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Synthesis of 2-Aza[6]helicene and Attempts To Synthesize 2,14-Diaza[6]helicene Utilizing Metal-Catalyzed Cycloisomerization

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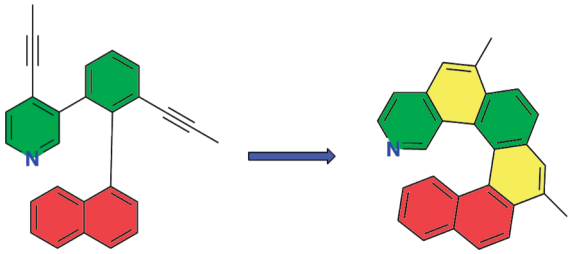


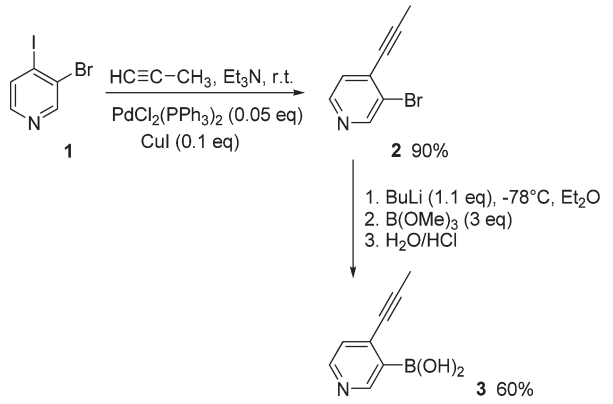
A modular synthetic approach leading to 2-aza[6]helicene is reported. It involves assembly of key hetero biphenylylnaphthalenes from functionalized building blocks and study of their metal catalyzed cycloisomerization.

Azahelicenes are a subgroup of helicenes, a fascinating class of compounds which possess a unique screw-shaped π-conjugated aromatic systems consisting of all ortho-annelated aromatic and heteroaromatic rings. Despite their chirality and possibility of coordination of the heteroatoms with metals, there are only scattered examples of using azahelicene derivatives in asymmetric catalysis.[1] Studies focused on their self-assembly,[2] basicities,[3] proton affinities,[4] complexation with silver(I),[5] and chiroptical properties controlled by metal coordination[6] have been performed. During the past few years, besides photochemical procedures,[7] only two examples of nonphotochemical synthesis of aza[6]helicenes have been elaborated, [2 + 2 + 2] cycloisomerization of triynes[5a,8] and Stille−Kelly reaction of dihalogenated *cis*-stilbene-type precursors.[9] To our best knowledge only one study of diaza-[6]helicene synthesis utilizing unsuccessful photocyclodehydrogenation of pyridine containing stilbene-type precursor and effective Stille−Kelly reaction of 2,7-bis(2-(pyridin-3-yl)-vinyl)naphthalene[3b] has been described up to now. Promising applications of azahelicenes in various branches of chemistry and material science might be envisaged, therefore, further research in the field and a larger scale preparation by simple methods is required.

Recently, we have developed an alternative approach to [6]helicene synthesis, which involves platinum-catalyzed double cycloisomerization of biphenylylnaphthalene derivatives.[10] We decided to continue exploring its potential to prepare aza[6]helicene and diaza[6]helicenes. Herein, we report on the synthesis of two nitrogen-containing biphenylylnaphthalenes, which were subjected to metal-catalyzed cycloisomerization. This modular method is again based on assembling from functionalized building blocks with final atom economic transformation.

3-Bromo-4-iodopyridine **1** prepared from commercially available 3-bromopyridine according to the literature procedure[11] was converted into **2** by Sonogashira coupling with propyne. Boronic acid **3** was obtained from **2** by lithiation in diethyl ether and subsequent reaction with $B(OMe)_3$ (Scheme 1).

SCHEME 1. Synthesis of Pyridine Building Block



Suzuki coupling of the triflate **4**[10] with the boronic acid **3** under standard conditions afforded azabiphenylylnaphthalene **5** in 35% yield (Scheme 2). This racemic diastereomers

(1) (a) Takenaka, N.; Sarangthem, R. S.; Captain, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 9708. (b) Šámal, M.; Míšek, J.; Stará, I. G.; Starý, I. *Collect. Czech. Chem. Commun.* **2009**, *74*, 1151.
(2) (a) Tanaka, K.; Kitahara, Y.; Suzuki, H.; Osuga, H. *Tetrahedron Lett.* **1996**, *37*, 5925. (b) Murguly, E.; McDonald, R.; Branda, N. R. *Org. Lett.* **2000**, *2*, 3169.
(3) (a) Staab, H. A.; Zirnstein, M. A.; Krieger, C. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 86. (b) Staab, H. A.; Diehm, M.; Krieger, C. *Tetrahedron Lett.* **1994**, *35*, 8357.
(4) Roithová, J.; Schröder, D.; Míšek, J.; Stará, I. G.; Starý, I. *J. Mass Spectrom.* **2007**, *42*, 1233.
(5) (a) Míšek, J.; Teplý, F.; Stará, I. G.; Tichý, M.; Šaman, D.; Císařová, I.; Vojtíšek, P.; Starý, I. *Angew. Chem., Int. Ed.* **2008**, *47*, 3188. (b) Míšek, J.; Tichý, M.; Stará, I. G.; Starý, I.; Schröder, D. *Collect. Czech. Chem. Commun.* **2009**, *74*, 323.
(6) Graule, S.; Rudolph, M.; Vanthuyne, N.; Autschbach, J.; Roussel, Ch.; Crassous, J.; Réau, R. *J. Am. Chem. Soc.* **2009**, *131*, 3183.
(7) (a) Staab, H. A.; Diehm, M.; Krieger, C. *Tetrahedron Let.* **1994**, *35*, 8357. (b) Aloui, F.; Abed, R. E.; Hassine, B. B. *Tetrahedron Lett.* **2008**, *49*, 1455. (c) Aloui, F.; Abed, R. E.; Marinetti, A.; Hassine, B. B. *Tetrahedron Lett.* **2008**, *49*, 4092.
(8) Andronova, A.; Szydlo, F.; Teplý, F.; Tobrmanová, M.; Volot, A.; Stará, I. G.; Starý, I.; Rulíšek, L.; Saman, D.; Cvačka, J.; Fiedler, P.; Vojtišek, P. *Collect. Czech. Chem. Commun.* **2009**, *74*, 189.
(9) Takenaka, N.; Sarangthem, R. S.; Captain, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 9708.
(10) Storch, J.; Sýkora, J.; Čermak, J.; Karban, J.; Císařová, I.; Ružička, A. *J. Org. Chem.* **2009**, *74*, 3090.
(11) Baxter, P. N. W. *Chem.—Eur. J.* **2003**, *9*, 2531.

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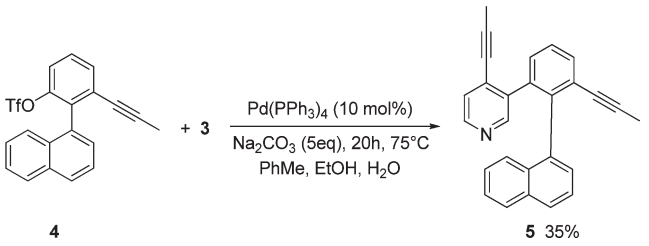
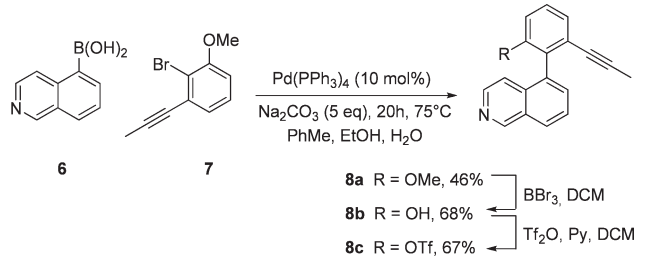
SCHEME 2. Construction of Azabiphenylylnaphthalene



behaves similarly as their carbo-analogue.[10] The free energy of activation of hindered rotation in **5** is slightly lower than that in the carbo-analogue[10] $-\Delta G^{\ddagger}_{300} = 14.5$ and 15.0 kcal·mol^{-1}, respectively (for the variable-temperature ^{1}H NMR analysis see Figures S6 and S7 in the Supporting Information), and thus, rapid rotation around the pyridine−phenyl bond at ambient temperature makes it impossible to separate the two diastereomers.

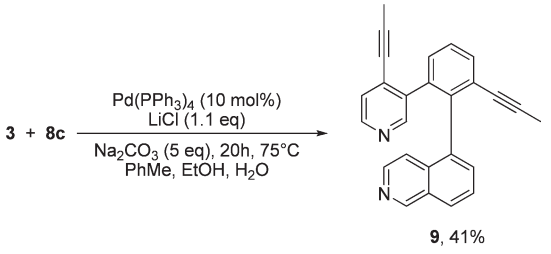
The multistep synthesis of isoquinoline building block started from isoquinolin-5-ylboronic acid[12] **6** prepared from 5-bromoisoquinoline[13] and 2-bromo-1-methoxy-3-(propyn-1-yl)benzene[10] **7** (Scheme 3). Suzuki coupling provided 5-(2-methoxy-6-(propyn-1-yl)phenyl)isoquinoline **8a** which was converted via ether cleavage into desired triflate **8c**.

SCHEME 3. Synthesis of Isoquinoline Building Block



Then, we could assemble the pyridylphenylisoquinoline backbone by the Suzuki coupling of boronic acid **3** and triflate **8c** under analogous conditions resulting in the formation of desired diastereomeric mixture of **9** in 41% yield (Scheme 4).

SCHEME 4. Synthesis of Azabiphenylylisoquinoline



In this case, the rotation barrier is much lower compared to **5**, and at ambient temperature, we can see average spectrum of both conformational isomers. The structure of **9** proposed by NMR spectroscopy was later confirmed by X-ray crystallography. The crystal lattice of **9** contains both enantiomers (space group *P*-1) (Figure 1).

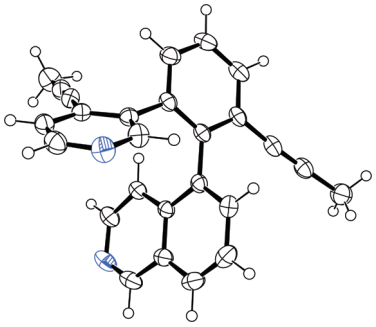


FIGURE 1. ORTEP projection of the crystal structure **9**.

Having **5** and **9** in hand, we could investigate their ability to undergo cycloisomerization to form aza- and diaza[6]helicenes (Table 1). Previously, we found that carbo-analogues were appropriate substrates for fast isomerization to [6]helicenes under platinum catalysis.[10] In the case of **5**, attempts for cycloisomerization by $PtCl_2$ or $PtCl_4$ failed (entries 1 and 2). Partial success was achieved with $InCl_3$ (entry 3) yielding half-cyclized molecule isolated as an addition product with HCl **12**, which could be formed during the reaction. Finally, we found that when the isomerization reaction was carried out with the catalyst mixture composed of $InCl_3$ and $PtCl_4$ (entry 4) the desired product **10** was successfully obtained in 80% yield. Unfortunately, the attempts for cycloisomerisation of azabiphenylylisoquinoline **9** using the same reaction conditions as for **5** (entries 4−7) did not work. The use of Au^I and Au^{III} catalysts[14] also did not bring any success (entries 8−17). Also, $Hg(OTf)_2$-catalyzed[15] enyne cycloizomerization gave no reaction. Attempts for electrophilic cyclization using iodonium chloride[16] provided only addition product **13**. Conversion of **9** into bis(pyridinium) dichloride by HCl leading to neglecting of potential coordination properties and subsequent attempts for cycloizomerization catalyzed by $PtCl_2$, $PtCl_4$, or $InCl_3$ also failed.

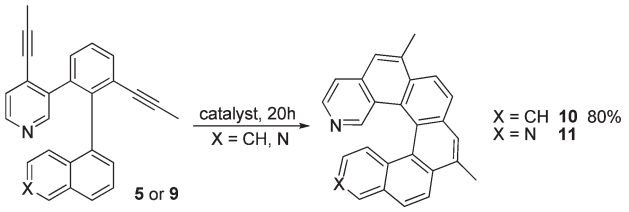
In conclusion, we have explored metal-catalyzed cycloisomerization of nitrogen-containing byphenylylnaphthalenes prepared by Suzuki coupling of functionalized building blocks. Our approach was successfully applied to the synthesis of 2-aza[6]helicene. Further efforts directed at achieving so far unsuccessful cycloisomerization of **9** yielding 2,14-diaza[6]helicene continue in our laboratories.

Experimental Section

3-(2-(Naphth-1-yl)-3-(propyn-1-yl)phenyl)-4-(propyn-1-yl)-pyridine (5). A mixture of $Pd(PPh_3)_4$ (200 mg, 0.17 mmol, 10 mol %) and triflate **4** (0.7 g, 1.8 mmol) in toluene (9 mL) was stirred for 5 min at room temperature under argon. Aqueous Na_2CO_3 (2 M, 4.5 mL, 9 mmol, 5 equiv) was added to the mixture, followed by the boronic acid **3** (0.36 g, 2.24 mmol, 1.2 equiv) in ethanol (9 mL).

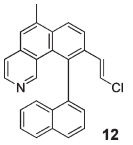
(12) Lee, I. Y. C.; Jung, M. H.; Lim, H. J.; Lee, H. W. *Heterocycles* **2005**, *65*, 2505.
(13) Gomtsyan, A.; Bayburt, E. K.; Schmidt, R. G.; Zheng, G. Z.; Perner, R. J.; Didomenico, S.; Koenig, J. R.; Turner, S.; Jinkerson, T.; Drizin, I.; Hannick, S. M.; Macri, B. S.; McDonald, H. A.; Honore, P.; Wismer, C. T.; Marsh, K. C.; Wetter, J.; Stewart, K. D.; Oie, T.; Jarvis, M. F.; Surowy, C. S.; Faltynek, C. R.; Lee, C. H. *J. Med. Chem.* **2005**, *48*, 744.
(14) (a) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402. (b) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (c) Nevado, C.; Echavarren, A. M. *Chem.—Eur. J.* **2005**, *11*, 3155.
(15) Nishizawa, M.; Takao, H.; Yadav, V. K.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 4563.
(16) Yao, T.; Campo, M. A.; Larock, R. C. *Org. Lett.* **2004**, *6*, 2677.

TABLE 1. Cycloisomerization Reaction Experiments

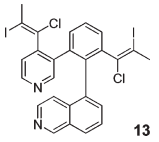


entry	substrate, X	catalyst (mol %), solvent	temp, °C	GC, %
1	CH	$PtCl_2$ (10), toluene	90	0
2	CH	$PtCl_4$ (10), toluene	90	0
3	CH	$InCl_3$ (10), toluene	90	40[a]
4	CH	$InCl_3$ (5), $PtCl_4$ (5), toluene	90	80
5	N	$PtCl_2$ (10), toluene	90	0
6	N	$PtCl_4$ (10), toluene	90	0
7	N	$InCl_3$ (10), toluene	90	0
8	N	AuCl (10), MeCN	70	0
9	N	AuCl (10), toluene	90	0
10	N	$AuCl(PPh_3)$ (10), DCM	rt	0
11	N	$AuCl(PPh_3)$ (10), AgOTf (10), $MeNO_2$	80	0
12	N	$AuCl(PPh_3)$ (10), AgOTf (10), DCM	rt	0
13	N	$AuCl(PPh_3)$ (10), $AgBF_4$ (10), DCM	rt	0
14	N	$AuCl_3$ (10), toluene	90	0
15	N	$AuCl_3$ (10), PPh_3 (10), DCM	rt	0
16	N	$AuCl_3$ (10), AgOTf (10), DCM	rt	0
17	N	$AuCl_3$ (10), $AgBF_4$ (10), DCM	rt	0
18	N	$Hg(OTf)_2$ (6), MeCN	60	0
19	N	$Hg(OTf)_2$ (10), tetramethylurea (30), MeCN	rt	0
20	N	ICl (3 equiv), DCM	−78 to rt	80[b]

[a]Isolated product.



[b]Isolated product.



The mixture was heated at 75 °C for 20 h and then cooled to room temperature, diluted with water, and extracted with ethyl acetate (3 × 30 mL). Combined organic extracts were dried and evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/petroleum ether, 2:1). Product was obtained as colorless oil (0.23 g, 35%): ^{1}H NMR (500 MHz; $C_2D_2Cl_4$, 75 °C) δ 8.10 (d, J = 5.1 Hz, 1H), 8.04 (s, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.68−7.64 (m, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.48−7.47 (m, 2H), 7.43− 7.35 (m, 3H), 7.32 (d, J = 6.8 Hz, 1H), 7.08 (d, J = 5.1 Hz, 1H), 1.99 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (125 MHz; $C_2D_2Cl_4$, 75 °C) δ 149.6 (d), 146.9 (d), 141.7 (s), 133.0 (s), 132.0 (s), 131.9 (d), 131.1 (s), 130.1 (d), 128.9 (s), 128.2 (d), 128.1 (s), 127.7 (d), 127.3 (d), 126.7 (d), 126.3 (d), 125.5 (d), 125.4 (s), 125.18 (d), 125.17 (s), 125.1 (d), 124.5 (d), 94.5 (s), 90.0 (s), 79.0 (s), 77.2 (s), 4.3 (q), 3.7 (q); EI-MS m/z 357 (84, M^+), 342, 327, 317, 171, 163, 150. Anal. Calcd for $C_{27}H_{19}N$: C, 90.72; H, 5.36; N, 3.92. Found: C, 90.52; H, 5.33; N, 3.87.

5-(2-(Propyn-1-yl)-6-(4-(propyn-1-yl)pyridin-3-yl)phenyl)-isoquinoline (9). A mixture of $Pd(PPh_3)_4$ (224 mg, 0.19 mmol, 10 mol %), LiCl (90 mg, 2.13 mmol, 1.1 equiv), and triflate **8c** (0.76 g, 1.94 mmol) in toluene (9.7 mL) was stirred for 5 min at room temperature under argon. Aqueous Na_2CO_3 (2 M, 4.85 mL, 44 mmol, 5 equiv) was added to the mixture, followed by the boronic acid **3** (1.39 g, 8.73 mmol, 4.5 equiv) in ethanol (9.7 mL). The mixture was heated at 75 °C for 20 h and then cooled to room temperature, diluted with water, and extracted with ethyl acetate (3 × 30 mL). Combined organic extracts were dried and evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/petroleum ether/acetone, 2:1:1 + 5% i-Pr_2NH). The product was obtained as a colorless oil (0.29 g, 41%) which solidified upon standing: ^{1}H NMR (500 MHz; $CDCl_3$) δ 9.17 (bs, 1H), 8.13 (d, J = 4.3 Hz, 1H), 8.1−7.9 (bm, 1H), 7.81 (bm, 1H), 7.63 (dd, J = 1.1, 7.6 Hz, 1H), 7.55−7.37 (bm, 4H), 7.47 (t, J = 7.7 Hz, 1H), 7.42 (dd, J = 1.3 7.8 Hz, 1H), 7.04 (bm, 1H), 1.93 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 154.9 (d), 152.5 (d), 147.6 (d), 142.4 (d), 140.0 (s), 137.9 (s), 137.5 (s), 136.1 (s), 134.6 (s), 132.3 (d), 132.2 (d), 131.2 (s), 130.3 (d), 128.2 (s), 127.5 (d), 127.3 (d), 126.2 (d), 125.8 (d), 125.3 (s), 119.2 (d), 94.7 (s), 90.4 (s), 78.6 (s), 77.0 (s), 4.6 (q), 4.0 (q); MS (EI) m/z 358 (100, M^+), 343, 228, 315, 301, 288, 274, 264, 250, 238, 224, 213, 200, 187, 178, 157, 151, 143, 137, 124, 112. Anal. Calcd for $C_{26}H_{18}N_2$: C, 87.12; H, 5.06; N, 7.82. Found: C, 87.04; H, 5.23; N, 7.79.

2-Aza-6,10-dimethyl[6]helicene (10). A solution of **5** (0.4 g, 1.12 mmol), $PtCl_4$ (18.9 mg, 0.056 mmol, 5 mol %), and $InCl_3$ (13 mg, 0.056 mmol, 5 mol %) in toluene (10 mL) was stirred for 20 h at 90 °C. The solvent was evaporated. Purification of the residue by column chromatography (ethyl acetate/petroleum ether, 50:50 − 67:33) gave 0.31 g (78%) of **10** as a colorless oil. ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.71 (s, 1H), 8.18 (d, J = 8.5 Hz, 1H), 8.15 (d, J = 5.4 Hz, 1H), 8.12 (d, J = 8.8 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.85 (s, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.66 (s, 1H), 7.50 (d, J = 5.4 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.23 (t, J = 7.4 Hz, 1H), 6.70 (t, J = 7.4 Hz, 1H), 2.95 (s, 3H), 2.92 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 150.0 (d), 142.5 (d), 137.7 (s), 134.7 (s), 134.3 (s), 132.8 (s), 131.9 (s), 131.1 (s), 130.1 (s), 129.1 (s), 128.4 (s), 128.3 (d), 128.2 (d), 128.0 (d), 127.3 (s), 127.2 (d), 126.9 (d), 125.7 (d), 125.1 (d), 124.7

(d), 124.1 (s), 123.0 (d), 122.5 (s), 122.0 (d), 119.3 (d), 20.7 (q), 20.0 (q); MS (EI) *m*/*z* 357 (91, M^+), 342, 327, 317, 171, 163, 150, 137. Anal. Calcd for $C_{27}H_{19}N$: C, 90.72; H, 5.36; N, 3.92. Found: C, 90.68; H, 5.41; N, 3.89.

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Supporting Information Available: Experimental procedures and spectroscopic details for **2**, **3**, **8a**−**c**; ^1H and ^{13}C NMR spectra for all compounds; X-ray diffraction data for **9**. This material is available free of charge via the Internet at http://pubs.acs.org.