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Homocoupling Reactions

The Regioselective Homocoupling of *meta*-Hydroxypyridines with Hypervalent Iodine(III)

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Abstract: The C–H homocoupling of *meta*-hydroxypyridines with phenyliodine(III) diacetate (PIDA) was carried out in dichloromethane at room temperature in the presence of cesium carbonate. The coupling reaction is highly regioselective with respect to the hydroxy group at the pyridine ring. Comparative control experiments with *meta*-alkoxypyridine suggest that the *meta*-hydroxy group at the pyridine ring plays a key role during the homocoupling reaction.

Biaryls containing the 2,2′-bipyridine motif have become extremely important building blocks for supramolecular chemistry, macromolecular chemistry, as well as nanoscience due to their interesting chemical and material properties.[1] Especially important is the 3,3′-dihydroxy-2,2′-bipyridine framework, whereby the O–H proton is hydrogen bonded to the nitrogen atom of the pyridyl ring in the ground state. It has been widely used for studying excited-state intramolecular proton transfer processes, which play an important role in many chemical and biological systems. Moreover, 6,6′-dimethyl-3,3′-dihydroxy-2,2′-bipyridine is an important intermediate for elaboration of more complex ligands with potential application in medicinal diagnostics, biological labeling, molecular detection, and optoelectronic materials due to their intense fluorescent properties.[2] The conventional synthesis of bipyridine by a coupling reaction using transitional metals generally requires the prefunctionalization of the pyridine (e.g., halide or metal).[3] Recently, the direct oxidative coupling of unfunctionalized pyridine derivatives using Raney nickel and palladium on carbon (Pd/C) has also been achieved.[4] One of the major limitations of using transitional metals as catalysts for the oxidative coupling reaction for nitrogen-containing heteroarenes is the catalyst deactivation, thus leading to a slow reaction and low yield.[5] Therefore, the coupling of pyridine derivatives to form bipyridines remains a significant challenge. As such, extensive research has been carried out to develop new protocols based on transitional metals for the coupling of heteroaryls by the appropriate choice of ligands, such as Buchwald phosphanes,[6] bulky tri-alkylphosphanes,[7] and other di-alkylarylphosphanes.[8]

Recently, hypervalent iodine(III) reagents have been used successfully for the metal-free oxidative coupling between two unfunctionalized electron-rich arenes and heteroarenes for the direct synthesis of biaryls. However, the direct coupling of two unfunctionalized electron-deficient heteroarenes using hypervalent iodine(III) has not been reported. Herein, we chose to study the homocoupling reaction of hydroxypyridine derivatives. Hydroxypyridine was chosen to mimic the known homocoupling reaction of phenol derivatives using hypervalent iodine(III) reagents. The phenolic oxygen has been reported to react with phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis(trifluoroacetate) (PIFA) to increase the electrophilicity of the ring which can be attacked by another electron-rich aromatic ring to give biaryl.[9] We therefore envisaged that hydroxypyridine derivatives can also undergo a similar oxidative C–H/C–H homocoupling reaction using hypervalent iodine(III) to form dihydroxy-2,2′-bipyridine derivatives. The number of possible homocoupling products from the reaction of a substituted *meta*-hydroxy pyridine are shown in Scheme 1. Herein, we report on the highly regioselective homocoupling reaction of *meta*-hydroxypyridine derivatives using phenyliodine(III) diacetate (PIDA) to yield 3,3′-dihydroxy-2,2′-bipyridine derivatives with high efficiency.

Among the hypervalent iodine(III) reagents, we chose to use PIDA as it is cheap and less air-sensitive. Initial experiments were conducted in the search for a suitable solvent (acetone, benzene, dichloromethane, ether, ethyl acetate, 1,1,1-trifluoroethanol, tetrahydrofuran) for the homocoupling reaction of 2-methyl-5-hydroxypyridine at room temperature. Dichloromethane was found to be the best solvent, albeit low yields (20–30%) were obtained. Next, we examined the effect of reaction temperature using PIDA (Table 1, entries 2, 4, 5), and room temperature afforded the best yield. Assessment of the various base additives that have been studied[10] for coupling reactions using PIDA indicated Cs_2CO_3 to be more favorable (Table 1, entries 6–8). We found that 0.5 equivalent of Cs_2CO_3 was sufficient for the reaction. Under optimum conditions, the homocoupling product, 6,6′-dimethyl-(2,2′-bipyridine)-3,3′-diol (**2**) could be obtained in 70% yield and with high regioselectivity, as determined by NMR spectroscopy (Table 1, entry 11).

The scope and regioselectivity of the homocoupling reaction for a variety of hydroxy-pyridines and their derivatives were then investigated under the optimal conditions as outlined in Table 2. 2- and 4-Hydroxypyridine, (Table 2, entries 3, 4**)** did not

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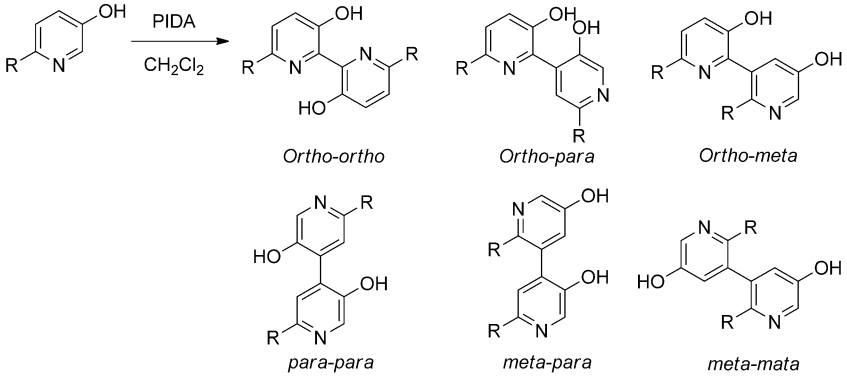
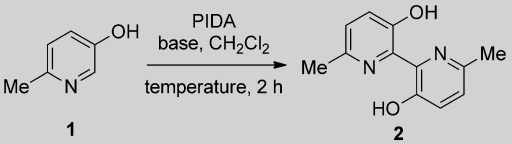


Scheme 1. Possible homocoupling product of substituted *meta*-hydroxypyridine.

Table 1. Optimization of the reaction conditions.



1 2

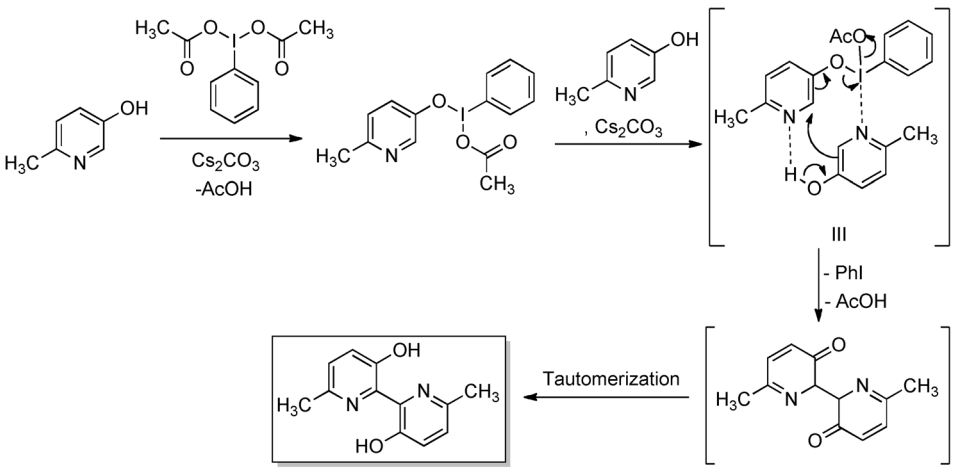
Entry	Pyridine [equiv]	PIDA [equiv]	*T* [°C]	Additives/ equiv	Yield [%][a]
1	1	0.5	rt	none	20
2	1	1	rt	none	30
3	1	2	rt	none	13
4	1	1	0 °C	none	15
5	1	1	40 °C	none	26
6	1	1	rt	Na_2CO_3/1 eq	36
7	1	1	rt	K_2CO_3/1 eq	24
8	1	1	rt	Cs_2CO_3/1.0 eq	41
9	1	1	rt	Cs_2CO_3/0.5 eq	47
10	2	1	rt	Cs_2CO_3/0.5 eq	52
11	3	1	rt	Cs_2CO_3/0.5 eq	70
12	4	1	rt	Cs_2CO_3/0.5 eq	72

[a] Yield estimated directly from the crude product by ^{1}H NMR spectroscopic analysis using 1,1,2,2-tetrachloroethane as an internal standard.

give rise to the homocoupling product dihydroxybipyridine, whereas 3-hydroxypyridine underwent a regioselective homocoupling reaction to give 3,3′-dihydroxy 2,2′-bipyridine (Table 2, entry 2). Thus, the homocoupling reaction is chemo- and regioselective for 3-hydroxypyridine. Next, various substituted *meta*-hydroxypyridines were examined for the homocoupling reaction under the same reaction conditions. Interestingly, all the 2-substituted-5-hydroxypyridine reacted smoothly to give regioselectively 6,6′-substituted-(2,2′-bipyridine)-3,3′-diol (Table 2, entries 1, 2, 5–10, and 13). The presence of an electron-withdrawing group at the 2-position slightly affected the reaction (Table 2, entry 10). Furthermore, we could synthesize poly-unfused aromatic rings readily from the homocoupling of 2-phenyl-5-hydroxypyridine (Table 2, entry 9). In the context of the *ortho*-regioselective homocoupling of 3-hydroxypyridine with respect to the hydroxy group, one may ask the question whether blocking this position would hamper the reaction. Here we found that no homocoupling product was obtained using 2-substituted-3-hydroxypyridine (Table 2, entries 11, 12). These results imply that substitution at the *ortho*-position with respect to the hydroxy group blocks the homocoupling reaction.

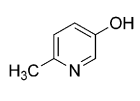
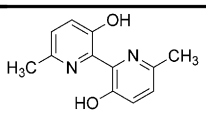
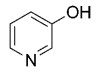
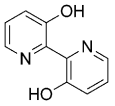
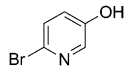
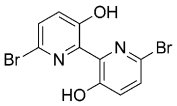
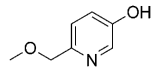
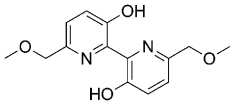
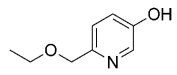
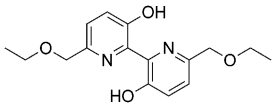
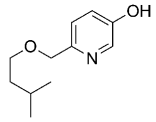
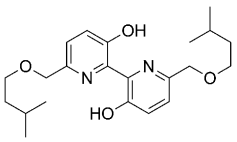
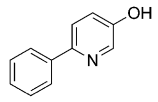
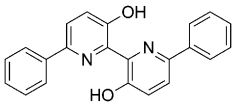
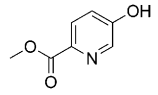
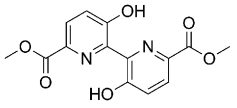
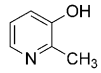
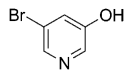
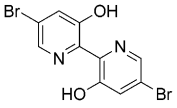
Two mechanisms may be postulated for the homocoupling reaction of hydroxypyridine with PIDA. One involves the reaction at the oxygen of the hydroxy group and the second involves the nitrogen of the pyridine ring to form the iodo(III) intermediates (Scheme 2). To gain further insights into the mechanism of the reaction, the hydroxy group was converted into the corresponding alkoxy derivatives. It was found that these ether derivatives did not undergo the homocoupling reaction (Table 3). The use of 2-methylpyridine itself also did not give rise to any coupling product. Based on this observation, we concluded that the hydroxy group at the *meta*-position of pyridine is essential for the homocoupling reaction with PIDA.

We further suggests a plausible mechanism to address the issue of regioselectivity (Scheme 2). The fact that the homocoupling reaction proceeded with excellent chemo- and regioselectivity suggests that the mechanism possibly involves an intramolecular concerted-like reaction, through the formation of intermediate **III** (Scheme 2). The intermediate **II** formed from the reaction of the hydroxy group with PIDA can coordinate with another molecule of the hydroxypyridine to form interme-



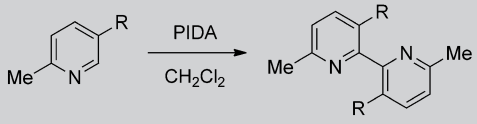
Scheme 2. Plausible mechanism for the homocoupling.

Table 2. Substrate scope of unactivated hydroxypyridyls for the homocoupling reaction.[a]

Entry	Substrate	Product	Yield [%][a]
1			70 (85)
2			32 (60)
3			0[b]
4			0[b]
5			49 (70)
6			69 (80)
7			64 (75)
8			66 (72)
9			66 (76)
10			46 (65)
11			0[b]
12			0[b]
13			53 (70)

[a] Unless otherwise mentioned, all reactions were carried out using substrate **1–8** (3.0 equiv), PIDA (1.0 equiv), and Cs_2CO_3 (0.5 equiv). Isolated yields. Yields estimated directly from the crude product by ^1H NMR spectroscopic analysis using 1,1,2,2-tetrachloroethane as an internal standard are given in parenthesis. [b] No coupling products were obtained.

Table 3. Investigation of the homocoupling reaction for the phenolic protection of hydroxypyridines.



Entry	R	Yield
1	H	No reaction
2	OMOM	No reaction
3	O*n*Bu	No reaction
4	Oallyl	No reaction
5	OBn	No reaction

diate **III**, which can then undergo a regioselective intramolecular reaction to form the product. The favorable coordination of the iodine group to the nitrogen of pyridine has been reported.[11] Thus, although the *ortho-ortho* regioselectivity of the homocoupling reaction seems surprising, it can be clearly explained. The addition of a protic polar solvent such as trifluoroethanol, which can disrupt the hydrogen-bonding pyridine coordination, was found to suppress the reaction. We also excluded the possibility of a radical reactivity through hypervalent iodine(III) induced single electron transfer (SET) because the addition of a radical scavenger such as 2,6-di-*tert*-butyl-4-methylphenol (BHT), TEMPO, and diphenylethylene (DPE) had no influence on the yield of the reaction.

Next, we performed a cross-over homocoupling reaction by using two different 6-substituted 3-hydroxypyridines (Scheme 3). We obtained three products that correspond to two homocoupling and one cross-coupling in a nearly 2:2:1 ratio. When the reaction was performed using a 6-substituted 3-hydroxypyridine and a differently 6-substituted 3-alkoxypyridine, only the homocoupling product from the 6-substituted 3-hydroxypyridine was obtained. These results of our cross-over coupling experiments clearly show that the reaction takes place intramolecularly and concerted-like.

In summary, a new metal-free selective homocoupling of *meta*-hydroxypyridine using iodine(III) has been developed. In this methodology, prefunctionalization of the pyridine is not required, and the coupling takes place exclusively at the *ortho*-position with respect to the hydroxypyridine. The 3,3′-dihydroxy-2,2′-bipyridine derivatives have been widely applied as ligands for coordination of transitional metals for many applications.

Experimental Section

General procedure for the preparation of pyridol derivatives (**2 a–i**). To a stirred solution of the pyridinol (**1 a–i**, 4.14 mmol, 3.0 equiv) in CH_2Cl_2 (8 mL) were added Cs_2CO_3 (0.69 mmol, 0.5 equiv) and PIDA (1.38 mmol, 1.0 equiv) at room temperature for 2 h. The solution was then filtered and washed with hot hexane, and then concentrated in vacuo. Purification of the residue by column chromatography on silica gel gave the corresponding bipyridium.

Acknowledgements

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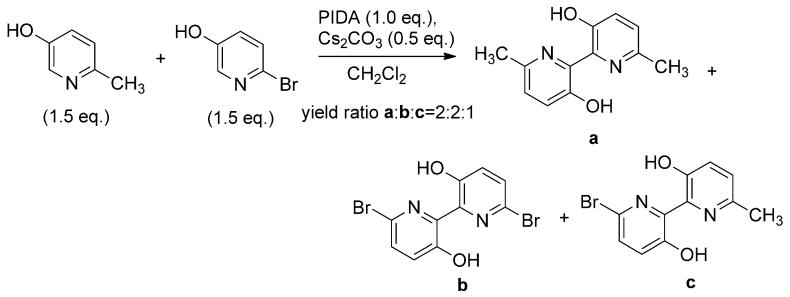

Scheme 3. Competitive homocoupling and crosscoupling.

Keywords: 3,3′-dihydroxy-2,2′-bipyridine · direct C–C bond formation · hypervalent iodine · *meta*-hydroxypyridines · metal-free C–H homocoupling reaction

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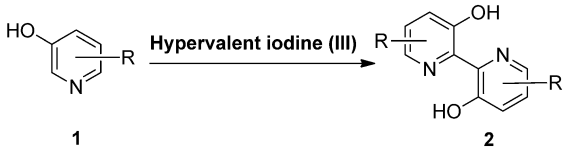

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The C–H homocoupling of *meta*-hydroxypyridines with phenyliodine(III) diacetate (PIDA) was carried out in dichloromethane at room temperature in the presence of cesium carbonate. The coupling reaction was found to be highly regioselective with respect to the hydroxy group at the pyridine ring.

Homocoupling Reactions

*Ping Syun Yang, Mi Ting Tsai, Meng Han Tsai, Chi Wi Ong**

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The Regioselective Homocoupling of *meta*-Hydroxypyridines with Hypervalent Iodine(III)