ORGANIC LETTERS

2007
Vol. 9, No. 4
559−562

Diverse Synthesis of Novel Bisterpyridines via Suzuki-Type Cross-Coupling

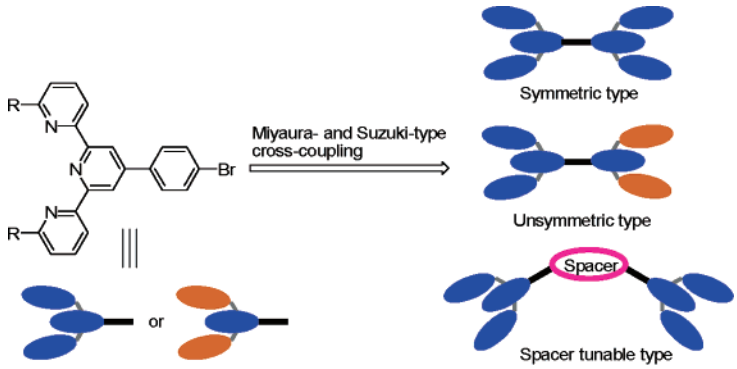
Fu She Han,[†] Masayoshi Higuchi,*[,†] and Dirk G. Kurth*[,†,‡]

Functional Modules Group, Organic Nanomaterials Center, National Institute for Materials Science, 1-1 Namiki, Tsukuba, Ibaraki 305-0044, Japan and Max-Planck-Institute of Colloids and Interfaces, Research Campus Golm, D-14424, Potsdam, Germany

higuchi.masayoshi@nims.go.jp; kurth@mpikg.mpg.de

Received November 16, 2006

ABSTRACT



A new protocol is presented for the synthesis of novel bisterpyridine derivatives using palladium-catalyzed Miyaura- and Suzuki-type cross-couplings as the key reactions. This protocol is quick, efficient, mild, and broadly applicable for the construction of versatile bisterpyridines by symmetric and unsymmetric introduction of various substituents in the pyridine rings as well as by tuning the spacers for bridging the two terpyridine moieties.

Metallo-supramolecular polymers have recently attracted growing interest within the domain of material and supramolecular chemistry,[1] molecular biology,[2] and nano science.[3] In this context, particular attention has been paid to the ditopic bisterpyridine derivatives because this type of compound is chemically and thermally stable and forms, as a tridentate ligands, stable complexes with a large variety of transition-metal ions, associated with a rich variety of interesting properties.[3a,4] However, versatile preparation of bisterpyridine-based coordination polymers has been seriously restricted due to the limited availability of suitable ligands, and studies have focused mainly on ligands such as 1,4-bis(2,2′:6′,2″-terpyridine-4-yl)benzene. To date, two strategies are commonly employed to synthesize bisterpyridine derivatives.[4a,5] One is the base-mediated aldol condensation of a dialdehyde with an acetylpyridine, for the

[†] National Institute for Materials Science.

[‡] Max-Planck-Institute of Colloids and Interfaces.

(1) Constable, E. C. In *Comprehensive Supramolecular Chemistry*; Lehn, J. M., Ed.; Pergamon, 1996; Vol. 9, pp 213−252.

(2) (a) Song, B.; Wang, G.; Tan, M.; Yuan, J. *J. Am. Chem. Soc.* **2006**, *128*, 13442−13450. (b) Hovinen, J.; Hakala, H. *Org. Lett.* **2001**, *3*, 2473−2476.

(3) (a) Kolb, U.; Büscher, K.; Helm, C. A.; Lindner, A.; Thünemann, A. F.; Menzel, M.; Higuchi, M.; Kurth, D. G. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 10202 − 10206. (b) Oh, M.; Mirkin, C. A. *Nature* **2005**, *438*, 651−654. (c) Kurth, D. G.; Higuchi, M. *Soft Matter* **2006**, *2*, 915−927.

(4) For a recent comprehensive review, see: (a) Andres, P. R.; Schubert, U. S. *Adv. Mater.* **2004**, *16*, 1043−1068 and references therein. For recent research articles, see: (b) Carlson, C. N.; Kuehl, C. J.; Da-Re, R. E.; Veauthier, J. M.; Schelter, E. J.; Milligan, A. E.; Scott, B. L.; Bauer, E. D.; Thompson, J. D.; Morris, D. E.; John, K. D. *J. Am. Chem. Soc.* **2006**, *128*, 7230−7241. (c) Lainé, P. P.; Bedioui, F.; Loiseau, F.; Chiorboli, C.; Campagna, S. *J. Am. Chem. Soc.* **2006**, *128*, 7510−7521. (d) Sénéchal-David, K.; Leonard, J. P.; Plush, S. E.; Gunnlaugsson, T. *Org. Lett.* **2006**, *8*, 2727−2730. (e) Coronado, E.; Galán-Mascarós, J. R.; Marti-Gastaldo, C.; Palomares, E.; Durrant, J. R.; Vilar, R.; Grätzel, M.; Nazeeruddin, M. K. *J. Am. Chem. Soc.* **2005**, *127*, 12351−12356. (f) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210−4212. (g) Baitalik, S.; Wang, X.; Schmehl, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 16304−16305. (h) Cui, Y.; He, C. *J. Am. Chem. Soc.* **2003**, *125*, 16202−16203.

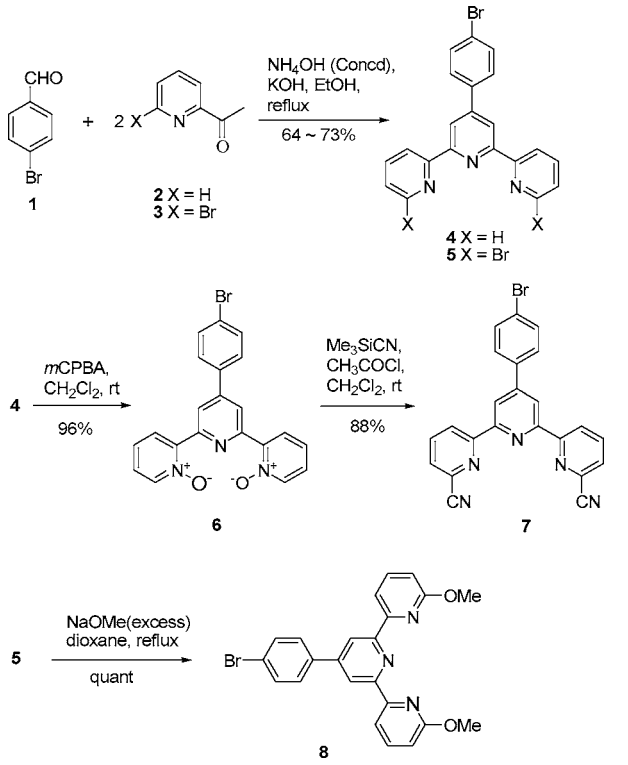
10.1021/ol062788h CCC: $37.00
Published on Web 01/25/2007

preparation of diazachalcone, followed by a bis-1,4-addition of the resulting azachalcone with a pyridinium nucleophile.[5] Another is the 4′-position substitution reactions of commericially available 4′-Cl (or OH) monoterpyridines.[4a] However, because of the frequent application of strong bases and/or employment of the bis-1,4-addition reaction in these conventional methods, their general application intrinsically suffers from many drawbacks such as the preparation of unsymmetric ligands, the introduction of functional groups at the ring periphery, and the availability of different spacers for bridging the two terpyridine moieties. These drawbacks, thereby, prevent flexible design and synthesis of bisterpyridines with structural and functional diversity.

Therefore, development of a general and efficient protocol for the synthesis of bisterpyridines is highly desirable. Herein, we describe a Suzuki coupling protocol, which permits the versatile synthesis of bisterpyridines. Although Suzuki coupling has been used in a broad range of sp^2 C−C bond formations,[6] only very few examples are reported for the construction of structurally unique bisterpyridines.[7]

Synthesis of monoterpyridine derivatives **4**, **5**, **7**, and **8** is outlined in Scheme 1. On the basis of a modified one-pot

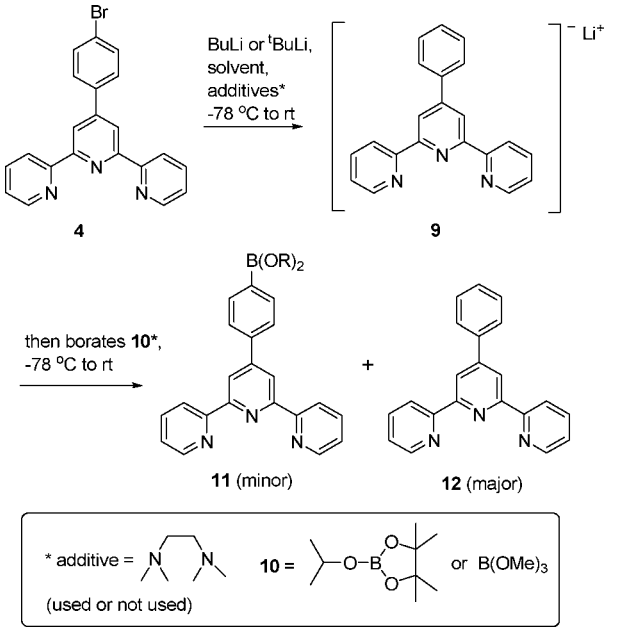
Scheme 1. Synthesis of Monoterpyridines



Kröhnke procedure,[8] 4-bromobenzaldehyde **1** and 2 equiv of 2-acetylpyridines (**2** or **3**) reacted sequentially in a Claisen−Schmidt aldol condensation,[8] a 1,4-addition, and an intramolecular dehydration, to afford the monoterpyridines **4** and **5,** respectively, in good yield. For further functionalization, the terpyridine **4** was oxidized with *m*-CPBA to give *N*,*N*″-dioxidized compound **6** in excellent yield. The resulting dioxide **6** was then subjected to a Reissert−Henze-type reaction[9] to produce the 6,6″-dicarbonitrile **7**. Alternatively, nucleophilic substitution of 6,6″-dibromo-terpyridine **5** with NaOMe gave the corresponding 6,6″-dimethoxyl derivative **8** in quantitative yield. The functional groups in pyridine rings, such as the bromide in **5**, the carbonitrile in **7**, and the methoxyl group in **8**, can be readily transformed into a number of other functional groups. The efficient synthesis makes these monoterpyridines attractive precursors for the construction of diverse bisterpyridine derivatives.

With these useful monoterpyridines in hand, our attention shifted first to the construction of symmetric bisterpyridines by using Suzuki-type cross-coupling. The first challenge here is to successfully synthesize the terpyridine boronic esters (acids), a class of compounds rarely reported.[7] We initially tried the classical reaction of a lithium reagent **9**, generated in situ from terpyridine **4** and BuLi or ^{t}BuLi, with a trialkyl borate **10** (Scheme 2).[10] However, extensive efforts under

Scheme 2. Preparation of Terpyridine Boronic Esters



various conditions proved to be fruitless, and only a small amount of boronic esters contaminated by some unknown impurities were obtained (ca. 30%). The major product was found to be the debrominated **12**[11] (>50%).

(5) (a) Vaduvescu, S.; Potvin, P. G. *Eur. J. Inorg. Chem.* **2004**, 1763−1769. (b) Constable, E. C.; Thompson, A. M. W. C. *J. Chem. Soc., Dalton Trans.* **1992**, 3467−2475. (c) Kröhnke, F. *Synthesis* **1976**, 1−24.

(6) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483 and references therein.

(7) After the submission of this manuscript, an example for the synthesis of fluorenyl-bridged unsubstituted bis- and tristerpyridines was reported using Suzuki cross-coupling. See: Yuan, S.; Chen, H.; Zhang, Y.; Pei, J. *Org. Lett.* **2006**, *8*, 5701−5704.

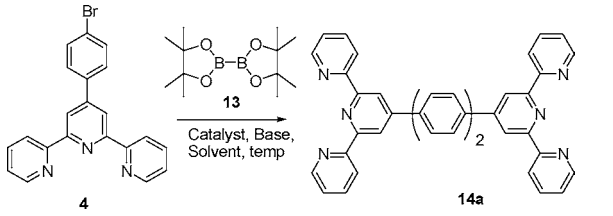
(8) Eryazici, I.; Moorefield, C. N.; Durmus, S.; Newkome, G. R. *J. Org. Chem.* **2006**, *71*, 1009−1014.

(9) Pauvert, M.; Collet, S. C.; Bertrand, M.; Guingant, A. Y.; Evain, M. *Tetrahedron Lett.* **2005**, *46*, 2983−2987.

(10) Jacob, J.; Sax, S.; Piok, T.; List, E. J. W.; Grimsdale, A. C.; Müllen, K. *J. Am. Chem. Soc.* **2004**, *126*, 6987−6995.

Our efforts then focused on a Miyaura-type cross-coupling strategy for the preparation of terpyridine boronic esters.[12] We were pleased to find that treatment of **4** with 1.1 equiv of bis(pinacolato)diboron **13** led to a smooth conversion of substrate **4** under all three different conditions tried (Table 1, entries 1−3). Careful spectroscopic analyses revealed that the product was a hard to separate mixture of **11** (major) and the dimerized product **14a** (minor).

Table 1. Optimization of the Suzuki Dimerization Coupling Reaction of Terpyridine **4** with Bis(pinacolato)diboron **13**[a]



entry	catalyst	base	°C/h	solvent	yield[c] (%)
1	$PdCl_2(dppf)$[b]	KOAc	80/6	DMSO	97[d]
2	$PdCl_2(PPh_3)_2$[b]	KOAc	80/6	DMSO	95[d]
3	$PdCl_2(PPh_3)_2$	KOAc	80/16	DMSO	95[d]
4	$PdCl_2(PPh_3)_2$	K_2CO_3	80/18	DMSO	89
5	$PdCl_2(PPh_3)_2$	K_2CO_3	80/18	DMF	88
6	$PdCl_2(PPh_3)_2$	K_2CO_3	100/16	DMSO	88
7	$PdCl_2(PPh_3)_2$	K_2CO_3	60/16	DMSO	51
8	$PdCl_2(PPh_3)_2$	K_2CO_3	80/20	dioxane	—[e]
9	$PdCl_2(PPh_3)_2$	$NaHCO_3$	80/20	DMSO	73
10	$PdCl_2(PPh_3)_2$	KF	80/20	DMSO	40

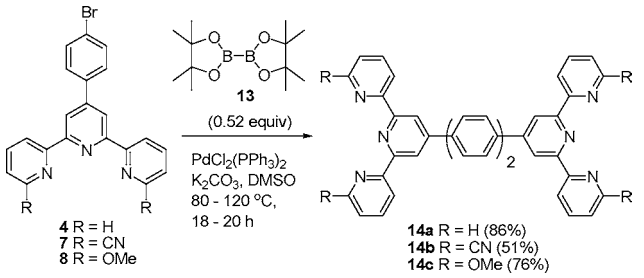
[a] Conditions for entries 1−3: 50 mg (0.128 mmol) of **4**, 1.1 equiv of bis(pinacolato)diboron **13**, 5 mol % of catalyst unless otherwise noted, 3.0 equiv of base, 80 °C. Conditions for entries 4−10: 50 mg (0.128 mmol) of **4**, 0.52 equiv of **13**, 5 mol % of catalyst, 3.0 equiv of base, 80 °C. [b]30 mol % of catalyst. [c]Isolated yield by column chromatography on basic Al_2O_3, unless otherwise noted. [d]Combined total yield of the mixture of **11** (major) and **14a** (minor). [e]Only a trace amount of product was detected by TLC.

The detection of **14a** is attractive because it implies that high-yielding dimerization would be possible via a one-pot tandem Miyaura boronic ester formation and Suzuki coupling if the reaction conditions such as the amount of boron reagent, bases, solvents, and temperature were properly controlled, thereby providing a much faster procedure for synthesizing bisterpyridines of the symmetric type than a stepwise one. Accordingly, the reaction conditions were further optimized using $PdCl_2(PPh_3)_2$ as catalyst instead of $PdCl_2(dppf)$ in standard Miyaura conditions.[13] It was immediately clear that the outcome of the reaction was markedly affected by base, solvent, and temperature (Table 1, entries 4−10). In general, use of stronger bases such as K_2CO_3 and of polar solvents such as DMSO and DMF (Table 1, entries 4 and 5) gave the dimerized product **14a** in a satisfactory yield. Thus, the final optimized conditions were 5 mol % of $PdCl_2(PPh_3)_2$, K_2CO_3, DMSO, and 80 °C. Under these conditions, **14a** was obtained in 86% yield when the reaction was scaled up to 300 mg.[14] The structure of **14a** is determined by standard spectroscopic techniques, including ^1H and ^{13}C NMR and mass spectrometry, as well as X-ray crystallographic analysis (Figure 1).[15]

Figure 1. X-ray crystal structure of **14a**. Displacement ellipsoids represent 50% probability.

Next, the methodology was extended to the synthesis of a range of symmetric bisterpyridines having various functional groups in the pyridine rings. As shown in Scheme 3, the dimerization occurred efficiently for both electron-deficient (**7**) and electron-rich (**8**) substrates to give **14b** and **14c**, respectively. The relatively low yield for **14b** is due to the extremely poor solubility in many solvents such as DMSO, DMF, THF, $CHCl_3$, CH_2Cl_2, and other protic solvents, resulting in a partial precipitation of the product from the reaction system.[16] When **5** was subjected to cross-coupling under the same conditions, a complex mixture was obtained, probably resulting from the competitive boronic ester formation of the bromides in benzene and pyridine rings as well as from the following competitive Suzuki coupling reactions.[17]

Scheme 3. Synthesis of Substituted Bisterpyridines



(11) Mutai, T.; Cheon, J.; Arita, S.; Araki, K. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1045−1050.

(12) (a) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447−3450. (b) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508−7510.

(13) Because use of $PdCl_2(dppf)$ afforded a product with the contamination of unremovable red color.

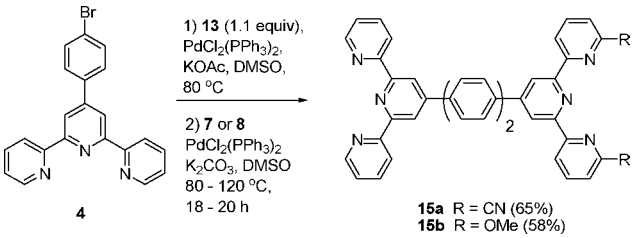
(14) Reaction at a larger scale was not tried.

(15) Crystal data for **14a** at 110 K: C42H28N6 (MW: 616.71), 0.20 × 0.05 × 0.04 mm^3, colorless needle crystal, monoclinic, space group *C*2/*c*, a = 28.0200(12) Å, b = 10.6337(3) Å, c = 10.9221(4) Å, V = 3201.6(2) $Å^3$, β = 100.330(3)°, Z = 4; final R1 = 0.0445 for all 15 519 reflections of $I > 2\sigma(I)$, wR2 = 0.1404 for all 15 519 reflections.

(16) Due also to the poor solubility, characterization of **14b** by NMR spectroscopy was difficult, but mass spectrometry revealed a characteristic peak corresponding to **14b** (see Supporting Information).

On the basis of the experiences for the synthesis of symmetric bisterpyridines **14a**−**c**, bisterpyridines of the unsymmetric type **15a**−**b** were also synthesized efficiently via a one-pot procedure involving boronic ester formation followed by in situ Suzuki cross-coupling (Scheme 4). Thus,

Scheme 4. Synthesis of Unsymmetric Bisterpyridines

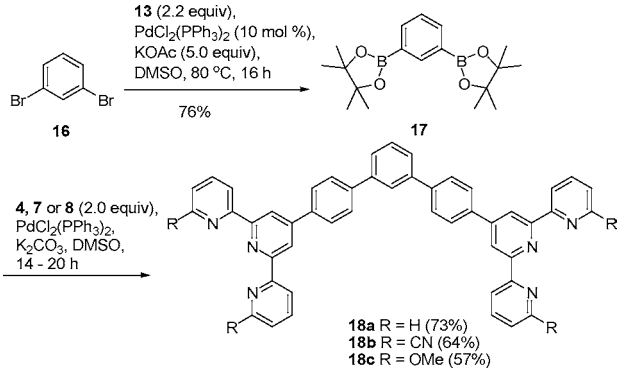


monoterpyridine **4** was treated with 1.1 equiv of bis(pinacolato)diboron **13** under modified Miyaura conditions[13] until the starting material had disappeared as monitored by TLC. Then, the reaction vessel was recharged in situ with 1.0 equiv of electron-deficient **7** (or electron-rich **8**), 5 mol % of $PdCl_2(PPh_3)_2$, and 3.0 equiv of K_2CO_3. The mixture was heated further under stirring until **7** (or **8**) had disappeared. Purification of the reaction mixtures afforded the desired unsymmetric bisterpyridine **15a** and **15b**, respectively, in good isolated yield. It should be noted that such types of unsymmetric ligands are anticipated to be interesting for the fabrication of metallo-supramolecular polymers containing different metal ions in a well-defined way, providing new materials with novel functions. However, it is extremely difficult to synthesize this type of ligands according to the established procedures.[4a,5]

Having established a robust Suzuki-type protocol accomplishing the synthesis of bisterpyridines of symmetrically and unsymmetrically substituted types, we became interested in extending this protocol to the construction of other new bisterpyridines by tuning the spacers for bridging the two terpyridine moieties. For this purpose, we adopted a Suzuki bis-coupling strategy as outlined in Scheme 5. Here, 1,3-diboronate **17** was prepared from 1,3-dibromobenzene **16** via Miyaura cross-coupling. Then, Suzuki bis-coupling of **17** with 2 equiv of **4** gave the corresponding bisterpyridine

(17) It was also reported that protonolysis of a C−B bond might occur when the boron atom is attached to a carbon adjacent to heteroatoms (see ref 9a), making the reaction more complicated.

Scheme 5. Synthesis of Bisterpyridines by Tuning Spacers



18a in good yields. Further exploration showed that the electron-deficient (**7**) and electron-rich (**8**) substrates are also compatible with this synthetic strategy, providing the corresponding coupling products **18b** and **18c**, respectively, in high yields.

In conclusion, we have developed a new protocol to access bisterpyridine derivatives using palladium-catalyzed Miyaura- and Suzuki-type cross-couplings as the key reactions. This protocol is shown to be quick, efficient, mild, and broadly applicable for the synthesis of a large variety of symmetrically and unsymmetrically functionalized, as well as spacer tunable bisterpyridines. Besides, the methoxyl and carbonitrile functionalities either in the monoterpyridines or in the bisterpyridines are ready for further versatile derivatization. As a result, flexible design and synthesis of bisterpyridine derivatives with structural and functional diversity are possible employing the newly developed methodology. On the other hand, the availability of a diverse class of valuable bisterpyridines allows the versatile fabrication of novel metallo-supramolecular polymers. This work along with the synthesis of structurally more complex bisterpyridines is currently underway.

Acknowledgment. We thank the Ministry of Education, Culture, Sports, Sciences, and Technology, Japan, for financial support.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR for all new compounds (except for **14b**) and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062788H