

NHC/Iron cooperative catalysis: aerobic oxidative esterification of aldehydes with phenols†‡

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Received 27th January 2011, Accepted 1st March 2011

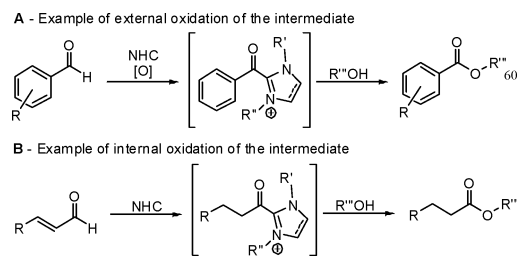
DOI: 10.1039/c1ob05151b

An NHC/iron cooperative catalytic system mediates the aerobic oxidative esterification of aldehydes with phenols. The use of equimolar amounts of reactants led to good to excellent isolated yields of esters.

Over the years *N*-heterocyclic carbenes (NHCs) have gained an important position within the field of catalysis, acting both as ligands for a variety of metal centres,¹ often yielding highly active catalysts,^{1,2} and as organocatalysts, especially for carbonyl group activation.³ In particular, umpolung of aldehyde groups to acyl anion equivalents is a well-established mode of NHC catalysis. Recently, the excellent ligand properties and organocatalytic activity of NHCs were further expanded with the discovery that NHCs and metals such as Ag, Ti, Mg and Pd can be involved in cooperative catalysis.⁴ Despite their high potential, cooperative methodologies are quite challenging due to the requirement for fine tuning of the Lewis basic and Lewis acidic properties of the catalysts.⁵ This is particularly challenging when using NHCs due to their exceptionally strong donor properties.⁶ Based on this we designed a study to test the possibility of iron, a metal currently at the centre of intense research,⁷ being used in conjunction with NHCs for cooperative metal/organocatalytic reactions.⁴⁻⁶

In recent years, the oxidative esterification of aldehydes with alcohols using NHC catalysts has been reported, opening a

new area of application of these versatile organocatalysts.³ In earlier work, the oxidation of the intermediate generated from the addition of the NHC to the aldehyde functionality has been achieved by coupling it with a reduction occurring elsewhere in the molecule. Examples include, saturation of the conjugated double bond in an α,β -unsaturated aldehyde,⁸ replacement of a leaving group by hydrogen,⁹ or a reductive ring opening.¹⁰ Alternatively, an external oxidizing agent may act as the terminal electron acceptor in this process (Scheme 1).



Scheme 1 Examples of the oxidation of the intermediate generated from the addition of the NHC to the aldehyde.

In previous work, a number of oxidants, such as MnO_2 ¹¹ and organic electron acceptors,¹² have been used to carry out the aldehyde to ester conversion. These methodologies normally use an excess of both oxidant and alcohol (5 to 10 fold excess). Such oxidative esterification methods have been mostly applied to alkyl aldehydes, despite the synthetic utility of aryl benzoates. Aryl benzoates have been prepared *via* the reaction of acyl halides, anhydrides or activated esters with phenol derivatives or *via* the esterification or transesterification reactions catalysed by strong acids or bases which considerably limit the reaction scope. Further methods for the synthesis of benzoates include the Baeyer–Villiger oxidation reaction, although low regioselectivities are obtained when asymmetric benzophenone derivatives are used.¹³ Thus, a catalysed process that allows the efficient direct esterification of aldehydes with phenols is highly desirable.

Recently we found that a NHC/iron catalytic system enables the aerobic oxidative coupling reaction between aldehydes and boronic acids in high yields using equimolar amounts of both reactants (Scheme 2).¹⁴

Extensive mechanistic studies carried out on this reaction suggested that phenol could be a possible intermediate in this reaction.¹⁴ Therefore, we initiated a study to establish the direct

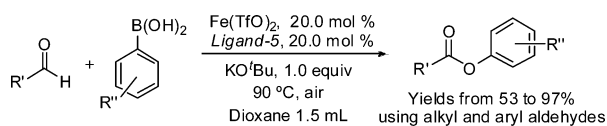
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† Electronic supplementary information (ESI) available: Computational details, the corresponding list of references and atomic coordinates for all optimised species and ¹H and ¹³C spectra of all compounds. See DOI: 10.1039/c1ob05151b

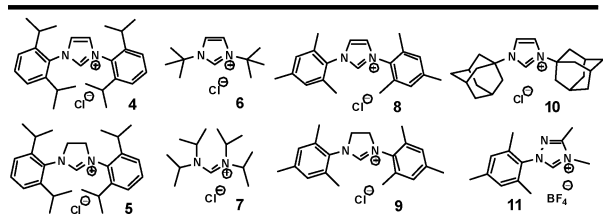
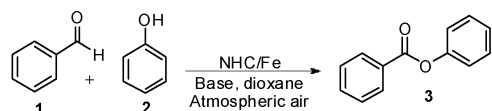
‡ **General method:** To a round bottom flask under N_2 freshly dried dioxane over sodium (1.5 mL), NHC ligand precursor (20 mol%) and sublimed KO^tBu or dried K_2CO_3 (0.247 mmol) were added. The mixture was allowed to react at room temperature for 20 min., after which $\text{Fe}(\text{TiO})_2$ or anhydrous FeCl_3 (20 mol%) was also added. The mixture was left reacting 5 min. at room temperature and then the phenol (0.25 mmol) and the aldehyde (0.25 mmol) were sequentially added. The N_2 atmosphere was removed and the mixture was heated at 90 °C. Typically, after a reaction time of 24 h the volatiles were removed under reduced pressure and the product isolated by preparative thin layer chromatography (Hexanes:AcOEt).



Scheme 2 Aerobic oxidative esterification of aldehydes with boronic acids.

oxidative esterification of aldehydes with phenols, catalyzed by a NHC/iron system using atmospheric O₂ as the terminal oxidant.

We began our study by evaluating the salts **4–10** as the NHC precursor using iron(II) triflate as the iron source (Scheme 3). Gratifyingly, **5** afforded the benzoate ester **3** in 82% yield using equimolar amounts of benzaldehyde and phenol (Table 1, entry 2). It is noteworthy that of the range of NHC precursors evaluated, only the N,N'-biarylimidazolium or imidazolium showed activity. The selection of the base also plays a pivotal role in the reaction efficiency. Simple tertiary amines such as triethylamine or DIPEA were unable to promote the reaction, and only anionic oxygen bases such as potassium *tert*-butoxide and potassium carbonate showed activity. Interestingly, replacing the phenol + base by preformed phenoxide anion led to degradation in yield (Table 1, entries 11–14). Decreasing the temperature or the quantity of iron was also detrimental for the yield (Table 1, entries 3 and 15–17). More importantly, the reaction did not proceed without the presence of **5** (Table 1, entry 18). On the other hand, without the iron source the benzoate ester **3** was isolated in 17% and 20% when using **5** and **9** respectively (Table 1, entries 1 and 4). These results clearly indicate that the NHC is involved in the activation of the aldehyde, though it is unable to deliver high yields of the benzoate ester **3** in the absence of the metal source.



Scheme 3 NHC–Fe catalysed oxidative aromatic esterification of aldehydes using phenols and imidazolium salts tested.

Once the optimized system had been established, we proceeded to evaluate the generality of our method using a number of substituted phenols and aldehydes (Table 2). As shown in Table 2, moderate to high yields (up to 89%) were obtained for a variety of aldehyde/phenol combinations. Aryl aldehydes are considerably more reactive than alkylic examples (Table 2, entry 19). From the results obtained, it is clear that the substitution pattern in the phenol plays an important role in the reactivity. For example the sterically hindered phenol **2f** (51%) displays a significantly reduced reactivity when compared with *para*-chloro substituted phenol **2d** (82%) (Table 2, entries 11 and 13). The same trend is observed when using hindered aryl aldehydes. The *ortho*-substituted aldehyde **1j** is quite unreactive presumably due to steric constraints imposed by the bulky NHC **5** used (Table 2, entry 17).

Table 1 Evaluation of the reaction conditions

Entry	NHC Precursor	Fe Source	Base	Yield ^a
1	5	None	^t BuOK	17%
2	5	Fe(OTf) ₂	^t BuOK	82%
3	5	Fe(OTf) ₂	^t BuOK	63% (70 °C)
4	9	None	^t BuOK	20%
5	9	Fe(OTf) ₂	^t BuOK	56%
6	4	None	^t BuOK	Traces
7	4	Fe(OTf) ₂	^t BuOK	22%
8	8	None	^t BuOK	Traces
9	8	Fe(OTf) ₂	^t BuOK	Traces
10	5	Fe(OTf) ₂ ^b	^t BuOK	89%
11	5	Fe(OTf) ₂	DIPEA	Traces
12	5	Fe(OTf) ₂	K ₂ CO ₃	77%
13	5	Fe(OTf) ₂	TEA	Traces
14	5	Fe(OTf) ₂	None ^c	40%
15	5 (5%)	Fe(OTf) ₂ (5%)	^t BuOK	Traces
16	5 (10%)	Fe(OTf) ₂ (10%)	^t BuOK	45%
17	5 (15%)	Fe(OTf) ₂ (15%)	^t BuOK	52%
18	None	Fe(OTf) ₂	^t BuOK	n.r.
19	PPh ₃	Fe(OTf) ₂	^t BuOK	n.r.
20	P ⁿ Bu ₃	Fe(OTf) ₂	^t BuOK	n.r.

^a Isolated yields. ^b Fe(OTf)₂ prepared from pure iron. ^c Preformed potassium phenoxide was used instead of phenol, also serving as base.

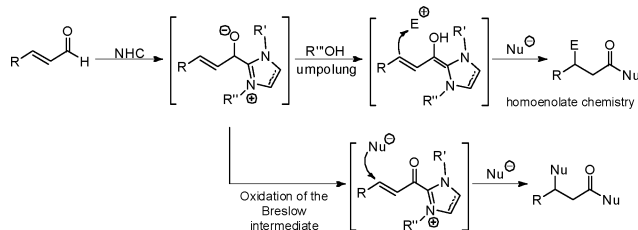
Table 2 Oxidative esterification of aldehydes and phenols

Entry	Aldehyde R ^a	Phenol R' ^b	Product	Yield ^c
1	Ph (1a)	H (2a)	3a	84% (74%) ^c
2	4-Cl-Ph (1b)	H (2a)	3b	77%
3	4-OMe-Ph (1c)	2b	3c	62%
4	4-Br-Ph (1d)	H (2a)	3d	59%
5	4-F-Ph (1e)	H (2a)	3e	82%
6	4-CN-Ph (1f)	H (2a)	3f	55%
7	4-Me-Ph (1g)	H (2a)	3g	85%
8	2-Naph (1h)	H (2a)	3h	89%
9	Ph (1a)	2b ^d	3i	83%
10	4-Br-Ph (1i)	4-Me (2c)	3j	65%
11	Ph (1a)	4-Cl (2d)	3k	82%
12	Ph (1a)	4-NO ₂ (2e)	3l	88%
13	Ph (1a)	2,4-Cl (2f)	3m	51%
14	Ph (1a)	4-F (2g)	3n	86%
15	Ph (1a)	4-Br (2h)	3o	87%
16	Ph (1a)	4-CF ₃ (2i)	3p	81%
17	2-Cl-Ph (1j)	H (2a)	3q	15%
18	Ph (1a)	4-CN (2j)	3r	86%
19	Cyclohexyl (1k)	4-F (2g)	3s	32%
20	Cinnamyl (1l)	H (2a)	3t	46%

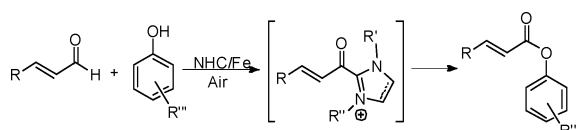
^a 1 eq. of aldehyde was used. ^b 1 eq. of phenol was used. ^c Isolated yields. ^d Instead of a substituted phenol, 2-naphthol (**2b**) was used. ^e The reaction was carried out in 0.5 mmol scale of aldehyde and phenol.

Encouraged by these results we focused on the aerobic esterification of cinnamaldehyde which has recently elicited considerable interest, as it potentially allows the *in situ* generation of an enone via oxidation, which can then undergo conjugate addition, *in lieu*

of the normal homoenolate reaction path. (Scheme 4).^{15,16} Most recently this approach was beautifully explored by Studer *et al.* with the reaction of various 1,3-dicarbonyl compounds and α,β -unsaturated aldehydes in the presence of stoichiometric amounts of the oxidant 3,3,5,5'-tetra-*tert*-butyldiphenoquinone.¹⁶ Based on this, we anticipated that under our standard conditions, the intermediate would be readily oxidised to the activated acyl group which would then react with phenol (Scheme 5).



Scheme 4 Oxidation of the intermediate resulting from the addition of NHCs to α,β -unsaturated aldehydes.



Scheme 5 NHC-Fe catalysed oxidative aromatic esterification of cinnamaldehydes using phenols.

Based on the aforementioned hypothesis we performed the reaction of cinnamaldehyde with phenol using the standard conditions developed for the arylation of aryl aldehydes. These conditions led to the desired reactivity, albeit in only 46% yield (Table 2, entry 20). Gratifyingly, using anhydrous FeCl_3 and K_2CO_3 , the yield of the ester was improved to 89%. Evaluation of the reaction scope revealed that electron donating groups in the cinnamaldehyde aromatic ring decreased the reactivity (Table 3, entries 1–3 and 6). However the phenol aromatic substitution had little impact on the reactivity and the desired esters were obtained in good to excellent yields (Table 3, entries 4–8).

We propose that the NHC adds to the aldehyde generating the intermediate I,¹⁷ which then undergoes an oxidation step mediated by an iron oxo species to form the acyl intermediate

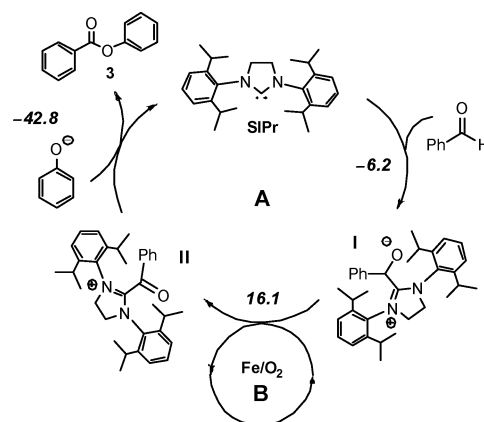
Table 3 Oxidative esterification of cinnamaldehydes and phenols

Entry	Aldehyde R ^a	Phenol R ^b	Product	Yield ^c
1	Ph (1a)	H (2a)	3t	89%
2	4-MeO-Ph	H (2a)	3u	55%
3	4-(Me) ₂ N-Ph	H (2a)	n.r.	n.r.
4	Ph (1a)	4-Br (2a)	3v	87%
5	Ph (1a)	4-Cl (2b)	3w	73%
6	4-MeO-Ph (1e)	4-Cl (2b)	3x	71%
7	Ph (1d)	4-F (2a)	3y	90%
8	Ph (1e)	3-Me (2a)	3z	84%

^a 1 eq. of aldehyde was used. ^b 1 eq. of phenol was used. ^c Isolated yields.

II.¹⁶ Subsequently, this intermediate reacts with the phenoxide to yield the aryl benzoate regenerating the NHC.

Preliminary DFT calculations¹⁸ were performed in order to gain a greater understanding of the reaction mechanism.¹⁹ The energy balance obtained for each of the three major steps of the mechanism represented in Scheme 2 (NHC from **5**, R = Ph, R' = H) indicate that only the oxidation step is thermodynamically unfavourable, ($\Delta E = 16.1 \text{ kcal mol}^{-1}$).²⁰ Both the initial attack of the NHC to benzaldehyde, yielding intermediate **I** ($\Delta E = -6.2 \text{ kcal mol}^{-1}$), as well as replacement of the NHC by phenoxide with formation of the ester and regeneration of free NHC ($\Delta E = -42.8 \text{ kcal mol}^{-1}$), correspond to exergonic reactions. According to these results, the putative role of the Fe complex as co-catalyst in the reaction, possibly through coordination of the oxidant (atmospheric O_2), represented by cycle B in Scheme 6, would take place in the less favourable step of the reaction. Of course, these are thermodynamic results and a full kinetic study is needed for an extended understanding of the reaction mechanism.



Scheme 6 Proposed catalytic cycle for the aerobic oxidative esterification of aldehydes with phenols catalysed by a NHC-Iron cooperative system. Energy balance (italics, kcal mol^{-1}) for each step obtained by DFT.

It should be noticed that calculations were performed for NHCs from precursors **4**, **5**, **8** and **9** (see Scheme 1), allowing the comparison between saturated and unsaturated NHC, on one hand, and between mesityl and 2,6-diisopropylphenyl as N-substituents, on the other. The corresponding energy balances are presented as ESI.† Unfortunately, the small differences found for the energy balance of equivalent reaction steps prevent any solidly based conclusions. In particular, the noticeable difference between the reactivity of saturated and unsaturated NHCs seems to be too subtle for the theory level employed here, with calculated ΔE values, for equivalent steps, within 2 kcal mol^{-1} (see ESI, Figure S1†).

Conclusions

In summary, we have developed an efficient methodology to prepare benzoate esters *via* the aerobic oxidative esterification of aryl aldehydes and cinnamaldehydes with phenols catalysed by a cooperative NHC/Fe system. This method uses equimolar amounts of both the aldehyde and phenol affording the desired benzoates in good to excellent yields.

Acknowledgements

The Fundação para a Ciência e Tecnologia and FEDER (PTDC/QUI-QUI/099389/2008; SFRH/BPD/46589/2008;/48219/2008; SFRH/BPD/65455/2009) are thanked for the financial support.

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