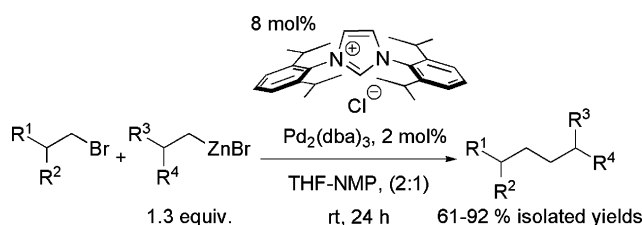


## Room-Temperature Negishi Cross-Coupling of Unactivated Alkyl Bromides with Alkyl Organozinc Reagents Utilizing a Pd/*N*-Heterocyclic Carbene Catalyst

Niloufar Hadei, Eric Assen B. Kantchev, Christopher J. O'Brien, and Michael G. Organ\*  
 Department of Chemistry, York University, 4700 Keele Street Toronto, ON, Canada M3J 1P3

organ@yorku.ca

Received June 25, 2005



A high-yielding cross-coupling reaction of unactivated alkyl bromides possessing  $\beta$ -hydrogens with alkylzinc halides utilizing a Pd/*N*-heterocyclic carbene (NHC) catalyst at room temperature is described. A variety of Pd sources, Pd<sub>2</sub>(dba)<sub>3</sub>, Pd(OAc)<sub>2</sub>, or PdBr<sub>2</sub>, with the commercially available ligand precursor 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr·HCl) successfully coupled 1-bromo-3-phenylpropane with *n*-butylzinc bromide in THF/NMP. An investigation of different NHC precursors showed that the bulky 2,6-diisopropylphenyl moiety was necessary to achieve high coupling yields (75–85%). The corresponding ethyl analogue was moderately active (11%). A range of unsymmetrical NHC precursors were prepared and evaluated. The ligand precursor containing one 2,6-diisopropylphenyl and one 2,6-diethylphenyl afforded the coupling product in 47% yield, clearly suggesting a direct relationship between the steric topography created by the flanking *N*-substituents and catalyst activity. Under optimal conditions, a number of alkyl bromides and alkylzinc halides possessing common functional groups (amide, nitrile, ester, acetal, and alkyne) were effectively coupled (61–92%). It is noteworthy that  $\beta$ -substituted alkyl bromides and alkylzinc halides successfully underwent cross-coupling. Also, under these conditions alkyl chlorides were unaffected.

### Introduction

Transition metal-catalyzed cross-coupling reactions of unsaturated organohalides and sulfonates with organometallic reagents are well-established and powerful methods for construction of carbon-carbon bonds.<sup>1</sup> While coupling of alkyl organometallic reagents has been known for some time, the use of unactivated alkyl chlorides, bromides, or tosylates possessing  $\beta$ -hydrogen atoms as coupling partners posed a greater challenge.<sup>2</sup> Numerous articles detailing couplings of unactivated alkyl halides with aryl,<sup>3</sup> vinyl,<sup>3f,h,4</sup> and alkynyl<sup>5</sup> organometallic derivatives have appeared recently. However, the coupling of

an alkyl halide with an alkyl organometallic reagent is, arguably, the most difficult to achieve, and it was not

(1) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley & Sons: New York, 2004.

(2) (a) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674–688. (b) Cárdenas, D. *J. Angew. Chem., Int. Ed.* **2003**, *42*, 384–387. (c) Kochi, J. K. *J. Organomet. Chem.* **2002**, *653*, 11–19. (d) Luh, T.-Y.; Leung, M.-K.; Wong, K.-T. *Chem. Rev.* **2000**, *100*, 3187–3204. (e) Cárdenas, D. *J. Angew. Chem., Int. Ed.* **1999**, *38*, 3018–3020 and references therein.

(3) (a) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686–3687. (b) Martin, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955–3957. (c) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297–1299. (d) Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788–7789. (e) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340–1341. (f) Tang, H.; Menzel, K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5079–5082. (g) Lee, J.-Y.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616–5617. (h) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527–12530. (i) Frisch, A. C.; Rataboul, F.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2003**, *687*, 403–409. (j) Terao, J.; Naitoh, Y.; Kuniyasu, H.; Kambe, N. *Chem. Lett.* **2003**, *32*, 890–891. (k) Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2003**, *125*, 5646–5647. (l) Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4056–4059. (m) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910–3912. (n) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662–13663. (o) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *123*, 4222–4223. (p) Cahiez, G.; Chaboche, C.; Jezequel, M. *Tetrahedron* **2000**, *56*, 2733–2737. (q) Giovanini, R.; Knochel, P. *J. Am. Chem. Soc.* **1998**, *120*, 11186–11187. (r) Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, 691–694.

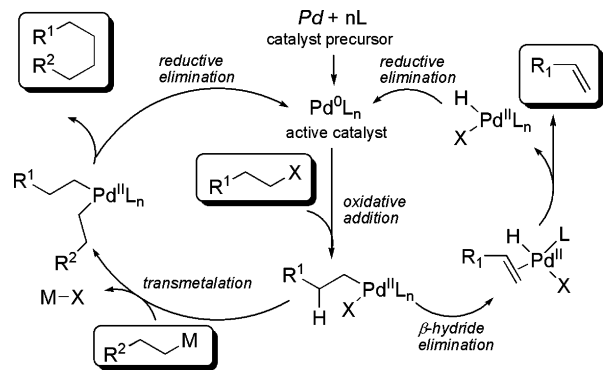
until the past few years that general, efficient protocols with broad functional group tolerance were developed.

Early investigations showed the possibility of cross-coupling reactions involving alkyl halides and alkyl Grignard reagents promoted by Fe,<sup>2c,6</sup> Cu,<sup>2c,7</sup> and Pd<sup>8</sup> catalysts. However, the range of substrates was limited as was functional group tolerance. Moreover, these reactions were often accompanied by significant byproduct formation. Later, improved alkyl/alkyl Kumada cross-coupling protocols based on Cu/Mn<sup>9</sup> or Cu<sup>3p</sup> catalysts were published. Very recently, an active catalyst for cross-couplings of alkyl halides (RCl, RBr) and tosylates with primary and secondary alkyl Grignard reagents employing Ni<sup>3k,o</sup> or Pd<sup>3j</sup> (1–3 mol %) and 1,3-butadiene (10–100 mol %) was disclosed by Kambe and co-workers. Also, the same group showed that a Cu/butadiene catalyst was suitable for coupling of alkyl bromides and fluorides, while alkyl chlorides, surprisingly, gave lower yields.<sup>3k</sup>

The first cross-coupling reaction of alkyl iodides possessing  $\beta$ -hydrogens with alkyl-9-BBN derivatives catalyzed by Pd(PPh<sub>3</sub>)<sub>4</sub> was reported in 1992.<sup>3r</sup> In a series of communications,<sup>3m,n,10</sup> Fu and co-workers reported the development of Pd-catalyzed protocols for a variety of primary alkyl chlorides, bromides, and tosylates with organoboron compounds. After extensive screening, Fu et al. discovered that PCy<sub>3</sub> (Cy = cyclohexyl) was the ligand of choice for alkyl halides (RBr, RCl),<sup>10b,c</sup> while alkyl tosylates required P(*t*-Bu)<sub>2</sub>Me.<sup>3m</sup> The latter phosphine ligand was shown to be effective with alkyl boronic acids instead of alkyl-9-BBN derivatives.<sup>3n</sup> A recent report revealed the first alkyl/alkyl Suzuki reaction with Pd/*N*-heterocyclic carbene (NHC) catalyst, although the yields were low to moderate.<sup>11</sup>

Knochel and co-workers pioneered the development of Ni-catalyzed alkyl/alkyl Negishi cross-coupling reactions. It was observed that primary alkyl iodides coupled with primary and secondary dialkylzinc derivatives in the presence of 10 mol % Ni(acac)<sub>2</sub>/3-trifluoromethylstyrene in THF/NMP.<sup>12</sup> Later, the method was extended to primary alkyl halides (RI, RBr) and primary and secondary alkylzinc iodides with a catalyst system composed of

### SCHEME 1. General Mechanism of Pd-Catalyzed Alkyl/Alkyl Cross-Coupling Reaction



Ni(acac)<sub>2</sub>/4-fluorostyrene/Bu<sub>4</sub>NI.<sup>13</sup> Similarly, Kambe observed that Ni/butadiene or Pd/butadiene catalyst was active in coupling a variety of primary alkyl bromides and tosylates with primary dialkylzinc reagents.<sup>14</sup> A Ni-catalyzed Negishi reaction with a Ni/terpyridine complex was published by Vicić et al.<sup>15</sup> Fu's group extended the Ni-catalyzed Negishi protocol to secondary halides (RI, RBr) using a Ni(cod)<sub>2</sub>/*s*-Bu-pybox catalyst.<sup>16</sup> This methodology was further developed into the first enantioselective alkyl/alkyl cross-coupling reaction of 2-bromopropionamides with organozinc halides.<sup>17</sup> Fu et al. also demonstrated that Pd(PCyp<sub>3</sub>)<sub>2</sub> (Cyp = cyclopentyl) is an effective catalyst for Negishi cross-couplings of primary alkyl halides (RCl, RBr, RI) and tosylates at 80 °C.<sup>3h</sup>

Compared to electrophiles possessing an unsaturated moiety at, or immediately adjacent to, the leaving group, alkyl halides are more reluctant to undergo oxidative addition.<sup>2e,18</sup> Recent mechanistic studies suggest that palladium insertion into an alkyl halide bond (oxidative addition) occurs via an S<sub>N</sub>2-type mechanism and is enhanced by an electron-rich palladium center.<sup>10a</sup> Hence, an active catalyst should readily insert into the carbon/halogen bond of the alkyl halide while suppressing  $\beta$ -hydride elimination from the oxidative addition intermediate which leads to unwanted alkene formation (Scheme 1). Following transmetalation, effective reductive elimination is dependent on the catalyst's steric environment.<sup>19</sup> The strong  $\sigma$ -donor properties of NHCs make this ligand class an attractive platform for development of catalysts for alkyl/alkyl cross-coupling reactions.<sup>20</sup> In addition, ease of synthesis and variable steric bulk allow easy tuning of the reactivity of the catalyst in the reductive elimination step (Figure 1). Previously, Pd/NHC catalysts were successfully employed in recent studies on Suzuki,<sup>11</sup> Kumada,<sup>3i</sup> and Sonogashira<sup>5b</sup> coupling reactions of bromoalkanes possessing  $\beta$ -hydrogens.

(4) (a) Wiskur, S. L.; Korte, A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 82–83. (b) Menzel, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 3718–3719.

(5) (a) Yang, L.-M.; Huang, L.-F.; Luh, T.-Y. *Org. Lett.* **2004**, *6*, 1461–1463. (b) Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642–13643.

(6) (a) Tamura, M.; Kochi, J. *J. Organomet. Chem.* **1971**, *31*, 289–309. (b) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303–305.

(7) (a) Nunamoto, S.; Kawakami, Y.; Yamashita, J. *J. Org. Chem.* **1983**, *48*, 1912–1914. (b) Tamura, M.; Kochi, J. K. *J. Organomet. Chem.* **1972**, *42*, 205–228. (c) Kochi, J. K.; Tamura, M. *J. Am. Chem. Soc.* **1971**, *93*, 1485–1487.

(8) (a) Castle, P. L.; Widdowson, D. A. *Tetrahedron Lett.* **1986**, *27*, 6013–6016. (b) Yuan, K.; Scott, W. J. *J. Org. Chem.* **1990**, *55*, 6188–6194. (c) Yuan, K.; Scott, W. J. *Tetrahedron Lett.* **1989**, *30*, 4779–4782.

(9) Donkervoort, J. G.; Vicario, J. L.; Jastrebski, J. T. B. H.; Gossage, R. A.; Cahiez, G.; van Koten, G. *J. Organomet. Chem.* **1998**, *558*, 61–69.

(10) (a) Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5749–5752. (b) Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945–1947. (c) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099–10100.

(11) Arentsen, K.; Caddick, S.; Cloke, F. G. N.; Herring, A. P.; Hitchcock, P. B. *Tetrahedron Lett.* **2004**, *45*, 3511–3515.

(12) (a) Giovannini, R.; Stüdermann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544–3553. (b) Giovannini, R.; Stüdermann, T.; Dussin, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2387–2390.

(13) Jensen, A. E.; Knochel, P. *J. Org. Chem.* **2002**, *67*, 79–85.

(14) (a) Terao, J.; Todo, H.; Watanabe, H.; Ikumi, A.; Kambe, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6180–6182. (b) Terao, J.; Nii, S.; Chowdhury, F. A.; Nakamura, A.; Kambe, N. *Adv. Synth. Catal.* **2004**, *346*, 905–908.

(15) Anderson, T. J.; Jones, G. D.; Vicić, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 8100–8101.

(16) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726–14727.

(17) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *126*, 4594–4595.

(18) Pearson, R. G.; Figdore, P. E. *J. Am. Chem. Soc.* **1980**, *102*, 1541–1547.

(19) Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 1991–1994.

(20) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290–1309.

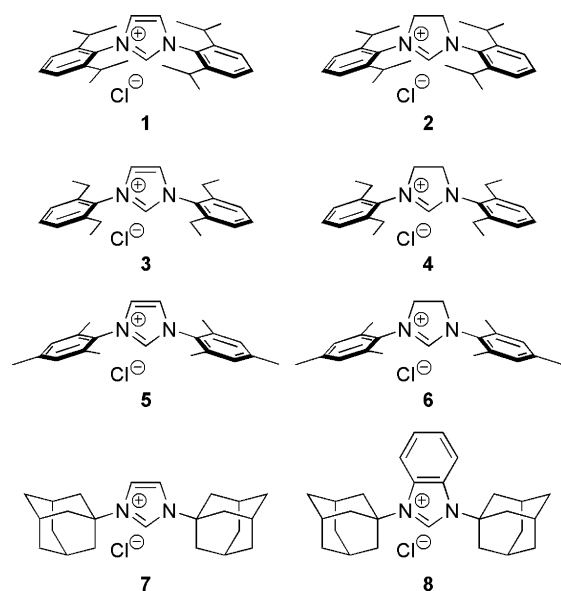


FIGURE 1. Symmetrical NHC ligand precursors.

Here we report the extension of the Pd/imidazolium salt protocol toward the cross-coupling reaction of unactivated alkyl bromides with alkylzinc halides at room temperature.<sup>21</sup>

## Results and Discussion

**Initial Optimization of the Catalytic Protocol.** We submitted the NHC precursor **1** into Negishi reaction conditions<sup>3h</sup> assuming that the alkylzinc reagent would facilitate the formation of active catalyst. We were delighted to find that cross-coupling occurred in high yield (Table 1, entry 1). Furthermore, the reaction proceeded with equal efficiency at room temperature (Table 1, entry 4).

Evaluation of the source of palladium demonstrated that Pd<sub>2</sub>(dba)<sub>3</sub> and Pd(OAc)<sub>2</sub> were equally effective at both 75 °C and room temperature (Table 1, entries 3 and 5). PdBr<sub>2</sub> was also successful, while other Pd precursors were less effective (Table 1, entries 7–10). Importantly, when couplings were performed outside of the protection of the glovebox using Pd(OAc)<sub>2</sub>, no erosion of yield was observed (Table 1, entry 6). Finally, a solvent study revealed a dependence on polar amide solvents (DMA, DMI, NMP, but not DMF) to achieve high yields (Table 1, entries 4 and 13–15), similar to earlier reports.<sup>3h,i,l,q,12,13,22</sup> However, ether solvents (THF, DME) proved ineffective (Table 1, entries 11 and 12).

**Investigation of the Effect of the NHC Ligand.** Following our initial success, we conducted a more detailed examination of the catalyst composition (Table 2). A few points are noteworthy. First, an investigation of the Pd/**1** ratio confirmed that a 1:2 ratio was optimal (Table 2, entries 1–5). Only slight variations in yield were observed when the Pd/**1** ratio was increased from 1:1 to 1:3. This suggests that only one catalytically active species was formed and the variation in yield was due to

TABLE 1. Effect of Reaction Conditions on the Yield of Alkyl/Alkyl Negishi Coupling

entry	change from standard conditions	yield (%) <sup>a</sup>
1	75 °C, 18 h	75
2	no ligand ( <b>1</b> ), 75 °C, 18 h	0.3
3	Pd(OAc) <sub>2</sub> , 75 °C, 18 h	75
4	<b>none</b>	<b>77</b>
5	Pd(OAc) <sub>2</sub>	75
6	Pd(OAc) <sub>2</sub> , no glovebox	73
7	PdBr <sub>2</sub>	74
8	Pd(OCOCF <sub>3</sub> ) <sub>2</sub>	40
9	PdCl <sub>2</sub>	19
10	[( $\pi$ -allyl)PdCl] <sub>2</sub>	6
11	substituted THF for NMP	0.4
12	substituted DME for NMP	0.4
13	substituted DMF for NMP	7
14	substituted DMI for NMP	71
15	substituted DMA for NMP	76

<sup>a</sup> GC yield against a calibrated internal standard (undecane); reactions were performed in duplicate, and the average yield was reported.

TABLE 2. Optimization of Catalyst Composition

entry	change from standard conditions <sup>a</sup>	yield (%) <sup>b</sup>
1	Pd/IPr ( <b>1</b> ), 1:1	53
2	Pd/IPr ( <b>1</b> ), 1:1.5	63
3	Pd/IPr ( <b>1</b> ), 1:2	76
4	Pd/IPr ( <b>1</b> ), 1:2.5	77
5	Pd/IPr ( <b>1</b> ), 1:3	74
6	SIPr ( <b>2</b> )	85 <sup>c</sup>
7	IEt ( <b>3</b> )	17
8	SIET ( <b>4</b> )	11
9	IMes ( <b>5</b> )	2.8
10	SIMes ( <b>6</b> )	1.2
11	IAd ( <b>7</b> )	0.6
12	BzIAd ( <b>8</b> )	0.3

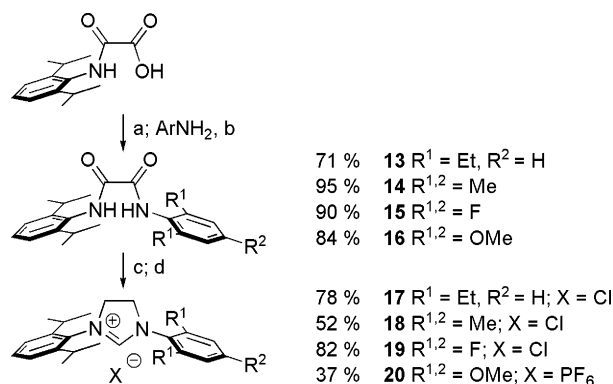
<sup>a</sup> The NHC precursors are shown in Figure 1. <sup>b</sup> GC yield against a calibrated internal standard (undecane); reactions were performed in duplicate, and the average yield was reported. <sup>c</sup> Even though SIPr showed higher yields in the model reaction, the cross-couplings of other substrates suffered from reduced reproducibility.

differing amounts of the active catalyst being produced in situ. We propose this to be a monoligated Pd/NHC species in accordance with recent studies.<sup>23</sup> Second, evaluation of different NHC ligand precursors showed a very strong dependence on the steric bulk of the N-substituents on the nitrogen atoms of the five-membered ring. We observed that the 2,6-diisopropylphenyl substituent was required for high coupling yields (Table 2,

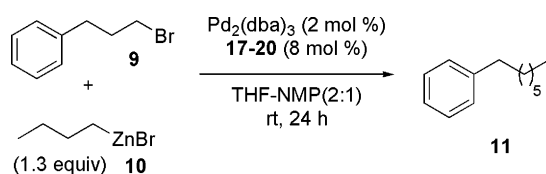
(21) Preliminary communication: Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3805–3808.

(22) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525–1532.

(23) (a) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366–374. (b) Campeau, L.-C.; Thansandote, P.; Fagnou, K. *Org. Lett.* **2005**, *7*, 1857–1860. The use of the known (IPr)<sub>2</sub>PdCl<sub>2</sub> complex (ref 23b) led to no cross-coupling product.

**SCHEME 2. Synthesis of Unsymmetrical NHC Precursors<sup>a</sup>**


<sup>a</sup> Reaction conditions: (a) (COCl)<sub>2</sub>, Cat. DMF, CH<sub>2</sub>Cl<sub>2</sub>, rt, 4 h. (b) Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to room temperature, 18 h. (c) BH<sub>3</sub>·THF, THF, reflux, 18 h. (d) **17–19**: HCl, HC(OEt)<sub>3</sub>, 120 °C, 2h; **20**: NH<sub>4</sub>PF<sub>6</sub>, HC(OEt)<sub>3</sub>, THF, 80 °C, 18 h.

**TABLE 3. Evaluation of Unsymmetrical Imidazolium Salts**


entry	ligand <sup>a</sup>	yield (%) <sup>b</sup>
1	SIPr ( <b>2</b> ) <sup>c</sup>	85
2	SIPr-Et ( <b>17</b> )	47
3	SIPr-Mes ( <b>18</b> )	23
4	SIPr-F <sub>3</sub> ( <b>19</b> )	1.6
5	SIPr-(MeO) <sub>3</sub> ( <b>20</b> )	3.4

<sup>a</sup> Scheme 2. <sup>b</sup> GC yield against a calibrated internal standard (undecane); reactions were performed in duplicate, and the average yield was reported. <sup>c</sup> SIPr result (Table 2, entry 6) included for comparison.

entries 1–6), irrespective of the nature of the carbene (imidazolium (**1**) versus 4,5-dihydroimidazolium (**2**)). The corresponding ethyl analogues **3**<sup>24</sup> and **4** were much less effective (Table 2, entries 7 and 8) and the mesityl carbenes derived from **5** and **6** were ineffective as previously observed<sup>3h,10b</sup> (Table 2, entries 9 and 10). The most sterically demanding adamantyl carbenes derived from **8** and **9**<sup>19</sup> did not yield any cross-coupling product (Table 2, entries 11 and 12). Whether this failure is due to the different topology imparted by adamantyl groups (compared to the 2,6-dialkylphenyl) or lack of Pd/NHC complex formation remains unclear at this point. Unfortunately, formation of Pd/NHC catalyst(s) of unknown amount(s) and composition when employing the Pd/imidazolium salt protocol seriously impedes further mechanistic studies.

**Preparation and Evaluation of Novel, Unsymmetrical NHC Ligands.** Intrigued by the effect of the bulky 2,6-diisopropylphenyl substituent, we decided to synthesize a range of unsymmetrical 4,5-dihydroimidazolium salts. One 2,6-diisopropylphenyl substituent was retained, and either a 2,6-disubstituted or 2,4,6-trisub-

**TABLE 4. Room Temperature Negishi Cross-Coupling Reactions of Unactivated Alkyl Bromides with Alkyl Zinc Reagents<sup>a</sup>**

entry	alkyl bromide	alkyl zinc reagent	yield (%) <sup>b</sup>
1			<b>21</b> 92
2			<b>22</b> 92
3			<b>23</b> 65
4			<b>21</b> 92
5			<b>24</b> 62
6			<b>25</b> 76
7			<b>26</b> 66
8			<b>27</b> 70
9			<b>28</b> 61
10			<b>29</b> 75
11			<b>30</b> 81
12			<b>31</b> 63
13			<b>31</b> 84

<sup>a</sup> Pd<sub>2</sub>(dba)<sub>3</sub> (2 mol %), IPr·HCl (8 mol %), *n*-butylzinc bromide (0.5 M in THF, 12 mol %) stirred for 1 h, alkyl bromide (0.5 mmol), alkylzinc reagent (0.5 M in THF, 0.65 mmol) in THF/NMP (2:1), rt, 24 h. <sup>b</sup> Isolated yield. Reactions were performed in duplicate, and the average yield was reported.

stituted aryl moiety bearing a range of alkyl groups, electron-donating (OMe), or electron-withdrawing substituents (F) was introduced on the other nitrogen (Scheme 2). Similar ligands have been prepared previously<sup>25</sup> and proved effective in Pd-catalyzed enolate arylation,<sup>25f</sup> Ru-catalyzed metathesis of alkenes,<sup>25b</sup> and asymmetric Cu-catalyzed allylic alkylation<sup>25b,c</sup> and 1,4-addition to conjugate enones.<sup>25a</sup> The corresponding imidazolium salts (**17–20**) were prepared (Scheme 2) in good yields and subjected to the reaction conditions outlined in Table 3. We observed that ligand precursor **17**, possessing the most sterically hindered arene substituents (2,6-diisopropylphenyl and 2,6-diethylphenyl), yielded 47% of product compared to 11% for the symmetrical diethyl analogue (Table 2, entry 8). Analogous yield increase (Table 3, entry 3, and Table 2, entry 10) was observed for the 2,6-diisopropylphenyl-mesityl de-

(24) Sprengers, J. W.; Wassenaar, J.; Clement, N. D.; Cavell, K. J.; Elsevier, C. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 2026–2029.

rivative (**18**) compared to the symmetrical mesityl NHC precursor (**5**). In contrast, even though the *o*-methoxy groups in **20** are similar in size to the ethyl groups in **17**, very little product was observed. Similarly, the 2,4,6-trifluoroanalogue **19** was ineffective.

**Preparative Scale Couplings of Alkyl Bromides with Organozinc Reagents.** Under optimized conditions, a variety of substrates were coupled in good to excellent yields at room temperature. The results (Table 4) indicate that a number of functional groups (esters, nitriles, amides, alkynes, and acetals) were tolerated. The addition of a small amount (12 mol %) of *n*-butylzinc bromide ensures reproducible catalyst formation.<sup>26</sup> However, we have one example that demonstrates that excellent yields may be obtained when *n*-butylzinc bromide activation was not employed.<sup>27</sup> Of particular interest is the coupling of  $\beta$ -substituted alkyl bromides and alkylzinc reagents (Table 4, entries 12 and 13).<sup>28</sup> Moreover, we observed that alkyl chlorides were unreactive under these conditions. Thus, we were able to selectively activate an alkyl bromide in the presence of an alkyl chloride (Table 4, entry 11).

## Conclusion

In conclusion, we have demonstrated the first high-yielding Negishi cross-coupling reaction utilizing NHC ligands. Additionally, this is also the first reported room-temperature palladium-catalyzed Negishi alkyl/alkyl coupling reaction. Since high-yielding coupling reactions can be routinely performed with general Schlenk technique, this further enhances the usefulness of this protocol. Interestingly, the topography created by the flanking *N*-substitutes was found to be of critical importance. The 2,6-diisopropylphenyl substituted NHC ligand was found to give the highest yields. Computational investigations are underway to ascertain the reason for this differing reactivity. We are currently expanding the scope of the Pd/NHC Negishi protocol to aryl and vinyl halides, pseudo-halides, and more elaborate zinc reagents. Selective activation of the halide or pseudo-halide would allow the sequential coupling of unsymmetrical electrophiles (e.g., Table 4, entry 11). Efforts aimed at convergent synthesis of complex molecules utilizing such a *linch pin*

approach to stitch together alkyl segments are currently in progress in our laboratory.

## Experimental Section

**General Procedure (Table 4).** A vial equipped with a stir bar was charged with Pd<sub>2</sub>(dba)<sub>3</sub> (9.2 mg, 0.010 mmol) and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr·HCl) (17 mg, 0.040 mmol) in a glovebox and capped with a septum. The vial was removed from the glovebox, and 0.3 mL of dry THF and 0.8 mL of dry NMP were added via syringe. After being stirred for 5–10 min at room temperature, *n*-butylzinc bromide (0.12 mL of a 0.5 M THF solution, 0.06 mmol) was added, and the reaction mixture was stirred for 1 h at room temperature, after which the alkylzinc reagent (1.3 mL of a 0.5 M THF solution, 0.65 mmol) and the alkyl bromide (0.50 mmol) were added. The septum was replaced with a Teflon-lined screw cap under an inert atmosphere, and the solution was stirred at room temperature for 24 h. The reaction mixture was then transferred to a separatory funnel with diethyl ether (10 mL), and the organic layer was successively washed with 1 M Na<sub>3</sub>EDTA solution (prepared from EDTA and 3 equiv of NaOH), water, and brine. After drying (anhydrous MgSO<sub>4</sub>), the solution was filtered and concentrated and the residue was purified by flash chromatography.

(Table 4, Entry 11). Following the general procedure, 5-cyano-5-methylhexylzinc bromide (1.3 mL of a 0.5 M THF solution; 0.65 mmol) and 1-bromo-6-chlorohexane (100 mg, 75  $\mu$ L, 0.5 mmol) provided 98.5 mg of **30**, 81% yield after column chromatography (3 vol % diethyl ether in pentane; *R*<sub>f</sub> 0.18). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  3.55 (t, *J* = 6.8 Hz, 2H), 1.77 (m, 2H), 1.55–1.39 (m, 4H), 1.35 (s, 6H), 1.34–1.27 (m, 12H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  125.3, 53.5, 45.2, 41.1, 32.6, 32.4, 29.6, 29.4, 28.8, 26.9, 26.7, 25.3. Anal. Calcd for C<sub>14</sub>H<sub>26</sub>ClN: C, 68.97; H, 10.75; N, 5.74. Found C, 69.34; H, 11.01; N, 5.40.

**General Coupling Procedure outside the Glovebox (Table 1, Entry 6).** A vial was charged with Pd(OAc)<sub>2</sub> (8.8 mg, 0.040 mmol), IPr·HCl (**1**) (34 mg, 0.080 mmol), and a stir bar in air. The vial was sealed with a septum and backfilled with Ar. Dry THF (0.60 mL) and dry NMP (1.60 mL) were added via syringe. After being stirred for 5–10 min at room temperature, *n*-butylzinc bromide (2.60 mL of a 0.5 M THF solution, 1.30 mmol) was added, and the reaction mixture was stirred at room temperature for an additional 1 h. 1-Bromo-3-phenylpropane (199 mg, 152  $\mu$ L, 1.00 mmol) and *n*-undecane (GC internal standard, 100  $\mu$ L) were added, the septum was replaced with a Teflon-lined screw cap under an inert atmosphere, and the reaction mixture was then stirred for 24 h at room temperature, diluted with hexane, and analyzed by GC/MS after passing through a short pad of silica gel. The yield was 73% of 1-heptylbenzene, with an average of two duplicate experiments. The <sup>1</sup>H NMR, GC retention time, and EI fragmentation pattern were identical to commercially available material.

**Acknowledgment.** We thank ORDCF and NSERC (Canada) for financial support, Dr. Howard N. Hunter for assistance with NMR, and Varian Canada for their collaborative in-kind donation (in part) of the GC/MS/MS 4000 to conduct the analyses in this report.

**Supporting Information Available:** Experimental procedures for preparation and characterization of compounds **4**, **13–20**, and **21–31** (Table 4) and representative procedures for Tables 1 and 2. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO051304C

(25) (a) Clavier, H.; Coutable, L.; Guillemin, J.-C.; Mauduit, M. *Tetrahedron: Asymmetry* **2005**, *16*, 921–924. (b) Van Veldhuizen, J. J.; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877–6882. (c) Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130–11131. (d) Waltman, A. W.; Grubbs, R. H. *Organometallics* **2004**, *23*, 3105–3107. (e) Dinger, M. B.; Nieczypor, P.; Mol, J. C. *Organometallics* **2003**, *22*, 5291–5296. (f) Glorius, F.; Altenhoff, G.; Goddard, R.; Lehmann, C. *Chem. Commun.* **2002**, 2704–2705.

(26) The steric nature of the organozinc reagent could affect the formation of the active catalyst. We observed significant variation in yield when the organozinc reagent participating in the cross-coupling reaction was used alone.

(27) The reaction depicted in Table 4, entry 4, yielded 87% of the cross-coupled product when *n*-butylzinc bromide catalyst activation was not employed.

(28) Secondary alkyl bromides and alkylzinc reagents are unreactive under these conditions.