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Ni-Catalyzed Mild Arylation of α-Halocarbonyl Compounds with Arylboronic Acids

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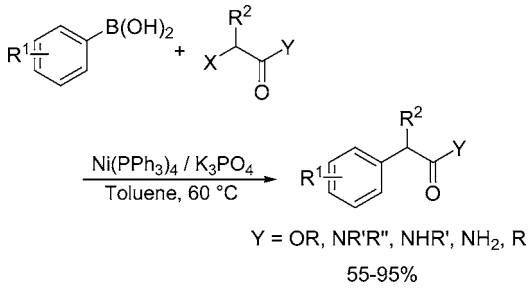
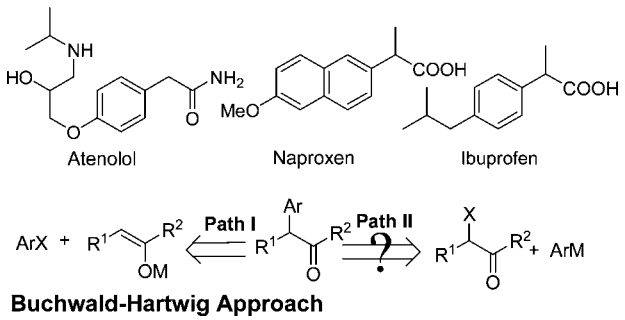
ABSTRACT



A simple yet powerful Ni catalyst can be used to promote direct arylations of α-halocarbonyl compounds, including a range of esters, amides, and ketones, with various arylboronic acids under mild conditions. The method tolerates *β*-hydrogens and functional groups in the substrates and offers reactivity and selectivity profiles that are complementary to those found in the well-established Buchwald–Hartwig approach.

α-Functionalization[1,2] using readily available α-halocarbonyl compounds represents one of the most versatile and valuable methods for organic synthesis. Direct arylation of these compounds would lead to efficient syntheses of the *β*-blocker drug, avenolol, and a number of important nonsteroidal anti-inflammatory drugs (NSAIDs) such as naproxen and ibuprofen (Scheme 1). Since 1997, Buchwald and Hartwig have pioneered palladium-catalyzed arylation of enolates of ketone, ester, or amide using aryl halides as electrophiles (Scheme 1, Path I).[3,4] Their method has received much attention because it could produce important synthetic building blocks that are otherwise inefficient to prepare by other technologies.[5] However, those enolate nucleophiles were usually generated from their corresponding carbonyl compounds by deprotonation of α-hydrogens with strong bases, conditions that could jeopardize the method's functional group tolerance capability. Very recently, Hartwig et al. reported a mild and efficient arylation protocol from Zn-enolate, silyl enol ether, and other precursors.[6−8] We anticipated that an alternative arylation strategy employing

Scheme 1. α-Arylation of Carbonyl Compounds and Its Potential Applications



(1) Millard, A. A.; Rathke, M. W. *J. Am. Chem. Soc.* **1977**, *99*, 4833−4835.
(2) Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 953−956.
(3) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382−12383.
(4) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108−11109.
(5) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234−245.

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α-halocarbonyl compounds as the electrophiles and ArM as the nucleophiles might achieve the same goal while at the same time offering a greater level of synthetic flexibility (Scheme 1, Path II). Moreover, such ArM precursors as $ArB(OR)_2$ are usually less toxic, fairly stable, readily available, and broadly compatible with an array of functional groups.[9−17]

Goossen and Deng et al. had previously investigated the reactions of α-bromoacetic acid derivatives with $ArB(OH)_2$ in the presence of palladium catalysts. The yields were moderate to good in most cases, but the substrates were limited to unsubstituted acetic acid derivatives.[18−20] α-Bromosulfoxides were also reported as suitable electrophiles to react with $ArB(OH)_2$.[21] In 2007, we disclosed α-alkynylation of α-bromoester or amides under mild conditions promoted by some palladium catalysts.[22] However, the substrates employed in all the aforementioned transformations have been limited to α-bromoacetic acid derivatives where *β*-hydride elimination was not an issue in catalysis. Very recently, Fu et al. reported an elegant approach of coupling α-halocarbonyl compounds with Csp^3-Zn and $ArSiF_3$ reagents, by employing Ni-based catalysts[23] ligated with pybox or amino alcohols.[24,25]

In our continued efforts to investigate arylations of α-halocarbonyl compounds bearing *β*-hydrogen with $ArB(OH)_2$, we found that homocoupling product biaryls were predominantly obtained.[26] In these cases, α-halocarbonyl compounds seemed to serve as agents in promoting oxidative homocoupling reactions,[26−28] rather than function effectively as coupling partners, which was in marked contrast to some cross-coupling systems we uncovered recently.[29] We proposed that the complexity of the reactions involving α-halocarbonyl compounds likely arose from the tautomerization between intermediates **IA** and **IB** (Figure 1), which were generated through oxidative addition of α-halocarbonyl compounds with the palladium catalysts. As illustrated in Figure 1, among the several reaction pathways initiated from oxidative addition and transmetalation intermediates, only path **B** to **D** offers the potential of arylating α-halocarbonyl compounds, while path **A** and path **B** to **C** would result in

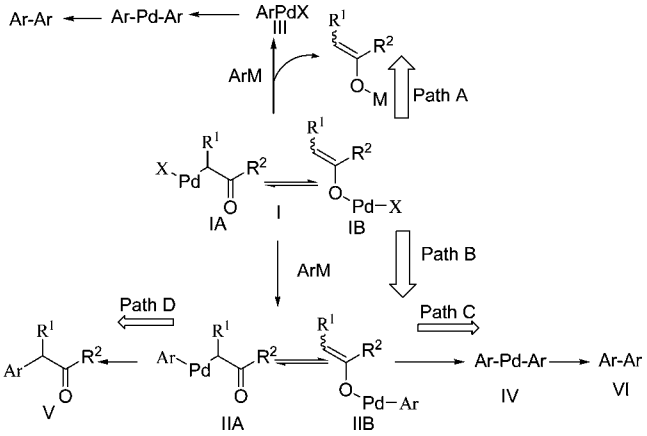
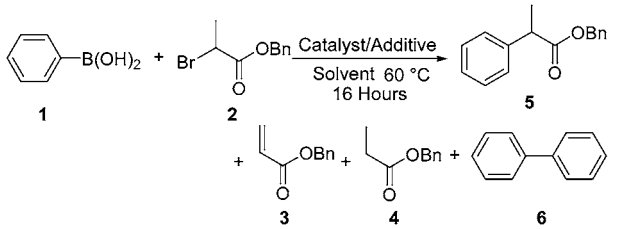


Figure 1. Possible reaction pathways involving α-halocarbonyl compounds.

Table 1. Arylation of α-Bromoesters with $PhB(OH)_2$[a]



entry	catalyst	additive	solvent	GC yield[%] 3	4	5	6
1	$Pd(PPh_3)_4$	K_2CO_3	THF	2	49	6	18
2			Toluene	<1	11	2	40
3			Dioxane	1	24	2	40
4			$ClCH_2CH_2Cl$	<1	9	2	29
5			DMF	2	19	<1	41
6			DMA	2	26	<1	43
7			CH_3CN	<1	14	<1	42
8			*iso*-PrOH	1	46	2	25
9			*t*-BuOH	<1	<1	<1	32
10		K_3PO_4	Toluene	<1	12	2	41
11		Cs_2CO_3		<1	14	1	39
12		KF		2	13	<1	31
13		CsF		<1	14	<1	27
14	$Ni(PPh_3)_4$	K_3PO_4		<1	11	82	6

[a] 1:2:catalyst = 2:1:0.05 (0.5 mmol scale); solvent 1 mL; additive 2 mmol; naphthalene 0.5 mmol. The yields were determined by GC.

(6) Su, W.; Raders, S.; Verkade, J. G.; Liao, X.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2006**, *45*, 5852−5855.
(7) Hama, T.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 4976−4985.
(8) Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824−15832.
(9) Murphy, J. M.; Tzschucke, C. C.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 757−760.
(10) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649−5651.
(11) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508−7510.
(12) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056−3058.
(13) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390−391.
(14) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. *Science* **2002**, *295*, 305−308.
(15) Mkhalid, I. A. I.; Conventry, D. N.; Albesa-Jove, D.; Batsanov, A. S.; Howard, J. A. K.; Perutz, R. N.; Marder, T. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 489−491.
(16) Paul, S.; Chotana, G. A.; Holmes, D.; Reichle, R. C.; Maleczka, R. E., Jr.; Smith, M. R., III. *J. Am. Chem. Soc.* **2006**, *128*, 15552−15553.
(17) Shimada, S.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2168−2171.
(18) Goossen, L. J. *Chem. Commun.* **2001**, 669−670.
(19) Liu, X.-X.; Deng, M.-Z. *Chem. Commun.* **2002**, 622−623.
(20) Duan, Y.-Z.; Deng, M.-Z. *Tetrahedron Lett.* **2003**, *44*, 3423−3426.
(21) Rodriguez, N.; Cuenca, A.; De Arellano, C. R.; Medio-Simon, M.; Peine, D.; Asensio, G. *J. Org. Chem.* **2004**, *69*, 8070−8076.
(22) Shi, W.; Liu, C.; Yu, Z.; Lei, A. *Chem. Commun.* **2007**, 2342−2344.
(23) Tamaru, Y. *Modern Organonickel Chemistry*; Wiley-VCH: Weinheim, Germany, 2005.
(24) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594−4595.
(25) Strotman, N. A.; Sommer, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3556−3558.
(26) Lei, A.; Zhang, X. *Tetrahedron Lett.* **2002**, *43*, 2525−2528.
(27) Lei, A.; Zhang, X. *Org. Lett.* **2002**, *4*, 2285−2288.
(28) Lei, A.; Srivastava, M.; Zhang, X. *J. Org. Chem.* **2002**, *67*, 1969−1971.

Table 2. Arylation of α-Bromoesters or Amides with $PhB(OH)_2$[a]

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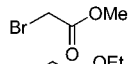
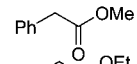
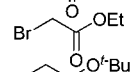
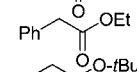
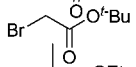
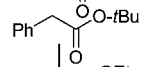
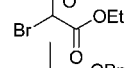
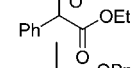
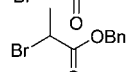
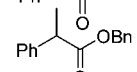
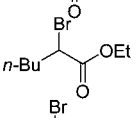
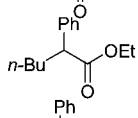
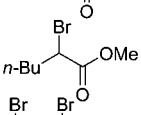
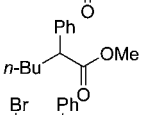
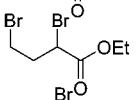
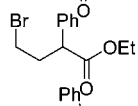
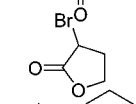
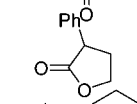
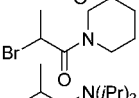
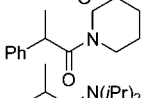
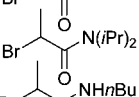
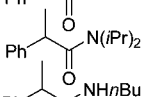
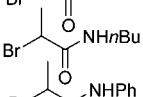
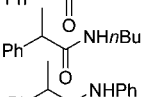
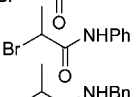
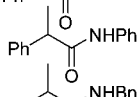
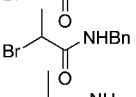
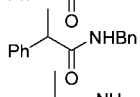
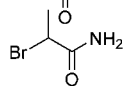
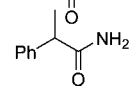
1			80[b]
2			93[b]
3			92[b]
4			78
5			80
6			95
7			77
8			72
9			74
10			61
11			71
12			70
13			68
14			65
15			75

[a] Reaction conditions: refer to Supporting Information, isolated yield. [b] GC yield.

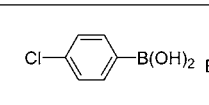
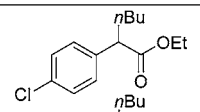
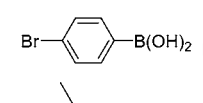
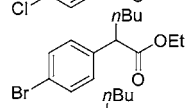
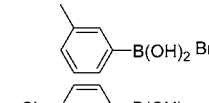
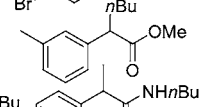
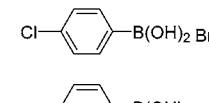
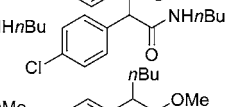
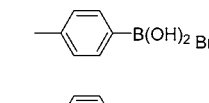
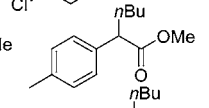
the formation of biaryl byproducts. Herein, we report a highly efficient and versatile catalytic system that was shown to differentiate well these competing pathways and lead to arylations of a series of α-halocarbonyl compounds bearing β-hydrogens with various arylboronic acids.

Our initial efforts focused on the reaction of β-hydrogen-bearing α-bromoester **2** with phenylboronic acid using $Pd(PPh_3)_4$ as the catalyst precursor.[30] As listed in Table 1, the formation of the desired arylation product **5** proved to be rather fruitless under a variety of conditions (<10% yield, Table 1, entries 1−13). The major byproduct was the biphenyl derived from homocoupling of phenylboronic acid. However, we were delighted to find that **5** could be obtained in 82% yield when $Ni(PPh_3)_4$ was used as the catalyst precursor in the presence of K_3PO_4 in toluene (Table 1, entry 14).

(29) Zhao, Y.; Wang, H.; Hou, X.; Hu, Y.; Lei, A.; Zhang, H.; Zhu, L. *J. Am. Chem. Soc.* **2006**, *128*, 15048−15049.

This finding prompted us to explore the utility of Ni-catalyzed arylations of a range of α-bromoesters and amides with phenylboronic acid. As summarized in Table 2, the Ni-$(PPh_3)_4$ catalytic system proved to be broadly applicable as in nearly all the cases the products were obtained in good to high yields. Arylations with bromoacetates appeared to be particularly efficient (Table 2, entries 1−3).[31] Those α-bromoesters bearing β-hydrogens were well-tolerated (Table 2, entries 4−9). The arylation of α-bromolactone formed the product in 74% yield using anhydrous K_3PO_4 with only a trace amount of biphenyl (<5%) detected by GC. It merits a note here that the role of the base seemed to be critical as no product could be isolated when the reaction was carried out in the presence of $K_3PO_4 \cdot 3H_2O$. The protocol could also be extended to α-bromoamides to afford arylated derivatives effectively (Table 2, entries 10−15). It is noteworthy that the free NH of primary and secondary amides was fairly compatible with these reaction conditions (Table 2, entries 12−15). Additionally, a substrate containing two Br atoms at the α- and γ-positions displayed good selectivity (Table 2, entry 8).

Table 3. Arylation of α-Bromoacetic Acid Derivatives with Arylboronic Acids[a]

entry	$ArB(OH)_2$	α-bromoacetic acid derivatives	product	yield(%)
1				95
2				75
3				74
4				90
5				72[b]
6				82[b]

[a] Reaction conditions: refer to Supporting Information, isolated yield. [b] At a 1.5 mmol scale, at 80 °C.

Furthermore, as shown in Table 3, we found that the method could be readily extended to substituted arylboronic acids to generate arylated products in good to excellent yields. For example, arylation of *p*-chlorobenzenylboronic acid with ethyl 2-bromohexanoate (Table 3, entry 1) afforded the product in 95% yield. It is noteworthy that the ArBr moiety was tolerated under these mild conditions, which may

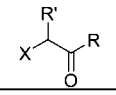
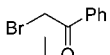
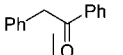
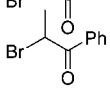
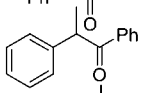
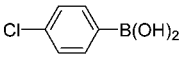
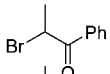
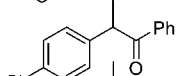
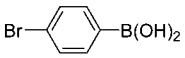
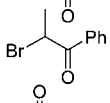
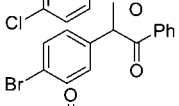
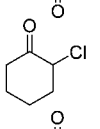
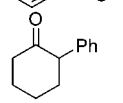
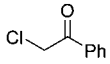
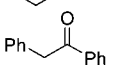
(30) Durandetti, M.; Gosmini, C.; Perichon, J. *Tetrahedron* **2006**, *63*, 1146−1153.

(31) Ten percent yields of the biphenyl was detected by GC in the reaction of the methyl bromoester (Table 2, entry 1). The reactions of the ethyl bromoester and the *tert*-butyl bromoacetate produced the biphenyl in 6 and 5% GC yields, respectively (Table 2, entries 2 and 3).

otherwise cause problems for its oxidative addition reactivity as reported in Buchwald−Hartwig approaches. The reaction produced the corresponding product in 75% yield (Table 3, entry 2).

The α-haloketones are also viable substrates for this process, as evidenced by the results compiled in Table 4.

Table 4. Ni-Catalyzed α-Arylation of Ketones[a]

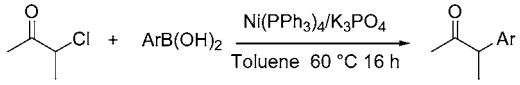
entry	$ArB(OH)_2$		product	yield (%)
1	$PhB(OH)_2$			66
2	$PhB(OH)_2$			87
3				68
4				55
5	$PhB(OH)_2$			75
6	$PhB(OH)_2$			63

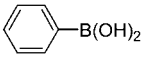
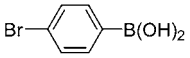
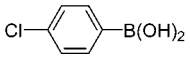
[a] Reaction conditions: refer to Supporting Information, isolated yield.

The reaction of 2′-bromoacetophenone with phenylboronic acid led to the formation of 1,2-diphenylethanone in 66% yield. Both 2′-chloroacetophenone and 2′-bromopropiophenone bearing a methyl group at the α-position afforded arylated products in high yields. Again, we observed that the halide moieties (ArCl and ArBr) were well-tolerated under these reaction condition.

Regioselective arylation using unsymmetric ketones such as butan-2-one represented a major challenge in the Buchwald−Hartwig approach employing palladium catalysts where the arylations tend to take place at less hindered sites when the ketones have two enolizable positions. In our system, remarkably, we found that the arylations could be controlled regioselectively. As shown in Table 5, the

Table 5. Arylation of 3-Chlorobutan-2-one[a]



entry	$ArB(OH)_2$	yields (%)
1		61
2		60
3		67

[a] Reaction conditions: refer to Supporting Information, GC yield.

reactions of 3-chlorobutan-2-one took place smoothly at the more hindered site to give the products in 60−67% yield, which offered complementary results to those of the Buchwald−Hartwig method (Table 5).

In conclusion, we have discovered that $Ni(PPh_3)_4$ served as a highly effective catalyst for the arylations of a wide variety of α-halocarbonyl compounds with various arylboronic acids. Compared to those Pd-catalyzed arylations using aryl halides, the Ni-based catalysis approach is notably more advantageous in that it is capable of bringing about arylations with readily available substrates and offering more robust profiles in such important issues as functional group tolerance and reaction selectivity. This method is simple, general, and practical and thus holds promise for the preparation of structurally diverse arylated carbonyl compounds. The mechanism is currently under investigation in our laboratory and will be reported in due course.

Acknowledgment. This work was assisted financially by the National Natural Science Foundation of China (20502020) and a startup fund from Wuhan University.

Supporting Information Available: Detailed experimental procedure and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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