Efficient Negishi Coupling Reactions of Aryl Chlorides Catalyzed by Binuclear and Mononuclear Nickel−N-Heterocyclic Carbene Complexes

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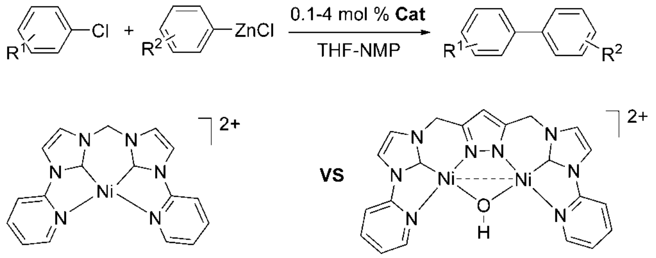

We describe the first nickel−N-heterocyclic carbene catalyzed Negishi cross-coupling reaction of a variety of unactivated aryl chlorides, heterocyclic chlorides, aryl dichlorides, and vinyl chloride. The mononuclear and binuclear nickel−NHC complexes supported by heteroarene-functionalized NHC ligands are found to be highly efficient for the coupling of unactivated aryl chlorides and organozinc reagents, leading to biaryls and terphenyls in good to excellent yields under mild conditions. For all aryl chlorides, the binuclear nickel catalysts show activities higher than those of mononuclear nickel complexes because of possible bimetallic cooperative effect.

Introduction

Transition-metal-catalyzed cross-coupling reactions between C_{sp2} centers have been extensively used for preparing pharmaceuticals and agrochemical intermediates.[1] In this context, there has been great development in palladium-catalyzed coupling reactions of a series of organometallic reagents (M = B, Sn, Si, Mg) for the construction of carbon−carbon bonds.[2] Metal-catalyzed cross-coupling of organozinc compounds with organic electrophiles, known as the Negishi reaction, has become one of the extremely powerful tools for C−C bond formation due to mild reaction conditions and good functional group tolerance.[3] Compared with the partners, organotin, organomagnesium, and organoboron reagents, which are investigated widely, organozinc reagents have been studied to a lesser extent. Though a few successful examples of Negishi coupling reactions of aryl bromides and iodides have been reported in the recent decade,[4] aryl chlorides are more attractive because they are more economic and easily accessible organic electrophiles. However, only a few catalytic systems show good activities for unactivated

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(1) (a) Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, 2004. (b) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (d) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (e) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

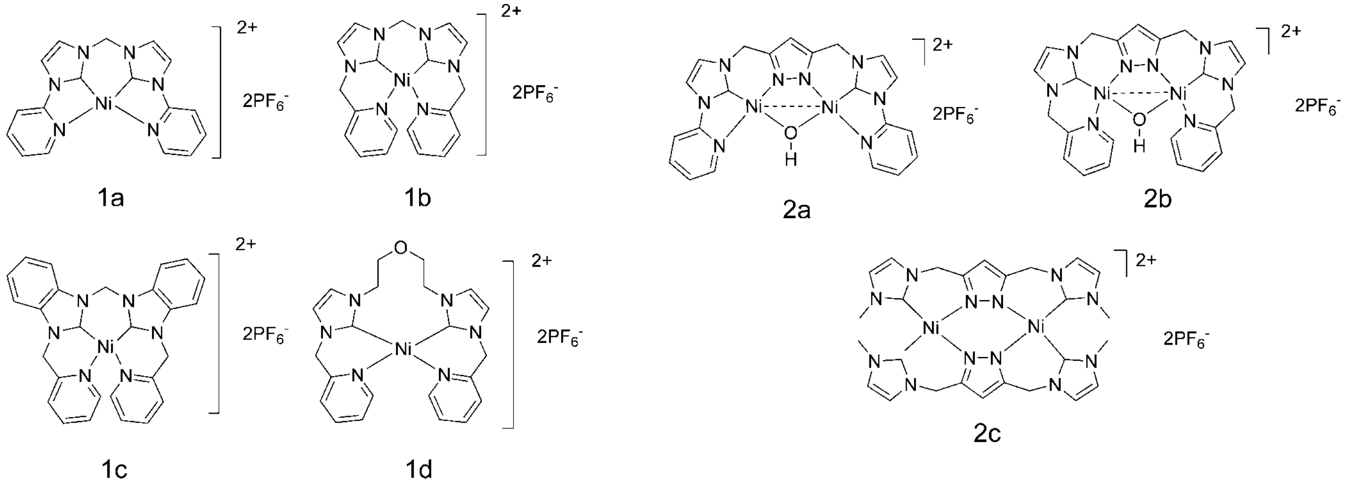
(2) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992. (c) Stille, J. K. *Angew. Chem., Int. Ed.* **1986**, *25*, 508. (d) Handy, S. T.; Zhang, X. *Org. Lett.* **2001**, *3*, 233. (e) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704. (f) Hiyama, T. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 10. (g) Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58.

(3) (a) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (b) Kobayashi, M.; Negishi, E. *J. Org. Chem.* **1980**, *45*, 5223. (c) Zeng, X.; Qian, M.; Hu, Q.; Negishi, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 2259. (d) Qian, M.; Huang, Z.; Negishi, E. *Org. Lett.* **2004**, *6*, 1531.

(4) (a) Sapountzis, I.; Dube, H.; Knochel, P. *Adv. Synth. Catal.* **2004**, *346*, 709. (b) Alimardanov, A.; Schmieder-van de Vondervoort, L.; de Vries, A. H. M.; de Vries, J. G. *Adv. Synth. Catal.* **2004**, *346*, 1812. (c) Herbert, J. M. *Tetrahedron Lett.* **2004**, *45*, 817. (d) Kondolff, I.; Doucet, H.; Santelli, M. *Organometallics* **2006**, *25*, 5219. (e) Huang, Z.; Qian, M.; Babinski, D. J.; Negishi, E.-I. *Organometallics* **2005**, *24*, 475. (f) Krascsenicsova, K.; Walla, P.; Kasak, P.; Uray, G.; Kappe, C. O.; Putala, M. *Chem. Commun.* **2004**, 2606. (g) Corley, E. G.; Conrad, K.; Murry, J. A.; Savarin, C.; Holko, J.; Boice, G. *J. Org. Chem.* **2004**, *69*, 5120. (h) Marquais, S.; Arlt, M. *Tetrahedron Lett.* **1996**, *37*, 5491. (i) Okano, M.; Amano, M.; Takagi, K. *Tetrahedron Lett.* **1998**, *39*, 3001. (j) Hoye, T. R.; Chen, M. *J. Org. Chem.* **1996**, *61*, 7940. (k) Liu, J.; Deng, Y.; Wang, H.; Zhang, H.; Yu, G.; Wu, B.; Zhang, H.; Li, Q.; Marder, T. B.; Yang, Z.; Lei, A. *Org. Lett.* **2008**, *10*, 2661. (l) Manolikakes, G.; Schade, M. A.; Hernandez, C. M.; Mayr, H.; Knochel, P. *Org. Lett.* **2008**, *10*, 2765.

10.1021/jo8018686 CCC: $40.75

CHART 1. Schematic Illustration of Nickel Catalysts 1a−d and 2a−c



aryl chlorides due to low reactivity of the C−Cl bond.[5] In this line, palladium-catalyzed Negishi coupling of unactivated aryl chlorides has recently been found to be successful under mild conditions.[6] A few nickel complexes also show good activities for unactivated aryl chlorides.[7] However, most of these nickel and palladium catalysts require environmentally unfriendly phosphine or phosphite ligands.[6,7]

Although N-heterocyclic carbenes (NHCs) have found wide applications in a number of organic transformations as an alternative to phosphines because of their excellent σ-donor properties, ease of synthesis, and variable steric bulk,[8,9] metal−NHC complex catalyzed Negishi cross-coupling reaction has not been well studied. Organ et al. reported the first $Pd_2(dba)_3$/1,3-di(diisopropylphenyl)imidazolium catalyzed Negishi cross-coupling reaction utilizing NHC ligands.[10] Nickel catalysts based on NHC ligands for Negishi cross-coupling reaction have not been known so far. Nickel is generally believed to be less efficient for coupling reactions than the corresponding palladium catalyst. The employment of hemilable heteroarene-functionalized NHC ligands would be a possible way to enhance the catalytic activities of nickel complexes since the dissociation of heteroarene allows the creation of unsaturated coordination site and the coordination of NHCs promotes the oxidative addition of substrates in the catalytic cycle.[8c,e] We have recently reported the synthesis and structural characterization of a few nickel complexes supported by multidentate NHC ligands, and their catalytic activities for Suzuki−Miyaura and Kumada−Corriu couplings have been briefly studied.[11] As a continuation, herein we describe the first Negishi cross-coupling reaction of unactivated aryl chlorides based on mononuclear and binuclear nickel−NHC complexes under mild conditions. The bimetallic catalysts exhibit strong cooperative catalytic activities for the coupling reaction.

Results and Discussion

To examine the catalytic efficiencies of the mononuclear nickel−NHC complexes **1a−d** and three binuclear nickel−NHC complexes, **2a−c**, we chose the coupling reaction of chlorobenzene and *p*-tolylzinc chloride as model reaction to optimize the reaction conditions and evaluate the catalytic activities of these nickel complexes. The structures of the seven nickel complexes are shown in Chart 1. The results are listed in Table 1 and illustrate the impact of a variety of reaction parameters on the Negishi coupling process. The results show that the desired biaryl was obtained in a yield of 80% when 3 mol % of mononuclear nickel complex **1a** was used at 80 °C in mixed THF/NMP within 5 h (Table 1, entry 1). When the catalyst loading was reduced to 2 mol %, the yield was not significantly changed (entry 2). However, further decrease of the catalyst loading to 1 or 0.5 mol % lowered the yields of the coupling product to 65% and 34%, respectively (entries 3 and 4). These data illustrate that the employment of 2 mol % of nickel catalyst is sufficient for the coupling of chlorobenzene and *p*-tolylzinc chloride. We have tried to prolong the reaction time, but the yield was not improved (entry 5). The effect of temperature

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(5) (a) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047. (b) Littke, A.; Fu, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (c) Cornils, B., Herrmann, W. A., Eds.; *Applied Homogeneous Catalysis with Organometallic Compounds*; VCH: Weinheim, 1996.

(6) (a) Herrmann, W. A.; Bohm, V. P. W.; Reisinger, C. P. *J. Organomet. Chem.* **1999**, *576*, 23. (b) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719. (c) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028. (d) Sirieix, J.; Ossberger, M.; Betzemeier, B.; Knochel, P. *Synlett* **2000**, 1613.

(7) (a) Lipshutz, B. H.; Blomgren, P. A. *J. Am. Chem. Soc.* **1999**, *121*, 5819. (b) Miller, J. A.; Farrel, R. P. *Tetrahedron Lett.* **1998**, *39*, 6441. (c) Walla, P.; Kappe, C. O. *Chem. Commun.* **2004**, 564. (d) Gavryushin, A.; Kofink, C.; Manolikakes, G.; Knochel, P. *Org. Lett.* **2005**, *7*, 4871. (e) Gavryushin, A.; Kofink, C.; Manolikakes, G.; Knochel, P. *Tetrahedron* **2006**, *62*, 7521. (f) Lipshutz, B. H.; Frieman, B. A.; Lee, C. T.; Lower, A.; Nihan, D. M.; Taft, B. R. *Chem. Asian J.* **2006**, *1*, 417. (g) Wang, L.; Wang, Z. X. *Org. Lett.* **2007**, *9*, 4335. (h) Schade, M. A.; Metzger, A.; Hug, S.; Knochel, P. *Chem. Commun.* **2008**, *26*, 3046.

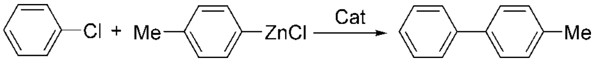
(8) (a) Bourisou, D.; Guerret, O. P.; Gabbaï, F.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39. (b) Jafarpour, L.; Nolan, S. P. *J. Organomet. Chem.* **2001**, *617−618*, 17. (c) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (d) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69. (e) Glorius, F., Ed.; *N*-Heterocyclic Carbenes in Transition Metal Catalysis. In *Topics in Organometallic Chemistry*; Springer: Berlin, 2007; Vol. 21, pp 1−218. (f) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2768.

(9) (a) Lee, D.-H.; Kim, J.-H.; Jun, B.-H.; Kang, H.; Park, J.; Lee, Y.-S. *Org. Lett.* **2008**, *10*, 1609. (b) Weck, M.; Jones, C. W. *Inorg. Chem.* **2007**, *46*, 1865. (c) Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 1991. (d) Lee, M.-T.; Lee, H. M.; Hu, C.-H. *Organometallics* **2007**, *26*, 1317. (e) Yang, C.; Nolan, S. P. *J. Org. Chem.* **2002**, *67*, 591. (f) Navarro, O.; Kelly, R. A., III; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194. (g) Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470. (h) Ray, L.; Shaikh, M. M.; Ghosh, P. *Organometallics* **2007**, *26*, 958. (i) Desmarets, C.; Schneider, R.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 3029.

(10) (a) Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3805. (b) Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *J. Org. Chem.* **2005**, *70*, 8503.

(11) (a) Xi, Z.; Zhang, X.; Chen, W.; Fu, S.; Wang, D. *Organometallics* **2007**, *26*, 6636. (b) Xi, Z.; Liu, B.; Chen, W. *J. Org. Chem.* **2008**, *73*, 3954. (c) Zhou, Y.; Xi, Z.; Chen, W.; Wang, D. *Organometallics*, submitted for publication.

TABLE 1. Reactions of PhCl with *p*-TolylZnCl Catalyzed by 1a−d, 2a−c[a]



entry	catalyst	catalyst amount (mol %)	*T* (°C)	time (h)	yield (%)
1	**1a**	3	80	5	80
2	**1a**	2	80	5	79
3	**1a**	1	80	5	65
4	**1a**	0.5	80	5	34
5	**1a**	2	80	10	79
6	**1a**	2	90	5	80
7	**1a**	2	100	5	81
8	**1a**	2	70	5	52
9	**1a**	2	80	5	38[b]
10	**1b**	2	80	5	71
11	**1c**	2	80	5	65
12	**1d**	2	80	5	72
13	**2a**	1	80	2	97
14	**2a**	0.5	80	2	94
15	**2a**	0.2	80	2	69
16	**2a**	0.1	80	2	34
17	**2a**	0.5	80	1	79
18	**2a**	0.5	80	2	40[b]
19	**2a**	0.5	100	2	95
20	**2b**	0.5	80	2	92
21	**2c**	0.5	80	2	75

[a] Reaction conditons: PhCl 1.0 mmol, *p*-tolylZnCl 1.2 mmol, THF/NMP (1:1) 3 mL. [b] In THF.

has also been investigated. The reaction at 80 °C proceeded smoothly and elevation of temperature to 100 °C showed no obvious improvement of the yields (entries 6−8). Similar to other known Negishi reactions,[6b,7d,e,g] the mixed THF/NMP solvent is more suitable than pure THF due to low solubility of organozinc reagent in THF (entry 9). Under the optimized conditions stated above, the catalytic activities of **1b−d** for the coupling of chlorobenzene and *p*-tolylzinc chloride were tested. We found that **1a** is more efficient than **1b−d** (entries 10−12). In these reactions, no side products such as homocoupling products were observed and the starting aryl chlorides were not consumed completely. The higher catalytic activity of **1a** is probably ascribed to the ease of dissociation of the coordinated pyridine groups of **1a** because of the internal strain due to the coplanarity of the four rings of bis(pyridylimidazolylidenyl)methane and the central nickel ion. For the other three nickel complexes the four pyridine and imidazolylidene rings are not coplanar due to flexibility of the ligands.

Further studies of the coupling reaction using binuclear nickel catalyst system were carried out under the optimized conditions. The results listed in Table 1 show that the coupling of chlorobenzene gave the coupling product in much higher yields by using only 0.5 mol % of the binuclear nickel complexes **2a,b** than 2 mol % of **1a−d**. The catalytic activity of **2c** is relatively poorer than that of **2a** and **2b**. This is probably because the two nickel ions of **2c** are tightly bonded by two 3,5-bis(*N*-methylimidazolylidenylmethyl)pyrazolate, which are dissociated with difficulty to generate coordinatively unsaturated active species. In contrast, nickel complexes **2a** and **2b** can easily dissociate pyridine groups and lose or break down the hydroxide bridge. The high efficiency of **2a** is illustrated by the moderate yield (69%) for unactivated chlorobenzene at a catalyst loading of 0.2 mol % (entry 15). Increasing the catalyst loading to 0.5 mol %, the coupling product can be obtained in nearly quantitative yield (entry 14). Further increase of the reaction temperature and the catalyst loading has little influence on the reaction rate and efficiency (entries 13 and 19). The coupling reactions in air using either **1a** or **2a** did not afford the desired products but homocoupling products of arylzinc reagents, and aryl chlorides were not consumed. Obviously, in the Negishi coupling the binuclear nickel complexes show activities higher than those of the mononuclear complexes since the former require lower catalyst loadings and shorter reaction times.

To examine the difference between the mononuclear and binuclear nickel complexes in the Negishi coupling reactions, we utilized **1a** and **2a** as catalysts for the study of the reactions between a variety of aryl chlorides and organozinc reagents under the optimized condition. The results are summarized in Table 2. As can be seen, both **1a** and **2a** were efficient for two heteroaryl chlorides. For example, 2-chloropyridine and 2-chloropyrimidine were easily coupled with *p*-tolylzinc chloride, and the products were produced in excellent yields when 1 mol % of **1a** was used (Table 2, entries 1 and 3). For the same heteroaryl chlorides, the corresponding products were afforded in nearly quantitative yields at 0.1 mol % loading of **2a** (entries 2 and 4). Both **1a** and **2a** showed good tolerance toward a few functional groups such as ketone, ester, and nitrile. Aryl chlorides bearing a cyanide function such as 4-chlorobenzonitrile and 3-chlorobenzonitrile reacted smoothly with *p*-tolylzinc chloride affording the desired products in more than 80% yields, whereas 2-chlorobenzonitrile gave 2-tolylbenzonitrile in lower yield because of steric hindrance when 2 mol % of **1a** was employed (entries 5, 7, and 9). The same reactions catalyzed by 0.5 mol % of **2a** under the same temperature led to the corresponding products in much higher yields even within shorter reaction time (entries 6, 8, and 10). It is worth noting that 2-tolylbenzonitrile derived from the coupling between 2-chlorobenzonitrile and *p*-tolylzinc chloride is a key intermediate for a few antihypertensive drugs.[12] Previous reports indicated that aryl chlorides containing a nitrile group are usually less active in nickel-catalyzed Negishi couplings due to the coordination of the nitrile group with the catalytically active metal center.[7e,g] 2-Tolylbenzonitrile can be obtained in nearly 90% yield even in the presence of 0.5 mol % loading of **2a**, providing a new protocol for the preparation of the important intermediate. The couplings of *p*-PhC(O)C$_6$H$_4$Cl and *p*-EtO$_2$CC$_6$H$_4$Cl were also successful to give the products in 95% and 93% yields, respectively (entries 18 and 20). Unfortunately, both **1a** and **2a** catalyzed Negishi reactions were found incompatible with NO$_2$ and CHO groups; in such cases only trace amount of the desired products could be detected by GC chromatography. The nickel catalysts are also applied to the coupling reactions of aryl chlorides bearing electron-donating groups. The coupling reactions of 4-chloroanisole and 2-chlorotoluene with *p*-tolylzinc chloride catalyzed by 2 mol % of **1a** afforded the corresponding products in 63% and 61% yields, respectively (entries 11 and 13). By replacing **1a** with **2a**, much higher yields of 2,4′-dimethylbiphenyl and 4-tolylanisole were obtained (entries 12 and 14). Experimental results show that we can apply the same protocol to the Negishi reaction of vinyl chlorides. The styrene derivative was produced in 85% and 96% yields when 1 mol % of **1a** and 0.1 mol % of **2a** were employed (entries 15 and 16).

As part of our study, the coupling reactions of steric hindered arylzinc reagent were also investigated. Reactions between

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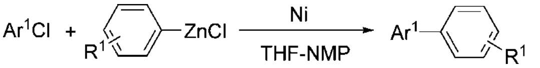
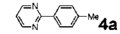
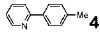
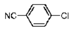
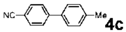
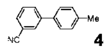
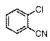
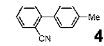
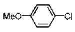
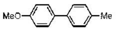
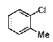
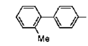
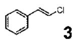
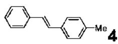
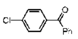
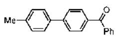
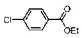
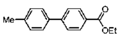
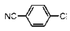
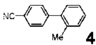
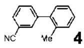
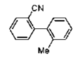
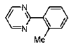
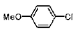
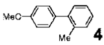
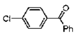
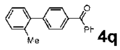
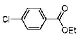
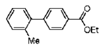
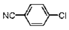
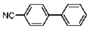
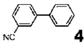
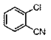
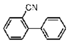
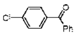
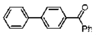
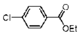
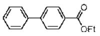
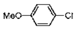
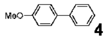
[12] (a) Goubet, D.; Meric, P.; Dormoy, J. R.; Moreau, P. *J. Org. Chem.* **1999**, *64*, 4516. (b) Kageyama, H.; Miyazaki, T.; Kimura, Y. *Synlett.* **1994**, 371. (c) Miller, J. A.; Farrell, R. P. *Tetrahedron Lett.* **1998**, *39*, 6441. (d) Walla, P.; Kappe, C. O. *Chem. Commun.* **2004**, 564.

TABLE 2. Cross-Coupling of Aryl Chlorides with Arylzinc Chlorides Catalyzed by 1a and 2a[a]



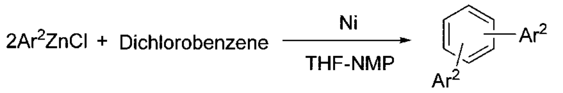
entry	Ar^1	R^1	product	cat (mol %)	time (h)	yield (%)
1	 **3a**	p-Me	 **4a**	**1a** (1)	5	91
2	**3a**	p-Me	**4a**	**2a** (0.1)	2	99
3	 **3b**	p-Me	 **4b**	**1a** (1)	5	90
4	**3b**	p-Me	**4b**	**2a** (0.1)	3	98
5	 **3c**	p-Me	 **4c**	**1a** (2)	5	84
6	**3c**	p-Me	**4c**	**2a** (0.5)	3	95
7	 **3d**	p-Me	 **4d**	**1a** (2)	5	83
8	**3d**	p-Me	**4d**	**2a** (0.5)	3	95
9	 **3e**	p-Me	 **4e**	**1a** (2)	12	69
10	**3e**	p-Me	**4e**	**2a** (0.5)	5	88
11	 **3f**	p-Me	 **4f**	**1a** (2)	5	63
12	**3f**	p-Me	**4f**	**2a** (0.5)	3	78
13	 **3g**	p-Me	 **4g**	**1a** (2)	12	61
14	**3g**	p-Me	**4g**	**2a** (0.5)	5	76
15	 **3h**	p-Me	 **4h**	**1a** (1)	5	85
16	**3h**	p-Me	**4h**	**2a** (0.1)	2	96
17	 **3i**	p-Me	 **4i**	**1a** (2)	5	83
18	**3i**	p-Me	**4i**	**2a** (0.5)	2	95
19	 **3j**	p-Me	 **4j**	**1a** (2)	5	71
20	**3j**	p-Me	**4j**	**2a** (0.5)	2	93
21	 **3l**	o-Me	 **4l**	**1a** (2)	5	69
22	**3l**	o-Me	**4l**	**2a** (0.5)	2	85
23	 **3m**	o-Me	 **4m**	**1a** (2)	5	68
24	**3m**	o-Me	**4m**	**2a** (0.5)	2	87
25	 **3n**	o-Me	 **4n**	**1a** (2)	24	31[b]
26	**3n**	o-Me	**4n**	**2a** (0.5)	24	79
27	 **3o**	o-Me	 **4o**	**1a** (1)	5	82
28	**3o**	o-Me	**4o**	**2a** (0.1)	3	97
29	 **3p**	o-Me	 **4p**	**1a** (2)	5	51
30	**3p**	o-Me	**4p**	**2a** (0.5)	3	71
31	 **3q**	o-Me	 **4q**	**1a** (2)	12	72
32	**3q**	o-Me	**4q**	**2a** (0.5)	3	86
33	 **3r**	o-Me	 **4r**	**1a** (2)	12	62
34	**3r**	o-Me	**4r**	**2a** (0.5)	3	81
35	 **3s**	H	 **4s**	**1a** (2)	5	80
36	**3s**	H	**4s**	**2a** (0.5)	2	92
37	 **3t**	H	 **4t**	**1a** (2)	5	81
38	**3t**	H	**4t**	**2a** (0.5)	2	93
39	 **3u**	H	 **4u**	**1a** (2)	12	66
40	**3u**	H	**4u**	**2a** (0.5)	10	78
41	 **3v**	H	 **4v**	**1a** (2)	5	80
42	**3v**	H	**4v**	**2a** (0.5)	2	92
43	 **3w**	H	 **4w**	**1a** (2)	5	71
44	**3w**	H	**4w**	**2a** (0.5)	2	90
45	 **3x**	H	 **4x**	**1a** (2)	5	61
46	**3x**	H	**4x**	**2a** (0.5)	2	77

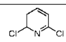
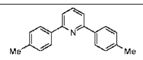
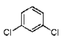
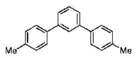
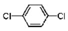
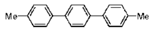
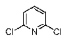
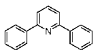
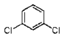
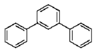
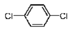
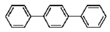
[a] Reaction conditions: aryl chloride 1.0 mmol, arylzinc reagent 1.5 mmol, THF/NMP (1:1) 3 mL, 80 °C. [b] 56% 2-chlorobenzonitrile was recovered.

o-tolylzinc chloride and aryl chloride containing functional groups such as CN, PhC(O), EtO$_2$C, OMe, and heterocyclic chloride were examined comparatively by using **1a** and **2a** (entries 21−34). The difference between **1a** and **2a** is that the influence of the steric hindrance of organozinc reagent for catalyst **1a** is more prominent than for **2a**. For example, in the case of **2a** o-tolylzinc chloride reacted with 4-chlorobenzonitrile, 3-chlorobenzonitrile, and 4-chloroanisole leading to the corresponding products **4e** (85%), **4m** (87%), and **4p** (71%) (entries 22, 24, and 30). In contrast, the yields of the coupling products lowered to ca. 60% when 2 mol % of **1a** was employed (entries 21, 23, and 29). Similarly, electron-poor aryl chlorides such as p-PhC(O)C$_6$H$_4$Cl, p-EtO$_2$CC$_6$H$_4$Cl, and 2-chloropyrimidine coupled with o-tolylzinc chloride catalyzed by **2a** affording the products in good to excellent yields (81−97%) (entries 28, 32, and 34), whereas the same products were obtained in moderate yields with **1a** (entries 27, 31, and 33). Especially, the difference between **1a** and **2a** is more apparent in the reaction of 2-chlorobenzonitrile and o-tolylzinc chloride. Complex **1a** is nearly ineffective (entry 25), whereas complex **2a** could give the product in a yield of 79% (entry 26). Finally, we have also studied the couplings between phenylzinc chloride with a few aryl chlorides. The data revealed that the reactivity of phenylzinc chloride was similar to that of p-tolylzinc chloride for both **1a** and **2a** (entries 35−46).

With our optimized reaction conditions, we can also synthesize terphenyl derivatives via one-pot double coupling of aryl dihalides (Table 3). For example, we can generate

TABLE 3. Cross-Coupling of Dichlorobenzene with Arylzinc Chlorides Catalyzed by 1a and 2a[a]



entry	dichlorobenzene	Ar^2	product	cat (mol %)	yield (%)
1	 **5a**	*p*-tolyl	 **6a**	**1a** (4)	88
2	**5a**	*p*-tolyl	**6a**	**2a** (0.5)	97
3	 **5b**	*p*-tolyl	 **6b**	**1a** (4)	78
4	**5b**	*p*-tolyl	**6b**	**2a** (1)	84
5	 **5c**	*p*-tolyl	 **6c**	**1a** (4)	76
6	**5c**	*p*-tolyl	**6c**	**2a** (1)	86
7	 **5d**	phenyl	 **6d**	**1a** (4)	82
8	**5d**	phenyl	**6d**	**2a** (0.5)	95
9	 **5e**	phenyl	 **6e**	**1a** (4)	76
10	**5e**	phenyl	**6e**	**2a** (1)	82
11	 **5f**	phenyl	 **6f**	**1a** (4)	75
12	**5f**	phenyl	**6f**	**2a** (1)	82

[a] Reaction conditions: dichlorobenzene 1.0 mmol, arylzinc reagent 3.0 mmol, THF/NMP (1:1) 3 mL, 80 °C.

1,3- and 1,4-ditolylbenzene in 76−86% yields from 1,3-dichlorobenzene and 1,4-dichlorobenzene with *p*-tolylzinc chloride (entries 3−6) using either **1a** or **2a**. Similarly, we can also obtain 1,3-terphenyl and 1,4-terphenyl in 75−82% yields (entries 9−12). Furthermore, we can produce 2,6-diaryl pyridine in excellent yield from 2,6-dichloropyridine and C_6H_5ZnCl or *p*-MeC_6H_4ZnCl (entries 2 and 8). Especially, 2,6-ditolylpyridine could be achieved in nearly quantitative yield by using 0.5 mol % of **2a** (entry 2). Obviously, the coupling of 1,3-dichlorobenzene and 1,4-dichlorobenzene is more difficult than that of heterocyclic dichlorides because of the electronic deficient nature of 2,6-dichloropyridine. Again, we found that complex **2a** also showed much better activities for the double couplings than **1a** under the same conditions.

Many efforts have been made in the design of cooperative metal catalysts because such catalysts are believed to exhibit an enhancement of catalytic activity in organic transformation and may serve as functional models for natural metalloenzymes.[13] The bimetallic nickel complex **2a** shows higher activity than **1a** with respect to their catalytic efficiency taking account of the much lower loading of **2a** and shorter reaction time. Such advantage is tentatively ascribed to the bimetallic cooperative effect. The two nickel centers are held together by a 3,5-bis(pyridylimidazolylidenylmethyl)pyrazolate ion and display a short distance (around 3.2 Å),[11c] which may allow the two nickel ions to get access to aryl chloride simultaneously, and thereafter bimetallic activation of inert C−Cl bond could be achieved.

In conclusion, we have described the first successful Negishi cross-coupling catalyzed by mononuclear and binuclear nickel complexes supported by N-heterocyclic carbenes under mild conditions. Both mononuclear and binuclear nickel−NHC complexes are effective for the coupling reactions of unactivated aryl chlorides, heterocyclic chlorides, and vinyl chloride with organozinc reagents leading to a wide range of biphenyls and terphenyls. The catalytic data show that binuclear nickel−NHC complexes are more active than mononuclear nickel−NHC complexes probably due to possible bimetallic cooperativity. All the Ni(II) complexes are air stable and can be easily prepared. We believe that these binuclear nickel−NHC catalytic systems could provide a complement to the protocols using expensive palladium and environmentally unfriendly phosphine or phosphite ligands in a number of organic transformations. Efforts are currently underway to clarify the origin of cooperative activity as well as the nature of active species for the catalytic coupling reaction.

Experimental Section

General Procedure for Negishi Reactions. A Schlenk tube was charged with nickel complexes **1a** or **2a** (0.01−2% mmol), anhydrous THF (1.5 mL), NMP (1.5 mL), and aryl chloride (1.0 mmol). To the solution was added a solution of arylzinc reagent (1.5 mL, 1.0 M in THF) at room temperature with stirring. After it was stirred at 80 °C for 2−12 h, the reaction was ceased by addition of water and several drops of HCl. Then the mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried by $MgSO_4$. The filtrate was concentrated by rotary evaporation, and the crude product was purified by column chromatography on sillca gel to afford the desired product.

2-*p*-Tolylpyrimidine (4a). ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.78 (d, $J = 4.8$ Hz, 2H), 8.34 (d, $J = 8.0$ Hz, 2H), 7.31 (d, $J = 8.0$ Hz, 2H), 7.15(d, $J = 4.8$ Hz, 1H), 2.42 (s, 3H) ppm. MS (EI, *m/z*): 170 [M^+].

Acknowledgment. We gratefully acknowledge the financial support of the NSF of China (Grant 20572096), Zhejiang Provincial Natural Science Foundation (R405066), and Qianjiang Project (2007R10006).

Supporting Information Available: Experimental details and spectroscopic data of compounds **4a**−**x**, **6a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) (a) Nielsen, L. P. C.; Stevenson, C. P.; Blackmond, D. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 1360. (b) Sammis, G. M.; Danjo, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 9928. (c) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 13632. (d) Gianneschi, N. C.; Cho, S.-H.; Nguyen, S. T.; Mirkin, C. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5503. (e) Dube, C. E.; Wright, D. W.; Armstrong, W. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2169. (f) Iranzo, O.; Kovalevsky, A. Y.; Morrow, J. R.; Richard, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 1988.

(14) Raminelli, C.; Gargalaka, J.; Silveira, C.; Camasseto, J. *Tetrahedron* **2007**, *63*, 8801.

(15) Chiu, P. L.; Lai, C.-L.; Chang, C.-F.; Hu, C.-H.; Lee, H. M. *Organometallics* **2005**, *24*, 6169.