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# Dehydrogenative Synthesis of 2,2'-Bipyridyls through Regioselective Pyridine Dimerization

Shuya Yamada,[a] Takeshi Kaneda,[a] Philip Steib,[a] Kei Murakami,*[a] and Kenichiro Itami*[a,b]

**Abstract:** 2,2'-Bipyridyls have been utilized as indispensable ligands in metal-catalyzed reactions. The most streamlined approach for the synthesis of 2,2'-bipyridyls is the dehydrogenative dimerization of unfunctionalized pyridine. In this communication, we report on the palladium-catalyzed dehydrogenative synthesis of 2,2'-bipyridyl derivatives. The Pd catalysis effectively works with Ag(I) salt as the oxidant in the presence of pivalic acid. A variety of pyridines regioselectively react at C2-positions. This dimerization method is applicable for challenging substrates such as sterically hindered 3-substituted pyridines where the pyridines regioselectively react at C2-position. The reaction enables concise synthesis of twisted 3,3'-disubstituted-2,2'-bipyridyls as an underdeveloped class of ligands.

2,2'-Bipyridyls[1] represent one of the most fundamental and privileged scaffolds in metal-catalyzed reactions. For example, 4,4'-di-*tert*-butyl-2,2'-bipyridyl (dtbpy) has been regarded as a highly active ligand for aromatic C–H borylation.[2] $Ru(bpy)_3$, a ruthenium complex with three 2,2'-bipyridyls, is known as an efficient catalyst for emerging photoredox-catalyzed reactions.[3] Moreover, we have found that 2,2'-bipyridyls play a key role in C–H functionalization reactions such as C–H arylation of 5-membered heteroaromatics[4a] and aromatic C–H imidation.[4b]

Typically, 2,2'-bipyridyls are synthesized from 2-halopyridines through cross-coupling reactions or reductive dimerization.[5] Although these methods are reliable and well-established, additional steps to prepare 2-halogenated pyridines are required and thereby it is usually an expensive and time-consuming process. Moreover, halogenation of pyridine ring systems generally suffers from poor regioselectivity and harsh reaction conditions.[6] Since the catalytic activity of 2,2'-bipyridyls is strongly affected by their structural deformation, rapid and divergent syntheses of 2,2'-bipyridyl derivatives are valuable for catalyst/ligand development.

Dehydrogenative dimerization reaction of unfunctionalized pyridine is the most straightforward and attractive route from atom- and step-economical point of view. Such dehydrogenative bipyridyl synthesis was originally accomplished by heating a metal catalyst such as Raney nickel or palladium on charcoal in the pyridine solvent (neat conditions).[7] To date, several transition-metal-catalyzed dehydrogenative dimerizations of pyridine have been reported. For example, Suzuki and co-workers developed the dehydrogenative dimerization of 4-substituted pyridine under ruthenium or ruthenium/cobalt catalysis with evolution of hydrogen gas.[8] The group of Weix reported a dimerization and trimerization reaction of pyridine in the presence of palladium on charcoal as a catalyst.[9] While these examples clearly demonstrated the synthetic advantage of dehydrogenative dimerization, they focused mainly on 4-substituted pyridines as substrates. Consequently, the development of a general and practical method through pyridine C–H functionalization[10] to synthesize hitherto inaccessible 2,2'-bipyridyls has been in high demand.

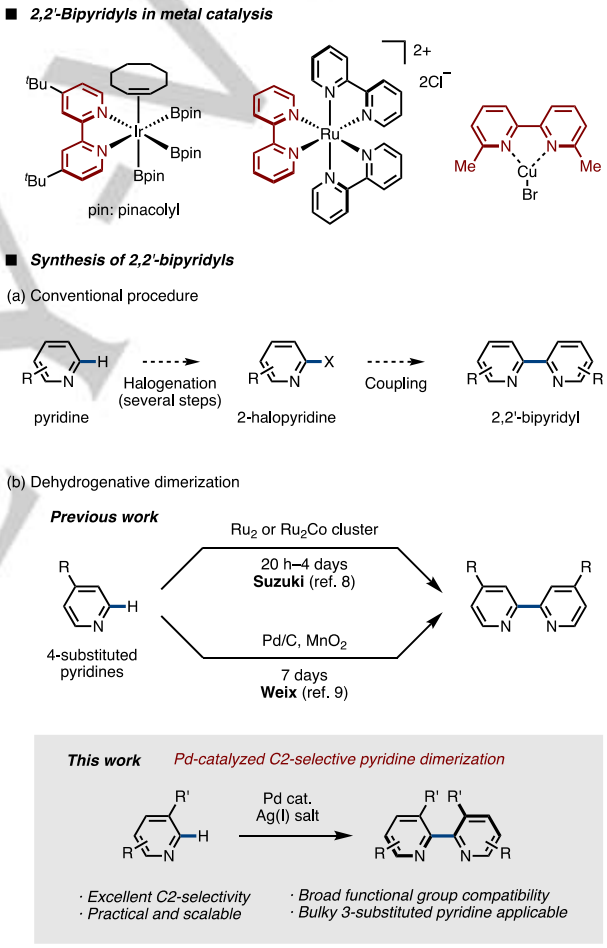


**Figure 1.** Representative 2,2'-bipyridyl ligands in transition metal catalysis and synthesis of 2,2'-bipyridyls.

To achieve this goal, we initiated our study on palladium-catalyzed pyridine dimerization. At first, we treated stoichiometric amount of palladium with pyridine. 4-*tert*-Butylpyridine (**1a**) was reacted with 0.50 mmol of $Pd(OAc)_2$ in cyclopentyl methyl ether (CPME) at 140 °C (Figure 2). The reaction smoothly proceeded to give 4,4'-di-*tert*-butyl-2,2'-bipyridyl (**2a**) in 98% NMR yield (0.49 mmol). Mechanistically, the reaction would initiate from a pyridine C2–H activation by palladium(II) acetate to form pyridylpalladium **A**. Successive palladation affords bis(pyridyl)palladium intermediate **B**, which

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undergoes reductive elimination to furnish product **2a** and Pd(0). We envisioned that the addition of an appropriate oxidant could perform this reaction in a catalytic manner.

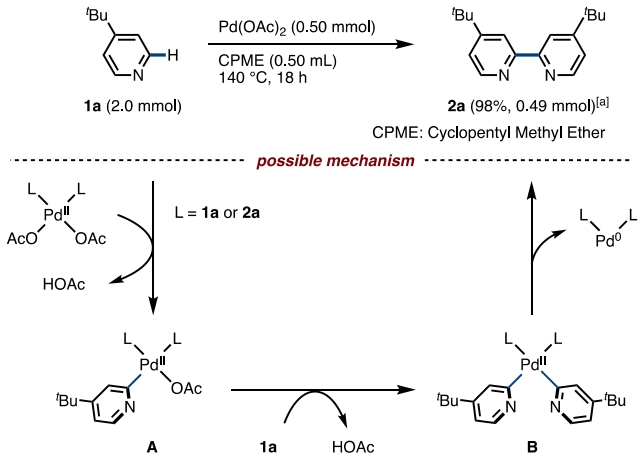
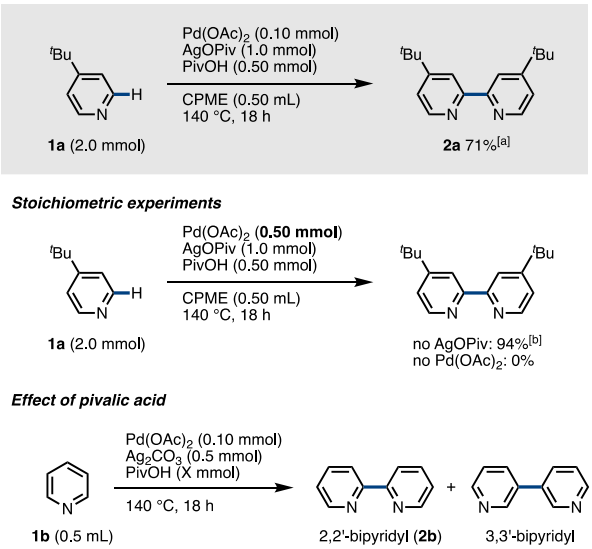



**Figure 2**. $Pd(OAc)_2$-mediated formation of **2a**. [a] $^1H$ NMR yield based on Pd using 1,1,2,2-tetrachloroethane as the internal standard.

After extensive investigation, we have established a palladium-catalyzed dehydrogenative dimerization of pyridines. The optimal conditions for the dimerization are the following: 4-*tert*-butylpyridine (**1a**) was heated in the presence of silver pivalate, pivalic acid, and catalytic amount of $Pd(OAc)_2$ in CPME at 140 °C providing **2a** in 71% isolated yield (Figure 3). In our previous study, we observed 2,2'-bipyridyl as a side product




| entry | X | 2,2'-bipyridyl (**2b**)[c] | 3,3'-bipyridyl[c] |
|---|---|---|---|
| 1 | 0 | 2% | 5% |
| 2 | 0.25 | 5% | 7% |
| 3 | 0.50 | 16% | 4% |
| 4 | 1.0 | 56% | trace |

**Figure 3.** Optimized conditions for pyridine dimerization. All $^1H$ NMR yields were determined using 1,1,2,2-tetrachloroethane as the internal standard. [a] Isolated yield based on Ag as the one electron oxidant. [b] $^1H$ NMR yield based on Pd. [c] $^1H$ NMR yield based on Ag.

when benzyl bromide was used as the oxidant.[11] Unfortunately, the use of organic halides were not sufficiently effective for the dimerization. After extensive screening of oxidants, silver salts were found to be the most effective to achieve the envisioned catalytic cycle. The choice of solvent was not essential for the reaction efficiency where the use of other solvents such as toluene, DMF and 1,4-dioxane resulted in similar yields as CPME (see SI for the details). We then performed control experiments to get insights into each reaction parameter. First, we confirmed the role of silver salt as the sacrificial oxidant. The reaction of **1a** using 0.50 mmol of $Pd(OAc)_2$ without AgOPiv gave **2a** in 94% yield. On the other hand, the dimerization of **1a** did not proceed without the addition of $Pd(OAc)_2$. Consequently, silver salt acted as the terminal oxidant to regenerate the Pd(II) intermediate in the catalytic cycle. Next, the effect of $PivO^-$/PivOH was investigated. The addition of PivOH was proved to enhance the reaction efficiency. Pyridine was reacted in the presence of catalytic amount of $Pd(OAc)_2$ and $Ag_2CO_3$ as the oxidant in CPME. In the absence of PivOH, the reaction was relatively slow and both regioisomers, 2,2'-bipyridyl (**2b**) and 3,3'-bipyridyl, were observed in the crude mixture. Increasing the amount of PivOH accelerated the C2-dimerization reaction. Finally, the yield of **2b** was raised to 56% when employing 1.0 mmol of pivalic acid. The satisfactory amount of PivOH would help to reproduce the reactive $Pd(OPiv)_2$ intermediate.[12]

We next investigated the substrate scope of the dimerization reaction (Table 1). Unsubstituted pyridine (**1b**) smoothly dimerized to give **2b** in 80% yield in the presence of 1,10-phenanthroline. Remarkably, as observed in the control experiments, no regioisomeric bipyridyls were observed in the crude mixture.[13] The reactions of 4-substituted pyridine under the optimized conditions were sluggish where the products **2c**, **2d** and **2e** were obtained in 46%, 47% and 41% yields, respectively. In order to improve the yields, we investigated the effect of ligands. Fortunately, the addition of dtbpy was effective where the product yields increased to 60% (**2c**), 56%(**2d**) and 70% (**2e**) yields, respectively. We postulated that the addition of a bidentate ligand would suppress the product inhibition, which could be caused by coordination of the resulting bipyridyl to the palladium catalyst. It is noteworthy that **1c** was a challenging substrate in dehydrogenative dimerization reaction.[8c] For the reaction of 4-phenylpyridine, the ligand effect on the product yield was not significant as **2f** was isolated in 56% yield without and 54% NMR yield with dtbpy. Sterically hindered 2-picoline participated in dimerization with dtbpy to afford **2g** albeit in low yield. 3-Picoline was converted to two regioisomers **2h** and **2h'** in 56% total yield with a ratio of 34:66. 3,5-Disubstituted pyridines were applicable for the dimerization. The reaction provided the corresponding products in moderate yields (**2i**, **2j** and **2j'**). It should be highlighted that regioisomers **2h**/**2h'** and **2j**/**2j'** are easily separable with the typical silica-gel purification. Other 6-membered heteroaromatics such as quinoline, pyrimidine and 2,6-dimethylpyrazine were applicable to give the dimerized products (**2k**–**2m**) in moderate yields. Unfortunately, our attempts to apply the dimerization protocol to unsymmetrical 2,2'-bipyridyl synthesis (cross-dehydrogenative coupling[11,14]) was not successful for the reaction between **1a** and **1i**; the dimerized products **2a**, **2i** and the desired cross-coupled product

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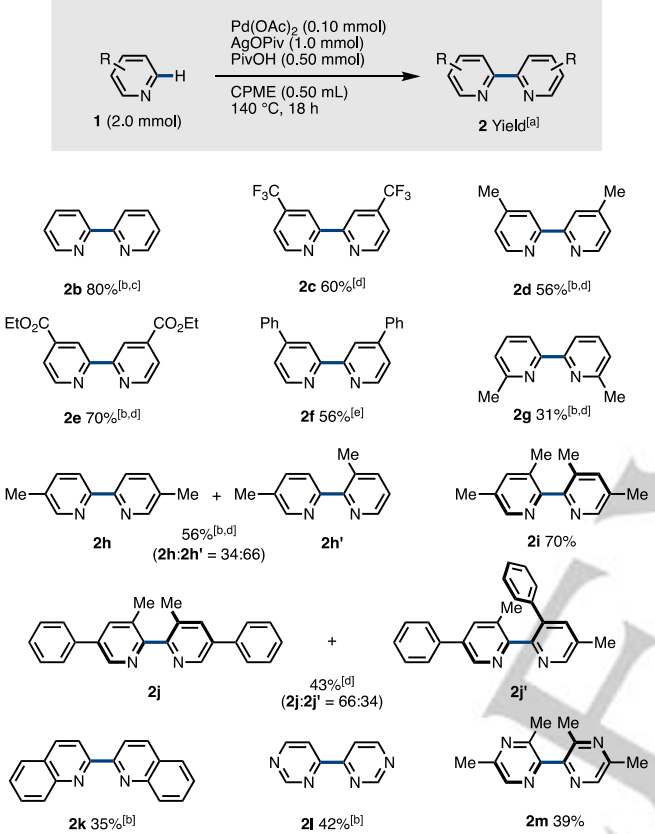
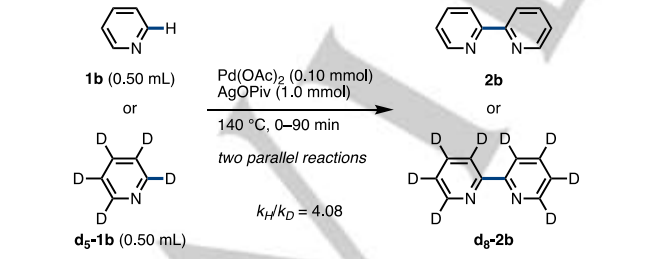
**2n** were provided as a mixture (see SI). Further studies on cross-dehydrogenative coupling are ongoing in our laboratory.

To gain some insight into the reaction mechanism, intermolecular kinetic isotope effect was investigated (Scheme 1). In parallel, pyridine (**1b**) or $d_5$-pyridine (**$d_5$-1b**) were subjected to the dimerization. A significant isotope effect ($k_H/k_D$ = 4.08) was observed between **1b** and **$d_5$-1b**. The results suggested that C–H bond cleavage would be the rate-determining step.

**Table 1.** Substrate scope of dimerization reaction of pyridine **1**.



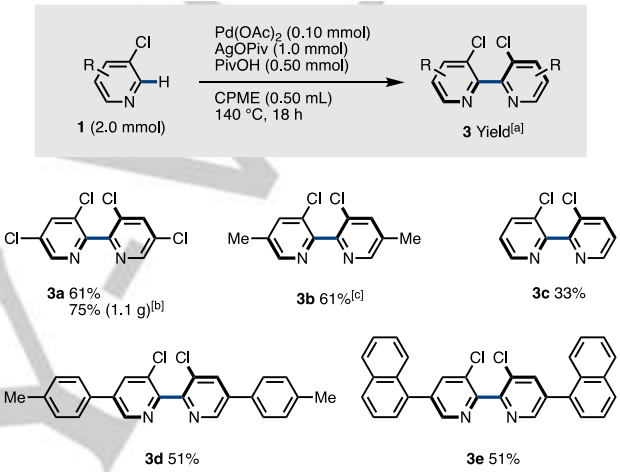

[a] Isolated yield based on Ag. [b] 0.50 mL of **1** was used instead of CPME. [c] 0.50 mmol of 1,10-phenanthroline was added as a ligand. [d] 0.10 mmol of dtbpy was added as a ligand. [e] 36 h.




**Scheme 1.** Kinetic isotope effect experiment

The efficient dimerization of sterically hindered pyridine **1i** and **1j** prompted us to study the dimerization of 3-chloropyridines (Table 2). 3,5-Dichloropyridine was found to dimerize predominantly at C2-position to give the corresponding 2,2'-bipyridyl **3a** in 61% yield. Gram scale preparation of **3a** was also feasible in 75% yield (1.1 g) where more concentrated conditions (20 mmol of 3,5-dichloropyridine in 1.0 mL CPME) were employed to increase the reaction rate. The dimerization of 3-chloro-5-methylpyridne, an unsymmetrically substituted pyridine, delivered **3b** as a major product with concomitant formation of regioisomer **3b'** in 17% yield (for the structure of **3b'**, see SI). 3-Chloropyridine underwent the C2-selective dimerization to furnish **3c** as the sole product.[15] When disubstituted pyridine derivatives bearing aryl and chloro groups were used as substrates, the corresponding dimerization occurred only at C2 position without formation of any regioisomers (**3d** and **3e**).[16]

**Table 2.** Substrate scope of dimerization reaction of 3-chloropyridines.

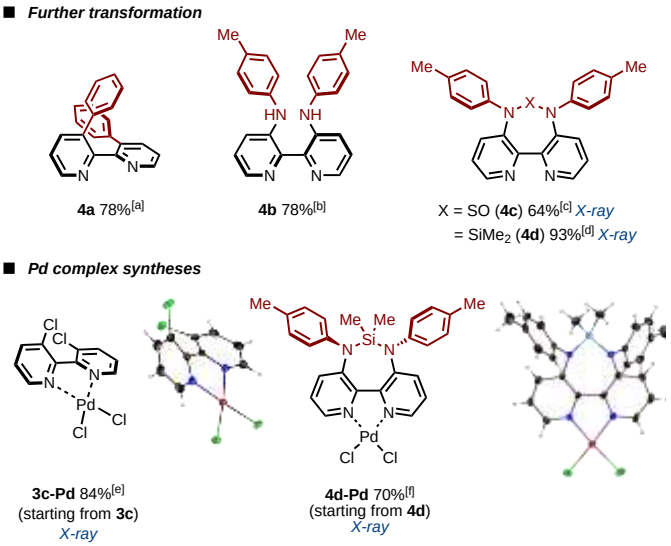



[a] Isolated yield based on Ag. [b] 20 mmol scale using 1.0 mL of CPME. [c] The regioisomer **3b'** was isolated in 17% yield (**3b**:**3b'** = 72:28).

3-Chloropyridine dimers **3** are convertible platforms to access various 3,3'-disubstituted-2,2'-bipyridyls, an underdeveloped class of bidentate ligands.[5a] Generally, such 2,2'-bipyridyls are synthesized through multistep transformation starting from 1,10-phenanthroline or the corresponding 3-substituted pyridine.[17] Setting 3,3'-dichloro-2,2'-bipyridyl (**3c**) as a model substrate, we demonstrated further derivatization (Figure 4). The Suzuki–Miyaura cross-coupling reaction with phenylboronic acid provided 3,3'-diphenyl-2,2'-bipyridyl (**4a**) in 78% yield. The twofold Buchwald–Hartwig amination of **3c** with *p*-toluidine produced **4b** in 78% yield. The resulting **4b** could react with electrophiles to give a new form of bipyridyls embedding the 7-membered ring. For example, the reaction of **4b** with thionyl chloride in the presence of triethylamine successfully introduced sulfinyl group to form **4c** in 64% yield. Dimethylsilyl group was installable to give **4d** in 93% yield. The structures of **4c** and **4d** were unambiguously confirmed by X-ray crystallographic analysis. Subsequently, twisted 2,2'-bipyridyls were treated with palladium chloride. Heating the mixtures of $PdCl_2$ and 2,2'-bipyridyls (**3c** or **4d**) afforded the corresponding palladium complexes **3c-Pd** or **4d-Pd**. In the $^1$H NMR spectra of these palladium complexes, the signals of hydrogen atoms on pyridine core appeared as three different signals, which reflected that both palladium complexes are axially $C_2$ symmetric molecules. Finally, the structures of **3c-Pd** and **4d-Pd** were confirmed by X-ray crystal structure analysis (for the structural

details, see SI). Overall, 3-chloropyridine dimers **3** are found to be promising platform for constructing axially twisted 2,2'-bipyridyl ligands.

**Figure 4.** Derivatization of **3c**.




[a] **3c**, $PhB(OH)_2$, $Pd(OAc)_2$, XPhos, $K_3PO_4$, $^nBuOH/H_2O$, 120 °C. [b] **3c**, *p*-toluidine, $Pd(OAc)_2$, dppf, $NaO^tBu$, toluene, 100 °C. [c] **4b**, $SOCl_2$, $NEt_3$, THF, rt. [d] **4b**, $SiMe_2Cl_2$, $^nBuLi$, THF, 0 °C to rt. [e] $PdCl_2$ (0.20 mmol), **3c** (1.0 equiv), MeOH (1.0 mL), 80 °C. [f] $PdCl_2$ (0.10 mmol), **4d** (1.0 equiv), MeCN (1.0 mL), 80 °C.

In summary, we have developed the Pd-catalyzed C2-selective dehydrogenative dimerization reaction of pyridines to afford the corresponding 2,2'-bipyridyls. The present catalysis enables rapid and scalable 2,2'-bipyridyl ligand syntheses with only simple reagents, thereby it benefits to practical synthetic applications. Remarkably, straightforward preparation of axially twisted 2,2'-bipyridyl ligands is feasible with our protocol, which stimulate the discovery of new application of twisted bidentate ligands.

## Acknowledgments

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**Keywords:** dehydrogenative coupling • C–H arylation • 2,2'-bipyridyl • palladium catalyst • pyridine functionalization

[1] a) C. Kaes, A. Katz, M. W. Hosseini, *Chem. Rev.* **2000**, *100*, 3553–3590; b) V. Marin, E. Holder, R. Hoogenboom, U. S. Schubert, *Chem. Soc. Rev.* **2007**, *36*, 618–635; c) H.-L. Kwong, H.-L. Yeung, C.-T. Yeung, W.-S. Lee, C.-S. Lee, W.-L. Wong, *Coord. Chem. Rev.* **2007**, *251*, 2188–2222.

[2] I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890-931.

[3] C. K. Preir, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363.

[4] a) S. Yanagisawa, K. Ueda, H. Sekizawa, K. Itami, *J. Am. Chem. Soc.* **2009**, *131*, 14622–14623.; b) T. Kawakami, K. Murakami, K. Itami, *J. Am. Chem. Soc.* **2015**, *137*, 2460–2463.

[5] Reviews for synthetic methods of 2,2'-bipyridyls: a) G. R. Newcome, A. K. Patri, E. Holder, U. S. Schubert, *Eur. J. Org. Chem.* **2004**, 235–254; b) M. Hapke, L. Brandt, A. Lützen, *Chem. Soc. Rev.* **2008**, *37*, 2782–2797. Selected examples: c) F. Havas, N. Leygue, M. Danel, C. Galup, C. Picard, *Tetrahedron* **2009**, *65*, 7673–7686; d) J. L. Oliveira, M. J. Silva, T. Florêncio, K. Urgin, S. Sengmany, E. Leónel, J.-Y. Nédélec, M. Navarro, *Tetrahedron* **2012**, *68*, 2383–2390; e) J. A. Buonomo, D. A. Everson, D. J. Weix, *Synthesis* **2013**, *45*, 3099–3102.

[6] a) S. M. McElvain, M. A. Goese, *J. Am. Chem. Soc.* **1943**, *65*, 2227–2233. For recent improved methods using pyridine *N*-oxide, see: b) S. E. Wengryniuk, A. Weickgenannt, C. Reiher, N. A. Strotman, K. Chen, M. D. Eastgate, P. S. Baran, *Org. Lett.* **2013**, *15*, 792–795; c) Y. Chen, J. Huang, T.-L. Hwang, M. J. Chen, J. S. Tedrow, R. P. Farrell, M. M. Bio, S. Cui, *Org. Lett.* **2015**, *17*, 2948–2951.

[7] For Raney Ni catalyst, see: a) G. M. Badger, W. H. F. Sasse, *J. Chem. Soc.* **1956**, 616–620. For Pd on charcoal catalyst, see: b) H. Rapoport, R. Iwamoto, J. R. Tretter, *J. Org. Chem.* **1960**, *25*, 372–373; c) P. K. Ghosh, T. G. Spiro, *J. Am. Chem. Soc.* **1980**, *102*, 5543–5549; d) H. Hagelin, B. Hedman, I. Orabona, T. Åkermark, B. Åkermark, C. A. Klug, *J. Mol. Catal. A: Chem.* **2000**, *164*, 137–146; e) J. Polin, E. Schmohel, V. Balzani, *Synthesis* **1998**, *1998*, 321–324.

[8] a) T. Kawashima, T. Takao, H. Suzuki, *J. Am. Chem. Soc.* **2007**, *129*, 11006–11007; b) T. Takao, T. Kawashima, H. Kanda, R. Okamura, H. Suzuki, *Organometallics* **2012**, *31*, 4817–4831; c) M. Nagaoka, T. Kawashima, H. Suzuki, T. Takao, *Organometallics* **2016**, *35*, 2348–2360.

[9] M. T. Robo, M. R. Prinsell, D. J. Weix, *J. Org. Chem.* **2014**, *79*, 10624–10628.

[10] a) P. C. Gros, Y. Fort, *Eur. J. Org. Chem.* **2009**, 4199–4209; b) Y. Nakao, *Synthesis* **2011**, *20*, 3209–3219; c) D. E. Stephens, O. V. Larionov, *Tetrahedron* **2015**, *71*, 8683–8716.; d) K. Murakami, S. Yamada, T. Kaneda, K. Itami, *Chem. Rev.* **2017**, *117*, 9302–9332.

[11] S. Yamada, K. Murakami, K. Itami, *Org. Lett.* **2016**, *18*, 2415–2418.

[12] For the acceleration of C–H bond metalation with carboxylate ligand, see: L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315–1345.

[13] Recent reports on catalytic homo-coupling reaction of azines: a) G.-L. Gao, W. Xia, P. Jain, J.-Q. Yu, *Org. Lett.* **2016**, *18*, 744–747; b) X.-W. Chen, H. Zhao, B. Xiong, H.-F. Jiang, P. H. Dixneuf, M. Zhang, *Org. Biomol. Chem.* **2017**, *15*, 6093–6097.

[14] For recent reviews on cross dehydrogenative coupling, see: a) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74–100; b) C. Liu, J. Yuan, M. Gao, S. Tang, W. Li, R. Shi, A. Lei, *Chem. Rev.* **2015**, *115*, 12138–12204; c) Y. Yang, J. Lan, J. You, *Chem. Rev.* **2017**, *117*, 8787–8863. Selected examples: d) X. Gong, G. Song, H. Zhang, Z. Li, *Org. Lett.* **2011**, *13*, 1766–1769; e) W.-C. Lee, T.-H. Wang, T.-G. Ong, *Chem. Commun.* **2014**, *50*, 3671–3673.

[15] Another approach with Glaser–Hay-type reactions: a) H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2009**, *131*, 17052–17053; b) T. Truong, J. Alvarado, L. D. Tran, O. Daugulis, *Org. Lett.* **2010**, *12*, 1200–1203.

[16] Cross-dehydrogenative coupling of 3-chloropyridine with 5-membered heteroaromatics showed the same regioselectivity: B. Liu, Y. Huang, J. Lan, F. Song, J. You, *Chem. Sci.* **2013**, *4*, 2163–2167.

[17] a) J. J. Rebek, T. Costello, R. Wattley, *J. Am. Chem. Soc.* **1985**, *107*, 7487–7493; b) R. P. Thummel, *Tetrahedron* **1991**, *47*, 6851–6886; c) P. N. W. Baxter, J. A. Connor, J. D. Wallis, D. C. Povey, A. K. Powell, *J. Chem. Soc., Perkin Trans. 1* **1992**, 1601–1606; d) A. M. W. C. Thompson, J. C. Jeffery, D. J. Liard, M. D. Ward, *J. Chem. Soc. Dalton Trans.* **1996**, 879–884; e) J. Durand, E. Zangrand, C. Carfagna, B. Milani, *Dalton Trans.* **2008**, 2171–2182.

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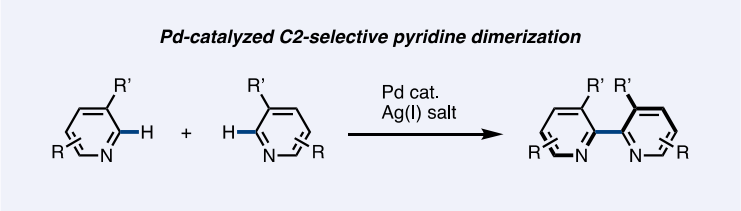


**Dehydrogenative dimerization**: The palladium-catalyzed dehydrogenative C2-selective dimerization reaction of pyridine is described. A variety of 2,2'-bipyridyls can be prepared directly from unfunctionalized pyridine without additional pre-halogenation or pre-metalation steps. The reaction is applicable to a series of sterically hindered 3-substituted pyridine derivatives. The reaction enables concise synthesis of twisted 3,3'-disubstituted-2,2'-bipyridyls as an underdeveloped class of ligands.

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