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Cobalt-Catalyzed Carbon-Carbon Bond Formation: Synthesis and Applications of Enantiopure Pyrrolidine Derivatives[1]

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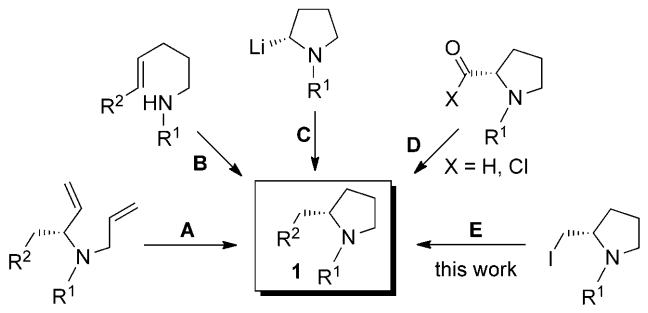
Abstract: In the presence of cobalt catalysts and tetramethylethylenediamine (TMEDA), the iodine atom in (*S*)-2-(iodomethyl)pyrrolidines was replaced by an aryl or an alkynyl group from the corresponding Grignard reagent, and the coupling products were obtained in good to excellent yields (16 examples; 75–94% yields). The scope and limitations of this protocol were examined. The stereochemistry of the pyrrolidines was unaffected by the reaction conditions. The coupling products are important building blocks of phenanthroindolizidine alkaloids. Palladium-catalyzed formal [4+2] cycloaddition of 2,2′-diiodobiphenyl with the thus-generated (*S*)-2-(3-trimethylsilyl-2-propynyl)pyrrolidine gave a good yield of the desilylated phenanthrene, which was then converted into unnatural (+)-(*S*)-tylophorine by the Pictet–Spengler cyclization.

Keywords: cobalt; palladium; phenanthrenes; pyrrolidines; tylophorine

Introduction

Enantiopure pyrrolidines **1**, an important class of compounds, and derivatives thereof are used as chiral ligands[2] and auxiliaries,[3] as well as chiral organocatalysts.[2a,c,4] Moreover, they are indispensable building blocks for bioactive molecules[5] and natural products, such as indolizidine[6] and securinega[7] alkaloids. The 2-substituted pyrrolidines **1** can be synthesized using the methods summarized in Scheme 1.[8,9] Cyclization of chiral amines gives highly enantiopure compounds **1**,[10] but the procedure for preparing their chiral precursors is highly complex (route A). Alternatively, **1** is easily accessible by either the metal-catalyzed enantioselective intramolecular hydroamination of alkenes (route B)[11] or by asymmetric functionalization of 2-lithiated pyrrolidines (route C).[12] To the best of our knowledge, routes B and C generally do not exhibit very high stereoselectivity, and the enantiomeric excess (*ee*) values of the products depend on the substituents. As alternative to the above synthetic methods, a low-cost enantiopure amino acid such as L-proline would be an ideal starting material for furnishing chiral **1**. Indeed, reactive (*S*)-2-formylpyrrolidine or its acid chloride derivative can also produce **1**, but more synthetic steps are required (route D).[13] The simple 2-(halomethyl)pyrrolidines are inert to common carbonide nucleophilies,[14,15] and they cannot be converted into the organometallic reagents needed for further carbon-carbon bond formation.[16] These inconveniences caused some synthetic plans to be changed or modified.[15] Although some 2-(halomethyl)pyrrolidine derivatives furnish the desired products **1** on reaction with stoichiometric amounts of organocopper reagents,[17] this reaction is not atom-economical,[18] and reaction by-products must be separated by HPLC.[17c] Therefore, a practical protocol for generating **1** directly from 2-(halomethyl)pyrrolidines



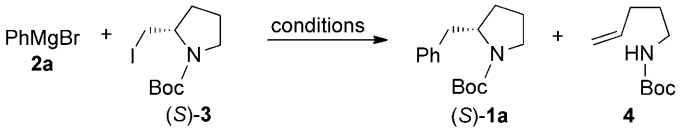
Scheme 1. Synthesis of enantiopure 2-substituted pyrrolidines **1**.

is needed. Fortunately, cobalt/iron-catalyzed coupling reactions of alkyl halides with Grignard reagents or organozinc species have proven useful in carbon-carbon bond formation.[19] Employing this method, we recently observed that enantiopure **1** can be directly generated from (*S*)-2-(iodomethyl)pyrrolidines in the presence of cobalt catalysts (route E). This study investigated the scope and limitations of this protocol, and the coupling product was used for preparing a bioactive molecule. Reactions of (*S*)-2-(iodomethyl)-pyrrolidines with aryl reagents were intensively explored because 2-(arylmethyl)pyrrolidines are important precursors for synthesizing phenanthroindolizidine alkaloids.

Results and Discussion

The starting material (*S*)-2-(iodomethyl)pyrrolidine (*S*)-**3** was obtained from Boc-L-proline by simple reduction and iodination.[20] Treating compound (*S*)-**3** with phenylmagnesium bromide (**2a**) gave an unsatisfactory yield of the desired product (*S*)-**1a** and furnished substantial amounts of by-product **4** (entry 1 in Table 1). Accordingly, the reaction conditions were systematically investigated by screening of numerous cobalt complexes, additives and reaction temperatures. The previous studies reported by Oshima[19g] and Cahiez[19a] provided very useful information. Cobalt complexes significantly improved the coupling reactions, and catalysts $Co(PPh_3)_2Cl_2$ and $Co(acac)_3$ (acac = acetylacetone) proved superior to $Co(OAc)_2$ and $Co(PPh_3)_3Cl$ (entries 3, 4, 6 and 12 in Table 1). Moreover, catalysis with $Co(PPh_3)_2Cl_2$ was slightly better than that with $Co(acac)_3$ because complete consumption of (*S*)-**3** gave a higher yield of (*S*)-**1a**. *N,N*-Tetramethylethylenediamine (TMEDA) was crucial in this reaction (entries 10–12 and 15 in Table 1). A small quantity of TMEDA (5 mol%) was sufficient for catalysis. When TMEDA was used as the solvent, neither (*S*)-**1a** nor **4** were obtained. In large quantities of TMEDA (11 equiv.) or in the absence of TMEDA, some (*S*)-**3** remained, and the amount of **4** increased. The reaction at either room temperature (*ca.* 25 °C) or at 40 °C was preferable to running the reaction at 0 °C. Under optimal conditions, the desired product (*S*)-**1a** was isolated in 84% yield (entry 12 in Table 1). Notably, phenylmagnesium bromide (**2a**) generated from a mixture of phenyllithium and $MgBr_2{\cdot}(THF)_n$ (ratio 1:1) caused the coupling reaction to become in-

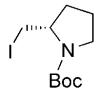
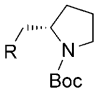
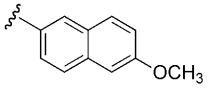
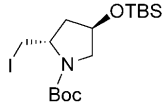
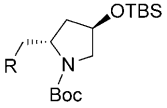
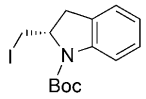
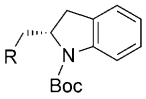
Table 1. Optimization of reaction conditions for the preparation of (*S*)-**1a**.[a]



Entry	Catalyst (mol%)	TMEDA (mol%)	Reagent (equiv.)	*T* [°C]	Conversion of **3** [%]	Ratio (**1a**:**3**:**4**:others)
1	–	–	PhMgBr (1.5)	25	53	15:47:15:23
2	–	neat	PhMgBr (1.5)	25	0	0:100:0:0
3	$Co(OAc)_2$ (5)	1100	PhMgBr (1.5)	25	100	69:0:29:2
4	$Co(acac)_3$ (5)	1100	PhMgBr (1.5)	25	93	76:7:15:2
5	$Co(acac)_3$ (5)	5	PhMgBr (1.3)	25	93	88:7:4:1
6	$CoCl(PPh_3)_3$ (10)	1100	PhMgBr (1.5)	25	90	79:10:9:2
7	$CoCl_2(PPh_3)_2$ (10)	1100	PhMgBr (1.5)	25	100	86:0:13:1
8	$CoCl_2(PPh_3)_2$ (10)	1100	PhMgBr (1.5)	0	100	64:0:36:0
9	$CoCl_2(PPh_3)_2$ (10)	1100	PhMgBr (1.5)	40	100	87:0:12:1
10	$CoCl_2(PPh_3)_2$ (5)	1100	PhMgBr (1.5)	25	100	76:0:22:2
11	$CoCl_2(PPh_3)_2$ (5)	250	PhMgBr (1.3)	25	100	90:0:9:1
12	$CoCl_2(PPh_3)_2$ (5)	5	PhMgBr (1.3)	25	100	92:0:7:1[b]
13	$CoCl_2(PPh_3)_2$ (5)	5	PhMgBr[c] (1.5)	25	55	53:45:1:1
14	$CoCl_2(PPh_3)_2$ (5)	5	PhMgBr[c] (1.5 + 0.5[d])	25	79	76:21:2:1
15	$CoCl_2(PPh_3)_2$ (5)	5	$ZnPh_2$[e] (1.3)	25	95	45:5:50:0
16	$CoCl_2(PPh_3)_2$ (5)	10	$ZnPh_2$[e] (1.3)	25	99	84:1:12:3[f]
17	$CoCl_2(PPh_3)_2$ (5)	–	PhMgBr (1.3)	25	86	68:14:15:3

[a] The reaction was conducted with (*S*)-**3** (0.50 mmol) in THF for 1 h if no otherwise specified. The ratio of product distribution was analyzed by GC MS. *Others* refer to unknown compounds containing a fragment of pyrrolidine.
[b] Product (*S*)-**1a** was isolated in 84% yield.
[c] **2a** was generated from PhLi and $MgBr_2{\cdot}(THF)_n$ (ratio 1:1, 1.5 equiv.).
[d] Additional **2a** (0.5 equiv.) was added into the reaction mixture after 50 min.
[e] Reaction was conducted with $ZnPh_2$, which was generated from the mixture of **2a** and $ZnBr_2$ (ratio 2:1), for 16 h.
[f] Product (*S*)-**1a** was isolated in 73% yield.

Table 2. Synthesis of pyrrolidine derivatives.[a]

Entry	Pyrrolidine	Grignard Reagent	R	Time	Product	Isolated Yield (%)
						
1	(−)-(*S*)-**3**[b]	**2a**	Ph	1 h	(+)-(*S*)-**1a**[c]	84
2	(−)-(*S*)-**3**[b]	**2b**	2-CH_3-C_6H_4[d]	1 h	(+)-(*S*)-**1b**[c]	93
3	(−)-(*S*)-**3**[b]	**2c**	4-F-C_6H_4	50 min	(−)-(*S*)-**1c**[c]	84
4	(−)-(*S*)-**3**[b]	**2d**	3-OCH_3-C_6H_4	50 min	(+)-(*S*)-**1d**[c]	89
5	(−)-(*S*)-**3**[b]	**2e**	3,5-$(OCH_3)_2$-C_6H_3	50 min	(+)-(*S*)-**1e**[c]	78
6	(−)-(*S*)-**3**[b]	**2f**	1-naphthyl	1 h	(+)-(*S*)-**1f**[c]	94
7	(−)-(*S*)-**3**[b]	**2 g**	2-naphthyl	40 min	(+)-(*S*)-**1g**[b]	78
8	(−)-(*S*)-**3**[b]	**2 h**		40 min	(+)-(*S*)-**1h**[c]	85
9	(−)-(*S*)-**3**[b]	**2i**	9-phenanthrenyl	30 min	(+)-(*S*)-**1i**[b,e]	92
10	(*R*/*S*)-**3**[b]	**2i**	9-phenanthrenyl	30 min	(*R*/*S*)-**1i**[b]	87
11	(−)-(*S*)-**3**[b]	**2j**	2-thiophenyl	16 h	(−)-(*S*)-**1j**[b]	61[f]
12	(−)-(*S*)-**3**[b]	**2k**	2-pyridinyl	16 h	(*S*)-**1k**	trace
						
13	(−)-(2*S*,4*R*)-**5**[b]	**2b**	2-CH_3-C_6H_4	40 min	(+)-(2*S*,4*R*)-**6b**[b]	93
14	(−)-(2*S*,4*R*)-**5**[b]	**2d**	3-OCH_3-C_6H_4	40 min	(−)-(2*S*,4*R*)-**6d**[b,e]	81
						
15	(−)-(*S*)-**7**[c]	**2c**	4-F-C_6H_4	40 min	(−)-(*R*)-**8c**[c]	92
16	(−)-(*S*)-**7**[c]	**2d**	3-OCH_3-C_6H_4	40 min	(−)-(*R*)-**8d**[c]	75
17	(−)-(*S*)-**7**[c]	**2f**	1-naphthyl	40 min	(+)-(*R*)-**8f**[c]	90

[a] Reactions were conducted with pyrrolidines (0.50 mmol), Grignard reagents **2** (RMgBr, 1.3 equiv.), $CoCl_2(PPh_3)_2$ (5 mol%) and TMEDA (5 mol%) in THF at room temperature unless otherwise specified.
[b] Two diastereomers were determined according to the ^{13}C NMR analysis.
[c] Single diastereomer was determined according to the ^{13}C NMR analysis.
[d] Reaction was conducted with 2-tolylmagnesium chloride.
[e] The compound can be converted into a single-diastereomer form when its $CDCl_3$ solution was immersed in a water bath (around 50 °C) for 4 h.
[f] Reaction was conducted with **2j** (4 equiv.).

efficient (entries 13 and 14 in Table 1). Diphenylzinc seemed to be less reactive than **2a** because it produced larger quantities of **4**. Although this limitation could be minimized by increasing the amount of TMEDA (10 mol%), (*S*)-**1a** was then obtained in only 73% yield (entries 15 and 16 in Table 1).

Tests of the reactivity of several Grignard reagents with (*S*)-2-(iodomethyl)pyrrolidine (*S*)-**3** under the optimal conditions herein generated most coupling products in good to excellent yields (Table 2). Both electron-rich and electron-deficient phenyl derivatives were efficiently attached to the pyrrolidine core. The yield was not decreased by sterically congested 2-tolyl, 1-naphthyl or 9-phenanthryl groups (entries 2, 6 and 10 in Table 2). Apparently, heteroaryl-Grignard reagents were less reactive compared to aryl reagents. The 2-thiophenyl reagent furnished **1k** in moderate yield; 2-pyridinylmagnesium bromide did not produce the desired coupling product (entries 11 and 12 in Table 2). Like (*S*)-**3**, other pyrrolidine derivatives, such as 3-silyloxypyrrolidine (*S*)-**5** and 2,3-dihydroindole (*S*)-**7**,[21] also gave satisfactory results (entries 13–17 in Table 2). Notably, coupling product (*R*/*S*)-**1i** was prepared from (*R*/*S*)-**3** for comparison of its optical properties with those of (*S*)-**1i**.

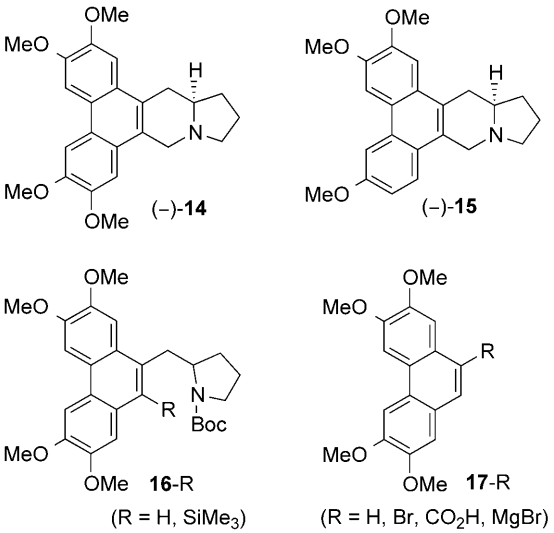
As expected, the coupling products maintained the same stereochemistry as observed in their starting materials. Chiral HPLC chromatograms and specific rotations confirmed that they were single enantiomers (see Supporting Information). The one exception was compound (*R*/*S*)-**1i**. The racemate showed two enan-

tiomers on chiral HPLC, and its specific rotation was approximately zero.

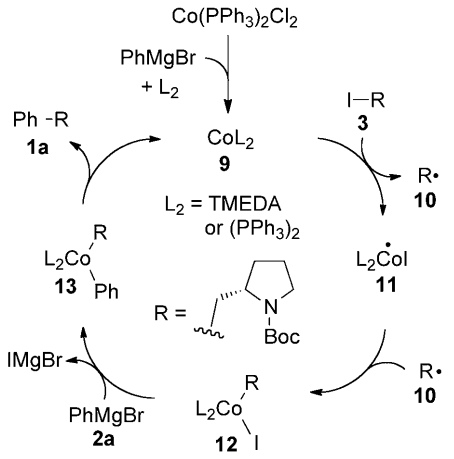
In Table 2, some coupling products showed two stereoisomers in their ^{13}C NMR spectra. This phenomenon was likely caused by the different configuration of the nitrogen atom in pyrrolidines, leading to the two diastereomers.[22] In this reaction, the number of diastereomers in the coupling products depended on their starting materials. Interestingly, two diastereomeric pyrrolidines can be easily converted into the single diastereomer at around 50 °C for 4 h or under milder conditions. The conversion process depends on the aryl substituents and the pyrrolidine backbone. Notably, the diastereomers do not play a critical role in their optical properties. Comparing (+)-(*S*)-**1i**, (−)-(*S*)-**3**, and (−)-(*R*)-**6d**, the specific rotations of single- and two-diastereomer samples are very similar (see Supporting Information).

Based on a literature precedent,[19e] the putative reaction mechanism for the formation of compound **1a** is presented in Scheme 2. In the presence of TMEDA, Grignard reagent **2a** reduces the pre-catalyst $Co(PPh_3)_2Cl_2$ to generate a reactive CoL_2 species **9**. Single electron transfer from **9** to pyrrolidine **3** gives a mixture of complex **11** and alkyl radical **10**. Combination of the latter two species affords intermediate **12**, which is transformed into cobalt complex **13** through phenylation with Grignard reagent **2a**. Reductive elimination of **13** yields the desired product **1a** and the reactive CoL_2 complex **9**.

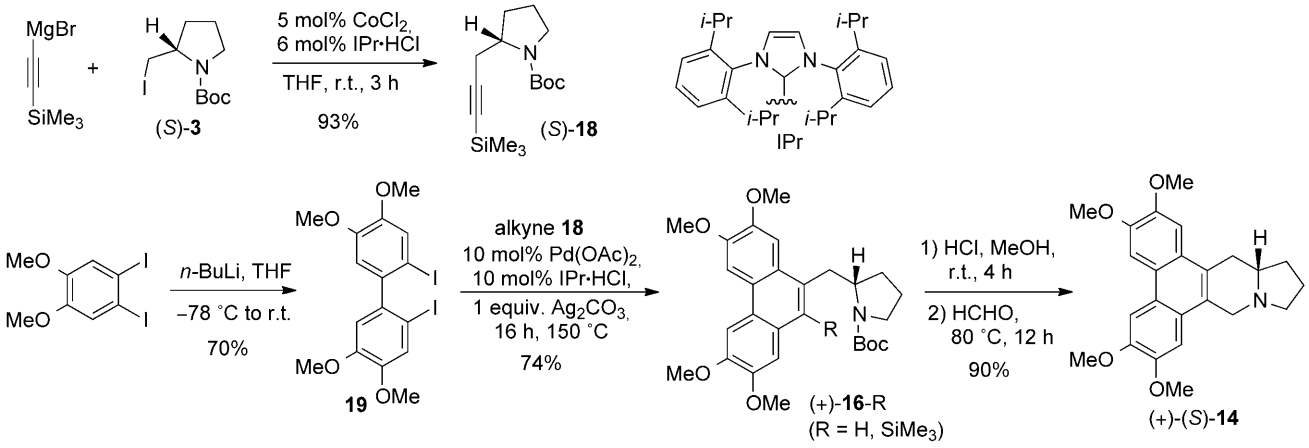
The phenanthroindolizidine alkaloids are structurally related natural products costructed by the fusion of a highly oxygenated phenanthrene ring to a saturated N-heterocycle.[23] Representative examples are tylophorine [(−)-(*R*)-**14**] and antofine [(−)-(*R*)-**15**], which are known for their important biological properties, including antitumor, anti-immune, and anti-inflammatory activities.[24] For instance, (*R*)-tylophorine [(*R*)-**14**] is effective against drug-sensitive and multi-drug-resistant cancer cells with an EC_{50} (half maximal effective concentration) of approximately 10^{-8} M.[25] Tylophorine (**14**) has been prepared by various synthetic approaches.[6,15a,26,27] Given the successful preparation of **1i**, the proposed protocol may be applicable to synthesize phenanthrene **16**-H, which can be converted into tylophorine (**14**) through the Pictet–Spengler reaction.[28] The proposed strategy would give the target molecule **14** in an unnatural form, i.e., (*S*)-tylophorine. Generally, both enantiomers of **14** have comparable antitumor activities, but a recent study indicated that (*S*)-tylophorine is more potent (3- to 4-fold) than its natural levorotatory analogue in some cell lines.[29] Like **1i**, **16**-H can be generated by a coupling reaction of **3** with the Grignard reagent **17**-MgBr. In this study, phenanthrene **17**-Br was prepared in several steps *via* **17**-CO_2H[27d] by decarboxylation[27g] and subsequent bromination,[27i] as described in the literature. The low-solubility of **17**-Br in THF or in a mixture of THF/toluene led to a highly diluted **17**-MgBr. Unfortunately, the cobalt-catalyzed coupling reaction of (*S*)-**3** with **17**-MgBr was very inefficient, and the former remained unchanged. This unsatisfactory result was likely caused by the low solubility of **17**-MgBr.



Alternatively, phenanthrene **16** may be accessible by Pd-catalyzed cycloaddition of 2,2′-diiodobiphenyl with an internal alkyne based on our recently developed method (Scheme 3).[30] The coupling reaction of (*S*)-2-(iodomethyl)pyrrolidine (*S*)-**3** with trimethylsilylethynylmagnesium bromide was conducted in the catalytic system $CoCl_2$/IPr·HCl in order to enhance the yield of alkyne **18**.[19d] Biphenyl **19** was easily generated from 4,5-diiodovetrol by treatment with *n*-butyllithium.[31] Pd-catalyzed cycloadditon of biphenyl **19** with alkyne **18** formed a mixture of phenanthrene **16**-$SiMe_3$ and its desilylated product **16**-H in 74%



Scheme 2. Proposed mechanism for the formation **1a**.



Scheme 3. Synthesis of tylophorine (+)-(*S*)-**14**.

yield. The latter was clearly the major product, and it became the sole product when the reaction was allowed to continue for long reaction times (24 h) or when the added amount of Ag_2CO_3 was increased. The Pictet–Spengler reaction converted the mixture of **16**-$SiMe_3$[28b] and **16**-H into (*S*)-**14** in 90% yield. It seems that the developed protocol for synthesizing tylophorine is more efficient compared with conventional methods.

Conclusions

This study presents a simple and efficient procedure for generating enantiopure functionalized pyrrolidines through a cobalt-catalyzed coupling reaction. Moreover, the resulting coupling product can be used to prepare (*S*)-tylophorine. Studies on the application of the protocol herein in the synthesis of bioactive molecules are currently under way.

Experimental Section

General Procedure for Cocatalyzed Cross-Coupling Reaction of Pyrrolidines with Aryl Grignard Reagents (GP1)

A solution of (−)-2-(iodomethyl)pyrrolidine (**3**, 155 mg, 0.50 mmol) and $Co(PPh_3)_2Cl_2$ (16.4 mg, 2.50 μmol) in THF (1.7 mL) was treated with TMEDA (0.4 mL from a dilute solution prepared from 0.1 mL of neat TMEDA in 10 mL of THF) at room temperature under nitrogen. To the resulting mixture, arylmagnesium bromide **2** (0.50 mmol) was slowly added within 5 min. After approximately 1 h, the reaction was quenched was saturated NH_4Cl solution (5 mL), and the solution was extracted with ethyl acetate (2×10 mL). The combined organic phases were dried over $MgSO_4$ and filtered. The solvents of the filtrate were removed under reduced pressure and the residue was subjected to chromatography on silica gel.

Procedure for Preparation of 2-(2-Propynyl)-pyrrolidine 18

A solution of trimethylsilylethyne (74.0 mg, 0.75 mmol) in THF (1.0 mL) at room temperature was treated with EtMgBr (0.25 mL, 3.0 M in THF, 0.75 mmol), and the reaction mixture was stirred at the same temperature for 30 min. The generated trimethylsilylethynylmagnesium bromide was transferred to a Schlenk flask, which contained $CoCl_2$ (3.2 mg, 25.0 μmol), IPr·HCl (13.0 mg, 30.0 μmol) and THF (0.5 mL). To the resulting mixture, a solution of (−)-2-(iodomethyl)pyrrolidine (**3**, 156 mg, 0.50 mmol) in THF (1 mL) was slowly added within 5 min. After 1 h, the reaction was quenched was saturated NH_4Cl solution (5 mL), and the solution was extracted with ethyl acetate (2×10 mL). The combined organic phases were dried over $MgSO_4$ and filtered. The solvents of the filtrate were removed under reduced pressure, and the residue was subjected to chromatography on silica gel. Eluting with hexane/ethyl acetate (8:1) gave **18** as a white solid; yield: 128 mg (93%).

Procedure for Pd-catalyzed Cycloaddition of 2,2′-Diiodobiphenyl 19 with Alkyne 18

A mixture of biphenyl **19** (158 mg, 0.30 mmol), alkyne **18** (126.7 mg, 0.45 mmol), $Pd(OAc)_2$ (6.7 mg, 30.0 μmol), IPr·HCl (12.8 mg, 30.0 μmol), Ag_2CO_3 (82.7 mg, 0.30 mmol) and *p*-xylene (1.5 mL) in a thick-walled Pyrex tube was purged with nitrogen for 5 min. The sealed tube was kept in an oil bath at 150 °C for 16 h. After cooling to room temperature, the solution was filtered through celite and washed with ethyl acetate. The solvent of the filtrate was removed under reduced pressure and the residue was subjected to chromatography on silica gel. Eluting with the solvent mixture hexane/ethyl aceate/CH_2Cl_2 (from 3:1:1 to 3:2:1) gave **16**-H (yield: 110 mg, 73%) and **16**-SiMe3 (yield: 6 mg, 1%).

Acknowledgements

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