



Nickel Catalysis

Nickel-Catalyzed Arylative Additions on 2-Alkynyl-*N*-Arylsulfonylanilides to Construct Functionalized Indoles

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Abstract: The addition of aryl iodides to 2-alkynyl-*N*-sulfonylanilides to form 2,3-difunctionalized *N*-arylsulfonylindoles can be catalyzed using a nickel catalyst ligated to a bis(cyclohexanyl)phosphinoferrocene. A variety of nickel complexes can be

Introduction

The ability of Group 10 metals to carry out catalyzed transformations within the discipline of synthetic organic chemistry has been transformative. Robust synthetic methods such as crosscoupling have been an unabashed success story, and thousands of scientists have used these techniques to build molecules of interest and of consequence.^[1] Although palladium-based catalyst systems remain the textbook standard for reactions of this type, the use of catalyst systems that are not based on palladium have been a focus of significant research effort.^[2] These efforts have been spurred by factors such as the scarcity and sustainability issues of palladium, its resulting effect on cost, and a desire to generate orthogonal reactivity patterns compared to the textbook version.^[3,4]

Our research group became interested in the use of nickel complexes as catalytic precursors within methods to construct or functionalize heterocyclic and heteroaromatic structures. Indoles are exemplary in their importance in both the realms of natural products and medicinal chemistry, and consequently became an engaging set of initial targets in our exploratory efforts.^[5] The elegant work of our academic and industrial colleagues to use catalysis for indole construction establishes important precedents and acts as inspiration and motivation.^[6] The palladium-catalyzed cyclizations of Larock and Cacchi developed in the 1990's established signature methods to form indoles with substitution patterns at C2 and C3 of the indole (Scheme 1).^[7,8] In the last decade, Matsubara and co-workers have presented their work to develop an addition of an orthonickelated aniline derivative across an alkyne.^[9] As a complement to this significant work, we were motivated to examine an arylative cyclization across an ortho-alkynylaniline derivative.

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used as precatalysts including a complex derived from inexpensive NiCl₂·6H₂O. Electron-rich aryl iodides are superior partners in this transformation.



Scheme 1. Representative examples of group 10 metal-catalyzed indole formation and this work.

Results and Discussion

A summary of initial explorations to carry out a nickel-catalyzed arylative cyclization across an *ortho*-alkynylaniline derivative is presented in Figure 1. Many undesired products could be formed in principle, and despite our best efforts, these were observed in practice as well. These reactions were complicated by unsufficient consumption of starting material and the formation of by-products such as 3-unsubstituted indoles as well as heterocycles formed by 6-*endo* cyclizations of the oxygen atom of an ambident amide or carbamate nucleophile.^[10] Isolated yields for the desired 3-aryl-substituted indole **B** topped out at around 30 % in reaction mixtures complicated by the presence of many by-products.

Our attention turned to 2-alkynyl-*N*-arylsulfonylamidylarenes in an attempt to reduce a number of competitive by-product

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sample condition set 1: $R^{1}=H$, $Ar=C_{6}H_{4}(p-Me)$; [(PPh₃)₂Ni(*o*-tol)Cl; AgSbF₆, K₂CO₃, dioxane, 100 °C: SM consumed, only **A** formed. sample condition set 2: $R^{1}=Me$, $Ar=C_{6}H_{4}(p-OMe)$; (dppf)Ni(cod); K₃PO₄ (1.5 equiv), CPME, 110 °C: ratio **A**:**B**:**C**:**D** = 0.4: 0.1: 0.14:1.0 sample condition set 3: $R^{1}=Me$, $Ar=C_{6}H_{4}(p-OMe)$; (dppf)Ni(cod); K₃PO₄ (3.0 equiv), CPME, 110 °C: ratio **A**:**B**:**C**:**D** = 0.5: 0.5: 0.1:0.2

Figure 1. By-products formed in exploratory Ni-catalyzed arylative indole formation.

reaction paths. Of reasonable concern was a base-promoted or metal-catalyzed background cyclization of these compounds to 3-unsubstituted indoles (cf. product **A** in Figure 1) as this cyclization is well-established in the experimental record.^[11] The exploratory results using *ortho*-alkynyl-*N*-carbamoylarenes in Figure 1 had established Ni(cod)₂ and potassium phosphate as a promising nickel precatalyst and alkaline additive. The optimization work is summarized in Equation 1 and Table 1.

Table 1. Optimization experiments for arylative cyclizations of 1.

Entry ^[a]	Х	Ligand ^[b]	Unreacted SM	Yield 2a ^[c]	Yield 2b
1	I	none	99 %	-	_
2	Ι	IPr•HCI	-	12 %	60 %
3	I	PPh₃	18 %	6 %	3 %
4	I	PCy ₃	14 %	9 %	10 %
5	I	dtbbpy	50 %	-	20 %
6	I	dppf	51 %	3 %	6 %
7	I	d(<i>i</i> Pr)pf	21 %	41 %	8 %
8	I	d(Cy)pf	-	51 %	18 %
9	I	m(Cy)pf	-	13 %	31 %
10	I	(Cy)xantphos	70 %	8 %	15 %
11 ^[c]	1	d(Cy)pf	-	69 %	5 %
12 ^[c]	Br	d(Cy)pf	25 %	11 %	26 %

[a] rxns were carried out as 0.2 $\mbox{ model}$ solutions in PhCH₃ on 1 mmol scale; reported yields are of isolated products. [b] none=no Ni(cod)₂ or ligand were used; *i*Pr-HCl = 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride; Ph= phenyl; Cy=cyclohexyl; dtbbp = 4,4'-di-*tert*-butyl-2,2'-bipyridine; dppf = 1,1'-bis(diphenylphosphino)ferrocene; d(*i*Pr)pf = 1,1'-bis[1,1'-bis[diisopropylphosphino)]ferrocene; d(Cy)pf = 1,1'-bis(dicyclohexylphosphino)ferrocene; m(Cy)pf = 1-(dicyclohexylphosphino)ferrocene; (Cy)xantphos = 4,5-Bis(dicyclohexylphosphino)-9,9-dimethylxanthene. [c] The rxn was run as a 0.1 $\mbox{ model}$ solution of **1** in cyclopentyl methyl ether (CPME).

The control reaction of alkyne **1** run in the absence of a Ni source or ligand gave no cyclization products in the timeframe that was examined (entry 1). The addition of monodentate ligands such as IPr, or phosphines gave poor yields of **2a** (entries 2–4). Catalyst systems derived with common bidentate ligands such as dtbbp and dppf did not react effectively with alkyne **1** (entries 5 and 6). A catalyst system that incorporated an electron-rich, bidentate phosphine, d(*i*Pr)pf or d(Cy)pf resulting in moderate conversions of the alkyne to the 3-aryl-substituted indole **2a** (entries 7 and 8). A structurally related catalyst system incorporating a monodentate phosphine, m(Cy)pf, only poorly converted the starting materials to **2** (entry 9). A xantphos ligand bearing cyclohexyl-substituted phosphines was uniformly

uneffective (entry 10). Switching the solvent from toluene to cyclopentyl methyl ether (CPME) but otherwise holding the catalyst conditions as in entry 8 allowed for the formation of indole **2a** in 69 % yield, a nice result (entry 11).^[12] Unfortunately, our reactions using aryl bromides, for example in entry 12, demonstrated that as yet they are not viable aryl halides for our nickelcatalyzed arylative cyclization.



With the conditions of nickel-catalyzed arylative indole formation established, a survey of a variety of aryl iodides with alkyne 1 was undertaken (Figure 2). The conditions used for this survey were identical to that Table 1, entry 11: 10 mol-% Ni(cod)₂, 10 mol-% d(Cy)pf, 3 equiv. of potassium phosphate as a 0.1 M of alkyne starting material in CPME. These reactions were often complicated by concurrent formation of indoles without substitution at the 3-position as well as a Ni catalyzed formation of a hexasubstituted benzene formed by trimerization of the alkyne starting material - these processes often made up the mass balance of reacted starting materials.^[13] A summary of the product distribution for a sampling of these reactions is provided in the Supplementary Information. Reactions with a variety of *p*-substituted aryl iodides demonstrated that although many reactions were viable, with yields ranging from charitably modest (26%) to good (63%), the highest yields involved reactions with electron donating substituents (compare examples 3a-3d with examples 3e-3i). These nickelcatalyzed reactions proceed in the presence of C-Br or C-F bonds and heterocycles (examples 3, 5-7). Electronically neutral aryl iodides such as p-iodotoluene, m-iodoxylene and 2-iodothiophene were modestly reactive partners (examples 3e, 4, 5). The importance of electron density at the carbon bearing the iodide function is reflected in the reactions producing examples 2 (69 %) and 3a (para-OR, 63 %), 8 (meta-OR, 24 %) and 9 (ortho-OR, 67 %); steric interactions did not seem to be problematic. Comparison of the reactions of o-iodoanisole and o-iodothioanisole to generate 9 and 10 in 67 % and 26 % yields respec-







Figure 2. Scope of nickel-catalyzed indole construction. [a] Unless otherwise noted, reactions were carried out on 1 mmol scale as described in the figure and yields represent isolated and purified compounds. [b] Yield is obtained as a mixture of the desired compound and the corresponding 3-unsubstituted indole derivative. Yields of purified compounds are lower. [c] 20 mol-% of Ni(cod)₂ and 20 mol-% of d(Cy)pf were used in the reaction. [d] 0.8 mmol of alkyne used.

tively underlined the importance of the electron-donating oxygen substituents. Other electron rich poly-oxygenated iodoarenes could be used to good effect (examples **11–12**).

Some structural variation in the *N*-sulfonyl group is tolerated, as the *p*-methoxyphenylsulfonyl group and the methanesulfonyl group were each tolerated (example **13**). Structural variation of the *ortho*-alkynylarylsulfonamide demonstrated that the reaction conditions are amenable to electron-withdrawing and donating substituents on the arene ring of the sulfonamide (indoles **14a**–**d**) or conjugated to the alkyne (indoles **14e** and **15c**), as well as alkyl substitution on the alkyne (indole **15a**). As exemplified in Equation 2, this Ni-catalyzed process was successful using an alkenyl iodide rather than an aryl iodide. The reaction with an analogous alkenyl trifluoromethylsulfonate was not successful.



The use of d(Cy)pfnickel(II) chloride, a bench-stable solid, as a precatalyst in a gram-scale process was also possible (Equation 3). The reaction was run using CPME from the bottle that had been sparged with nitrogen gas for 30 min. This yield of this process was comparable to that using a Ni(cod)₂ precursor. The formation of a 2,3-diarylindole from a 3-iodoindole and an arylboronic acid using the same nickel catalyst system took place in 8 % yield (Equation 4).



A complicating Ni-catalyzed side-reaction that is observed along with the formation of indoles is an oligomerization of the alkyne function of the starting materials to form hexasubstituted benzene derivatives. This concurrent process consumes some of the 2-alkynylsulfonanilide starting material. The experimental observation that electron-rich iodides react more quickly to produce 3-substituted indoles in greater yields is consistent with some experimental investigations of other processes that incorporate putative oxidative additions to organonickel complexes.^[14] A hypothetical mechanistic rationale that is presented in Scheme 2. Either Ni⁰ d(Cy)pf and Ni(cod)₂, Ni^{II} d(Cy)pfNiX₂ or Ni¹ [d(Cy)pfNiX] are precatalysts to Ni systems that can, to various extents, catalyze alkyne trimerization or the arylative indolization reaction. Interestingly, preformed d(Cy)pfNi(o-tol)Cl complexes that are viable cross-coupling catalytic precursors do not generate catalytic systems of particularly useful efficiency. The overall steps are currently speculated to follow the mechanistic guides of the Pd-catalyzed Cacchi proc-





ess: oxidative addition, alkyne amination and reductive elimination. The putative intermediate **19** can undergo reductive elimination, while the formation of an analogous intermediate in Equation 4 seems to be problematic.



Scheme 2. Hypothetical mechanistic rationale.

As would be reasonably anticipated, the indoles can be further synthetically manipulated (Scheme 3). The robust *p*-toluenesulfonyl protecting group in **2a** could be deprotected from the indole nitrogen atom using TBAF.^[15] A Buchwald-Hartwig cross-coupling between morpholine and the aryl chloride function in **14d** generates an indole that might be challenging to generate using a standard Cacchi reaction.



Scheme 3. Synthetic manipulation of indoles.

Conclusion

In summary, nickel complexes ligated to d(Cy)pf can catalyze an arylative addition to 2-alkynyl-*N*-arylsulfonylanilides to form 2,3-disubstituted indoles. Compared to a cross-coupling between an aryl halide and an organometallic, this reaction requires a careful partitioning between the desired process and several undesired reactions involving the alkyne function of the 2-alkynyl-*N*-sulfonylanilide starting material. Even so, the efficiency of these reactions can be high yielding when aryl iodides having electron-donating substituents are used as partners. This unusual reactivity pattern coupled with the need to partition the starting material into one of several different catalysis paths makes the exploration of mechanistic details of this process and an expansion of the scope of this process an important subject of future work.

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 Nickel-Catalyzed Arylative Additions on 2-Alkynyl-*N*-Arylsulfonylanilides to Construct Functionalized Indoles



The addition of aryl iodides to 2-alkynyl-*N*-sulfonylanilides to form 2,3-difunctionalized *N*-arylsulfonylindoles can be catalyzed using a nickel catalyst ligated to a bis(cyclohexanyl)phosphinoferrocene. A variety of nickel complexes can be used as precatalysts including a complex derived from inexpensive NiCl₂•6H₂O. Electron-rich aryl iodides are superior partners in this transformation.

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