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TEMPO Oxoammonium Salt-Mediated Dehydrogenative Povarov/Oxidation Tandem Reaction of N-Alkyl Anilines

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ABSTRACT

The synthesis of a variety of substituted quinolines from N-alkyl anilines by a one-pot dehydrogenative Povarov/oxidation tandem reaction with mono- and 1,2-disubstituted aryl and alkyl olefins was developed. A simple protocol using cheap and benign iron(III)chloride as the Lewis acid catalyst and a TEMPO oxoammonium salt as a nontoxic, mild, efficient oxidant is reported.

In the past few years, Cross Dehydrogenative Coupling reactions (CDCs)[1] have been established as powerful synthetic tools, allowing the direct generation of a new C–C bond from two C–H bonds. This approach has started to revolutionize the way of tackling organic synthesis, since prefunctionalization in the reaction partners is not required and C–H bonds are ubiquitous in organic molecules. Consequently, the use of simpler starting materials, as well as the development of more atom-economic processes and the less waste generation constitute its major advance. However, one of the main issues in CDC is still the limited substrate scope, being basically restricted to more or less activated diarylmethanes or benzylic C–H bonds alpha to a heteroatom such as in tetrahydroisoquinolines or isochromanes. Recently, it has been shown that glycine derivatives[2] and N-alkyl anilines[3] are also good substrates in CDC reactions with malonates, ketones, heteroaromatic compounds, and alkynes as typical nucleophiles. However, it would be of added synthetic value to extend their use to the synthesis of more interesting N-containing compounds, such as bioactive heterocycles by employing less usual nucleophiles in CDC such as simple olefins.[4] Although the use of olefins is still scarce in this chemistry, they are widely available reagents, making them very interesting for developing general CDC reactions.

On the other hand, substituted quinolines are important scaffolds present in many biologically active compounds, including natural products and synthetic drugs.[5] As a consequence of their proven interesting bioactivity, many different strategies for the preparation of quinolines have been developed.[6] Among them, the Povarov reaction followed by oxidation is widely recognized.[6a,b,7] Nevertheless, the last oxidation step, which involves a formal removal of four hydrogens from the tetrahydroquinoline intermediate, is still challenging. Typically, harsh conditions or large amounts (e.g., MnO_2), expensive (e.g., Pd-based), or toxic oxidants (e.g., DDQ, nitrobenzene, etc.)

(1) Selected reviews: (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (b) Scheuermann, C. J. *Chem. Asian J.* **2009**, *5*, 436. (c) Klussmann, M.; Sureshkumar, D. *Synthesis* **2011**, 353. (d) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (e) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215.

(2) (a) Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7075. (b) Xie, J.; Huang, Z.-Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 10181.

(3) See, for example: (a) Li, H.; He, Z.; Guo, X.; Li, W.; Zhao, X.; Li, Z. *Org. Lett.* **2009**, *11*, 4176. (b) Han, W.; Ofial, A. R. *Chem. Commun.* **2009**, *40*, 6023. (c) Han, W.; Mayer, P.; Ofial, A. R. *Adv. Synth. Catal.* **2010**, *352*, 1667. (d) Yang, F.; Li, J.; Xie, J.; Huang, Z.-Z. *Org. Lett.* **2010**, *12*, 5214.

(4) (a) Song, C.-X.; Cai, G.-X.; Farrell, T. R.; Jiang, Z.-P.; Li, H.; Gan, L.-B.; Shi, Z.-J. *Chem. Commun.* **2009**, 6002. (b) Li, H.; Li, W.; He, Z.; Li, Z. *Angew. Chem., Int. Ed.* **2011**, *50*, 2975. (c) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 6447.

(5) See, for example: (a) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*, 2nd ed.; Wiley-VCH: Weinheim, 2003; p 316. (b) Musiol, R.; Serda, M.; Hensel-Bielowka, S.; Polanski, J. *Curr. Med. Chem.* **2010**, *17*, 1960.

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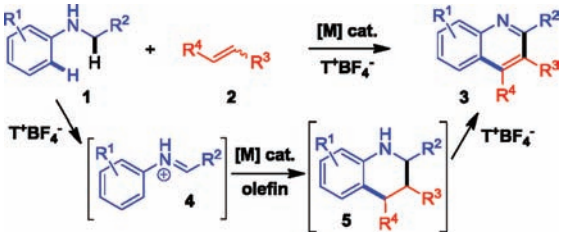
are employed. Therefore, the identification of more efficient and environmentally benign oxidants for this transformation is highly desirable.

We herein report on an alternative one-pot method for the synthesis of quinolines from N-alkyl anilines and olefins by a one-pot dehydrogenative coupling–aromatic substitution–oxidation sequence reaction using a TEMPO salt ($T^+BF_4^-$)[8,9] as a highly efficient, mild and nontoxic oxidant. This oxidant will be then involved in two dehydrogenative processes (Scheme 1): (i) the formation of an iminium ion intermediate **4**, which will undergo the CDC reaction in the presence of an olefin **2** as nucleophile and (ii) the final aromatization step of the intermediate **5** to form the quinoline unit **3**.

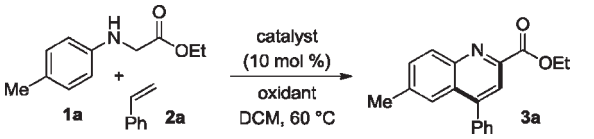
Scheme 1. One-pot Dehydrogenative Approach



Initially, the reaction between glycine **1a** and styrene (**2a**) was chosen as a model reaction and several Lewis acid metal catalysts and oxidants were tested (Table 1). Under slightly modified conditions of our recently reported CDC reaction with α,β-unsaturated aldehydes:[9b] **1a** (1 equiv), 2 equivalents of **2a**, 10 mol % of metal catalyst and 2 equivalents of $T^+BF_4^-$ as oxidant in DCM at 60 °C, the clean formation of quinoline **3a** was observed.

The use of $Cu(OTf)_2$ as catalyst provided the desired quinoline **3a** in a promising 64% yield (entry 1). Considering that the more environmentally friendly iron species are well-known to promote electrophilic aromatic substitution reactions we next explored the corresponding Fe(II)triflate and Fe(III)chloride salts as catalysts.[10] Although both complexes were active, we were pleased to find out that cheap and commercially available $FeCl_3$ was the most active catalyst, leading to quinoline **3a** in an excellent 93% yield (entry 4).[11]

Table 1. Optimization of the Reaction of **1a** with Styrene[a]



entry	catalyst	oxidant (equiv)	time (h)	yield of **3** (%)[b]
1	$Cu(OTf)_2$	$T^+BF_4^-$ (2)	24	64
2	$Fe(OTf)_2$	$T^+BF_4^-$ (2)	24	55
3	$FeCl_3 \cdot 6H_2O$	$T^+BF_4^-$ (2)	24	91
4	**$FeCl_3$**	**$T^+BF_4^-$ (2)**	**16 (20)**	**93 (93)**[c]
5	$FeCl_3$	$T^+BF_4^-$ (2)/air[d]	18	86
6		$T^+BF_4^-$ (2)	16	51[e]
7	$FeCl_3$	DDQ (2)	24	7
8	$FeCl_3$	$(t\text{-BuO})_2$ (2)	24	30
9	$FeCl_3$	air[d]	24	3
10	$FeCl_3$	O_2 (1 atm)	16	41[e,f]

[a] **1a** (0.1 mmol), catalyst (10 mol %), **2a** (0.2 mmol) and oxidant in DCM (1 mL). [b] Isolated yield. [c] 0.5 mmol scale reaction in brackets. [d] Reaction under air atmosphere. [e] Reaction stopped after 16 h. [f] Higher temperatures (≤110 °C) or O_2 pressure (3 atm) gave no improvements.

The reaction was not sensitive to moisture or aerobic conditions, permitting the use of $FeCl_3 \cdot 6H_2O$ or nondry solvents (91% yield, entry 3) and conducting the reaction under air atmosphere (86% yield, entry 5) maintaining the same level of efficiency. Moreover, the reaction also proceeded in the absence of iron catalyst, probably by an acid-mediated reaction. Nevertheless, **3a** was obtained in a significantly lower 51% yield (entry 6). For that reason, we decided to continue the study using $FeCl_3$ as a catalyst. Subsequently, other typical oxidants for CDC reactions were tested; however, the TEMPO oxoamonium salt $T^+BF_4^-$ turned out to be the most efficient. Thus, DDQ, peroxides such as $(t\text{-BuO})_2$, and air were not competent oxidants for this reaction, leading to quinoline **3a** in only 7, 30 and 3%, respectively (entries 7–9). On the other hand, the use of oxygen (1–3 atm) permitted the formation of **3a** in a decent 41% yield (entry 10).[12]

(6) For reviews on quinoline synthesis, see: (a) Jones, G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., McKillop, A., Eds.; Pergamon Press: Oxford, 1996; Vol. 5, p 167. (b) Larsen, R. D. In *Science of Synthesis*; Black, D. S., Ed.; Thieme: Stuttgart, 2005; Vol. 15, pp 389 and 551. (c) Kouznetsov, V. V.; Vargas Méndez, L. Y.; Meléndez Gómez, C. M. *Curr. Org. Chem.* **2005**, *9*, 141. (d) Madapa, S.; Tusi, Z.; Batra, S. *Curr. Org. Chem.* **2008**, *12*, 1116. (e) Marco-Contelles, J.; Pérez-Mayoral, E.; Samadi, A.; Carreiras, M. D.; Soriano, E. *Chem. Rev.* **2009**, *109*, 2652.

(7) For recent examples with alkynes: (a) Huang, H.; Jiang, H.; Chen, K.; Liu, H. *J. Org. Chem.* **2009**, *74*, 5476. (b) Cao, K.; Zhang, F.-M.; Tu, Y.-Q.; Zhuo, X.-T.; Fan, C.-A. *Chem.—Eur. J.* **2009**, *15*, 6332. (c) Desrat, S.; van de Weghe, P. *J. Org. Chem.* **2009**, *74*, 6728. (d) Kulkarni, A.; Török, B. *Green Chem.* **2010**, *12*, 875 and references cited therein. Povarov's initial work:(e) Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656.

(8) T^+BF_4- preparation, see for example: (a) Yonekuta, Y.; Oyaizu, K.; Nishide, H. *Chem. Lett.* **2007**, *36*, 866. For comprehensive reviews on oxoammonium chemistry:(b) Bobbitt, J. M.; Brückner, C.; Merbouh, N. Oxoammonium- and nitroxide-catalyzed oxidations of alcohols. In *Organic Reactions*; Denmark, S. E., Ed.; Wiley: New York, 2009; Vol. 74, p 103. (c) Tebben, L.; Studer, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 5034.

(9) For our previous works on CDC using $T^+BF_4^-$ as oxidant, see: (a) Richter, H.; García Mancheño, O. *Eur. J. Org. Chem.* **2010**, 4460. (b) Richter, H.; Rohlmann, R.; García Mancheño, O. *Chem.—Eur. J.* **2011**, *17*, 11622.

(10) For recent reviews and highlights on iron catalysis, see: (a) *Iron Catalysis in Organic Chemistry*; Plietker, B., Ed.; Wiley-VCH: Weinheim, 2008. (b) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (c) Correa, A.; García Mancheño, O.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (d) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317. (e) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500. (f) Fürstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 1364. (g) Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061. (h) García Mancheño, O. *Angew. Chem., Int. Ed.* **2011**, *50*, 2216.

(11) The reaction in DCE gave a slightly lower yield of 80%.

(12) The reaction with 10 mol % TEMPO salt and NaOCl (2 equiv) as co-oxidant at 60 °C gave as major product the corresponding ortho-chlorinated aniline (29%), along with 17% of **1a** recovered.

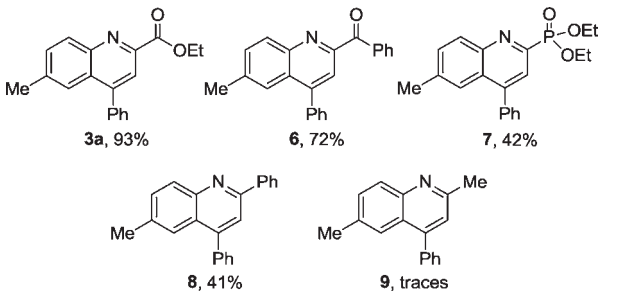
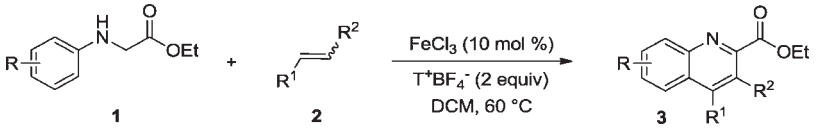


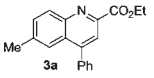
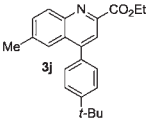
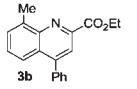
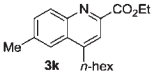
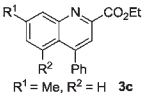
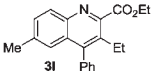
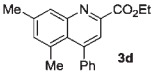
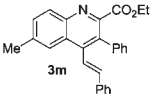
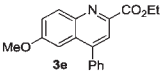
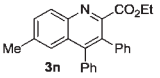
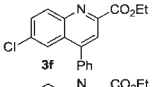
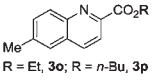
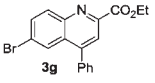
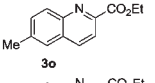
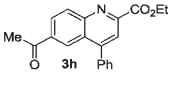
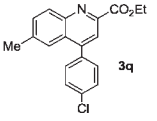
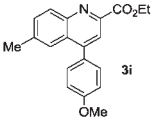
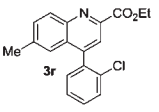
Figure 1. Effect of the substitution at the N-alkyl group.

Having identified the optimal reaction conditions ($FeCl_3$ as catalyst and 2 equivalents of $T^+BF_4^-$ at 60 °C), the substitution of the N-alkyl group at the aniline was next investigated (Figure 1). The ester function was then changed to another electron withdrawing group such as ketone (72%, **6**) and phosphonate (42%, **7**) or to an aryl (Ph, 40%, **8**) or alkyl group (Me, traces, **9**).[13] In general, lower yields or no desired reactivity was observed, indicating the ester substitution is optimal.

The scope of the reaction with ethyl glycine **1** was then explored (Table 2). The substitution at the aniline ring was studied first (entries 1−8). Para (93%), ortho (38%) and meta (42%, 1.6:1 regioisomers) substituents were tolerated (entries 1−3, respectively), although the para substitution gave the best results in terms of reactivity and selectivity. Both electron donating (entries 4−5) and electron withdrawing groups (entries 6−8) were compatible, providing the corresponding quinolines **3** in good yields (73−84%). Interestingly, functional moieties such as chloro, bromo or an acetyl group behave well under these oxidative conditions. Next, a variety of substituted olefins **2** were applied

Table 2. Scope of the Reaction of Glycines **1** with Olefins **2**[a]



entry	R, R^1,R^2	product **3**	yield (%)[b]	entry	R, R^1,R^2	product **3**	yield (%)[b]
1	4-MePh, Ph, H	 **3a**	93	10	4-MePh, 4-*t*-BuPh, H	 **3j**	86
2	2-MePh, Ph, H	 **3b**	38[c,d]	11	4-MePh, *n*-hex, H	 **3k**	66
3	3-MePh, Ph, H	 R^1 = Me, R^2 = H **3c**; R^1 = H, R^2 = Me **3c'**	42[c] (**3c**:**3c'** = 1.6:1)	12	4-MePh, Ph, Et	 **3l**	58
4	3,5-diMePh, Ph, H	 **3d**	68	13	4-MePh, PhCH=CH, Ph,	 **3m**	44
5	4-MeOPh, Ph, H	 **3e**	84	14	4-MePh, Ph, Ph	 **3n**	29[c]
6	4-ClPh, Ph, H	 **3f**	73	15	4-MePh, OBu, H	 R = Et, **3o**; R = *n*-Bu, **3p**	82[c,f] (47, **3o**; 35, **3p**)
7	4-Br, Ph, H	 **3g**	73	16	4-MePh, OEt, H	 **3o**	64[c]
8	4-COMePh, Ph, H	 **3h**	75[e]	17	4-MePh, 4-ClPh, H	 **3q**	83
9	4-MePh, 4-OMePh, H	 **3i**	76	18	4-MePh, 2-ClPh, H	 **3r**	77

[a] **1** (1 equiv), olefin **2** (2 equiv), $FeCl_3$ (10 mol %), and $T^+BF_4^-$ (2 equiv) in DCM (0.1 M) at 60 °C. [b] Isolated yield. [c] 4 equiv of olefin were used. [d] Methylene bis-quinoline **10** was also formed in 23% (see Scheme 2). [e] 2.5 equiv. of $T^+BF_4^-$ at 70 °C. [f] Isolated yields of **3o** and **3p** in brackets.

in the reaction with **1a** (entries 9–18). The electronic nature of the substituents at the aromatic ring of different styrenes did not have a significant impact on the reaction, leading to the corresponding quinolines in similar good yields of 76–86% (electron donating: entries 9–10; and electron withdrawing: entries 17–18).

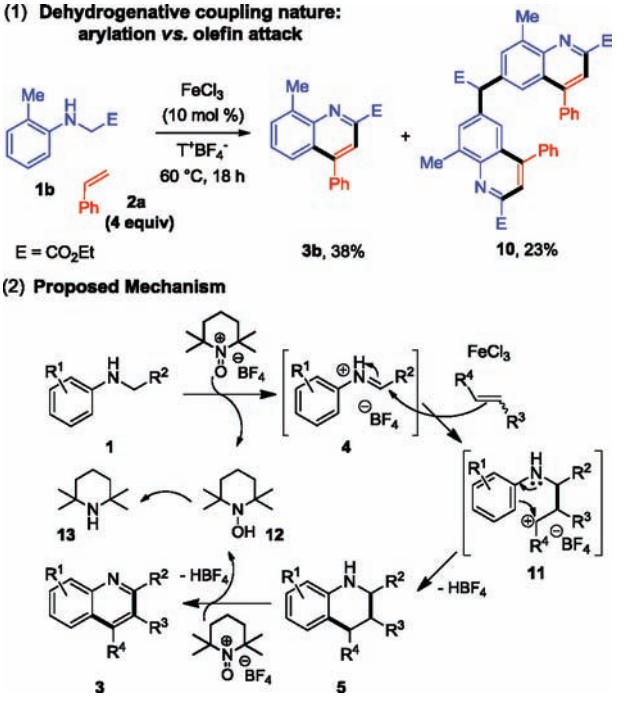
Olefins with linear aliphatic chains such as *n*-hexyl reacted well, providing quinoline **3k** in 66% yield (entry 11). Interestingly, 1,2-disubstituted olefins were also suitable. Thus, *β*-ethyl styrene lead to 2,3,4-trisubstituted quinoline **3l** in a remarkable 58% yield (entry 12). On the other hand, 1,2-aryl alkenyl and 1,2-diaryl substituted olefins such as 1,4-diphenyl butadiene and stilbene turned to be less reactive providing **3m** and **3n** in 44% and 29% yield, respectively (entries 13–14). Finally, the reaction with *n*-butyl and ethyl vinyl ethers was also explored (entries 15 and 16). Then, C-4 unsubstituted quinolines were exclusively obtained by elimination of the corresponding alcohol. This was confirmed by the formation in good overall yield (82%) of a mixture of quinolines with ethyl (**3o**, 47%) and *n*-butyl (**3p**, 35%) esters when using *n*-butyl vinyl ether as nucleophile (entry 15).

To get some insights into the mechanism of this one-pot sequential process, the role of $T^+BF_4^-$ as oxidant was studied. As expected, the reaction of **1a** with only 1.2 equivanlents of $T^+BF_4^-$ was notably less efficient (51%) showing the need of at least 2 equiv of this oxidant for achieving high performance in both key steps: the iminium ion formation and the oxidation of the tetrahydroquinoline intermediate. Additionally, the reaction proceeded relatively slower at room temperature, making it possible to isolate after 13 h the tetrahydroquinoline **5a** in a 33% yield along with 48% of **3a**. However, **5a** could be then converted to the corresponding quinoline **3a** upon treatment with an extra equivalent of oxidant.[14] Furthermore, we could prove the dehydrogenative coupling nature of the transformation by the formation of diarylmethane derivative **10** by a double CDC arylation followed by double dehydrogenative Povarov-type reaction in the reaction with 2-methyl substituted aniline derivative **1b** (Scheme 2, eq 1; Table 2, entry 2).[14] Consequently, a mechanism implying a multistep sequence is proposed (Scheme 2, eq 2). After the first in situ generation of an iminium ion **4** mediated by the TEMPO salt, a nucleophilic attack of the olefin to form a carbocation **11** occurs. This highly reactive intermediate undergoes an intramolecular electrophilic aromatic substitution reaction to form a tetrahydroquinoline **5**, which then is finally further dehydrogenated to form the corresponding quinoline **3**. Interestingly, some overpressure in the reaction vessel was observed after the reaction and the conversion with the time of N-hydroxy TEMPO **12** to amine **13** could be followed by GC-MS, which might indicate certain evolution of H_2. Further investigations aiming the elucidation of the dehydrogenative nature of this TEMPO salt-mediated reaction are currently undergoing in our laboratory.

(13) Although the reaction with *p*-toluidine and ethyl glyoxalate to form the Schiff base in situ is possible (71%, **3a**), the advantage of starting from **1** is to be able to introduce groups such as phosphonates (**7**), etc., which not accessible by the in situ approach.

(14) For more details, see Supporting Information.

Scheme 2. Mechanistic Insights



In summary, we have developed a one-pot dehydrogenative synthesis of quinolines using a TEMPO oxoammonium salt as highly efficient, mild and nontoxic oxidant. The combination of cheap and available $FeCl_3$ catalyst with $T^+BF_4^-$ as formal hydrogen acceptor was successfully employed. This approach allows the direct reaction of simple N-alkyl anilines, such as ethyl glycines, with a variety of mono- and 1,2-disubstituted aryl and alkyl olefins. A mechanism implying a multistep sequence in which the TEMPO oxoammonium salt participates in both the first and the last stage is proposed. This oxidant seems to be crucial for both the in situ generation of a reactive iminium ion and the final dehydrogenation of the tetrahydroquinoline to form the corresponding heteroaromatic compound.

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Supporting Information Available. Experimental procedures, characterization and NMR spectra of compounds and further mechanistic aspects. This material is available free of charge via the Internet at http://pubs.acs.org.