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A Nickel Catalyst for the Addition of Organoboronate Esters to Ketones and Aldehydes

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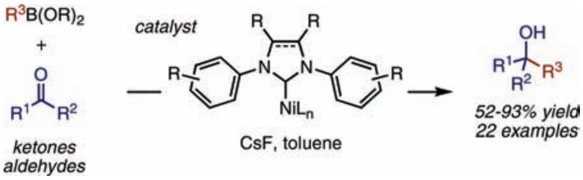
ABSTRACT



A $Ni(cod)_2$/IPr catalyst promotes the intermolecular 1,2-addition of arylboronate esters to unactivated aldehydes and ketones. Diaryl, alkyl aryl, and dialkyl ketones show good reactivity under mild reaction conditions (≤80 °C, nonpolar solvents, no strong base or acid additives). A dramatic ligand effect favors either carbonyl addition (IPr) or C−OR cross-coupling (PCy_3) with aryl ether substrates. A Ni(0)/Ni(II) catalytic cycle initiated by the oxidative cyclization of the carbonyl substrate is proposed.

Boronic acids and their derivatives have emerged as privileged organometallic nucleophiles in a wide variety of late transition metal-catalyzed reactions, including Suzuki−Miyaura cross-couplings, 1,4-conjugate additions, and carbon−heteroatom bond formation.[1] Despite substantial advances in C−X and C−H metalation chemistry,[2] the shelf-stability, functional group compatibility, widespread commercial availability, and ease of functionalization[3] of boronic acids confer on them significant practical advantages over lithium, magnesium, aluminum, or zinc organometallics. Unfortunately, for the most prototypical of organometallic reactions, 1,2-addition to carbonyls, boronic acids remain limited substrates. Since the first report of Rh-catalyzed addition of boronic acids to aldehydes by the Miyaura group,[4] and despite recent developments,[5] the 1,2-addition of boronic acids to the less reactive ketones has to date been largely limited to activated substrates and intramolecular reactions, or must be preceded by boron-to-zinc transmetalation.[6,7]

Herein, we report that a simple $Ni(cod)_2$/IPr·HCl system (IPr: 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) catalyzes the 1,2-addition of organoboronate esters to unactivated ketones and aldehydes under mild conditions. For example, phenylboronate ester **2a** reacts with 2-acetylnaphthalene (**1a**) in toluene at 80 °C in the presence of $Ni(cod)_2$, IPr·HCl,

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(2) Recent reviews: (a) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3802–3824. (b) Knochel, P.; Dohle, W.; Gommermann, N.; Kniesel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302–4320.

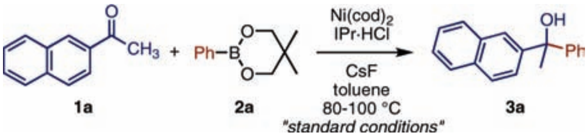
(3) Recent examples: (a) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 14084–14085. (b) Ihara, H.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 7502–7503.

(4) Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 3279–3280.

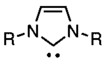
(5) Selected references: Rh: (a) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683–1686. (b) Ueda, M.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 4450–4452. (c) Fürstner, A.; Krause, H. *Adv. Synth. Catal.* **2001**, *343*, 343–350. Pd: (d) Kuriyama, M.; Shimazawa, R.; Shirai, R. *J. Org. Chem.* **2008**, *73*, 1597–1600. Ru: (e) Yamamoto, Y.; Kurihara, K.; Miyaura, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4414–4416. Fe: (f) Zou, T.; Pi, S.-S.; Li, J.-H. *Org. Lett.* **2009**, *11*, 453–456. Cu: (g) Tomita, D.; Kanai, M.; Shibasaki, M. *Chem. Asian J.* **2006**, *1*, 161–166. Pt: (h) Liao, Y.-X.; Xing, C.-H.; He, P.; Hu, Q.-S. *Org. Lett.* **2008**, *10*, 2509–2512. Ni: (i) Takahashi, G.; Shirakawa, E.; Tsuchimoto, T.; Kawakami, Y. *Chem. Commun.* **2005**, 1459–1461. (j) Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2005**, *7*, 4689–4691. (k) Arao, T.; Kondom, K.; Aoyama, T. *Tetrahedron Lett.* **2007**, *48*, 4115–4117.

10.1021/ol9017613 CCC: $40.75

Table 1. Discovery of Nickel Catalysis and Influence of Parameters[a]



deviation from "standard conditions"		yield (%)[b]
	none	> 95
Substrate in place of **2a**	PhB(OH)$_2$, PhBF$_3$K, PhSnMe$_3$	≤ 23
Precatalyst in place of Ni(cod)$_2$	Ni(acac)$_2$, NiCl$_2$(dme), NiF$_2$, (IPr)Ni(allyl)Cl, Pd(OAc)$_2$, Pd$_2$(dba)$_3$	< 5
Ligand in place of IPr	no ligand, ^{t}BuNHC·HBF$_4$, AdNHC·HCl IMes·HCl, SIMes·HCl, SIPr·HCl	≤ 16 36-48
Additive in place of CsF	KF CsOH, Cs$_2$CO$_3$	< 5 35-62
Catalyst loading and temperature	0.5% Ni(cod)$_2$, 1% IPr·HCl, 80 °C 1% Ni(cod)$_2$, 2% IPr·HCl, 80 °C 10% Ni(cod)$_2$, 10% IPr·HCl, 23 °C	57 78 56



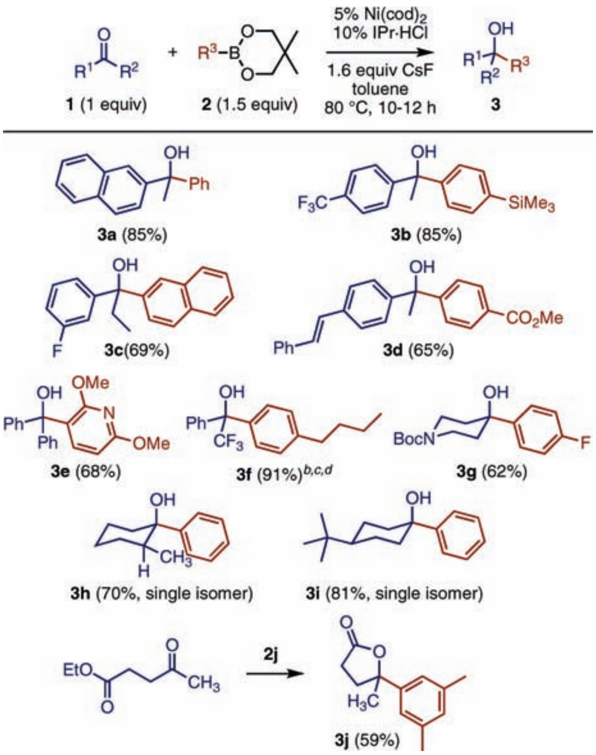
IPr: R = 2,6-(*i*-Pr)$_2$C$_6$H$_3$
IMes: R = 2,4,6-Me$_3$C$_6$H$_2$
^{t}BuNHC: R = *t*-butyl
AdNHC: R = 1-adamantyl
SIPr: R = 2,6-(*i*-Pr)$_2$C$_6$H$_3$ (ring saturated)
SIMes: R = 2,4,6-Me$_3$C$_6$H$_2$ (ring saturated)

[a] See the Supporting Information for details. Standard conditions for optimization studies: **1** (0.1 mmol), **2** (0.2 mmol), CsF (0.3 mmol), Ni(cod)$_2$ (10 μmol), IPr·HCl (13 μmol), toluene (1 mL), 80−100 °C, 10−12 h. [b] Determined by GC analysis.

and CsF to furnish the addition product **3a** in quantitative yield (Table 1). Under these conditions, neither α-arylation of **1a** nor homocoupling of **2a** occurs. Listed in Table 1 are some examples of variations from the standard conditions (see the Supporting Information for an extensive list of reaction conditions). Other nucleophiles such as trifluoroborates and stannanes are essentially unreactive, while boronic acids and pinacolboronate esters give lower yields. Catalysis requires both a Ni(0) precatalyst and a bulky NHC ligand. Comparable results are obtained with either the free carbene or the more convenient air-stable IPr•HCl. The addition of CsF, which presumably assists the transmetalation of the organoboron reagent to the Ni catalyst, was required to reach high conversions with ketone substrates.[8] Addition also proceeds at room temperature, albeit less rapidly. In some cases, the catalyst loading can be lowered to 1 mol % without an appreciable reduction in yield, at the expense of extended reaction times. The reaction proceeds best in toluene or benzene, but acceptable yields can be achieved in MTBE, THF, or *n*-hexane.[8]

With an efficient catalyst system in hand, the scope of applicable ketone substrates (**1**) as well as arylboronate esters (**2**) was examined on a preparative scale (1 mmol), with **1** (1.0 equiv), **2** (1.5 equiv), Ni(cod)$_2$ (5 mol %), IPr•HCl (10 mol %), and CsF (1.6 equiv) in toluene at 80 °C (Scheme 1). Unactivated diaryl (**3e**), aryl alkyl (**3a−d**), and dialkyl (**3g−j**) ketones, as well as activated trifluoromethyl ketones (**3f**), react to give the corresponding tertiary alcohols in moderate to excellent yields. Addition to a substituted cyclohexanone (**3h** and **3i**) takes place with virtually complete diastereoselectivity. Addition of **2j** to ethyl levulinate was followed by intramolecular cyclization to give lactone **3j**.

Scheme 1. Ni-Catalyzed Addition to Ketones[a]



[a] Reagents and conditions: carbonyl compound (**1**: 1.0 mmol), boronate (**2**: 1.5 mmol), CsF (1.6 mmol), Ni(cod)$_2$ (0.05 mmol), IPr•HCl (0.10 mmol), toluene (3 mL). Isolated yields. [b] 10% Ni(cod)$_2$. [c] IPr (1:1 L:Ni) in place of IPr•HCl. [d] without CsF.

As expected, aldehydes are considerably more reactive, allowing the reaction to be performed at room temperature with both aryl (**3k−p**, **3t**) and alkyl (**3q−s**) aldehydes (Scheme 2). Lower temperatures enable the addition to

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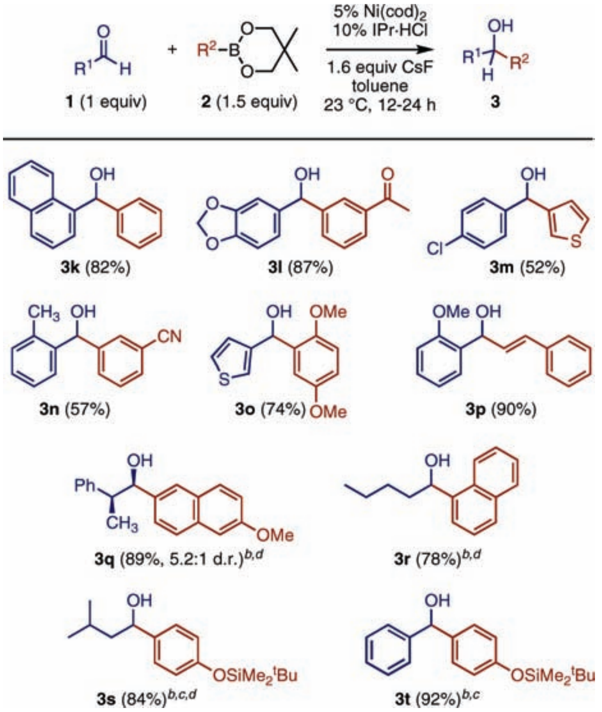
(6) Selected references: Electronically activated ketones: (a) He, P.; Lu, Y.; Dong, C.-G.; Hu, Q.-S. *Org. Lett.* **2007**, *9*, 343–346. (b) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353–3356. (c) Martina, S. L. X.; Jagt, R. B. C.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Chem. Commun.* **2006**, 4093–4095. (d) Motoki, R.; Tomita, D.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 8083–8086. Strain-activated ketones: (e) Matsuda, T.; Makino, M.; Murakami, M. *Org. Lett.* **2004**, *6*, 1257–1259. Intramolecular additions: (f) Liu, G.; Lu, X. *J. Am. Chem. Soc.* **2006**, *128*, 16504–16505. B-to-Zn transmetalation: (g) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850–14851. Rare examples of intermolecular additions to unactivated ketones, albeit limited in scope: (h) Ueura, K.; Miyamura, S.; Satoh, T.; Miura, M. *J. Organomet. Chem.* **2006**, *691*, 2821–2826. (i) Facchetti, S.; Cavallini, I.; Funaioli, T.; Marchetti, F.; Iuliano, A. *Organometallics* **2009**, *28*, 4150–4158.

(7) For recent progress in catalytic allylboration of carbonyls, see: (a) Hall, D. G. *Pure Appl. Chem.* **2008**, *80*, 913–927. (b) Kanai, M.; Wada, R.; Shibuguchi, T.; Shibasaki, M. *Pure Appl. Chem.* **2008**, *80*, 1055–1062.

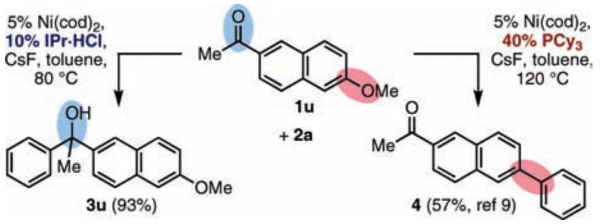
(8) See the Supporting Information for details.

Scheme 2. Ni-Catalyzed Addition to Aldehydes at Room Temperature[a]

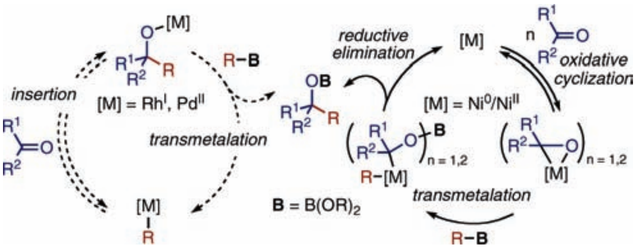


[a] Reagents and conditions: carbonyl compound (**1**: 1.0 mmol), boronate (**2**: 1.5 mmol), CsF (1.6 mmol), Ni(cod)$_2$ (0.05 mmol), IPr·HCl (0.10 mmol), toluene (3 mL). Isolated yields. [b] IPr (1:1 L:Ni) in place of IPr·HCl. [c] Without CsF. [d] Slow addition of aldehyde.

Scheme 3. Ligand-Controlled Orthogonal Arylation



Scheme 4. Proposed Mechanism



proceed selectively in the presence of other electrophiles including aryl chlorides (**3m**), ketones (**3l**), and nitriles (**3n**). Addition also takes place with alkenylboronate ester (**2p**) to furnish allylic alcohol **3p** in high yield. Synthetically useful levels of diastereoselectivity can be obtained when α,α-disubstituted aldehydes are used (**3q**). The addition to aldehydes does not require the presence of CsF, allowing fluoride-sensitive silyl ethers to participate in the reaction (**3s** and **3t**).

The choice of the bulky and strongly donating IPr ligand is critical not only for reactivity but also for the selectivity of the 1,2-addition reaction.[8] Tobisu, Chatani, and coworkers have recently reported that Ni(cod)$_2$/PCy$_3$ catalyzes the cross-coupling of arylboronate esters with aryl ethers.[9] Replacement of PCy$_3$ for IPr, under essentially identical reaction conditions, results in a complete reversal of selectivity with substrate **1u** to favor the carbonyl addition product **3u** in place of the C−OMe cross-coupling product **4** (Scheme 3).

Addition of organoboron reagents to aldehydes and ketones proceeds through a transmetalation-insertion mechanism for d^8 metal catalysts [Rh(I), Pd(II)], where the insertion is reversible and the reverse reaction (β-carbon elimination) has in many cases been found to be favorable for ketones (Scheme 4, left).[10]

Evidence from preliminary mechanistic investigations argues against the involvement of a transmetalation-insertion cycle for the Ni(cod)$_2$/IPr system (see detailed experiments and extended discussion in the Supporting Information): (i) addition does not occur with Ni(II) precatalysts; (ii) reaction of the carbonyl substrate with the catalyst precedes that of the organoboron substrate;[11] (iii) the observed rate law is first order in catalyst, zeroth order in carbonyl substrate, and approximately zeroth order in boronate ester, which is inconsistent with a two-step transmetalation-insertion cycle;[12] and (iv) byproducts that would arise from β-carbon elimination (aryl group scrambling) are not found in the reaction mixture.

We rather favor an alternate mechanism based on the oxidative cyclization of Ni(0) and substrate carbonyl(s) to afford an oxanickelacycle, followed by transmetalation with the boronate ester and reductive elimination (Scheme 4, right).[8] The 1,2-oxanickelirane pathway ($n = 1$) has been postulated in related reactions,[5i−k,13] although formation of

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(10) Mechanistic studies: (a) Krug, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1674–1679. (b) Krug, C.; Hartwig, J. F. *Organometallics* **2004**, *23*, 4594–4607. (c) Zhao, P.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 3124–3125. (d) Zhao, P.; Hartwig, J. F. *Organometallics* **2008**, *27*, 4749–4757. Tertiary alcohols as organometallic surrogates through β-carbon elimination: (e) Nishimura, T.; Katoh, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 4937–4939. (f) Iwasaki, M.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 4463–4469.

(11) Tsou, T. T.; Huffman, J. C.; Kochi, J. K. *Inorg. Chem.* **1979**, *18*, 2311–2316.

(12) Kinetic data were obtained for the addition of phenylboronate **2a** to *p*-anisaldehyde in the absence of CsF. The observed lack of dependence of the reaction rate on the concentration of both substrates within the range of concentration relevant to catalytic reactions is likely indicative of saturation kinetics. See the Supporting Information for a detailed discussion of the catalytic reaction kinetics.

the cyclic intermediate can require the assistance of an oxophilic Lewis acid.[14] The Ogoshi group has recently reported a Ni(cod)$_2$/IPr-catalyzed Tishchenko reaction that proceeds through a 1,4,2-dioxanickelolane intermediate ($n = 2$),[15] which supports its plausible participation in the 1,2-addition reaction. Both Ni(0)/Ni(II) redox cycles are nevertheless consistent with the experimental evidence, and their viability has been confirmed by kinetic modeling.[8]

Although these preliminary experiments remain insufficient to establish the reaction mechanism unequivocally, the Ni(cod)$_2$/IPr•HCl system constitutes a simple, practical, and comparatively inexpensive catalyst for the intermolecular 1,2-addition of boronic acid derivatives to unactivated ketones and aldehydes under remarkably mild conditions. Expansion of the scope of this reaction, elucidation of the reaction mechanism, and the development of catalytic asymmetric variants[16] are the object of ongoing efforts in our laboratory.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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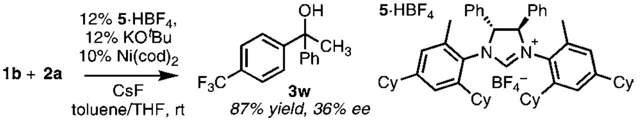
(14) (a) Ogoshi, S.; Oka, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2004**, *126*, 11802–11803. (b) Ogoshi, S.; Ueta, M.; Arai, T.; Kurosawa, H. *J. Am. Chem. Soc.* **2005**, *127*, 12810–12811. (c) Ogoshi, S.; Tonomori, K.; Oka, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2006**, *128*, 7077–7086. (d) Ogoshi, S.; Kamada, H.; Kurosawa, H. *Tetrahedron* **2006**, *62*, 7583–7588. (e) McCarren, P. R.; Liu, P.; Cheong, P. H.-Y.; Jamison, T. F.; Houk, K. N. *J. Am. Chem. Soc.* **2009**, *131*, 6654–6655.

(15) (a) Hoshimoto, Y.; Ogoshi, S. Nickel-catalyzed Coupling Reactions of Aldehydes. *Abstracts of Papers*, 89th Meeting of the Chemical Society of Japan, Chiba; The Chemical Society of Japan: Tokyo, Japan, 2009; 2-F3−20. See also: (b) Stone, F. G. A. *Pure Appl. Chem.* **1972**, *30*, 551–573. (c) Stone, F. G. A. *J. Organomet. Chem.* **1975**, *100*, 257–271. (d) Han, R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **1997**, *119*, 8135–8136. (e) Ogoshi, S.; Arai, T.; Ohashi, M.; Kurosawa, H. *Chem. Commun.* **2008**, 1347–1349.

(16) To date, best results have been obtained with chiral NHC ligand **5**:



For synthesis and applications of **5**•HBF$_4$ see: Chaulagain, M. R.; Sormunen, G. J.; Montgomery, J. *J. Am. Chem. Soc.* **2007**, *129*, 9568–9569.