JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Transition-Metal-Free BF_3-Mediated Regioselective Direct Alkylation and Arylation of Functionalized Pyridines Using Grignard or Organozinc Reagents

Quan Chen, Xavier Mollat du Jourdin, and Paul Knochel*

Department of Chemistry, Ludwig-Maximilians-Universität, Butenandtstr. 5-13, 81377 Munich, Germany

Supporting Information

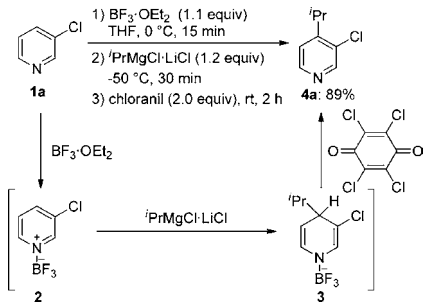
ABSTRACT: A formal regioselective cross-coupling of various pyridines with alkyl and aryl groups can be achieved by a BF_3·OEt_2-mediated addition of Grignard or organozinc reagents to pyridines bearing various substituents (chloro, bromo, cyano, vinyl, phenyl, carbethoxy, nitro, etc.) followed by an oxidative aromatization mediated by chloranil. Good regioselectivity and wide functional group tolerance make this method very versatile for the preparation of polyfunctional pyridines. No transition-metal catalyst is required in these coupling reactions.

Pyridines are an important class of *N*-heterocycles including many bioactive compounds[1] and functional materials.[2] The direct functionalization of these heterocyclic scaffolds has been achieved by numerous methods, including C−H activation,[3] radical reaction,[4] and directed metalation.[5] Nevertheless, these approaches always require the addition of catalytic or stoichiometric amounts of transition metals, most of which are expensive and nonenvironmentally benign. Besides, such transition-metal catalyzed procedures are frequently accompanied by side reactions such as homocoupling and β-hydride elimination. Moreover, especially for the pharmaceutical industry, the removal of harmful transition-metal contamination is often costly and difficult.[6]

To avoid using transition metals, oxidative Chichibabin-type two-step strategies (nucleophilic addition followed by oxidative aromatization) represent one of the most expedient methods for the direct functionalization of pyridine derivatives.[7] Yet, a preactivation of the pyridine ring such as *N*-oxidation, *N*-acylation, or *N*-alkylation is usually required.[8] Especially for hard nucleophiles such as organolithium, Grignard, and organozinc reagents, the nucleophiles add mostly to the C(2)-position of the pyridine ring. The formation of a small but not negligible amount of a 4-substituted product is often observed, lowering somewhat the synthetic value of these methods.[9] As a solution, we report a novel *transition-metal-free* BF_3·OEt_2[10] mediated regioselective synthesis of 4-substituted pyridine derivatives using LiCl activated Grignard[11] or organozinc reagents.[12]

Thus, treatment of 3-chloropyridine (**1a**) with BF_3·OEt_2 (1.1 equiv, THF, 0 °C, 15 min) affords the Lewis pair (**2**). Subsequent addition of ^{i}PrMgCl·LiCl (1.2 equiv, −50 °C, 0.5 h) leads to the tentative intermediate (**3**), which was conveniently aromatized by the low toxic[13] chloranil[14] (2.0 equiv, 25 °C, 2 h) affording the 3-chloro-4-isopropylpyridine (**4a**) in 89% isolated yield. The regioisomeric 2-substitution product is not observed (Scheme 1).

Scheme 1. Selective Addition of a Grignard Reagent to 1a



BF_3 facilitates this addition reaction considerably, and without this Lewis acid, no reaction occurs.[15]

The presence of LiCl has a beneficial effect since the addition of EtMgCl·LiCl provides the product (**4b**) in 94% NMR yield (NMR determination with internal standard calibration). In the absence of LiCl, EtMgCl furnishes the desired product (**4b**) in only 67% NMR yield (Table 1, entry 1). A range of primary and secondary alkylmagnesium derivatives add in the presence of LiCl to 3-chloropyridine (**1a**) to furnish regiospecifically the 4-substituted products (**4c**−**f**) in 70−94% yield (entries 2−5). Notably, even a tertiary alkyl group such as a *tert*-butyl group can be introduced to nicotinonitrile (**1b**) in 70% yield (entry 6). In order to exclude a radical pathway, we used hex-5-en-1-ylmagnesium chloride (**5**) as a radical clock, but no cyclized product was obtained and only the linear substituted pyridine (**4h**) was obtained in 76% NMR yield (entry 7). Several other 3-substituted pyridines such as 3-bromopyridine (**1c**), ethyl nicotinate (**1d**), 3-phenylpyridine (**1e**), and 3-vinylpyridine (**1f**) add ^{i}PrMgCl·LiCl, leading to the desired 4-substituted pyridines (**4i**−**l**) in 47−79% yield (entries 8−11).

Also, 2-chloropyridine (**1g**) adds ^{i}PrMgCl·LiCl in the C(4)-position to afford the corresponding disubstituted pyridine (**4m**) in 76% NMR yield. Interestingly, the 2-chloro substituent is inert under these conditions (entry 12). Similarly, a 1,2,3-trisubstituted pyridine (**4n**) can be readily prepared in 93% isolated yield (entry 13).

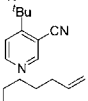
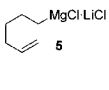
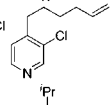
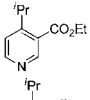
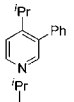
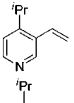
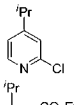
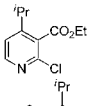
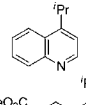
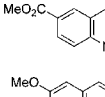
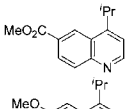
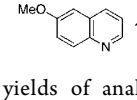
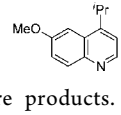
In the case of quinoline, the addition of ^{i}PrMgCl·LiCl occurs with good regioselectivity to afford the 4-substituted quinolines (**4o**−**q**) in 78−86% isolated yield (entries 14−16). Yet, <10% of the corresponding 2-substituted quinolines[16] have also been isolated.[17]

To expand the scope of this reaction, we have investigated the use of alkylzinc reagents[12c] for the nucleophilic addition. The addition of OctZnBr·$MgCl_2$·LiCl to nicotinonitrile (**1b**) led to an

Received: February 1, 2013
Published: March 18, 2013

dx.doi.org/10.1021/ja401146v | J. Am. Chem. Soc. 2013, 135, 4958−4961

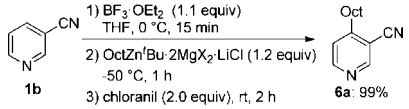
Table 1. Direct Alkylation of Pyridine Derivatives Using Grignard Reagents

Entry	Substrate	Grignard Reagent	Product	Yield %[a]
1		**1a** EtMgCl·LiCl	 **4b**	(94, 67[b])
2		**1a** OctMgBr·LiCl	 **4c**	94
3		**1a** *c*-HexMgBr·LiCl	 **4d**	70
4		**1a** *c*-PentMgCl·LiCl	 **4e**	89
5		**1a**  MgBr·LiCl	 **4f**	91
6		**1b** ^{t}BuMgCl·LiCl	 **4g**	70
7		**1a**  MgCl·LiCl **5**	 **4h**	44[c] (76)
8		**1c** ^{i}PrMgCl·LiCl	 **4i**	67
9		**1d** ^{i}PrMgCl·LiCl	 **4j**	79
10		**1e** ^{i}PrMgCl·LiCl	 **4k**	72
11		**1f** ^{i}PrMgCl·LiCl	 **4l**	47
12		**1g** ^{i}PrMgCl·LiCl	 **4m**	53[c] (76)
13		**1h** ^{i}PrMgCl·LiCl	 **4n**	93
14		**1i** ^{i}PrMgCl·LiCl	 **4o**	80
15		**1j** ^{i}PrMgCl·LiCl	 **4p**	86
16		**1k** ^{i}PrMgCl·LiCl	 **4q**	78

[a]Isolated yields of analytically pure products. NMR yields are given in parentheses. [b]The reaction is performed with EtMgCl. [c]The low isolated yield is caused by a difficult chromatographical separation.

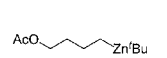
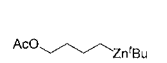
unsatisfactory reaction with uncompleted conversion. However, by forming the mixed diorganozinc reagent OctZn^tBu, readily prepared by adding ^{t}BuMgCl to Oct$ZnBr{\cdot}MgCl_2{\cdot}LiCl$, we obtained a fast and quantitative addition to nicotinonitrile (**1b**) at −50 °C. After oxidative treatment with chloranil, the desired 4-substituted pyridine (**6a**) was obtained in 99% yield (Scheme 2). The *tert*-butyl group plays in all these reactions the role of a nontransferable ligand.[18] It should be noticed that although the *tert*-butyl group bears 9 *β*-hydrogens, no significant *β*-hydride elimination is observed in these reactions, since no transition metal is present. This enables us to avoid using more expensive nontransferable ligands such as neopentyl, neophyl,[18b] or trimethylsilylmethyl,[18a,c] which bears no *β*-hydrogen.

Scheme 2. Selective Addition of an Organozinc Reagent to Nicotinonitrile



Thus, a variety of functionalized zinc reagents react under these conditions and highly functionalized products were obtained in 60−93% yield. Remarkably, functionalized mixed diorganozinc reagents with an acetoxy, a carbethoxy,[19] or a cyano group can be prepared and used without problems (Table 2).

Table 2. Direct Alkylation of Pyridine Derivatives Using Alkylzinc Reagents

Entry	Substrate	Zinc Reagent[a]	Product	Yield %[b]
1	 **1a**		 **6b**	93
2	 **1d**		**6c**	79
3	**1a**		**6d**	68
4	**1a**		**6e**	60
5	**1a**		**6f**	85
6[c]	**1c**		**6g**	63
7	**1a**		**6h**	86

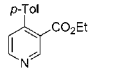
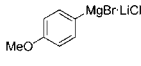
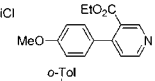
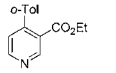
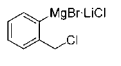
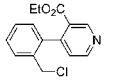
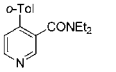
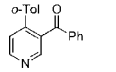
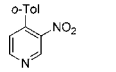
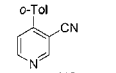
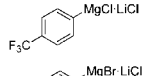
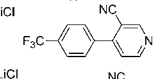
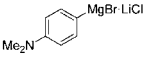
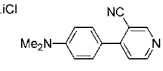
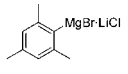
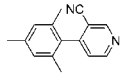
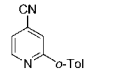
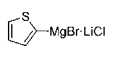
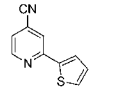
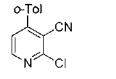
[a]$2MgX_2{\cdot}LiCl$ is omitted for clarity. [b]Isolated yields of analytically pure products. [c]The reaction was carried in an 8 mmol scale.

Next, we have examined the arylation of functionalized pyridines (Table 3). Here, arylmagnesium reagents proved to give the best results and a smooth addition is obtained with a variety of Grignard reagents leading to polyfunctional 4-arylated pyridines (**7a**−**n**; 42−99%). Remarkably, a number of functional groups are tolerated in the starting pyridines such as an ester (entries 1−4), an amide (entries 5), a ketone (entry 6), a nitro[8g] (entry 7), and a cyano group (entries 8−14). In a large scale (8 mmol) reaction, 2-chloromethylphenylmagnesium bromide[20] adds to ethyl nicotinate (**1d**) and leads to the pyridine (**7d**) in 83% isolated yield (entry 4). Both Grignard reagents with electron-withdrawing (entry 9) or -donating groups (entry 10) afford 4-arylated pyridines (**7i** and **7j**) in high yields. Even a bulky Grignard reagent such as mesitylmagnesium bromide reacts efficiently with nicotinonitrile (**1b**) and furnishes the 4-mesitylnicotinonitrile (**7k**) in 98% isolated yield (entry 11). For a 4-substituted starting pyridine such as isonicotinonitrile (**1o**), the addition of a Grignard reagent cannot occur at C(4) but proceeds at C(2) and furnishes the corresponding product in acceptable yields (entries 12 and 13). Finally, 2-chloronicotinonitrile (**1p**) is converted to the 1,2,3-trisubstituted pyridine (**7n**) in 57% isolated yield (entry 14).

To introduce a more functionalized aryl group, *p*-$EtO_2C{-}C_6H_4MgCl{\cdot}LiCl$ (**9**) was prepared *in situ* via an iodine/magnesium exchange.[11a] In a reversed addition procedure, a mixture of

dx.doi.org/10.1021/ja401146v | J. Am. Chem. Soc. 2013, 135, 4958−4961

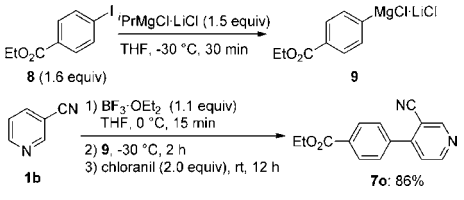
Table 3. Direct Arylation of Pyridine Derivatives Using Grignard Reagents

Entry	Substrate	Grignard Reagent	Product	Yield %[a]
1		**1d**	*p*-TolMgBr·LiCl		**7a**	80
2		**1d**			**7b**	81
3		**1d**	*o*-TolMgBr·LiCl		**7c**	83
4[b]		**1d**			**7d**	83
5		**1l**	*o*-TolMgBr·LiCl		**7e**	87
6		**1m**	*o*-TolMgBr·LiCl		**7f**	68
7		**1n**	*o*-TolMgBr·LiCl		**7g**	58
8		**1b**	*o*-TolMgBr·LiCl		**7h**	97
9		**1b**			**7i**	89
10		**1b**			**7j**	99
11		**1b**			**7k**	98
12		**1o**	*o*-TolMgBr·LiCl		**7l**	45
13		**1o**			**7m**	42
14		**1p**	*o*-TolMgBr·LiCl		**7n**	57

[a]Isolated yields of analytically pure products. [b]The reaction was carried in a 8 mmol scale.

nicotinonitrile (**1b**) and BF_3·OEt_2 was added to the Grignard reagent **9** to furnish a dual-functionalized pyridine (**7o**) in 86% isolated yield (Scheme 3).

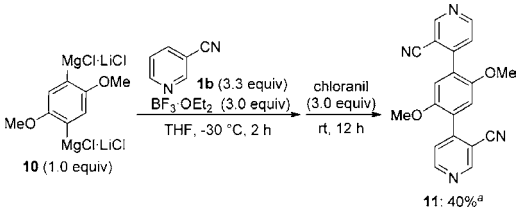
Scheme 3. Selective Addition of a Functionalized Grignard Reagent to Nicotinonitrile



Nicotinonitrile oligomers are usually used as functional materials, but their synthesis is always complex.[21] Surprisingly, with the aid of BF_3·OEt_2, a dimagnesiated species (**10**)[11b] reacts with 2 equiv of nicotinonitrile and affords a fluorescent compound **11** in one step (Scheme 4).

Also, nicotinamides are widely used as building blocks for many pharmaceuticals. However, the direct functionalization of nicotinamides always relies on transition-metal catalyzed procedures.[3f,22] Here,

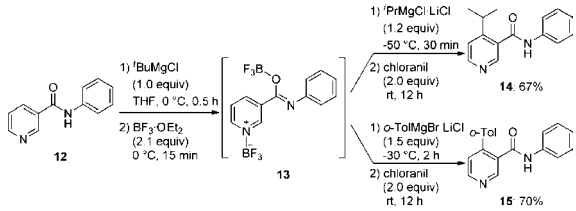
Scheme 4. Double Addition to Nicotinonitriles Using a 1,4-Dimagnesiated Aromatic Reagent[a]



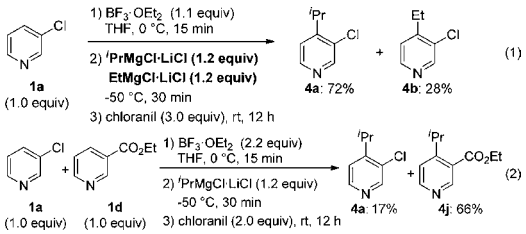
[a]Yield based on Grignard reagent.

1 equiv of ^{t}BuMgCl is used to deprotonate the amide nitrogen and 2 equiv of BF_3·OEt_2 are added, leading to the tentative intermediate **13**. Both alkyl and aryl Grignard reagents react with **13**, and the desired products (**14**–**15**) are obtained in good yields (Scheme 5).

Scheme 5. Direct Alkylation and Arylation of Nicotinamide



To explore some mechanistic details of this reaction, 3-chloropyridine (**1a**) was reacted with premixed ^{i}PrMgCl·LiCl and EtMgCl·LiCl in equal amounts. Interestingly, the bulkier isopropyl adduct (**4a**) is mainly formed (eq 1). It indicates that, rather than steric effects, the nucleophilicity and aggregation of the Grignard reagents play a more important role in these additions to pyridines. Besides, more electron-deficient ethyl nicotinate (**1d**) undergoes the addition of the Grignard reagent more readily (ca. 4 times) than 3-chloropyridine (**1a**) (eq 2).



In summary, we have developed a transition-metal-free BF_3·OEt_2-mediated functionalization of pyridines with functionalized alkyl and aryl groups. An excellent C(4)-regioselectivity makes this method a complement to previously reported ones. This reaction is practical and can be performed at a larger scale with no decrease in yield. Further mechanistic and synthetic studies are underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental details, ^{1}H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

paul.knochel@cup.uni-muenchen.de

dx.doi.org/10.1021/ja401146v | J. Am. Chem. Soc. 2013, 135, 4958–4961

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Fonds der Chemischen Industrie and the European Research Council (ERC-227763) and Sonderforschungbereich (SFB-749) of the German Science Foundation (DFG) for financial support and Rockwood Lithium (Frankfurt) for the generous gift of chemicals.

■ REFERENCES

(1) (a) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043. (b) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627. (c) Bagley, M. C.; Glover, C.; Merritt, E. A. *Synlett* **2007**, 2459. (d) Hill, M. D. *Chem.—Eur. J.* **2010**, *16*, 12052. (e) Hardin Narayan, A. R.; Sarpong, R. *Org. Biomol. Chem.* **2012**, *10*, 70.

(2) (a) Yokoyama, A.; Nishiyama, I.; Yoshizawa, A. *Ferroelectrics* **1993**, *148*, 139. (b) Skrypink, Y. G.; Doroshenko, T. F. *Mater. Sci.* **1996**, *32*, 537. (c) Tsutsumi, H.; Okada, K.; Oishi, T. *Electrochim. Acta* **1996**, *41*, 2657. (d) Bangcuyo, C. G.; Rampey-Vaughn, M. E.; Quan, L. T.; Angel, S. M.; Smith, M. D.; Bunz, U. H. F. *Macromolecules* **2002**, *35*, 1563. (e) Vetrichelvan, M.; Valiyaveettil, S. *Chem.—Eur. J.* **2005**, *11*, 5889.

(3) (a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (b) Larivée, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52. (c) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448. (d) Tobisu, M.; Hyodo, I.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 12070. (e) Nakao, Y.; Yamada, Y.; Kashihara, N.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 13666. (f) Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275. (g) Xiao, B.; Liu, Z.-J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 616.

(4) (a) Minisci, F.; Giordano, C.; Vismara, E.; Levi, S.; Tortelli, V. *J. Am. Chem. Soc.* **1984**, *106*, 7146. (b) Minisci, F.; Fontana, F.; Vismara, E. *J. Heterocycl. Chem.* **1990**, *27*, 79. (c) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 13194. (d) Molander, G. A.; Colombel, V.; Braz, V. A. *Org. Lett.* **2011**, *13*, 1852. (e) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herle, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, *492*, 95.

(5) (a) Schlosser, M.; Mongin, F. *Chem. Soc. Rev.* **2007**, *36*, 1161. (b) Haag, B.; Mosrin, M.; Ila, H.; Malakhov, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 9794.

(6) (a) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889. (b) Welch, C. J.; Albaneze-Walker, J.; Leonard, W. R.; Biba, M.; DaSilva, J.; Henderson, D.; Laing, B.; Mathre, D. J.; Spencer, S.; Bu, X.; Wang, T. *Org. Process Res. Dev.* **2005**, *9*, 198.

(7) (a) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223. (b) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141. (c) Andersson, H.; Olsson, R.; Almqvist, F. *Org. Biomol. Chem.* **2011**, *9*, 337. (d) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642. (e) Jeffrey, J. L.; Sarpong, R. *Org. Lett.* **2012**, *14*, 5400.

(8) *N*-Oxidation: (a) Kato, T.; Yamanaka, H. *J. Org. Chem.* **1965**, *30*, 910. (b) Kellogg, R. M.; Van Bergen, T. J. *J. Org. Chem.* **1971**, *36*, 1705. (c) Schiess, P.; Ringele, P. *Tetrahedron Lett.* **1972**, *13*, 311. (d) Andersson, H.; Almqvist, F.; Olsson, R. *Org. Lett.* **2007**, *9*, 1335. (e) Andersson, H.; Gustafsson, M.; Boström, D.; Olsson, R.; Almqvist, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 3288. (f) Andersson, H.; Sainte-Luce Banchelin, T.; Das, S.; Olsson, R.; Almqvist, F. *Chem. Commun.* **2010**, *46*, 3384. (g) Zhang, F.; Duan, X.-F. *Org. Lett.* **2011**, *13*, 6102. (h) Hussain, M.; Sainte-Luce Banchelin, T.; Andersson, H.; Olsson, R.; Almqvist, F. *Org. Lett.* **2013**, *15*, 54. *N*-Acylation: (i) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315. (j) Akiba, K.; Iseki, Y.; Wada, M. *Tetrahedron Lett.* **1982**, *23*, 429. (k) Comins, D. L. *Tetrahedron Lett.* **1983**, *24*, 2807. (l) Shing, T.-L.; Chia, W.-L.; Shiao, M.-J.; Chau, T.-Y. *Synthesis* **1991**, 849. (m) Chia, W.-L.; Shiao, M.-J. *Tetrahedron Lett.* **1991**, *32*, 2033. (n) Mangeney, P.; Gosmini, R.; Raussou, S.; Commerçon, M. *Tetrahedron Lett.* **1993**, *34*, 6399. (o) Krapcho, A. P.; Waterhouse, D. J.; Hammach, A.; Di Domenico, R.; Menta, E.; Oliva, A.; Spinelli, S. *Synth. Commun.* **1997**, *27*, 781. (p) Comins, D. L.; King, L. S.; Smith, E. D.; Février, F. C. *Org. Lett.* **2005**, *7*, 5059. *N*-Alkylation: (q) Loska, R.; Mąkosza, M. *J. Org. Chem.* **2007**, *72*, 1354. Others: (r) Katritzky, A. R.; Zhang, S.; Kurz, T.; Wang, M. *Org. Lett.* **2001**, *3*, 2807. (s) Corey, E. J.; Tian, Y. *Org. Lett.* **2005**, *7*, 5535.

(9) (a) Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829. (b) Legault, C.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 6360.

(10) (a) Maruyama, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1977**, *99*, 8068. (b) Aubrecht, K. B.; Winemiller, M. D.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 11084. (c) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275. (d) Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 46. (e) Jaric, M.; Haag, B. A.; Unsinn, A.; Karaghiosoff, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 5451. (f) Jaric, M.; Haag, B. A.; Manolikakes, S. M.; Knochel, P. *Org. Lett.* **2011**, *13*, 2306.

(11) (a) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333. (b) Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 6802. (c) Piller, F. M.; Metzger, A.; Schade, M. A.; Hagg, B. A.; Gavryushin, A.; Knochel, P. *Chem.—Eur. J.* **2009**, *15*, 7192.

(12) (a) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6040. (b) Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, *128*, 9998. (c) Blümke, T. D.; Piller, F. M.; Knochel, P. *Chem. Commun.* **2010**, *46*, 4082. (d) Metzger, A.; Bernhardt, S.; Manolikakes, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 4665.

(13) The LD_{50} of chloranil orally for rats is similar to that of acetic acid; see The Merck Index.

(14) (a) Krasovskiy, A.; Tishkov, A.; del Amo, V.; Mayr, H.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 5010. (b) del Amo, V.; Dubbaka, S. R.; Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 7838.

(15) Other Lewis acids such as $B(C_6F_5)_3$, $AlEt_2Cl$, and $AlMe_3$ decompose quickly together with Grignard reagents and cannot give any desired product.

(16) See Supporting Information.

(17) For other substrates such as pyridine, 3-picoline, and 2-methoxypyridine, the addition is very slow and only affords a trace amount of the desired products. A 4-substituted substrate such as ethyl isonicotinate does not give any addition product.

(18) (a) Berger, S.; Langer, F.; Lutz, C.; Knochel, P.; Mobley, T. A.; Reddy, C. K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1496. (b) Lutz, C.; Jones, P.; Knochel, P. *Synthesis* **1999**, 312. (c) Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E. *Synlett* **2005**, *11*, 1794.

(19) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368.

(20) Haag, B.; Peng, Z.; Knochel, P. *Org. Lett.* **2009**, *11*, 4270.

(21) (a) Li, N.; Wang, P.; Lai, S.-L.; Liu, W.; Lee, C.-S.; Lee, S.-T.; Liu, Z. *Adv. Mater.* **2010**, *22*, 527. (b) You, J.; Lo, M.-F.; Liu, W.; Ng, T.-W.; Lai, S.-L.; Wang, P.; Lee, C.-S. *J. Mater. Chem.* **2012**, *22*, 5107.

(22) Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428.