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Transition-metal-free synthesis of 3-(1-pyrrolidinyl)quinolines and 3-(1-pyrrolidinyl)quinoline 1-oxides *via* a one-pot reaction of 3-(1-pyrrolidinyl)crotonates with nitrobenzenes†

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A carbanion of *tert*-butyl 3-(1-pyrrolidinyl)crotonate adds to nitrobenzenes to form σ^H-adducts, which in the presence of pivaloyl chloride and triethylamine are converted into 3-(1-pyrrolidinyl)quinolines or 3-(1-pyrrolidinyl)quinoline 1-oxides depending on the nitrobenzene structure. This is the first methodology in which a quinoline ring is constructed from a substrate bearing a pyrrolidinyl ring. Starting from optically pure enamines, the method allows synthesis of the corresponding chiral products without racemisation.

Introduction

Quinoline is a key building block in many naturally occurring and synthetically prepared compounds that have important practical applications.[1] Thus, the synthesis of substituted quinolines is still of substantial interest.[2] In recent years quinoline derivatives bearing a 1-pyrrolidinyl substituent at the 3-position have attracted attention due to their biological activity and potential applications as antimicrobials (antimalarial activity),[3] hepatitis C virus polymerase inhibitors,[4] antineoplastic (antitumor) agents,[5] as well as compounds for osteoporosis treatment.[6] Representative structures are shown in Fig. 1.

General methods for the synthesis of 3-(1-pyrrolidinyl)-quinolines consist of transition-metal-catalyzed replacement of halogen (mostly bromine) (Fig. 2, path **a**),[4,7] reaction of 3-aminoquinoline with 4-chlorobutyryl chloride followed by reduction with LiAlH₄ (path **b**),[3] ring-closing metathesis in 3-diallylaminoquinolines followed by hydrogenation (path **c**),[3] and alkylation of 3-aminoquinoline with 1,4-dibromobutane (path **d**).[3] One of the drawbacks of the recently developed methods for the synthesis of heterocycles, including quinolines, is the use of transition metal catalysts, which often requires arduous removal of the catalyst, particularly if the product has potential pharmaceutical applications.[8] Thus new transition-metal-free methodologies are still in demand.

Institute of Organic Chemistry Polish Academy of Sciences, ul. Kasprzaka 44/52, 01-224 Warsaw, Poland. E-mail: robert.bujok@icho.edu.pl, krzysztof.wojciechowski@icho.edu.pl

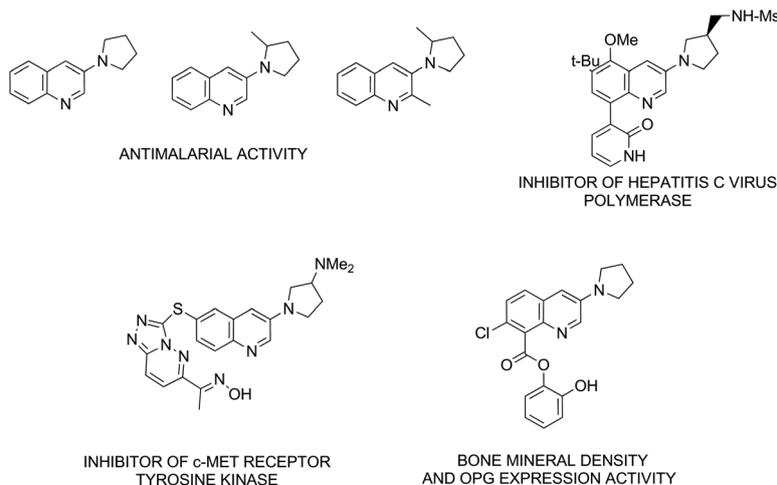†Electronic supplementary information (ESI) available. See DOI: 10.1039/c6ob02658c

Quinoline 1-oxides are usually obtained *via* direct oxidation of quinolines with peracids. Such oxidation will be ineffective if the quinoline derivative contains an amino group. Less widespread are methods in which the quinoline 1-oxides are formed as a result of interaction of the nitro group with adjacent substituents in *ortho*-substituted nitroarenes.[9] To the best of our knowledge, the synthesis of 3-(1-pyrrolidinyl)quinoline-1-oxides is still unexplored.

During our studies on reactions of carbanions with nitroarenes we have developed numerous methods for the synthesis of heterocycles, especially indoles and quinolines.[10,11] Particularly effective for the synthesis of quinolines were methods in which the σ^H-adducts formed by addition of allyl carbanions to nitroarenes were subsequently treated with a silylating agent[12] such as trialkylchlorosilane or bis-trimethyl-silylacetamide (BSA) or with an acyl chloride, preferably pivaloyl chloride.[12c]

Results and discussion

In this paper we present an efficient one-pot method for the synthesis of 3-(1-pyrrolidinyl)quinoline-2-carboxylic acid esters and the corresponding quinoline 1-oxides directly from nitrobenzenes. Unlike all the literature methods for the synthesis of 3-(1-pyrrolidinyl)quinoline, in this procedure a quinoline ring is constructed. Nitrobenzenes are cheap, commercially available starting materials, while quinoline derivatives are less abundant, so this synthesis is an interesting alternative to literature methodologies.

As a carbanion precursor we have chosen *tert*-butyl 3-(1-pyrrolidinyl)crotonate **1** prepared from *tert*-butyl acetoacetate and pyrrolidine in an excellent yield by simple mixing of

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Fig. 1 Selected 3-(1-pyrrolidinyl)quinolines exhibiting biological activity.
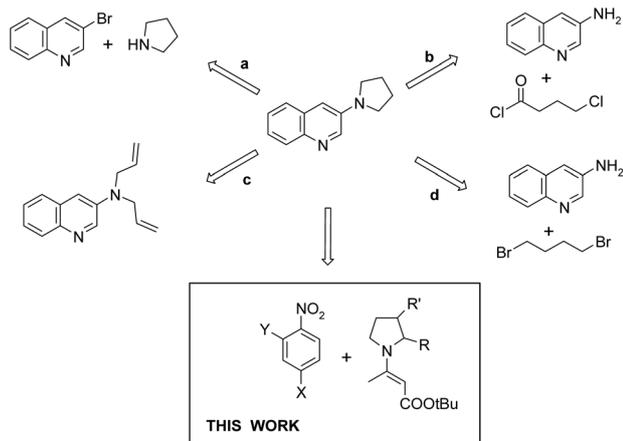

Fig. 2 Synthetic strategies towards 3-(1-pyrrolidinyl)-quinolines.

equimolar amounts of the reagents without solvent (Scheme 1). ^{1}H NMR and nuclear Overhauser effect (1D-NOE) experiments proved the exclusive formation of the *E*-isomer.

As a model nitroarene for testing the reaction conditions we have chosen 2,4-dichloronitrobenzene, because earlier studies on vicarious nucleophilic substitution of hydrogen in nitroarenes revealed its relatively high electrophilicity.[13]

In the initial experiment (Table 1) we used potassium *tert*-butoxide as a base for the generation of the carbanion and pivaloyl chloride to acylate the formed σ[H]-adduct. The reaction was carried out in THF at −70 °C. Unfortunately, this attempt
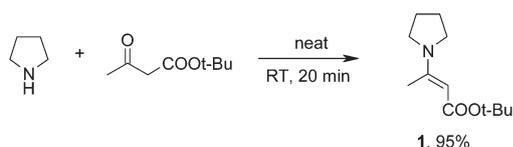
Scheme 1 Synthesis of enamine **1**.

Table 1 Effect of base on the yield of product **2a**
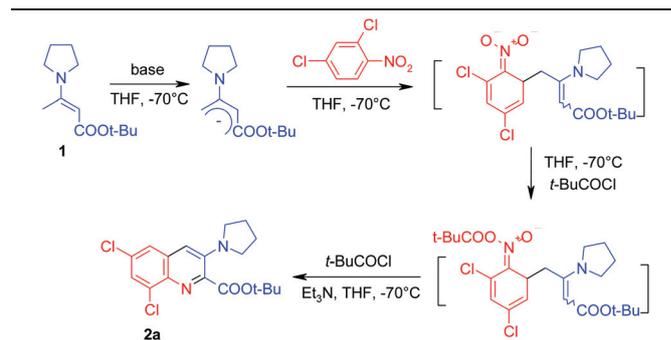
Base	Yield[a]
t-BuOK	0
LDA	24
n-BuLi	Traces of **2a** (TLC)
n-BuLi/NMP	12
n-BuLi/TMEDA	18
n-BuLi/HMPA	57

[a] The isolated yields are given.

was unsuccessful – no reaction with 2,4-dichloronitrobenzene occurred. Probably, potassium *tert*-butoxide is too weak a base to deprotonate the enamine **1**. Indeed, when we used a stronger base, namely lithium diisopropylamide, the expected *tert*-butyl 6,8-dichloro-3-(1-pyrrolidinyl)quinoline-2-carboxylate **2a** was obtained, but the yield was rather low (24%) and a large amount of by-products was formed. In the case of *n*-butyl-lithium only traces of the product **2a** (TLC) were observed in the absence of any compounds, decreasing the degree of aggregation of the base.

n-Butyllithium exists as a tetramer[14] in hexane/THF solution and HMPA is known to be the most effective reagent[14] that breaks organo-lithium oligomers and increases the activity of the organolithium compound. Taking this into consideration, we carried out the reaction with *n*-butyllithium in

the presence of 1 equivalent of HMPA. In this case, treatment of the formed σ[H]-adduct with triethylamine and pivaloyl chloride resulted in the formation of the ester **2a** in 57% yield. Attempts to replace HMPA by other reagents (*N*-methylpyrrolidone (NMP) and TMEDA) were not successful – yields have not exceeded 20%. Because of the multistep nature of the investigated reaction, we have found the result obtained in the presence of HMPA to be satisfactory and applied these conditions[15] to screen the scope of the reaction (Table 2).

The reactions of 2,4-disubstituted nitrobenzenes with the enamine **1** led to the expected quinoline derivatives **2a–2e** in 54–67% yields. As mentioned above, these are the overall yields of several steps.

Surprisingly, 4-substituted nitrobenzenes with no substituents at the 2-position react under analogous conditions to the enamine **1** to give *tert*-butyl 6-substituted 3-pyrrolidinyl-2-carboxylate-quinoline 1-oxides **3a–3h** instead of the expected quinolines. The reaction is of general character – 4-substituted nitrobenzenes with electron-withdrawing (CF$_3$, Cl) and electron-donating groups (CH$_3$, *t*-Bu) give quinoline 1-oxides, usually in *ca.* 50% yield.

In the case of the 2-chloronitrobezene complex a mixture of compounds was formed and no attempt was made to separate them. The mixture was formed probably due to the attack of the carbanion on the 4-position of 2-chloronitrobenzene.

To show the utility of our approach we have obtained carbanion precursors containing chiral pyrrolidines. Commercially available *N*-Boc-L-prolinol and *N*-Boc-D-prolinol were chosen for this purpose. Optically pure enamines **(S)-1a** and **(R)-1a**

were prepared in very good overall yields (Scheme 5; for details see the ESI†). Some of the biologically active quinolines contain substituents at the 3-position of the pyrrolidine ring, so the corresponding enamines **(S)-1b** and **(R)-1b** were also obtained (Scheme 2).

Chiral enamines **(S)-1a**, **(R)-1a**, **(S)-1b** and **(R)-1b** react with nitrobenzenes in a similar manner to achiral enamine **1**. Reaction with 2,4-disubstituted nitrobenzenes led to the corresponding non-racemic quinolines **4a–4d** and reaction with 4-substituted nitrobenzenes led to non-racemic quinoline 1-oxides **5a–5c**. The yields are somewhat lower than for achiral enamine **1**, but the results are still acceptable considering the complex nature of the obtained structures (Table 3).
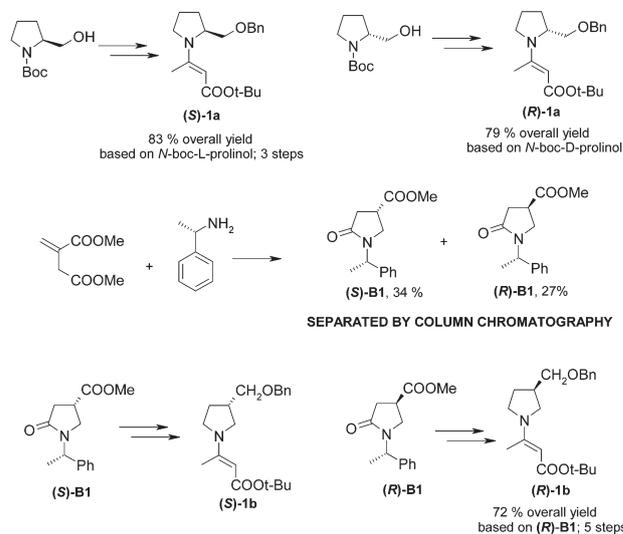
Scheme 2 Synthesis of optically pure enamines **(S)-1a**, **(R)-1a**, **(S)-1b** and **(R)-1b** (details are given in the ESI).

Table 2 Synthesis of *tert*-butyl 3-(1-pyrrolidinyl)quinoline-2-carboxylates **2a–2e** and *tert*-butyl 3-pyrrolidinyl-2-carboxylate-quinoline 1-oxides **3a–3h**[15]

			Yield[a]	
Product	X	Y	**2**	**3**
2a	Cl	Cl	57	—
2b	F	F	61	—
2c	Cl	OMe	67	—
2d	CH$_3$	Cl	54	—
2e	CH$_3$	F	55	—
3a	CF$_3$	H	—	38
3b	Cl	H	—	50
3c	I	H	—	50
3d	F	H	—	53
3e	SPh	H	—	50
3f	Ph	H	—	48
3g	CH$_3$	H	—	40
3h	*t*-Bu	H	—	33

[a] The isolated yields are given.

Table 3 Synthesis of optically pure *tert*-butyl 3-(1-pyrrolidinyl)-quinoline-2-carboxylates **4a–4d** and *tert*-butyl 3-pyrrolidinyl-2-carboxylate-quinoline 1-oxides **5a–5c**[15]

					Yield[a]	
Product	X	Y	R	R′	**4**	**5**
4a	Cl	Cl	(*S*)-CH$_2$OBn	H	37	—
4b	Cl	OMe	(*S*)-CH$_2$OBn	H	43	—
5a	I	H	(*S*)-CH$_2$OBn	H	—	35
5b	F	H	(*S*)-CH$_2$OBn	H	—	41
5c	F	H	(*R*)-CH$_2$OBn	H	—	40
4c	Cl	OMe	H	(*S*)-CH$_2$OBn	57	—
4d	F	F	H	(*R*)-CH$_2$OBn	40	—

[a] The isolated yields are given.

To verify the optical purity of the non-racemic products, the R-enantiomer of quinoline **4b** and the R-enantiomer of quinoline-1-oxide **5b** were synthesized and both enantiomers of the examined compounds were converted to diastereomeric salts with R-Mosher's acid. Diagnostic signals of each salt formed from the corresponding enantiomer could be clearly recognized in ^{1}H NMR spectra. Only one diastereoisomer was detected in each case, which proved that all the examined compounds are optically pure (Fig. 3).

The surprising selectivity of the reactions (in all cases only quinoline or quinoline 1-oxide was obtained depending on the structure of the nitrobenzene; a mixture of these products was never observed) suggests that two different mechanisms operate. To gain an insight into the mechanisms, a few control experiments were carried out.

First of all, reactions of 2,4-dichloronitrobenzene and 4-chloronitrobenzene with enamine **1** under standard conditions but in the absence of pivaloyl chloride were carried out. In both cases no reaction was observed. These results indicate that σ[H]-adducts formed from these nitrobenzenes do not undergo further reactions in the absence of t-BuCOCl and substrates are recovered after the hydrolysis of σ[H]-adducts during aqueous work-up. So in the presence of pivaloyl chloride both σ[H]-adducts are acylated and these intermediates are subsequently transformed into quinolines or quinoline 1-oxides depending on the character of the Y substituent (Scheme 3).

Acylated σ[H]-adduct (**I**) probably undergoes elimination of the pivalate anion. The formed nitroso group enters an intramolecular Ehrlich-Sachs[12a,e] reaction resulting in the formation of the corresponding 1-pivaloyloxy-dihydroquinoline derivative (**II**) (Scheme 4). When Y ≠ H due to steric interaction of the Y substituent and the bulky pivaloyloxy group, elimination of the pivalate anion takes place and quinoline **2a** is formed.

The formation of quinolone 1-oxides seems more difficult to explain. It could arise from nitro compound (**III**) (Scheme 5) via its intramolecular cyclization;[12c,16] however, experiments conducted in the absence of t-BuCOCl proved that the addition
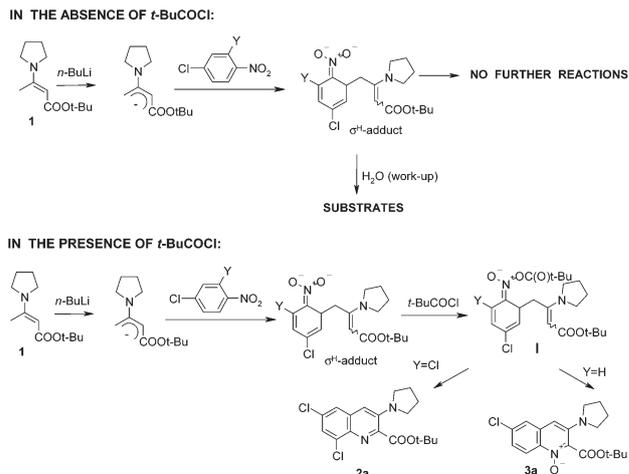
Scheme 3 Behaviour of σ[H]-adducts in the absence of pivaloyl chloride and in the presence of the reagent.
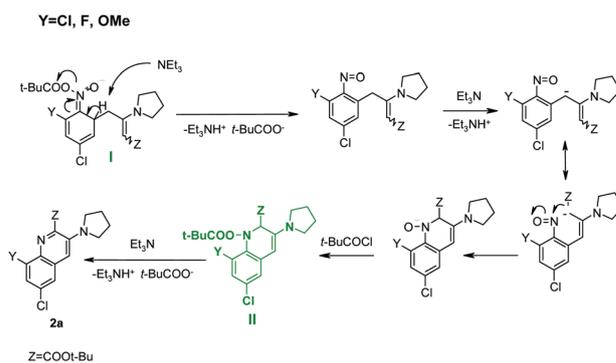
Scheme 4 Plausible mechanism for the synthesis of quinoline **2a**.
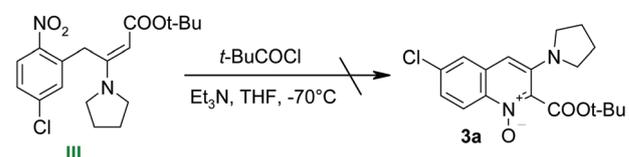
Scheme 5 Attempted conversion of nitrocompound (**III**) into quinoline 1-oxide **3a** under conditions employed for of synthesis of quinolines.

of the carbanion to nitroarene was reversible and the spontaneous oxidation of the σ[H]-adduct did not occur (Scheme 3).

On the other hand the intermediate (**III**) might be formed from other than σ[H]-adduct intermediates and then it could cyclize to quinoline 1-oxide **3a**. To check this hypothesis an appropriate nitrocompound (**III**) was synthesized and exposed to reaction conditions (Scheme 5). Product **3a** was not formed under these conditions – only the substrate and a moderate amount of polar by-products were observed. Thus quinoline 1-oxides are not formed via nitro-compound (**III**).

Based on these data, we suppose that 1-pivaloyloxy-dihydroquinoline derivative (**II**) is oxidized to 1-pivaloyloxy-quinoline
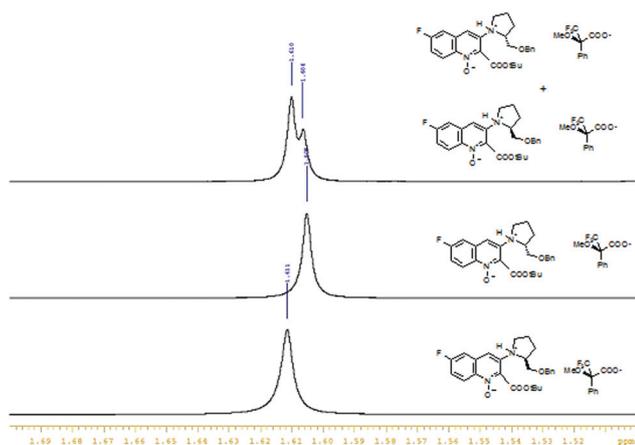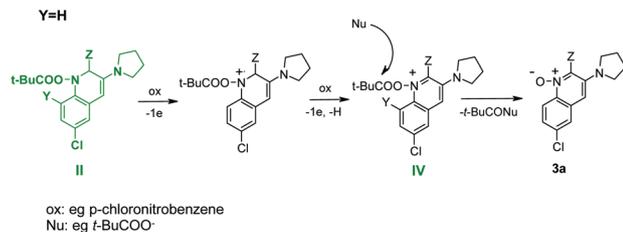

Fig. 3 Diagnostic signals of diastereoisomeric salts formed from **5b**, **5c** and R-Mosher's acid.

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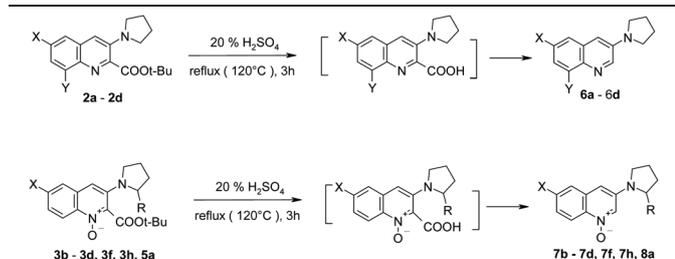**Scheme 6** Plausible mechanism for synthesis of quinoline 1-oxide **3a**.

(**IV**) by a nitrocompound (always used in excess) and then the pivaloyl group is attacked by a nucleophile (*e.g.* *t*-BuCOO⁻) leading to product **3a** (Scheme 6).

The *tert*-butoxycarbonyl group can be easily removed from compounds **2–3** by refluxing in 20% aqueous sulfuric acid. Hydrolysis and subsequent decarboxylation occurred, giving the expected products in good to excellent yields (81–97%) (Table 4).

The hydrolysis/decarboxylation domino reaction was also successfully performed for non-racemic quinoline 1-oxide **5a** – the expected product **8a** was obtained in 79% yield.
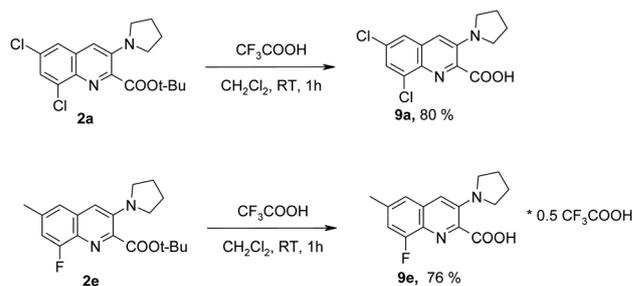
It is worth noting that treating a solution of *tert*-butyl esters **2a**, **2e** in dichloromethane with trifluoroacetic acid at room temperature resulted in the formation of the corresponding acids **9a**, **9e** in good yields of *ca.* 80% (Scheme 7). Elemental analysis indicated that compound **9a** was obtained as a free base (no fluorine present). In the case of compound **9e**, elemental analysis and ¹⁹F NMR spectroscopy suggest that the product contains "0.5 molecules" of trifluoroacetic acid.

Scheme 7 Transformation of COO*t*-Bu group into COOH group (the isolated yields are given).[18]

Probably, 2 molecules of compound **9e** are coordinated by 1 molecule of trifluoroacetic acid.

Conclusions

We have developed a one-pot, transition-metal-free method for the synthesis of 3-(1-pyrrolidinyl)quinolines or 3-(1-pyrrolidinyl)-quinoline 1-oxides depending on the structure of the starting materials (2,4-disubstituted or 4-substituted nitrobenzenes). This is the first methodology in which a quinoline ring is constructed from a substrate bearing a pyrrolidinyl ring. The method allows direct synthesis of complicated structures from easily available enamines and commercial nitrobenzenes. Starting from optically pure enamines the method allows synthesis of the corresponding chiral products without racemisation.

Acknowledgements

Table 4 Hydrolysis/decarboxylation domino reaction of *tert*-butyl 3-(1-pyrrolidinyl)quinoline-2-carboxylates **2a–2d** and *tert*-butyl 3-pyrrolidinyl-2-carboxylate-quinoline 1-oxides **3b–3h** and **5a** [17]

X	Y	R	Substrate	Product	Yield[a]
Cl	Cl	H	**2a**	**6a**	93
F	F	H	**2b**	**6b**	92
Cl	OMe	H	**2c**	**6c**	91
CH₃	Cl	H	**2d**	**6d**	93
Cl	H	H	**3b**	**7b**	81
I	H	H	**3c**	**7c**	87
F	H	H	**3d**	**7d**	97
Ph	H	H	**3f**	**7f**	84
t-Bu	H	H	**3h**	**7h**	91
I	H	(*S*)-CH₂OBn	**5a**	**8a**	79

[a] The isolated yields are given.

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15 To a solution of the enamine **1** (0.317 g, 1.5 mmol) and HMPA (0.35 mL, 0.357 g, 2.0 mmol) in dry THF (10 mL) at −70 °C under argon, 2.5 M BuLi in hexane (0.67 mL, 1.67 mmol) was added in portions in 4 min and the solution was stirred at −70 °C for 30 min. A solution of the nitroarene (3.0 mmol) in THF (1.7 mL) was added and the resultant mixture was stirred for 10 min at −70 °C. Et_3N (1.0 mL, 7.2 mmol) was added and then pivaloyl chloride (0.85 mL, 6.9 mmol) was added in portions (7 min). After the addition was complete, the solution was stirred at −70 °C for 2 h. The cooling bath was removed, water (10 mL) was added and the mixture was stirred for 5 min, then extracted with AcOEt (30 mL), dried and evaporated. The products were purified by column chromatography (SiO_2, hexane/AcOEt).

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17 A suspension of compounds **2–5** (0.2–0.4 mmol) in 20% H_2SO_4 (2–4 mL) was heated to reflux for 3 h. The mixture was cooled to RT and diluted with water (15 mL) and solid K_2CO_3 was added in portions to achieve pH = 10. The mixture was extracted with AcOEt (2 × 25 mL), and the combined extracts were dried and evaporated. The crude products were washed with pentane or Et_2O. The obtained products were pure according to ^{1}H NMR.

18 To a solution of compound **2a** (0.358 mmol) in CH_2Cl_2 (3.8 mL), trifluoroacetic acid (1.0 mL) was added and the solution was stirred at RT for 1 h. The solvent was evaporated and the crude product was washed with Et_2O. The obtained product was pure according to ^{1}H NMR.

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