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Nickel-Catalyzed Asymmetric α-Arylation and Heteroarylation of Ketones with Chloroarenes: Effect of Halide on Selectivity, Oxidation State, and Room-Temperature Reactions

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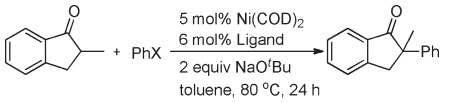
Supporting Information

ABSTRACT: We report the α-arylation of ketones with a range of aryl chlorides with enantioselectivities from 90 to 99% ee catalyzed by the combination of $Ni(COD)_2$ and (*R*)-BINAP and the coupling of ketones with a range of heteroaryl chlorides with enantioselectivities up to 99% ee catalyzed by $Ni(COD)_2$ and (*R*)-DIFLUORPHOS. The analogous reactions of bromoarenes occur with much lower enantioselectivities. Mechanistic studies showed that the difference in the rates of decomposition of the arylnickel(II) halide intermediates to $\{[(R)\text{-BINAP}]NiX\}_2$ likely accounts for the difference in the enantioselectivities of the reactions of bromoarenes and chloroarenes. This catalyst decomposition can be overcome by conducting the reactions with $[(R)\text{-BINAP}]Ni(\eta^2\text{-NC-Ph})$ (**4**), which undergoes oxidative addition to haloarenes at room temperature.

The α-arylation of ketones has become a mainstream synthetic method, but asymmetric α-arylation of carbonyl compounds remains a challenge.[1,2] Several catalysts for the coupling of specific classes of ketones with aryl halides have been reported,[3] and improved selectivities have been achieved by using aryl triflates instead of aryl bromides.[4] However, simple systems that catalyze a wide range of couplings of ketones with aryl halides have not been reported, and catalysts suitable for asymmetric α-heteroarylation with nitrogen heterocycles, arguably more important for applications in medicinal chemistry than asymmetric α-arylation, have not been identified.

Most asymmetric couplings of enolates with aryl halides have been conducted with Pd catalysts.[4−10] Asymmetric couplings of enolates with aryl halides and pseudohalides catalyzed by Ni complexes have been limited to those of electron-poor aryl triflates and to reactions of aryl halides with γ-lactones.[4,11,12] While investigating simple Ni catalysts for asymmetric α-arylation with heteroaryl halides, we identified a dramatic effect of the halide on the enantioselectivity: the coupling of 2-methyl-1-indanone with 2-chloropyridine occurred in higher yield and with much higher enantioselectivity than the analogous reaction of 2-bromopyridine, which is typically more reactive for cross-coupling. This observation led us to identify the most general system for the asymmetric α-arylation of ketones, a system for asymmetric α-heteroarylation of ketones, and an ability to distinguish between catalysis by Ni(0) and Ni(I). We report the combination of the scope of Ni-catalyzed asymmetric α-arylation and heteroarylation of a series of cyclic ketones with a range of aryl and heteroaryl chlorides and mechanistic studies that reveal the origins of the difference in enantioselectivity. These mechanistic studies, in turn, led to a system for asymmetric α-arylations of both chloroarenes and bromoarenes at room temperature.

Table 1. Screening of Ligands and Electrophiles for Ni-Catalyzed Asymmetric α-Arylation of 2-Methyl-1-indanone[a]



entry	PhX	Ligand	yield (%)	ee (%)	entry	PhX	Ligand	yield (%)	ee (%)
1	PhBr	**L1**	61	76	7	PhI	**L1**	36	37
2	PhBr	**L2**	40	47	8	PhOTf	**L1**	33	70
3	PhBr	**L3**	53	50	9	PhCl	**L1**	78	93
4	PhBr	**L4**	44	42	10	PhCl	**L3**	67	94
5	PhBr	**L5**	55	60	11	PhCl	**L5**	77	96
6	PhBr	**L6**	59	60	12	PhCl	**L6**	80	94

[a] Conditions: 2-methyl-1-indanone (0.200 mmol), PhX (0.400 mmol), NaO^tBu (0.400 mmol), $Ni(COD)_2$ (0.010 mmol), and ligand (0.012 mmol) in toluene (1.0 mL) at 80 °C; ee was determined by chiral HPLC analysis; ligands: (*R*)-BINAP (**L1**), (*R*)-XylBINAP (**L2**), (*R*)-SEGPHOS (**L3**), (*R*)-DM-SEGPHOS (**L4**), (*R*)-P-Phos (**L5**), (*R*)-DIFLUORPHOS (**L6**).

Reactions of 2-methyl-1-indanone with phenyl halides and phenyl triflate catalyzed by complexes generated from $Ni(COD)_2$ and a series of bidentate phosphine ligands (**L1**−**L6**) are summarized in Table 1. We focused initially on reactions of 2-methyl-1-indanone because published enantioselective α-arylations of this ketone with aryl bromides catalyzed by the combination of BINAP and Pd occurred with variable selectivities[5] and the corresponding reactions with aryl triflates catalyzed by $Pd(dba)_2$ and DIFLUORPHOS occurred with only modest ee's (55−84%).[4]

Reactions of bromobenzene catalyzed by the combination of $Ni(COD)_2$ and bisphosphines containing biaryl backbones occurred in only modest yields (40−61%) and with low enantioselectivities (42−76% ee) (entries 1−6). The reaction of iodobenzene catalyzed by $Ni(COD)_2$ and (*R*)-BINAP occurred in low yield with low ee (entry 7), and the analogous reaction of phenyl triflate occurred in low yield with modest ee (entry 8). In contrast, the reaction of chlorobenzene (entries 9−12) occurred in much higher yields (67−80%) and with high enantioselectivities (93−96% ee). Moreover, reactions of aryl chlorides conducted with ligands **L1**, **L3**, **L5**, and **L6** all occurred

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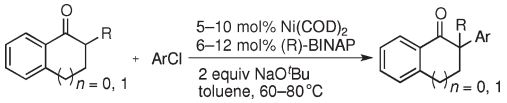
Table 2. Asymmetric α-Arylation of Indanones and Tetralones with Chloroarenes Catalyzed by Ni(COD)$_2$/(*R*)-BINAP[a]



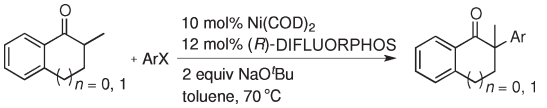
entry	ArX	yield (%)	ee (%)
n = 0, R = CH_3			
1[b]	3-CF_3	75	96
2[b]	4-CF_3	81	95
3[b]		58	92
4	3-F	72	94
5	4-F	75	95
6[b]		41	99
7[b]		82	96
8		73	98
9[b]	3-OMe	79	96
10[b]	4-OMe	81	96
n = 0, R = CH_2Ph			
14		89	99
15		77	98
16		83	98
n = 1, R = CH_3			
17	3-CF_3	74	96
18	4-CF_3	80	94
19		73	90
20		61	96
21	3-OMe	69	92
22	4-OMe	72	97
n = 0, R = CH_2CH_3			
11		66	92
12		77	98
13		72	94
n = 1, R = CH_2Ph			
23		76	94
24		72	98
25		53	99

[a] Conditions: indanone or tetralone (0.200 mmol), chloroarene (0.400 mmol), NaO^{t}Bu (0.400 mmol), and Ni(COD)$_2$ (0.010 mmol)/(*R*)-BINAP (0.012 mmol) for indanones or Ni(COD)$_2$ (0.020 mmol)/(*R*)-BINAP (0.024 mmol) for tetralones in toluene (1.0 mL) at 80 °C for 36 h for indanones or 48 h for tetralones; ee was determined by chiral HPLC analysis. [b] Run at 60 °C.

with similar enantioselectivities. These results indicate that the leaving group in the aryl electrophile significantly affects both the yield and enantioselectivity of the reactions in Table 1 catalyzed by the combination of Ni(COD)$_2$ and the bisphosphines.

Because of the accessibility and low cost of (*R*)-BINAP and chloroarenes, we studied the scope of the asymmetric α-arylation with a range of chloroarenes catalyzed by the combination of Ni(COD)$_2$ and (*R*)-BINAP (Table 2). We studied reactions of 1-indanones and 1-tetralones bearing different substituents (Me, Et, and Bn) on the carbon α to the carbonyl group. A range of electron-rich, electron-neutral, and electron-deficient chloroarenes reacted to give the corresponding coupled products in good isolated yields (58−83%) with high enantiomeric excess (90−99%). Reactions of ketones containing various substituents at the α-carbon of 1-indanone and 1-tetralone (e.g., see entries 2, 11, and 14) occurred with similarly high enantioselectivity for electronically varied chloroarenes (e.g., see entries 11−16). For reactions occurring in moderate yield (e.g., entries 6, 20, and 25), the starting ketones were not fully converted. Side products of ketone self-condensation and β-H elimination were not observed by GC−MS. The reaction of 2-methyl-1-indanone with chlorobenzene run on a 2.0 mmol scale occurred in similarly high yield (80%)

Table 3. Asymmetric Heteroarylation of Ketones with Heteroaryl Halides Catalyzed by Ni(COD)$_2$/(*R*)-DIFLUORPHOS[a]



entry	ArX	yield (%)	ee (%)	entry	ArX	yield (%)	ee (%)
	n = 0				*n* = 1		
1	X = Br	69	57	13	X = Br	73	55
2	X = Cl	93	97	14	X = Cl	89	99
3		54	91	15		68	94
4	R = OMe	75	41	16	R = OMe	72	35
5	R = Me	87	94	17	R = Me	86	98
6	R' = CF_3	85	81	18	R' = CF_3	85	96
7	R' = F	86	98	19	R' = F	89	99
8	R' = CN	87	21	20	R' = CF_3	84	93
9		76	96	21		54	96
10		54	95	22		45	97
11		90	99	23		87	99
12		85	90	24		79	92

[a] Conditions: indanone or tetralone (0.200 mmol), chloro- or bromoarene (0.400 mmol), NaO^{t}Bu (0.400 mmol), and Ni(COD)$_2$ (0.020 mmol)/(*R*)-DIFLUORPHOS (0.024 mmol) in toluene (1.0 mL) at 70 °C for 28 h; ee was determined by chiral HPLC analysis.

and with similarly high enantioselectivity (96% ee) as reactions run on smaller scale. Thus, these coupling reactions can be performed on a scale that would allow practical application in synthesis.

To determine the absolute configurations of the arylation products, we compared the optical rotations of 2-methyl-2-phenyl-2,3-dihydro-1*H*-inden-1-one obtained using the Ni(COD)$_2$/(*R*)-BINAP catalyst (entry 7) and the Pd(dba)$_2$/(*R*)-DIFLUORPHOS catalyst.[4] The values of the optical rotation of the products by these two catalysts are both negative. Thus, the α-arylation of ketones catalyzed by these Ni and Pd catalyst systems lead to the same enantiomers. These relative configurations contrast with those obtained in arylations of γ-lactones, for which Ni and Pd catalysts have been reported to form products with opposite configurations.[11]

Asymmetric α-heteroarylation is as important as asymmetric α-arylation because heteroaromatic units are ubiquitous in medicinal chemistry and can be reduced to saturated heterocycles. However, asymmetric α-heteroarylation is more challenging than asymmetric α-arylation because ligation of heteroarenes can lead to poisoning of the catalyst or displacement of the chiral ligand to form an achiral catalyst.[13,14] Because this Ni catalyst contains a bidentate ligand, rather than the monodentate ligands of some Pd systems for asymmetric α-arylation,[7,9,10] we hypothesized that Ni−bisphosphine systems would be suitable for asymmetric α-heteroarylation.

Initial studies of asymmetric heteroarylation showed that the reaction of 2-methyl-1-indanone with 2-bromopyridine under the conditions for the arylation of 2-methyl-1-indanone in Table 2 did not yield the coupled product. However, the same reaction

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conducted with (*R*)-DIFLUORPHOS (**L6**) in place of (*R*)-BINAP (**L1**) gave the desired product in 69% isolated yield but with only 57% ee (Table 3, entry 1). Most striking, the same reaction conducted with 2-chloropyridine in place of 2-bromopyridine afforded the heteroarylation product in 93% yield with 97% ee (entry 2). The leaving group had a similar effect on the heteroarylation of 2-methyl-1-tetralone (entries 13 and 14). Thus, further studies of the asymmetric coupling of ketones with heteroaryl electrophiles were conducted with heteroaryl chlorides.

The reactions of a series of nitrogen- and sulfur-containing heteroaryl chlorides possessing an electron-withdrawing group (i.e., $-CF_3$, $-CN$, or $-F$) or an electron-donating group (i.e., $-OMe$ or $-Me$) with 2-methyl-1-indanone and 2-methyl-1-tetralone are summarized in Table 3. In general, these reactions occurred with high enantioselectivities (90−99% ee) and in modest to high yields (45−93%). The few exceptions included the reactions of 2-chloro-6-methoxypyridine (entries 4 and 16) and the reactions of two electron-poor 2-chloropyridines. 2-Chloro-6-methoxypyridine has the potential to chelate the Ni center; the reactions of isosteric 2-chloro-6-methylpyridine afforded products with high ee's (entries 5 and 17). The low ee's of entries 6 and 8 appear to be caused by competing uncatalyzed nucleophilic aromatic substitutions between the sodium enolate of 2-methyl-1-indanone and the activated 2-chloropyridine bearing a highly electron-withdrawing group at the 2-position [see the Supporting Information (SI) for background reactions].

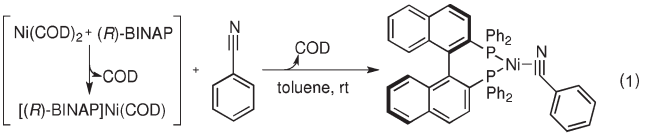
To understand the effect of the leaving group on the yield and enantioselectivity, we monitored by ^{31}P NMR spectroscopy the reactions of 2-methyl-1-indanone with 4-chlorobenzotrifluoride and 4-bromobenzotrifluoride in the presence of NaO^{t}Bu catalyzed by Ni(COD)$_2$ and (*R*)-BINAP at 60 °C. Two Ni species, [(*R*)-BINAP]$_2$Ni and [(*R*)-BINAP]Ni(COD), were detected in both reactions. Stoichiometric reactions of [(*R*)-BINAP]$_2$Ni with 4-chloro- or 4-bromobenzotrifluoride at 60 °C did not occur. The same reaction of [(*R*)-BINAP]Ni(COD) led to complete consumption of the Ni complex within 1 h, but no new species was detected by ^{31}P NMR spectroscopy. These data suggest that [(*R*)-BINAP]$_2$Ni is not the active catalyst and that [(*R*)-BINAP]Ni(COD) reacts with bromo- or chloroarenes to give products that are thermally labile toward the generation of Ni(I) species in the absence of enolate at elevated temperatures.

To determine whether catalyst decomposition relates to the difference in reactivity of bromoarenes and chloroarenes, we monitored the enantiomeric excess as a function of time. As shown in Figure S1 in the SI, the ee of the product from reaction of the bromoarene decreased from 92 to 60% during the course of the reaction, while that of the product from reaction of the chloroarene remained above 94%. These data are consistent with the hypothesis that the catalyst decomposes during the reaction of the bromoarene to a second species that catalyzes the reaction with lower enantioselectivity.

To determine the species that accounts for the high enantioselectivity and to identify potential modes of decomposition, we studied the formation and reactivity of arylnickel halide complexes. The reactions of [(*R*)-BINAP]Ni(COD) with the series of chloroarenes in Table 2 at room temperature showed that only 4-chlorobenzonitrile reacted to give a stable arylnickel chloride complex. [(*R*)-BINAP]Ni(Cl)(C$_6$H$_4$-4-CN) (**1**) was isolated from this reaction in 77% yield.

We speculated that the cyano group in 4-chlorobenzonitrile plays a role in triggering the oxidative addition reaction. Indeed, the reaction of [(*R*)-BINAP)]Ni(COD) (generated in situ) with 4-chlorobenzotrifluoride in the presence of a catalytic amount of benzonitrile (15 mol %) afforded [(*R*)-BINAP]Ni(Cl)(C$_6$H$_4$-4-CF$_3$) (**2**) in 75% isolated yield (the structure of **2** is shown in Figure S2). The bromide congener, [(*R*)-BINAP]Ni(Br)(C$_6$H$_4$-4-CF$_3$) (**3**), was isolated in 80% yield by an analogous procedure.

To determine the origin of the effect of benzonitrile on the oxidative additions of chloroarenes to [(*R*)-BINAP]Ni(COD), we studied the reaction of [(*R*)-BINAP]Ni(COD) with benzonitrile in toluene. The ^{31}P NMR spectrum of the reaction containing 2 equiv of benzonitrile led to the conversion of ~45% of [(*R*)-BINAP]Ni(COD) to the new species [(*R*)-BINAP]Ni(η^2-NC-Ph) (**4**). Addition of 20 equiv of benzonitrile to the same mixture led to 95% conversion of [(*R*)-BINAP]Ni(COD) and an 86% isolated yield of **4** (eq 1). Single-crystal X-ray diffraction (XRD) (Figure S3) confirmed its structural assignment. This complex is stable on its own at room temperature but reacts rapidly with chloroarenes. Isolated **4** reacted with 5 equiv of 4-chlorobenzotrifluoride in toluene at room temperature to form **2** in quantitative yield within 5 min, as determined by ^{31}P NMR spectroscopy.

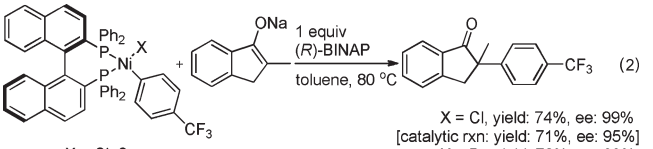


(1)

4: isolated yield: 92%

Benzonitrile also promoted the catalytic asymmetric α-arylation. The reaction of 2-methyl-1-indanone with 4-chlorobenzotrifluoride in the presence of NaO^{t}Bu catalyzed by the combination of 5 mol % Ni(COD)$_2$, 6 mol % (*R*)-BINAP, and 20 mol % PhCN at room temperature led to full conversion of 2-methyl-1-indanone within 3 h and a 92% isolated yield of the 2-aryl indanone with >99% ee. The same reaction at room temperature without added benzonitrile afforded less than 5% product after 3 h.

Because of the ambiguity of the oxidation state of the Ni species in cross-coupling reactions, we assessed the competence of the arylnickel(II) halide compounds as intermediates in asymmetric α-arylation. To do so, we conducted the stoichiometric reaction of [(*R*)-BINAP]Ni(X)(C$_6$H$_4$-4-CF$_3$) [X = Cl (**2**), Br, (**3**)] with the sodium enolate of 2-methyl-1-indanone at 80 °C in the presence of 1 equiv of (*R*)-BINAP (eq 2) to trap a Ni(0) product. The reaction of **2** afforded the α-aryl indanone in 74% yield with 99% ee in 3 h. This yield and ee match those of the corresponding catalytic reaction (71% yield and 95% ee), indicating that **2** is kinetically and chemically competent to be an intermediate in the catalytic process. The same reaction of **3** yielded the α-aryl indanone in 72% yield with 99% ee. These values are much *higher* than those of the corresponding catalytic reaction (38% yield and 39% ee). This result provides further evidence that **3** decomposes in the catalytic system to form a less reactive and selective catalyst for the asymmetric coupling of aryl bromides.



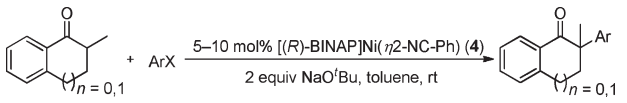
(2)

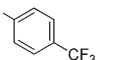
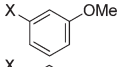
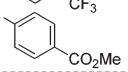
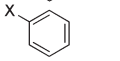
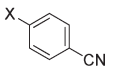
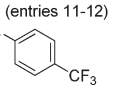
X = Cl, **2**
X = Br, **3**

X = Cl, yield: 74%, ee: 99%
[catalytic rxn: yield: 71%, ee: 95%]
X = Br, yield: 72%, ee: 99%
[catalytic rxn: yield: 38%, ee: 39%]

To identify this less reactive and selective species, we studied the thermal reactivity of arylnickel chloride and bromide complexes **2** and **3**. Both complexes fully decomposed in THF within 2 days at room temperature to form {[(*R*)-BINAP]Ni(μ-X)}$_2$ [X = Cl (**5**), 69%; Br (**6**), 71%] with concomitant release of

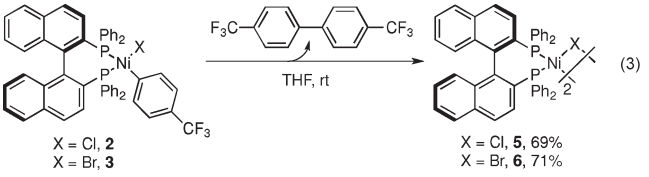
Table 4. Room-Temperature Asymmetric α-Arylation of Ketones with Chloro- and Bromoarenes Catalyzed by [(*R*)-BINAP]Ni(η^2-NC-Ph)[a]



entry	ArX	X	yield (%)	ee (%)	entry	ArX	X	yield (%)	ee (%)
n = 0, (entries 1-10)					7[c]		Cl	92	>99
1[b]		Cl	91	>99	8[c]		Br	96	>99
2[c]		Br	95	>99	9[b]		Cl	72	>99
3[b]		Cl	64	98	10[c]		Br	50	98
4[c]		Br	74	99	*n* = 1, (entries 11-12)				
5[b]		Cl	93	99	11[b]		Cl	59	95
6[c]		Br	61	98	12[b]		Br	74	83

[a] Conditions: ketone (0.200 mmol), ArX (0.400 mmol), NaO^{t}Bu (0.400 mmol), and [(*R*)-BINAP]Ni(η^2-NC-Ph) (0.010 mmol, 5% or 0.020 mmol, 10%) in toluene (1.0 mL); ee was determined by chiral HPLC analysis. [b] 10 mol % catalyst. [c] 5 mol % catalyst.

4,4′-bis(trifluoromethyl)-1,1′-biphenyl (detected by GC–MS) (eq 3). Both **5** and **6** are paramagnetic, and their structures were determined by single-crystal XRD (see the SI for structural data).



The reactions of 2-methyl-1-indanone with electronically varied chloro- and bromoarenes catalyzed by Ni(I) halides **5** and **6** (Table S1 in the SI) were slower than those catalyzed by nitrile complex **4**. Reactions catalyzed by **5** or **6** did not occur at room temperature, and the reactions at 80 °C formed the α-aryl indanones in low yields (13–49%). Moreover, the product ee's were only 50–89% for reactions of the chlorides catalyzed by **5** and 7–51% for reactions of the bromides catalyzed by **6**. These data imply that the loss of activity and enantioselectivity during the reactions of bromides results from competing reactions catalyzed by accumulating Ni(I) species.

The oxidative additions of chloro- and bromoarenes to **4** at room temperature suggest that the catalytic process could also occur at this mild temperature.[15] As shown in Table 4, both chloro- and bromoarenes reacted with 2-methyl-1-indanone in high yields and enantioselectivities (entries 1–10) at room temperature. Under these mild conditions, the difference in enantioselectivities with chloro- and bromoarenes was small for most reactions. The reaction of 2-methyl-1-tetralone with 4-chlorobenzotrifluoride, however, did occur with significantly higher enantioselectivity than that of 4-bromobenzotrifluoride (entries 11 and 12).

In summary, the α-arylations of ketones with aryl and heteroaryl chlorides catalyzed by the combination of Ni(COD)$_2$ and (*R*)-BINAP (for α-arylation) or (*R*)-DIFLUORPHOS (for α-heteroarylation) occur with high enantioselectivity. In contrast to the usual reactivity of haloarenes, bromoarenes reacted with lower yield and enantioselectivity than the corresponding chloroarenes, most likely because of greater reactivity of the bromoarene through a less selective catalyst formed by decomposition of the Ni(0) or Ni(II) species. Like the dibenzylidene acetone in electron-rich L$_2$Pd(dba) complexes,[16,17] the COD in [(*R*)-BINAP]Ni(COD) and related complexes is slow to dissociate and makes the oxidative addition of haloarenes to the Ni(0) species slow. However, the discrete Ni(0) precursor [(*R*)-BINAP]Ni(η^2-NC-Ph) (**4**) adds chloro- and bromoarenes rapidly at room temperature, and this high rate allows the α-arylation of ketones also to occur at room temperature and attenuate the decomposition to form the less selective Ni(I) species. Future work will focus on asymmetric α-arylation reactions of other types of carbonyl compounds and on additional cross-coupling reactions initiated with discrete Ni(0) complexes ligated by benzonitrile and bidentate phosphines.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, characterizations of all compounds, and X-ray crystallographic data (CIF) for compounds **2**, **4**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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