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NHC−Iron-Catalyzed Aerobic Oxidative Aromatic Esterification of Aldehydes using Boronic Acids

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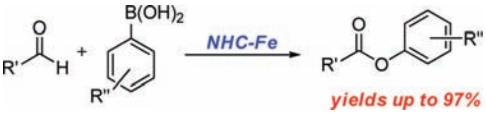
ABSTRACT



NHC−iron complexes prepared in situ very efficiently afforded benzoates via the aerobic oxidative aromatic esterification of aldehydes with boronic acids. This method uses equimolar amounts of both the aldehyde and the boronic acid allowing the preparation of benzoates in yields up to 97%.

N-Heterocyclic carbenes (NHCs), which are neutral, two-electron donor (σ-donating) species with reduced π-back-bonding tendency, are very useful ligands for homogeneous catalysis mediated by transition metals such as palladium, rhodium, platinum, or ruthenium.[1] Despite the immense utility of these catalytic systems, precious metals are quite expensive and often very toxic, which constitutes a serious drawback, namely in the context of large-scale production. Therefore, the discovery of old and new reactions catalyzed by cheap and nontoxic metals such as iron has become a major goal for organic chemistry.[2]

Ligands play a pivotal role in the modulation of the metal center reactivity. This is particularly true for iron as it displays different oxidation states and is amenable to ligation with nitrogen-, oxygen-, or phosphine-based ligands.[2] Over the years, NHCs have been generally overlooked as ligands for catalysis based on iron complexes.[1a] This reality is changing, and among the recent reports on this topic,[3] the highly successful cross-coupling reaction of Grignard reagents with aryl and heteroaryl halides to give unsymmetrical biaryls catalyzed by iron fluorides, and a saturated NHC ligand (SIPr) disclosed by Nakamura et al. has brought NHCs ligands into the limelight of iron catalysis.[4]

In line with our interest in this family of ligands,[5] we initiated a program in order to evaluate NHC−Fe systems

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(1) (a) González, S. D.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612. (b) Hahn, F. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 1348. (c) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (d) N-Heterocyclic Carbenes in Transition Metal Catalysis. In *Topics in Organometallic Chemistry*; Glorius, F., Ed.; Springer: Berlin, Heidelberg, 2007; Vol. 21. (e) *N-Heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; Wiley-VCH: Weinheim, 2006. (f) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem.* **2008**, *47*, 3317.

(2) (a) Bolm, C.; Legros, J.; Paih, J. L.; Zani, L. *Chem. Rev.* **2004**, *114*, 6217. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 1364. (c) Czaplik, W. M.; Mayer, M.; Cvengrš, J.; von Wangelin, A. J. *ChemSusChem* **2009**, *2*, 396.

(3) (a) Scepaniak, J. J.; Youg, J. A.; Bontchev, R. P.; Smith, J. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1364. (b) Liu, B.; Xia, Q.; Chen, W. *Angew. Chem., Int. Ed.* **2009**, *48*, 5513. (c) Danopoulos, A. A.; Wright, J. A.; Motherwell, W. B. *Chem. Commun.* **2005**, 784. (d) Louie, J.; Grubbs, R. H. *Chem. Commun.* **2000**, 1479. (e) McGuinness, D. S.; Gibson, V. C.; Steed, J. W. *Organometallics* **2004**, *23*, 6288. (f) Hatakeyama, T.; Nakamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 9844. (g) Plietker, B.; Dieskau, A.; Möws, K.; Jatsch, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 198.

(4) Hatakeyama, T.; Hashimoto, S.; Ishizuka, K.; Nakamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 11949.

(5) (a) Gois, P. M. P.; Trindade, A. F.; Veiros, L. F.; Andre, V.; Duarte, M. T.; Afonso, C. A. M.; Caddick, S.; Cloke, F. G. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 5750. (b) Trindade, A. F.; Gois, P. M. P.; Veiros, L. F.; Andre, V.; Duarte, M. T.; Afonso, C. A. M.; Caddick, S.; Cloke, F. G. N. *J. Org. Chem.* **2008**, *73*, 1076. (c) Esposito, O.; Gois, P. M. P.; Lewis, A. K.; de, K.; Caddick, S.; Cloke, F. G. N.; Hitchcock, P. B. *Organometallics* **2008**, *27*, 6411. (d) Gomes, L. F. R.; Trindade, A. F.; Candeias, N. R.; Gois, P. M. P.; Afonso, C. A. M. *Tetrahedron Lett.* **2008**, *49*, 7372.

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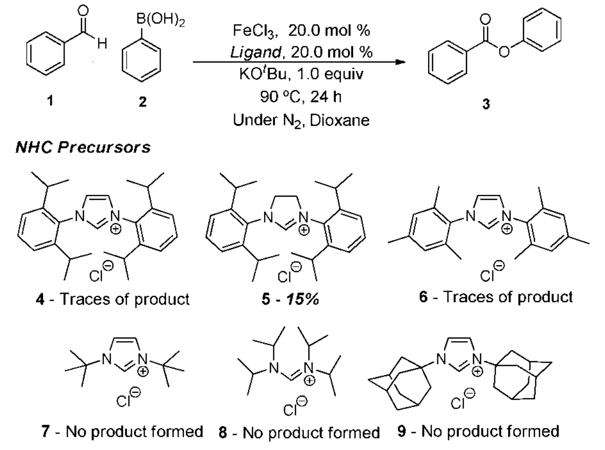
Scheme 1. Ligand Evaluation Using $FeCl_3$ as the Iron Source

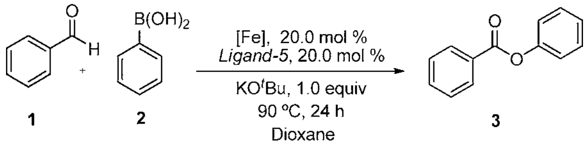


as catalysts for the direct oxidative aromatic esterification of aldehydes.

The ester functionality is present ubiquitously in the structure of important natural and synthetic molecules and for this reason constitutes an important synthetic target. The existent strategies to prepare carboxylic esters under mild conditions usually involve the activation of the carboxylic acid as an acyl halide, anhydride, or activated ester followed by nucleophilic substitution. The direct oxidative esterification of aldehydes remains as an attractive possibility to readily access esters.[6] Recently, Darcel et al. reported the one-pot oxidative esterification of aldehydes using $Fe(ClO_4)_3{\cdot}xH_2O$ and H_2O_2 in the presence of different alcohols.[7] Less attention though has been paid to the synthesis of aryl benzoate derivatives despite their importance as building blocks of numerous active compounds and as cross coupling partners.[8] Usually, these compounds are prepared via esterification or transesterification reactions which normally involve strong acidic or basic conditions limiting the reaction scope.[9] The Baeyer−Villiger oxidation reaction is another classical method to prepare benzoate derivatives though low regioselectivities are obtained when asymmetric benzophenoes derivatives are used.[10] Fully aware of these limitations Wu, Cheng et al. reported the NHC−palladium-catalyzed aromatic esterification of aldehydes with boronic acids in toluene at 120 °C under air.[8] Despite the vast potential of this reaction, only modest yields were obtained, typically between 5 and 68%. Therefore, we envisioned that iron could be a more successful catalyst than palladium for this important transformation as iron is known for its rich redox chemistry.[11]

We initiated our study reacting benzaldehyde with phenylboronic acid in the presence of NHC precursor **4** and $FeCl_3$ in dioxane at 90 °C and under a N_2 atmosphere. Very disappointingly, we only detected the formation of ester **3** in traces amounts. Screening different ligands, the yield of **3** was improved to 15% when using imidazolium **5**. Bulkier NHCs generated from **7**−**9** afforded no product (Scheme 1).

Table 1. Iron Source Evaluation Using NHC Precursor **5**



entry	ligand	iron source	yield[a] (%)
1	5	$FeCl_3$	41
2	5	$FeCl_3{\cdot}6H_2O$	39
3	5	$FeCl_2{\cdot}4H_2O$	62
4	5	$Fe(OTf)_2$	95
5	5	$Fe(NO_3)_3{\cdot}9H_2O$	22
6	5	TPPFeCl	no product
7	5	$Fe(acac)_2$	no product
8	no ligand	$Fe(OTf)_2$	no product
9	5	No iron	no product
10[b]	5	$Fe(OTf)_2$	80
11[c]	5	$Fe(OTf)_2$	48
12[d]	5	$Fe(OTf)_2$	76
13[e]	5	$CuSO_4{\cdot}5H_2O$	no product

[a] Isolated yield after preparative thin-layer chromatography (hexanes/AcOEt). Reaction conditions: benzaldehyde (0.247 mmol), phenylboronic acid (0.247 mmol), iron (20.0 mol %), **5** (20.0 mol %), KO*t*Bu (0.247 mmol), dioxane 1.5 mL, 90 °C for 24 h. [b] The same reaction conditions as in footnote *a* with the following exception: 80 °C for 24 h. [c] The same reaction conditions as in footnote *a* with the following exception: iron (10.0 mol %) and **5** (10.0 mol %). [d] The same reaction conditions as in footnote *a* with the following exception: iron (15.0 mol %) and **5** (15.0 mol %). [e] The same reaction conditions as in footnote *a* with the following exception: $CuSO_4{\cdot}5H_2O$ (20.0 mol %).

Having identified the most efficient ligand, we performed exactly the same reaction under air. The presence of air was crucial for this reaction as the yield was improved up to 41% (Table 1, entry 1). Performing the reaction using Schlenk line techniques, no product was obtained. Therefore, the screening of different iron sources was carried out in the presence of air (Table 1, entries 2−7). Very gratifyingly, $Fe(OTf)_2$ afforded the desired ester in 95% isolated yield using equimolar amounts of benzaldehyde and phenylboronic acid. The importance of both the ligand and the iron source was undoubtedly demonstrated as without one of them the

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(6) Kovi, K. E.; Wolf, C. *Chem.*−*Eur. J.* **2008**, *14*, 6302.

(7) Wu, X.-F.; Darcel, C. *Eur. J. Org. Chem.* **2009**, 1144.

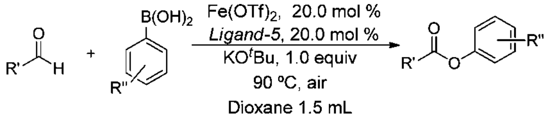
(8) Qin, C.; Wu, H.; Chen, J.; Liu, M.; Cheng, J.; Su, W.; Ding, J. *Org. Lett.* **2008**, *10*, 1537.

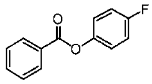
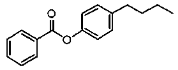
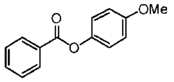
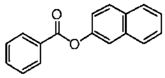
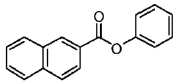
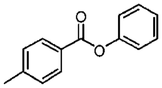
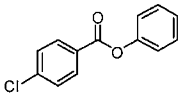
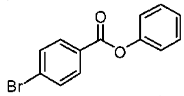
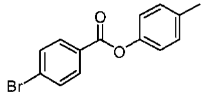
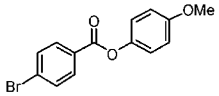
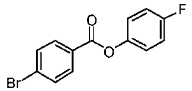
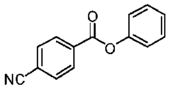
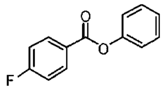
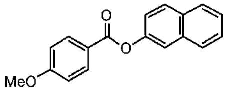
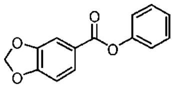
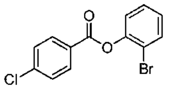
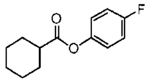
(9) (a) Sarvari, M. H.; Sharghi, H. *Tetrahedron* **2005**, *61*, 10903. (b) Tamaddon, F.; Amrollahi, M. A.; Sharafat, L. *Tetrahedron Lett.* **2005**, *46*, 7841. (c) Shah, S. T. A.; Khan, K. M.; Hussain, H.; Anwar, M. U.; Fecker, M.; Voelter, W. *Tetrahedron* **2005**, *61*, 6652. (d) Oohashi, Y.; Fukumoto, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1508.

(10) (a) Olah, G. A.; Wang, Q.; Trivedi, N. J.; Prakash, G. K. S. *Synthesis* **1991**, 739. (b) Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Narsaiah, A. V. *Chem. Lett.* **2004**, *33*, 248. (c) Kotsuki, H.; Arimura, K.; Araki, T.; Shinohara, T. *Synlett* **1999**, 462. (d) Toda, F.; Yagi, M.; Kiyoshige, K. *J.Chem. Soc., Chem. Commun.* **1988**, 958.

(11) Selected examples: (a) Li, Y. Z.; Li, B.-J.; Lu, X.-Y.; Lin, S.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3817. (b) Li, Z.; Yu, R.; Li, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7497. (c) Shi, F.; Tse, M. K.; Li, Z.; Beller, M. *Chem.*−*Eur. J.* **2008**, *14*, 8793. (d) Nakanishi, M.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 861. (e) Meyer, N. J.; Lough, A. J.; Morris, R. H. *Chem.*−*Eur. J.* **2009**, *15*, 5605.

Table 2. Methodology Scope Using the Optimized Conditions



Entry	Product	Yield[a]
1		**10** - 91%[b]
2		**11** - 72%
3		**12** - 97%
4		**13** - 92%[b]
5		**14** - 85%
6		**15** - 85%
7		**16** - 89% **16** - 73%[c]
8		**17** - 71%
9		**18** - 81%[d]
10		**19** - 64%
11		**20** - 70%
12		**21** - 75%
13		**22** - 80%
14		**23** - 80%
15		**24** - 72%
16		**25** - 15%
17		**26** - 53%

[a] Isolated yield after preparative thin-layer chromatography (hexanes/AcOEt). Reaction conditions: aldehyde (0.247 mmol), boronic acid (0.247 mmol), $Fe(OTf)_2$ (20.0 mol %), **5** (20.0 mol %), KO^{t}Bu (0.247 mmol), dioxane 1.5 mL, 90 °C for 24 h. [b] Reaction time = 6 h. [c] The reaction was performed on a 1 mmol scale maintaining the standard reaction conditions. [d] 1.2 equiv of boronic acid was used.

reaction simply fails (Table 1, entries 8 and 9). Decreasing the temperature and the quantity of iron was also detrimental for the yield (Table 1, entries 10−12). Finally, no product was formed when a copper source instead of iron was used (Table 1, entry 13).

With the optimum reaction conditions at hand, the protocol was extended to different aldehydes. As shown in Table 2, the aerobic oxidative aromatic esterification of benzaldehyde proceeded in good to excellent yieds using boronic acids regardless of their electonic nature (Table 2, entries 1−5). The reaction was also quite tolerant concerning the electronic nature of the aldehyde aryl substituents. For instance, 4-cyanobenzaldehyde and 4-fluorobenzaldehyde afforded the ester in 75% and 80% yield, respectively (Table 2, entries 12 and 13), and aldehydes bearing electron-donating substituents such as piperonal or 4-methoxybenzaldehyde were readily converted in the esters in yields up to 80% (Table 2, entries 14 and 15). Conversely, ortho substitution in the boronic acid resulted in a poor yield of ester **25** (Table 2, Entry 16). Finally, cyclohexanecarboxaldehyde was also converted into the corresponding phenyl ester, proving that this protocol is not exclusive for aromatic aldehydes (Table 2, entry 17).

Recently, Li et al. reported the 1,2-addition of boronic acids to electron-deficient aryl aldehydes in the presence of $FeCl_3$ and a phosphine ligand.[12] This clearly shows that the NHC ligand plays a crucial role in the aerobic oxidative aromatic esterification of aldehydes.[13] As shown in Table 1, entry 9, when NHC was used without an iron source no ester was formed. Apart from the aldehyde, which was isolated in 53% yield, and benzoic acid, no other products were isolated from the reaction mixture. This result indicates that the NHC is most probably involved in the in situ generation of a catalytic active NHC−iron complex.

In order to probe the reaction mechanism, we performed the reaction between benzaldehyde and phenylboronic acid in the presence of $H_2{}^{18}O$. The existence of water in the media was quite detrimental for the reaction yield as the ester **3** was obtained in only 10% yield. The ESI-MS and MS^2 spectrum of the ester **3** revealed the incorporation of ^{18}O (2:1) in the $[Ph-C{=}^{18}O]^+$ fragment. This incorporation probably results from the in situ isotopic labeling of the aldehyde with $H_2{}^{18}O$ prior to the reaction and indicates that the carbonyl functionality is the same in the aldehyde and ester. This result suggests that the sequence of events is not the oxidation of the aldehyde to the carboxylic acid followed by a cross coupling with the boronic acid. This was further demonstrated by the unsuccessful attempt of reacting benzoic acid with phenylboronic acid (Scheme 2). Furthermore, when the alcohol **28** was submitted to our catalytic system it afforded a rather complex mixture in which no ester was identified; indeed, the major product formed was the ketone

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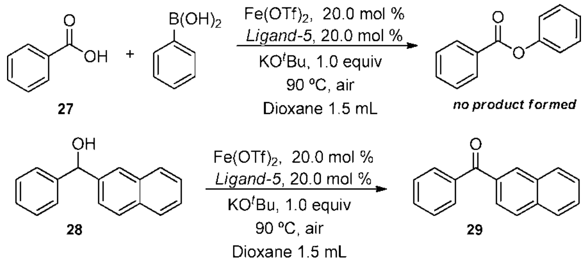
(12) Zou, T.; Pi, S.-S.; Li, J. H. *Org. Lett.* **2009**, *11*, 453.

(13) Selected examples: (a) Yu, H.; Fu, Y.; Guo, Q.; Lin, Z. *Organometallics* **2009**, *28*, 4443. (b) Popp, B. V.; Wendlandt, J. E.; Landis, C. R.; Stahl, S. S. *Angew. Chem.* **2007**, *46*, 601. (c) Gligorich, K. M.; Sigman, M. S. *Chem. Commun.* **2009**, 3854. (d) Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006**, *39*, 221. (e) Urkan, K. B.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 3146.

29 in 21% yield (Scheme 2). This clearly highlighted the fact that the ester formation does not occur via the 1,2-addition of boronic acids to aldehydes.

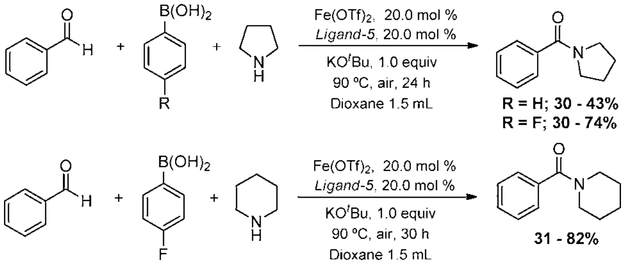
Scheme 2. Attempts To Prepare Aryl Benzoate from Benzoic Acid and Aromatic Secondary Alcohols



Finally, in our standard reaction conditions (without aldehyde) we did not observe a clear conversion of boronic acid into phenol, though when we performed the reaction between phenol and benzaldehyde under the optimized reaction conditions, the ester **3** was obtained in 88% suggesting that phenol may indeed be an intermediate of this transformation. On the basis of the aforementioned, a plausible mechanism for the benzoate esters formation may involve the in situ generation of phenol species from the boronic acid followed by the oxidative esterification of the aldehyde.

Once the synthesis of this family of compounds was established, we considered that the aryl benzoate could also be used as a scaffold to prepare other molecules via displacement of the phenol moiety. Therefore we attempted the one-pot synthesis of amides directly from the aldehyde. By simply adding an amine to the reaction mixture we were able to convert the aldehyde into amides **30** and **31** (Scheme 3). This transformation proceeds via the ester formation followed by the reaction with the amine. This was demonstrated by the fact that no reaction took place in the absence of boronic acid and a less reactive ester, formed with phenylboronic acid, afforded the amide **30** in only 43%.

Scheme 3. One-Pot Synthesis of Amides



In summary, we have developed an efficient methodology to prepare benzoates and amides via the aerobic oxidative aromatic esterification of aldehydes catalyzed by NHC−Fe using boronic acids. This method uses equimolar amounts of both the aldehyde and the boronic acids affording the desired benzoates in yields up to 97%. The relatively mild conditions, the use of air as the oxidant, and the possibility of using aldehydes with multiple electronic profiles including the alkylic ones constitutes a considerable improvement over the existing methods.

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

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