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Iron-Catalyzed Oxidative Tandem Reactions with TEMPO Oxoammonium Salts: Synthesis of Dihydroquinazolines and Quinolines

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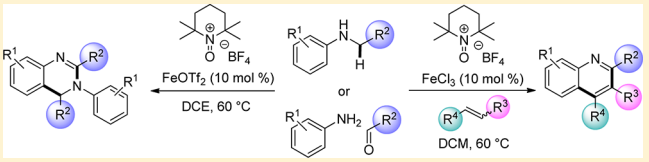
Supporting Information

ABSTRACT: A straightforward iron-catalyzed divergent oxidative tandem synthesis of dihydroquinazolines and quinolines from *N*-alkylanilines using a TEMPO oxoammonium salt as a mild and nontoxic oxidant has been developed. $Fe(OTf)_2$ was the Lewis acid catalyst of choice for the formation of dihydroquinazolines, whereas $FeCl_3$ led to better results for the synthesis of quinolines. This divergent approach implies that, for both syntheses, direct oxidative functionalization of a α-$C(sp^3)$–H bond of the *N*-alkylanilines occurs, leading to C–N bond formation or C–C bond formation upon homocondensation or reaction with simple olefins, respectively. Cyclization followed by a final oxidation generates these classes of interesting bioactive heterocycles in one synthetic transformation. Additionally, the one-pot multicomponent synthesis of quinolines from anilines, aldehydes, and olefins has also been successfully developed under these mild oxidative conditions.



INTRODUCTION

The development of efficient and sustainable synthetic methods is of great importance for modern organic chemistry in both academia and industry.[1] The scientific efforts already being made in this direction are having a significant impact in the way organic molecules are built up. One of the most appealing current approaches involves the direct functionalization of C–H bonds of simple starting materials.[2] In these processes, prefunctionalizations and multiple tedious purification steps can be avoided while enhancing the step economy of the transformation. In this regard, the dehydrogenative or oxidative coupling of C–H bonds has recently been established as a powerful and elegant synthetic approach for the direct generation of C–C and C–heteroatom bonds.[3] However, the selective and effective functionalization of unreactive $C(sp^3)$–H bonds remains a challenge in organic synthesis. Organic peroxides, quinones (e.g., DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone), and more recently dioxygen are typically used as oxidants for achieving such transformations.[3] Alternatively, our group has introduced a TEMPO oxoammonium salt ($T^+BF_4^-$, 2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate)[4] as a mild, nontoxic hydrogen acceptor for oxidative C–H coupling reactions. This oxidant has been used efficiently in Fe- and Cu-catalyzed oxidative C–C couplings of benzylic $C(sp^3)$–H bonds adjacent to a heteroatom with enolizable pronucleophiles.[5] We are devoted to broadening the substrate scope and synthetic applicability of C–H bond coupling reactions as part of our ongoing research program on oxidative C–H functionalizations with TEMPO salts. Along this line, we have recently focused our attention on the oxidative synthesis of N-heterocycles. In our initial studies, the use of simple olefins as weak nucleophiles for the metal-free synthesis of oxazinones from benzylic carbamates was reported.[6] This chemistry was recently extended to the metal-catalyzed synthesis of quinolines using $T^+BF_4^-$ as oxidant and glycine derivatives as substrates.[7]

Herein we describe the divergent oxidative synthesis of dihydroquinazolines and quinolines from preformed or in situ generated *N*-alkylaniline derivatives upon homocondensation or reaction with olefins, respectively. These tandem transformations involve oxidative C–C or C–N coupling followed by cyclization and oxidation and employ inexpensive iron Lewis acid catalysts in combination with $T^+BF_4^-$ as an efficient, mild, and nontoxic oxidant.

RESULTS AND DISCUSSION

Dihydroquinazolines by Oxidative C–N Coupling/Cyclization/Oxidation. The quinazoline core is an important structural moiety present in a large number of synthetic and natural products with an extensive spectrum of bioactivities.[8] For example, several quinazoline derivatives exhibit potent anticancer, anti-inflammatory, antibiotic, or antiviral activity, among others. Although well-established multistep processes to synthesize these heterocyclic compounds have been described,[9] it would still be highly desirable to develop more simple and step-economical methods for their preparation. Along this line, we decided to explore the simple homocondensation of *N*-alkylanilines under oxidative conditions using TEMPO oxoammonium salts for the synthesis of dihydroquinazolines. An ethyl acetate group was selected as the substitution pattern at the aniline for these studies. As the standard test reaction, we chose the C–N coupling/cyclization/oxidation tandem reac-

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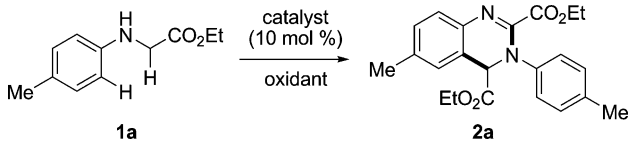
tion of N-substituted *p*-toluidine **1a** in the presence of different Lewis acid catalysts and oxidants (Table 1).

Table 1. Optimization of the Reaction Conditions[a]



1a **2a**

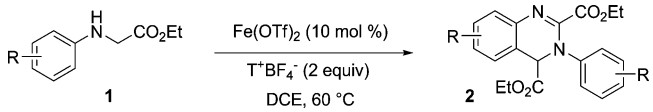
entry	catalyst	oxidant (equiv)	T (°C)	yield of **2a** (%)[b]
1		$T^+BF_4^-$ (2)	60	
2	$FeCl_3$	$T^+BF_4^-$ (2)	60	60
3	$AlCl_3$	$T^+BF_4^-$ (2)	60	
4	$InCl_3$	$T^+BF_4^-$ (2)	60	
5	$Cu(OTf)_2$	$T^+BF_4^-$ (2)	60	60
6	**$Fe(OTf)_2$**	**$T^+BF_4^-$ (2)**	**60**	**95 (70)**[c]
7	$Fe(OTf)_2$	$T^+BF_4^-$ (2)	40	72
8	$Fe(OTf)_2$	$T^+BF_4^-$ (1.5)	60	67
9	$Fe(OTf)_2$	O_2 (1 atm)	60	60[d]
10	$Fe(OTf)_2$	$Ph_3C^+BF_4^-$ (2)	60	10
11	$Fe(OTf)_2$	DDQ (2)	60	
12	$Fe(OTf)_2$	*t*-BuOOH (2)	60	

[a]Reaction conditions: **1** (0.1 mmol), catalyst (10 mol %), and oxidant in DCE (0.2 M), 24 h. [b]GC yield. [c]Isolated yield by column chromatography in parentheses. [d]Concomitant formation of an overoxidized byproduct.[10]

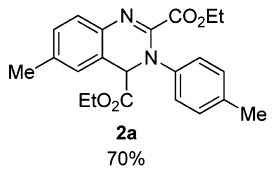
In the first attempts, 2 equiv of $T^+BF_4^-$ as oxidant in DCE at 60 °C was used. The reaction did not proceed in the absence of catalyst (entry 1), whereas the dihydroquinazoline **2a** was formed in a good yield of 60% (GC) in the presence of 10 mol % of inexpensive $FeCl_3$ as the Lewis acid catalyst (entry 2). Surprisingly, widely employed Lewis acids such as $AlCl_3$ and $InCl_3$ led to no conversion or decomposition of **1a**. On the other hand, metal triflate catalysts led to a cleaner reaction. $Cu(OTf)_2$ provided the same yield as $FeCl_3$ (entries 5 and 2), whereas $Fe(OTf)_2$ gave the best results (entry 6). Using this Lewis acid, **2a** was formed in an excellent 95% GC and 70% isolated yield. Decreasing the temperature to 40 °C or the amount of oxidant to 1.5 equiv resulted in lower yields (entries 7 and 8). Interestingly, the reaction proceeded using oxygen as the sole oxidant; however, an overoxidized cyclic byproduct, which was difficult to separate from **2a**, was also formed under these conditions (entry 9).[10] Remarkably, the TEMPO salt used showed excellent reactivity and selectivity, in contrast to the other oxidants tested. The well-known hydrogen abstractor trityl cation ($Ph_3C^+BF_4^-$, entry 10) produced **2a** in only 10% yield, while other typical oxidants for oxidative radical C−H coupling reactions such as DDQ and *t*-BuOOH did not provide the desired product (entries 11 and 12).

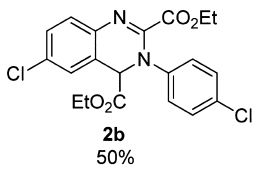
Having identified the optimal reaction conditions, 10 mol % of $Fe(OTf)_2$ and 2 equiv of $T^+BF_4^-$ in DCE at 60 °C for 24 h, the scope of the reaction was explored with different substituted anilines **1** (Table 2). In addition to the standard *p*-methyl substitution (**2a**, 70%), halogens such as Cl, Br, and F were also tolerated, leading to the desired dihydroquinazolines **2b−d** in 50−56% isolated yield. On the other hand, the more electron-withdrawing CF_3 group provided the quinazoline derivative **2e** in an enhanced 64% yield. Moreover, redox-sensitive substituents, such an acetyl group, were suitable in this reaction, with the corresponding quinazoline **2g** being delivered in 58% yield. It is worth mentioning that acid labile groups such as nitrile (**2f**, 50%) and ethyl ester (**2h**, 31%) in the *para*

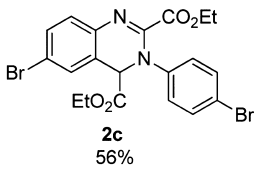
Table 2. Scope of the Reaction[a,b]

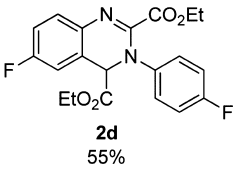


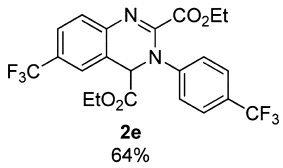
1 **2**

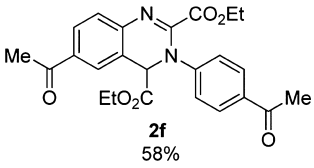

2a 70%

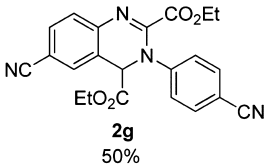

2b 50%

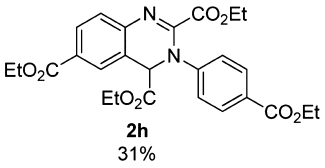

2c 56%

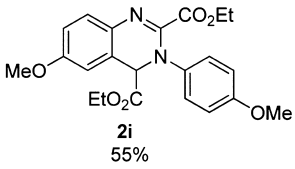

2d 55%

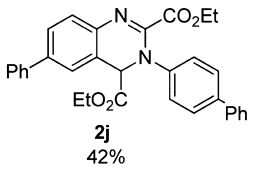

2e 64%

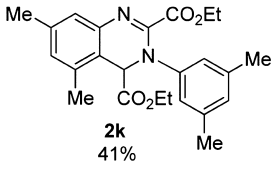

2f 58%

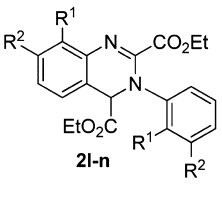

2g 50%


2h 31%


2i 55%


2j 42%


2k 41%


2l-n

n.o. (decomp./polymer)
2l R^1 = Me, R^2 = H
2m R^1 = OMe, R^2 = H
2n R^1 = H, R^2 = OMe

[a]Reaction conditions: **1** (0.1 mmol), $Fe(OTf)_2$ (10 mol %), and oxidant in DCE (0.2 M), 24 h. [b]Isolated yields by column chromatography. n.o. = not observed.

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position also worked well; however, slightly lower yields of the product were obtained. Electron-donating substituents at the aniline, such as *p*-methoxy, *p*-phenyl, and 3,5-dimethyl groups, also provided quinazolines **2** in moderate yields (41−55%). On the other hand, the monosubstituted *o*-methyl and *o*- and *m*-methoxy substrates (**1l−m**) led to a complex reaction mixture, in which the desired product could not be identified. This can be explained by the higher reactivity of these electron-rich anilines toward both oxidation and aromatic nucleophilic substitution.

Quinolines by Oxidative C−C Coupling/Cyclization/Oxidation. Quinolines are important heterocycles present in a large number of synthetic and natural biologically active compounds.[11] Therefore, several synthetic strategies for their synthesis have been developed,[12] such as the well-established Povarov reaction[13] between imines and olefins (hetero Diels−Alder) followed by oxidation. It is important to mention that the final oxidation step, the dehydrogenation of the tetrahydroquinoline intermediate (Povarov product), is still rather challenging, since it requires the formal removal of four hydrogen atoms. After the initial success in the oxidative synthesis of dihydroquinazolines, we studied the formation of two C−C bonds by reacting anilines **1** with simple olefins **3** in the presence of a TEMPO oxoammonium salt as a mild oxidant.[7a,14] A dehydrogenative cyclization−oxidation sequence would then lead to the quinoline scaffold.

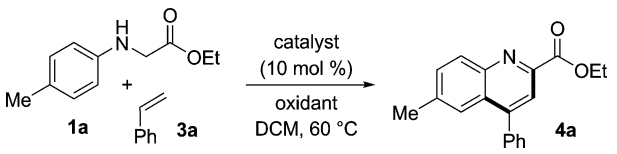
The reaction between aniline **1a** and styrene (**3a**) was initially studied in the presence of iron Lewis acid catalysts, such as $Fe(OTf)_2$ and $FeCl_3$ species, at 60 °C in dichloromethane in a pressure Schlenk tube (Table 3). Although quinoline **4a** was formed even without a Lewis acid catalyst using 2 equiv of $T^+BF_4^-$ as oxidant (entry 1), the reaction stalled after 16 h, leading to the product in a moderate yield of 51%. On the other hand, performing the reaction in the presence of 10 mol % of the inexpensive Lewis acid $FeCl_3$ resulted in complete conversion, delivering **4a** in a outstanding yield of 93% (entry 4). The suitability of a range of alternative oxidants was tested. Another oxoammonium salt derivative possessing an acetylamido group, 4-$AcNHT^+BF_4^-$,[15] was not as effective as $T^+BF_4^-$, producing **4a** in significantly lower yield of 69% (entry 5). The reaction was found to be sensitive to the TEMPO oxoammonium counterion, with ^-OTf, $^-ClO_4$, or TFA^- leading to reduced yields (entries 6−8). Once again, test reactions with standard oxidants such as DDQ, DTBP, O_2, and air were carried out (entries 9−12); however, none of them led to satisfactory conversions. Interestingly, this transformation does not seem to be moisture and air sensitive, since the reactions with hydrated $FeCl_3$ or under an air atmosphere provided similarly good results (entries 13 and 3, respectively).

Next, the substitution of the *N*-alkyl group at the aniline was investigated (Figure 1). Under the optimized reaction conditions (10 mol % of $FeCl_3$, 2 equiv of **3a**, and 2 equiv of $T^+BF_4^-$ at 60 °C), the ester unit was replaced by other electron-withdrawing groups such as phenyl ketone and ethyl phosphonate, providing the corresponding substituted quinolines in good to moderate yields (72% of **4aa** and 42% of **4ba**, respectively). On the other hand, labile subtituents such as an electron-withdrawing nitrile or an oxazolidinone led to a low yield of the desired product (**4ca**, −CN, 17%) or to no reaction at all. Alternatively, a simple *N*-alkyl substituent such as benzyl provided quinoline **4ea** in a moderate 41% yield, whereas an ethyl residue led to decomposition of the starting material.

With these results, aniline substrates bearing an ethyl ester substituent at the nitrogen were selected for further scope and limitation studies (Table 4). The reaction of styrene with a number of ethyl glycines **1** was first explored (first row). Halogens such as Br and Cl and acetyl and methoxy groups in the *para* position were well tolerated, providing the corresponding quinolines **4** in good yields (73−84%). Substitution in the *meta* postion, however, proved to be less efficient in terms of reactivity and selectivity, leading to slightly inferior yields (**4f,g**, 52−68%) and lower regioselectivities (1.6:1 ratio of **4g** to **4g′**).

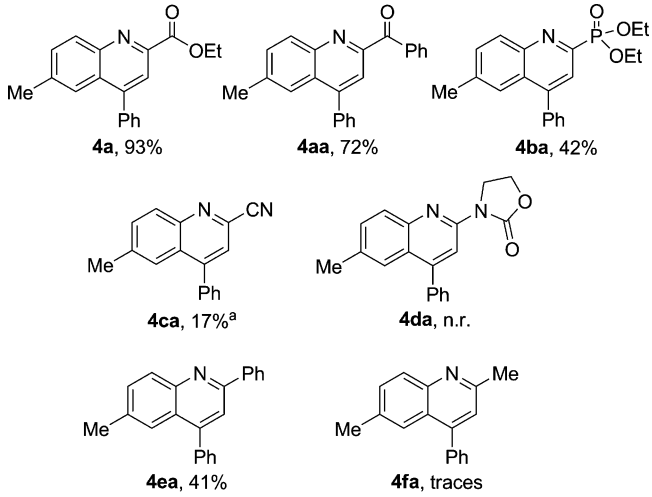
Afterward, a variety of styrenes **3** were reacted with **1a** (second row). The electronic and steric nature of the

Table 3. Optimization of the Reaction of 1a with Styrene[a]



entry	catalyst	oxidant (equiv)	*t* (h)	yield of **4a** (%)[b]
1		$T^+BF_4^-$ (2)	16/24	51[c]
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)**[d]
5	$FeCl_3$	$AcNHT^+BF_4^-$ (2)	24	69
6	$FeCl_3$	$AcNHT^+OTf^-$ (2)	24	40
7	$FeCl_3$	$AcNHT^+ClO_4^-$ (2)	24	58
8	$FeCl_3$	$AcNHT^+TFA^-$ (2)	24	<5
9	$FeCl_3$	DDQ (2)	24	7
10	$FeCl_3$	(*t*-BuO)$_2$ (2)	24	30
11	$FeCl_3$	O_2 (1 atm)	16/24	41[c]
12	$FeCl_3$	air[e]	24	3
13	$FeCl_3$	$T^+BF_4^-$ (2)/air[e]	18	86
14	$FeCl_3$	$T^+BF_4^-$ (2)	18	80[f]

[a]Conditions: **1a** (0.10 mmol), **3a** (0.20 mmol), Fe catalyst (10 mol %), and oxidant in DCM (1 mL). [b]Isolated yield. [c]The reaction stopped after 16 h. [d]0.50 mmol scale reaction in parentheses. [e]Reaction in an air atmosphere. [f]Reaction in DCE.



[a] Reaction at r.t. (6% yield at 60 °C).

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

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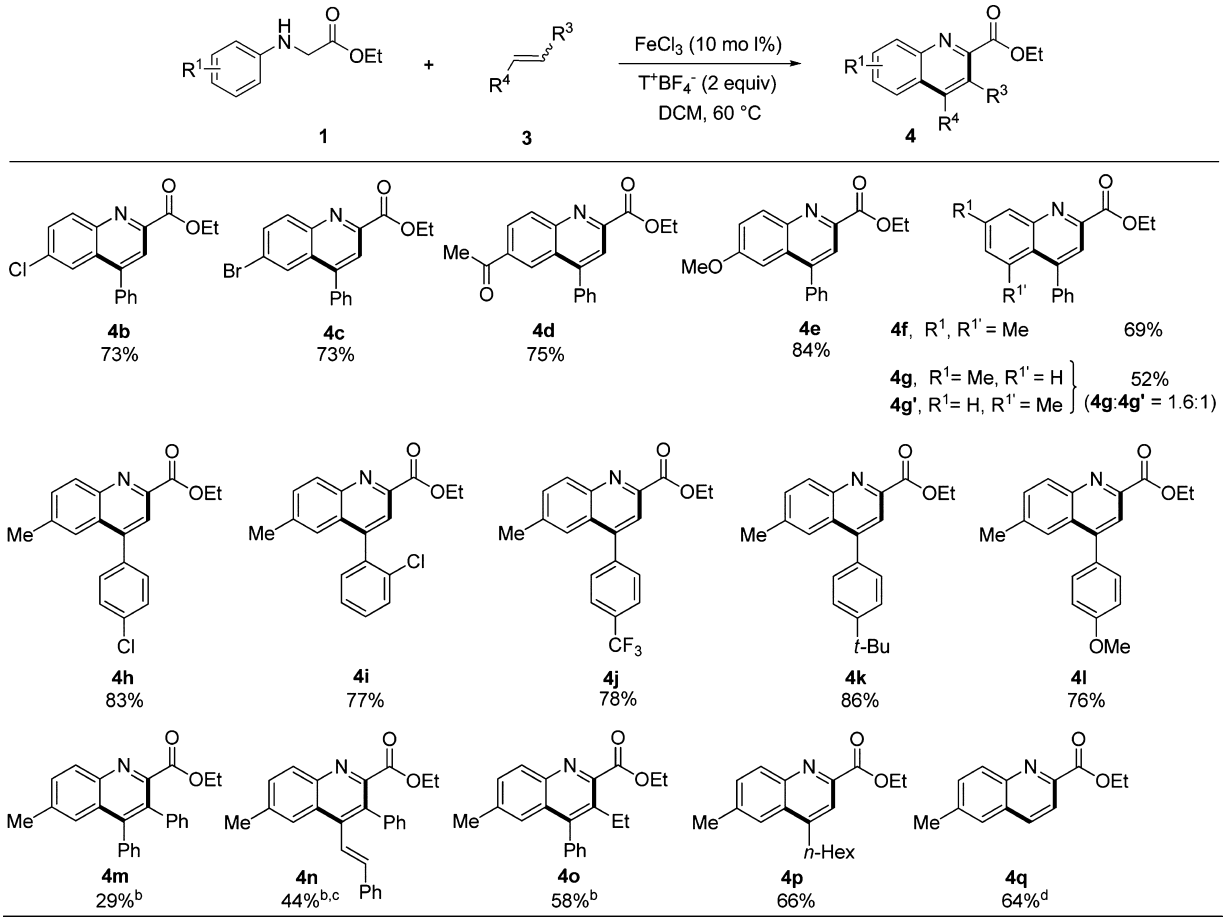
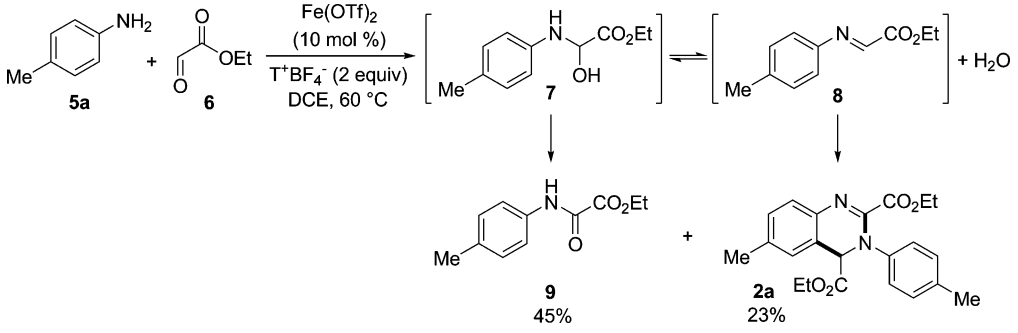
Table 4. Scope of the Reaction of 1 with Olefins 3[a]



[a]Conditions: **1** (1 equiv), **3** (2 equiv), $FeCl_3$ (10 mol %), and $T^+BF_4^-$ (2 equiv) in DCM (0.1 M) at 60 °C. [b]4 equiv of olefin was used. [c]No trace of the regioisomer of **4n** was detected by NMR. [d]Reaction with ethyl vinyl ether.

Scheme 1. One-Pot Reaction between Aniline 5a and Glyoxalate 6



substituents at the styrene ring did not have a great influence on the reaction outcome, although the electron-rich styrenes react more easily than the electron-deficient ones. Consequently, the corresponding quinolines **4h–l** were isolated in comparably good yields (76–86%).

Highly challenging 1,2-disubstituted olefins and olefins with linear aliphatic chains were also suitable reactants (third row). Although stilbene showed a low reactivity (**4m**, 29%), *β*-alkenyl and *β*-ethyl styrenes reacted more readily, leading to 2,3,4-trisubstituted quinolines **4n,o** in remarkable yields of 44% and 58%, respectively. 1-Octene also reacted well, providing quinoline **4p** in a good 66% yield. Finally, the reaction with ethyl vinyl ether was also explored. This substrate led exclusively to the C-3 and C-4 unsubstituted quinoline **4q** resulting from elimination of ethanol, in 64% yield.

Multicomponent One-Pot Synthesis. The in situ formation of an imine-type intermediate duning the course of the reaction led us to investigate the possibility of synthesizing dihydoquinazolines directly from aniline **5a** and ethyl glyoxalate (**6**) in a one-pot process (Scheme 1).[16,17] Unfortunately, this one-pot transformation was not efficient, leading to the overoxidation of the starting material as major reaction pathway (**9**, 45%). The formation of this product can be explained by a facile oxidation of the hemiaminal intermediate **7**, formed prior to the formation of imine **8**.

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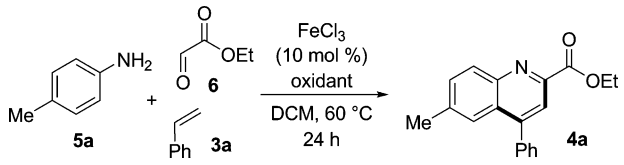
The three-component[18] oxidative synthesis of quinolines from anilines, aldehydes, and various olefins was investigated next.[19] Initially, the selected model reaction between *p*-toluidine (**5a**), ethyl glyoxalate (**6**), and styrene (**2a**) in the presence of $FeCl_3$ as a Lewis acid catalyst at 60 °C in dichloromethane was used in a brief optimization study (Table 5). The TEMPO oxoammonium salt $T^+BF_4^-$ (entries 1−3) proved again to be a more efficient oxidant than O_2 (entry 4). Consequently, the use of catalytic amounts of $T^+BF_4^-$ (10 mol %) in combination with O_2 as terminal oxidant only provided **4a** in low yield (38%, entry 5). Moreover, the use of a slight excess of ethyl glyoxalate (**6**; 1.2 equiv) was beneficial for the reaction (entry 1 vs 2). Importantly, 2 equiv of the oxidant was also required to attain full conversion (entry 1 vs 2), leading to a similarly high yield of the quinoline **4a** in comparison to the previous method starting from the *N*-alkylaniline (90% vs 93% yield).

Table 5. Optimization of the Multicomponent Reaction To Form Quinoline 4a[a]

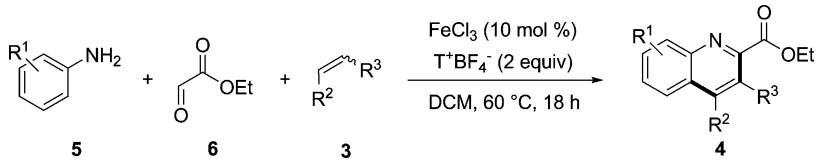


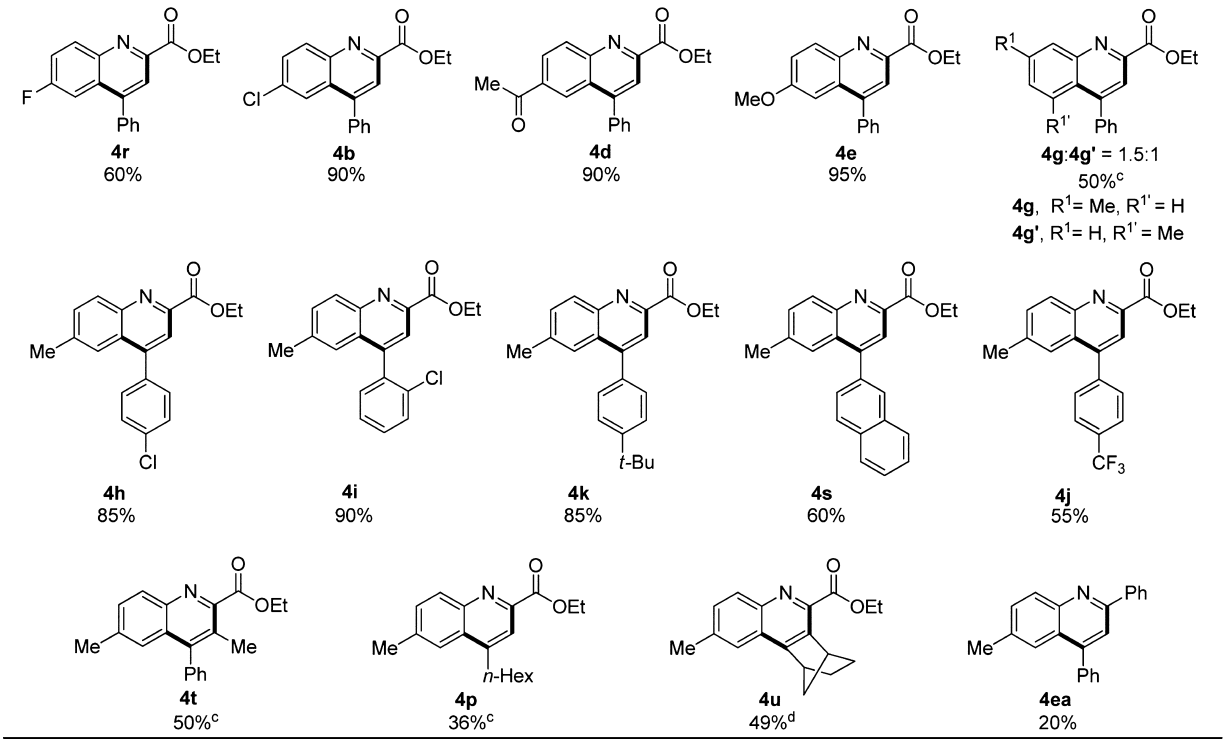
entry	oxidant (equiv)	**6** (equiv)	yield of **4a** (%)[b]
1	$T^+BF_4^-$ (2)	1.0	71
2	$T^+BF_4^-$ (2)	1.2	90
3	$T^+BF_4^-$ (1.2)	1.2	72
4	O_2 (1 atm)	1.2	15
5	O_2 (1 atm)/ $T^+BF_4^-$ (0.1)	1.2	38

[a]Conditions: **5a** (0.2 mmol), **6** (1.0−1.2 equiv), **3a** (2 equiv), $FeCl_3$ (10 mol %) and oxidant in DCM (2 mL). [b]Isolated yield.

With the optimized conditions for the multicomponent synthesis in hand, the scope of the reaction was next explored (Table 6). The effect of the substitution of the aniline on the reaction with styrene was first investigated (first row). The introduction of an electron-withdrawing group such as fluoro in the *para* position led to a lower yield (60%, **4r**), while a chloro, acetyl, or methoxy group provided the desired quinolines **4b,d,e** in excellent yields of 90−95%. As expected, methyl substitution at the *meta* position significantly hindered the reaction (50%). Moreover, a 1.5/1 mixture of the possible regioisomers **4g** and **4g′** was formed. On the other hand, reactions with different styrenes generally provided the corresponding quinolines in high yields (second row; **4h,i,k,s**), except for the electron-poor 4-CF_3-substituted styrene, which led to **4j** in only 55% yield. Finally, the reaction with the more challenging 1,2-disubstituted alkenes and olefins

Table 6. Scope of the One-Pot Multicomponent Reaction[a,b]





[a]Conditions: **5** (0.20 mmol), **6** (0.24 mmol), **2a** (0.40 mmol), $FeCl_3$ (10 mol %), and $T^+BF_4^-$ (0.40 mmol) in DCM (2 mL) for 18 h. [b]Isolated yields. [c]5 equiv of olefin was used. [d]4 equiv of olefin was used.

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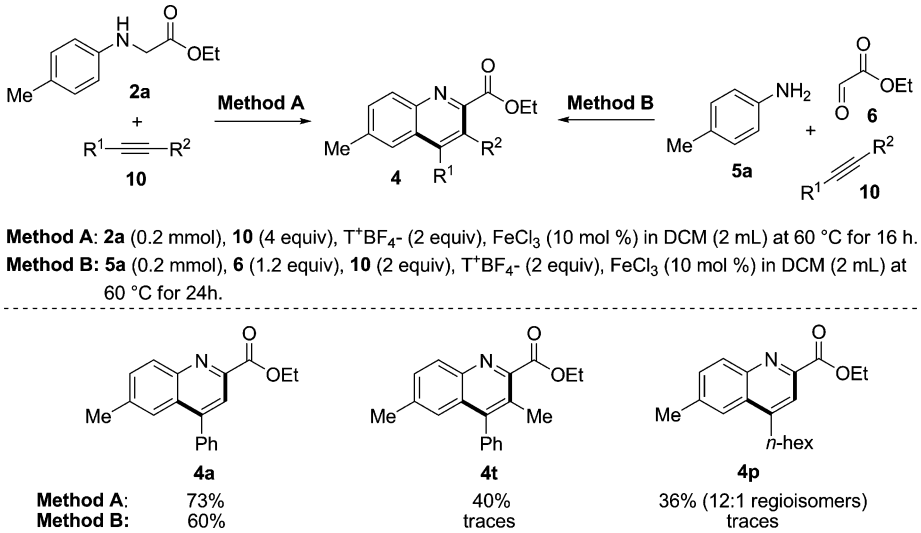
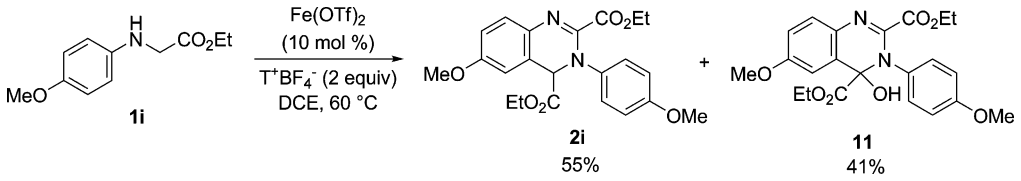
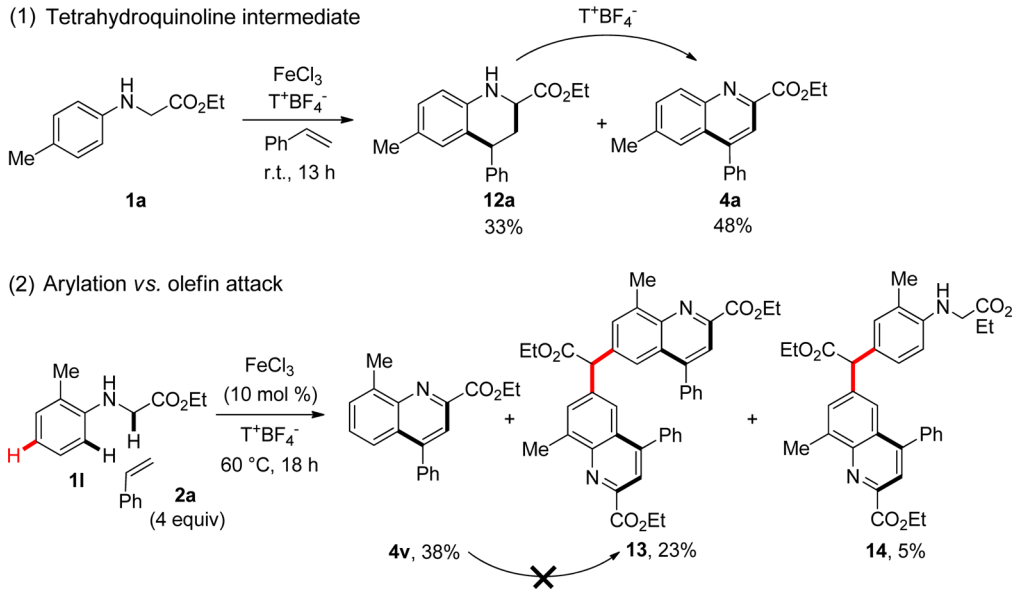
Scheme 2. Synthesis of Quinolines Using Alkynes



Scheme 3. Homocondensation of 1l: Formation of the Side Product 11



Scheme 4. Isolation of the Povarov-Type Intermediate and C−H Arylation vs Cyclization Reaction



bearing solely alkyl groups such as 1-octene and norbornene were explored (third row). Fortunately, in these cases the corresponding quinolines **4** could still be obtained in moderate yields (36−50%) upon reaction with a larger excess of the olefin (4−5 equiv). The reaction with benzaldehyde was also possible; however, a lower yield of **4ea** (20%) was obtained using the one-pot protocol in comparison to the method using *N*-alkylaniline **1a** 41% (see Figure 1).

Reaction with Alkynes. Finally, the reaction between terminal and internal alkynes **10** with the preformed *N*-alkylaniline **2a** (method A) and under the one-pot conditions with the aniline **5a** and ethyl glyoxalate (**6**) (method B) was explored (Scheme 2).[20] The reactions with alkynes were not as clean as those using alkenes, and several unidentified byproducts were formed, including various amounts of the oxidized starting material (**9**) under method B conditions. As a result, the same quinolines **4** were obtained in significantly lower yields. Moreover, the one-pot approach (method B) proved to be only suitable when using phenylacetylene (**10a**), providing **4a** in a moderate 60% yield. On the other hand, method A seemed to be more general, allowing for the formation of quinolines **4t** and **4p** with the less reactive 1-

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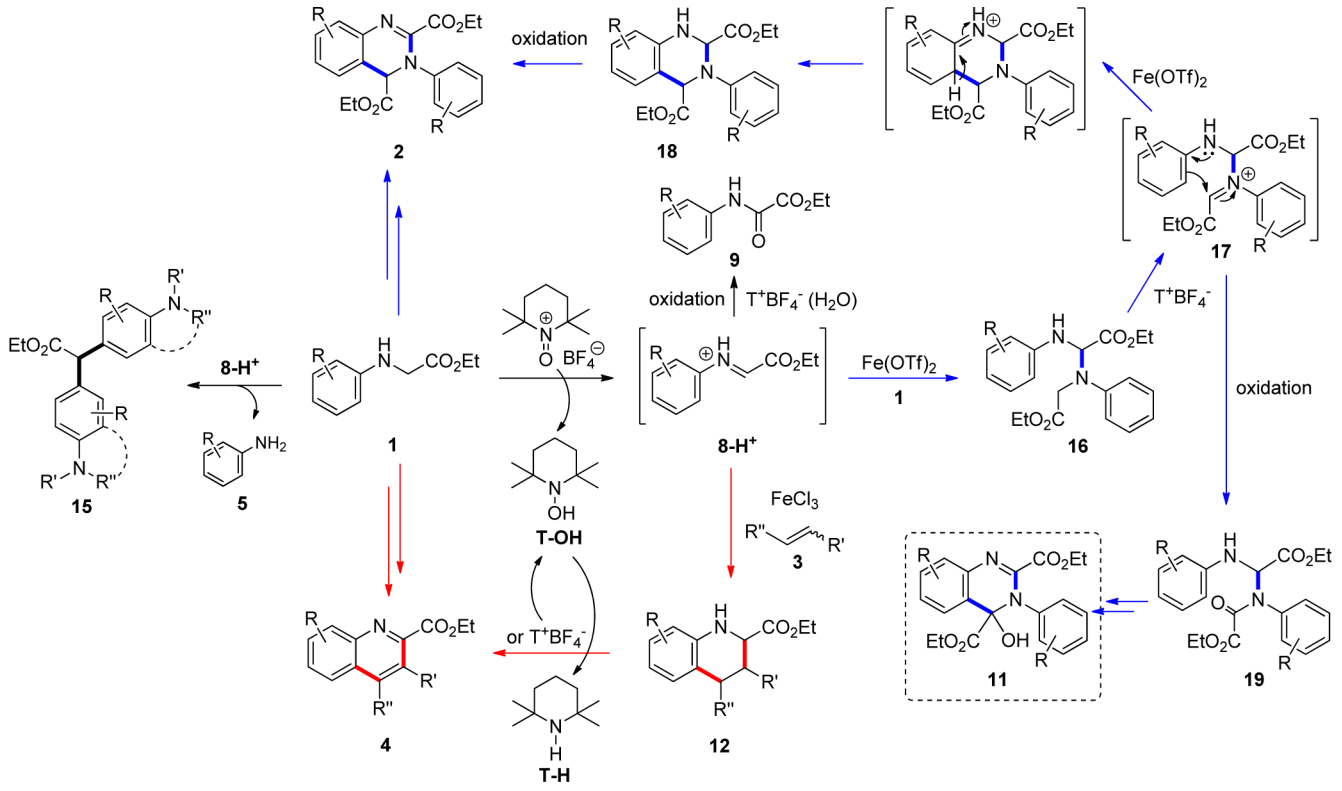
Scheme 5. Proposed Mechanism for the Synthesis of Dihydroquinazolines, Quinolines, and Diarylmethane Derivatives



phenyl-1-propyne (**10t**) and 1-octyne (**10p**) in 36−40% yield. Interestingly, when using **10p**, we could observe for the first time the formation of the C3 regioisomer along with the expected C4-*n*-hexyl-substituted quinoline **4p** (12:1 ratio of **4p** to **4p′**).

Mechanistic Considerations. During the development of the oxidative synthesis of dihydroquinazolines **2**, the occasional formation of a hydroxydihydroquinazoline side product of type **11** was observed (Scheme 3). This compound might be formed by a further oxidation at the α position of the second *N*-alkylaniline unit after the initial C−N bond formation step. Then, this carbonyl intermediate might undergo a subsequent Friedel−Crafts-type cyclization and oxidation, leading to the final dihydroquinazoline skeleton possessing the additional hydroxyl group. This finding sheds some light on the mechanism of the reaction. Thus, instead of a concerted cycloaddition between two in situ formed imine derivatives, a stepwise nucleophilic addition of the amine **1** to an imine followed by an intramolecular Friedel−Crafts-type reaction is most likely involved.

On the other hand, a different scenario can be imagined in the reaction of *N*-alkylanilines **1** with olefins **3**. Since no intermediate derived from a stepwise nucleophilic addition of the olefin to form the first C−C bond was detected, only the Povarov product tetrahydroquinoline **12a** being observed, a concerted cycloaddition is proposed to take place. When the reaction with **1a** was performed at room temperature, the Povarov product **12a** could be isolated in 33% yield along with the corresponding quinoline **4a** (Scheme 4, eq 1). As expected, **12a** is an intermediate in the synthesis, and it could be quantitatively converted into the corresponding quinoline **4a** upon treatment with an extra 1 equiv of the $T^+BF_4^-$ oxidant. Moreover, in the reaction with the 2-methyl-substituted aniline derivative **1l**, the formation of diarylmethane derivatives **13** and **14** was also observed. This demonstrates the dehydrogenative nature of this coupling reaction. Moreover, since the quinoline **4v** could not be converted into **13** upon treatment under the standard coupling conditions, **13** and **14** have to be formed by an initial double dehydrogenative arylation in the *para* position with the loss of a molecule of *o*-toluidine followed by dehydrogenative Povarov-type reactions to form the quinoline rings (Scheme 4, eq 2).

The exact role of the iron catalyst in both transformations is not completely clear. However, considering that the formation of the corresponding iminium ion **8-H**$^+$ is achieved with $T^+BF_4^-$ in the absence of the iron catalyst, it is more likely that it actively participates as a Lewis acid in the cyclization and/or C−N bond formation rather than as a co-oxidant in the oxidative step. Interestingly, the use of the metal catalyst is crucial in the formation of dihydroquinazolines **2** (Table 1), whereas in the case of quinolines **4** the iron catalyst is required for improved performance and to achieve full conversions (Table 3).

It is also important to note that, in the synthesis of quinolines **4**, the conversion of the oxoammonium salt $T^+BF_4^-$ to *N*-hydroxy TEMPO (**T-OH**) and then the corresponding 2,2,6,6-tetramethylpiperidine (**T-H**) could be followed by GC-MS. Due to the redox-instability of the **T-OH**, it was oxidized to TEMPO radical by exposure to air.[4] Therefore, both the TEMPO radical and the amine **T-H** (mainly as the **T-H·HBF$_4$** salt) had to be removed by chromatography after the reaction. In the case of the synthesis of dihydroquinazolines **T-H** was not formed in large amounts and the main recovered compound was the TEMPO radical.

On the basis of the above observations, a multistep reaction mechanism is proposed for the divergent synthesis of dihydroquinazolines and quinolines (Scheme 5). After the first TEMPO salt mediated in situ formation of an iminium ion

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8-H$^+$, a nucleophilic attack of the nitrogen of another molecule of aniline **1** (blue pathway) or cycloaddition with an olefin **3** (red pathway) takes place. In the case of the dihydroquinazoline synthesis, the addition product **16** can again be oxidized to the iminium derivative **17** (or carbonyl compound **19**) and be further activated by the Lewis acid, promoting the cyclization reaction to generate corresponding tetrahydroquinazoline intermediates of type **18**. These species are not redox stable and will be readily oxidized to the final product dihydroquinazoline **2** (or the side product **11**). On the other hand, quinolines **4** are formed via final aromatization by dehydrogenation of the Povarov intermediate **12**. Finally, the formation of diarylmethanes **15** (including structures **13** and **14**) can be explained by a prompt arylation reaction of an iminium intermediate **8-H$^+$** with two further molecules of aniline **1** when the *para* position of the *N*-alkylaniline **1**, an electron-rich arene, is available. Subsequently, after activating the aniline as a leaving group by protonation of the resulting intermediate, the corresponding diarylmethanes **15** are formed. Compound **15** can then undergo a Povarov reaction with an olefin present in the reaction mixture to form stepwise the mono- and bis-quinoline-containing compounds **13** and **14** (see Scheme 4).

CONCLUSIONS

In conclusion, a straightforward divergent oxidative synthesis of dihydroquinazolines and quinolines using a TEMPO oxoammonium salt as a nontoxic, highly efficient, and mild oxidant has been developed. The combination of inexpensive $FeCl_3$ or readily available $Fe(OTf)_2$ catalysts with $T^+BF_4^-$ as a formal hydrogen acceptor was successfully employed. This approach allows for the direct homocondensation of simple *N*-alkylanilines or their reaction with a variety of monosubstituted and 1,2-disubstituted olefins to generate valuable N-containing heterocycles in one synthetic step. A mechanism involving a multistep sequence is proposed, in which an iminium species, obtained by initial α-oxidation of *N*-alkylanilines with the TEMPO salt, is the key intermediate in both synthetic processes. Moreover, this kind of key intermediate could be formed in situ from the corresponding anilines and aldehydes, allowing the development of a one-pot multicomponent synthesis of quinolines under mild oxidative conditions.

EXPERIMENTAL SECTION

General Methods. NMR spectra were acquired on a 300 or 400 MHz spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$; 7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR), and spin−spin coupling constants (J) are given in Hz. ^{13}C NMR spectra were acquired on a broad-band-decoupled mode. Mass spectra were recorded using electrospray ionization (ESI$^+$) techniques and a MicroTOF mass analyzer. Analytical thin-layer chromatography (TLC) was performed using precoated aluminum-backed plates and visualized by ultraviolet irradiation or $KMnO_4$ dip. The wavenumbers (ν) of recorded IR signals are quoted in cm^{-1}. Dichloromethane was distilled over CaH_2. Commercially available reagents were used without further purification. $T^+BF_4^-$ [4b,5a] and *N*-alkylanilines **1aa**[21] ($-CH_2COPh$), **1ba**[22] ($-CH_2PO(OEt)_2$), **1ca**[23] ($-CH_2CN$), **1da**[24] ($-CH_2$-oxazolidinone), **1ea**[25,26] ($-CH_2Ph$), and **1fa**[26] ($-CH_2Et$) were prepared following literature procedures. Except for the reactions carried out under an air or O_2 atmosphere, the catalytic reactions were performed in sealed tubes under an argon atmosphere.

General Procedure for the Synthesis of Dihydroquinazolines 2. A sealed tube equipped with a magnetic stirring bar, $Fe(OTf)_2$ (10 mol %), aniline **1** (0.2 mmol, 1.0 equiv), $T^+BF_4^-$ (0.40 mmol, 2.0 equiv), and DCE (0.5 mL) were added under an argon atmosphere. The reaction mixture was then stirred at 60 °C for 24 h. The crude reaction mixture was directly purified by column chromatography on silica gel.

*Diethyl 6-Methyl-3-(p-tolyl)-3,4-dihydroquinazoline-2,4-dicarboxylate (**2a**).*[16] According to the general procedure using **1a** (38.6 mg, 0.20 mmol, 1.0 equiv), the title compound **2a** was obtained after FC (pentane/EtOAc 8/1 → 6/1) as a yellow solid (26.6 mg, 0.07 mmol, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 8.2 Hz, 3H), 7.05−6.94 (m, 3H), 5.31 (s, 1H), 4.28−4.08 (m, 4H), 2.33 (s, 3H), 2.33 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.05 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 162.6, 146.6, 141.2, 137.6, 137.4, 136.3, 130.4, 130.0 (2C), 127.0, 125.9, 122.9 (2C), 120.4, 63.5, 62.1, 62.1, 21.3, 21.0, 14.1, 13.8. HRMS (ESI+): calcd for $C_{22}H_{24}N_2O_4$ + Na^+ $[M + Na]^+$ m/z 403.1628, found 403.1621. IR: ν_{max} 2982, 2928, 2868, 1734, 1619, 1584, 1573, 1512, 1493, 1381, 1333, 1289, 1256, 1234, 1184, 1080, 1021, 922, 855, 825, 737, 646, 616.

*Ethyl 2-Oxo-2-(p-tolylamino)acetate (**9**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.84 (s, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 4.41 (q, J = 7.1 Hz, 2H), 2.33 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.2, 153.8, 135.4, 133.9, 129.8, 119.9, 63.8, 21.1, 14.1. HRMS (ESI+): calcd for $C_{11}H_{13}NO_3$ + Na^+ $[M + Na]^+$ m/z 230.0788, found 230.0802. IR: ν_{max} 3337, 2915, 1732, 1700, 1597, 1543, 1515, 1288, 1175, 816, 698.

*Diethyl 6-Chloro-3-(4-chlorophenyl)-3,4-dihydroquinazoline-2,4-dicarboxylate (**2b**).*[16] According to the general procedure using **1b** (42.7 mg, 0.20 mmol, 1 equiv), the title compound **2b** was obtained after FC (pentane/EtOAc 8/1 → 6/1) as a yellow solid (20.9 mg, 0.05 mmol, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41−7.29 (m, 4H), 7.23 (d, J = 2.1 Hz, 1H), 7.12−6.98 (m, 2H), 5.29 (s, 1H), 4.34−4.08 (m, 4H), 1.25 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 161.9, 146.7, 141.8, 138.4, 132.7, 132.4, 129.9, 129.7 (2C), 127.4, 126.5, 124.4 (2C), 121.8, 62.9, 62.5, 62.5, 14.1, 13.7. HRMS (ESI+): calcd for $C_{20}H_{18}Cl_2N_2O_4$ + Na^+ $[M + Na]^+$ m/z 443.0536, found 443.0528. IR: ν_{max} 2982, 2938, 2906, 2360, 2342, 1736, 1607, 1580, 1564, 1491, 1476, 1422, 1380, 1332, 1282, 1253, 1188, 1093, 1074, 1015, 915, 852, 832, 788, 752, 729, 651, 552.

*Diethyl 6-Bromo-3-(4-bromophenyl)-3,4-dihydroquinazoline-2,4-dicarboxylate (**2c**).*[16] According to the general procedure using **1c** (51.6 mg, 0.20 mmol, 1 equiv), the title compound **2c** was obtained after FC (pentane/EtOAc 8/1 → 6/1) as a yellow solid (28.8 mg, 0.06 mmol, 56%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52−7.43 (m, 3H), 7.38 (d, J = 2.1 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.07−6.87 (m, 2H), 5.28 (s, 1H), 4.54−3.69 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 161.9, 146.7, 142.3, 138.8, 132.9, 132.6 (2C), 129.5, 127.7, 124.7 (2C), 122.1, 120.6, 120.2, 62.7, 62.6 (2C), 14.1, 13.7. HRMS (ESI+): calcd for $C_{20}H_{18}Br_2N_2O_4$ + Na^+ $[M + Na]^+$ m/z 532.9506, found 532.9512. IR: ν_{max} 2981, 2936, 2906, 2361, 2339, 1735, 1603, 1577, 1561, 1489, 1473, 1420, 1378, 1331, 1281, 1252, 1188, 1069, 1013, 909, 851, 825, 785, 729, 646, 632, 545.

*Diethyl 6-Fluoro-3-(4-fluorophenyl)-3,4-dihydroquinazoline-2,4-dicarboxylate (**2d**).* According to the general procedure using **1d** (39.4 mg, 0.20 mmol, 1 equiv), the title compound **2d** was obtained after FC (pentane/EtOAc 8/1 → 6/1) as a white solid (20.9 mg, 0.06 mmol, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (dd, J = 8.7, 5.3 Hz, 1H), 7.18−7.00 (m, 5H), 6.95 (dd, J = 8.3, 2.8 Hz, 1H), 5.31 (s, 1H), 4.50−3.76 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H), 1.06 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3, 162.2, 161.6 (d, ^1J = 247.7 Hz), 161.2 (d, ^1J = 247.6 Hz); 139.6 (d, ^4J = 3.0 Hz), 136.3 (d, ^4J = 2.9 Hz), 127.9 (d, ^3J = 8.4 Hz), 125.7 (d, ^3J = 8.5 Hz, 2C), 121.7 (d, ^3J = 8.5 Hz), 116.8 (d, ^2J = 22.5 Hz), 116.5 (d, ^2J = 22.9 Hz, 2C), 116.4, 113.5 (d, ^3J = 24.2 Hz), 63.5 (d, ^4J = 1.3 Hz), 62.6, 62.5, 14.2, 13.8. HRMS (ESI+): calcd for $C_{20}H_{18}F_2N_2O_4$ + Na^+ $[M + Na]^+$ m/z 411.1127, found 411.1131. IR: ν_{max} 3072, 2984, 2939, 2907, 2876, 2360, 2343, 1736, 1618, 1596, 1578, 1508, 1488, 1433, 1395, 1382, 1369, 1334, 1290, 1222, 1186, 1159, 1138, 1096, 1079, 1016, 959, 924, 840, 809, 741, 704, 639, 619, 564.

*Diethyl 6-(Trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)-3,4-dihydroquinazoline-2,4-dicarboxylate (**2e**).* According to the general

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procedure using **1e** (9.4 mg, 0.20 mmol, 1.0 equiv), the title compound **2e** was obtained after FC (pentane/EtOAc 8/1) as a yellow solid (31.4 mg, 0.06 mmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72−7.60 (m, 3H), 7.59−7.50 (m, 2H), 7.21 (d, J = 8.1 Hz, 2H), 5.43 (s, 1H), 4.36−4.07 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H), 1.08 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 161.7, 147.8, 146.1 (q, ^5J = 1.3 Hz), 142.5 (q, ^5J = 1.3 Hz), 129.6 (q, ^2J = 32.9 Hz), 128.8 (q, ^2J = 33.2 Hz), 126.94 (q, ^3J = 3.6 Hz, 2C), 126.6, 124.5 (q, ^1J = 272.0 Hz), 124.2 (q, ^3J = 3.8 Hz), 123.9 (q, ^1J = 272.0 Hz), 122.9 (3C), 121.3, 62.9, 62.9, 62.8, 14.1, 13.7. ^{19}F NMR (282 MHz, $CDCl_3$): δ −62.37, −62.42. HRMS (ESI+): calcd for $C_{22}H_{18}F_6N_2O_4$ + H^+ [M + H]$^+$ m/z 489.1244, found 489.1244. IR: ν_{max} 2986, 1739, 1619, 1587, 1571, 1520, 1428, 1322, 1258, 1193, 1163, 1116, 1068, 1017, 910, 844, 735, 649, 612, 589.

*Diethyl 6-Acetyl-3-(4-acetylphenyl)-3,4-dihydroquinazoline-2,4-dicarboxylate (**2f**).* According to the general procedure using **1f** (44.3 mg, 0.20 mmol, 1 equiv), the title compound **2f** was obtained after FC (pentane/EtOAc 4/1 → 1/1) as a yellow solid (25.2 mg, 0.06 mmol, 58%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01−7.87 (m, 4H), 7.53 (d, J = 8.2 Hz, 1H), 7.15 (d, J = 8.5 Hz, 2H), 5.45 (s, 1H), 4.34−4.05 (m, 4H), 2.60 (s, 6H), 1.23 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.6 (2C), 169.0, 161.9, 147.8, 147.0, 143.6, 136.2, 134.8, 130.3, 130.0 (2C), 127.1, 126.3, 122.0 (2C), 121.3, 62.9, 62.8, 62.8, 26.74, 26.7, 14.2, 13.8. HRMS (ESI+): calcd for $C_{24}H_{24}N_2O_6$ + Na^+ [M + Na]$^+$ m/z 459.1527, found 459.1500. IR: ν_{max} 3062, 2983, 2937, 2361, 2341, 1737, 1679, 1602, 1576, 1555, 1510, 1421, 1394, 1381, 1360, 1335, 1290, 1254, 1186, 1086, 1017, 958, 916, 840, 791, 729, 617, 593, 577.

*Diethyl 6-Cyano-3-(4-cyanophenyl)-3,4-dihydroquinazoline-2,4-dicarboxylate (**2g**).* According to the general procedure using **1g** (40.8 mg, 0.20 mmol, 1 equiv), the title compound **2g** was obtained after FC (pentane/EtOAc 4/1 → 3/1) as a white solid (19.9 mg, 0.05 mmol, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72−7.51 (m, 5H), 7.22−7.14 (m, 2H), 5.38 (s, 1H), 4.35−4.15 (m, 4H), 1.26 (t, J = 7.0 Hz 3H), 1.14 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 161.3, 147.8, 146.5, 143.2, 133.8, 133.8, 130.9, 127.1, 123.0, 121.9, 118.3, 118.0, 111.2, 110.4, 63.3, 62.2, 29.9, 14.2, 13.9. HRMS (ESI+): calcd for $C_{22}H_{18}N_4O_4$ + Na^+ [M + Na]$^+$ m/z 425.1220, found 425.1225. IR: ν_{max} 2995, 2924, 2853, 2227, 1737, 1606, 1576, 1557, 1508, 1486, 1426, 1394, 1382, 1369, 1334, 1289, 1258, 1191, 1126, 1094, 1079, 1016, 912, 844, 729, 665, 648, 594, 577.

*Triethyl 3-(4-(Ethoxycarbonyl)phenyl)-3,4-dihydroquinazoline-2,4,6-tricarboxylate (**2h**).* According to the general procedure using **1h** (50.3 mg, 0.20 mmol, 1 equiv), the title compound **2h** was obtained after FC (pentane/EtOAc 6/1) as a yellow solid (14.7 mg, 0.03 mmol, 31%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08−8.03 (m, 3H), 7.99−7.95 (m, 1H), 7.51 (br d, J = 7.8 Hz, 1H), 7.13 (br d, J = 8.2 Hz, 2H), 5.45 (s, 1H), 4.42−4.32 (m, 4H), 4.28−4.12 (m, 4H), 1.40 (t, J = 7.1 Hz, 3H), 1.39 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 165.8, 165.7, 162.0, 147.8, 146.9, 143.4, 131.2, 131.2, 129.6, 128.4, 128.3, 126.2, 122.0, 121.0, 62.9, 62.8, 62.7, 61.4, 61.3, 29.8, 14.5, 14.4, 14.2, 13.9. HRMS (ESI+): calcd for $C_{26}H_{28}N_2O_8$ + Na^+ [M + Na]$^+$ m/z 519.1738, found 519.1726. IR: ν_{max} 2982, 2937, 2907, 2875, 1738, 1712, 1608, 1580, 1561, 1511, 1425, 1392, 1383, 1367, 1334, 1256, 1178, 1100, 1077, 1018, 910, 855, 823, 711, 732, 701, 649, 611.

*Diethyl 6-Methoxy-3-(4-methoxyphenyl)-3,4-dihydroquinazoline-2,4-dicarboxylate (**2i**).* According to the general procedure using **1i** (42.7 mg, 0.20 mmol, 1 equiv), the title compound **2i** was obtained after FC (pentane/EtOAc 8/1 → 6/1 → 4/1) as a white solid (22.6 mg, 0.06 mmol, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, J = 8.7 Hz, 1H), 7.13−7.00 (m, 2H), 6.94−6.83 (m, 3H), 6.74 (d, J = 2.8 Hz, 1H), 5.31 (s, 1H), 4.32−4.04 (m, 5H), 3.80 (s, 4H), 3.79 (s, 4H), 1.24 (t, J = 7.1 Hz, 3H), 1.06 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 162.7, 158.9, 158.3, 145.9, 136.9, 136.9, 127.5, 125.3 (2C), 121.4, 115.2, 114.7 (2C), 111.6, 64.1, 62.2, 62.1, 55.7, 55.7, 14.2, 13.9. HRMS (ESI+): calcd for $C_{22}H_{24}N_2O_6$ + Na^+ [M + Na]$^+$ m/z 435.1527, found 435.1524. IR: ν_{max} 2981, 2937, 2838, 2360, 2343, 1734, 1691, 1615, 1580, 1510, 1493, 1464, 1382, 1286, 1237, 1182, 1151, 1111, 1079, 1020, 854, 835, 798, 736, 574.

*Diethyl 4-Hydroxy-6-methoxy-3-(4-methoxyphenyl)-3,4-dihydroquinazoline-2,4-dicarboxylate (**10**).* White solid (17.5 mg, 0.04 mmol, 41%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, J = 8.7 Hz, 1H), 7.41 (d, J = 8.7 Hz, 1H), 7.06 (d, J = 9.0 Hz, 1H), 6.98 (dd, J = 8.6, 2.8 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 7.4 Hz, 1H), 6.61 (d, J = 2.7 Hz, 1H), 5.12 (s, 1H), 4.08 (q, J = 7.1 Hz, 2H), 4.02 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 1.10 (t, J = 7.1 Hz, 3H), 0.99 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 162.6, 159.8, 158.6, 145.5, 133.2, 131.9, 131.5, 129.7, 128.1, 123.6, 116.9, 114.1 (2C), 109.2, 85.6, 63.9, 62.1, 55.7, 55.6, 13.9, 13.8. HRMS (ESI+): calcd for $C_{22}H_{24}N_2O_7$ + H^+ [M + H]$^+$ m/z 429.1656, found 429.1659. IR: ν_{max} 3475, 2981, 2840, 1737, 1620, 1494, 1377, 1228, 1193, 1165, 1031, 837.

*Diethyl 3-([1,1′-Biphenyl]-4-yl)-6-phenyl-3,4-dihydroquinazoline-2,4-dicarboxylate (**2j**).* According to the general procedure using **1j** (51.1 mg, 0.20 mmol, 1 equiv), the title compound **2j** was obtained after FC (pentane/EtOAc 7/1) as a yellow solid (21.2 mg, 0.04 mmol, 41%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64−7.52 (m, 8H), 7.46 (ddt, J = 13.1, 6.2, 1.9 Hz, 5H), 7.40−7.32 (m, 2H), 7.23−7.17 (m, 2H), 5.50 (s, 1H), 4.37−4.09 (m, 4H), 1.26 (t, J = 7.1 Hz, 3H), 1.07 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 162.6, 146.9, 142.8, 140.5, 140.2, 140.0, 139.4, 139.3, 129.0 (2C), 129.0 (2C), 128.5 (2C), 128.2, 127.7 (2C), 127.7 (2C), 127.1, 127.0, 126.6, 125.3, 123.2, 121.2, 110.1, 63.5, 62.4, 62.4, 14.2, 13.8. HRMS (ESI+): calcd for $C_{32}H_{28}N_2O_4$ + H^+ [M + H]$^+$ m/z 505.2122, found 505.2124. IR: ν_{max} 3060, 3032, 2981, 2935, 2905, 1734, 1617, 1575, 1562, 1520, 1479, 1418, 1393, 1381, 1368, 1333, 1269, 1253, 1187, 1165, 1078, 1021, 1009, 910, 840, 764, 727, 696, 645, 601, 560.

*Diethyl 3-(3,5-Dimethylphenyl)-5,7-dimethyl-3,4-dihydroquinazoline-2,4-dicarboxylate (**2k**).* According to the general procedure using **1k** (41.5 mg, 0.20 mmol, 1 equiv), the title compound **2k** was obtained after FC (pentane/EtOAc 8/1 → 6/1) as a yellow solid (15.3 mg, 0.04 mmol, 37%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13 (s, 1H), 6.93 (s, 1H), 6.85 (s, 1H), 6.69 (s, 2H), 5.43 (s, 1H), 4.30−4.10 (m, 4H), 2.38 (s, 3H), 2.31 (s, 3H), 2.29 (s, 6H), 1.23 (t, J = 7.1 Hz, 3H), 1.08 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 162.6, 146.9, 143.8, 140.3, 139.3 (2C), 138.8, 134.6, 130.5, 127.7, 124.3, 120.0 (2C), 117.3, 62.1, 62.0, 60.5, 21.4 (2C), 21.1, 18.7, 14.1, 13.7. HRMS (ESI+): calcd for $C_{24}H_{28}N_2O_4$ + Na^+ [M + Na]$^+$ m/z 431.1941, found 431.1942. IR: ν_{max} 2983, 2921, 2857, 1740, 1730, 1593, 1564, 1468, 1446, 1398, 1377, 1365, 1339, 1306, 1249, 1229, 1204, 1191, 1099, 1037, 1020, 857, 842, 793, 702, 681, 662, 593.

General Procedure A for the Synthesis of Quinolines from *N*-Alkylanilines. A mixture of **1** (0.5 mmol), olefin **3** (1.0 mmol, 2.0 equiv) or alkyne **10** (4.0 equiv), $FeCl_3$ (8.0 mg, 0.05 mmol, 10 mol %), and $T^+BF_4^-$ (243.0 mg, 1.0 mmol, 2 equiv) in dry DCM (5.0 mL) in a Schlenk tube under an argon atmosphere was stirred at 60 °C. Once the starting material was consumed (monitored by GC-MS or TLC), the solvent was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel.

General Procedure B for the Synthesis of Quinolines via a Three-Component Reaction. In a pressure Schlenk tube equipped with a magnetic stirring bar, aniline **5** (0.2 mmol, 1.0 equiv) and $FeCl_3$ (3.2 mg, 0.02 mmol, 10 mol %) were dissolved in dry DCM (2 mL) under an argon atmosphere. After the addition of ethyl glyoxalate **6** (48 μL, 0.24 mmol, 1.2 equiv; 50% in toluene), olefin **3** or alkyne **10** (0.4 mmol, 2.0 equiv), and $T^+BF_4^-$ (97.2 mg, 0.4 mmol, 2.0 equiv) the solution was stirred at 60 °C for 18 h. The crude reaction mixture was directly purified by column chromatography to obtain the corresponding quinoline derivative **4**.

*Ethyl 6-Methyl-4-phenylquinoline-2-carboxylate (**4a**)..*[7a,14] According to the general procedure A using **1a** (96.6 mg, 0.50 mmol, 1.0 equiv) and styrene (**3a**; 115 μL, 1.00 mmol, 2.0 equiv), the title compound **4a** was obtained after FC (pentane/EtOAc 5/1) as a white solid (135.9 mg, 0.47 mmol, 93%). According to the general procedure B using 4-methylaniline (**5a**; 21.4 mg, 0.2 mmol, 1.0 equiv) and styrene (**3a**; 46 μL, 0.4 mmol, 2.0 equiv), the title compound **4a** was obtained after FC (pentane/EtOAc 8/1) as a white solid (51.3 mg, 0.18 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, J = 8.6 Hz, 1H), 8.10 (s, 1H), 7.71 (s, 1H), 7.62 (dd, J = 8.7, 1.7 Hz, 1H), 7.60−

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7.46 (m, 5H), 4.56 (q, J = 7.1 Hz, 2H), 2.49 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 149.0, 146.9, 146.8, 139.0, 137.8, 132.4, 130.9, 129.6, 128.7, 128.6, 127.8, 124.4, 121.5, 62.2, 22.1, 14.4. HRMS (ESI): calcd for $C_{19}H_{17}NO_2 + Na^+$ $[M + Na]^+$ m/z 314.1151, found 314.1146. IR: ν_{max} 3060, 2979, 2912, 1708, 1496, 1445, 1246, 1231, 1107, 1026, 825, 755, 700.

*Ethyl 6-Methyl-4-phenyl-1,2,3,4-tetrahydroquinoline-2-carboxylate (**11a**).*[7a] According to the general procedure A in the reaction at room temperature for 13 h using **1a** (19.0 mg, 0.10 mmol, 1.0 equiv) and styrene (**3a**; 23 μL, 0.20 mmol, 2.0 equiv), the title compound **11a** was isolated after FC (pentane/EtOAc 10/1) as a white solid and as a 5/1 mixture of two diastereomers (10.0 mg, 0.03 mmol, 33%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.17 (m, 4H, major and 4H, minor), 7.15−7.04 (m, 1H, major and 1H, minor), 6.89 (dd, J = 8.1, 2.0 Hz, 1H, major), 6.84 (d, J = 8.1 Hz, 1H, minor), 6.67 (d, J = 1.5 Hz, 1H, major), 6.62 (d, J = 8.1 Hz, 1H, major), 6.58 (d, J = 8.1 Hz, 1H, minor), 6.43 (s, 1H, minor), 4.41 (s, 1H, major and 1H, minor), 4.27−4.08 (m, 3H, major and 3H, minor), 3.85 (dd, J = 10.3, 3.7 Hz, 1H, major), 2.55 (ddd, J = 12.9, 5.4, 3.2 Hz, 1H, minor), 2.33 (ddd, J = 12.8, 4.4, 3.8 Hz, 1H, major), 2.20 (ddd, J = 12.9, 10.3, 5.2 Hz, 1H, major and 1H, minor), 2.15 (s, 3H, major), 2.08 (s, 3H, minor), 1.25 (t, J = 7.1 Hz, 3H, major), 1.26−1.21 (t, J = 7.1 Hz, 3H, minor); ^{13}C NMR (100 MHz, $CDCl_3$) (only peaks of the major diastereomer): δ 172.9, 145.0, 141.3, 129.97, 128.9, 128.7, 128.2, 127.2, 126.8, 124.3, 115.0, 61.5, 54.4, 44.0, 35.3, 20.6, 14.3. HRMS (ESI): calcd for $C_{19}H_{21}NO_2 + H^+$ $[M + H]^+$ m/z 296.1645, found 296.1642. IR: ν_{max} 3400, 3055, 2972, 2898, 1711, 1376, 1253, 1135, 1115, 770, 703.

*(6-Methyl-4-phenylquinolin-2-yl)(phenyl)methanone (**4aa**).*[7a] According to the general procedure A using **1aa** (23.0 mg, 0.10 mmol, 1.0 equiv) and styrene (**3a**; 23 μL, 0.20 mmol, 2.0 equiv), the title compound **4aa** was obtained after FC (pentane/EtOAc 5/1) as a white solid (23.0 mg, 0.07 mmol, 72%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (dd, J = 8.4, 1.3 Hz, 2H), 8.17 (d, J = 8.6 Hz, 1H), 8.03 (s, 1H), 7.76 (s, 1H), 7.69−7.60 (m, 2H), 7.59−7.46 (m, 7H), 2.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.1, 153.5, 149.0, 146.0, 139.0, 138.0, 136.4, 133.1, 132.4, 131.6, 130.8, 129.7, 128.8, 128.7, 128.3, 127.6, 124.7, 121.2, 22.2. HRMS (ESI): calcd for $C_{23}H_{17}NO + Na^+$ $[M + Na]^+$ m/z 346.1202, found 346.1208. IR: ν_{max} 3054, 1655, 1597, 1575, 1492, 1443, 1359, 1249, 1149, 1003, 951, 825, 728.

*Diethyl (6-Methyl-4-phenylquinolin-2-yl)phosphonate (**4ba**).*[7a] According to the general procedure A using **1ba** (26.0 mg, 0.10 mmol, 1.0 equiv) and styrene (**3a**; 23 μL, 0.20 mmol, 2.0 equiv), the title compound **4ba** was obtained after FC (pentane/EtOAc 2/1) as a white solid (15.0 mg, 0.04 mmol, 42%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 8.6 Hz, 1H), 7.90 (d, J = 5.2 Hz, 1H), 7.70 (s, 1H), 7.61 (dd, J = 8.7, 1.9 Hz, 1H), 7.58−7.44 (m, 5H), 4.46−4.00 (m, 4H), 2.49 (s, 3H), 1.61−1.03 (td, J = 7.1, 0.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 150.0, 148.0, 147.9, 147.6, 147.4, 138.8, 137.7, 132.3, 130.6, 129.7, 128.7, 128.7, 127.2, 127.1, 124.5, 123.9, 123.6, 63.2, 63.2, 22.1, 16.5, 16.5. ^{31}P NMR (162 MHz, $CDCl_3$): δ 11.15. HRMS (ESI): calcd for $C_{20}H_{22}NO_3P + Na^+$ $[M + Na]^+$ m/z 378.1230, found 378.1230. IR: ν_{max} 2982, 1489, 1392, 1248, 1049, 1020, 967, 793, 702.

*6-Methyl-4-phenylquinoline-2-carbonitrile (**4ca**).* According to the general procedure A using **1ca** (29.0 mg, 0.20 mmol) and styrene (**3a**; 46 μL, 0.40 mmol, 2 equiv), the title compound **4ca** was obtained after FC (pentane/EtOAc 5/1) as a white solid (8.0 mg, 0.03 mmol, 17%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (d, J = 8.6 Hz, 1H), 7.72−7.70 (m, 1H), 7.67 (dd, J = 8.6, 1.9 Hz, 1H), 7.59−7.53 (m, 3H), 7.52−7.45 (m, 2H), 2.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.6, 147.6, 140.2, 136.6, 133.5, 132.4, 130.2, 129.5, 129.3, 129.0, 127.5, 124.7, 123.7, 117.9, 22.3. HRMS (ESI): calcd for $C_{17}H_{12}N_2 + Na^+[M + Na]^+$ m/z 267.0893, found 267.0902. IR: ν_{max} 3061, 2995, 2227, 1720, 1605, 1373, 1252, 1151, 1024, 841, 705.

*6-Methyl-2,4-diphenylquinoline (**4ea**).*[7a] According to the general procedure A using **1ea** (20.0 mg, 0.10 mmol, 1.0 equiv) and styrene (**3a**; 23 μL, 0.20 mmol, 2.0 equiv), the title compound **4ea** was obtained after FC (pentane/EtOAc 10/1) as a white solid (12.0 mg, 0.04 mmol, 41%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23−8.11 (m, 1H), 7.79 (s, 1H), 7.66 (s, 1H), 7.62−7.34 (m, 3H), 2.49 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.1, 148.7, 147.5, 139.8, 138.8, 136.4, 131.9, 129.9, 129.7, 129.3, 128.9, 128.7, 128.4, 127.6, 125.8, 124.5, 119.6, 22.0. HRMS (ESI): calcd for $C_{22}H_{17}N + H^+$ $[M + H]^+$ m/z 296.1434, found 296.1434. IR: ν_{max} 3053, 1587, 1544, 1488, 1449, 1357, 1079, 1027, 878, 826, 756, 700.

*Ethyl 6-Chloro-4-phenylquinoline-2-carboxylate (**4b**)..*[7a,14] According to the general procedure A using **1b** (21.0 mg, 0.10 mmol, 1.0 equiv) and styrene (**3a**; 23 μL, 0.20 mmol, 2.0 equiv), the title compound **4b** was obtained after FC (pentane/EtOAc 4/1) as a white solid (23.0 mg, 0.07 mmol, 73%). According to the general procedure B using 4-chloroaniline (**3b**; 25.5 mg, 0.2 mmol, 1.0 equiv) and styrene (**3a**; 46 μL, 0.4 mmol, 2.0 equiv), the title compound **4b** was obtained after FC (pentane/EtOAc 10/1) as a white solid (56.1 mg, 0.18 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, J = 9.0 Hz, 1H), 8.14 (s, 1H), 7.92 (d, J = 2.3 Hz, 1H), 7.71 (dd, J = 9.0, 2.3 Hz, 1H), 7.61−7.39 (m, 5H), 4.56 (q, J = 7.1 Hz, 2H), 1.48 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3, 149.1, 148.2, 146.9, 136.9, 133.8, 132.9, 129.6, 129.2, 129.0, 129.0, 128.0, 123.4, 122.2, 62.5, 14.5. HRMS (ESI): calcd for $C_{18}H_{14}ClNO_2 + Na^+$ $[M + Na]^+$ m/z 334.0605, found 334.0607. IR: ν_{max} 3062, 2981, 1717, 1453, 1374, 1240, 1139, 1107, 831, 700.

*Ethyl 6-Bromo-4-phenylquinoline-2-carboxylate (**4c**)..*[7a,14] According to the general procedure A using **1c** (26.0 mg, 0.10 mmol, 1.0 equiv) and styrene (**3a**; 23 μL, 0.20 mmol, 2.0 equiv), the title compound **4c** was obtained after FC (pentane/EtOAc 4/1) as a white solid (26.0 mg, 0.07 mmol, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, J = 9.0 Hz, 1H), 8.14 (s, 1H), 8.10 (d, J = 2.1 Hz, 1H), 7.85 (dd, J = 9.0, 2.1 Hz, 1H), 7.66−7.42 (m, 5H), 4.56 (q, J = 7.1 Hz, 2H), 1.48 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3, 149.2, 148.1, 146.6, 137.0, 135.0, 132.8, 131.2, 129.6, 129.2, 129.0, 128.6, 124.7, 122.2, 62.5, 14.5. HRMS (ESI): calcd for $C_{18}H_{14}BrNO_2 + Na^+$ $[M + Na]^+$ m/z 380.0085, found 380.0083. IR: ν_{max} 3056, 1721, 1484, 1445, 1371, 1249, 1140, 1110, 1024, 829, 707.

*Ethyl 6-Acetyl-4-phenylquinoline-2-carboxylate (**4d**).*[7a] According to the general procedure A using **1f** (23.0 mg, 0.10 mmol, 1.0 equiv) and styrene (**3a**; 23 μL, 0.20 mmol, 2.0 equiv), the title compound **4d** was obtained after FC (pentane/EtOAc 2/1) as a white solid (24.0 mg, 0.08 mmol, 75%). According to the general procedure B using 4′-aminoacetophenone (**5d**) (27.0 mg, 0.2 mmol, 1.0 equiv) and styrene (**3a**; 46 μL, 0.4 mmol, 2.0 equiv), the title compound **4d** was obtained after FC (pentane/EtOAc 10/1) as a white solid (58.4 mg, 0.18 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, J = 1.7 Hz, 1H), 8.44 (d, J = 8.9 Hz, 1H), 8.31 (dd, J = 8.9, 1.9 Hz, 1H), 8.19 (s, 1H), 7.83−7.38 (m, 5H), 4.58 (q, J = 7.1 Hz, 2H), 2.62 (s, 3H), 1.50 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 165.2, 151.8, 150.1, 149.8, 136.9, 136.5, 131.8, 129.7, 129.4, 129.1, 128.3, 127.7, 127.2, 122.1, 62.7, 26.9, 14.5. HRMS (ESI): calcd for $C_{20}H_{17}NO_3 + Na^+$ $[M + Na]^+$ m/z 342.1101, found 342.1096. IR: ν_{max} 2985, 1733, 1680, 1402, 1244, 1229, 1141, 1024, 843, 772.

*Ethyl 6-Methoxy-4-phenylquinoline-2-carboxylate (**4e**)..*[7a,14] According to the general procedure A using **1i** (21.0 mg, 0.10 mmol, 1.0 equiv) and styrene (**3a**; 23 μL, 0.20 mmol, 2.0 equiv), the title compound **4e** was obtained after FC (pentane/EtOAc 5/1) as a white solid (26.0 mg, 0.08 mmol, 84%). According to the general procedure B using 4-anisidine (**5e**;24.6 mg, 0.2 mmol, 1.0 equiv) and styrene (**3a**; 46 μL, 0.4 mmol, 2.0 equiv), the title compound **4e** was obtained after FC (pentane/EtOAc 10/1) as a white solid (57.6 mg, 0.18 mmol, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (d, J = 9.3 Hz, 1H), 8.09 (s, 1H), 7.61−7.46 (m, 5H), 7.43 (dd, J = 9.3, 2.8 Hz, 1H), 7.21 (d, J = 2.8 Hz, 1H), 4.55 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 1.47 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 159.6, 148.2, 145.5, 144.4, 138.0, 132.8, 129.4, 129.3, 128.9, 128.8, 122.9, 121.9, 103.4, 62.2, 55.6, 14.5. HRMS (ESI): calcd for $C_{19}H_{17}NO_3 + H^+$ $[M + H]^+$ m/z 308.1281, found 308.1282. IR: ν_{max} 2976, 1729, 1616, 1472, 1220, 1103, 1025, 839, 707.

*Ethyl 5,7-Dimethyl-4-phenylquinoline-2-carboxylate (**4f**).*[7a] According to the general procedure A using **1k** (21.0 mg, 0.10 mmol, 1.0 equiv) and styrene (**3a**; 23 μL, 0.20 mmol, 2.0 equiv), the title compound **4f** was obtained after FC (pentane/EtOAc 5/1) as a white

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solid (21.0 mg, 0.07 mmol, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.92 (s, 1H), 7.50−7.39 (m, 3H), 7.39−7.28 (m, 2H), 7.22 (s, 1H), 4.53 (q, J = 7.1 Hz, 2H), 2.51 (s, 3H), 2.00 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 150.2, 149.7, 146.4, 142.1, 140.0, 135.2, 134.3, 129.0, 128.9, 128.1, 125.6, 122.8, 62.3, 24.4, 21.5, 14.5. HRMS (ESI): calcd for $C_{20}H_{19}NO_2$ + H^+ $[M + H]^+$ m/z 306.1484, found 306.1484. IR: ν_{max} 2976, 1708, 1470, 1372, 1338, 1244, 1135, 1026, 867, 708.

*Ethyl 7-Methyl-4-phenylquinoline-2-carboxylate (**4g**) and Ethyl 5-Methyl-4-phenylquinoline-2-carboxylate (**4g′**).*[7a] According to the general procedure A using **1o** (19.0 mg, 0.10 mmol, 1.0 equiv) and styrene (**3a**; 23 μL, 0.20 mmol, 2.0 equiv), the title regioisomers **4g** and **4g′** were obtained after FC (pentane/EtOAc 10:1) as a 1.6/1 mixture and a white solid (12.0 mg, 0.04 mmol, 42%). According to the general procedure B using 3-methylaniline (**5g**; 21.9 μL, 0.2 mmol, 1.0 equiv) and styrene (**3a**; 46 μL, 0.4 mmol, 2.0 equiv), the title regioisomers **4g** and **4g′** were obtained after FC (pentane/EtOAc 8/1) as a 1/1.5 mixture and a white solid (30.2 mg, 0.10 mmol, 50%) (1.6/1 dr mixture). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, J = 8.5 Hz, 1H, minor), 8.16 (s, 1H, major), 8.08 (s, 1H, major), 7.99 (s, 1H, minor), 7.86 (d, J = 8.6 Hz, 1H, major), 7.66 (dd, J = 8.4, 7.1 Hz, 1H), 7.59−7.50 (m, 3H, major and 3H, minor), 7.49−7.32 (m, 3H, major and 3H, minor), 4.56 (q, J = 7.1 Hz, 2H, major), 4.55 (q, J = 7.1 Hz, 1H, minor), 2.58 (s, 3H, major), 2.04 (s, 3H, minor), 1.49 (t, J = 7.1 Hz, 3H, major), 1.47 (t, J = 7.1 Hz, 3H, minor). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 165.4, 150.3, 149.5, 149.4, 148.5, 147.8, 146.4, 141.9, 140.4, 137.7, 135.6, 131.8, 131.0, 130.1, 129.6, 129.6, 128.8, 128.7, 128.1, 128.1, 127.4, 125.9, 125.4, 123.4, 120.6, 62.2, 24.5, 21.7, 14.4. HRMS (ESI): calcd for $C_{19}H_{17}NO_2$ + Na^+ $[M + Na]^+$ m/z 314.1151, found 314.1147. IR: ν_{max} 2975, 2919, 1712, 1443, 1377, 1377, 1250, 1133, 1111, 1038, 777, 767, 709.

*Ethyl 4-(4-Chlorophenyl)-6-methylquinoline-2-carboxylate (**4h**)..*[7a,14] According to the general procedure A using **1a** (19.0 mg, 0.10 mmol, 1.0 equiv) and 4-chlorostyrene (**3b**; 24 μL, 0.20 mmol, 2.0 equiv), the title compound **4h** was obtained after FC (pentane/EtOAc 5/1) as a white solid (27.0 mg, 0.08 mmol, 83%). According to the general procedure B using 4-methylaniline (**5a**; 21.4 mg, 0.2 mmol, 1.0 equiv) and 4-chlorostyrene (**3b**; 50.4 μL, 0.4 mmol, 2.0 equiv), the title compound **4h** was obtained after FC (pentane/EtOAc 10/1) as a white solid (56.6 mg, 0.17 mmol, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, J = 9.2 Hz, 1H), 8.06 (s, 1H), 7.67−7.59 (m, 2H), 7.57−7.50 (m, 2H), 7.50−7.42 (m, 2H), 4.56 (q, J = 7.1 Hz, 2H), 2.50 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 147.7, 147.0, 146.8, 139.3, 136.2, 134.9, 132.6, 131.1, 130.9, 129.0, 127.6, 124.1, 121.4, 62.3, 22.1, 14.5. HRMS (ESI): calcd for $C_{19}H_{16}ClNO_2$ + Na^+ $[M + Na]^+$ m/z 348.0762, found 348.0747. IR: ν_{max} 2987, 1710, 1595, 1491, 1381, 1252, 1149, 1111, 1087, 1016, 822.

*Ethyl 4-(2-Chlorophenyl)-6-methylquinoline-2-carboxylate (**4i**).*[7a] According to the general procedure A using **1a** (19.0 mg, 0.10 mmol, 1.0 equiv) and 2-chlorostyrene (**3c**; 24 μL, 0.20 mmol, 2.0 equiv), the title compound **4i** was obtained after FC (pentane/EtOAc 5/1) as a white solid (25.0 mg, 0.08 mmol, 77%). According to the general procedure B using 4-methylaniline (**5a**; 21.4 mg, 0.2 mmol, 1.0 equiv) and 2-chlorostyrene (**3c**; 51.3 μL, 0.4 mmol, 2.0 equiv), the title compound **4i** was obtained after FC (pentane/EtOAc 10/1) as a pale red solid (57.6 mg, 0.18 mmol, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, J = 8.7 Hz, 1H), 8.06 (s, 1H), 7.65−7.56 (m, 2H), 7.51−7.39 (m, 2H), 7.37−7.31 (m, 1H), 7.28 (br s, 1H), 4.56 (qd, J = 7.1, 1.0 Hz, 2H), 2.47 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.4, 146.8, 146.4, 146.3, 139.2, 136.4, 133.2, 132.6, 131.2, 130.8, 130.0, 129.9, 127.9, 126.9, 124.3, 121.9, 62.2, 22.0, 14.4. HRMS (ESI): calcd for $C_{19}H_{16}ClNO_2$ + Na^+ $[M + Na]^+$ m/z 348.0762, found 348.0744. IR: ν_{max} 2985, 1711, 1556, 1475, 1435, 1370, 1248, 1228, 1151, 1128, 1107, 1057, 1025, 900, 825, 763, 734, 685, 622, 591, 521.

*Ethyl 4-(4-(Trifluoromethyl)phenyl)-6-methylquinoline-2-carboxylate (**4j**).* According to the general procedure A using **1a** (19.0 mg, 0.10 mmol, 1.0 equiv) and 4-(trifluoromethyl)styrene (**3d**; 34.4 mg, 0.20 mmol, 2.0 equiv), the title compound **4j** was obtained after FC (pentane/EtOAc 6/1) as a white solid (28.0 mg, 0.08 mmol, 78%). According to the general procedure B using 4-methylaniline (**5a**; 21.4 mg, 0.2 mmol, 1.0 equiv) and *p*-(trifluormethyl)styrene (**3d**; 68.9 μL, 0.4 mmol, 2.0 equiv), the title compound **4j** was obtained after FC (pentane/EtOAc 10/1) as a pale yellow solid (41.1 mg, 0.11 mmol, 55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 8.7 Hz, 1H), 8.08 (s, 1H), 7.86−7.49 (m, 7H), 4.56 (q, J = 7.1 Hz, 2H), 2.49 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 147.3 147.0, 146.9, 139.7, 138.7, 133.0, 132.7, 131.4 (q, ^2J = 32.6 Hz), 131.2, 129.3, 127.5, 126.4 (q, ^3J = 3.8 Hz), 125.5 (q, ^3J = 3.8 Hz), 124.0 (q, ^1J = 272.5 Hz), 123.0, 121.5, 62.4, 22.2, 14.5. ^{19}F NMR (282 MHz, $CDCl_3$): δ −62.59. HRMS (ESI): calcd for $C_{19}H_{17}NO_3$ + Na^+ $[M + Na]^+$ m/z 330.1101, found 330.1088. IR: ν_{max} 2977, 2926, 1721, 1379, 1315, 1286, 1244, 1188, 1167, 1108, 1078, 1025, 895, 826, 811, 705.

*Ethyl 4-(4-(tert-Butyl)phenyl)-6-methylquinoline-2-carboxylate (**4k**).*[7a] According to the general procedure A using **1a** (19.0 mg, 0.10 mmol, 1.0 equiv) and 4-(*tert*-butyl)styrene (**3e**; 37 μL, 0.20 mmol, 2.0 equiv), the title compound **4k** was obtained after FC (pentane/EtOAc 5/1) as a white solid (30.0 mg, 0.09 mmol, 86%). According to the general procedure B using 4-methylaniline (**5a**; 21.4 mg, 0.2 mmol, 1.0 equiv) and 4-(*tert*-butyl)styrene (**3e**; 77.1 μL, 0.4 mmol, 2.0 equiv), the title compound **4k** was obtained after FC (pentane/EtOAc 10/1) as a white solid (60.6 mg, 0.17 mmol, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, J = 8.7 Hz, 1H), 8.10 (s, 1H), 7.78 (s, 1H), 7.64−7.59 (m, 1H), 7.59−7.54 (m, 2H), 7.51−7.44 (m, 2H), 4.55 (q, J = 7.1 Hz, 2H), 2.50 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H), 1.42 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 151.7, 149.0, 146.8, 146.7, 138.8, 134.7, 132.3, 130.8, 129.3, 127.9, 125.6, 124.5, 121.4, 62.1, 34.8, 31.3, 22.0, 14.4. HRMS (ESI): calcd for $C_{23}H_{25}NO_2$ + Na^+ $[M + Na]^+$ m/z 370.1778, found 370.1764. IR: ν_{max} 2965, 1738, 1581, 1495, 1365, 1225, 1108, 840.

*Ethyl 4-(4-Methoxyphenyl)-6-methylquinoline-2-carboxylate (**4l**).*[7a] According to the general procedure A using **1a** (19.0 mg, 0.10 mmol, 1.0 equiv) and 4-methoxystyrene (**3f**; 27 μL, 0.20 mmol, 2.0 equiv), the title compound **4l** was obtained after FC (pentane/EtOAc 5/1) as a white solid (27.0 mg, 0.08 mmol, 83%). Chromatography: pentane/ethyl acetate 5/1.ield: 76%, pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, J = 8.7 Hz, 1H), 8.08 (s, 1H), 7.75 (s, 1H), 7.61 (dd, J = 8.7, 1.9 Hz, 1H), 7.52−7.43 (m, 2H), 7.26 (s, 1H), 7.12−7.04 (m, 2H), 4.56 (q, J = 7.1 Hz, 2H), 3.92 (s, 3H), 2.50 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 160.0, 148.8, 146.8, 138.8, 132.3, 130.8, 130.8, 130.0, 128.0, 124.4, 121.3, 114.1, 110.0, 62.2, 55.4, 22.0, 14.4. HRMS (ESI): calcd for $C_{20}H_{19}NO_3$ + Na^+ $[M + Na]^+$ m/z 344.1257, found 344.1247. IR: ν_{max} 2969, 1714, 1610, 1514, 1376, 1247, 1174, 1128, 1110, 1026, 828.

*Ethyl 6-Methyl-3,4-diphenylquinoline-2-carboxylate (**4m**).*[7a] According to the general procedure A using **1a** (19.0 mg, 0.10 mmol, 1.0 equiv) and *trans*-stylbene (**3g**; 150 μL, 0.80 mmol, 4.0 equiv), the title compound **4m** was obtained after FC (pentane/EtOAc 4/1) as a white solid (11.0 mg, 0.03 mmol, 29%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (d, J = 8.6 Hz, 1H), 7.59 (dd, J = 8.6, 1.8 Hz, 1H), 7.34 (s, 1H), 7.33−7.27 (m, 3H), 7.20−7.14 (m, 3H), 7.14−7.05 (m, 3H), 4.12 (q, J = 7.1 Hz, 2H), 2.44 (s, 3H), 0.97 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 150.8, 147.6, 145.2, 138.4, 137.2, 136.1, 132.4, 131.7, 130.3, 130.3, 129.8, 128.0, 127.8, 127.7, 127.7, 127.2, 125.4, 61.8, 22.1, 13.8. HRMS (ESI): calcd for $C_{25}H_{21}NO_2$ + Na^+ $[M + Na]^+$ m/z 390.1465, found 390.1465. IR: ν_{max} 3059, 2979, 1735, 1489, 1375, 1303, 1243, 1174, 1109, 1034, 824.

*(E)-Ethyl 6-Methyl-4-phenyl-3-styrylquinoline-2-carboxylate (**4n**).*[7a] According to the general procedure A using **1a** (19.0 mg, 0.10 mmol, 1.0 equiv) and (1*E*,3*E*)-1,4-diphenylbuta-1,3-diene (**3h**; 165 mg, 0.80 mmol, 4.0 equiv), the title compound **4n** was obtained after FC (pentane/EtOAc 10/1) as a yellow oil (17.0 mg, 0.04 mmol, 44%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (d, J = 8.6 Hz, 1H), 8.06 (s, 1H), 7.61 (dd, J = 8.6, 1.7 Hz, 1H), 7.46−7.27 (m, 10H), 7.07 (d, J = 16.7 Hz, 1H), 6.77 (d, J = 16.7 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 2.56 (s, 3H), 0.99 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 150.7, 145.7, 143.0, 138.5, 138.3, 137.4, 136.7, 132.2, 130.9, 130.3, 130.3, 128.9, 128.6, 128.3, 127.8, 126.8, 126.7, 124.5, 123.4, 61.7, 22.3, 13.8. HRMS (ESI): calcd for $C_{27}H_{23}NO_2$ + H^+ $[M + Na]^+$

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m/*z* 394.1802, found 394.1798. IR: ν_{max} 2980, 1732, 1558, 1493, 1372, 1303, 1240, 1155, 1118, 1020, 826, 749, 734, 698.

*Ethyl 3-Ethyl-6-methyl-4-phenylquinoline-2-carboxylate (**4o**).*[7a] According to the general procedure A using **1a** (19.0 mg, 0.10 mmol, 1.0 equiv) and *β*-ethylstyrene (**3i**; 106 mg, 0.80 mmol, 4.0 equiv), the title compound **4o** was obtained after FC (pentane/EtOAc 4/1) as a white solid (19.0 mg, 0.06 mmol, 58%). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.01 (d, *J* = 8.6 Hz, 1H), 7.56−7.37 (m, 4H), 7.28−7.13 (m, 2H), 6.96 (s, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 2.64 (q, *J* = 7.5 Hz, 2H), 2.31 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H), 0.98 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 167.5, 150.4, 147.8, 144.0, 137.8, 136.5, 132.3, 131.5, 129.3, 129.2, 128.5, 128.4, 128.0, 124.9, 62.0, 23.0, 21.9, 15.8, 14.2. HRMS (ESI): calcd for $C_{21}H_{21}NO_2$ + H^+ $[M + H]^+$ *m*/*z* 320.1645, found 320.1647. IR: ν_{max} 2989, 1707, 1625, 1570, 1479, 1355, 1300, 1244, 1186, 1152, 1070, 1043, 878, 820, 750, 706.

*Ethyl 4-Hexyl-6-methylquinoline-2-carboxylate (**4p**).*[7a] According to the general procedure A using **1a** (19.0 mg, 0.10 mmol, 1.0 equiv) and 1-octene (**3j**; 32 *μ*L, 0.20 mmol, 2.0 equiv), the title compound **4p** was obtained after FC (pentane/EtOAc 5/1) as a white solid (20.0 mg, 0.07 mmol, 66%). According to the general procedure B using **5a** (21.4 mg, 0.2 mmol, 1.0 equiv) and 1-octene (**3j**; 157.0 *μ*L, 1.0 mmol, 5.0 equiv), the title compound **4p** was obtained after FC (pentane/EtOAc 10/1) as a pale yellow oil (21.6 mg, 0.07 mmol, 36%). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.19 (d, *J* = 8.7 Hz, 1H), 7.99 (s, 1H), 7.80 (s, 1H), 7.58 (dd, *J* = 8.7, 1.8 Hz, 1H), 4.55 (q, *J* = 7.1 Hz, 2H), 3.09 (dd, *J* = 8.0, 7.7 Hz, 2H), 2.58 (s, 3H), 1.86−1.63 (m, 2H), 1.49 (t, *J* = 7.1 Hz, 3H), 1.55−1.40 (m, 2H), 1.39−1.27 (m, 4H), 0.96−0.84 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 165.9, 149.4, 147.0, 146.3, 138.4, 131.93, 131.2, 128.6, 122.3, 120.6, 62.1, 32.3, 31.6, 29.9, 29.3, 22.6, 22.1, 14.4, 14.1. HRMS (ESI): calcd for $C_{19}H_{25}NO_2$ + H^+ $[M + H]^+$ *m*/*z* 300.1958, found 300.1959. IR: ν_{max} 2929, 2859, 1718, 1591, 1446, 1372, 1318, 1283, 1246, 1215, 1168, 1110, 1078, 1023, 936, 896, 825, 793, 705.

*Ethyl 6-Methylquinoline-2-carboxylate (**4q**).*[7a] According to the general procedure A using **1a** (19.0 mg, 0.10 mmol, 1.0 equiv) and ethyl vinyl ether (**3k**; 20 *μ*L, 0.20 mmol, 2.0 equiv), the title compound **4q** was obtained after FC (pentane/EtOAc 5/1) as a white solid (13.8 mg, 0.07 mmol, 64%). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.20 (d, *J* = 8.6 Hz, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.66−7.58 (m, 1H), 4.55 (q, *J* = 7.1 Hz, 1H), 2.56 (s, 2H), 1.49 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 165.5, 147.3, 146.2, 138.9, 136.5, 132.6, 130.4, 129.4, 126.3, 121.1, 62.2, 21.8, 14.4. HRMS (ESI): calcd for $C_{13}H_{13}NO_2$ + Na^+ $[M + Na]^+$ *m*/*z* 238.0838, found 238.0833. IR: ν_{max} 2973, 2929, 2871, 1717, 1444, 1371, 1318, 1295, 1249, 1214, 1133, 1104, 826.

*Ethyl 6-Fluoro-4-phenylquinoline-2-carboxylate (**4r**).* According to the general procedure B using 4-fluoroaniline (**5h**; 19 *μ*L, 0.2 mmol, 1.0 equiv) and styrene (**3a**; 46 *μ*L, 0.4 mmol, 2.0 equiv), the title compound **4r** was obtained after FC (pentane/EtOAc 5/1) as an orange solid (34.3 mg, 0.12 mmol, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.40−8.35 (m, 1H), 8.15 (s, 1H), 7.58−7.49 (m, 7H), 4.56 (q, *J* = 7.1 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 165.4, 162.0 (d, *J* = 251.1 Hz), 149.4 (d, *J* = 6.0 Hz), 147.4 (d, *J* = 2.9 Hz), 145.4, 137.2, 133.9 (d, *J* = 9.5 Hz), 129.5, 129.1, 129.0, 129.0 (d, *J* = 3.6 Hz), 121.9, 120.6 (d, *J* = 26.1 Hz), 109.3 (d, *J* = 23.3 Hz), 62.5, 14.5. ^{19}F NMR (282 MHz, $CDCl_3$): *δ* −109.0. HRMS (ESI): calcd for $C_{18}H_{14}FNO_2$ + Na^+ $[M + Na]^+$ *m*/*z* 318.0901, found 318.0887. IR: ν_{max} 3053, 2986, 2920, 1714, 1624, 1494, 1464, 1377, 1353, 1249, 1230, 1194, 1137, 1102, 1029, 906, 872, 835, 789, 756, 702.

*Ethyl 4-(2-Naphthyl)-6-methylquinoline-2-carboxylate (**4s**).* According to the general procedure B using 4-methylaniline (**5a**; 21.4 mg, 0.20 mmol, 1.0 equiv) and 2-vinylnaphthalene (**3l**; 61.7 mg, 0.4 mmol, 2.0 equiv), the title compound **4s** was obtained after FC (pentane/EtOAc 4/1) as a white solid (40.5 mg, 0.12 mmol, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.30 (d, *J* = 8.7 Hz, 1H), 8.20 (s, 1H), 8.06−7.99 (m, 2H), 7.96 (dddd, *J* = 8.8, 7.3, 4.1, 1.9 Hz, 2H), 7.75−7.72 (m, 1H), 7.66−7.62 (m, 2H), 7.62−7.56 (m, 2H), 4.58 (q, *J* = 7.1 Hz, 2H), 2.48 (s, 3H), 1.50 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 165.8, 149.1, 147.1, 147.0, 139.2, 135.4, 133.4, 133.2, 132.5, 131.1, 129.0, 128.4, 128.4, 128.1, 128.0, 127.4, 127.0, 126.9, 124.6, 121.8, 62.4, 22.2, 14.6. HRMS (ESI): calcd for $C_{23}H_{19}NO_2$ + H^+ $[M + H]^+$ *m*/*z* 342.1489, found 342.1494. IR: ν_{max} 3053, 2981, 1716, 1586, 1503, 1373, 1258, 1222, 1148, 1110, 1027, 821, 748.

*Ethyl 3,6-Dimethyl-4-phenylquinoline-2-carboxylate (**4t**).*[14] According to the general procedure B using 4-methylaniline (**5a**; 21.4 mg, 0.2 mmol, 1.0 equiv) and *cis*-*β*-methylstyrene (**3m**; 129.9 *μ*L, 1.0 mmol, 5.0 equiv), the title compound **4t** was obtained after FC (pentane/EtOAc 10/1) as a pale red solid (29.1 mg, 0.10 mmol, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.07 (d, *J* = 8.6 Hz, 1H), 7.57−7.45 (m, 4H), 7.25−7.20 (m, 2H), 7.10 (s, 1H), 4.53 (q, *J* = 7.1 Hz, 2H), 2.38 (s, 3H), 2.29 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 167.6, 150.6, 148.0, 144.4, 138.0, 137.0, 131.4, 129.7, 129.3, 128.8, 128.30, 128.1, 126.4, 124.8, 62.1, 22.0, 17.0, 14.4. HRMS (ESI): calcd for $C_{20}H_{19}NO_2$ + H^+ $[M + H]^+$ *m*/*z* 306.1489, found 306.1499. IR: ν_{max} 2987, 1713, 1626, 1568, 1489, 1367, 1299, 1246, 1191, 1154, 1073, 1044, 876, 822, 746, 704.

*Ethyl 2-Methyl-7,8,9,10-tetrahydro-7,10-methanophenanthridine-6-carboxylate (**4u**).* According to the general procedure B using 4-methylaniline (**5a**; 21.4 mg, 0.20 mmol, 1.0 equiv) and norbornene (**3n**; 75 mg, 0.8 mmol, 4.0 equiv), the title compound **4v** was obtained after FC (pentane/EtOAc 4/1) as a white solid (27.7 mg, 0.05 mmol, 49%). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.14 (d, *J* = 8.8 Hz, 1H), 7.73−7.64 (m, 1H), 7.50 (dd, *J* = 8.8, 2.0 Hz, 1H), 4.53 (td, *J* = 7.1, 2.1 Hz, 2H), 2.56 (s, 4H), 2.15−2.04 (m, 2H), 1.85 (dt, *J* = 9.0, 2.0 Hz, 1H), 1.68 (dt, *J* = 9.0, 1.4 Hz, 1H), 1.49 (t, *J* = 7.1 Hz, 3H), 1.33−1.26 (m, 1H), 1.17−1.09 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 166.3, 155.8, 145.4, 141.4, 141.0, 138.1, 131.6, 131.0, 124.4, 122.3, 61.9, 49.6, 43.6, 41.3, 26.9, 25.8, 22.1, 14.6. HRMS (ESI): calcd for $C_{18}H_{19}NO_2$ + H^+ $[M + H]^+$ *m*/*z* 282.1489, found 282.1494. IR: ν_{max} 2956, 2873, 1712, 1447, 1304, 1240, 1195, 1075, 1037, 820.

*Ethyl 8-Methyl-4-phenylquinoline-2-carboxylate (**4v**).*[7a] According to the general procedure A using **1l** (19.0 mg, 0.10 mmol, 1.0 equiv) and styrene (**3a**; 23 *μ*L, 0.2 mmol, 2.0 equiv), the title compound **4w** was obtained after FC (pentane/EtOAc 10/1 → 4/1) as a white solid (11 mg, 0.04 mmol, 38%). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.10 (s, 1H), 7.79 (dd, *J* = 8.5, 0.6 Hz, 1H), 7.69−7.60 (dt, *J* = 6.9, 1.1 Hz, 1H), 7.56−7.44 (m, 6H), 4.53 (q, *J* = 7.1 Hz, 2H), 2.95 (s, 3H), 1.49 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 165.9, 150.0, 147.5, 146.7, 139.3, 138.2, 130.2, 129.8, 128.7, 128.7, 128.4, 127.9, 123.8, 121.2, 62.1, 18.4, 14.5. HRMS (ESI): calcd for $C_{19}H_{17}NO_2$ + Na^+ $[M + Na]^+$ *m*/*z* 314.1151, found 314.1152. IR: ν_{max} 2925, 1706, 1444, 1373, 1252, 1129, 1115, 1035, 768, 706.

*Diethyl 6,6′-(2-Ethoxy-2-oxoethane-1,1-diyl)bis(8-methyl-4-phenylquinoline-2-carboxylate) (**12**).*[7a] Brown oil (15 mg, 0.02 mmol, 23%). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.08 (s, 2H), 7.66 (s, 2H), 7.55 (s, 2H), 7.47−7.37 (m, 10H), 5.15 (s, 1H), 4.52 (q, *J* = 7.1 Hz, 4H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.88 (s, 6H), 1.48 (t, *J* = 7.1 Hz, 6H), 1.13 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 171.5, 165.7, 149.7, 146.8, 139.7, 138.0, 137.8, 130.8, 129.6, 128.6, 128.6, 127.6, 123.2, 121.4, 62.0, 61.6, 57.5, 18.4, 14.4, 14.0. HRMS (ESI): calcd for $C_{42}H_{38}N_2O_6$ + Na^+ $[M + Na]^+$ *m*/*z* 689.2622, found 689.2628. IR: ν_{max} 2980, 1734, 1713, 1488, 1464, 1443, 1377, 1246, 1151, 1117, 1026, 765, 701.

*Ethyl 6-(2-Ethoxy-1-(4-((2-ethoxy-2-oxoethyl)amino)-3-methylphenyl)-2-oxoethyl)-8-methyl-4-phenylquinoline-2-carboxylate (**13**).*[6a]. Brown solid (2.7 mg, 0.005 mmol, 5%). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.07 (s, 1H), 7.72 (d, *J* = 1.6 Hz, 1H), 7.59 (s, 1H), 7.53−7.47 (m, 5H), 7.01 (m, 2H), 6.40 (d, *J* = 8.2 Hz, 1H), 4.95 (s, 1H), 4.51 (q, *J* = 7.1 Hz, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.16 (dd, *J* = 7.1, 0.9 Hz, 2H), 3.91 (s, 2H), 2.88 (s, 3H), 2.16 (s, 3H), 1.48 (t, *J* = 7.1 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). HRMS (ESI): calcd for $C_{34}H_{36}N_2O_6$ + Na^+ $[M + Na]^+$ *m*/*z* 591.2466, found 591.2464.

General Procedure for the Synthesis of *N*-Ethyl Acetate Substituted Anilines 1.[27] In an ordinary vial equipped with a magnetic stirring bar, aniline **5** (1.0 equiv), ethyl bromoacetate (1.0 equiv), sodium acetate (1.0 equiv), and ethanol (6.6 M) were added. After the reaction mixture was stirred at 85−90 °C overnight, the solvent was removed in vacuo. The residue was dissolved in DCM and

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washed with saturated NaCl (aqueous), the aqueous layer was washed two times with DCM, and the combined organic layers were dried over $MgSO_4$. Finally, the residue was purified by column chromatography.

*Ethyl 2-((4-Methylphenyl)amino)acetate (**1a**).* Following the general procedure, *p*-toluidine (**5a**; 1.07 g, 10.0 mmol, 1.0 equiv) was treated with ethyl bromoacetate (1.1 mL, 10.0 mmol, 1.0 equiv) and sodium acetate (900 mg, 10.0 mmol, 1.0 equiv) in ethanol (1.5 mL). **1a** was isolated by column chromatography (pentane/EtOAc: gradient 30/1 to 6/1) as a white solid (1.70 g, 8.8 mmol, 88%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.83−6.74 (m, 2H), 6.62−6.55 (m, 2H), 4.23 (q, J = 7.1 Hz, 2H), 3.86 (s, 2H), 3.74 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 152.8, 141.4, 115.0 (2C), 114.5 (2C), 61.4, 55.9, 47.0, 14.3. HRMS (ESI+): calcd for $C_{11}H_{15}NO_2$ + Na^+ $[M + Na]^+$ m/z 216.0995 found 216.0997. IR: ν_{max} 3379, 2980, 2897, 2861, 1725, 1619, 1524, 1450, 1366, 1325, 1216, 1182, 1031, 807.

*Ethyl 2-((4-Chlorophenyl)amino)acetate (**1b**).* Following the general procedure, 4-chloroaniline (1.27 g, 10.00 mmol, 1.0 equiv) was treated with ethyl bromoacetate (1.1 mL, 10.00 mmol, 1.0 equiv) and sodium acetate (900 mg, 10.00 mmol, 1.0 equiv) in ethanol (1.5 mL). **1b** was isolated by column chromatography (pentane/EtOAc: gradient 20/1 to 6/1) as a white solid (780 mg, 3.65 mmol, 37%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20−7.09 (m, 2H), 6.59−6.45 (m, 2H), 4.26 (br s, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.87 (s, 2H), 1.30 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 145.7, 129.3 (2C), 123.1, 114.3 (2C), 61.6, 46.1, 14.3. HRMS (ESI+): calcd for $C_{10}H_{12}ClNO_2$ + Na^+ $[M + Na]^+$ m/z 236.0449, found 236.0429. IR: ν_{max} 3377, 3001, 2989, 1730, 1606, 1506, 1450, 1347, 1220, 1179, 1094, 1024, 823, 803.

*Ethyl 2-((4-Bromophenyl)amino)acetate (**1c**).* Following the general procedure, 4-bromoaniline (1.72 g, 10.00 mmol, 1.0 equiv) was treated with ethyl bromoacetate (1.1 mL, 10.00 mmol, 1.0 equiv) and sodium acetate (900 mg, 10.00 mmol, 1.0 equiv) in ethanol (1.5 mL). **1c** was isolated by column chromatography (pentane/EtOAc: gradient 20/1 to 5/1) as a white solid (850 mg, 3.29 mmol, 33%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (dd, J = 8.9, 1.0 Hz, 2H), 6.46 (d, J = 8.7 Hz, 2H), 4.25 (br s, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.83 (s, 2H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 146.1, 132.2 (2C), 114.8 (2C), 110.2, 61.6, 46.0, 14.3. HRMS (ESI+): calcd for $C_{10}H_{12}BrNO_2$ + Na^+ $[M + Na]^+$ m/z 279.9944, found 279.9942. IR: ν_{max} 3375, 3050, 3000, 2984, 1718, 1600, 1502, 1449, 1371, 1346, 1225, 1180, 1071, 1022, 815, 802.

*Ethyl 2-((4-Fluorophenyl)amino)acetate (**1d**).* Following the general procedure, 4-fluoroaniline (480 μL, 5.00 mmol, 1.0 equiv) was treated with ethyl bromoacetate (554 μL, 5.00 mmol, 1.0 equiv) and sodium acetate (410 mg, 5.00 mmol, 1.0 equiv) in ethanol (10 mL). **1d** was isolated by column chromatography (pentane/EtOAc: gradient 10/1 to 4/1) as a pale orange solid (619.5 mg, 3.14 mmol, 63%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.99−6.81 (m, 2H), 6.62−6.47 (m, 2H), 4.24 (q, J = 7.1 Hz, 2H), 4.18 (br s, 1H), 3.86 (s, 2H), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 156.3 (d, ^1J = 235.7 Hz), 143.52 (d, ^4J = 1.8 Hz), 115.9 (d, ^2J = 22.4 Hz, 2C), 114.0 (d, ^3J = 7.5 Hz), 61.5, 46.6, 14.3. ^{19}F NMR (282 MHz, $CDCl_3$): δ −127.22. HRMS (ESI+): calcd for $C_{10}H_{12}FNO_2$ + Na^+ $[M + Na]^+$ m/z 220.0744, found 220.0738. IR: ν_{max} 3382, 2993, 1724, 1511, 1450, 1369, 1349, 1255, 1206, 1144, 1025, 815, 783.

*Ethyl 2-((4-(Trifluoromethyl)phenyl)amino)acetate (**1e**).* Following the general procedure, 4-(trifluoromethyl)aniline (403 mg, 2.50 mmol, 1.0 equiv) was treated with ethyl bromoacetate (276 μL, 2.50 mmol, 1.0 equiv) and sodium acetate (205 mg, 2.50 mmol, 1.0 equiv) in ethanol (0.4 mL). **1e** was isolated by column chromatography (pentane/EtOAc: gradient 10/1 to 3/1) as a white solid (375.5 mg, 1.52 mmol, 61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (dd, J = 8.6, 1.0 Hz, 2H), 6.53 (dd, J = 8.6, 1.0 Hz, 2H), 4.56 (br s, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.85 (s, 2H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 149.5, 126.8 (q, ^3J = 3.8 Hz, 2C), 121,4 (q, ^1J = 271.0 Hz), 119.8 (q, ^2J = 32.6 Hz), 112.2 (2C), 61.8, 45.3, 14.3. ^{19}F NMR (282 MHz, $CDCl_3$): δ −61.18. HRMS (ESI+): calcd for $C_{11}H_{12}F_3NO_2$ + Na^+ $[M + Na]^+$ m/z 270.0712, found 270.0710. IR: ν_{max} 3391, 2990, 1727, 1616, 1538, 1320, 1222, 1191, 1146, 1095, 1064, 831, 812.

*Ethyl 2-((4-Acetylphenyl)amino)acetate (**1f**).* Following the general procedure, 1-(4-aminophenyl)ethanone (338 mg, 2.50 mmol, 1.0 equiv) was treated with ethyl bromoacetate (276 μL, 2.50 mmol, 1.0 equiv) and sodium acetate (205 mg, 2.50 mmol, 1.0 equiv) in ethanol (0.4 mL). **1f** was isolated by column chromatography (pentane/EtOAc: gradient 20/1 to 2/1) as a white solid (273 mg, 1.23 mmol, 49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87−7.80 (m, 2H), 6.60−6.53 (m, 2H), 4.27 (br s, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.95 (s, 2H), 2.50 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 170.4, 150.9, 130.9 (2C), 127.7, 111.9 (2C), 61.8, 45.2, 26.2, 14.3. HRMS (ESI+): calcd for $C_{12}H_{15}NO_3$ + Na^+ $[M + Na]^+$ m/z 244.0944, found 244.0947. IR: ν_{max} 3370, 2977, 1718, 1668, 1528, 1528, 1350, 1272, 1251, 1174, 1018, 952, 836, 805.

*Ethyl 2-((4-Cyanophenyl)amino)acetate (**1g**).* Following the general procedure, 4-aminobenzonitrile (590 mg, 5.0 mmol, 1.0 equiv) was treated with ethyl bromoacetate (553 μL, 5.0 mmol, 1.0 equiv) and sodium acetate (410 mg, 5.0 mmol, 1.0 equiv) in ethanol (0.75 mL). **1g** was isolated by column chromatography (pentane/EtOAc: gradient 20/1 to 2/1) as a white solid (347 mg, 1.7 mmol, 34%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47−7.42 (m, 2H), 6.63−6.48 (m, 2H), 4.82 (br s, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.92 (s, 2H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 150.1, 133.9 (2C), 120.3, 112.6 (2C), 100.1, 62.0, 45.0, 14.3. HRMS (ESI+): calcd for $C_{11}H_{12}N_2O_2$ + Na^+ $[M + Na]^+$ m/z 227.0791, found 227.0790. IR: ν_{max} 3375, 2997, 2213, 1723, 1603, 1523, 1378, 1227, 1175, 1021, 832, 816.

*Ethyl 4-((2-Ethoxy-2-oxoethyl)amino)benzoate (**1h**).* Following the general procedure, ethyl 4-aminobenzoate (413 mg, 2.50 mmol, 1.0 equiv) was treated with ethyl bromoacetate (280 μL, 2.50 mmol, 1.0 equiv) and sodium acetate (205 mg, 2.50 mmol, 1.0 equiv) in ethanol (10 mL). **1h** was isolated by column chromatography (pentane/EtOAc: gradient 20/1 to 4/1) as a white solid (184 mg, 0.73 mmol, 29%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94−7.82 (m, 2H), 6.61−6.49 (m, 2H), 4.77 (s, 1H), 4.28 (dq, J = 16.7, 7.1 Hz, 4H), 3.93 (s, 2H), 1.35 (t, J = 7. Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 166.8, 150.7, 131.6 (2C), 119.7, 111.8 (2C), 61.7, 60.4, 45.2, 14.5, 14.3. HRMS (ESI+): calcd for $C_{13}H_{17}NO_4$ + Na^+ $[M + Na]^+$ m/z 274.1050, found 274.1055. IR: ν_{max} 3376, 2985, 1737, 1682, 1602, 1527, 1449, 1277, 1228, 1175, 1107, 1021, 845, 771.

*Ethyl 2-((4-Methoxyphenyl)amino)acetate (**1i**).* Following the general procedure, 4-methoxyaniline (616 mg, 5.00 mmol, 1.0 equiv) was treated with ethyl bromoacetate (554 μL, 5.00 mmol, 1.0 equiv) and sodium acetate (410 mg, 5.00 mmol, 1.0 equiv) in ethanol (10 mL). **1i** was isolated by column chromatography (pentane/EtOAc: gradient 20/1 to 2/1) as a white solid (888 mg, 4.25 mmol, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10−6.92 (m, 2H), 6.63−6.48 (m, 2H), 4.25 (q, J = 7.1 Hz, 2H), 4.16 (br s, 1H), 3.89 (s, 2H), 2.26 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 144.9, 129.9 (2C), 127.5, 113.3 (2C), 61.3, 46.3, 20.5, 14.3. HRMS (ESI+): calcd for $C_{11}H_{15}NO_3$ + Na^+ $[M + Na]^+$ m/z 232.0944, found 232.0947. IR: ν_{max} 3382, 2989, 2941, 1727, 1514, 1439, 1371, 1266, 1210, 1144, 1023, 821.

*Ethyl 2-([1,1′-Biphenyl]-4-ylamino)acetate (**1j**).* Following the general procedure, [1,1′-biphenyl]-4-amine (425 mg, 2.50 mmol, 1.0 equiv) was treated with ethyl bromoacetate (280 μL, 2.50 mmol, 1.0 equiv) and sodium acetate (205 mg, 2.50 mmol, 1.0 equiv) in ethanol (10 mL). **1j** was isolated by column chromatography (pentane/EtOAc: gradient 10/1 to 4/1) as an orange solid (469.3 mg, 1.83 mmol, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58−7.51 (m, 2H), 7.50−7.44 (m, 2H), 7.44−7.36 (m, 2H), 7.33−7.21 (m, 1H), 6.77−6.63 (m, 2H), 4.38 (br s, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.95 (s, 2H), 1.32 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 146.5, 141.2, 131.3, 129.0, 128.9, 128.8, 128.2, 127.2, 126.5, 126.3, 122.2, 113.4, 61.6, 46.0, 14.4. HRMS (ESI+): calcd for $C_{16}H_{17}NO_2$ + Na^+ $[M + Na]^+$ m/z 278.1151, found 278.1148. IR: ν_{max} 3389, 3058, 2985, 2906, 1727, 1611, 1531, 1492, 1438, 1375, 1254, 1202, 1026, 824, 754.

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*Ethyl 2-((3,5-Dimethylphenyl)amino)acetate (**1k**).* Following the general procedure, 3,5-dimethylaniline (0.31 mL, 2.5 mmol, 1.0 equiv) was treated with ethyl bromoacetate (276 μL, 2.5 mmol, 1.0 equiv) and sodium acetate (205 mg, 2.5 mmol, 1.0 equiv) in ethanol (0.4 mL). **1k** was isolated by column chromatography (pentane/EtOAc: gradient 20/1 to 4/1) as a white solid (400 mg, 1.93 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.43 (dt, *J* = 1.5, 0.8 Hz, 1H), 6.27 (dd, *J* = 1.3, 0.7 Hz, 2H), 4.25 (q, *J* = 7.1 Hz, 2H + br s, 1H), 3.89 (s, 2H), 2.25 (d, *J* = 0.7 Hz, 6H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 147.1, 139.1 (2C), 120.5, 111.3 (2C), 61.4, 46.2, 21.6 (2C), 14.3. HRMS (ESI+): calcd for $C_{12}H_{17}NO_2$ + Na^+ [M + Na]$^+$ *m*/*z* 230.1151, found 230.1151. IR: ν_{max} 3377, 2987, 2917, 1732, 1601, 1520, 1474, 1442, 1382, 1367, 1354, 1212, 1195, 1027, 812.

*Ethyl 2-(o-Tolylamino)acetate (**1l**).* Following the general procedure, *o*-toluidine (536 μL, 5.0 mmol, 1.0 equiv) was treated with ethyl bromoacetate (553 μL, 5.0 mmol, 1.0 equiv) and sodium acetate (410 mg, 5.0 mmol, 1.0 equiv) in ethanol (0.75 mL). **1l** was isolated by column chromatography (pentane/EtOAc: gradient 30/1 to 10/1) as a white solid (970 mg, 5.0 mmol, 99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (dd, *J* = 16.8, 8.8 Hz, 2H), 6.71 (t, *J* = 7.3 Hz, 1H), 6.49 (d, *J* = 8.4 Hz, 1H), 4.27 (br s. 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.95 (s, 2H), 2.22 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 145.2, 130.4, 127.3, 122.7, 117.9, 110.0, 61.5, 46.1, 17.5, 14.3. HRMS (ESI+): calcd for $C_{11}H_{15}NO_2$ + Na^+ [M + Na]$^+$ *m*/*z* 216.0995, found 216.0998. IR: ν_{max} 3423, 2981, 1737, 1607, 1587, 1515, 1453, 1372, 1348, 1207, 1152, 1024, 746.

*Ethyl 2-((2-Methoxyphenyl)amino)acetate (**1m**).* Following the general procedure, 2-methoxyaniline (0.28 mL, 2.5 mmol, 1.0 equiv) was treated with ethyl bromoacetate (276 μL, 2.5 mmol, 1.0 equiv) and sodium acetate (205 mg, 2.5 mmol, 1.0 equiv) in ethanol (0.4 mL). **1m** was isolated by column chromatography (pentane/EtOAc: gradient 20/1 to 2/1) as a white solid (418 mg, 2.0 mmol, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.86 (td, *J* = 7.5, 1.6 Hz, 1H), 6.79 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.71 (ddd, *J* = 8.0, 7.3, 1.6 Hz, 1H), 4.93 (br s, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.93 (s, 2H), 3.86 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 147.3, 137.2, 121.3, 117.6, 110.1, 109.8, 61.4, 55.6, 45.9, 14.4. HRMS (ESI+): calcd for $C_{11}H_{15}NO_3$ + Na^+ [M + Na]$^+$ *m*/*z* 232.0944, found 232.0945. IR: ν_{max} 3370, 2981, 2842, 1727, 1607, 1569, 1500, 1448, 1325, 1255, 1199, 1054, 1032, 761.

*Ethyl 2-((3-Methoxyphenyl)amino)acetate (**1n**).* Following the general procedure, 3-methoxyaniline (0.28 mL, 2.5 mmol, 1.0 equiv) was treated with ethyl bromoacetate (276 μL, 2.5 mmol, 1.0 equiv) and sodium acetate (205 mg, 2.5 mmol, 1.0 equiv) in ethanol (0.4 mL). **1n** was isolated by column chromatography (pentane/EtOAc: gradient 20/1 to 2/1) as a white solid (428 mg, 2.05 mmol, 82%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10 (t, *J* = 8.1 Hz, 1H), 6.28 (ddd, *J* = 26.2, 8.1, 2.1 Hz, 2H), 6.16 (t, *J* = 2.3 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 2H), 3.77 (s, 3H + br s, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 160.9, 148.5, 130.2, 106.1, 103.5, 99.2, 61.5, 55.2, 45.9, 14.3. HRMS (ESI+): calcd for $C_{11}H_{15}NO_3$ + Na^+ [M + Na]$^+$ *m*/*z* 232.0944, found 232.0941. IR: ν_{max} 3372, 2977, 2936, 2837, 1728, 1609, 1579, 1497, 1452, 1369, 1323, 1276, 1258, 1201, 1168, 1050, 1030, 845, 758.

*Ethyl 2-(m-Tolylamino)acetate (**1o**).* Following the general procedure, *m*-toluidine (536 μL, 5.0 mmol, 1.0 equiv) was treated with ethyl bromoacetate (553 μL, 5.0 mmol, 1.0 equiv) and sodium acetate (410 mg, 5.0 mmol, 1.0 equiv) in ethanol (0.75 mL). **1o** was isolated by column chromatography (pentane/EtOAc: gradient 20/1 to 2/1) as a white solid (690 mg, 3.6 mmol, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18−7.00 (m, 1H), 6.65−6.55 (m, 1H), 6.44 (dd, *J* = 9.2, 1.9 Hz, 2H), 4.26 (q, *J* = 7.2 Hz, 3H + br s, 1H), 3.90 (s, 2H), 2.30 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 147.2, 139.2, 129.3, 119.2, 113.9, 110.2, 61.4, 46.0, 21.7, 14.3. HRMS (ESI+): calcd for $C_{11}H_{15}NO_2$ + Na^+ [M + Na]$^+$ *m*/*z* 216.0995 found 216.0993. IR: ν_{max} 3383, 2982, 1729, 1617, 1600, 1587, 1519, 1496, 1448, 1364, 1349, 1333, 1260, 1218, 1030, 866, 766.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For some reviews, see for example: (a) Anastas, P- T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686. (b) Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. *Green Chem.* **2002**, *4*, 521. (c) Horváth, I. T.; Anastas, P. T. *Chem. Rev.* **2007**, *107*, 2169. (d) Li, C.-J.; Trost, B. M. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 13197. See also: (e) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory; Practice*; Oxford University Press: New York, 2000.

(2) For selected recent representative general reviews on C−H bond functionalizations, see: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (b) Gunay, A.; Theopold, K. H. *Chem. Rev.* **2010**, *110*, 1060. (c) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (d) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, *110*, 824. (e) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725. (f) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681. (g) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315 and references cited therein.

(3) For selected reviews on dehydrogenative coupling reactions, see: (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) Shi, W.; Liu, C.; Lei, A. *Chem. Soc. Rev.* **2011**, *40*, 2761. (f) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (g) Jones, K. M.; Klussmann, M. *Synlett* **2012**, *23*, 159. (h) Rohlmann, R.; García Mancheño, O. *Synlett* **2013**, *24*, 6 and references cited therein.

(4) Reviews on *N*-oxoammonium chemistry: (a) Bobbitt, J. M.; Flores, M. C. L. *Heterocycles* **1988**, *27*, 509. (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. For a recent review on TEMPO chemistry, see: (c) Tebben, L.; Studer, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 5034.

(5) (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.

(6) Richter, H.; Fröhlich, R.; Daniluic, C.-G.; García Mancheño, O. *Angew. Chem., Int. Ed.* **2012**, *51*, 8656.

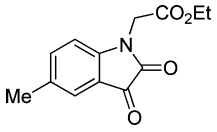
(7) (a) Richter, H.; García Mancheño, O. *Org. Lett.* **2011**, *13*, 6066. For other uses of glycines and *N*-alkylanilines in CDC, see for example: (b) Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7075. (c) Li, H.; He, Z.; Guo, X.; Li, W.; Zhao, X.; Li, Z. *Org. Lett.* **2009**, *11*, 4176. (d) Han, W.; Ofial, A. R. *Chem. Commun.* **2009**, *40*, 6023. (e) Han, W.; Mayer, P.; Ofial, A. R. *Adv. Synth. Catal.* **2010**, *352*, 1667. (f) Xie, J.; Huang, Z.-Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 10181. (g) Yang, F.; Li, J.; Xie, J.; Huang, Z.-Z. *Org. Lett.* **2010**, *12*, 5214.

(8) For quinazolines in medicinal chemistry, see for example: (a) Foster, B. A.; Coffrey, H. A.; Morin, M. J.; Rastinejad, F. *Science*

1999, *286*, 2507. (b) Lewerenz, A.; Hentschel, S.; Vissiennon, Z.; Michael, S.; Nieber, K. *Drug Dev. Res.* **2003**, *58*, 420. (c) Doyle, L. A.; Ross, D. D. *Oncogene* **2003**, *22*, 7340. (d) Gundla, R.; Kazemi, R.; Sanam, R.; Muttineni, R.; Sarma, J. A. R. P.; Dayam, R.; Neamati, N. *J. Med. Chem.* **2008**, *51*, 3367. (e) Lüth, A.; Löwe, W. *Eur. J. Med. Chem.* **2008**, *43*, 1478. For a recent example on bioactive dihydroquinazoline derivatives, see: (f) Patterson, S.; Alphey, M. S.; Jones, D. C.; Shanks, E. J.; Street, I. P.; Frearson, J. A.; Wyatt, P. G.; Gilbert, I. H.; Fairlamb, A. H. *J. Med. Chem.* **2011**, *54*, 6514 and references cited therein.

(9) For selected examples on the synthesis of dihydroquinazolines, see: (a) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 14254. (b) Huang, C.; Fu, Y.; Fu, H.; Jiang, Y.; Zhaoa, Y. *Chem. Commun.* **2008**, 6333. (c) Kabri, Y.; Gellis, A.; Vanelle, P. *Green Chem.* **2009**, *11*, 201. (d) Portela-Cubillo, F.; Scott, J. S.; Walton, J. C. *J. Org. Chem.* **2009**, *74*, 4934. (e) Li, J.; Chen, X.; Shi, X.; Ma, S.; Li, Q.; Zhang, Q.; Tang, J. *Org. Lett.* **2009**, *11*, 1193. (f) Zhang, J.; Zhu, D.; Yu, C.; Wan, C.; Wang, Z. *Org. Lett.* **2010**, *12*, 2841. (g) Sarma, R.; Prajapati, D. *Green Chem.* **2011**, *13*, 718 and references cited therein.

(10) A dioxoindoline derivative was also formed as an overoxidized byproduct in the reaction under an O_2 atmosphere (1 atm) in 10−20% yield. Its structure and analytical data are shown below. *Ethyl 2-(5-methyl-2,3-dioxoindolin-1-yl)acetate*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50−7.42 (m, 1H), 7.39 (ddd, J = 8.1, 1.9, 0.9 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 4.46 (s, 2H), 4.24 (q, J = 7. Hz, 2H), 2.34 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.9, 167.0, 158.4, 148.3, 139.0, 134.2, 126.1, 117.8, 110.0, 62.3, 41.5, 20.9, 14.3; HRMS (ESI+) calcd for $C_{13}H_{13}NO_4$ + Na^+ $[M + Na]^+$ m/z 270.0737, found 270.0739.



(11) See for example: (a) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2003; p 316. (b) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 223. (c) Musiol, R.; Serda, M.; Hensel-Bielowka, S.; Polanski, J. *Curr. Med. Chem.* **2010**, *17*, 1960. (d) Kaur, K.; Jain, M.; Reddy, R. P.; Jain, R. *Eur. J. Med. Chem.* **2010**, *45*, 3245. (e) Solomon, V. R.; Lee, H. *Curr. Med. Chem.* **2011**, *18*, 1488 and references cited therein.

(12) For reviews on quinoline synthesis: (a) Jones, G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., McKillop, A., Eds.; Pergamon Press: Oxford, U.K., 1996; Vol. *5*, p 167. (b) Larsen, R. D. In *Science of Synthesis*; Black, D. S., Ed.; Thieme: Stuttgart, 2005; Vol. *15*, pp 389, 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.

(13) (a) Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656. For its use in the synthesis of tetrahydroquinolines, see: (b) Reymond, S.; Cossy, J. *Chem. Rev.* **2008**, *108*, 5359.

(14) Jia, X.; Peng, F.; Qing, C.; Huo, C.; Wang, X. *Org. Lett.* **2012**, *14*, 4030.

(15) Mercadante, M. A.; Kelly, C. B.; Bobbitt, J. M.; Tilley, L. J.; Leadbeater, N. E. *Nat. Protoc.* **2013**, *8*, 666.

(16) Chen, X. M.; Wei, H.; Yina, L.; Li, X. S. *Chin. Chem. Lett.* **2010**, *21*, 782.

(17) The heterocoupling of two kinds of *N*-alkylanilines **1** was also investigated. However, inseparable mixtures of all possible homo- and heterocoupling products were obtained (e.g., in the reaction with **1a** and **1d** a 2/1/2 mixture of homo-**2a**, homo-**2d**, and hetero-**2ad** was formed).

(18) Multicomponent reactions (MCR): (a) Zhu, J.; Bienaymé, H. *Multicomponent Reaction*; Wiley-VCH: Weinheim, Germany, 2005. See also: (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (c) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134 and references cited therein.

(19) For synthesis of quinolines via MCR, see for example: (a) Nakajima, T.; Inada, T.; Shimizu, I. *Heterocycles* **2006**, *69*, 497. (b) Sueki, S.; Okamoto, C.; Shimizu, I.; Seto, K.; Furukawa, Y. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 385. (c) Kumar, A.; Rao, V. K. *Synlett* **2011**, 2157. (d) Reddy, T. R.; Reddy, L. S.; Reddy, G. R.; Yarbagi, K.; Lingappa, Y.; Rambabu, D.; Krishna, G. R.; Reddy, C. M.; Kumar, K. S.; Pal, M. *Green Chem.* **2012**, *14*, 1870 and references cited therein.

(20) For Fe-catalyzed multicomponent synthesis of quinolines with alkynes, see for example: (a) Patil, S. S.; Patil, S. V.; Bobade, V. D. *Synlett* **2011**, 2379. (b) Zhang, J.; Wang, L.-M.; Mao, D.; Wang, W.-B.; Zhang, L.; Wu, S.-Y.; Xie, Y.-S. *Tetrahedron* **2011**, *67*, 8465. (c) Cao, K.; Zhang, F.-M.; Tu, Y.-Q.; Zhuo, X.-T.; Fan, C.-A. *Chem. Eur. J.* **2009**, *15*, 6332 and references cited therein.

(21) Fourrey, J.-L.; Beauhaire, J.; Yuan, C. W. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1841.

(22) Keglevich, G.; Szekrényi, A. *Lett. Org. Chem.* **2008**, *5*, 616.

(23) Prieur, E.; Azzouz, R.; Deguest, G.; Fruit, C.; Bischoff, L.; Marsais, F. *Tetrahedron Lett.* **2008**, *49*, 437.

(24) Aciro, C.; Davies, S. G.; Garner, A. C.; Ishii, Y.; Key, M.-S.; Ling, K. B.; Prasad, R. S.; Roberts, P. M.; Rodriguez-Solla, H.; O'Leary-Steele, C.; Russell, A. J.; Sanganee, H. J.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Tetrahedron* **2008**, *64*, 9320.

(25) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164.

(26) Marzaro, G.; Guiotto, A.; Chilin, A. *Green Chem.* **2009**, *11*, 774.

(27) Anderson, W. K.; Bhattacharjee, D.; Houston, D. M. *J. Med. Chem.* **1989**, *32*, 119.