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Communications

Indoline Synthesis via Coupling of Phenethyl Grignard Reagents with Organoazides Mediated by (Alkylphosphine)nickel(II) Complexes

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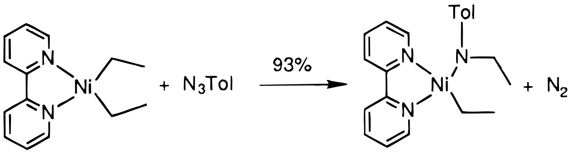
Summary: The room-temperature reaction of $(PMe_3)_2Ni(CH_2CMe_2\text{-}o\text{-}C_6H_4)$ (**3**) *with 3 equiv of p-tolyl azide* ($TolN_3$) *results in evolution of* N_2 *and clean formation of the N-p-tolylindoline derivative* $TolNCH_2CMe_2\text{-}o\text{-}C_6H_4$ (**4a**), *isolated in 82% yield. The reaction almost certainly proceeds via insertion of an "NTol" fragment from* $TolN_3$ *into the Ni−C(aryl) bond to give an intermediate azametallacycle* $[L_nNi(NTol\text{-}o\text{-}C_6H_4\text{-}CMe_2CH_2)]$ (**5**), *which then undergoes C,N-reductive elimination to afford the indoline* **4a**.

Numerous synthetic approaches to the indoline and indole classes of molecules have been developed over the years because of the prevalence of these structural motifs in natural product chemistry (cf., the indole alkaloids) and indole dyes.[1] Most indoline and indole syntheses have accessed these compounds via conventional organic synthetic routes,[1,2] but several groups have recently reported procedures to these molecules using metal-mediated, organometallic protocols for key synthetic steps.[3] In this report we demonstrate a simple new route to *N*-arylindoline derivatives based on nickel(II) phosphine chemistry.

We have been exploring the use of organoazides as "NR" transfer reagents to alkylnickel complexes in reactions that yield new nickel amido complexes.[4] A typical example of this transformation is shown in eq 1, in which N_3Tol reacts cleanly with $(bpy)Ni(Et)_2$ (bpy = 2,2′-bipyridine) to give $(bpy)Ni\{N(Tol)Et\}(Et)$ and N_2.[4] We have furthermore demonstrated that the resulting alkylnickel(II) amides, especially those in which the alkyl and amido moieties are tethered together in azametallacycles, undergo oxidatively-induced reduc-



(1)

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[1] (a) Glasby, J. S. In *Encyclopedia of the Alkaloids*; Plenum Press: New York, 1975. (b) Horwell, D. C. *Tetrahedron* **1980**, *36*, 3123. (c) Fransk, R. W. *Prog. Chem. Org. Nat. Prod.* **1979**, *38*, 1. (d) Sumpter, W. C.; Miller, F. M. *Chem. Heterocycl. Compd.* **1954**, *8*, 171.

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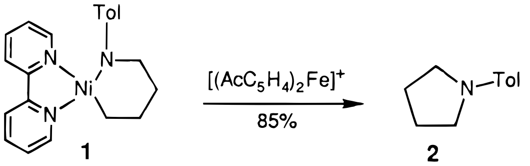
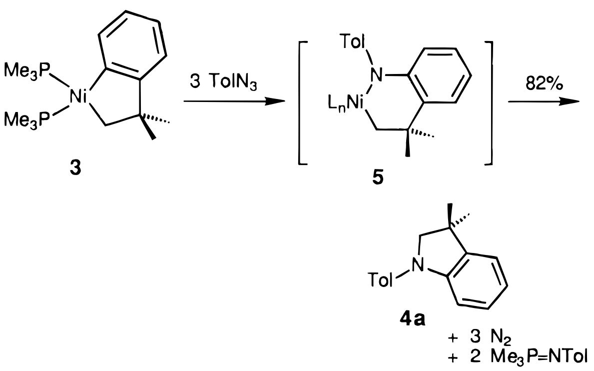
tive-elimination reactions that form new C−N bonds very efficiently.[5] An example of such a C−N reductive elimination is depicted in eq 2. Reaction of (bpy)$\overline{\text{Ni}\{\text{N(Tol)CH}_2\text{CH}_2\text{CH}_2\text{CH}_2}\}$ (**1**) with the one-electron oxidant 1,1′-diacetylferrocenium tetrafluoroborate ([(Ac$C_5H_4)_2$Fe][BF_4]) gives *N*-*p*-tolylpyrrolidine (**2**) in high isolated yield.[5] We have shown that oxidation of Ni(II) to Ni(III) triggers the reductive elimination event and that, in the absence of external oxidants (O_2, I_2, or [$(AcC_5H_4)_2Fe^+$]), **1** is quite thermally stable, decomposing only at temperatures above 130 °C.[6]



1 **2** (2)

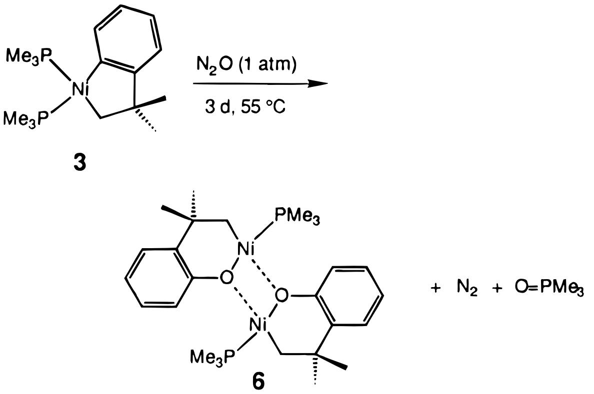
The thermal stability of **1** toward reductive elimination is intriguing in the light of recent reports of facile C,N-reductive eliminations that form arylamines in palladium-catalyzed cross-coupling reactions.[7] In these Pd−triarylphosphine systems, mechanistic evidence supports three-coordinate species of the type [(PAr_3)Pd(R)(NR'_2)] as the intermediates from which reductive elimination occurs to give RNR'_2.[8] Since the chelating nature of the bipyridine ligand in **1** and related complexes inhibits ligand dissociation to give a three-coordinate intermediate, we have investigated the reactivity of organoazides with several alkylphosphine complexes of organonickel metallacycles, anticipating that these might be prone to thermal reductive elimination reactions, and we report here on the findings of these studies.

Addition of *p*-tolyl azide (3 equiv) to diethyl ether solutions of $(PMe_3)_2\overline{\text{Ni}(\text{CH}_2\text{CMe}_2\text{-}o\text{-C}_6\text{H}_4})$ (**3**)[9] results in N_2 evolution and a change in the color of the solution from red to dark yellow. Removal of the solvent and inspection of the residue by ^{1}H and ^{31}P NMR spectroscopies clearly indicated (i) that the PMe_3 ligands had been completely converted to $Me_3P = NTol$ and (ii) that the major organic product was the *N*-*p*-tolyldimethylindoline Tol$\overline{\text{NCH}_2\text{CMe}_2\text{-}o\text{-C}_6\text{H}_4}$ (**4a**).[10] Chromatography of the reaction residue on silica gel allowed for isolation of pure **4a** in 82% yield (eq 3).



3 **5** **4a** (3)

Although no intermediates were detected in the formation of **4a**, the mechanism undoubtedly involves insertion of the "TolN" fragment from the azide into the Ni−C(aryl) bond of **3** to give an intermediate azanickelacyclohexene moiety (**5**, eq 3) followed by C,N-reductive elimination to give **4a**. This can be inferred from precedent provided by two related systems. We have shown that nitrous oxide (isoelectronic with N_3-Tol) reacts with **3** to afford dimeric **6** in good yield along with N_2 and O=PMe_3 (eq 4).[11] This robust (aryloxy)nickelacycle retains one of the two original PMe_3 ligands of **3**, and the oxygen-atom insertion occurs regioselectively to give an aryloxide (not alkoxide) moiety. What factors are likely responsible for the instability of an intermediate like **5** with respect to its spontaneous reductive elimination to form **4a** while **6** is quite stable? First, complex **6** is an oxygen analogue of **5** except that it has dimerized via bridging aryloxide linkages (to give a Ni_2O_2 core) resulting in a stable 16-electron, d^8 complex; the sterically encumbering aryl substituent on nitrogen in **5** would prohibit a similar dimerization. Second, because the reaction between $TolN_3$ and PMe_3 to form TolN=PMe_3 is an extremely facile one while the corresponding reaction between N_2O and PMe_3 to give O=PMe_3 is very slow, both PMe_3 ligands of **3** are rapidly consumed by reaction with *p*-tolyl azide and are therefore unavailable as stabilizing ligands (as in compound **6**).[12]



3 **6** (4)

Further convincing support for the indoline-formation sequence depicted in eq 3 is found in an analogous reaction between N_3Ph and (bpy)$\overline{\text{Ni}(\text{CH}_2\text{CMe}_2\text{-}o\text{-C}_6\text{H}_4})$ (**7**) that proceeds regioselectively with "PhN" insertion into the Ni−C(aryl) bond to give (bpy)$\overline{\text{Ni}(\text{NPh-}o\text{-C}_6\text{H}_4\text{CMe}_2\text{CH}_2})$ (**8**). As was the case in the **1** → **2** transformation (eq 2), oxidation of **8** by [$(AcC_5H_4)_2Fe^+$] affords the *N*-phenylindoline **4b** in excellent yield (eq 5).[5]

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(5) Koo, K.; Hillhouse, G. L. *Organometallics* **1995**, *14*, 4421.

(6) The thermal decomposition of **1** does not yield **2** but rather products derived from β-hydrogen eliminations: Zhong, A.; Koo, K.; Hillhouse, G. L. Unpublished results.

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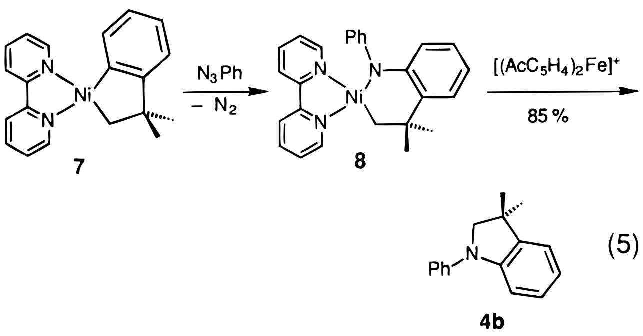
(10) Complete synthetic procedures and spectral data are reported in the Supporting Information.

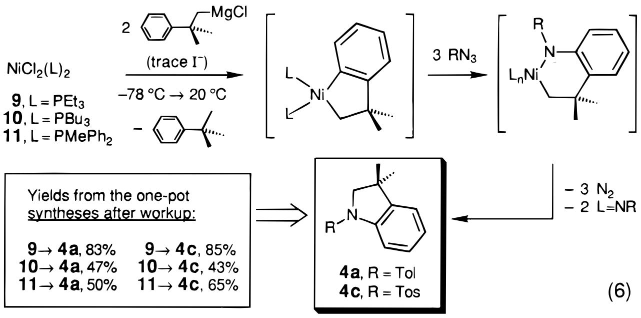
(11) Koo, K.; Hillhouse, G. L.; Rheingold, A. L. *Organometallics* **1995**, *14*, 456.

(12) If fewer than 3 equiv of N_3Tol are allowed to react with **3**, the reaction still proceeds according to eq 3, giving diminished yields of **4a** along with unreacted **3**.



(5)

We have adapted the synthetic protocols of the three key reactions in this system (metallacycle formation, "NR" insertion into a Ni−C bond, and N,C-reductive elimination) into a simple one-pot synthesis of *N*-aryl- and *N*-tosylindolines, as outlined in eq 6. Sequential treatment of an ether solution of $NiCl_2(L)_2$ (**9**, L = PEt_3; **10**, L = PBu_3; **11**, L = $PMePh_2$)[13] with 2 equiv of $ClMgCH_2CMe_2Ph$ at −78 °C followed by warming to 20 °C and addition of 3 equiv of RN_3 (R = p-C_6H_4Me, SO_2-p-C_6H_4Me) affords pure $TolNCH_2CMe_2$-o-C_6H_4 (**4a**) or $TosNCH_2CMe_2$-o-C_6H_4 (**4c**) after chromatographic workup.[14] The metallacycle formation from the phenethyl Grignard reagent and $NiCl_2(L)_2$ requires a trace of iodide and is essentially identical to Carmona's method of preparing **3**.[9] For convenience, we carried out these reactions using alkylphosphines less volatile than PMe_3 (i.e., PEt_3, PBu_3, and $PMePh_2$), although the intermediate nickelacycles are not readily isolated in good yields with these ligands.[15] The isolated yields of the indolines range from 43 to 85% based on $NiCl_2(L)_2$ and decrease with increasing phosphine bulk. It is noteworthy that the alkylphosphine complexes used in this study have square-planar $NiCl_2(L)_2$ geometries. The tetrahedral complex $NiCl_2(PPh_3)_2$, however, was not effective in this reaction, giving Grignard coupling products instead of the (required) neophyl metallacycle.



(6)

In summary, we have shown that square-planar organonickel phosphine metallacycles can react with organoazides to eliminate N_2 with insertion of the imide (NR) fragment into a Ni−C bond. The resulting (amido)nickel intermediates are unstable with respect to a spontaneous reductive elimination reaction that forms a new N−C bond. Using this chemistry, we have developed a one-pot, high-yield synthesis of the indolines $TolNCH_2CMe_2$-o-C_6H_4 and $TosNCH_2CMe_2$-o-C_6H_4 from the corresponding organic azides ($TolN_3$ and $TosN_3$), $ClMgCH_2CMe_2Ph$, and $NiCl_2(L)_2$ (L = PEt_3, PBu_3, or $PMePh_2$).

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Supporting Information Available: Text describing synthetic details and spectral data for the new compounds (4 pages). Ordering information is given on any current masthead page.

OM960286+

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(14) A typical one-pot synthetic protocol is described here for the preparation of **4a** from **9**. (See the Supporting Information for complete synthetic procedures and spectral data.) To a suspension of $(PEt_3)_2$-$NiCl_2$ (**9**, 0.30 g, 0.82 mmol) in Et_2O (40 mL) was added MgI_2 (10 mg) under an Ar counterflow. The $MgClCH_2CMe_2C_6H_5$ (1.6 mL, 1.0 M in Et_2O) was added to the reaction mixture at −78 °C with stirring, and the resultant solution was slowly warmed to room temperature. During the warming, the color changed to reddish-yellow from dark red. After an additional 2 h of stirring at room temperature, $TolN_3$ (0.28 mL, 2.5 mmol) was added to the mixture via syringe, the solution was stirred for 2 h and filtered, and the volatiles were removed under vacuum. The residue was extracted with Et_2O (30 mL), the extracts were evaporated, and the residue was chromatographed on silica gel (eluent: n-hexane/ethyl acetate, 5:1) to give $TolN(CH_2CMe_2$-o-$C_6H_4)$ (**4a**, 0.15 g, 83%) as a yellow oil. The formation of $Et_3P = NTol$ was identified by ^{31}P NMR spectroscopy (202.5 MHz, δ 47.8).

(15) Attempts to isolate $(PR_3)_2Ni(CH_2CMe_2$-o-$C_6H_4)$ (R = Et, Bu) gave the highly soluble compounds as red oils. $(PMePh_2)_2Ni(CH_2CMe_2$-o-$C_6H_4)$ was isolated as an orange powder in modest yield.