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Improved synthesis of electron deficient bipyridines

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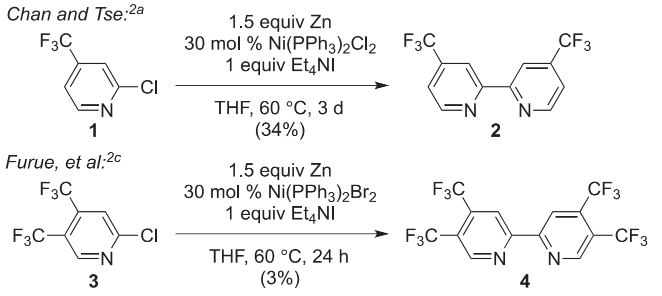
ABSTRACT

Symmetric bipyridines commonly serve as ligands for various types of catalytic processes. Nickel catalyzed Ullmann 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), $NiCl_2{\cdot}6H_2O$, and Ph_3P. 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.

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 Ullmann 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.



Scheme 1. Previously reported syntheses of bis- and tetra-CF_3 substituted bipyridines via 2-chloropyridines.

Results and discussion

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**.

Improving the synthesis of $bpy(CF_3)_2$ (2)

We first examined the synthesis of compound **2**. At 30 mol % the literature synthesis of **2** already used relatively high loadings of $Ni(PPh_3)_2Cl_2$.[2a] Nonetheless, we sought to determine if stoichiometric Ni catalyst load would afford a significant increase in the yield of compound **2** (Scheme 2). We were pleased to see that this change led to a 50% boost in yield, but recognized that if 1 equiv

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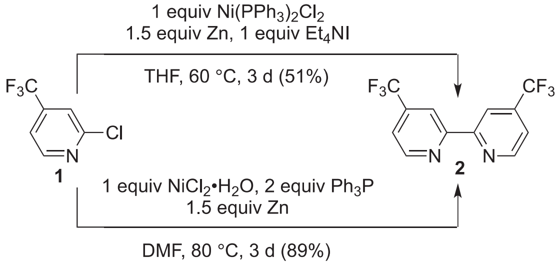
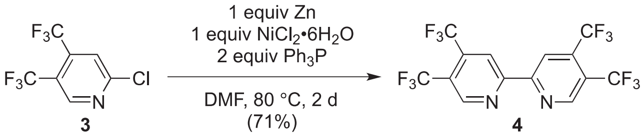


Scheme 2. Improved synthesis of bpy$(CF_3)_2$ (**2**).



Scheme 3. Improved synthesis of bpy$(CF_3)_4$ (**4**).

of Ni(II) would be necessary a more economical replacement for Ni$(PPh_3)_2Cl_2$ would also be required.

An obvious alternative would be to form $Ni(PPh_3)_2Cl_2$ from $NiCl_2$ and PPh_3 in situ as $NiCl_2{\cdot}6H_2O$ and PPh_3 are both readily available in kilogram quantities at a fraction the cost of the pre-assembled catalyst. We chose DMF as the solvent[6] to enable higher reaction temperatures and possibly eliminate the need for Et_4NI 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]

Improving the synthesis of bpy$(CF_3)_4$ (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 (ttfbpy) (**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 h 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$(CF_3)_3CH_3$.[8] Presumably the excess Zn lead to reduction of one of the CF_3 groups,[9] perhaps under Ni catalysis.[10] Given this outcome, we then reduced the load of Zn to 1 equiv. This eliminated the byproduct formation and afforded bpy$(CF_3)_4$ (**4**) in 71% isolated yield[7,11] (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%).

Conclusions

Through the use of stoichiometric Ni(II), yields for the preparation of two CF_3 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 $NiCl_2{\cdot}6H_2O$ and PPh_3 provided an economical alternative to $Ni(PPh_3)_2Cl_2$. We also note that the stoichiometry of Zn used in these Ullmann couplings is impactful as excess Zn can lead to unwanted reduction of the CF_3 group. This should be noted when designing syntheses of extremely electron deficient bipyridines or biaryls under similar conditions.

Acknowledgments

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Supplementary data

Supplementary data (experimental details for the preparation of **2** and **4**, the preparations of putative structure assignment of bpy$(CF_3)_3CH_3$, 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/10.1016/j.tetlet.2016.04.023.

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6. Neither $NiCl_2{\cdot}6H_2O$ or DMF were dried prior to use.
7. See Supplementary material for experimental details.
8. See Supplementary material for the putative structure assignment of the isomers of bpy$(CF_3)_3CH_3$.
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11. *Representative experimental:* In a Schlenk flask, $NiCl_2{\cdot}6H_2O$ (238 mg, 1.0 mmol) and PPh_3 (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. Activated[12] 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 CH_2Cl_2 (3 × 20 mL). The combined organics were washed with water (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. The residue was purified on a silica gel column (4:1 hexane/CH_2Cl_2) giving 152 mg (71%) of **4** as a white solid; mp 127–120 °C.[13] ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (s, 2H), 8.96 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 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); ^{19}F NMR (470 MHz, $CDCl_3$) δ −59.2 (q, $J = 12.2$ Hz), −61.6 (q, $J = 12.2$ Hz).
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13. A small sample was recrystallized from Et_2O at rt and an X-ray crystal structure was obtained and deposited in the Cambridge Crystallographic Data Centre and allocated deposition number CCDC 1044026.