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Hao Li, Jossian Oppenheimer, Milton R. Smith III, Robert E. Maleczka Jr.

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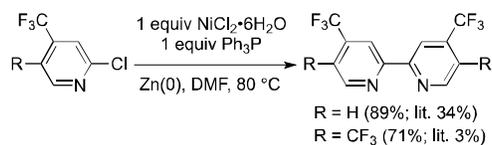
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Hao Li, Jossian Oppenheimer, Milton R. Smith, III, and Robert E. Maleczka, Jr.





Improved Synthesis of Electron Deficient Bipyridines

Hao Li,^a Jossian Oppenheimer,^b Milton R. Smith, III,^a and Robert E. Maleczka, Jr.^{a*}

^a Department of Chemistry, Michigan State University, 578 S. Shaw Lane, East Lansing, Michigan, 48824, United States

^b The Dow Chemical Company, Process Chemistry & Development, Core R&D, Midland, Michigan 48674, United States

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ABSTRACT

Symmetric bipyridines commonly serve as ligands for various types of catalytic processes. Nickel catalyzed Ullman couplings are often used to prepare such bipyridines, however for electron deficient substrates low conversions and/or yields are often reported. We herein report an improved synthesis of trifluoromethyl substituted bipyridines using stoichiometric amounts of Zn(0), NiCl₂·6H₂O, and Ph₃P. This modified procedure enables a >20 fold improvement over the previously reported yield for the synthesis of 4,4',5,5'-tetrakis(trifluoromethyl)-2,2'-bipyridine.

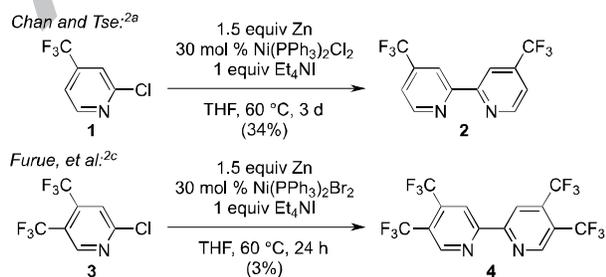
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1. Introduction

Symmetric bipyridine ligands are common to a variety of metal-mediated processes. Among these trifluoromethyl substituted bipyridines have found use in dye-sensitized solar cells and other applications.¹ Their preparation is often achieved through nickel catalyzed Ullman coupling of a 2-halopyridine, however low yields are often observed when such pyridines are electron deficient.² While the poor reactivity of some electron deficient pyridines can be mitigated by palladium or copper catalysis,³ procedures for the efficient synthesis of bipyridines from 2-chloropyridines bearing trifluoromethyl substituents have remained elusive. We hereby report economic syntheses of 4,4'-bis(trifluoromethyl)-2,2'-bipyridine (btfbpy) and 4,4',5,5'-tetrakis(trifluoromethyl)-2,2'-bipyridine (ttfbpy) that proceed in synthetically useful yields.

2. Results and Discussion

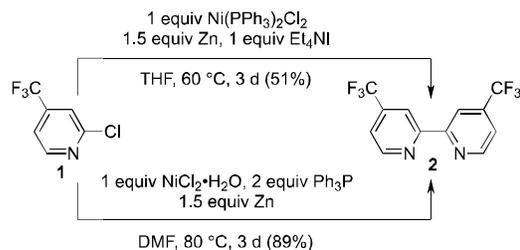
Scheme 1. Previously reported syntheses of *bis*- and *tetra*-CF₃ substituted bipyridines via 2-chloropyridines.



During the course of our research on Ir-catalyzed borylations,⁴ we came across the need for electron deficient bipyridine ligands. We were specifically interested in 4,4'-bis(trifluoromethyl)-2,2'-bipyridine (**2**) and 4,4',5,5'-tetrakis(trifluoromethyl)-2,2'-bipyridine (**4**). While literature preparations exist for both **2**^{2a} and **4**,^{2c} we were disappointed with the reported yields, especially the 3% yield for **4** (Scheme 1). Even though our plans for these ligands were catalytic in nature, the need to explore their reactivity across a series of experiments, the high cost of 2-chloropyridines **1** and **3**, and the anticipated scale of the final application,⁵ demanded better yields for the synthesis of these ligands, especially **4**.

2.1. Improving the synthesis of bpy(CF₃)₂ (**2**)

Scheme 2. Improved synthesis of bpy(CF₃)₂ (**2**).



We first examined the synthesis of compound **2**. At 30 mol % the literature synthesis of **2** already used relatively high loadings of Ni(PPh₃)₂Cl₂.^{2a} Nonetheless, we sought to determine if stoichiometric Ni catalyst would afford a significant increase in the yield of compound **2** (Scheme 2). We were please

* Corresponding author. Tel.: +1-517-353-0834; fax: +1-517-353-1793; e-mail: maleczka@chemistry.msu.edu

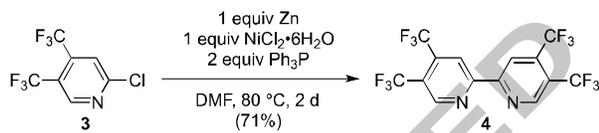
to see that this change led to a 50% boost in yield, but recognized that if 1 equiv of Ni(II) would be necessary a more economical replacement for Ni(PPh₃)₂Cl₂ would also be required.

An obvious alternative would be to form Ni(PPh₃)₂Cl₂ from NiCl₂ and PPh₃ in situ as NiCl₂•6H₂O and PPh₃ are both readily available in kilogram quantities at a fraction the cost of the preassembled catalyst. We chose DMF as the solvent⁶ to enable higher reaction temperatures and possibly eliminate the need for Et₃Ni by virtue of better solubility. As Scheme 2 shows, these modifications not only made the reaction more economical, but also improved the reaction outcome as **2** was isolated in 89% yield.⁷

2.2. Improving the synthesis of bpy(CF₃)₄ (**4**)

Deeming the synthesis of **2** efficient enough for our needs, we then turned to the more challenging 4,4',5,5'-tetrakis(trifluoromethyl)-2,2'-bipyridine (tfbpy) (**4**). Directly applying the modified conditions improved the isolated yield of **4** from **3**^{2c} to 31%. We attempted to further optimize the reaction by doubling the zinc load. After 48 hours of heating, GC-MS indicated the full consumption of **3**, but the desired product was not found. Instead, two byproducts were isolated in a combined 18% yield, for which all spectroscopic data pointed to isomeric structures of bpy(CF₃)₃CH₃.⁸ Presumably the excess Zn led to reduction of one of the CF₃ groups,⁹ perhaps under Ni catalysis.¹⁰ Given this outcome, we then reduced the load of Zn to 1 equivalent. This eliminated the byproduct formation and afforded bpy(CF₃)₄ (**4**) in 71% isolated yield¹¹ (Scheme 3), representing a >20 fold increase over the previously reported yields for this compound.^{2c} Usefully this procedure could be run at 10 mmol scale with little change in the isolated yield (67%).

Scheme 3. Improved synthesis of bpy(CF₃)₄ (**4**).



3. Conclusions

Through the use of stoichiometric Ni(II), yields for the preparation of two CF₃ substituted electron deficient bipyridine ligands have been significantly improved over those previously reported. The downside of needing 1 equiv of catalyst was minimized by the finding that NiCl₂•6H₂O and PPh₃ provided an economical alternative to Ni(PPh₃)₂Cl₂. We also note that the stoichiometry of Zn used in these Ullman couplings is impactful as excess Zn can lead to unwanted reduction of the CF₃ group. This should be noted when designing syntheses of extremely electron deficient bipyridines or biaryls under similar conditions.

Acknowledgments

We thank the Dow Chemical Company for funding, Shawn Feist (Dow) for helpful discussions and Dr. Richard Staples (MSU) for crystallographic analysis.

References and notes

- For recent examples see: (a) Coe, B. J.; Helliwell, M.; Raftery, J.; Sanchez, S.; Peers, M. K.; Scrutton, N. S. *Dalton Trans.* **2015**, *44*, 20392–20405. (b) Takizawa, S.-y.; Shimada, K.; Sato, Y.; Murata, S. *Inorg. Chem.* **2014**, *53*, 2983–2995. (c) Steves, J. E.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 15742–15745. (d) Gueden-Silber, T.; Klein, K.; Seitz, M. *Dalton Trans.* **2013**, *42*, 13882–13888.

- (a) Chan, K. S.; Tse, A. K. S. *Synth. Commun.* **1993**, *23*, 1929–1934. (b) Iyoda, M.; Otsuka, H.; Sato, K.; Nisato, N.; Oda, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 80–87. (c) Furue, M.; Maruyama, K.; Oguni, T.; Naiki, M.; Kamachi, M. *Inorg. Chem.* **1992**, *31*, 3792–3795. (d) McFarland, S. A.; Lee, F. S.; Cheng, K. A. W. Y.; Cozens, F. L.; Schepp, N. P. *J. Am. Chem. Soc.* **2005**, *127*, 7065–7070. (e) Crouch, R. D.; Nelson, T. D. *Cu, In Ni, and Pd Mediated Homocoupling Reactions in Biaryl Syntheses: The Ullmann Reaction*, John Wiley & Sons: New York, 2004.
- (a) Coe, B. J.; Peers, M. K.; Scrutton, N. S. *Polyhedron* **2015**, *96*, 57–65. (b) Schultz, D. M.; Sawicki, J. W.; Yoon, T. P. *Beilstein J. Org. Chem.* **2015**, *11*, 61–65. (c) Benson, E. E.; Grice, K. A.; Smieja, J. M.; Kubiak, C. P. *Polyhedron* **2013**, *58*, 229–234. (d) Hsu, C. M.; Li, C. B.; Sun, C. H. *J. Chin. Chem. Soc.-Taip.* **2009**, *56*, 873–880.
- (a) Jayasundara, C. R. K.; Unold, J. M.; Oppenheimer, J.; Smith, M. R., III; Maleczka, R. E.; Jr. *Org. Lett.* **2014**, *16*, 6072–6075. (b) Ghaffari, B.; Preshlock, S. M.; Plattner, D. L.; Staples, R. J.; Maligres, P. E.; Krska, S. W.; Maleczka, R. E.; Jr.; Smith, M. R., III *J. Am. Chem. Soc.* **2014**, *136*, 14345–14348. (c) Mkhali, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890–931. (d) Roš, A.; Fernández, R.; Lassaletta, J. M. *Chem. Soc. Rev.* **2014**, *43*, 3229–3243.
- (a) Bisht, R.; Chattopadhyay, B. *J. Am. Chem. Soc.* **2016**, *138*, 84–87. (b) Smith, M. R., III; Maleczka, R. E., Jr.; Li, H.; Jayasundara, C.; Oppenheimer, J. U.S. Pat. Appl. 2015, US 20150065743 A1 20150305. (c) Oppenheimer, J.; Maleczka, R. E.; Smith, M. R.; Li, H.; Sabasovs, D. 246th American Chemical Society National Meeting, September 8–12, Indianapolis, IN; The Division of Organic Chemistry of the American Chemical Society: Washington, DC, 2013; ORGN 381.
- Neither NiCl₂•6H₂O or DMF were dried prior to use.
- See the Supplementary Material for experimental details.
- See the Supplementary Material for the putative structure assignment of the isomers of bpy(CF₃)₃CH₃.
- Greene, J. L., Jr.; Montgomery, J. A. *J. Med. Chem.* **1963**, *6*, 294–297.
- Zhao, W.; Wu, J.; Cao, S. *Adv. Synth. Catal.* **2012**, *354*, 574–578.
- Representative Experimental: In a Schlenk flask, NiCl₂•6H₂O (238 mg, 1.0 mmol) and PPh₃ (524 mg, 2.0 mmol) were dissolved in 5 mL of reagent grade DMF. The resulting blue solution was sparged by argon for 30 min. Activated¹² zinc dust (65 mg, 1.0 mmol) was added and the mixture was stirred with further argon sparging for 30 min. To the resulting red-brown slurry was added 2-chloro-4,5-bis(trifluoromethyl)pyridine (**3**) (250 mg, 1 mmol). The Schlenk flask was connected to an argon manifold through a water cooled condenser and heated in an 80 °C oil bath for 48 h, at which time GC-MS showed full consumption of **3**. The reaction was then poured into a beaker containing 2 mL ammonia (24%, aq) and 20 g ice. The resulting mixture was extracted with CH₂Cl₂ (3 x 20 mL). The combined organics were washed with water (2 x 50 mL), dried over MgSO₄, filtered, and concentrated on a rotary evaporator. The residue was purified on a silica gel column (4:1 hexane/ CH₂Cl₂) giving 152 mg (71%) of **4** as a white solid; mp 127–120 °C; ¹H NMR (500 MHz, CDCl₃) δ 9.20 (s, 2 H), 8.96 (s, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 157.9, 148.9 (q, J = 6.7 Hz), 137.8 (q, J = 36 Hz), 123.8 (q, J = 32 Hz), 122.1 (q, J = 274 Hz), 121.5 (q, J = 275 Hz), 119.2 (q, J = 5.7 Hz); ¹⁹F NMR (470 MHz, CDCl₃) δ –59.2 (q, J = 12.2 Hz), –61.6 (q, J = 12.2 Hz).
- Yamamura, S.; Toda, M.; Hirata, Y. *Org. Synth.* **1973**, *53*, 86.
- A small sample was recrystallized from Et₂O at rt and an x-ray crystal structure was obtained and deposited in the Cambridge Crystallographic Data Centre and allocated deposition number CCDC 1044026.

Supplementary Material

Supplementary material (experimental details for the preparation of **2** and **4**, the preparations of putative structure assignment of bpy(CF₃)₃CH₃, NMR spectra, and X-ray crystallographic data for **4**) associated with this article can be found, in the online version, at <http://dx.doi.org/xx.xxxx/j.tetlet.2015.xx.xxx>.

- An improved synthesis of trifluoromethyl substituted bipyridines is reported
- Trifluoromethyl substituted 2-chloropyridines undergo efficient Ullman couplings
- >20 fold improvement in yield for coupling of bis-CF₃ bipyridines
- An inexpensive source of nickel can be used
- No purification or drying of reagents and solvents required