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New Metal-Catalyzed Synthesis of Quinoline and Chromene Skeletons[‡]

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Alkoxy-functionalized butadienylboronic esters have been synthesized starting from α,β-unsaturated acetals and cross-coupled with both *N*-protected and *N*-unprotected 2-bromo- and 2-iodoaniline, and with 2-iodophenol. In particular, *N*-tosyl-protected dienylanilines can be transformed under mild conditions into quinolines and quinolinones, in the presence of a Pd^{II} catalyst. Moreover, the cross-coupling reaction between butadienylboronic esters and iodophenol directly affords chromenes that can be successively transformed into chromenones.

Introduction

Organic molecules containing C–N and C–O bonds are of significant importance and frequently show interesting properties as pharmaceutically and biologically active substances, dyes and fine chemicals.[1] Quinolines and their derivatives have long been developed as antimalarial agents since the discovery of cinchona alkaloids.[2] Classical synthetic routes to quinolines rely on the preparation of intermediate imines that tautomerize to dienamines, and finally undergo aromatic electrophilic cyclization, according to the historic Combes procedure,[3] on the Skraup reaction, in which the diketone is replaced by an α,β-unsaturated carbonyl compound,[4] on the Friedländer synthesis, or others.[5]

Synthetic organic reactions catalyzed by transition-metal complexes have progressed enormously over the last few years, and highly regio- and stereoselective methods have been developed in order to carry out the syntheses of complicated natural products and pharmaceutically active compounds, as well as functional molecules. Over the past few years much effort has gone into developing Pd-catalyzed reactions of aryl halides with amines[6] and alcohols.[7] Initial works were focused on the intermolecular C–N and C–O bond constructions, and more recently, this cross-coupling chemistry has undergone optimization, particularly with the development of new ligand systems, and intramolecular versions have been utilized for the synthesis of heterocyclic compounds containing nitrogen[8] and oxygen[9]. The cyclization works well with aromatic and activated amines (amides and sulfonamides), and this methodology has been used to construct various nitrogen-containing heterocycles.[10] More recently, the applicability of Pd-catalyzed asymmetric allylic alkylation (AAA) reaction of phenol-derived allylic carbonates to the synthesis of chiral chromans was demonstrated.[11] Finally, an expedient preparation of chromane derivatives has been realized by employing an indium-mediated intramolecular addition.[12]

During the past few years, we have reported that the lithium/potassium mixed base LIC-KOR (Schlosser's superbase: LIC = butyllithium, KOR = potassium *tert*-butoxide),[13] chemoselectively promotes the conversion of α,β-unsaturated acetals into 1-alkoxybuta-1,3-dienes,[14] inducing a stereoselective conjugate elimination that is initiated by the metalation reaction at the γ-allylic position of the unsaturated substrate. Moreover, the elimination product can be further selectively metalated at its α-position by conducting the former elimination reaction in the presence of at least 2 equiv. of the LIC-KOR base: the produced nucleophile can be finally quenched with various electrophiles, yielding functionalized butadienyl derivatives.[15] By resorting to this procedure, we have described different functionalized unsaturated systems.[16] More recently, the arylation of α,β-unsaturated carbonyl compounds by a Heck reaction has been described.[17] The reactivity of α-metalated alkoxydienes with trialkylboranes and trialkyl borates as electrophiles has also been reported.[18]

In the course of our recent studies, we have developed a new synthesis of quinoline and chromene systems, which forms the subject of this paper.

[‡] The results reported are taken from the Ph. D. Thesis of Chiara Zavattaro

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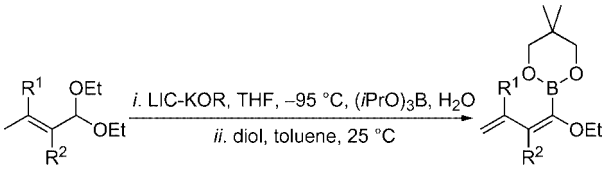
Results and Discussion

Synthesis of Quinoline Systems

Our procedure consists of three steps: (i) the synthesis of the dienylboronates, which starts from α,β-unsaturated acetals in the presence of the LIC-KOR superbase; (ii) the Suzuki cross-coupling reaction, which involves a properly *N*-protected *o*-haloaniline; (iii) the Pd^{II}-catalyzed cyclization process.

Synthesis of the Dienyl Boronates

The dienylboronates **2a**–**c** were synthesized starting from the diethyl acetal of but-2-enal (**1a**), 3-methylbut-2-enal (**1b**), and 2-methylbut-2-enal (**1c**), respectively, in the presence of the LIC-KOR reagent. Typically, treatment of crotonaldehyde diethyl acetal (**1a**) at –95 °C with Schlosser's LIC-KOR base readily gives α-metalated 1-ethoxybuta-1,3-diene. Subsequent reaction with triisopropyl borate leads to immediate disappearance of the deep red color due to the metalated diene. Aqueous workup of the reaction mixture affords intermediate dienylboronic acid, which, in order to address its instability, was trapped with 2,2-dimethylpropane-1,3-diol to give the corresponding boronic ester **2a** (Scheme 1).



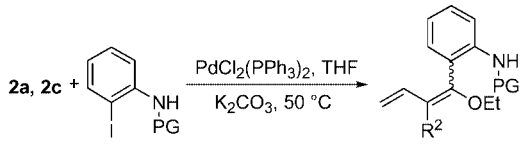
1a: R^1, R^2 = H
1b: R^1 = Me, R^2 = H
1c: R^1 = H, R^2 = Me

2a: R^1, R^2 = H (70%)
2b: R^1 = Me, R^2 = H (85%)
2c: R^1 = H, R^2 = Me (85%)

Scheme 1. Synthesis of (1-ethoxy-1,3-butadienyl)boronates.

Suzuki Cross-Coupling

By exploiting the particular reactivity of 1,3-dienylboronate derivatives, we have successfully carried out their cross-coupling with 2-bromo- and 2-iodoaniline under different experimental conditions. The results obtained in order to evaluate the effect of the solvent, temperature, catalyst and base are reported in Table 1. Scheme 2 shows the results obtained under the best experimental conditions (Entry 7), using the boronates **2a** and **2c** and *N*-protected or unprotected 2-iodoanilines.



PG = H, Ac, TFA, Ts

3a: R^2 = H, PG = H (49%)
3c: R^2 = Me, PG = Ts (75%)
3d: R^2 = H, PG = Ac (85%)
3e: R^2 = H, PG = TFA (68%)
3f: R^2 = H, PG = Ts (94%)

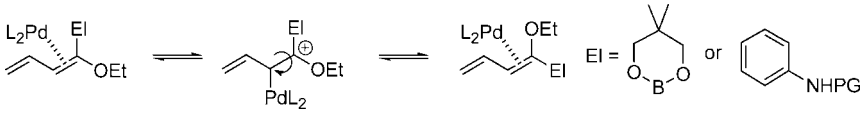
Scheme 2. Synthesis of dienylanilines by Suzuki cross-coupling.

When the coupling reaction was carried out with *N*-Ts-protected aniline **3c** and **3f**, only (*E*)-arylated products were obtained, while with *N*-Ac- and *N*-TFA-protected aniline **3d** and **3e**, respectively, the dienic moiety underwent partial isomerization, and both (*E*)- and (*Z*)-arylated derivatives were isolated.[19] The isomerization probably takes place according to the Pd-catalyzed process proposed in Scheme 3.[20]

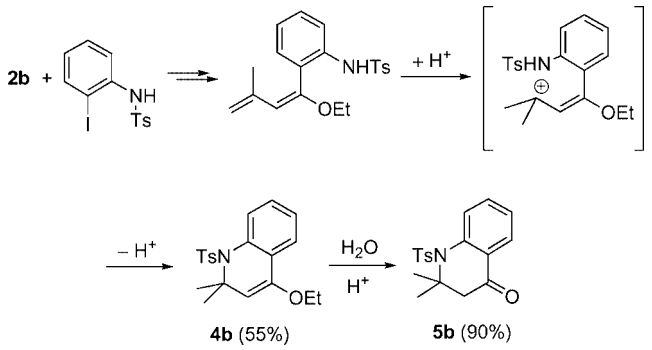
The Suzuki reaction was performed on protected anilines in order to decrease the tendency of the amino group to form stable Pd^{II} complexes.[21] Acylation, and especially tosylation of amines was found to eliminate the basicity and thus the complexation strength, therefore allowing smooth reaction using catalytic quantities of Pd complexes. It must be mentioned that, while the dienylboronates **2a** and **2c** give the corresponding arylated derivatives **3a** and **3c**, substrate **2b** directly affords the cyclization product **4b** even in THF at 55 °C, probably through the formation of the highly stable intermediate carbocation (see Scheme 4). Traces of HCl are likely to be provided by the Pd^{II} catalyst.[22]

Table 1. Suzuki cross-coupling of boronate **2a** with 2-bromo- and 2-iodoaniline, as a function of different experimental conditions.

Entry	Halogen	Solvent	Base (M)	*T* [°C]	*t* [h]	Catalyst (%)	Yield [%]
1	Br	dioxane	Et_3N (2 M)	80	15	$Pd(dba)_3$ (1.5), $P(tBu)_3$ (3.5)	0
2	Br	DMSO	Cs_2CO_3 (2 M)	80	15	$Pd(dba)_3$ (1.5), $P(tBu)_3$ (3.5)	0
3	Br	THF	K_2CO_3 (2 M)	50	15	$Pd(OAc)_2$ (5), PCy_3 (10)	0
4	Br	DMSO	KF (2 M)	100	15	$Pd(OAc)_2$ (5), dppp (0.005)	19
5	Br	toluene	K_2CO_3 (2 M)	50	15	$PdCl_2(PPh_3)_2$	24
6	I	THF	K_2CO_3 (1 M)	50	15	$PdCl_2(PPh_3)_2$	33
7	I	THF	K_2CO_3 (2 M)	50	15	$PdCl_2(PPh_3)_2$	49



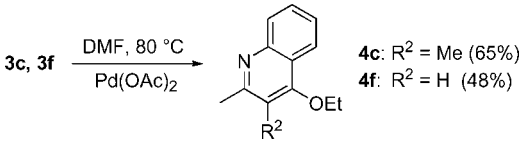
Scheme 3. Pd-catalyzed (*E*)/(*Z*) isomerization of 1-ethoxy-1,3-butadienyl derivatives.



Scheme 4. Direct synthesis of cyclic derivative **4b** through the formation of a stable carbocation.

Cyclization Reaction

The cyclization step has been investigated on the dienylanilines **3c**–**3f** in DMF at 80 °C using $Pd(OAc)_2$ as a catalyst, under an inert gas. The cyclization step takes place only on *N*-Ts-protected derivatives **3c** and **3f**, whereas the dienylanilines **3d** and **3f** do not react, because the Ac and TFA groups are not reactive enough, for reasons that will become apparent upon examination of Scheme 6 (poorer leaving groups). The protected dienylanilines cyclize to afford quinoline-type skeletons (Scheme 5).



Scheme 5. Pd-catalyzed synthesis of quinoline-type skeletons.

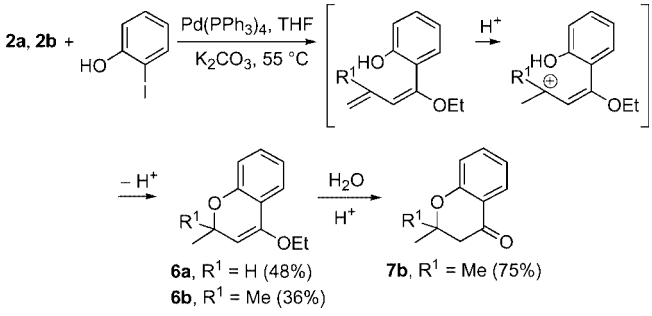
Similar results concerning the synthesis of nitrogen heterocycles by the Pd-catalyzed cross-coupling of 2-alkenylanilines with vinylic triflates and halides have been reported recently.[23]

The first step of the mechanistic pathway involves probably the formation a π-complex **A** between Pd^{II} and the dienyl fragment. The π-complex successively undergoes heterocyclization and conversion to the σ-complex **B**. According to the information reported in the literature for similar reactions, the cyclization process can be terminated by a β-eliminative step to afford HX and Pd^0.[24] The latter could then be reoxidized to Pd^{II} by Cu^{II}, benzoquinone, or air, in order to promote the reaction once again.[10a,10b,18c,25] In the present case, on the contrary, the reaction proceeds without the need for a re-oxidation. This is due to the fact that intermediate **C** can re-add HPdX to the exocyclic double bond with opposite regiochemistry **D**, and finally directly generate the quinoline skeleton through elimination of Pd(OAc)Ts, which restarts the catalytic cycle without requiring any re-oxidation process (Scheme 6).[26]

This is rendered possible by the excellent leaving group characteristics of the sulfinate ion. It is now apparent why amides do not participate in this reaction, as expulsion of an acyl anion is extremely unfavorable. Thus, the judicious combination of reaction conditions and suitable *N*-protecting/activating groups allows this novel tandem annulation reaction to proceed under facile conditions without the need for complex Pd re-oxidation schemes.

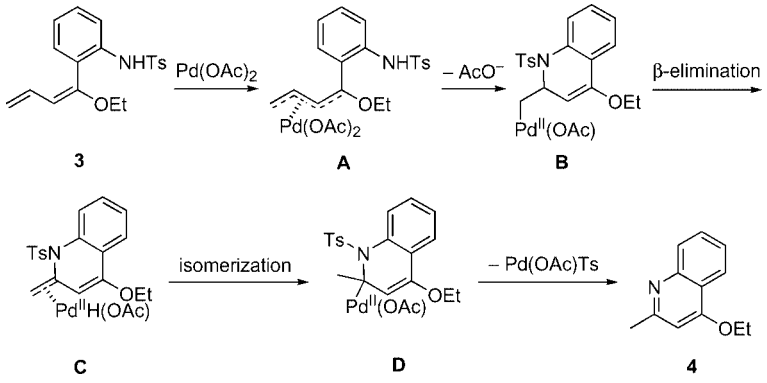
Synthesis of Chromene-Type Skeletons

Two chromenes have been synthesized starting from dienylboronates and 2-iodophenol in the presence of a Pd catalyst, as shown in Scheme 7.



Scheme 7. Pd-catalyzed synthesis of chromene-type skeletons.

It was impossible to isolate the cross-coupling intermediate, because the cyclization to the chromene skeleton occurs readily. It is uncertain whether the latter is Pd- or acid-catalyzed. Derivative **6b** was smoothly hydrolyzed to 2,2-dimethylchroman-4-one (**7b**), which is known to be an important building block for the synthesis of many pharmaceutically important structures.[27]



Scheme 6. Proposed mechanism for the novel Pd-catalyzed cyclization.

Conclusion

We have developed a tandem Suzuki coupling/cyclization between dienylboronates and *o*-haloanilines derivatives or *o*-halophenols, which leads to the direct formation of substituted quinoline and chromenes, respectively. Additional studies are necessary to further assess the general synthetic utility of our new annulation protocol.

Experimental Section

General Remarks: Flasks and all equipment used for the generation and reaction of moisture-sensitive compounds were flame-dried under argon. Where a temperature of –95 °C is indicated, a slush bath of liquid nitrogen/acetone was used; room temp. stands for 25 °C. THF was distilled from benzophenone ketyl prior to its use. BuLi (1.6 M solution in hexanes) was obtained from Aldrich. *t*BuOK was sublimed in vacuo (0.1 Torr) prior to use. All commercially obtained reagents were used as received. All the acetals and ethoxydienes were prepared as described previously. Products were purified by preparative column chromatography on Merck silica gel 60 with light petroleum ether (boiling range 40–60 °C)/diethyl ether as eluent. ^{1}H NMR spectra were recorded at 200 MHz in $CDCl_3$, using TMS as internal standard. Coupling constants (*J*) are given in Hz and coupling patterns are described by abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), br. s (broad singlet). ^{13}C NMR spectra were recorded at 50.2 MHz in $CDCl_3$, and chemical shifts were determined relative to the residual solvent peak (δ = 77.0 ppm). GC-MS spectra were obtained with a mass-selective detector HP-5970B instrument operating at an ionizing voltage of 70 eV connected to an HP-5890GC cross-linked methyl silicone capillary column (25 m × 0.2 mm × 0.33 μm film thickness).

General Procedure for the Synthesis of Butadienylboronic Esters:[28] To a cooled solution (–95 °C) of *t*BuOK (1.4 g, 12.5 mmol) in anhydrous THF (10 mL) acetal **1a**–**c** (5.0 mmol) and BuLi (7.8 mL, 12.5 mmol) were consecutively added dropwise whilst stirring. After 2 h, the purple-red solution was treated with triisopropyl borate (10.0 mmol, 2.4 mL). The solution was warmed to room temp. and then quenched with saturated aqueous NH_4Cl (10 mL). The organic phase was diluted with Et_2O and then washed with brine. After drying (Na_2SO_4) and evaporation of the solvent, the crude product was diluted with toluene (30 mL) and treated with 2,2-dimethyl-1,3-propanediol (5 mmol, 0.52 g). The mixture was stirred at room temp. under an inert gas overnight. The organic phase was diluted with Et_2O and washed with H_2O. Drying (Na_2SO_4) and removal of the solvent gave the crude reaction product, which was then purified by column chromatography.

General Procedure for the Synthesis of Dienylbenzeneamines 3a, 3c–3f: Boronate [0.210 g (**2a**), 0.224 g (**2c**), 1 mmol], 2-iodoaniline (0.219 g, 1 mmol), and $(PPh_3)_2PdCl_2$ (0.035 g, 5% mol) were added to a solution of THF (10.0 mL) and 2 M aqueous K_2CO_3 (1.0 mL), which had been previously degassed with argon for 10 min. The resulting orange solution was heated to 50 °C overnight, then cooled to room temp., H_2O (10 mL) was then added to the mixture which was extracted with Et_2O (2 × 10 mL). The collected organic layers were washed with brine (2 × 10 mL) and dried (K_2CO_3), and the solvent was removed. The reaction product was purified by column chromatography on deactivated SiO_2 (Et_3N, 1%; light petroleum ether/Et_2O, 9:1).

2-[(*E*)-1-Ethoxybuta-1,3-dienyl]benzeneamine (3a): Yield 0.093 g (49%) of a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.18 [d, *J* = 7.7, 1 H; superimposed on δ = 7.22–7.15 ppm (m, 1 H)], 6.80–6.70 (m, 2 H), 6.18 (dt, *J* = 16.9, 10.5 Hz, 1 H), 5.69 (d, *J* = 10.5 Hz, 1 H), 5.09 (dd, *J* = 16.9, 1.8 Hz, 1 H), 4.81 (dd, *J* = 10.5, 1.8 Hz, 1 H), 3.93 (q, *J* = 7.0 Hz, 2 H), 1.56 (br. s, 2 H), 1.33 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 156.3, 144.6, 133.7, 131.0, 129.8, 120.8, 117.9, 115.8, 112.5, 105.1, 63.4, 14.7 ppm. MS: *m*/*z* (%) = 189 (42) [M$^+$], 188 (18), 160 (100) [M$^+$ – 29], 144 (27), 132 (44), 120 (29). $C_{12}H_{15}NO$ (189.25): calcd. C 76.16, H 7.99, N 7.40; found C 77.01, H 7.80, N 7.15.

2-[(*E*)-1-Ethoxy-2-methylbuta-1,3-dienyl]-*N*-tosylbenzeneamine (3c): Yield 0.0.27 g (75%) as a yellow-brown oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.7 Hz, 1 H), 7.54 (d, *J* = 8.7 Hz, 2 H), 7.3–7.2 (m, 1 H), 7.1–7.0 (m, 4 H), 5.65 (dd, *J* = 17.4, 10.6, 1 H), 5.00 (dd, *J* = 17.4, 1.4, 1 H), 4.72 (dd, *J* = 10.6, 1.4, 1 H), 4.50 (br. s, 1 H), 3.41 (q, *J* = 6.6, 2 H), 2.33 (s, 3 H), 1.84 (s, 3 H), 1.17 (t, *J* = 6.6, 3 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 149.0, 147.4, 143.6, 136.1, 135.4, 132.2, 129.3, 127.1, 126.3, 125.7, 124.1, 121.9, 113.4, 112.3, 65.4, 21.4, 14.9, 10.6 ppm. MS: *m*/*z* (%) = 357 (8) [M$^+$], 342 (100), 174 (19), 159 (10), 155 (31), 91 (30). $C_{20}H_{23}NO_3S$ (357.47): calcd. C 67.20, H 6.49, N 3.92; found C 67.80, H 6.75, N 3.20.

***N*-{2-[(*E*)-1-Ethoxybuta-1,3-dienyl]phenyl}acetamide (3d):** Yield 0.107 g (63%) of white solid [(*E*) isomer: see ref.[19]] and 0.037 g (22%) of a yellow oil [(*Z*) isomer: see ref.[19]]. ^{1}H NMR [200 MHz, $CDCl_3$, (*E*) isomer]: δ = 8.31 (d, *J* = 7.8 Hz, 1 H), 7.82 (br. s, 1 H), 7.38 (td, *J* = 7.8, 1.6, 1 H), 7.27 (dd, *J* = 7.8, 1.6, 1 H), 7.11 (t, *J* = 7.8, 1 H), 6.11 (dt, *J* = 16.8, 10.6 Hz, 1 H), 5.76 (d, *J* = 10.6 Hz, 1 H), 5.15 (dd, *J* = 16.8, 1.8 Hz, 1 H), 4.88 (dd, *J* = 10.6, 1.8 Hz, 1 H), 3.97 (q, *J* = 7.0 Hz, 2 H), 2.13 (s, 3 H), 1.40 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, mixture of isomers): δ = 154.8, 154.0 153.4, 151.6, 133.9, 133.5, 132.2, 131.2, 130.3, 129.9, 129.8, 129.5, 125.8, 125.6, 125.5, 125.3, 121.4, 120.4, 120.1, 118.7, 118.0, 115.2, 112.9, 106.9, 67.0, 63.9, 14.6, 14.2 ppm. MS: *m*/*z* (%) = 231 (46) [M$^+$], 202 (14), 188 (27), 160 (100), 146 (38). ^{1}H NMR [200 MHz, $CDCl_3$, (*Z*) isomer]: δ = 8.55 (br. s, 1 H), 8.47 (d, *J* = 8.2 Hz, 1 H), 7.4–7.3 (m, 2 H), 7.18 (t, *J* = 7.4, 1 H), 7.17 (dt, *J* = 16.8, 10.2 Hz, 1 H), 5.80 (d, *J* = 10.6 Hz, 1 H), 5.32 (dd, *J* = 16.8, 1.8 Hz, 1 H), 5.16 (dd, *J* = 9.8, 1.6 Hz, 1 H), 3.61 (q, *J* = 7.0 Hz, 2 H), 2.15 (s, 3 H), 1.26 (t, *J* = 7.0 Hz, 3 H) ppm. MS: *m*/*z* (%) = 231 (57) [M$^+$], 202 (16), 188 (29), 160 (100), 146 (42). $C_{14}H_{17}NO_2$ (231.29): calcd. C 72.70, H 7.41, N 6.06; found C 71.01, H 6.95, N 6.40.

***N*-{2-[(*E*)-1-Ethoxybuta-1,3-dienyl]phenyl}2,2,2-trifluoroacetamide (3e):** Yield 0.193 g (68%) of a mixture of (*E*) and (*Z*) isomers (5:1 ratio), that were not separated, as a yellow oil. ^{1}H NMR [200 MHz, $CDCl_3$, mixture of (*E*)* and (*Z*) isomer]: δ = 9.80 (br. s, 1 H), 8.96* (br. s, 1 H), 8.31 (d, *J* = 8.2 Hz, 1 H), 8.17* (d, *J* = 8.4 Hz, 1 H), 8.09 (dd, *J* = 8.2, 1.6 Hz, 1 H), 7.74 (dd, *J* = 8.2, 1.6 Hz, 1 H), 7.33* (td, *J* = 8.0, 1.8 Hz, 1 H), 7.25* (dd, *J* = 8.0, 1.8 Hz, 1 H), 7.18* (dd, *J* = 8.0, 1.8 Hz, 1 H), 7.14 (td, *J* = 8.0, 1.8 Hz, 1 H), 6.88 (td, *J* = 8.2, 1.6 Hz, 1 H), 6.77 (td, *J* = 16.8, 10.2 Hz, 1 H), 6.07* (td, *J* = 16.8, 10.5 Hz, 1 H), 5.81 (d, *J* = 10.2 Hz, 1 H), 5.70* (d, *J* = 10.5 Hz, 1 H), 5.23 (dd, *J* = 16.8, 1.5 Hz, 1 H), 5.10* [dd, *J* = 16.8, 1.5 Hz, 1 H; superimposed on 1 H of the minor (*Z*) isomer], 4.83* (dd, *J* = 10.5, 1.5 Hz, 1 H), 3.90* (q, *J* = 7.0 Hz, 2 H), 3.61 (q, *J* = 7.0 Hz, 2 H), 1.30* (t, *J* = 7.0 Hz, 3 H), 1.18 (t, *J* = 7.0 Hz, 1 H) ppm. ^{13}C NMR [50.3 MHz, $CDCl_3$, major (*E*) isomer]: δ = 154.4 (q, $^2J_{C,F}$ = 36.96 Hz), 153.4, 133.5, 132.2, 131.2, 130.3, 125.8, 125.3, 121.4, 115.7 (q, $^1J_{C,F}$ = 289.1 Hz), 115.2, 106.9, 63.9, 14.2 ppm. MS: (*E*) isomer: *m*/*z* (%) = 285 (100) [M$^+$], 257 (15), 242 (27), 238 (23), 216 (52); (*Z*) isomer: *m*/*z* (%) = 285 (17) [M$^+$], 271 (16), 270 (100), 242 (93), 145 (17). $C_{14}H_{14}F_3NO_2$

(285.26): calcd. C 58.95, H 4.95, N 4.91; found C 58.01, H 4.85, N 4.70.

2-[(*E*)-1-Ethoxybuta-1,3-dienyl]phenyl-*N*-tosylbenzenamine (3f): Yield 0.32 g (94%) of **3d** as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.58 (d, J = 8.4 Hz, 1 H), 7.43 (d, J = 8.7 Hz, 2 H), 7.3–7.1 (m, 1 H), 7.1–7.0 (m, 4 H), 5.55 (dt, J = 16.6, 10.4 Hz, 1 H), 5.40 (d, J = 10.4, Hz, 1 H), 4.90 (dd, J = 16.6, 2.2 Hz, 1 H), 4.61 (dd, J = 10.4, 2.2 Hz, 1 H), 4.12 (br. s, 1 H), 3.73 (q, J = 7.0 Hz, 2 H), 2.18 (s, 3 H), 1.24 (t, J = 6.8 Hz, 1 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 153.6, 143.6, 135.9, 134.8, 132.2, 131.0, 129.7, 129.4, 127.0, 126.8, 124.5, 122.5, 113.6, 106.5, 63.6, 21.2, 14.3 ppm. MS: *m*/*z* (%) = 343 (3) [M$^+$], 329 (23), 328 (100), 160 (15), 155 (32). $C_{19}H_{21}NO_3S$ (343.44): calcd. C 66.45, H 6.16, N 4.08; found C 67.01, H 6.85, N 3.95.

General Procedure for the Synthesis of Quinolines 4c and 4f: $Pd(OAc)_2$ (0.0056 g, 5%mol) and dienylaniline [0.18 g (**3c**), 0.17 g (**3f**), 0.50 mmol] were consecutively added to a solution of DMF (3.0 mL) and 2 M aqueous K_2CO_3 (1.0 mL), which had been previously degassed with argon for 10 min. The mixture was heated to 80 °C for 5 h. After that period, the mixture was cooled to room temperature and filtered through Celite, then the solvent was evaporated to afford the crude reaction product, that was purified by column chromatography on deactivated SiO_2 (Et_3N, 1%, light petroleum ether/EtOAc, 6:1).

4-Ethoxy-2-methylquinoline (4f): Yield 0.045·g (48%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.17 (d, J = 7.8 Hz, 1 H), 7.95 (d, J = 7.8 Hz, 1 H), 7.66 (t, J = 7.8 Hz, 1 H), 7.43 (t, J = 7.8, 1 H), 6.61 (s, 1 H), 4.25 (q, J = 7.0 Hz, 2 H), 2.70 (s, 3 H), 1.57 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 161.6, 160.1, 148.7, 129.7, 127.9, 124.6, 121.7, 119.9, 101.0, 63.9, 29.7, 14.5 ppm. MS: *m*/*z* (%) = 187 (76) [M$^+$], 159 (100), 130 (24), 120 (9). $C_{12}H_{13}NO$ (187.24): calcd. C 76.98, H 7.00, N 7.48; found C 78.01, H 6.85, N 6.70.

4-Ethoxy-2,3-dimethylquinoline (4c): The crude reaction product was purified by column chromatography on deactivated SiO_2 (Et_3N, 1%, light petroleum ether/EtOAc, 6:1) to give pure **4c** (0.065 g, 65%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.1, 1 H), 7.62 (t, J = 8.1, 1 H), 7.46 (t, J = 8.1, 1 H), 7.26 (d, J = 8.1, 1 H), 4.10 (q, J = 6.6 Hz, 2 H), 2.70 (s, 3 H), 2.38 (s, 3 H) 0.88 (t, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 160.6, 159.8, 147.6, 128.9, 126.7, 125.2, 122.8, 121.7, 121.3, 70.1, 24.1, 15.7, 12.3 ppm. MS: *m*/*z* (%) = 201 (100) [M$^+$], 173 (78), 144 (52), 130 (16), 77 (17). $C_{13}H_{15}NO$ (201.26): calcd. C 77.58, H 7.51, N 6.96; found C 76.20, H 8.01, N 6.02.

Typical Procedure for the Synthesis of 4-Ethoxy-1,2-dihydro-2,2-dimethyl-1-tosylquinoline (4b): Boronate **2b** (0.58 g, 2.6 mmol) and 2-iodo-*N*-tosylaniline (0.720 g, 1.93 mmol), and $PdCl_2(PPh_3)_2$ (0.068 g, 5% mol) were used. The reaction then was carried out as above reported for quinoline **4a**, to afford pure **4b** (0.38 g, 55%) as a white solid (m.p. 104–106 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.65 (dd, J = 7.8, 1.6 Hz, 1 H), 7.44 (td, J = 7.8, 1.6 Hz, 1 H), 7.70 (td, J = 7.8, 1.6 Hz, 1 H), 7.2–7.1 (m, 3 H), 7.07 (d, J = 8.1, 2 H), 4.24 (s, 1 H), 3.31 (q, J = 6.7 Hz, 2 H), 2.36 (s, 3 H), 1.48 (s, 6 H), 1.20 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 149.7, 142.6, 137.9, 136.8, 129.8, 128.7, 128.2, 128.0, 127.5, 126.7, 121.8, 104.0, 62.5, 58.61, 29.2, 21.3, 14.2 ppm. MS: *m*/*z* (%) = 187 (68), 159 (100), 158 (13), 130 (22), 77 (12). $C_{20}H_{23}NO_3S$ (357.47): calcd. C 67.20, H 6.49, N 3.92; found C 68.05, H 5.99, N 4.08.

Typical Procedure for the Synthesis of 2,3-Dihydro-2,2-dimethyl-1-tosylquinolin-4(1*H*)-one (5b): Quinoline **4b** (0.30 g, 0.84 mmol) was dissolved in $CHCl_3$, then a catalytic quantity of Amberlyst-15® (1.0–1.5 mg) was added, and the mixture was stirred. After 4.5 h, the chromene reagent disappeared (GC control). Amberlyst-15® was filtered off and the solvent evaporated, then the crude quinolinone was purified by column chromatography on SiO_2 (petroleum ether/Et_2O, 9:1) to give pure **5b** (0.25 g, 90%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.96 (d, J = 7.8 Hz, 1 H), 7.72 (t, J = 7.8 Hz, 1 H), 7.63 (t, J = 7.8 Hz, 1 H), 7.43 [d, J = 8.1 Hz, 2 H, superimposed on δ = 7.4–7.3 ppm (m, 1 H)], 7.24 (d, J = 8.1, 2 H), 2.40 (s, 3 H), 2.28 (s, 2 H), 1.45 (s, 6 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 194.1, 144.1, 142.7, 138.2, 134.1, 130.4, 129.9, 128.6, 127.2, 126.9, 126.4, 60.4, 48.9, 28.3, 21.5 ppm. MS: *m*/*z* (%) = 329 (11) [M$^+$], 274 (14), 265 (41), 174 (100), 155(17), 91 (46). $C_{18}H_{19}NO_3S$ (329.41): calcd. C 65.63, H 5.81, N 4.25; found C 66.20, H 5.05, N 4.80.

General Procedure for the Synthesis of Chromenes 6a and 6b: Boronate [0.27 g (**2a**), 0.29 g (**2b**), 1.3 mmol] and 2-bromophenol (0.17 g, 1.0 mmol) were added to THF (10 mL) which had been degassed with argon for 10 min, then $Pd(PPh_3)_4$ (0.058 g, 5% mol) and K_2CO_3 (0.21 g, 1.5 mmol) were consecutively added. The resulting solution was stirred at 80 °C overnight, and then cooled to room temperature. H_2O (10 mL) was added, the mixture extracted with Et_2O (2 × 10 mL), and then washed with 10% aqueous NaOH (2 × 10 mL); the collected organic layers were treated with charcoal, filtered and dried (K_2CO_3). After evaporation of the solvent, the crude reaction product was purified by column chromatography on neutral Al_2O_3 (light petroleum ether/Et_2O, 9:1).

Ethoxy-2-methyl-2*H*-chromene (6a): Yield 0.091 g (48%) as a yellow-green oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.36 (dd, J = 7.8, 1.6 Hz, 1 H), 7.06 (td, J = 7.8, 1.6 Hz, 1 H), 6.80 (td, J = 7.8, 1.6 Hz, 1 H), 6.72 (dd, J = 7.8, 1.6 Hz, 1 H), 4.99 (qd, J = 6.4, 3.0 Hz 1 H), 4.52 (d, J = 3.0 Hz, 1 H), 3.79 (q, J = 7.0 Hz, 2 H), 1.43–1.26 (m, 6 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 154.6, 149.2, 129.8, 122.0, 120.6, 115.7, 110.1, 95.2, 72.2, 62.7, 22.4, 14.4 ppm. MS: *m*/*z* (%) = 190 (25) [M$^+$], 175 (68), 161 (17), 147 (100). $C_{12}H_{14}O_2$ (190.24): calcd. C 75.76, H 7.42; found C 74.85, H 7.95.

4-Ethoxy-2,2-dimethyl-2*H*-chromene (6b): (0.075 g, 36%) as a yellow-green oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.37 (dd, J = 7.6, 1.6 Hz, 1 H), 7.08 (td, J = 7.6, 1.6 Hz, 1 H), 6.80 (td, J = 7.6, 1.6 Hz, 1 H), 6.71 (dd, J = 7.6, 1.6 Hz, 1 H), 4.53 (s, 1 H), 3.79 (q, J = 6.8 Hz, 2 H), 1.38 (s, 6 H), 1.36 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 153.6, 148.1, 129.5, 121.9, 120.2, 119.2, 116.1, 99.6, 77.3, 62.6, 29.2 (2 C), 14.5 ppm. MS: *m*/*z* (%) = 204 (19) [M$^+$], 189 (79), 161 (100), 121 (10). $C_{13}H_{16}O_2$ (204.26): calcd. C 76.44, H 7.90; found C 76.99; H,7.45.

Typical Procedure for the Synthesis of 2,3-Dihydro-2,2-dimethylchromen-4-one (7b): Chromene **6b** (0.045 g, 0.22 mmol) was dissolved in $CHCl_3$, then a catalytic quantity of Amberlyst-15® (1.0–1.5 mg) was added, and the mixture was stirred. After 2 h, the chromene reagent disappeared (GC control). The resin was filtered off and the solvent evaporated, then the crude chromenone was purified by column chromatography on SiO_2 (petroleum ether/Et_2O, 9:1) to give pure **7b** (0.029 g, 75%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.79 (d, J = 7.8 Hz, 1 H), 7.40 (t, J = 7.8 Hz, 1 H), 6.92 (t, J = 7.8 Hz, 1 H), 6.86 (d, J = 7.8 Hz, 1 H), 2.66 (s, 2 H), 1.36 (s, 6 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 192.6, 159.9, 136.1, 126.5, 120.6, 120.2, 118.3, 79.1, 48.9, 26.7 (2 C) ppm. MS: *m*/*z* (%) = 176 (59) [M$^+$], 161 (100), 121 (52), 120 (51), 93 (10), 92 (40). $C_{11}H_{12}O_2$ (176.21): calcd. C 74.98, H 6.86; found C 75.75, H 7.10.

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[1] J. P. Collman, B. M. Trost, T. R. Verhoeven, in *Comprehensive Organometallic Chemistry* (Eds.: G. Wilkinson, F. G. A. Stone), Pergamon Press, Oxford, **1982**, vol. 8, p. 892; and references cited therein.
[2] P. M. S. Chauhan, S. K. Srivastava, *Curr. Med. Chem.* **2001**, *8*, 1535–1542; F. S. Yates, in *Comprehensive Heterocyclic Chemistry* (Eds.: A. J. Boulton, A. McKillop), Pergamon Press, New York, **1984**, vol. 2, chapter 2.09.
[3] A. Combes, *Bull. Soc. Chim. Fr.* **1888**, *49*, 89–92; J. Born, *J. Org. Chem.* **1972**, *37*, 3952–3953.
[4] Z. H. Skraup, *Ber. Dtsch. Chem. Ges.* **1880**, *13*, 2086–2087; R. H. F. Manske, M. Kulka, *Org. React.* **1953**, *7*, 80–99.
[5] P. Friedlaender, *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 2572–2575; R. P. Thummel, *Synlett* **1992**, 1–12.
[6] a) J. F. Hartwig, *Synlett* **1997**, 329–340; b) M. Kosugi, M. Kameyama, T. Migita, *Chem. Lett.* **1983**, 927–928; c) A. S. Guram, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 7901–7902; d) F. Paul, J. Patt, J. F. Hartwig, *J. Am. Chem. Soc.* **1994**, *116*, 5969–5970; e) J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995**, *36*, 3609–3612.
[7] Q. Shelby, N. Kataoka, G. Mann, J. Hartwig, *J. Am. Chem. Soc.* **2000**, *122*, 10718–10719.
[8] a) J. P. Wolfe, R. A. Rennels, S. L. Buchwald, *Tetrahedron* **1996**, *52*, 7525–7546; b) A. van den Hoogenband, J. A. J. den Hartog, J. H. M. Lange, J. W. Terpstra, *Tetrahedron Lett.* **2004**, *45*, 8535–8537; c) A. Neogi, T. P. Majhi, R. Mukhopadhyay, P. Chattopadhyay, *J. Org. Chem.* **2006**, *71*, 3291–3294, and references therein.
[9] a) M. Palucki, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 10333–10334; b) N. Kataoka, Q. Shelby, J. P. Stambuli, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 5553–5566.
[10] a) L. S. Hegedus, G. F. Allen, J. J. Bozell, E. L. Waterman, *J. Am. Chem. Soc.* **1978**, *100*, 5800–5807; b) R. C. Larock, T. R. Hightower, L. A. Hasvold, K. P. Peterson, *J. Org. Chem.* **1996**, *61*, 3584–3585; c) S. Cacchi, G. Fabrizi, L. M. Parisi, *Heterocycles* **2002**, *58*, 667–682; d) G. Balme, D. Bouyssi, T. Lomberget, N. Monteiro, *Synthesis* **2003**, 2115–2134; e) G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, *104*, 2285–2309; f) G. Kirsch, S. Hesse, A. Comel, *Curr. Org. Synth.* **2004**, *1*, 47–63; g) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127–2198.
[11] B. M. Trost, H. G. Shen, L. Dong, J.-P. Surivet, *J. Am. Chem. Soc.* **2003**, *125*, 9276–9277.
[12] H.-Y. Kang, Y.-T. Kim, Y.-K. Yu, J. H. Cha, Y. S. Cho, H. Y. Kohb, *Synlett* **2004**, 45–48.
[13] a) M. Schlosser, *J. Organomet. Chem.* **1967**, *8*, 9–16; b) M. Schlosser, *Mod. Synth. Methods* **1992**, *6*, 227–271; c) A. Mordini, in *Advances in Carbanion Chemistry* (Ed.: V. Snieckus), JAI Press, Inc., Greenwich, CT, **1992**, vol. 1, pp. 1–45; d) M. Schlosser, F. Faigl, L. Franzini, H. Geneste, G. Katsoulos, G. Zhong, *Pure Appl. Chem.* **1994**, *66*, 1439–1446; e) L. Lochmann, *Eur. J. Inorg. Chem.* **2000**, 1115–1126.
[14] P. Venturello, *J. Chem. Soc., Chem. Commun.* **1992**, 1032–1033.
[15] C. Prandi, P. Venturello, *J. Org. Chem.* **1994**, *59*, 3494–3496; C. Prandi, P. Venturello, *J. Org. Chem.* **1994**, *59*, 5458–5462.
[16] a) P. Balma Tivola, A. Deagostino, C. Prandi, P. Venturello, *J. Chem. Soc., Perkin Trans. 1* **2001**, 437–441; b) A. Deagostino, C. Prandi, P. Venturello, *Curr. Org. Chem.* **2003**, *7*, 821–839.
[17] A. Deagostino, C. Prandi, P. Venturello, *Org. Lett.* **2003**, *5*, 3815–3817.
[18] a) P. Balma Tivola, A. Deagostino, C. Prandi, P. Venturello, *Chem. Commun.* **2001**, 1536–1537; b) P. Balma Tivola, A. Deagostino, C. Prandi, P. Venturello, *Org. Lett.* **2002**, *4*, 1275–1277; c) A. Deagostino, C. Prandi, C. Zavattaro, P. Venturello, *Eur. J. Org. Chem.* **2003**, 2612–2616; d) A. Deagostino, M. Migliardi, E. G. Occhiato, C. Prandi, C. Zavattaro, P. Venturello, *Tetrahedron* **2005**, *61*, 3429–3436.
[19] In the case of cross-coupling derivative **3d** both (*E*) and (*Z*) isomers have been characterized, and the stereochemistry has been deduced on the basis of NOESY experiments (see Experimental Section).
[20] One of the referees suggested to interrupt the coupling reaction before completion, in order to allow the isolation of the stereomeric mixture of boronates. Accordingly, we have treated boronate **2a** under the same experimental conditions of the synthesis of derivatives **3d** and **3e** in the absence of iodoaniline, and checked the composition of the reaction mixture by GC analysis. We have found that after 16 h, the (*E*)/(*Z*) ratio was about 95:5, which is, however, far from the composition of the isomeric mixture of products **3d** and **3e**. In Scheme 3 we therefore suggest that the isomerization could occur either on the boronate or on the coupling product. The possibility that isomerization might proceed by protonation of the dienyl fragment, without requiring the intervention of Pd^{II}, has also to be considered. At this moment we have no explanation for the results regarding cross-coupling product **3c** and **3f**.
[21] T. E. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675–703.
[22] We advance the hypothesis of a H^+-promoted cyclization reaction, since a THF suspension of K_2CO_3 can be likely considered a weak proton scavenger.
[23] R. C. Larock, P. Pace, H. Yang, C. E. Russel, S. Cacchi, G. Fabrizi, *Tetrahedron* **1998**, *54*, 9961–9980.
[24] a) L. S. Hegedus, G. F. Allen, E. L. Waterman, *J. Am. Chem. Soc.* **1976**, *98*, 2674–2676; b) E. M. Beccalli, G. Broggini, M. Martinelli, G. Paladino, *Tetrahedron* **2005**, *61*, 1077–1082.
[25] J. E. Bäckvall, P. G. Andersson, *J. Am. Chem. Soc.* **1990**, *112*, 3683–3685.
[26] The reaction reported in Scheme 6 has also been carried out using **3a** in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), and no significant increase in reaction rate and yield has been observed.
[27] T. Tímár, A. Lévai, T. Eszenyí, P. Sebók, *J. Heterocycl. Chem.* **2000**, *37*, 1389–1417.
[28] For a detailed typical procedure, see ref.[18b]

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