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A Heterogeneous-Catalyst-Based, Microwave-Assisted Protocol for the Synthesis of 2,2′-Bipyridines

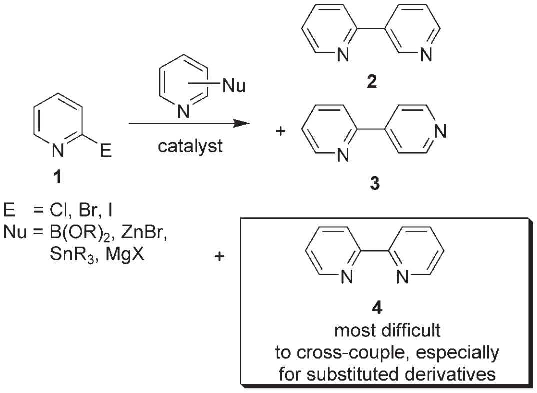
Lucas R. Moore and David A. Vicic*[a]

Abstract: A new method of preparing 2,2′-bipyridines with short reaction times by using microwave assistance and heterogeneous catalysts has been developed. With a Negishi-like protocol, it was found that Ni/Al_2O_3–SiO_2 afforded 2,2′-bipyridine products in up to 86 % yield in 1 h. Palladium supported on alumina also provided yields of 2,2′-bipyridines comparable to those seen for homogeneous PEPPSI^{TM} (1,3-diisopropylimidazol-2-ylidene)(3-chloropyridyl)palladium(II)dichloride) and tetrakis(triphenylphosphanyl)palladium complexes.

Keywords: C–C coupling · heterogeneous catalysis · microwaves · nickel · palladium

Introduction

Carbon–carbon and carbon–heteroatom coupling reactions have been shown to be incredibly useful synthetic tools for a variety of synthetic applications, such as the synthesis of natural products and pharmaceuticals.[1,2] The success of a coupling reaction is limited to the activity of the catalyst for a particular transformation, which in most cases is directly correlated to the ligands coordinated to the metal. The synthesis of new heterocycles, such as those containing pyridine rings, is especially important for the pharmaceutical industry. Whereas $C_{pyridyl}$–C_{aryl} cross-couplings are well-known with palladium, certain aspects of bipyridyl synthesis have always been problematic. Scheme 1 describes the general cross-coupling methods used to prepare different isomers of the bipyridyl family. Methods of preparing bipyridyls **2** and **3** are well-known,[6–11] but strikingly absent are reliable ways of preparing unsymmetrically substituted 2,2′-bipyridyls **4** that are broad in scope. This is presumably due to the fact that bipyridyls are effective transition-metal binding agents, so any homogeneous metal-catalyzed reaction to produce them would suffer from marked product-inhibition effects. Thus, a high-yielding method of constructing the bipyridyl framework would not only be important for drug-discovery endeavors, but would also significantly affect the field of inorganic chemistry, in which polypyridyl ligands are used quite frequently.[3–6]



Scheme 1. Scope of cross-coupling of 2-halopyridines with pyridyl nucleophiles, which is highly dependent on substitution pattern.

Current protocols for the preparation of 2,2′-bipyridines involve lithiation–addition,[7,8] radical-anion coupling,[9] Stille,[10,11] Suzuki,[12] Kumada,[13,14] and Negishi[15–19] reactions. All these methods have limitations,[15] and most employ homocoupling[20–27] methodologies. Some cross-couplings have been reported, but all involve extremely extended reaction times.[15–19,28] Heller and co-workers reported yields of 2,2′-bipyridines of 56–87 % when Stille coupling was used, but these results involve heating under reflux in toluene for 48 h.[28] Fang and Hanan reported yields of 68–98 % when a Negishi protocol was used, with reaction times of 18–40 h and temperatures ranging from room temperature to 60 °C.[15] Herein we report a convenient protocol for

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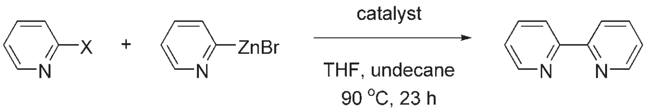
the preparation of 2,2′-bipyridines by using heterogeneous palladium and nickel catalysts with the assistance of microwave irradiation. The major advantages of these conditions are ease of product separation and extremely fast reaction times relative to previously reported procedures.

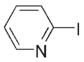
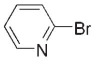
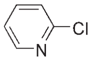
Results and Discussion

Attempts were made to synthesize 2,2′-bipyridine under thermal conditions with the use of heterogeneous palladium and nickel catalysts suspended in THF. When either nickel or palladium supported on carbon, silica, and alumina was applied, no activity was observed for the coupling of iodo-, bromo-, or chloropyridines with either pyridylzinc bromide or pyridinium-*N*-oxide,[29] even at temperatures of reflux (90 °C) for 23 h with 5 mol % catalyst loading (Table 1, entries 7–12, 19–24, and 31–36). However, when the amount of nickel was increased to 50 mol % supported on silica or an alumina–silica mixture (Table 1, entries 1–3, 13–15, and 25–27), some conversion to the desired 2,2′-bipyridines was observed, which indicates that optimization of these initial nickel reactions may provide more respectable yields (see below). Increasing the amount of palladium to 50 mol % gave no increase in product formation for the thermal reactions (Table 1, entries 4–6, 16–18, and 28–30). Interestingly, crystallization of (bpy)$ZnBr_2$ (bpy = 2,2′-bipyridyl) from THF (as determined by X-ray crystallography) was observed at the conclusion of every successful reaction, which could provide a crude way of rapidly determining which set of conditions are promising. Because of the ability of bipyridines to bind avidly to transition metals, all crude product mixtures for this study were treated with ammonium hydroxide to release free bipyridines before chromatography.

Given that some conversion into 2,2′-bipyridine products was observed with 50 mol % nickel loading in the thermal reactions, we explored the possibility of using microwaves to increase yields further. The results are summarized in Table 2. The yield of 2,2′-bipyridines rose to the 80 % range; the most practical conditions involved $Ni/Al_2O_3–SiO_2$ as the catalyst with no phosphine required (Table 2, entry 1 c). One hour was chosen as the time limit for irradiation because we saw significantly less conversion at 20 min. PPh_3 had little effect on the yield of this reaction (Table 2, entry 1 a); however, the addition of the more electron-rich phosphine P-(tBu)$_3$ actually lowered the observed yields (Table 2, entry 1 b). The pyridyl zinc nucleophile and the nickel catalyst are needed for the reaction to proceed, as control reactions performed in the absence of these reagents resulted in no product formation (Table 2, entries 2 and 3). A huge steric effect was seen with these reactions, however, as placement of a methyl group in either the 6- or the 3-position of the pyridyl bromide shut down catalysis entirely and produced no homocoupled product (Table 2, entries 4 and 5).

Table 1. Thermal synthesis of bipyridines by heterogeneously catalyzed Negishi coupling.[a]



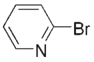
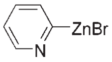
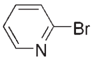
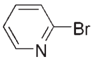
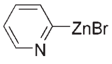
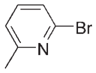
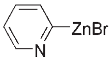
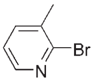
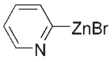
Pyr–X	Entry	Catalyst	Catalyst [mol %]	Ligand	Yield [%]
	1	$Ni/Al_2O_3–SiO_2$	50	–	39
	2	Ni/C	50	–	0
	3	Ni/SiO_2	50	–	41
	4	Pd/Al_2O_3	50	–	0
	5	Pd/C	50	–	0
	6	Pd/SiO_2	50	–	0
	7	Pd/Al_2O_3	5	PPh_3	0
	8	Pd/C	5	PPh_3	0
	9	Pd/SiO_2	5	PPh_3	0
	10	Pd/Al_2O_3[b]	5	PPh_3	0
	11	Pd/C[b]	5	PPh_3	0
	12	Pd/SiO_2[b]	5	PPh_3	0
	13	$Ni/Al_2O_3–SiO_2$	50	–	38
	14	Ni/C	50	–	0
	15	Ni/SiO_2	50	–	21
	16	Pd/Al_2O_3	50	–	0
	17	Pd/C	50	–	0
	18	Pd/SiO_2	50	–	0
	19	Pd/Al_2O_3	5	PPh_3	0
	20	Pd/C	5	PPh_3	0
	21	Pd/SiO_2	5	PPh_3	0
	22	Pd/Al_2O_3[b]	5	PPh_3	0
	23	Pd/C[b]	5	PPh_3	0
	24	Pd/SiO_2[b]	5	PPh_3	0
	25	$Ni/Al_2O_3–SiO_2$	50	–	41
	26	Ni/C	50	–	0
	27	Ni/SiO_2	50	–	39
	28	Pd/Al_2O_3	50	–	0
	29	Pd/C	50	–	0
	30	Pd/SiO_2	50	–	0
	31	Pd/Al_2O_3	5	PPh_3	0
	32	Pd/C	5	PPh_3	0
	33	Pd/SiO_2	5	PPh_3	0
	34	Pd/Al_2O_3[b]	5	PPh_3	0
	35	Pd/C[b]	5	PPh_3	0
	36	Pd/SiO_2[b]	5	PPh_3	0

[a] Amount of 2-halopyridine used was 0.67 mmol. A 1:1 metal/phosphine ratio was used. [b] Nucleophile was pyridyl *N*-oxide instead of 2-pyridylzinc bromide.

We also wondered whether the microwave conditions could help the palladium-catalyzed heterogeneous reactions, and the results of this study are summarized in Table 3. Yields comparable to those found with the nickel-supported thermal reactions were obtained at 250 W (Table 3, entries 4 and 6), and a catalyst loading of only 5 mol % was required. These yields were increased to 66–72 % with an increase in wattage to 300 W (Table 3, entries 1 a and 3). This wattage was maintained throughout the course of the reaction. The Pd/Al_2O_3-catalyzed coupling of 2-bromopyridine under microwave conditions gave a yield comparable to that found with homogeneous [$Pd(PPh_3)_4$] (Table 3, entry 1 g) and greater than that found for PEPPSI^{TM}-catalyzed coupling (Table 3, entry 1 h) under the same conditions. Applications of more-polar solvents proved to be unsuccessful with yields

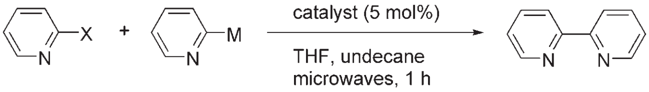
Table 2. Microwave-assisted synthesis of 2,2′-bipyridines with Ni-supported catalysts.[a]

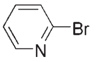
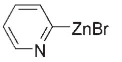
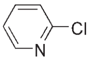
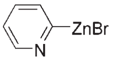
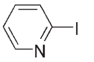
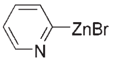
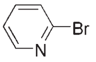
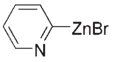
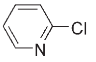
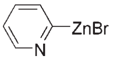
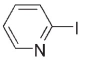
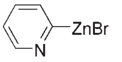
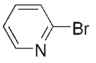
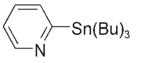
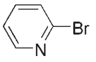
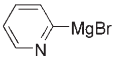
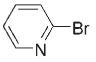
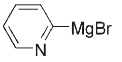
$$\text{pyridyl bromide} + (\text{pyridyl})\text{ZnBr} \xrightarrow[\text{microwave, 300 W, THF, 1h}]{\text{catalyst (50 mol\%)}} \text{2,2'-bipyridyl product}$$

Entry	Electrophile	Nucleophile	Catalyst	Yield [%]	Phosphine
1 a			Ni/Al_2O_3-SiO_2	86	PPh_3
1 b			Ni/Al_2O_3-SiO_2	39	P(*t*Bu)$_3$
1 c			Ni/Al_2O_3-SiO_2	84	None
1 d			Ni/C	34	PPh_3
1 e			Ni/SiO_2	82	PPh_3
2		none	Ni/Al_2O_3–SiO_2	0	–
3			none	0	–
4			Ni/Al_2O_3–SiO_2	0	–
5			Ni/Al_2O_3–SiO_2	0	–

[a] Amount of 2-halopyridine used was 0.67 mmol. A 1:1 metal/phosphine ratio was used.

Table 3. Microwave-assisted synthesis of bipyridines with Pd and Fe catalysts.[a]



Entry	Electrophile	Nucleophile	Catalyst	Yield [%]	Conditions
1 a			Pd/Al_2O_3	66	300 W
1 b			Pd/Al_2O_3	28[b]	300 W
1 c			Pd/Al_2O_3	4[c]	300 W
1 d			Pd/Al_2O_3	28	275 W, $ZnBr_2$
1 e			Pd/C	7	300 W
1 f			Pd/SiO_2	32	300 W
1 g			[Pd(PPh_3)$_4$]	62	300 W
1 h			PEPPSI™	45	300 W
2			Pd/Al_2O_3	0	300 W
3			Pd/Al_2O_3	72	300 W
4			Pd/Al_2O_3	40	250 W, PPh_3
5			Pd/Al_2O_3	5	250 W, PPh_3
6			Pd/Al_2O_3	30	250 W, PPh_3
7			Pd/Al_2O_3	0	300 W, PPh_3
8			Pd/Al_2O_3	0	300 W
9			$FeCl_3/SiO_3$	2	300 W

[a] Amount of 2-halopyridine used was 0.67 mmol. A 1:1 metal/phospine ratio was used. [b] Dioxane as solvent. [c] DMF as solvent. DMF = *N*,*N*-dimethylformamide.

dropping to 28 % for dioxane (Table 3, entry 1 b) and 4 % for DMF (Table 3, entry 1 c). Even at 300 W, Stille and Kumada coupling of 2-bromopyridine with 2-pyridyltributyltin or 2-pyridylmagnesium bromide were unsuccessful (Table 3, entries 7 and 8) when a palladium catalyst was applied. Iron is known to be an effective catalyst for Kumada-like cross-couplings,[30,31] but a heterogeneous iron-supported catalyst only afforded 2 % yield (Table 3, entry 9).

Finally, we tested the ability of supported palladium to prepare unsymmetrically substituted 2,2′-bipyridines (Table 4). Some homocoupling of both the electrophile and nucleophile was observed, but the major product in all cases was that resulting from cross-coupling. The desired product was obtained in 33 % yield with the methyl group located in the 6-position (Table 4, entry 1).

Yields approaching those of a nonsubstituted electrophile were obtained when the methyl group was in the 3-position, and similar yields were also obtained when the methyl group was placed in the 5-position (Table 4, entries 2 and 3). Although no homocoupling was observed during the reaction of 2-bromo-4-methyl-pyridine, a 36 % yield was obtained for the desired product (Table 4, entry 4).

Conclusions

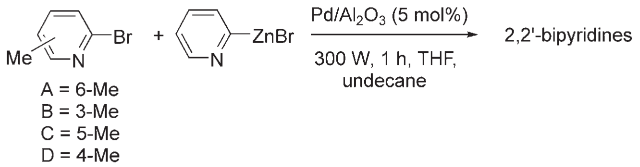
A convenient new protocol employing heterogeneous catalysts and microwave irradiation to prepare 2,2′-bipyridines has been discovered. The major benefits of this reaction are ease of product purification and particularly short reaction times. Heterogeneous Pd/Al_2O_3 has proven to be as effective in the Negishi coupling of 2-bromopyridines with pyridylzinc bromide to two commonly used homogeneous catalysts: [Pd(PPh_3)$_4$] and PEPPSI™. Ni/Al_2O_3–SiO_2 provided the best yields of bipyridine product, but at much higher catalyst loadings.

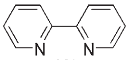
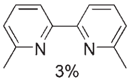
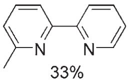
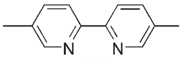
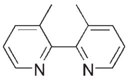
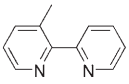
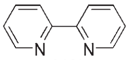
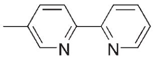
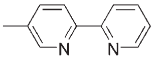
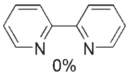
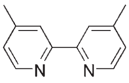
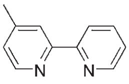
Experimental Section

All reagents were mixed in a glovebox under an atmosphere of nitrogen prior to irradiation. THF was distilled over sodium and benzophenone followed and then stored in the glovebox. Both pyridylzinc and magnesium bromide were purchased from Rieke Metals and were used without further purification. PEPPSI™ was purchased from Sigma Aldrich, nickel supported on carbon (graphite) was purchased from Alfa Aesar, and all other catalysts were purchased from Strem Chemicals. All the catalysts were used without further purification. Microwave reactions were carried out while a temperature of 90 °C was maintained by using a CEM Discover System with an Explorer autosampler attachment. Undecane was applied as the internal standard.

Representative example of the microwave-assisted reactions with 5 mol % catalyst: While in the glovebox, the desired 2-halopyridine (0.67 mmol), metal catalyst (0.0335 mmol), pyridylzinc bromide (0.5 M in THF, 1.36 mL, 0.68 mmol), distilled THF (4 mL), and undecane (0.05 mL, 0.24 mmol) were added to a 10-mL CEM crimp-top vial equipped with a stirrer bar. The reaction vial was placed in a CEM Discover microwave

Table 4. Microwave-assisted synthesis of unsymmetrical bipyridines.[a]



Entry	Electrophile	Homocoupling product		Cross-coupling product
		Nucleophile	Electrophile	
1	A	 9%	 3%	 33%
2	B	 3%	 2%	 53%
3	C	 20%	 7%	 49%
4	D	 0%	 0%	 36%

[a] Amount of 2-halopyridine used was 0.67 mmol.

reactor with the following specifications: power = 300 W, time = 60 min. The crude reaction mixtures were allowed to stir with ammonium hydroxide (30 wt %, 2 mL) for 30 min to remove any bipyridines that may be coordinated to Zn. A sample of the crude mixture was then removed and filtered through a silica plug followed by rinsing with diethyl ether. The yields of the reactions were calculated by GC on a Shimadzu GC-17A chromatograph (with undecane as the internal standard).

Representative example of the thermal reactions with 5 mol % catalyst: All reagent concentrations were kept the same as in the previously mentioned microwave procedure; however, 25-mL reaction vials were used along with a Radleys 12 Reaction Station carousel that allowed heating under reflux (90 °C) in nitrogen. The reactions were heated under reflux for 24 h, after which they were cooled to room temperature. The workup procedure described above was then followed.

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