RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2014, **4**, 19602

Deproto-metallation using mixed lithium–zinc and lithium–copper bases and computed CH acidity of 2-substituted quinolines†

Nada Marquise,[a] Guillaume Bretel,[a] Frédéric Lassagne,[a] Floris Chevallier,*[a] Thierry Roisnel,[b] Vincent Dorcet,[b] Yury S. Halauko,*[c] Oleg A. Ivashkevich,[c] Vadim E. Matulis,[d] Philippe C. Gros[e] and Florence Mongin*[a]

Received 24th March 2014
Accepted 14th April 2014

DOI: 10.1039/c4ra02583k

www.rsc.org/advances

2-Substituted quinolines were synthesized, and their deproto-metallation using the bases prepared by mixing LiTMP with either $ZnCl_2$·TMEDA (1/3 equiv.) or CuCl (1/2 equiv.) was studied. With phenyl and 2-naphthyl substituents, the reaction occurred at the 8 position of the quinoline ring, affording the corresponding iodo derivatives or 2-chlorophenyl ketones using the lithium–zinc or the lithium–copper combination, respectively. With a 4-anisyl substituent, a dideprotonation at the 8 and 3′ position was noted using the lithium–zinc base. With 3-pyridyl, 2-furyl and 2-thienyl substituents, the reaction took place on the substituent, at a position adjacent to its heteroatom. 2-Chlorophenyl-2-phenyl-8-quinolyl ketone could be cyclized under palladium catalysis. The experimental results were analyzed with the help of the CH acidities of the substrates, determined in THF solution using the DFT B3LYP method.

Introduction

Quinolines are key heterocycles present in numerous natural products and biologically active compounds.[1] In addition, derivatives are widely used in different fields, *e.g.* as biocides, dyes, rubber chemicals and corrosion inhibitors.[2] Deprotonative lithiation[3] has been developed in the quinoline series,[4] in general with recourse to substituents capable of directing the reaction to specific sites through acidifying and/or coordinating effects. Due to the low LUMO level of such substrates, very low temperatures are often required in the protocoles employed.

Efficient tools for the deproto-metallation of sensitive aromatic compounds have recently emerged. In particular, synergic combinations of lithium reagents and softer metal compounds such as bimetal ate compounds, salt-activated metal amides, and pairs of metal amides have appeared as promising alternatives to lithium bases,[5] and notably in the quinoline series.[6]

In the search of new bimetal ate bases, our group developed $(TMP)_2CuLi(\pm LiCl)$ (TMP = 2,2,6,6-tetramethylpiperidido),[7] a lithiocuprate prepared *in situ* from CuCl and LiTMP. Besides its possible use at room temperature, one main advantage of using the base is the possible trapping of the formed arylmetal species by aroyl chlorides to directly afford ketones.

Our group also developed the use of the TMP-based pair of metal amides, *in situ* prepared by mixing $ZnCl_2$·TMEDA (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) with LiTMP (3 equiv.),[8] and supposed to be a 1 : 1 LiTMP·2LiCl(±TMEDA)–$Zn(TMP)_2$ mixture.[9] By complementing each other in deproto-metallation reactions, this mixture of lithium and zinc amides allows sensitive substrates to be mono- or di- deproto-metallated, as evidenced by subsequent iodolysis.[7c,8,10] In addition, compared with both heteroleptic amido-organo lithium zincates[10d] and salt-activated hindered zinc amides,[5d] the above combination allows the conversion of less activated substrates.

Synthesis of 2-substituted quinolines, *e.g.* 2-arylquinolines, was recently simplified with the one-pot Friedländer access from 2-nitroarylcarbaldehydes.[11] We thus decided to study the deprotonative metallation of the substrates **1** (Scheme 1) using

[a]*Chimie et Photonique Moléculaires, Institut des Sciences Chimiques de Rennes, UMR 6226 Université de Rennes 1, CNRS, Bâtiment 10A, Case 1003, Campus Scientifique de Beaulieu, 35042 Rennes, France. E-mail: floris.chevallier@univ-rennes1.fr; florence.mongin@univ-rennes1.fr; Fax: +33-2-2323-6955*

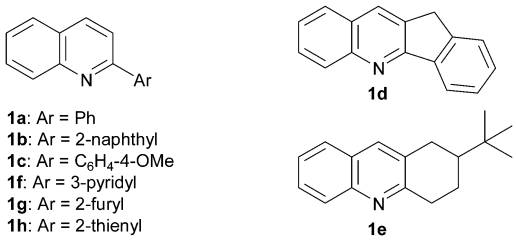
[b]*Centre de DIFfractométrie X, Institut des Sciences Chimiques de Rennes, UMR 6226 Université de Rennes 1, CNRS, Bâtiment 10B, Campus de Beaulieu, 35042 Rennes, France*

[c]*UNESCO Chair of Belarusian State University, 14 Leningradskaya Str., Minsk, 220030, Belarus. E-mail: hys@tut.by*

[d]*Research Institute for Physico-Chemical Problems of Belarusian State University, 14 Leningradskaya Str., Minsk, 220030, Belarus. Fax: +375-17-2264696*

[e]*HECRIN, SRSMC, Université de Lorraine-CNRS, Boulevard des Aiguillettes, 54506, Vandoeuvre-Lès-Nancy, France*

† Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR spectra, calculated values of the Gibbs energies $\Delta_{acid}G$ [kcal mol^{-1}] for deprotonation at the corresponding positions of the investigated quinolines, and cartesian coordinates of molecular geometry for the most stable rotamer form of selected quinolines (on example of **1f**, **1h**) (neutral molecule, gas phase) optimized at B3LYP/6-31G(d) level of theory. CCDC 981282–981288. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra02583k



Scheme 1 Quinolines **1** for which the deproto-metallation was studied.

both the lithium–zinc and the lithium–copper base in order to prepare iodo derivatives and ketones, respectively, after direct trapping. We earlier showed that the regioselectivity of the reactions for related substrates is partly determined by the acidity of the different hydrogens in their molecules.[7c,10j] Similarly, here we tried to rationalize the outcome of reactions by using the CH acidities in THF of the quinoline-based substrates calculated by means of the isodesmic reaction approach within the density functional theory (DFT) framework.

Results and discussions

Synthetic aspects

To reach the target quinolines **1**, the conditions reported by Li, Mulvihill and co-workers were employed.[11] Thus, 2-nitrobenzaldehyde was reduced using iron in the presence of catalytic aqueous HCl, and the obtained 2-aminobenzaldehyde was condensed *in situ* with ketones to form either 2-substituted or 2,3-disubstituted quinolines in high yields (Table 1). The structure of **1e** was confirmed by X-ray diffraction analysis (Fig. 1, left).‡

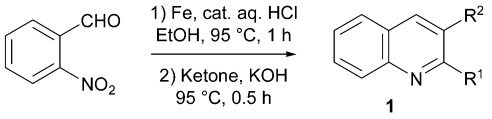
The lithium–zinc TMP-based mixture of amides, prepared *in situ* from $ZnCl_2$·TMEDA (0.5 equiv.) and LiTMP (1.5 equiv.), was first attempted for the deproto-metallation of the quinolines **1**. Previous studies aimed at optimizing the reaction on different substrates showed that THF is the most suitable solvent, and 2 h a sufficient reaction time for a reaction performed at room temperature.[7c,10a,b] In addition, iodolysis was similarly identified as an efficient quenching mode for the arylmetal compounds thus generated.[10d]

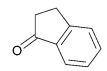
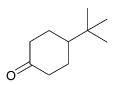
Upon treatment under these conditions, 2-phenyl and 2-naphthylquinoline **1a,b** were converted to the corresponding 8-iodo derivatives **2a,b** in 74 and 54% yield, respectively (Scheme 2). The product **2a** was identified unequivocally by X-ray diffraction (Fig. 1, right).‡ Functionalization at the 8 position had previously been observed by deproto-lithiation[4] or -magnesiation[6f,12] of quinolines, but in general either in the presence of a directing group at the 7 position or in the absence of free/accessible position on the quinoline ring. For bare quinoline, deproto-metallation using the Kondo's TMP-zincate LiZn(TMP)(*t*-Bu)$_2$ followed by iodolysis was reported, and showed the formation of both the 2- and 8-iodo regioisomers in a 3 : 7 ratio.[13] A substituted 2 position together with the absence of directing group on the pyridine ring leads to a reaction at the 8 position in the case of **1a,b**.

Anisole being easily *ortho*-deprotonated under similar reaction conditions,[10d] it was interesting to involve in the deprotonation–iodination sequence 2-(4-methoxyphenyl)quinoline (**1c**). Under the same reaction conditions, the diiodide **3c** was obtained in 61% yield (Scheme 3). Such a double

‡ CIF files available in the ESI: CIF files of **1e** (CCDC 981282), **2a** (981283), **2h** (981284), **3h** (981285), **4a** (981286), **4b** (981287), and **5a** (981288).

Table 1 Synthesis of the quinoline substrates **1**



Entry	Ketone	Product (R^1, R^2)	Yield[a] (%)
1	PhCOMe	**1a** (Ph, H)	99
2	2-NaphthylCOMe	**1b** (2-naphthyl, H)	90
3	4-MeOC$_6$H$_4$COMe	**1c** (4-MeOC$_6$H$_4$, H)	95
4		**1d** (C$_6$H$_4$-2-CH$_2$)	87
5		**1e** ((CH$_2$)$_2$C(*t*-Bu)CH$_2$)	91
6	3-PyridylCOMe	**1f** (3-pyridyl, H)	89
7	2-FurylCOMe	**1g** (2-furyl, H)	100
8	2-ThienylCOMe	**1h** (2-thienyl, H)	80

[a] After purification.

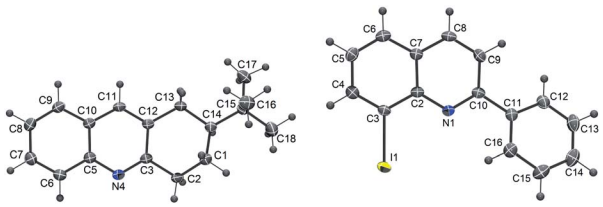
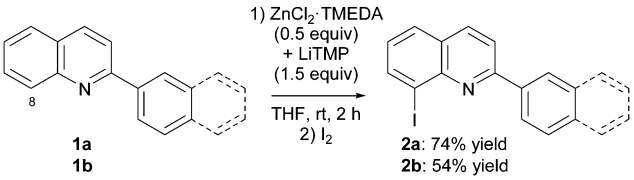
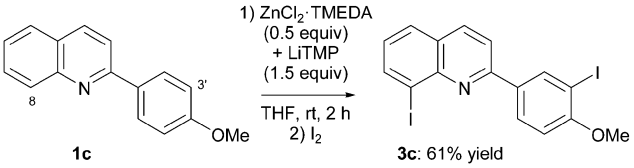


Fig. 1 ORTEP diagram (50% probability) of **1e** and **2a**.



Scheme 2 Deproto-metallation of **1a,b** followed by iodination.



Scheme 3 Deproto-metallation of **1c** followed by iodination.

functionalization generally does not take place using monometal lithium bases, but is a reaction commonly observed using the present lithium–zinc base.[10e,g,j]

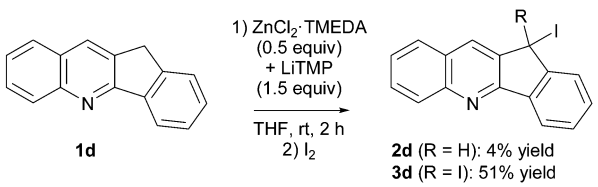
In the case of 11*H*-indeno[1,2-*b*]quinoline (**1d**), no more ring deprotonation was noted due to the presence of more acidic benzylic hydrogens. Under the same reactions conditions, the mono and diiodide **2d** and **3d** were isolated in 4 and 51% yield, respectively (Scheme 4). From 2-*tert*-butyl-1,2,3,4-tetrahydroacridine (**1e**), a complex mixture of iodides was formed, a result probably due to a larger number of deprotonation sites in this case.

By switching from 2-phenylquinoline (**1a**) to 2-(3-pyridyl)-quinoline (**1f**), the regioselectivity of the reaction was completely modified. The deproto-metallation no more took place on the quinoline ring but on its pyridine substituent. In addition, the two sites next to the pyridine ring were unregioselectively attacked, with a preference for the less hindered 6 position (product **2f**, 47% yield) over the 2 position (product **2f′**, 20% yield) (Scheme 5).

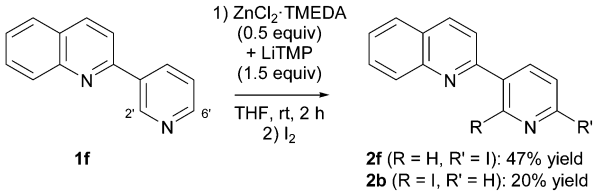
When submitted to the same reaction conditions, 2-(2-furyl) quinoline (**1g**) was attacked at the furan ring, next to oxygen, to afford the iodo derivative **2g** in 71% yield (Scheme 6).

2-(2-Thienyl)quinoline (**1h**) had previously been deproto-lithiated using butyllithium in ethereal solvents, either to give a mixture resulting from a reaction at the 3′ or 5′ position at 0 °C (trapping with chlorotrimethylsilane),[3a] or to furnish the product functionalized at the 5′ position at −78 °C (interception by DMF).[14]

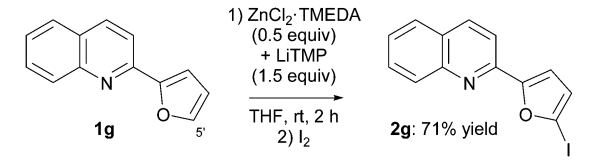
By using the lithium–zinc base as before, the bis(heterocycle) **1h** was functionalized at the thienyl ring. The corresponding monoiodide **2h** and diiodide **3h** were isolated in 52 and 12% yield, respectively (Scheme 7 and Fig. 2).



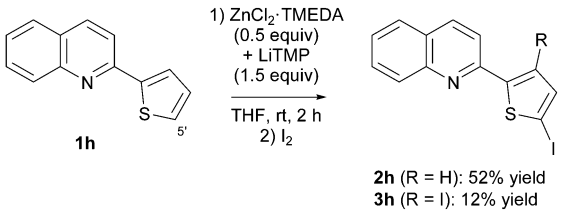
Scheme 4 Deproto-metallation of **1d** followed by iodination.



Scheme 5 Deproto-metallation of **1f** followed by iodination.



Scheme 6 Deproto-metallation of **1g** followed by iodination.



Scheme 7 Deproto-metallation of **1h** followed by iodination.

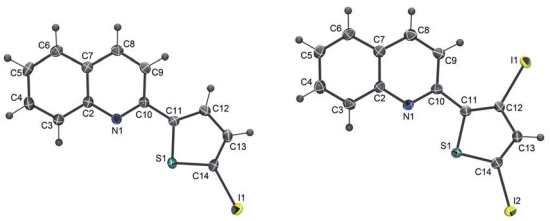
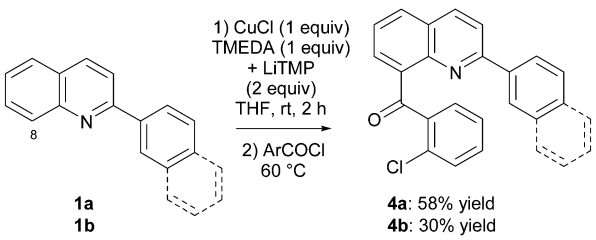


Fig. 2 ORTEP diagrams (50% probability) of **2h** and **3h**.

In order to reach other kinds of functionalization by direct trapping after deproto-metallation, we turned to another base. It was decided to attempt the use of the lithiocuprate prepared *in situ* from CuCl and LiTMP (2 equiv.) on some of the quinoline substrates in order to prepare ketone derivatives by interception with an aroyl chloride.[7]

Previous studies established THF containing TMEDA (1 equiv.) as the most suitable solvent, and 2 h as a sufficient reaction time for a reaction performed at room temperature.[7] First, the TMP-based lithiocuprate, prepared *in situ* from CuCl (1 equiv.) and LiTMP (2 equiv.), was evaluated for the deproto-metallation of 2-phenyl and 2-naphthylquinoline **1a,b**. Both substrates were functionalized at their 8 position, affording after trapping with 2-chlorobenzoyl chloride the ketones **4a,b** in 58 and 30% yield, respectively (for the latter, recovery of starting material was also noted) (Scheme 8 and Fig. 3). Similarly, 2-(2-thienyl)quinoline (**1h**) was converted to the ketone **4h**, isolated in 62% yield (Scheme 9).

It is possible to involve the generated heterocyclic iodides in different transition metal-catalyzed coupling reactions,[15] and the chloro ketones in intramolecular direct arylation through palladium-catalysed C–H bond activation.[16] To attempt the conversion of 8-(2-chlorobenzoyl)-2-phenylquinoline (**4a**) to the



Scheme 8 Deproto-metallation of **1a,b** followed by aroylation.

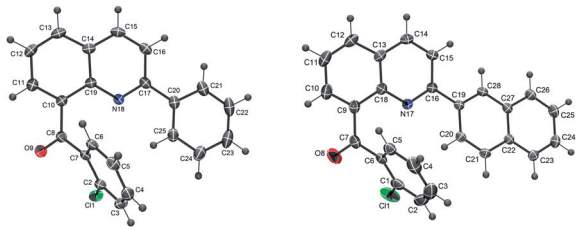
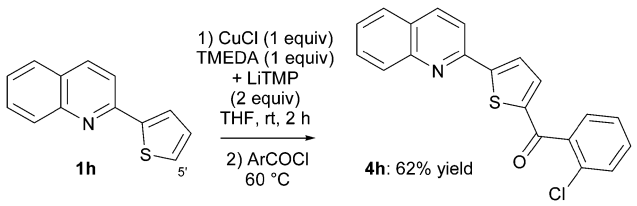


Fig. 3 ORTEP diagrams (50% probability) of **4a** and **4b**.

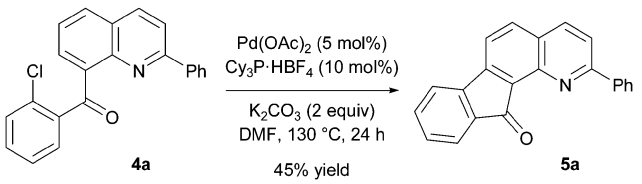


Scheme 9 Deproto-metallation of **1h** followed by aroylation.

fluorenone **5a**, we proceeded as reported for the cyclization of 2-chloro diaryl aniline to carbazole.[17] Using catalytic amounts of $Pd(OAc)_2$, Cy_3P (Cy = cyclohexyl) as an electron-rich and bulky trialkyl phosphine, K_2CO_3 as a base and DMF as solvent at 130 °C afforded the tetracycle **5a** in a moderate 45% yield due to the competitive formation of 8-benzoyl-2-phenylquinoline in 30% yield (Scheme 10 and Fig. 4).

Computational aspects

Unfortunately, both experimental and computational data on CH acidity for quinoline and its derivatives are scanty. The main reasons are the necessity of using very strong bases at low temperatures, the possible side reactions of the generated carbanions and also the acidity closeness between different C–H bonds in such condensed aromatics. A brief review of papers, devoted to experimental and theoretical investigation of CH acidity in azines, is presented in our previous publication.[7c] For such aromatic substrates, one should especially mention the



Scheme 10 Cyclization to **5a**.

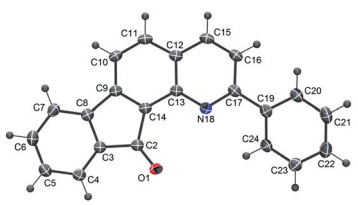


Fig. 4 ORTEP diagrams (50% probability) of **5a**.

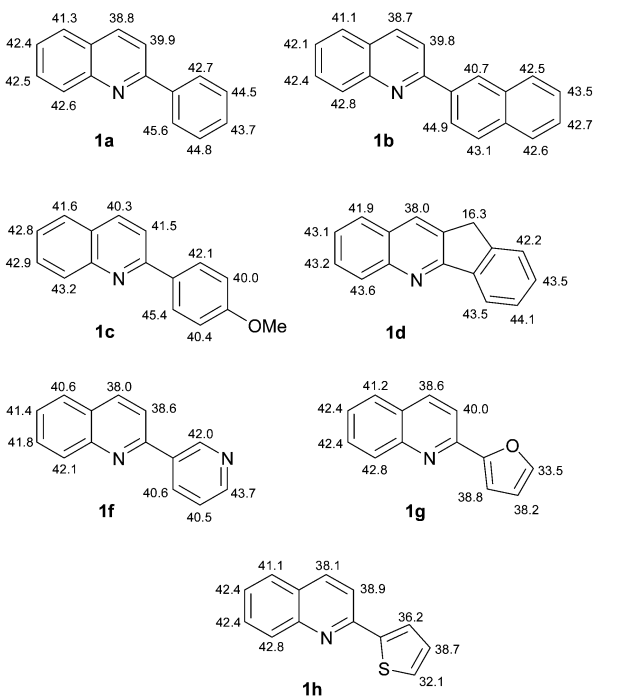
pK_a values experimentally found for 4-methylquinoline and several alkylpyridines in THF,[18] and for substituted arenes and fluorenes in CH_3CN.[19] Some experimental gas-phase acidities of condensed heteroaromatics including bare quinoline were also reported.[20] To the long-standing semi-empirical studies of the deprotonation energies of nitrogen heterocycles,[21] DFT calculations of pK_a values of benzo-azines[22] and -quinuclidines[23] were recently added.

In the present paper, the DFT calculations of CH acidity of the different quinolines, both in gas phase (see ESI†) and in THF solution (Scheme 11), are presented. The gas phase acidities $\Delta_{acid}G$ and pK_a values in THF solution of all the substrates were calculated using the theoretical protocol thoroughly described previously.[24] This approach already proved to be worthy for substituted azines[7c] and biaryl compounds.[10j]

All the calculations were performed by using the DFT B3LYP method. The geometries were fully optimized using the 6-31G(d) basis set. No symmetry constraints were implied. In order to perform stationary points assessment and to calculate zero-point vibrational energies (ZPVE) and thermal corrections, the Hessian matrix eigenvalues were calculated at the same level of theory. The single point energies were found using the 6-311+G(d,p) basis set and tight convergence criteria. The gas phase Gibbs energies (G^0_{298}) were calculated for each isolated species using the following equation:

$$G^0_{298} = E + \mathrm{ZPVE} + H_{0\rightarrow 298} - \mathrm{TS}^0_{298}.$$

The gas phase acidities $\Delta_{acid}G$ were determined as the Gibbs energies of deprotonation of the substrates R–H ($\mathrm{R–H_{(g)}} \rightarrow \mathrm{R^-_{(g)}} + \mathrm{H^+_{(g)}}$) by the following formula:



Scheme 11 Calculated values of pK_a (THF) of the quinoline substrates.

$$\Delta_{acid}G = G^0_{298}(R^-) + G^0_{298}(H^+) - G^0_{298}(RH).$$

The solvent effects were treated by using the polarized continuum model (PCM) with the default parameters for THF.[25] The PCM energies E_{PCM} were also calculated at the B3LYP/6-311+G(d,p) level using geometries optimized for isolated structures. The Gibbs energies in solution G_s were calculated for each species by the formula:

$$G_s = G^0_{298} + E_{PCM} - E.$$

To cancel the majority of calculation errors, the pK_a values were calculated by means of the following isodesmic reaction:

$$R\text{–}H_{(s)} + Het^-_{(s)} \rightarrow R^-_{(s)} + Het\text{–}H_{(s)},$$

where Het–H is an appropriate heterocycle with experimentally determined pK_a values. In the present study, pyridine was chosen as the reference compound owing to its structural similarity and expected pK_a proximity.

It could be shown easily that the Gibbs energies of the isodesmic reactions ($\Delta_r G_s$) and the corresponding pK_a values are linked together by the following equation:

$$pK_a(R-H) = 40.2 + \frac{\Delta_r G_s}{RT}\frac{1}{\ln 10}.$$

The CH acidity of the methoxy group for the substrate **1c** was not considered here since it was expected to be significantly lower and there was no sign of its deprotonation in the experiment. The calculations on **1e** were also skipped due to the obvious prevalence of benzylic acidity in deprotonation.

It is obvious that, with the exception of **1a** and **1d**, all the investigated arylquinolines exist in form of several rotamers. So, the data on Scheme 11 (and ESI†) refer to the most stable ones. Among these molecules with several rotamers, the naphthyl derivative **1b** is likely to exist in the stretched form, **1f** and **1g** with remote heteroatoms, while for the sulfur-containing compound **1h** the *syn*-form should prevail. These findings are in agreement with those for arylated azoles.[10k]

There are several potential deprotonation sites in the investigated substrates. When comparing the CH acidity in gas-phase (see ESI†) and in THF solution (Scheme 11), the correlation can be easily seen. The analysis of the obtained results shows that CH acidity increases logically with the introduction of electron-withdrawing groups, and decreases for electron-donating ones.

The calculated values of gas-phase acidity of the investigated quinolines mostly lie within the range of 375 to 390 kcal mol^{-1} (see ESI†). Such $\Delta_{acid}G$ values are typical of very weak acids and correspond to those found previously in experiment for bare quinoline[20] (exp. 376.9 kcal mol^{-1} *vs.* calc. 377.3 kcal mol^{-1}, position 4) as well as for computed ones.[22] When analyzing the pK_a values distribution for a common quinolinic part of the molecules, one can see some general trends. The most acidic hydrogen is at the position 4, while the least acidic is at the 8.

Discussion

The calculations of the CH acidities in THF of **1a–d** and **1f–h** (Scheme 11) allowed us to comment on the regioselectivities observed in the course of the reactions involving these substrates.

The calculations performed on the quinoline derivatives **1a,b** show that the hydrogens at the two free positions of the pyrido ring are more acidic than those of the benzo and aryl rings. Nevertheless, reactions did not lead to any 3- and 4-substituted quinolines but to the 8-iodo and 8-(2-chlorobenzoyl) derivatives **2a,b** and **4a,b**, respectively using the lithium–zinc (Scheme 2) and lithium–copper (Scheme 8) bases. Such reactions at the 8 position could be due to the presence of a nitrogen able to coordinate a metal, either favouring the approach of the base and/or stabilizing the arylmetal compound formed. Recently, C–H borylation of quinoline derivatives was similarly observed at the C8 position.[26]

Using the lithium–zinc base under the same reaction conditions with the substrate **1c** led to the formation of the diiodide **3c** (Scheme 3). When a methoxy group is present on the phenyl ring, the *ortho* sites are acidified by its inductive effect and their pK_a values become similar to those of the quinoline pyrido hydrogens. This could explain the formation of a heteroaryl compound metallated both at the 8 position *peri* to the quinoline nitrogen and at the 3′ position *ortho* to the methoxy group.

From the substrate **1d** and the lithium–zinc base, the diiodide **3d** was predominately formed (Scheme 4). This can be rationalized in terms of a huge pK_a values difference in favour of benzylic hydrogens. pK_a (THF) values less than 20 are typical of those for fluorenes with acceptor substituents.[19] The same effect, enhanced by a larger number of potential deprotonation sites, was noted in the case of **1e**, leading to a mixture of iodides.

In the case of the substrate **1f**, with a 3-pyridyl group connected to the 2 position of the quinoline ring, deproto-metallation was only observed on the pyridine group in spite of higher acidities at the quinoline pyrido ring (Scheme 5). Such a result could be rationalized by a coordination exerted by the pyridine nitrogen toward a metal, either intermolecularly (approach of the metallic base) or intramolecularly (internal stabilization of the metallated species). The result suggests a more unlikely coordination by the quinoline nitrogen, maybe for steric reasons.

Upon treatment by the lithium–zinc and lithium–copper base, the quinolines 2-substituted by a 2-furyl and 2-thienyl group **1g,h** were functionalized on the five-membered ring, and mainly at the 5′ position (Schemes 6, 7 and 9). The reason why there is no functionalization at the 8 position of the quinoline ring could be in relation with the presence of a clearly more acidic site at the position adjacent to the furan and thiophene heteroatom.

These results, together with earlier findings for azines[7c] and biaryls,[10j] lead us to the following conclusions. The pK_a values obtained by our theoretical protocol are useful for the reaction outcome prediction. When using amido-based bimetallic bases

in THF solution, it seems that there is a boundary corresponding to a pK_a value of *ca.* 36. Consequently, the substrates with C–H bonds of enough acidity are deprotonated at the most acidic site in THF at moderate temperatures. The other option implies a substitution at a position adjacent to the ring nitrogen through metal complexation for weak CH acids (this course of the reaction could be enhanced by using less polar solvents at low temperatures).

Conclusions

Upon treatment with the lithium–zinc base prepared *in situ* from $ZnCl_2 \cdot TMEDA$ (0.5 equiv.) and LiTMP (1.5 equiv.), different 2-arylquinolines were deproto-metallated, as evidenced by subsequent interception by iodine. In the presence of unsubstituted phenyl and naphthyl substituents, a single reaction at the 8 position was noted; in contrast, with a 4-anisyl group bearing a substituent able to acidify the neighbouring hydrogens, a double functionalization took place at both the 8 and 3′ position. When a 3-pyridyl, a 2-furyl or a 2-thienyl was connected to the 2 position of the quinoline ring, the reaction occurred on this heteroaryl substituent, next to nitrogen, oxygen or sulfur, respectively. The iodo derivatives could be elaborated, for example by Suzuki cross-coupling as shown recently in the pyrazole series.[10e]

Using the corresponding lithiocuprate generated from CuCl (1 equiv.) and LiTMP (2 equiv.), a similar regioselectivity was observed. 2-Chlorophenyl ketones could be prepared, and a subsequent palladium-catalysed cyclization to polycycle demonstrated.

The CH acidities of the substrates in THF solution, which were calculated using a continuum solvation model, were used to rationalize the outcome of the reactions. The related substances could be preliminary functionalized to enhance the regioselectivity of deproto-metallation.

Experimental

General methods

Metallation reactions were performed under an argon atmosphere. THF was distilled over sodium/benzophenone. Column chromatography separations were achieved on silica gel (40–63 μm). Melting points were measured on a Kofler apparatus. IR spectra were taken on a Perkin-Elmer Spectrum 100 spectrometer. ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance III spectrometer at 300 and 75 MHz, respectively. ^{1}H chemical shifts (δ) are given in ppm relative to the solvent residual peak, ^{13}C chemical shifts are relative to the central peak of the solvent signal.[27] Mass spectra (HRMS) measurements were performed at the CRMPO (Centre Régional de Mesures Physiques de l'Ouest) of Rennes using a Waters Q-TOF 2 instrument.

General procedure 1 for the synthesis of the substituted quinolines 1a–h[11]

To 2-nitrobenzaldehyde (1.5 g, 10 mmol) in EtOH (20 mL) was added iron powder (2.2 g, 40 mmol) and 0.1 N aqueous HCl (5 mL, 0.5 mmol). The mixture was then stirred at 95 °C for 1 h. The required ketone (10 mmol) was then added. KOH (0.67 g, 12 mmol) was introduced portionwise (**Caution!** Potential exotherm) before stirring at 95 °C for 30 min. The mixture was cooled to room temperature, diluted with CH_2Cl_2 (300 mL) and filtered over silica. The filtrate was dried over $MgSO_4$, and the solvents were removed under vacuum. The crude product was purified by chromatography over silica gel (eluent: 4 : 1 heptane–AcOEt).

2-Phenylquinoline (1a). 2-Phenylquinoline (**1a**) was prepared from acetophenone (1.2 mL) using the general procedure 1, and was isolated in 99% yield (2.0 g) as a white solid: mp 85 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.46–7.56 (m, 4H), 7.73 (m, 1H), 7.84 (dd, 1H, J = 1.2 and 8.1 Hz), 7.89 (d, 1H, J = 8.6 Hz), 8.15–8.18 (m, 3H), 8.23 (d, 1H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 119.1, 126.4, 127.3, 127.6, 127.7 (2C), 129.0 (2C), 129.4, 129.8, 129.9, 136.9, 139.8, 148.4, 157.5. These data are analogous to those obtained from a commercial sample.

2-(2-Naphthyl)quinoline (1b). 2-(2-Naphthyl)quinoline (**1b**) was prepared from 2-acetonaphthone (1.7 g) using the general procedure 1, and was isolated in 90% yield (2.3 g) as a white solid: mp 160 °C (lit.[28] 162–163 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.54 (m, 3H), 7.76 (m, 1H), 7.78–7.93 (m, 2H), 8.02 (m, 3H), 8.24 (m, 2H), 8.3 (m, 1H), 8.63 (d, 1H, J = 1.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 119.2, 125.2, 126.4, 126.8, 127.2, 127.3, 127.6, 127.8, 128.3, 128.7, 128.9, 129.8, 129.9, 133.6, 134.0, 136.9, 137.0, 148.5, 157.2. The NMR data are analogous to those previously described.[28]

2-(4-Methoxyphenyl)quinoline (1c). 2-(4-Methoxyphenyl)-quinoline (**1c**) was prepared from 4-methoxyacetophenone (1.5 g) using the general procedure 1, and was isolated in 95% yield (2.2 g) as a yellow solid: mp 124 °C (lit.[29] 123–125 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) 3.89 (s, 3H), 7.05 (d, 2H, J = 8.9 Hz), 7.50 (m, 1H), 7.71 (m, 1H), 7.81 (m, 1H), 7.84 (d, 1H, J = 8.7 Hz), 8.13 (m, 1H), 8.14 (d, 2H, J = 8.9 Hz), 8.18 (d, 1H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 55.5, 114.3 (2C), 118.7, 126.0, 127.0, 127.6, 129.0 (2C), 129.6, 129.7, 132.4, 136.7, 148.4, 157.0, 160.9. The NMR data are analogous to those previously described.[29]

11*H*-Indeno[1,2-*b*]quinoline (1d). 11*H*-Indeno[1,2-*b*]quinoline (**1d**) was prepared from 1-indanone (1.3 g) using the general procedure 1, and was isolated in 87% yield (1.9 g) as a yellow solid: mp 166 °C (lit.[30] 164–166 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) 4.01 (s, 2H), 7.49 (m, 3H), 7.59 (m, 1H), 7.70 (m, 1H), 7.80 (m, 1H), 8.15 (s, 1H), 8.21 (d, 1H, J = 8.5 Hz), 8.30 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 34.1, 122.1, 125.6, 125.8, 127.5, 127.6, 127.9, 128.9, 129.2, 130.1, 131.2, 134.7, 140.5, 145.2, 148.2, 161.8. These data are analogous to those previously described.[30]

2-*tert*-Butyl-1,2,3,4-tetrahydroacridine (1e). 2-*tert*-Butyl-1,2,3,4-tetrahydroacridine (**1e**)[31] was prepared from 4-*tert*-butylcyclohexanone (1.5 g) using the general procedure 1, and was isolated in 88% yield (2.1 g) as a white solid: mp 91 °C; IR (ATR): 3870, 3753, 3620, 3194, 2945, 2923, 2548, 2313, 2051, 1618, 1601, 1494, 1428, 1416, 1365, 1234, 1159, 955, 931, 782, 765, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 0.99 (s, 9H), 1.57 (m, 2H), 2.15 (m, 1H), 2.70 (m, 1H), 3.03 (m, 2H), 3.25 (m, 1H), 7.41 (dd, 1H, J = 7.0 and 8.0 Hz), 7.59 (dd, 1H, J = 7.0 and 8.1 Hz), 7.67 (d, 1H, J = 8.1 Hz), 7.79 (s, 1H), 7.97 (d, 1H, J = 8.0 Hz);

^{13}C NMR ($CDCl_3$, 75 MHz) 24.6, 27.3 (3C), 30.8, 32.6, 34.4, 44.6, 125.5, 126.9, 127.2, 128.3, 128.5, 131.2, 135.2, 146.6, 159.4.

2-(3-Pyridyl)quinoline (1f). 2-(3-Pyridyl)quinoline (**1f**) was prepared from 3-acetylpyridine (1.1 g) using the general procedure 1, and was isolated in 89% yield (1.8 g) as a yellow solid: mp 68 °C (lit.[29] 69–72 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.45 (ddd, 1H, J = 0.8, 4.8 and 8.0 Hz), 7.55 (ddd, 1H, J = 1.1, 6.9 and 8.1 Hz), 7.75 (ddd, 1H, J = 1.3, 6.9 and 8.4 Hz), 7.84 (br dd, 1H, J = 1.3 and 8.1 Hz), 7.87 (d, 1H, J = 8.6 Hz), 8.17 (br d, 1H, J = 8.4 Hz), 8.25 (br d, 1H, J = 8.6 Hz), 8.50 (ddd, 1H, J = 1.8, 2.3 and 8.0 Hz), 8.70 (dd, 1H, J = 1.8 and 4.8 Hz), 9.35 (dd, 1H, J = 0.8 and 2.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 118.6, 123.7, 126.9, 127.4, 127.6, 129.8, 130.1, 135.0, 135.2, 137.2, 148.5, 148.9, 150.3, 154.7. The NMR data are analogous to those previously described.[29]

2-(2-Furyl)quinoline (1g). 2-(2-Furyl)quinoline (**1g**) was prepared from 2-acetylfuran (1.1 g) using the general procedure 1, and was isolated in 100% yield (2.0 g) as a yellow solid: mp 94 °C (lit.[32] 94 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) 6.59 (dd, 1H, J = 1.8 and 3.4 Hz), 7.24 (br d, 1H, J = 3.4 Hz), 7.49 (ddd, 1H, J = 1.1, 6.9 and 8.1 Hz), 7.63 (dd, 1H, J = 0.7 and 1.8 Hz), 7.70 (ddd, 1H, J = 1.3, 6.9 and 8.4 Hz), 7.77 (br dd, 1H, J = 1.3 and 8.1 Hz), 7.82 (d, 1H, J = 8.5 Hz), 8.15 (br d, 1H, J = 8.4 Hz), 8.16 (br d, 1H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 110.2, 112.3, 117.5, 126.3, 127.2, 127.6, 129.4, 129.9, 136.7, 144.2, 148.1, 149.1, 153.7. These data are analogous to those previously described.[32]

2-(2-Thienyl)quinoline (1h). 2-(2-Thienyl)quinoline (**1h**) was prepared from acetyl thiophene (1.3 g) using the general procedure 1, and was isolated in 80% yield (1.7 g) as a yellow solid: mp 129 °C (lit.[30] 130–132 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.16 (m, 1H), 7.17 (m, 2H), 7.73–7.80 (m, 4H), 8.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 117.7, 125.9, 126.2, 127.3, 127.6, 128.2, 128.7, 129.3, 129.9, 136.7, 145.5, 148.2, 152.4. These data are analogous to those previously described.[30]

General procedure 2 for the deprotonative metallation using the lithium–zinc base followed by iodination

To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.26 mL, 1.5 mmol) in THF (3 mL) was added BuLi (about 1.6 M hexanes solution, 1.5 mmol). After 15 min at 0 °C, $ZnCl_2$·TMEDA (0.13 g, 0.50 mmol) was added, and the mixture was stirred for 15 min at this temperature before introduction of the substrate (1.0 mmol). After 2 h at room temperature, a solution of I_2 (0.38 g, 1.5 mmol) in THF (5 mL) was added. The mixture was stirred overnight before addition of an aqueous saturated solution of $Na_2S_2O_3$ (10 mL) and extraction with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure before purification by flash chromatography on silica gel (the eluent is given in the product description).

8-Iodo-2-phenylquinoline (2a). 8-Iodo-2-phenylquinoline (**2a**) was obtained from 2-phenylquinoline (**1a**, 0.21 g) using the general procedure 2 (eluent: 9 : 1 heptane–AcOEt) in 74% yield (0.25 g) as a yellow solid: mp 89 °C; IR (ATR): 2349, 1596, 1483, 1284, 954, 835, 760, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.23 (dd, 1H, J = 7.4 and 8.0 Hz), 7.48–7.58 (m, 3H), 7.80 (dd, 1H, J = 1.3 and 8.0 Hz), 7.95 (d, 1H, J = 8.6 Hz), 8.13 (d, 1H, J = 8.6 Hz), 8.33–8.38 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 104.7, 119.2, 127.5, 127.7, 127.8, 128.4, 128.9, 129.0, 129.1, 129.9, 137.5, 138.7, 140.1, 146.7, 157.7.

8-Iodo-2-(2-naphthyl)quinoline (2b). 8-Iodo-2-(2-naphthyl)-quinoline (**2b**) was obtained from 2-(2-naphthyl)quinoline (**1b**, 0.26 g) using the general procedure 2 (eluent: 1 : 1 heptane–CH_2Cl_2) in 54% yield (0.21 g) as a yellow solid: mp 210 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.19 (dd, 1H, J = 7.5 and 8.0 Hz), 7.53 (m, 2H), 7.74 (dd, 1H, J = 1.2 and 8.0 Hz), 7.88–8.09 (m, 5H), 8.34 (dd, 1H, J = 1.2 and 7.5 Hz), 8.60 (dd, 1H, J = 1.7 and 8.6 Hz), 8.68 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 104.8, 119.3, 125.2, 126.4, 127.0, 127.3, 127.5, 127.7, 127.8, 128.4, 128.7, 129.0, 133.5, 134.2, 136.0, 137.5, 140.1, 146.8, 157.5; HRMS (ESI): calcd for $C_{19}H_{12}IN$ $[M + H]^+$ 381.0014, found 381.0012.

8-Iodo-2-(3-iodo-4-methoxyphenyl)quinoline (3c). 8-Iodo-2-(3-iodo-4-methoxyphenyl)quinoline (**3c**) was obtained from 2-(4-methoxyphenyl)quinoline (**1c**, 0.24 g) using the general procedure 2 (eluent: 4 : 1 heptane–AcOEt) in 61% yield (0.30 g) as a yellow solid: mp 158 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 3.97 (s, 3H), 6.98 (d, 1H, J = 8.7 Hz), 7.22 (dd, 1H, J = 7.5 and 8.0 Hz), 7.78 (dd, 1H, J = 1.2 and 8.0 Hz), 7.86 (d, 1H, J = 8.6 Hz), 8.1 (d, 1H, J = 8.6 Hz), 8.33 (dd, 1H, J = 1.2 and 7.5 Hz), 8.37 (dd, 1H, J = 2.2 and 8.7 Hz), 8.74 (d, 1H, J = 2.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 56.7, 86.5, 104.5, 111.0, 118.6, 127.5, 127.6, 128.4, 129.3, 133.2, 137.7, 138.9, 140.3, 146.7, 155.9, 159.7; HRMS (ESI): calcd for $C_{16}H_{11}I_2NO$ $[M + H]^+$ 486.8930, found 486.8927.

11-Iodo-11*H*-indeno[1,2-*b*]quinoline (2d). 11-Iodo-11*H*-indeno[1,2-*b*]quinoline (**2d**) was obtained from 11*H*-indeno[1,2-*b*]quinoline (**1d**, 0.22 g) using the general procedure 2 (eluent: 4 : 1 heptane–AcOEt) in 4% yield (14 mg) as a yellow solid: mp 211 °C (rapidly decomposes by loss of iodine); IR (ATR): 3742, 3417, 3238, 2925, 2329, 1717, 1621, 1459, 1380, 1257, 1175, 1138, 856, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 5.51 (s, 1H), 7.48–7.55 (m, 3H), 7.71 (ddd, 1H, J = 1.4, 6.9 and 8.4), 7.81 (m, 1H), 7.88 (dd, 1H, J = 1.2 and 8.1), 8.23 (br d, 1H, J = 8.4), 8.33 (m, 2H).

11,11-Diiodo-11*H*-indeno[1,2-*b*]quinoline (3d). 11,11-Diiodo-11*H*-indeno[1,2-*b*]quinoline (**3d**) was obtained from 11*H*-indeno-[1,2-*b*]quinoline (**1d**, 0.22 g) using the general procedure 2 (eluent: 4 : 1 heptane–AcOEt) in 51% yield (0.24 g) as an orange liquid: IR (ATR): 3333, 2933, 2345, 1713, 1621, 1604, 1578, 1387, 1039, 924, 864, 766 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.52–7.91 (m, 6H), 8.12 (m, 1H), 8.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 26.2, 122.0, 124.3, 126.6, 127.4, 128.3, 130.0, 130.4, 130.7, 131.8, 132.3, 132.7, 135.8, 137.6, 144.0, 150.8; HRMS (ESI): calcd for $C_{16}H_9I_2N$ $[M + H]^+$ 468.8824, found 468.8820.

2-(6-Iodo-3-pyridyl)quinoline (2f). 2-(6-Iodo-3-pyridyl)quinoline (**2f**) was obtained from 2-(3-pyridyl)quinoline (**1f**, 0.21 g) using the general procedure 2 (eluent: 4 : 1 heptane–AcOEt) in 47% yield (0.16 g) as a yellow solid: mp 151 °C; IR (ATR): 2925, 1737, 1420, 1380, 1015, 793, 757 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.57 (ddd, 1H, J = 0.9, 7.0 and 7.9 Hz), 7.76 (ddd, 1H, J = 1.3, 7.0 and 8.4 Hz), 7.85 (m, 3H), 8.16 (m, 2H), 8.26 (d, 1H, J = 8.6 Hz), 9.07 (d, 1H, J = 2.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 118.3, 119.2, 127.3, 127.6, 127.7, 129.6, 130.5, 134.5, 135.2, 136.8,

137.8, 148.2, 149.7, 153.5; HRMS (ESI): calcd for $C_{14}H_9IN_2$ $[M + H]^+$ 331.9810, found 331.9804.

2-(2-Iodo-3-pyridyl)quinoline (2f′). 2-(2-Iodo-3-pyridyl)quinoline (**2f′**) was obtained from 2-(3-pyridyl)quinoline (**1f**, 0.21 g) using the general procedure 2 (eluent: 4 : 1 heptane–AcOEt) in 20% yield (66 mg) as a yellow solid: mp 108 °C; IR (ATR): 3039, 2922, 2849, 1740, 1594, 1570, 1555, 1548, 1501, 1421, 1380, 1046, 1025, 834, 802, 728 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.40 (dd, 1H, $J = 4.7$ and 7.6 Hz), 7.62 (ddd, 1H, $J = 1.2$, 6.9 and 8.1 Hz), 7.70 (d, 1H, $J = 8.5$ Hz), 7.78 (ddd, 1H, $J = 1.5$, 6.9 and 8.3 Hz), 7.80 (dd, 1H, $J = 2.0$ and 7.6 Hz), 7.90 (dd, 1H, $J = 1.2$ and 8.1 Hz), 8.16 (br d, 1H, $J = 8.3$ Hz), 8.27 (br d, 1H, $J = 8.5$ Hz), 8.43 (dd, 1H, $J = 2.0$ and 4.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 120.3, 122.4, 123.1, 127.3, 127.4, 127.8, 129.7, 130.3, 136.4, 137.8, 143.1, 147.9, 150.3, 158.6; HRMS (ESI): calcd for $C_{14}H_9IN_2$ $[M + H]^+$ 331.9810, found 331.9802.

2-(5-Iodo-2-furyl)quinoline (2g). 2-(5-Iodo-2-furyl)quinoline (**2g**) was obtained from 2-(2-furyl)quinoline (**1g**, 0.20 g) using the general procedure 2 (eluent: 9 : 1 heptane–AcOEt) in 71% yield (0.23 g) as a brown solid: mp 159 °C; IR (ATR): 1595, 1500, 1066, 1013, 780 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 6.75 (d, 1H, $J = 3.4$ Hz), 7.17 (d, 1H, $J = 3.4$ Hz), 7.50 (ddd, 1H, $J = 1.2$, 6.9 and 8.1 Hz), 7.70 (ddd, 1H, $J = 1.3$, 6.9 and 8.7 Hz), 7.78 (dd, 1H, $J = 1.3$ and 8.1 Hz), 7.82 (d, 1H, $J = 8.6$ Hz), 8.09 (br d, 1H, $J = 8.7$ Hz), 8.16 (br d, 1H, $J = 8.6$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 90.5, 112.8, 117.3, 123.2, 126.6, 127.4, 127.7, 129.2, 130.2, 137.1, 147.8, 147.9, 159.0; HRMS (ESI): calcd for $C_{13}H_8INO$ $[M + H]^+$ 320.9651, found 320.9652.

2-(5-Iodo-2-thienyl)quinoline (2h). 2-(5-Iodo-2-thienyl)quinoline (**2h**) was obtained from 2-(2-thienyl)quinoline (**1h**, 0.21 g) using the general procedure 2 (eluent: 3 : 2 heptane–CH_2Cl_2) in 52% yield (0.18 g) as a yellow solid: mp 156 °C; IR (ATR): 1595, 1499, 1418, 819, 782 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.31 (d, 1H, $J = 3.9$ Hz), 7.38 (d, 1H, $J = 3.9$ Hz), 7.50 (ddd, 1H, $J = 1.2$, 6.9 and 8.1 Hz), 7.71 (ddd, 1H, $J = 1.5$, 6.9 and 8.4 Hz), 7.72 (d, 1H, $J = 8.6$ Hz), 7.78 (br d, 1H, $J = 8.1$ Hz), 8.07 (br d, 1H, $J = 8.4$ Hz), 8.15 (br d, 1H, $J = 8.6$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 78.3, 117.0, 126.4, 126.9, 127.3, 127.6, 129.2, 130.1, 136.9, 138.1, 148.0, 151.3, 151.3.

2-(3,5-Diiodo-2-thienyl)quinoline (3h). 2-(3,5-Diiodo-2-thienyl)quinoline (**3h**) was obtained from 2-(2-thienyl)quinoline (**1h**, 0.21 g) using the general procedure 2 (eluent: 3 : 2 heptane–CH_2Cl_2) in 12% yield (56 mg) as a yellow solid: mp 156 °C; IR (ATR): 1590, 1493, 1422, 1321, 949, 785, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.35 (s, 1H), 7.55 (ddd, 1H, $J = 1.2$, 6.9 and 8.1 Hz), 7.73 (ddd, 1H, $J = 1.3$, 6.9 and 8.5 Hz), 7.82 (dd, 1H, $J = 1.3$ and 8.1 Hz), 8.10 (br d, 1H, $J = 8.5$ Hz), 8.23 (br d, 1H, $J = 8.7$ Hz), 8.29 (d, 1H, $J = 8.7$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 79.6, 103.5, 117.5, 127.2, 127.5, 127.7, 128.4, 137.6, 138.1, 140.5, 146.7, 151.1, 152.1.

General procedure 3 for the deprotonative metallation using the lithium–copper base followed by aroylation

A stirred cooled (0 °C) solution of LiTMP prepared at 0 °C in THF (3 mL) from 2,2,6,6-tetramethylpiperidine (0.34 mL, 2.0 mmol) and BuLi (1.6 M hexanes solution, 2.0 mmol) was treated with TMEDA (0.15 mL, 1.0 mmol) and CuCl (99 mg, 1.0 mmol). The mixture was stirred for 15 min at 0 °C before introduction of the required substrate (1.0 mmol). After 2 h at rt, a solution of 2-chlorobenzoyl chloride (0.25 mL, 2.0 mmol) in THF (3 mL) was added. The mixture was stirred at 60 °C overnight before addition of a 1 M aqueous solution of NaOH (10 mL) and extraction with Et_2O (2 × 20 mL). After washing the organic phase with an aqueous saturated solution of NH_4Cl (10 mL) and drying over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure, and the product was isolated after purification by flash chromatography on silica gel (the eluent is given in the product description).

8-(2-Chlorobenzoyl)-2-phenylquinoline (4a). 8-(2-Chlorobenzoyl)-2-phenylquinoline (**4a**) was obtained from 2-phenylquinoline (**1a**, 0.21 g) using the general procedure 3 (eluent: 19 : 1 heptane–AcOEt) in 58% yield (0.20 g) as a yellow powder; mp 126 °C; IR (ATR): 3627, 3496, 3056, 2607, 1665, 1584, 1544, 1437, 1344, 1288, 1239, 1074, 1033, 817, 751, 700, 688 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.15–7.32 (m, 6H), 7.42 (dd, 2H, $J = 1.5$ and 8.2 Hz), 7.52 (dd, 1H, $J = 7.3$ and 8.0 Hz), 7.57–7.60 (m, 1H), 7.76 (d, 1H, $J = 8.7$ Hz), 7.88 (dd, 1H, $J = 1.4$ and 8.1 Hz), 8.07 (dd, 1H, $J = 1.5$ and 7.2 Hz) 8.08 (d, 1H, $J = 8.7$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 118.6 (CH), 126.1 (CH), 126.8 (CH), 127.0 (C), 127.4 (2CH), 128.5 (2CH), 129.7 (CH), 130.4 (CH), 130.7 (CH), 131.3 (CH), 131.8 (CH), 131.9 (CH), 132.1 (C), 136.9 (CH), 138.3 (C), 138.5 (C), 141.5 (C), 145.9 (C), 156.4 (C), 197.2 (C); HRMS (ASAP): calcd for $C_{22}H_{15}{}^{35}ClNO$ $[M + H]^+$ 344.0842, found 344.0842.

8-(2-Chlorobenzoyl)-2-(2-naphthyl)quinoline (4b). 8-(2-Chlorobenzoyl)-2-(2-naphthyl)quinoline (**4b**) was obtained from 2-(2-naphthyl)quinoline (**1b**, 0.26 g) using the general procedure 3 (eluent: 4 : 1 heptane–AcOEt) in 30% yield (0.12 g) as a yellow powder: mp 192 °C; IR (ATR): 3050, 2345, 1673, 1590, 1558, 1284, 1265, 1036, 933, 827, 809, 755, 744, 727 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.40–7.53 (m, 5H), 7.60–7.75 (m, 4H), 7.81–7.87 (m, 2H), 8.02–8.06 (m, 2H), 8.14 (s, 1H), 8.67 (dd, 1H, $J = 1.5$ and 7.2 Hz), 8.26 (d, 1H, $J = 8.7$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 118.9 (CH), 124.8 (CH), 126.2 (CH), 126.3 (CH), 126.8 (CH), 126.9 (CH), 127.0 (CH), 127.7 (CH), 128.1 (CH), 128.9 (CH), 130.5 (CH), 130.8 (CH), 131.5 (CH), 131.8 (CH), 131.9 (CH), 132.2 (C), 133.4 (C), 134.1 (C), 136.0 (C), 136.9 (CH), 137.9 (C), 138.4 (C), 141.5 (C), 146.1 (C), 156.3 (C), 197.3 (C); HRMS (ESI): calcd for $C_{26}H_{17}{}^{35}ClNO$ $[M + H]^+$ 394.0999, found 394.1009.

2-(5-(2-Chlorobenzoyl)-2-thienyl)quinoline (4h). 2-(5-(2-Chlorobenzoyl)-2-thienyl)quinoline (**4h**) was obtained from 2-(2-thienyl)quinoline (**1h**, 0.21 g) using the general procedure 3 (eluent: 9 : 1 heptane–AcOEt) in 62% yield as a yellow powder: mp 160 °C; IR (ATR): 3750, 3060, 2329, 1646, 1592, 1471, 1426, 1300, 1263, 1237, 1049, 854, 820, 761, 749, 739, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.25–7.45 (m, 6H), 7.59–7.71 (m, 4H), 7.8 (d, 1H, $J = 8.4$ Hz), 8.1 (d, 1H, $J = 8.5$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 117.8 (CH), 126.3 (CH), 126.7 (CH), 127.1 (CH), 127.7 (CH), 127.8 (C), 129.0 (CH), 129.6 (CH), 130.3 (CH), 130.4 (C), 131.3 (CH), 131.4 (CH), 136.4 (CH), 137.1 (CH), 138.4 (C), 144.5 (C), 148.1 (C), 151.0 (C), 154.5 (C), 187.3 (C); HRMS (ESI): calcd for $C_{20}H_{12}{}^{35}ClNOS$ $[M + H]^+$ 350.0406, found 350.0411.

2-Phenyl-11*H*-indeno[1,2-*h*]quinolin-11-one (5a). A degassed mixture of K_2CO_3 (0.28 g, 2.0 mmol), $Pd(OAc)_2$ (11 mg, 5 mol%, 50 μmol), $Cy_3P{\cdot}HBF_4$ (37 mg, 10 mol%, 0.10 mmol), 8-(2-chlorobenzoyl)-2-phenylquinoline (**4a**, 0.34 g, 1.0 mmol) in DMF (4 mL) was heated at 130 °C for 24 h. After filtration over a celite pad, washing using CH_2Cl_2 (3 × 10 mL), and removal of the solvents under reduced pressure, the product was isolated after purification by flash chromatography on silica gel (eluent: 9 : 1 heptane–AcOEt) in 45% yield (0.14 g) as a yellow powder; mp 164 °C; IR (ATR): 3623, 2921, 2345, 1704, 1601, 1547, 1462, 1312, 1278, 1175, 1152, 844, 758, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.34 (1H, dt, $J = 0.9$ and 7.3 Hz), 7.45–7.59 (m, 5H), 7.69–7.73 (m, 2H), 7.89 (d, 1H, $J = 8.7$ Hz), 7.98 (d, 1H, $J = 8.1$ Hz), 8.15 (d, 1H, $J = 8.7$ Hz), 8.36–8.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 118.5 (CH), 118.7 (CH), 120.4 (CH), 124.1 (CH), 127.1 (C), 127.9 (2CH), 128.5 (C), 129.0 (2CH), 130.0 (CH), 130.3 (CH), 134.1 (CH), 134.7 (C), 135.5 (CH), 137.3 (CH), 138.8 (C), 143.1 (C), 144.9 (C), 149.7 (C), 159.9 (C), 192.8 (C); HRMS (ASAP): calcd for $C_{22}H_{14}NO$ $[M + H]^+$ 308.1075, found 308.1074.

Crystallography

The samples were studied with graphite monochromatized Mo-Kα radiation ($\lambda = 0.71073$ Å). X-ray diffraction data were collected at $T = 150(2)$ K using APEXII Bruker-AXS diffractometer. The structure was solved by direct methods using the SIR97 program,[33] and then refined with full-matrix least-square methods based on F2 (SHELX-97)[34] with the aid of the WINGX program.[35] All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. H atoms were finally included in their calculated positions. Molecular diagrams were generated by ORTEP-3 (version 2.02).

Crystal data for 1e. $C_{17}H_{21}N$, $M = 239.35$, monoclinic, $P2_1/a$, $a = 12.2168(5)$, $b = 8.6679(3)$, $c = 12.9252(5)$ Å, $\beta = 98.611(2)°$, $V = 1353.27(9)$ Å^3, $Z = 4$, $d = 1.175$ g cm^{-3}, $\mu = 0.067$ mm^{-1}. A final refinement on F^2 with 3090 unique intensities and 166 parameters converged at $\omega R(F^2) = 0.107$ ($R(F) = 0.0406$) for 2454 observed reflections with $I > 2\sigma(I)$.

Crystal data for 2a. $C_{15}H_{10}IN$, $M = 331.14$, orthorhombic, $Pbcn$, $a = 11.1278(3)$, $b = 12.2969(4)$, $c = 18.3090(6)$ Å, $V = 2505.36(13)$ Å^3, $Z = 8$, $d = 1.756$ g cm^{-3}, $\mu = 2.532$ mm^{-1}. A final refinement on F^2 with 2861 unique intensities and 154 parameters converged at $\omega R(F^2) = 0.0607$ ($R(F) = 0.0295$) for 2261 observed reflections with $I > 2\sigma(I)$.

Crystal data for 2h. $C_{13}H_8INS$, $M = 337.16$, monoclinic, $P2_1/n$, $a = 6.0678(2)$, $b = 9.6385(3)$, $c = 19.7538(5)$ Å, $\beta = 94.1170(10)°$, $V = 1152.31(6)$ Å^3, $Z = 4$, $d = 1.943$ g cm^{-3}, $\mu = 2.928$ mm^{-1}. A final refinement on F^2 with 2632 unique intensities and 145 parameters converged at $\omega R(F^2) = 0.0457$ ($R(F) = 0.0207$) for 2393 observed reflections with $I > 2\sigma(I)$.

Crystal data for 3h. $C_{13}H_7I_2NS$, $M = 463.06$, monoclinic, $P2_1/c$, $a = 4.1495(2)$, $b = 12.4526(5)$, $c = 25.0266(9)$ Å, $\beta = 90.217(2)°$, $V = 1293.17(9)$ Å^3, $Z = 4$, $d = 2.378$ g cm^{-3}, $\mu = 5.000$ mm^{-1}. A final refinement on F^2 with 2962 unique intensities and 154 parameters converged at $\omega R(F^2) = 0.0698$ ($R(F) = 0.0259$) for 2662 observed reflections with $I > 2\sigma(I)$.

Crystal data for 4a. $C_{22}H_{14}ClNO$, $M = 343.79$, monoclinic, $P2_1/c$, $a = 7.6161(4)$, $b = 10.4578(4)$, $c = 20.7837(8)$ Å, $\beta = 98.336(2)°$, $V = 1637.88(12)$ Å^3, $Z = 4$, $d = 1.394$ g cm^{-3}, $\mu = 0.242$ mm^{-1}. A final refinement on F^2 with 3738 unique intensities and 226 parameters converged at $\omega R(F^2) = 0.0924$ ($R(F) = 0.0402$) for 2991 observed reflections with $I > 2\sigma(I)$.

Crystal data for 4b. $C_{26}H_{16}ClNO$, $M = 393.85$, monoclinic, $P2_1/c$, $a = 12.2577(4)$, $b = 7.6576(2)$, $c = 20.6631(7)$ Å, $\beta = 102.2370(10)°$, $V = 1895.46(10)$ Å^3, $Z = 4$, $d = 1.38$ g cm^{-3}, $\mu = 0.219$ mm^{-1}. A final refinement on F^2 with 4335 unique intensities and 262 parameters converged at $\omega R(F^2) = 0.1087$ ($R(F) = 0.043$) for 3362 observed reflections with $I > 2\sigma(I)$.

Crystal data for 5a. $C_{22}H_{13}NO$, $M = 307.33$, monoclinic, $P2_1/n$, $a = 11.9851(4)$, $b = 8.0059(3)$, $c = 16.6683(8)$ Å, $\beta = 110.6260(10)°$, $V = 1496.83(10)$ Å^3, $Z = 4$, $d = 1.364$ g cm^{-3}, $\mu = 0.084$ mm^{-1}. A final refinement on F^2 with 3420 unique intensities and 218 parameters converged at $\omega R(F^2) = 0.107$ ($R(F) = 0.0422$) for 2679 observed reflections with $I > 2\sigma(I)$.

Acknowledgements

We are grateful to the Agence Nationale de la Recherche for financial support to NM and GB. FM thanks the Institut Universitaire de France and Rennes Métropole for financial support. We also thank Thermo Fischer for generous gift of 2,2,6,6-tetramethylpiperidine.

Notes and references

1 T. Eicher, S. Hauptmann and A. Speicher, *The Chemistry of Heterocycles*, Wiley-VCH, New York, 2nd edn, 2003.
2 J. A. Joule and K. Mills, *Heterocyclic Chemistry*, Wiley-Blackwell, Chichester, 5th edn, 2010.
3 (*a*) H. W. Gschwend and H. R. Rodriguez, *Org. React.*, 1979, **26**, 1–360; (*b*) P. Beak and V. Snieckus, *Acc. Chem. Res.*, 1982, **15**, 306–312; (*c*) V. Snieckus, *Chem. Rev.*, 1990, **90**, 879–933; (*d*) T. G. Gant and A. I. Meyers, *Tetrahedron*, 1994, **50**, 2297–2360; (*e*) M. Schlosser, *Organometallics in Synthesis*, ed. M. Schlosser, Wiley, 2nd edn, 2002, ch. I.
4 (*a*) F. Mongin and G. Queguiner, *Tetrahedron*, 2001, **57**, 4059–4090; (*b*) J.-M. L'Helgoual'ch, F. Chevallier and F. Mongin, *Targets Heterocycl. Syst.*, 2007, **11**, 155–180; (*c*) F. Chevallier and F. Mongin, *Top. Heterocycl. Chem.*, 2013, **31**, 93–130.
5 (*a*) R. E. Mulvey, *Organometallics*, 2006, **25**, 1060–1075; (*b*) R. E. Mulvey, F. Mongin, M. Uchiyama and Y. Kondo, *Angew. Chem., Int. Ed.*, 2007, **46**, 3802–3824; (*c*) R. E. Mulvey, *Acc. Chem. Res.*, 2009, **42**, 743–755; (*d*) B. Haag, M. Mosrin, H. Ila, V. Malakhov and P. Knochel, *Angew. Chem., Int. Ed.*, 2011, **50**, 9794–9824; (*e*) F. Mongin and M. Uchiyama, *Curr. Org. Chem.*, 2011, **15**, 2340–2361; (*f*) F. Mongin and A. Harrison-Marchand, *Chem. Rev.*, 2013, **113**, 7563–7727; (*g*) R. E. Mulvey, *Dalton Trans.*, 2013, **42**, 6676–6693.
6 See for example: (*a*) M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff and P. Knochel, *Angew. Chem., Int. Ed.*, 2010, **49**, 5451–5455; (*b*) M. Jeganmohan and P. Knochel, *Angew. Chem., Int. Ed.*, 2010, **49**, 8520–8524; (*c*)

C. J. Rohbogner, S. Wirth and P. Knochel, *Org. Lett.*, 2010, **12**, 1984–1987; (*d*) M. Jaric, B. A. Haag, S. M. Manolikakes and P. Knochel, *Org. Lett.*, 2011, **13**, 2306–2309; (*e*) S. M. Manolikakes, M. Jaric, K. Karaghiosoff and P. Knochel, *Chem. Commun.*, 2013, **49**, 2124–2126; (*f*) C. Metallinos and K. Stromski, *Top. Heterocycl. Chem.*, 2013, **31**, 65–92.

7 (*a*) T. T. Nguyen, F. Chevallier, V. Jouikov and F. Mongin, *Tetrahedron Lett.*, 2009, **50**, 6787–6790; (*b*) T. T. Nguyen, N. Marquise, F. Chevallier and F. Mongin, *Chem.–Eur. J.*, 2011, **17**, 10405–10416; (*c*) K. Snégaroff, T. T. Nguyen, N. Marquise, Y. S. Halauko, P. J. Harford, T. Roisnel, V. E. Matulis, O. A. Ivashkevich, F. Chevallier, A. E. H. Wheatley, P. C. Gros and F. Mongin, *Chem.–Eur. J.*, 2011, **17**, 13284–13297; (*d*) N. Marquise, P. J. Harford, F. Chevallier, T. Roisnel, A. E. H. Wheatley, P. C. Gros and F. Mongin, *Tetrahedron Lett.*, 2013, **54**, 3154–3157; (*e*) N. Marquise, P. J. Harford, F. Chevallier, T. Roisnel, V. Dorcet, A.-L. Gagez, S. Sablé, L. Picot, V. Thiéry, A. E. H. Wheatley, P. C. Gros and F. Mongin, *Tetrahedron*, 2013, **69**, 10123–10133.

8 J. M. L'Helgoual'ch, A. Seggio, F. Chevallier, M. Yonehara, E. Jeanneau, M. Uchiyama and F. Mongin, *J. Org. Chem.*, 2008, **73**, 177–183.

9 P. García-Álvarez, R. E. Mulvey and J. A. Parkinson, *Angew. Chem., Int. Ed.*, 2011, **50**, 9668–9671.

10 (*a*) A. Seggio, M.-I. Lannou, F. Chevallier, D. Nobuto, M. Uchiyama, S. Golhen, T. Roisnel and F. Mongin, *Chem.–Eur. J.*, 2007, **13**, 9982–9989; (*b*) A. Seggio, F. Chevallier, M. Vaultier and F. Mongin, *J. Org. Chem.*, 2007, **72**, 6602–6605; (*c*) G. Dayaker, A. Sreeshailam, F. Chevallier, T. Roisnel, P. Radha Krishna and F. Mongin, *Chem. Commun.*, 2010, **46**, 2862–2864; (*d*) K. Snégaroff, S. Komagawa, F. Chevallier, P. C. Gros, S. Golhen, T. Roisnel, M. Uchiyama and F. Mongin, *Chem.–Eur. J.*, 2010, **16**, 8191–8201; (*e*) F. Chevallier, Y. S. Halauko, C. Pecceu, I. F. Nassar, T. U. Dam, T. Roisnel, V. E. Matulis, O. A. Ivashkevich and F. Mongin, *Org. Biomol. Chem.*, 2011, **9**, 4671–4684; (*f*) G. Dayaker, D. Tilly, F. Chevallier, G. Hilmersson, P. C. Gros and F. Mongin, *Eur. J. Org. Chem.*, 2012, 6051–6057; (*g*) F. Chevallier, T. Blin, E. Nagaradja, F. Lassagne, T. Roisnel, Y. S. Halauko, V. E. Matulis, O. A. Ivashkevich and F. Mongin, *Org. Biomol. Chem.*, 2012, **10**, 4878–4885; (*h*) A. Sreeshailam, G. Dayaker, D. V. Ramana, F. Chevallier, T. Roisnel, S. Komagawa, R. Takita, M. Uchiyama, P. Radha Krishna and F. Mongin, *RSC Adv.*, 2012, **2**, 7030–7032; (*i*) D. Tilly, K. Snégaroff, G. Dayaker, F. Chevallier, P. C. Gros and F. Mongin, *Tetrahedron*, 2012, **68**, 8761–8766; (*j*) R. R. Kadiyala, D. Tilly, E. Nagaradja, T. Roisnel, V. E. Matulis, O. A. Ivashkevich, Y. S. Halauko, F. Chevallier, P. C. Gros and F. Mongin, *Chem.–Eur. J.*, 2013, **19**, 7944–7960; (*k*) E. Nagaradja, F. Chevallier, T. Roisnel, V. Dorcet, Y. S. Halauko, O. A. Ivashkevich, V. E. Matulis and F. Mongin, *Org. Biomol. Chem.*, 2014, **12**, 1475–1487.

11 A.-H. Li, E. Ahmed, X. Chen, M. Cox, A. P. Crew, H.-Q. Dong, M. Jin, L. Ma, B. Panicker, K. W. Siu, A. G. Steinig, K. M. Stolz, P. A. R. Tavares, B. Volk, Q. Weng, D. Werner and M. J. Mulvihill, *Org. Biomol. Chem.*, 2007, **5**, 61–64.

12 N. Boudet, J. R. Lachs and P. Knochel, *Org. Lett.*, 2007, **9**, 5525–5528.

13 Y. Kondo, M. Shilai, M. Uchiyama and T. Sakamoto, *J. Am. Chem. Soc.*, 1999, **121**, 3539–3540.

14 X. Qu, Q. Liu, X. Ji, H. Chen, Z. Zhou and Z. Shen, *Chem. Commun.*, 2012, **48**, 4600–4602.

15 (*a*) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359–1469; (*b*) V. Ritleng, C. Sirlin and M. Pfeffer, *Chem. Rev.*, 2002, **102**, 1731–1770; (*c*) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094–5115.

16 (*a*) L.-C. Campeau, M. Parisien, A. Jean and K. Fagnou, *J. Am. Chem. Soc.*, 2006, **128**, 581–590; (*b*) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174–238; (*c*) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792–9826; (*d*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147–1169.

17 M. R. Netherton and G. C. Fu, *Org. Lett.*, 2001, **3**, 4295–4298.

18 R. R. Fraser, T. S. Mansour and S. Savard, *J. Org. Chem.*, 1985, **50**, 3232–3234.

19 A. Kütt, I. Leito, I. Kaljurand, L. Sooväli, V. M. Vlasov, L. M. Yagupolskii and I. A. Koppel, *J. Org. Chem.*, 2006, **71**, 2829–2838.

20 M. Meot-Ner, J. F. Liebman and S. A. Kafafi, *J. Am. Chem. Soc.*, 1988, **110**, 5937–5941.

21 J. C. Del Valle and J. L. G. De Paz, *J. Mol. Struct.: THEOCHEM*, 1992, **86**, 481–491.

22 K. Shen, Y. Fu, J.-N. Li, L. Liu and Q.-X. Guo, *Tetrahedron*, 2007, **63**, 1568–1576.

23 S. Kheirjou, A. Abedin, A. Fattahi and M. M. Hashemi, *Comput. Theor. Chem.*, 2014, **1027**, 191–196.

24 V. E. Matulis, Y. S. Halauko, O. A. Ivashkevich and P. N. Gaponik, *J. Mol. Struct.: THEOCHEM*, 2009, **909**, 19–24.

25 E. Cances, B. Mennucci and J. Tomasi, *J. Chem. Phys.*, 1997, **107**, 3032–3041.

26 S. Konishi, S. Kawamorita, T. Iwai, P. G. Steel, T. B. Marder and M. Sawamura, *Chem.–Asian J.*, 2014, **9**, 434–438.

27 H. E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem.*, 1997, **62**, 7512–7515.

28 A. M. Berman, J. C. Lewis, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2008, **130**, 14926–14927.

29 R.-G. Xing, Y.-N. Li, Q. Liu, Y.-F. Han, X. Wei, J. Li and B. Zhou, *Synthesis*, 2011, 2066–2072.

30 A.-H. Li, D. J. Beard, H. Coate, A. Honda, M. Kadalbajoo, A. Kleinberg, R. Laufer, K. M. Mulvihill, A. Nigro, P. Rastogi, D. Sherman, K. W. Siu, A. G. Steinig, T. Wang, D. Werner, A. P. Crew and M. J. Mulvihill, *Synthesis*, 2010, 1678–1686.

31 A. Canas-Rodriguez, R. G. Canas and A. Mateo-Bernardo, *An. Quim., Ser. C*, 1987, **83**, 24–27.

32 R. Martinez, D. J. Ramon and M. Yus, *Tetrahedron*, 2006, **62**, 8988–9001.

33 A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori and R. Spagna, *J. Appl. Crystallogr.*, 1999, **32**, 115–119.
34 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 2008, **64**, 112–122.
35 L. J. Farrugia, *J. Appl. Crystallogr.*, 2012, **45**, 849–854.