# Direct, Catalytic, and Regioselective Synthesis of 2-Alkyl-, Aryl-, and Alkenyl-Substituted *N*-Heterocycles from *N*-Oxides

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ⓢ Supporting Information

ABSTRACT: A one-step transformation of heterocyclic *N*-oxides to 2-alkyl-, aryl-, and alkenyl-substituted *N*-heterocycles is described. The success of this broad-scope methodology hinges on the combination of copper catalysis and activation by lithium fluoride or magnesium chloride. The utility of this method for the late-stage modification of complex *N*-heterocycles is exemplified by facile syntheses of new structural analogues of several antimalarial, antimicrobial, and fungicidal agents.
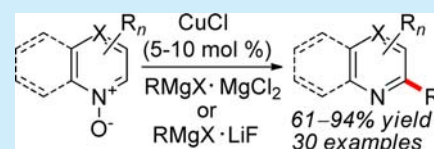
Substituted *N*-heterocycles are important structural motifs of bioactive compounds and advanced materials.[1] Hence, methods that allow for regioselective construction of C−C bonds to *N*-heterocycles have attracted continuous attention.[2] In particular, introduction of substituents in the C2-position of pyridines, quinolines, and related six-membered nitrogenous heterocycles is an important strategy in heterocyclic synthesis that represents a significant synthetic challenge.[3] One of the most commonly used strategies is based on transition-metal-catalyzed coupling reactions of organometallic reagents with 2-haloazines,[4] which are prepared from the corresponding *N*-oxides[5] (Scheme 1). However, despite its widespread use, this

Scheme 1. Methods of Synthesis of 2-Substituted *N*-Heterocycles from *N*-Oxides
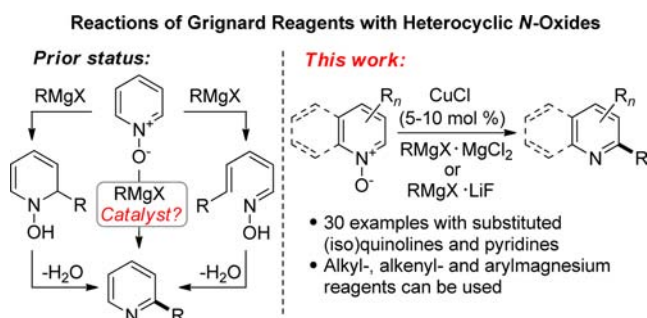
route has significant drawbacks. The synthesis of 2-haloazines from the *N*-oxides is low yielding due to poor regioselectivity. In addition, although significant progress has been achieved in the development of catalytic coupling reactions of 2-haloazines, most of the methods focus on construction of aryl−heteroaryl bonds. A more recent strategy that has been developed by Fagnou and other groups entails Pd-catalyzed CH functionalization of the heterocyclic *N*-oxides.[6] However, a reduction of the N−O bond is required to produce the corresponding 2-substituted *N*-heterocycles, and excess *N*-oxide is needed to achieve good yields. It would be, therefore, advantageous to devise a direct one-step method for regioselective conversion of

heterocyclic *N*-oxides to 2-substituted *N*-heterocycles. We herein report a coupling reaction of heterocyclic *N*-oxides with Grignard reagents that directly affords 2-aryl-, alkyl-, and alkenyl-substituted *N*-heterocycles regioselectively and in good to excellent yields.
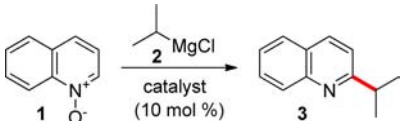
Grignard reagents have previously been known to react with heterocyclic *N*-oxides to give predominantly, depending on reaction conditions and the structure of the heterocyclic core, variable ratios of addition and ring-opening products (Scheme 1). Based on early work by Kellog,[7a] Shiess,[7b] and Kato,[8] Almqvist and Olsson[9] as well as Duan[10] have significantly improved the versatility of the method and showed that both products can subsequently be converted to 2-alkyl- and aryl-substituted *N*-heterocycles on treatment with dehydrating reagents in a stepwise fashion.

We began our study by examining the reaction between quinoline *N*-oxide and isopropylmagnesium chloride (Table 1) in diethyl ether. While formation of product **3** was not observed upon reaction of **1** and **2** in the absence of a catalyst, a yield of 53% was achieved in the presence of 10 mol % of copper(I) chloride. Iron(II) chloride was less effective, leading to complex reaction mixtures and a 36% yield of **3**. Attempts to augment the activity of the copper and iron catalysts by using phosphine, NHC, and amine ligands were not successful. Similarly, cobalt and nickel exhibited no appreciable catalytic activity (entries 5−7). Further experiments showed that copper(I) chloride was superior to other copper(I) and copper(II) salts (e.g., entries 8 and 9).

Solvents were found to have a notable effect on the reaction efficiency. Ethereal solvents (diethyl ether and methyl *tert*-butyl ether) proved to be the optimal reaction media, while formation of substantial amounts of side products was observed in tetrahydrofuran (THF), toluene (entries 10 and 11), and other nonethereal solvents. Ambient temperature (23 °C) was found to be optimal, while diminished yields of coupling

Table 1. Optimization of the Reaction Conditions.[a]

entry	catalyst	additive[b]	solvent	temp (°C)	yield (%)
1			Et$_2$O	23	0
2	CuCl		Et$_2$O	23	53
3	FeCl$_2$		Et$_2$O	23	36
4[c]	FeCl$_2$/SIMes		THF	23	0
5	CoCl$_2$		Et$_2$O	23	6
6	Ni(PPh$_3$)$_2$Cl$_2$		THF	23	3
7	NiCl$_2$·dme		Et$_2$O	23	0
8	CuCl$_2$		Et$_2$O	23	17
9	CuBr		Et$_2$O	23	21
10	CuCl		THF	23	45
11	CuCl		PhMe	23	38
12	CuCl		Et$_2$O	0	44
13	CuCl		Et$_2$O	−20	25
14	CuCl		Et$_2$O	50	42
15	CuCl	LiCl	Et$_2$O	23	67
16	CuCl	ZnBr$_2$	Et$_2$O	23	0
17	CuCl	tmeda	Et$_2$O	23	2
18	**CuCl**	**MgCl$_2$**	**Et$_2$O**	23	**95**
19	CuCl	MgF$_2$	Et$_2$O	23	37
20	**CuCl**	**LiF**	**Et$_2$O**	23	**96**

[a]Reaction conditions: 1 (0.17 mmol), 2 (1.5 equiv), catalyst (10 mol %) in solvent (1 mL) under Ar for 12 h. [b]1.5 equiv. [c]SIMes =1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene.

product 3 were observed at lower (−20 and 0 °C) and higher (50 °C, in a sealed vessel) temperatures (entries 13 and 14).

In an effort to improve the yield, we then turned our attention to additives, since it is known that the reactivity of organomagnesium[11] and organocopper[12] species can be modulated by Lewis acids and bases.

Encouragingly, addition of LiCl improved the yield to 67%. At the same time, zinc bromide and *N,N,N′,N′*-tetramethylethylenediamine (tmeda) completely suppressed the coupling (entries 16 and 17). Surprisingly, when the reaction was run in the presence of magnesium chloride, a clean conversion of *N*-oxide 1 into product 3 took place (entry 18, 95% yield). It is interesting that other magnesium salts (e.g., fluoride, entry 19) were much less effective. On the other hand, lithium fluoride exhibited comparable efficiency to magnesium chloride (entry 20).

After completion of the optimization study, we set out to explore the scope of the novel method with other Grignard reagents (16 reagents) and heterocyclic *N*-oxides (12 substrates) (Figure 1).

The reaction generally shows a broad scope for both counterparts. Thus, both primary and secondary alkylmagnesium halides proved to be suitable nucleophiles for the reaction with substituted quinoline, pyridine, and isoquinoline *N*-oxides giving rise to the corresponding products in a highly regioselective fashion.

Similarly, arylmagnesium halides afforded the desired products in good yields; e.g., the *o*-tolyl group can be installed in 61% yield. 2-Propenylmagnesium bromide also proved to be a suitable nucleophile. With respect to the *N*-oxide counterparts, quinoline, isoquinoline, pyridine, phenanthridine, pyrazine, and quinoxaline *N*-oxides are viable substrates.
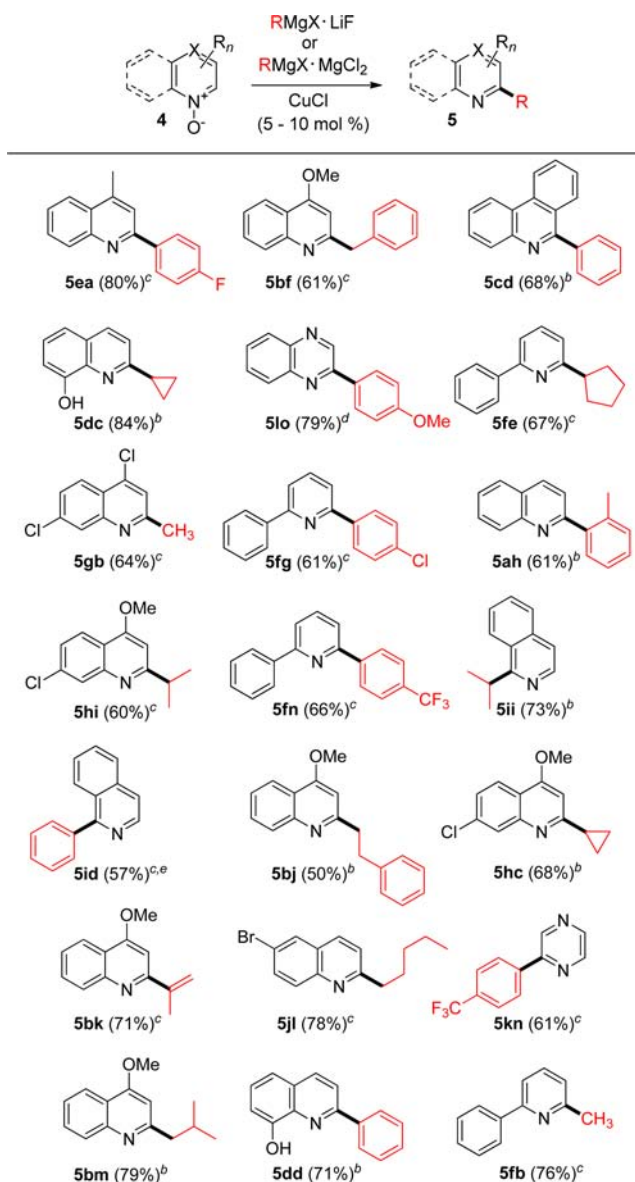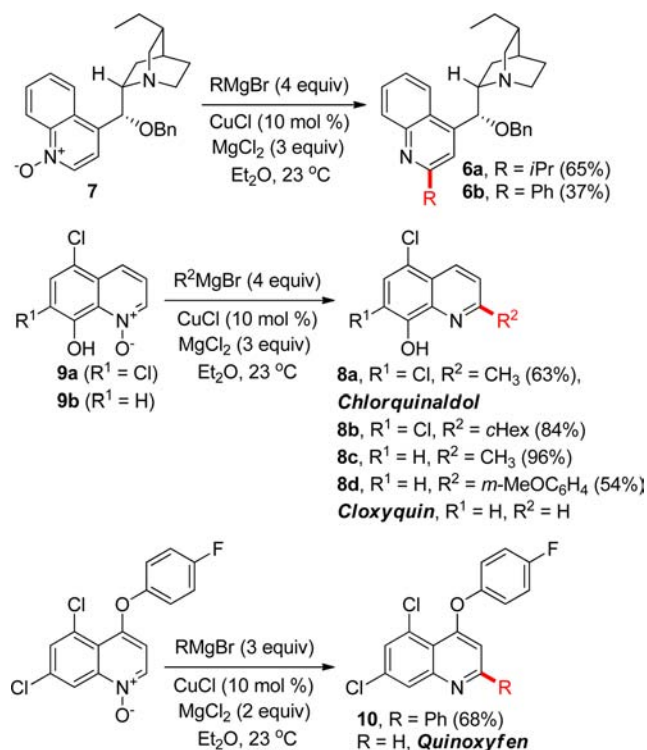

Figure 1. Scope of the Azine *N*-Oxides and Grignard Reagents. (a) Reaction conditions: 4 (0.17−1.3 mmol), RMgX (1.5−4 equiv), MgCl$_2$ or LiF (1.5−4 equiv), catalyst (5−10 mol %), Et$_2$O (*c* = 0.2 M), at 23 °C under Ar for 12 h. (b) RMgCl was used as a nucleophile. (c) The reaction was run with RMgBr. (d) RMgI was used. (e) The reaction was run with LiF as an additive.

Halogenated substrates undergo chemoselective reaction at the C2-position with Grignard reagents under these conditions, including 4-chloroquinoline that is known to be prone to facile nucleophilic displacement of the 4-chloro group.[13] The hydroxy group is also well tolerated, provided that an additional equivalent of a Grignard reagent is added. The reaction has been successfully carried out on preparative scale (e.g., 3 g of 2-phenylquinoline from 1 and phenylmagnesium chloride) with a 94% yield.

The new method has been used for the synthesis of several derivatives of biologically relevant heterocycles. 2′-Isopropyl- and 2′-phenyl-substituted dihydrocinchonidine derivatives 6a,b have been prepared from *N*-oxide 7 in 65 and 37% yields (Scheme 2).

Similarly, antimicrobial drug chlorquinaldol 8a (63%) and the 2-cyclohexyl analogue 8b (84%) have been accessed from

Scheme 2. Synthesis of 2-Substituted Derivatives of Cinchonidine, Chlorquinaldol, Cloxyquin, and Quinoxyfen

Scheme 3. Preparation of 2-Substituted Derivatives of Amodiaquine and Chloroquine

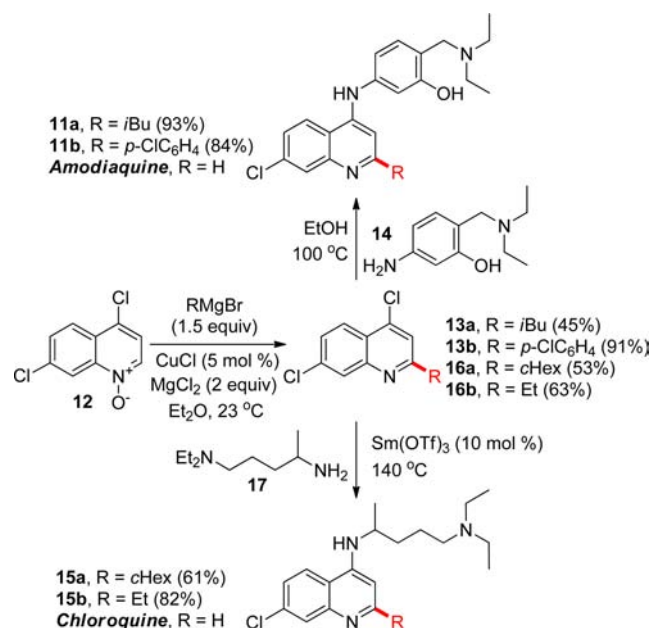late-stage modification of several antimalarial, antimicrobial, and fungicidal agents.

N-oxide **9a** as well as 2-methyl and 2-(*m*-methoxyphenyl) derivatives **8c,d** of an antimicrobial drug cloxyquin from *N*-oxide **9b**. In addition, the 2-phenyl derivative of selective agrochemical fungicide quinoxyfen (Quintec) **10** has been prepared in 68% yield.

The chemoselective preference for the C2-addition in 4-chloroquinoline *N*-oxides has been exploited for a regioselective synthesis of new structural analogues of antimalarial drugs amodiaquine and chloroquine (Scheme 3). Both 4-amino-quinolines have long been considered as the most important drugs for the treatment and prophylaxis of malaria.[14] However, the emergence of widespread parasite resistance to these drugs in every region where *P. falciparum* is prevalent has spurred interest in new 4-aminoquinolines with improved pharmaco-logical profiles.[15] In addition, chloroquine has recently demonstrated promising antitumor,[16] antirheumatic,[17] and antiviral activities.[18]

The amodiaquine derivatives **11a,b** were prepared in 42 and 77% combined yields from *N*-oxide **12** in two steps. The copper-catalyzed reaction with a Grignard reagent and magnesium chloride was followed by a condensation of quinolines **13** with aniline **14**. Similarly, chloroquine derivatives **15a,b** that bear 2-cyclohexyl and 2-ethyl groups have been synthesized in two steps by way of converting *N*-oxide **12** into quinolines **16**, followed by a samarium triflate catalyzed displacement reaction with amine **17**.

In conclusion, we have developed a direct catalytic synthesis of 2-substituted nitrogenous heterocycles from Grignard reagents and *N*-oxides. Magnesium chloride and lithium fluoride have been identified as additives that drastically improve the chemoselectivity of the reaction. The reported transformation of heterocyclic *N*-oxides to 2-substituted heterocycles can be used to access heterocyclic scaffolds of practical synthetic and medicinal value as exemplified by facile

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Notes

The authors declare no competing financial interest.

REFERENCES

(1) (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930. (b) Vieth, M.; Siegel, M. G.; Higgs, R. E.; Watson, I. A.; Robertson, D. H.; Savin, K. A.; Durst, G. L.; Hipskind, P. A. *J. Med. Chem.* **2004**, *47*, 224–232. (c) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361.

(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. (e) Ji, X.; Huang, H.; Li, Y.; Chen, H.; Jiang, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 7292–7296. (f) Hyodo, I.; Tobisu, M.; Chatani, N. *Chem.—Asian J.* **2012**, *7*, 1357–1365. (g) Zhuo, F.-F.; Xie, W.-W.; Yang, Y.-X.; Zhang, L.; Wang, P.; Yuan, R.; Da, C.-S. *J. Org.*

Chem. **2013**, 78, 3243−3249. (h) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, 130, 2448.

(3) (a) 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, 95−99. (b) Liu, B.; Huang, Y.; Lan, J.; Songa, F.; You, J. *Chem. Sci.* **2013**, 4, 2163−2167. (c) Yao, B.; Song, R.-J.; Liu, Y.; Xie, Y.-X.; Li, J.-H.; Wang, M.-K.; Tang, R.-Y.; Zhang, X.-J.; Deng, C.-L. *Adv. Synth. Catal.* **2012**, 354, 1890−1896. (d) Ren, X.; Wen, P.; Shi, X.; Wang, Y.; Li, J.; Yang, S.; Yan, H.; Huang, G. *Org. Lett.* **2013**, 15, 5194−5197.

(4) (a) Bonnet, V.; Mongin, F.; Trecourt, F.; Queguiner, G.; Knochel, P. *Tetrahedron* **2002**, 58, 4429−4438. (b) Lutzen, A.; Hapke, M. *Eur. J. Org. Chem.* **2002**, 14, 2292−2297. (c) Slagt, V. F.; de Vries, A. H. M.; de Vries, J. G.; Kellogg, R. M. *Org. Process Res. Dev.* **2010**, 14, 30−47. (d) Iglesias, M. J.; Prieto, A.; Nicasio, M. C. *Org. Lett.* **2012**, 14, 4318−4321. (e) Kuzmina, O. M.; Steib, A. K.; Flubacher, D.; Knochel, P. *Org. Lett.* **2012**, 14, 4818−4821. (f) Kuzmina, O. M.; Steib, A. K.; Markiewicz, J. T.; Flubacher, D.; Knochel, P. *Angew. Chem., Int. Ed.* **2013**, 52, 4945−4949. (g) Steib, A. K.; Kuzmina, O. M.; Fernandez, S.; Flubacher, D.; Knochel, P. *J. Am. Chem. Soc.* **2013**, 135, 15346−15349.

(5) (a) Ash, M. L.; Pew, R. G. *J. Heterocycl. Chem.* **1981**, 18, 939−940. (b) Mittelbach, M. *Synthesis* **1988**, 479−480. (c) Singh, B.; Lesher, G. Y.; Pennock, P. O. *J. Heterocycl. Chem.* **1990**, 27, 1841−1842. (d) Hurst, D. T. *Adv. Heterocycl. Chem.* **1993**, 58, 227−269. (e) Constable, E. C.; Seddon, K. R. *Tetrahedron* **1983**, 39, 291−295. (f) Koenig, T.; Wieczorek, J. S. *J. Org. Chem.* **1968**, 33, 1530−1532. (g) Vozza, J. *J. Org. Chem.* **1962**, 27, 3856−3860. (h) Yamanaka, H.; Arak, T.; Sakamoto, T. *Chem. Pharm. Bull.* **1988**, 36, 2244−2247. (i) Wengryniuk, S. E.; Weickgenannt, A.; Reiher, C.; Strotman, N. A.; Chen, K.; Eastgate, M. D.; Baran, P. S. *Org. Lett.* **2013**, 15, 792−795.

(6) (a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, 127, 18020. (b) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, 45, 7781−7786. (c) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2007**, 46, 8872. (d) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, 130, 9254−9256. (e) Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y. *J. Am. Chem. Soc.* **2009**, 131, 13888−13889. (f) Xiao, B.; Liu, Z.-J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, 135, 616−619.

(7) (a) Kellogg, R. M.; Van Bergen, T. J. *J. Org. Chem.* **1971**, 36, 1705−1708. (b) Schiess, P.; Ringele, P. *Tetrahedron Lett.* **1972**, 311−312.

(8) Kato, T.; Yamanaka, H. *J. Org. Chem.* **1965**, 30, 910−913.

(9) (a) Hussain, M.; Banchelin, T. S.-L.; Andersson, H.; Olsson, R.; Almqvist, F. *Org. Lett.* **2013**, 15, 54−57. (b) Andersson, H.; Olsson, R.; Almqvist, F. *Org. Biomol. Chem.* **2011**, 9, 337−346. (c) Andersson, H.; Banchelin, T. S.-L.; Das, S.; Gustafsson, M.; Olsson, R.; Almqvist, F. *Org. Lett.* **2010**, 12, 284−286. (d) Andersson, H.; Banchelin, T.S.-L.; Das, S.; Olsson, R.; Almqvist, F. *Chem. Commun.* **2010**, 46, 3384−3386. (e) Andersson, H.; Gustafsson, M.; Bostrom, D.; Olsson, R.; Almqvist, F. *Angew. Chem., Int. Ed.* **2009**, 48, 3288−3291. (f) Andersson, H.; Wang, X.; Bjorklund, M.; Olsson, R.; Almqvist, F. *Tetrahedron Lett.* **2007**, 48, 6941−6944. (g) Andersson, H.; Almqvist, F.; Olsson, R. *Org. Lett.* **2007**, 9, 1335−1337.

(10) (a) Zhang, S.; Liao, L. Y.; Zhang, F.; Duan, X. F. *J. Org. Chem.* **2013**, 78, 2720−2725. (b) Zhang, F.; Zhang, S.; Duan, X.-F. *Org. Lett.* **2012**, 14, 5618−5620. (c) Zhang, F.; Duan, X.-F. *Org. Lett.* **2011**, 13, 6102−6105.

(11) (a) Farkas, J. J.; Stoudt, S. J.; Hanawalt, E. M.; Pajerski, A. D.; Richey, H. G. *J. Organometallics* **2004**, 23, 423−427. (b) Hanawalt, E. M.; Farkas, J. J.; Richey, H. G. *J. Organometallics* **2004**, 23, 416−422. (c) Westerhausen, M. *Dalton Trans.* **2006**, 40, 4755−4768.

(12) (a) Kleijn, H.; Elsevier, C. J.; Westmijze, H.; Meijer, J.; Vermeer, P. *Tetrahedron Lett.* **1979**, 3101−3102. (b) Marfat, A.; McGuirk, P. R.; Helquist, P. *J. Org. Chem.* **1979**, 44, 3888−3901. (c) Davies, R. P. *Coord. Chem. Rev.* **2011**, 255, 11−12.

(13) (a) Pino, P.; Piccolo, O.; Straub, B.; Consiglio, G.; Dich, C. T. *Helv. Chim. Acta* **1982**, 65, 2102−2109. (b) Wendeborn, S.; Winkler, T.; Foisy, I. *Tetrahedron Lett.* **2000**, 41, 6387−6391. (c) Matsumoto, K.; Kannami, M.; Inokuchi, D.; Kurata, H.; Kawase, T.; Oda, M. *Org. Lett.* **2007**, 9, 2903−2906.

(14) O'Neill, P. M.; Barton, V. E.; Ward, S. A.; Chadwick, J. In *Treatment and Prevention of Malaria*; Staines, H. M., Krishna, S., Eds.; Springer: Basel, 2012; pp 19−44.

(15) (a) Winstanley, P. A.; Ward, S. A.; Snow, R. W. *Microb. Infect.* **2002**, 4, 157−164. (b) Martin, R. E.; Marchetti, R. V.; Cowan, A. I.; Howitt, S. M.; Bröer, S.; Kirk, K. *Science* **2009**, 325, 1680−1682.

(16) Solomon, V. R.; Lee, H. *Eur. J. Pharmacol.* **2009**, 625, 220−233.

(17) Augustijns, P.; Geusens, P.; Verbeke, N. *Eur. J. Clin. Pharmacol.* **1992**, 42, 429−433.

(18) Savarino, A.; Di, T. L.; Donatelli, I.; Cauda, R.; Cassone, A. *Lancet Infect. Dis.* **2006**, 6, 67−69.