ORGANIC LETTERS

2011
Vol. 13, No. 14
3556–3559

New Ligands That Promote Cross-Coupling Reactions between Aryl Halides and Unactivated Arenes

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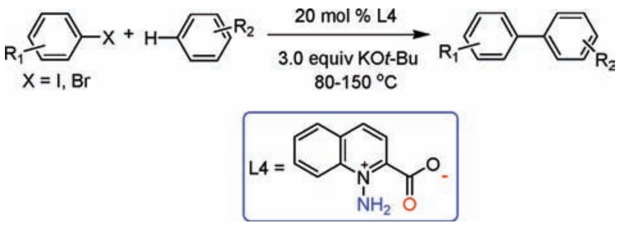
Received April 8, 2011

ABSTRACT



Several ligands were designed to promote transition-metal-free cross-coupling reactions of aryl halides with benzene derivatives. Among the systems probed, quinoline-1-amino-2-carboxylic acid was found to serve as an excellent catalyst for cross-coupling between aryl halides and unactivated benzene. Reactions using this inexpensive catalytic system displayed a high functional group tolerance as well as excellent chemoselectivities.

Selective functionalization of aromatic compounds through substitution at C$-$H bonds is an important goal in modern organic synthesis.[1] As part of the studies aimed at this goal, transition-metal catalyzed arylation reactions between arenes and aryl halides have been developed to construct biaryl compounds.[2,3] However, the presence of

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(1) For recent reviews of C$-$H transformation, see: (a) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077–1101. (b) Jones, W.; Fehe, F. *Acc. Chem. Res.* **1989**, *22*, 91–100. (c) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35–41. (d) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193. (e) Lewis, L. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013–1025. (f) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (h) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826. (i) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. (j) Dyker, G. *Handbook of C$-$H Transformations*; Wiley-VCH: Weinheim, 2005.

(2) For recent reviews of metal-catalyzed cross-coupling reactions, see: (a) Meijere, A.; Diederich, F. *Metal-catalyzed cross-coupling reactions, completely revised and enlarged*, 2nd ed.; Wiley-VCH: Weinheim, 2004. (b) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447–2464. (c) Daugulis, O.; Do, H. Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (e) Li, B. J.; Yang, S. D.; Shi, Z.-J. *Synlett* **2008**, 949–957.

(3) For recent examples of the use of metal-catalyzed cross-coupling in the construction of biaryl compounds, see: (a) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057. (b) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972–4973. (c) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754–8756. (d) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496–16497. (e) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066–6067. (f) Turner, G.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996–8000. (g) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128–1129. (h) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185–15192. (i) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926–2927. (j) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676–17677. (k) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593–1597. (l) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2925–2928. (m) Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3296–3300. (n) Join, B.; Yamamoto, T.; Itami, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 3644–3647. (o) Tobisu, M.; Hyodo, I.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 12070–12071. (p) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2202–2205. (r) Vallée, F.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 1514–1516.

10.1021/ol2009208

transition-metal impurities in the final products of these processes is a significant problem when these reactions are employed to prepare pharmaceutical agents. In 2008, Itami and his co-workers described a new procedure for carrying out "transition-metal-free" cross-coupling reactions between aryl halides and heterocyclic compounds.[4] In subsequent and recent efforts, two classes of ligands, including DMEDA,[5] 1,10-phenanthroline,[6] and its derivatives,[7] have been found to promote transition-metal-free processes for the synthesis of biaryl targets. Although these reactions proceed with acceptable yields, the requirement for high temperatures and the limited substrate range and low selectivities impede their general synthetic utility. Consequently, a highly desirable aim of studies in this area is the development of versatile and simple ligands that lead to improvements in the efficiency and generality of transition-metal free cross-coupling reactions between aryl halides and unactivated arenes. Below, we describe the results of a preliminary investigation of the use of quinoline-1-amino-2-carboxylic acid (**L4**) as a ligand for cross-coupling reactions of aryl iodides and bromides with unactivated arenes that do not require the assistance of any transition metals.

The design of this study was guided by the assumption that the ligands coordinating to metal centers played a key role in governing the efficiencies of catalyst systems that promote cross-coupling reactions of aryl halides with arenes. An analysis of the results of previous studies showed that the ligands probed thus far contain bidentate chelating centers that have the capability of coordinating with a K ion to form five-membered ring structures.[8] Based on this consideration, we believed that novel ligands possessing appropriately functionalized pyridine and related N-amino or N-oxide ring systems (**L1**–**L5** in Figure 1) would be capable of promoting cross-coupling processes owing to the fact that these substances would participate in forming six-membered ring chelates with the potassium ion.

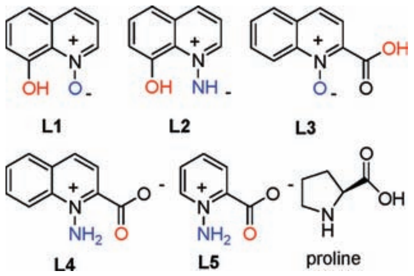
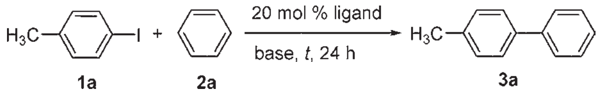


Figure 1. Structure of designed ligands.

The cross-coupling reaction of 4-methyliodobenzene and benzene was selected to evaluate the catalytic activities of systems comprised of the designed ligands. Reactions were carried out in benzene using 20 mol % of the ligands and 3.0 equiv of KO*t*-Bu at 80 °C (Table 1, entries 1–7). Importantly, this coupling reaction did not occur when ligands were absent (entry 7). The results showed that the highest yield (88%, entry 4) was obtained when quinoline-1-amino-2-carboxylic acid (**L4**) was employed. The high efficiency of this process might be due to the fact that **L4** possesses a rigid conformation that strongly complexed to the potassium ion via a six-membered ring chelate. Using **L4** as the ligand and benzene as the solvent, reactions employing other bases, including K_2CO_3, NaO*t*-Bu, and KOH, were explored. Bases weaker than KO*t*-Bu were found to be much less effective, and no coupling product was formed in these cases (Table 1, entries 8–10). The results of this preliminary investigation demonstrated that the optimal conditions for the cross-coupling reaction of 4-methyliodobenzene with benzene involved the use of 20 mol % **L4** and 3.0 equiv of KO*t*-Bu.

Table 1. Designed Ligands for the Cross-Coupling Reaction of *p*-Tolyl Iodide with Benzene[a]



entry	ligand	base	*t* (°C)	yield (%)[b]
1	L1	KO*t*-Bu	80	34
2	L2	KO*t*-Bu	80	47
3	L3	KO*t*-Bu	80	64
4	L4	KO*t*-Bu	80	88
5	L5	KO*t*-Bu	80	60
6	Proline	KO*t*-Bu	80	67
7	None	KO*t*-Bu	80	0
8	L4	K_2CO_3	80	0
9	L4	NaO*t*-Bu	80	0
10	L4	KOH	80	0

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (2 mL), 20 mol % ligand, base (3.0 mmol), Ar, 80 °C, 24 h. [b] Isolated yield.

The scope of reactions, promoted by the KO*t*-Bu/**L4** catalyst system under the optimal conditions described above, was explored next. As can be seen from the results displayed in Table 2, coupling reactions of most of the substrates examined took place in 60%–88% yields. For example, coupling reactions of various methoxy and methyl substituted iodobenzenes with benzene occurred in excellent yields (80%–88%) (entries 1–4). Even coupling reactions of sterically hindered 2-iodotoluene and 2-iodoanisole took place in good yields (66%–84%) (entries 5, 6). This finding represents an improvement over the reported results.[5] Polysubstituted electron-rich aryl

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[4] Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4673–4676.

[5] Liu, W.; Cao, H.; Zhang, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwong, F. Y.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 16737–16740.

[6] Sun, C.-L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X. Y.; Huang, K.; Zheng, S. F.; Li, B.-J.; Shi, Z.-J. *Nat. Chem.* **2010**, *2*, 1044–1049.

[7] Shirakawa, E.; Itoh, K.; Higashino, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 15537–15539.

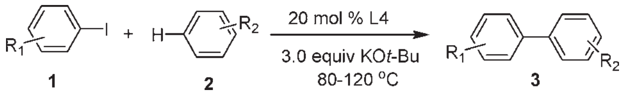
[8] Studer, A.; Curran, D. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 5018–5022.

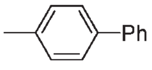
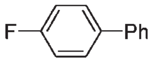
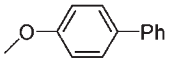
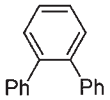
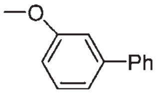
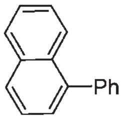
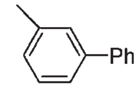
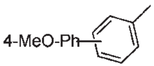
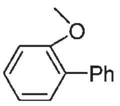
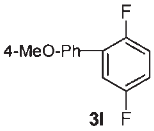
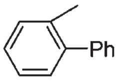
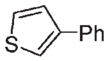
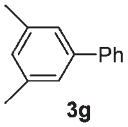
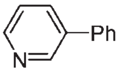
iodides also participated in this ligand-induced coupling process (entry 7). Interestingly, the catalyst system promoted highly selective reactions when a variety of other potentially reactive groups were present in the substrate. For example, a cross-coupling reaction of 4-fluoro-1-iodobenzene with benzene yielded the corresponding fluorine-containing product selectively in 80% isolated yield. This is a highly desirable outcome for the synthesis of complex molecules using sequential orthogonal cross-couplings (entry 8).

Significantly, by raising the temperature to 120 °C, a cross-coupling reaction of *o*-diiodobenzene with benzene (entry 9), a typically challenging substrate combination,[5] took place smoothly. In addition, direct arylation reactions of other challenging substrate combinations,[5,7] comprised of unactivated arenes (*eg*., toluene, and 1,4-difluorobenzene), took place in good yields by using the new catalyst system (entries 11, 12). Finally, even cross-coupling reactions of heterocyclic iodides with benzene were promoted by the new catalyst system. In these cases, heteroaryl iodides, such as 3-iodothiophene and 3-iodopyridine, coupled with benzene efficiently to generate the corresponding adducts (entry 13, 14).

The new catalytic system was also found to be applicable to cross-coupling reactions of aryl bromides (Table 3). All of the aryl bromides examined reacted with benzene at 120 °C to furnish the corresponding biaryls in good yields. Moreover, high yields were also obtained when aryl bromides with electron-donating groups were used as reactants (entries 1–7). Noteworthy is the observation that

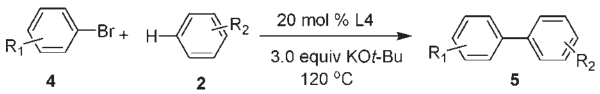
Table 2. Direct Arylation Reactions of Arenes with Aryl Iodides[a]

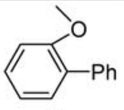
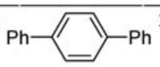
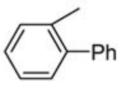
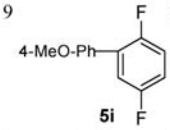
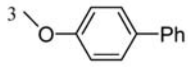
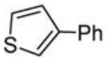
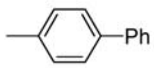
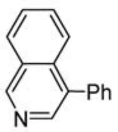
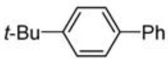
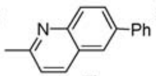
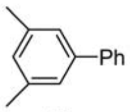
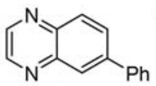
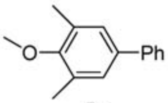


entry	product	time (h)	yield [b](%)	entry	product	time (h)	yield [b](%)
1	 **3a**	24	88	8	 **3h**	24	80[c]
2	 **3b**	24	85	9	 **3i**	24	47[c]
3	 **3c**	28	80	10	 **3j**	10	67
4	 **3d**	24	81	11	 **3k** (o/m/p = 2/3/5)	10	48[c]
5	 **3e**	24	84[c]	12	 **3l**	44	78
6	 **3f**	24	66[c]	13	 **3m**	24	81[c]
7	 **3g**	24	74[c]	14	 **3n**	24	75[c]

[a] Reaction conditions: 1 (1.0 mmol), **2** (2 mL), 20 mol % ligand, KO*t*-Bu (3.0 mmol), Ar, 80 °C, 24 h. [b] Isolated yield. [c] At 120 °C.

Table 3. Direct Arylation Reactions of Arenes with Aryl Bromides[a]



entry	product	time (h)	yield [b](%)	entry	product	time (h)	yield [b](%)
1	 **5a**	36	87	8	 **5h**	24	56
2	 **5b**	30	57	9	 **5i**	24	64
3	 **5c**	48	87	10	 **5j**	16	63[c]
4	 **5d**	24	81	11	 **5k**	18	87
5	 **5e**	12	85[c]	12	 **5l**	24	58
6	 **5f**	12	67[c]	13	 **5m**	14	60
7	 **5g**	24	70				

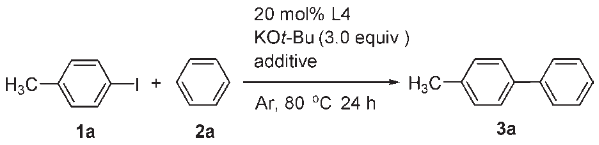
[a] Reaction conditions: **4** (1.0 mmol), **2** (2 mL), 20 mol % ligand, KO*t*-Bu (3.0 mmol), Ar, 120 °C, 24 h. [b] Isolated yield. [c] At 150 °C.

reaction of 2-bromotoluene with benzene at 120 °C, a typically difficult process,[5,6] gave the coupling product in 57% yield (entry 2). In addition, double coupling also took place in a 56% yield when 1,4-dibromobenzene was used as the substrate. Further, the new catalytic system was found to successfully promote coupling reactions of heterocyclic bromides with benzene (entries 10−13).

Based on the above observation, we propose that quinoline-1-amino-2-carboxylic acid (**L4**) serves to catalyze the radical formation as a consequence of its ability to strongly complex to potassium via a six-membered ring chelate. To verify this proposal, tetramethylpiperidine *N*-oxide (TEMPO), a typical radical scavenger, was added to the reaction mixture (Table 4). No coupling product formed in this case indicated that the transformation proceeded via radical intermediates. In the absence of L4, AIBN served to initiate the coupling process that formed the desired coupling product, albeit in a lower yield (Table 4).

Lastly, we investigated the effects of trace metal impurities. For this purpose, different metals, such as Cu and Fe, were examined for their ability to promote the cross-coupling reaction of 4-methyliodobenzene with benzene (Table 4). In the cases when 10% CuI or 10% Fe(acac)$_2$ was present in the reaction mixture, the coupling process took place in comparably lower yields. These findings suggest that transition-metal complexes do not participate in these cross-coupling reactions.

Table 4. Radical Trapping and Transition-Metal Effects on the Cross-Coupling Reaction of *p*-Tolyl Iodide with Benzene[a]

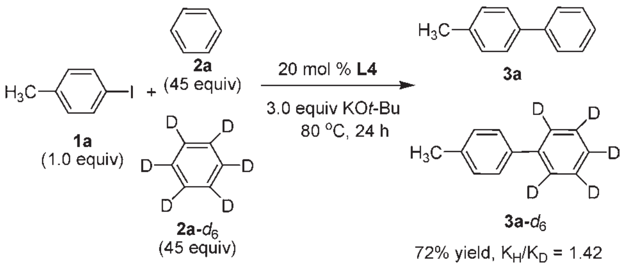


entry	ligand	base	additive	yield (%)[b]
1	L4	KO*t*-Bu	TEMPO (1.0 equiv)	0
2	none	KO*t*-Bu	AIBN	28
3	L4	KO*t*-Bu	10% CuI	75
4	L4	KO*t*-Bu	10% Fe(acac)$_2$	51
5	L4	KO*t*-Bu	none	88

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (2 mL), 20 mol % ligand, KOt-Bu (3.0 mmol), Ar, 80 °C, 24 h. [b] Isolated yield.

Furthermore, as described in the Supporting Information, we formulated a possible mechanism for the **L4**-catalyzed cross-coupling between aryl halides and the unactivated arenes. To understand the proposed radical pathway and clarify the rate-determining step, we tested the competition reaction between C_6H_6 (45 equiv) and C_6D_6 (45 equiv), as shown in Scheme 1. The observed low K_H/K_D value (1.42) implies that the rate-determining step is the single electron transfer process.

Scheme 1. Kinetic Isotopic Effects Experiment



In summary, a combination of quinoline-1-amino-2-carboxylic acid and KO*t*-Bu is identified as an effective catalytic system for promoting transition-metal-free cross-coupling reactions of aryl halides with unactivated benzenes. Particularly noteworthy are the observations which show that this inexpensive catalytic system displays high functional group tolerance and selectivity when multiple potentially reactive groups are present in the substrates. Finally, mechanistic studies indicate the operation of a radical pathway in this process.

Acknowledgment. This project was supported by the National Natural Science Foundation (Nos. 20802078, 20972160, and 20772035), National Basic Research Program of China (2009CB940900), Shanghai University Distinguished Professor (Eastern scholars) Program (DF2009-02), Pujiang Talent Plan Project (09PJ1409200), and National Major Scientific and Technological Program for Drug Discovery (2009ZX-09103-101).

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