ORGANIC
LETTERS

2012
Vol. 14, No. 13
3352–3355

Nickel-Catalyzed Reductive Coupling of Aryl Halides with Secondary Alkyl Bromides and Allylic Acetate

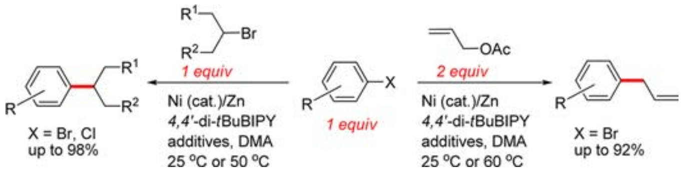
Shulin Wang, Qun Qian, and Hegui Gong*

Department of Chemistry, Shanghai University, 99 Shang-Da Road,
Shanghai 200444, China

hegui_gong@shu.edu.cn

Received May 14, 2012

ABSTRACT



A room-temperature Ni-catalyzed reductive method for the coupling of aryl bromides with secondary alkyl bromides has been developed, providing C(sp^2)−C(sp^3) products in good to excellent yields. Slight modification of this protocol allows efficient coupling of activated aryl chlorides with cyclohexyl bromide and aryl bromides with allylic acetate.

The construction of secondary alkyl−aryl C−C bonds has achieved significant success using Ni-catalyzed cross-coupling of secondary alkyl halides with aryl metallic reagents.[1,2] Recently, transition-metal-catalyzed coupling of secondary alkyl-metallics with aryl halides has also attracted considerable attention.[3] Both strategies require the catalytic system to prevail over the challenges residing in alkyl coupling partners, e.g., β-elimination and slow reductive elimination.[3e,4]

Direct coupling of aryl and alkyl halides that does not need preprepared organometallic reagents has also led to efficient production of aryl and alkyl C−C bonds. These include Co-, Fe-, and Pd-catalyzed in situ Kumada and Negishi processes[5] and Co- and Ni-catalyzed reductive coupling protocols.[6,7] The nickel methods are pioneered by Durandetti's electrochemical and Weix's elegant chemical reductive conditions for activated and unactivated halides, respectively.[7] However, secondary alkyl halides generally delivered the products in less than 70% yields.[8] Although Weix's Ni-catalyzed reductive method discloses that the coupling of iodobenzene with 2-bromoheptane is high yielding, an expensive phosphine ligand is inevitable at elevated temperature. use of equimolar secondary alkyl and aryl bromides, on the other hand, results in less than 60% yields solely using bipyridine ligands.

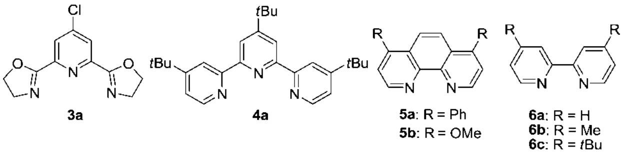


Figure 1. Structures of ligands.

We herein report highly efficient reductive coupling of equimolar secondary alkyl bromides with aryl bromides at

---

(1) For selected reviews, see: (a) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656–2670. (b) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674–688. (c) Hu, X. *Chem. Sci.* **2011**, *2*, 1867.

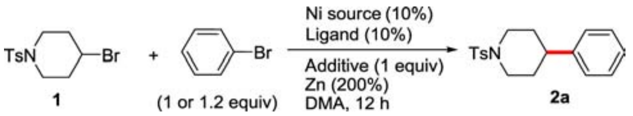
(2) For selected examples, see: (a) Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510–511. (b) Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 1264–1266. (c) Strotman, N. A.; Stefan Sommer, S.; Gregory C. Fu, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3556–3558. (d) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340–1341. (e) Oelke, A. J.; Sun, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 2966–2969. (f) Gong, H.; Gagné, M. R. *J. Am. Chem. Soc.* **2008**, *130*, 12177–12183. (g) Vechorkin, O.; Proust, V.; Hu, X. *J. Am. Chem. Soc.* **2009**, *131*, 9756.

(3) For examples, see: (a) Smith, S. C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 9334. (b) Han, C.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 7532. (c) Thaler, T.; Haag, B.; Gavryushin, A.; Schober, K.; Hartmann, E.; Gschwind, R. M.; Zipse, H.; Mayer, P.; Knochel, P. *Nature Chem.* **2010**, *2*, 125. (d) Joshi-Pangu, A.; Ganesh, M.; Biscoe, M. R. *Org. Lett.* **2011**, *13*, 1218. (e) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417.

(4) Breitenfeld, J.; Vechorkin, O.; Corminboeuf, C.; Scopelliti, R.; Hu, X. *Organometallics* **2010**, *29*, 3686–3689.

10.1021/ol3013342

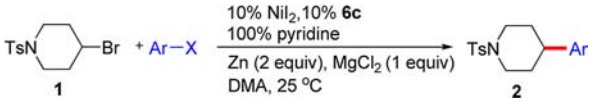
Table 1. Optimization for the Reaction of **1** and PhBr[a]

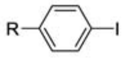
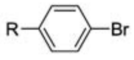
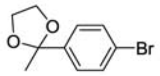
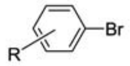
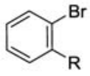
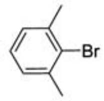
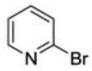
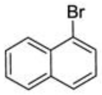
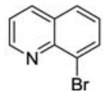


entry	Ni/ligand/temp (°C)	additive (mol %)	yield[b] (%)
1[c]	Ni(acac)$_2$/**3a**/80	none	32
2[c]	Ni(acac)$_2$/**3a**/80	MgCl$_2$ (100)	53
3[c]	NiI$_2$/**3a**/80	MgCl$_2$ (100)	60
4[c]	NiI$_2$/**4a**/80	MgCl$_2$ (100)	<30
5[c]	NiI$_2$/**5a**/80	MgCl$_2$ (100)	47
6[c]	NiI$_2$/**5b**/80	MgCl$_2$ (100)	54
7[c]	NiI$_2$/**6a**/80	MgCl$_2$ (100	57
8[c]	NiI$_2$/**6b**/80	MgCl$_2$ (100)	54
9[c]	NiI$_2$/**6c**/80	MgCl$_2$ (100)	59
10[d]	NiI$_2$/**6c**/80	MgCl$_2$ (100)/Py (1:1)[e]	69
11[d]	**NiI$_2$/6c/25**	**MgCl$_2$ (100)/Py (1:1)**[e]	**92**
12[d]	NiI$_2$/**6c**/25	Py (100)[e]	89
13[d]	NiI$_2$/**6c**/25	MgCl$_2$ (100)/Py (10:1)[e]	46

[a] Reaction conditions: **1** (0.15 mmol, 100 mol %), PhBr (0.15 or 0.16 mmol), Ni source (10 mol %), ligand (10 mol %), Zn (200 mol %), MgCl$_2$ (100 mol %), pyridine (100 mol %), DMA (1 mL). [b] Isolated yields. [c] 1.2 equiv of PhBr. [d] 1 equiv of PhBr. [e] Py = pyridine.

Table 2. Scope and Limitation of Aryl Bromides[a]



entry	Ar−X	product	yield[b]
1		**2a,** R = H:	33%
2		**2b,** R = OMe:	55%
3		**2b,** R = OMe:	91%
4		**2c,** R = OH:	60%
5		**2d,** R = CH$_3$C(O):	56%
6		**2e**	72%
7		**2f**, R = 3-OMe:	79%
8		**2g**, R = 2-OMe:	83%
9		**2h**, R = Cl:	67%
10		**2i**, R = NH$_2$:	71%
11		**2j**, R = F:	80%
12		**2k**, R = MeO(O)CCH$_2$:	98%
13		**2l**, R = MeO(O)C:	44%
14		**2m**	ND[c]
15		**2n**	38%
16		**2o**	73%
17		**2p**	96%

[a] Reaction conditions: **1** (0.15 mmol, 100 mol %), PhBr (100 mol %), NiI$_2$ (10 mol %), **6c** (10 mol %), Zn (200 mol %), MgCl$_2$ (100 mol %), pyridine (100 mol %), DMA (1 mL). [b] Isolated yields. [c] Not detected.

ambient temperature. Simple modification of the reaction conditions allowed efficient coupling of electron-deficient aryl chlorides with cyclohexyl bromide as well as allylation of aryl bromides with allylic acetate. The present work should serve a complementary means to the concurrent methods for the coupling of aryl and alkyl electrophiles.

In the course of our early effort on the Ni-catalyzed reductive coupling of two electrophiles,[9] we initially discovered that use of Cl-PyBox **3a** ligand alone provides the desired alkylaryl product **2a** in nearly 32% yield under Ni(acac)$_2$/Zn/DMA (DMA = *N*,*N*-dimethylacetamide) conditions for the coupling of 1 equiv of **1** with 1.2 equiv of PhBr at 80 °C (Table 1, entry 1).[10] The yield could be boosted to 53% by addition of 1 equiv of MgCl$_2$ (entry 2). Use of NiI$_2$ raised the yield to 60% (entry 3). Other tridentate and bidentate ligands such as **4a**, **5a**,**b**, and **6a**−**c** were inferior (Figure 1 and entries 4−9).[10] Inspired by Weix and Gosmini's reductive coupling procedures where pyridine necessitates the coupling of organo halides, we reasoned that a combination of a bidentate ligand and pyridine should be effective for this coupling event.[7b,11] However, only moderate improvement was observed when 1 equiv of pyridine was used (entry 10). A dramatic increase of the yield to 92% was eventually observed by lowering the temperature to 25 °C (entry 11).[10] With no MgCl$_2$, the reaction still proved to be highly effective (entry 12). Employment of 1 equiv of pyridine seemed to be critical as only 46% of yield was obtained using 10% pyridine (entry 13). With no or a low ratio of pyridine, significant homocoupling of **1** was observed, suggesting that pyridine can promote the reactivity of phenylbromide.

With the optimized conditions in hand, the limitation and scope of the aryl bromides were examined for the

---

(5) (a) Krasovskiy, A.; Duplais, C.; Lipshutz, B. H. *J. Am. Chem. Soc*. **2009**, *131*, 15592–15593. (b) Czaplik, W. M.; Mayer, M.; von Wangelin, A. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 607–610. (c) Amatore, M.; Gosmini, C. *Chem. Commun*. **2008**, 5019. (d) Duplais, C.; Krasovskiy, A.; Wattenberg, A.; Lipshutz, B. H. *Chem. Commun*. **2010**, 562. (e) Czaplik, W. M.; Mayer, M.; Jacobi von Wangelin, A. *Synlett* **2009**, 2931.

(6) Amatore, M.; Gosmini, C. *Chem.*−*Eur. J.* **2010**, *16*, 5848.

(7) (a) Durandetti, M.; Nédélec, J.-Y.; Périchon. *J. Org. Chem*. **1996**, *61*, 1748–1755. (b) Everson, D. A.; Shrestha, R.; Weix, D. J. *J. Am. Chem. Soc*. **2010**, *132*, 920–921. (c) Yan, C.-S.; Peng, Y.; Xu, X.-B.; Wang, Y.-W. *Chem.*—*Eur. J.* **2012**, *18*, 6039–6048. (d) Everson, D. A.; Jones, B. A.; Weix, D. J. *J. Am. Chem. Soc*. **2012**, *134*, 6146–6159.

(8) Although the cobalt/phosphine-catalyzed method gave a high yield for bromocyclohexane, it is limited to activated aryl halides (ref 6).

(9) (a) Yu, X.; Yang, T.; Wang, S.; Xu, H.; Gong, H. *Org. Lett*. **2011**, *13*, 2138. (b) Dai, Y.; Wu, F.; Zang, Z.; You, H.; Gong, H. *Chem.*—*Eur. J.* **2012**, *16*, 808. (c) Wu, F.; Lu, W.; Qian, Q.; Ren, Q.; Gong, H. *Org. Lett*. **2012**, *14*, 3044. (d) Yin, H.; Zhao, C.; You, H.; Lin, Q.; Gong, H. *Chem. Commun*. 2012, in press (DOI: 10.1039/C2CC33232A).

(10) See the Supporting Information for details.

(11) Qian, X.; Auffrant, A.; Felouat, A.; Gosmini, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10402.

coupling with **1** (Table 2). In general, aryl iodides were less effective (entries 1 and 2). Aryl bromides bearing electron-donating substituents, e.g., **2b**,**c**,**e**−**k**, delivered much better yields than those substituted with electron-withdrawing groups, e.g., **2d**,**l** (entries 3−13). The reaction conditions also tolerate acidic phenol and free amines as evident in **2c** and **2i**. The sterically more hindered 2,6-dimethylbromobenzene did not generate desired product **2m** (entry 14). 2-Bromopyridine only gave rise to a low yield for **2n**, probably due to the deactivated aromatic ring (entry 15). In addition to the benzene rings, 1-bromonaphthalene was also compatible, giving **2o** in 73%. 8-Bromoquinoline gave the coupling product in 96% yield, implying that coordination of the 1-nitrogen to nickel center played an important role (entries 16−17).

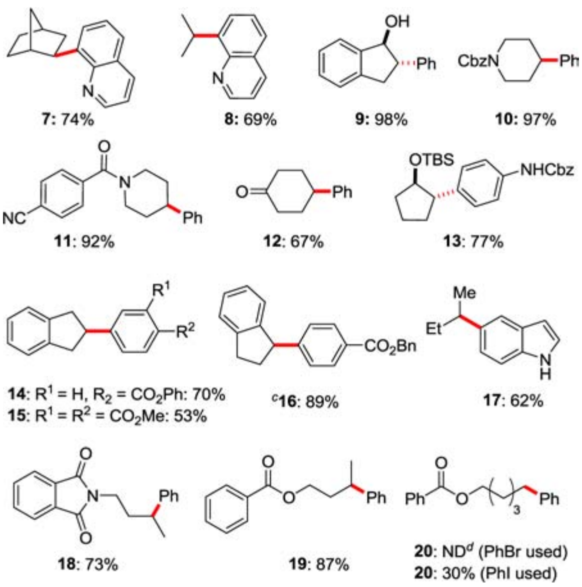
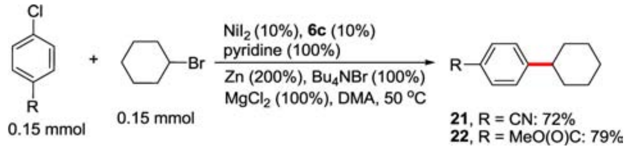


Figure 2. Coupling of aryl bromides with secondary alkyl bromides. (a) Reaction conditions: Ar-X (0.15 mmol, 100 mol %), PhBr (100 mol %), NiI_2 (10 mol %), **6c** (10 mol %), Zn (200 mol %), $MgCl_2$ (100 mol %), pyridine (100 mol %), DMA (1 mL). (b) Isolated yields. (c) 1-Chloro-2,3-dihydro-1*H*-indene was used. (d) Not detected.

An investigation of the scope of the alkyl halides and other aromatic systems is summarized in Figure 2. The cyclic and the open-chain secondary bromides were both efficient, providing **7**−**19** in good to excellent yields. Notably, benzylic chloride such as 1-chloro-2,3-dihydro-1*H*-indene also delivered **16** in excellent yield even with electron-deficient aryl bromide. The coupling of primary bromide with aryl bromides and iodides was not satisfactory. No or low yields were observed for **20** using PhBr or PhI, respectively. This is possibly due to less stable primary alkyl radical is involved.[12]

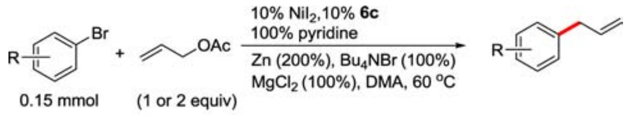
Extension of the coupling strategy to the less reactive aryl chlorides was also performed (Scheme 1). It was determined that only aryl chlorides bearing electron-withdrawing groups were effective at 50 °C. The presence of Bu_4NBr was indispensable, without which no products was detected.[13] The modified reaction conditions allowed the coupling of 4-cyano- and 4-(methoxycarbonyl)phenyl chlorides with cyclohexyl bromide to generate **21** and **22** in 72% and 79% yields, respectively. These results offset the shortcomings of low coupling efficiency using electron-deficient aryl bromides (vide supra).

Scheme 1. Coupling of Activated Ar-Cl with Cyclohexyl Bromide[a,b]



[a] Reaction conditions: ArCl (0.15 mmol, 100 mol %), cyclohexyl bromide (100 mol %), NiI_2 (10 mol %), **6c** (10 mol %), Zn (200 mol %), Bu_4NBr (100 mol %), $MgCl_2$ (100 mol %), pyridine (100 mol %), DMA (1 mL). [b] Isolated yields.

Scheme 2. Coupling of Ar-Br with Allylic Acetate[a,b]



ArBr/ allyl-OAc:	1:2	1:1
23, R = 3,4-dimethoxy:	75%	40%
24, R = 3,4,5-trimethoxy:	79%	NA[c]
25, R = 2-MeOC(O):	92% (90%)[d]	70%

[a] Reaction conditions: ArBr (0.15 mmol, 100 mol %), allylic acetate (100 or 200 mol %), NiI_2 (10 mol %), **6c** (10 mol %), Zn (200 mol %), Bu_4NBr (100 mol %), $MgCl_2$ (100 mol %), pyridine (100 mol %), DMA (1 mL). [b] Isolated yields. [c] Not available. [d] The yield in parentheses was achieved at 25 °C.

Finally, it was interesting to identify that the modified coupling conditions for activated aryl chlorides were highly effective for the coupling of aryl bromides with allylic acetate (Scheme 2). With 2 equiv of allylic acetate at 60 °C, aryl bromides containing electron-rich substituents gave allylated products **23** and **24** in fairly good yields, which were less effective than those with electron-withdrawing groups as evident in **25**. High coupling yield for **25** was even obtained at room temperature. Use of 1 equiv of allylic acetate, significantly eroded the coupling yields, e.g., 40% for **23** and 70% for **25**. The Ni-catalyzed conditions seem to be more effective than the analogous Co-catalyzed reductive and Fe-catalyzed domino Kumada methods.[14]

In summary, we have developed a highly efficient protocol for the coupling of secondary alkyl halides with aryl

---

(12) Coupling of (bromomethyl)cyclopropane with 8-bromoquinoline only generated ring-opening product, and 1 equiv of TEMPO completely inhibited the reaction of **1** with PhBr, indicating a possible radical process for alkyl halides.

(13) The role of $MgCl_2$ and BuNBr may possibly account for activation of Zn by removing salts on the surface.

halides, which provides a complementary solution to the unresolved issue in the previous studies on the coupling of aryl bromides with secondary alkyl bromides. Extension of the coupling strategy to the allylation of aryl bromides with allylic acetate is also highly effective, which may offer a convenient synthetic strategy for functionalization of aromatic rings.

Acknowledgment. Dr. Hongmei Deng (Shanghai University) is thanked for use of the NMR facility. Financial support was provided by the Chinese NSF (Nos. 2097209 and 21172140), the Program for Professor of Special Appointment (Eastern Scholar) at Shanghai Institutions of Higher Learning, Shanghai Education Committee (No. 10YZ04), and Shanghai Leading Academic Discipline Project (No. S30107).

Supporting Information Available. Spectral data of new compounds and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(14) (a) Gomes, P.; Gosmini, C.; Périchon, J. *Org. Lett.* **2003**, *5*, 1043–1045. (b) Mayer, M.; Czaplik, W. M.; Jacobi von Wangelin, A. *Adv. Synth. Catal.* **2010**, *352*, 2147.

The authors declare no competing financial interest.