5, 34.0, 82.2, 116.9, 120.4, 121.5, 124.2, 125.5, 126.2, 128.3, 128.5, 132.4, 134.6, 141.5, 145.2, 146.2, 150.6; HRMS (ESI^{+}) Calcd for $C_{20}H_{23}OS$ $[M+H]^{+}$ 311.1464. Found 311.1464.



3l

IR (ATR): 3335, 1508, 1084, 918, 758 cm^{-1}; ^{1}H NMR: δ = 0.85 (t, *J* = 7.2 Hz, 3H), 1.30 (tt, *J* = 7.2, 7.2 Hz, 2H), 1.41-1.67 (m, 6H), 2.29-2.50 (m, 5H), 7.02-7.06 (m, 1H), 7.16-7.28 (m, 6H), 7.44-7.48 (m, 1H); ^{13}C NMR: δ = 13.8, 21.3, 23.2, 23.7, 25.2, 31.4, 82.9, 119.8, 121.5, 125.6, 128.2, 128.6, 129.1, 131.8, 137.0, 137.4, 143.0, 149.2, 149.6; HRMS ($APCI^{+}$) Calcd for $C_{21}H_{25}O$ $[M+H]^{+}$ 293.1900. Found 293.1890.

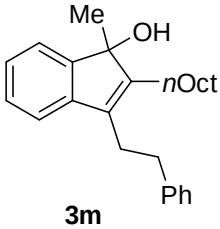
The Synthesis of 2,3-Dialkylsubstituted Indenol 3m from 1-Octene, 4-Phenyl-1-butyne, and *o*-Iodoacetophenone (2a)



3m

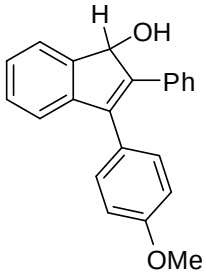
Under an nitrogen atmosphere, a solution of 1-octene (145.9 mg, 1.30 mmol) in THF (2.0 mL) was added to $(H\text{-}9\text{-}BBN)_2$ (158.6 mg, 0.65 mmol), and then the mixture was stirred for 1 h at room temperature. In another flask, *n*-BuLi (0.69 mL, 1.6 M in hexane,

1.10 mmol) was added dropwise to a solution of 4-phenylbut-1-yne (143.2 mg, 1.10 mmol) in THF (2 mL) at -78 ℃. After stirred for 30 minutes at this temperature, the two solutions were combined and then the cooling bath was removed. After being stirred for 1 h at room temperature, (dpephos)PdCl(π-allyl) (7.21 mg, 0.010 mmol) and a solution of o-iodoacetophenone (246.1 mg, 1.00 mmol) in toluene (2 mL) were added. The reaction mixture was stirred for 1 h at 50 ℃. To the mixture were added aqueous H_2O_2 (1 mL, 30 wt%), aqueous NaOH (1 mL, 20 wt%), and MeOH (1 mL) at 0 ℃. After being stirred for 2 h at room temperature, the resulting mixture was quenched by adding water and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed by brine, dreid over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 10/1) to afford the indenol **3m** (332.3 mg, 0.92 mmol, 92% yield).



3m

IR (ATR): 3335, 1456, 1078, 752, 698 cm^{-1}; ^1H NMR: δ = 0.96 (t, *J* = 6.8 Hz, 3H), 1.29-1.56 (m, 15H), 1.60 (s, 1H), 2.08-2.27 (m, 2H), 2.74-2.81 (m, 2H), 2.87-2.94 (m, 2H), 7.19-7.28 (m, 5H), 7.29-7.36 (m, 3H), 7.42 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR: δ = 14.1, 22.6, 23.4, 24.7, 27.7, 29.3, 29.4, 29.5, 30.4, 31.9, 34.5, 82.5, 118.6, 121.3, 125.2, 126.0, 128.2, 128.3, 128.4, 135.1, 141.7, 142.5, 148.9, 149.4; HRMS (EI^+) Calcd for $C_{26}H_{34}O_4$ $[M]^+$ 362.2610. Found 362.2619.

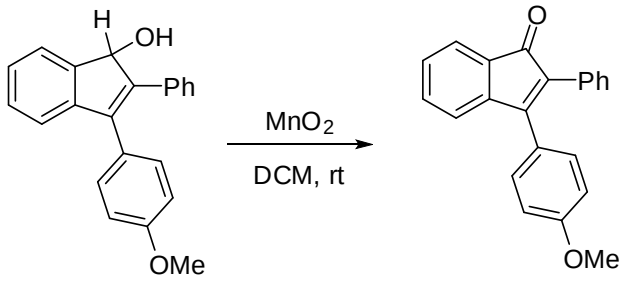


3n

IR (ATR): 3354, 1508, 1246, 764, 692 cm^{-1}; ^1H NMR: δ = 1.85 (bs, 1H), 3.86 (s, 3H), 5.67 (s, 1H), 6.92-6.97 (m, 2H), 7.18-7.38 (m, 10H), 7.63-7.66 (m, 1H); ^{13}C NMR: δ = 55.2, 77.3, 114.3, 120.6, 123.7, 126.3, 126.8, 127.2, 128.3, 128.7, 129.2, 130.3, 134.2, 139.3, 143.2, 144.0, 144.3, 159.2; HRMS ($APCI^-$) Calcd for $C_{22}H_{17}O_2$ $[M-H]^-$ 313.1234. Found 313.1237.

The ^{1}H, ^{13}C NMR and HRMS spectra were agreed with the reported value.[15]

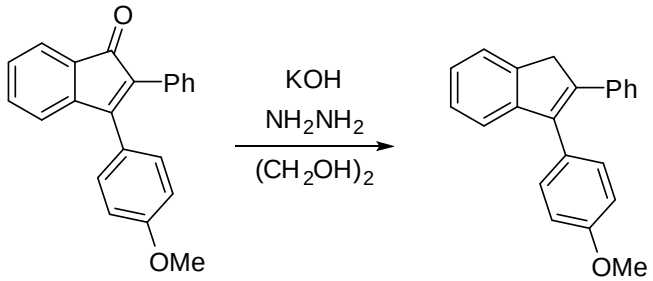
Synthesis of indenone 4 and indene 5



3n **4**

MnO_2 (170 mg, 2 mmol) was dried under vacuum for 5 h at 120 ℃. Under an argon atomosphere, the solution of indenol **3n** (31.4 mg, 0.1 mmol) was added at room temperature. After being stirred for 3 h, the reaction mixture was filtered through a pad of celite, and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 10/1) to afford the indenone **4** (29.9 mg, 0.096 mmol, 96% yield).

The ^{1}H, ^{13}C NMR spectra were agreed with the reported value.[16]



4 **5**

Under an argon atomosphere, an ethylene glycol solution (1 mL) of indenone **4** (31.2 mg, 0.1 mmol), hydrazine (0.4 mL), and 2N KOH aq (10 μL, 0.02 mmol) was stirred for 5 h at 150 ℃, and water was added. The aqueous layer was extracted with AcOEt (3 times), washed with water (once), brine (once), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 4/1) to afford the indene **5** (17.6 mg, 0.059 mmol, 59% yield).

The ^{1}H, ^{13}C NMR spectra were agreed with the reported value.[5]

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List of Publication

Chapter 1.

Solar-Driven Incorporation of Carbon Dioxide into α-Amino Ketones
Naoki Ishida, Yasuhiro Shimamoto, and Masahiro Murakami
Angew. Chem. Int. Ed., **2012**, *51*, 11750-11752

Chapter 2.

1,5-Rhodium Shift in Rearrangement of *N*-Arenesulfonylazetidin-3-ols into Benzosultams
Naoki Ishida, Yasuhiro Shimamoto, Takaaki Yano, Masahiro Murakami
J. Am. Chem. Soc., **2013**, *135*, 19103-19106

Chapter 3.

Stereoselective Synthesis of (*E*)-(Trisubstituted alkenyl)borinic Esters: Stereochemistry Reversed by Ligand in the Palladium-Catalyzed Reaction of Alkynylborates with Aryl Halides
Naoki Ishida, Yasuhiro Shimamoto, and Masahiro Murakami
Org. Lett., **2009**, *11*, 5434-5437

Chapter 4.

Iterative Approach to Oligo(arylenevinylene)s Containing Tetrasubstituted Vinylene Units
Naoki Ishida, Yasuhiro Shimamoto, and Masahiro Murakami
Org. Lett., **2010**, *12*, 3179-3181

Chapter 5.

Regioselective Construction of Indene Skeletons by Palladium-Catalyzed Annulation of Alkynylborates with *o*-Iodophenyl Ketones
Yasuhiro Shimamoto, Hanako Sunaba, Naoki Ishida, and Masahiro Murakami
Eur. J. Org. Chem., **2013**, 1421-1424

Other Publication

Construction of Indole Skeletons by Sequential Actions of Sunlight and Rhodium on α-Amino Acetophenones
Naoki Ishida, David Nečas, Yasuhiro Shimamoto, and Masahiro Murakami
Chem. Lett., **2013**, *42*, 1076