Synthetic Methods

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Assembly of Substituted 2-Alkylquinolines by a Sequential Palladium-Catalyzed C–N and C–C Bond Formation

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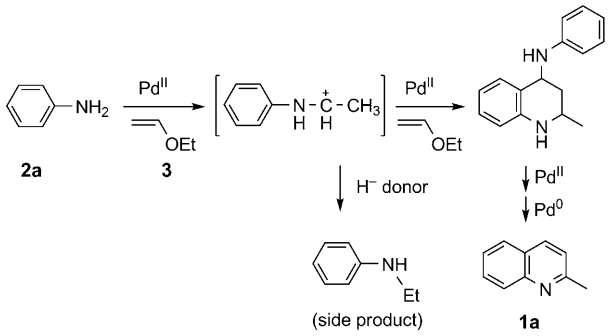
The quinoline unit represents an important structural motif found in a variety of biologically active compounds.[1] For example, 2-methylquinoline (**1a**) is employed in the design of pharmaceuticals and related compounds such as antischizophrenia (e.g., PF-2545920),[2] antitumor (e.g., lavendamycin methyl ester),[3] and anti-HIV agents (e.g., styrylquinoline),[4] as well as nociceptin receptor antagonists (e.g., JTC-801).[5]

Cyanine dyes derived from substituted 2-methylquinolines are utilized as electronic and optoelectronic materials.[6] Tris(8-quinolinolato)aluminum is most widely used as an excellent green-emitting material,[7a,b] and functionalization of the quinoline ring provides full-spectrum fluorescent materials.[7c,d]

Since the substituents on the quinoline rings have a great influence on the properties of these compounds, efficient methods for the preparation of a diverse range of substituted 2-alkylquinolines are highly desirable. Traditionally, these compounds are synthesized by using reactions of functionalized anilines with α,β-unsaturated carbonyl compounds at elevated temperatures under strongly acidic conditions.[8–10] Although the improvement of these harsh conditions has recently been addressed by metal-catalyzed approaches,[11] these new methods are confined because of a lack of generality and limited functional-group tolerance. As examples of the synthesis of 2-alkylquinolines by metal-catalyzed intermolecular reactions, Beller and co-workers have developed the formation of 2-benzyl-3-phenylquinoline by the rhodium-catalyzed reaction of aniline with styrene.[11e] Later, Yi and Yun reported the formation of 2-methylquinoline by the ruthenium-catalyzed reaction of aniline with ethylene.[11d] However, the generality of these excellent reactions has not been examined. The functionalization of unsubstituted 2-alkylquinolines is another commonly used approach, although in most cases it suffers from a lack of regioselectivity.

Herein, we report a highly efficient new method for the construction of substituted 2-alkylquinolines by the $PdCl_2$-catalyzed reaction of anilines with alkenyl ethers. To the best of our knowledge, this report represents the first application of alkenyl ethers in the metal-mediated synthesis of quinolines. We have envisioned the reaction consisting of three sequential steps: 1) a hydroamination catalyzed by the Lewis acid $PdCl_2$ (C–N bond formation), 2) a subsequent $PdCl_2$-catalyzed tetrahydroquinoline ring formation (C–C bond formation), and 3) a palladium-catalyzed aromatization, thus resulting in the formation of the desired compound in one step.

A typical example of the reaction of an aniline with an alkenyl ether is shown in Scheme 1. The reaction of aniline (**2a**) with ethyl vinyl ether (**3**, 3 equiv) in the presence of



Scheme 1. Formation of 2-methylquinoline (**1a**) from aniline (**2a**) and ethyl vinyl ether (**3**).

$PdCl_2$ (5 mol%) in acetonitrile (MeCN; reflux in air, 5 h) afforded 2-methylquinoline (**1a**, 76%) accompanied by the side product *N*-ethylaniline (24%). The yield of **1a** was increased to 82% by prolonged reflux in the presence of Pd/C (Table 1, entry 1), which hindered the formation of the side product. In the early stages of the reaction we observed the formation of **1a** and its tetrahydroderivatives (*cis* and *trans*), but the hydroamination products were not isolated, thus indicating that the aromatization step is the slowest and, thus, the rate-determining step of the three sequential steps mentioned above. From HPLC analysis of the reaction mixtures, we suggest that the formation of **1a** proceeds through the mechanism shown in Scheme 1 (see the Supporting Information for further details).

During the optimization of the reaction conditions, it was found that $PdCl_2$ (finely powdered immediately before the reaction) or $[PdCl_2(MeCN)_2]$ were the most effective catalysts among those examined ($PdCl_2$, $Pd(OAc)_2$, PdI_2, $[PdCl_2(MeCN)_2]$, $[Pd(PPh_3)_2Cl_2]$, and Pd/C), and MeCN was the best solvent among those tested (MeCN, EtCN, PrCN, toluene, *N*,*N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO)). The yield of **1a** was highest at a molar ratio of **2a**/**3** = 1:3 and a concentration of 1 mmol **2a** in 5 mL MeCN (0.2 M).

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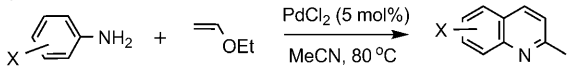
Table 1: Synthesis of substituted 2-methylquinolines.[a]



2 **3** **1**

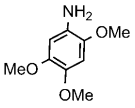
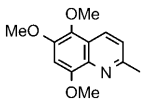
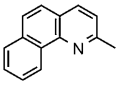
Entry	Aniline (X)	*t* [h]	Product	Yield [%][b]	Entry	Aniline (X)	*t* [h]	Product	Yield [%][b]
1	**2a** (H)	24	**1a**	82[d]	9	**2i** (3-F)	24	**1i**	72
2	**2b** (4-Me)	24	**1b**	82	10	**2j** (4-Cl)	24	**1j**	70
3	**2c** (3-Me)	24	**1c**	81	11	**2k** (3-Cl)	24	**1k**	68
4	**2d** (2-Me)	24	**1d**	75	12	**2l** (4-Br)	24	**1l**	66
5	**2e** (4-OMe)	24	**1e**	86	13	**2m** (4-COOMe)[c]	24	**1m**	79
6	**2f** (3-OMe)	48	**1f**	62	14	**2n** (4-CONMe$_2$)[c]	24	**1n**	85
7	**2g** (2-OMe)	4	**1g**	74	15	**2o** (4-COMe)[c]	24	**1o**	80
8	**2h** (4-F)	24	**1h**	77	16	**2p** (4-COPh)[c]	24	**1p**	77

[a] Reaction conditions: substituted aniline (1 mmol), **3** (3 mmol), $PdCl_2$ (5 mol%), and Pd/C (20 mg) in MeCN (5 mL) were heated in air at 80°C. [b] Yields were determined by HPLC. [c] Yields from reaction in the absence of Pd/C. [d] A threefold scale-up resulted in almost no change in the yield. [e] Data for the formation of substituted *N*-ethylaniline (side product) are shown in the Supporting Information.

Under these optimized conditions, we examined the scope and limitation of our reaction for the synthesis of substituted 2-methylquinolines (Table 1). The reaction works well, regardless of the electron-donating or electron-withdrawing nature of the substituents on the aniline ring. The reactions of *para*-substituted anilines afforded 6-substituted 2-methylquinolines in yields ranging from 66% to 86% (Table 1, entries 2, 5, 8, 10, and 12–16). Interestingly, the products of the reaction with *meta*-substituted anilines were not a mixture of 5- and 7-substituted 2-methylquinolines, but only 7-substituted 2-methylquinolines in yields ranging from 62% to 81% (Table 1, entries 3, 6, 9, and 11). This result could be ascribed to the steric effect of the substituent at the transition state of the C–C bond formation that leads to the tetrahydroquinoline ring (see the Supporting Information). It is noteworthy that the reaction with *o*-Me- and *o*-OMe-substituted anilines afforded 8-substituted 2-methylquinolines in yields of around 75% (Table 1, entries 4 and 7), although no reaction of *o*-F-, *o*-Cl-, and *o*-COOMe-substituted anilines with **3** was observed.

To further demonstrate the scope of our reaction for the preparation of polysubstituted 2-methylquinolines, we examined the reactions of 2,4,5-trimethoxyaniline (**5**) and 1-naphthylamine (**7**), and obtained 5,6,8-trimethoxy-2-methylquinoline (**4**) and 2-methylbenzo[*h*]quinoline (**6**), respectively, in satisfactory yields (Table 2). Compound **4** is a useful intermediate for the synthesis of lavendamycin [3] and streptonigrin,[12] and compound **6** is expected to become an attractive new ligand for novel phosphorescent Ir complexes (electroluminescent materials).[13]

Table 2: Synthesis of 5,6,8-trimethoxy-2-methylquinoline (**4**) and 2-methylbenzo[*h*]quinoline (**6**).[a]

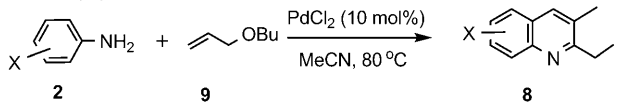
Entry	Aniline		Product		*t* [h]	Yield [%][b]
1	**5**		**4**		96	71
2	**7**		**6**		4	66

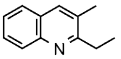
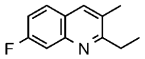
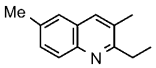
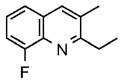
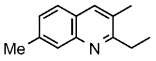
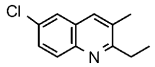
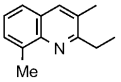
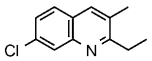
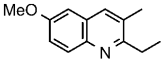
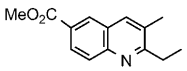
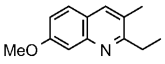
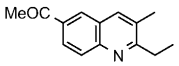
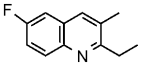
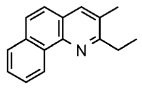
[a] Reaction conditions: substituted aniline (1 mmol), **3** (3 mmol), and $PdCl_2$ (3 mol%) in MeCN (5 mL) were heated in air at 80°C. [b] Yields were determined by HPLC. [c] Data for the formation of substituted *N*-ethylaniline (side product) are shown in the Supporting Information.

To extend the applicability of our reaction, we also employed allyl and propenyl ethers. We examined the reaction between substituted anilines **2** and allyl *n*-butyl ether (**9**) by using the reaction conditions shown in Table 1. We found that the reaction worked well by using 10 mol% $PdCl_2$ to provide substituted 2-ethyl-3-methylquinolines **8** (Table 3). The π-allyl Pd complex was not detected by ^{1}H NMR spectroscopy and HPLC analysis of the reaction mixtures.

As shown in Table 3, the reaction of substituted anilines with allyl ether **9** works well, regardless of the electron-

Table 3: Synthesis of substituted 2-ethyl-3-methylquinolines **8**.[a]

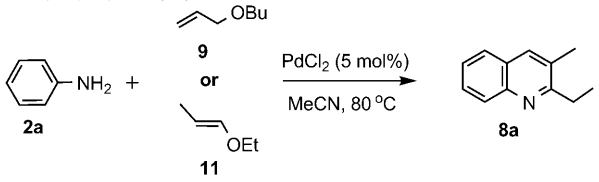


Entry	Aniline (X)	*t* [h]		Product	Yield [%][b]	Entry	Aniline (X)	t [h]		Product	Yield [%][b]
1	**2a** (H)	48	**8a**		62	8	**2i** (3-F)	48	**8i**		58
2	**2b** (4-Me)	24	**8b**		63	9	**2q** (2-F)	48	**8q**		15
3	**2c** (3-Me)	48	**8c**		73	10	**2j** (4-Cl)	48	**8j**		55
4	**2d** (2-Me)	48	**8d**		29	11	**2k** (3-Cl)	48	**8k**		56
5	**2e** (4-OMe)	24	**8e**		59	12	**2m** (4-CO_2Me)	24	**8m**		65
6	**2f** (3-OMe)	48	**8f**		65	13	**2o** (4-COMe)	24	**8o**		72
7	**2h** (4-F)	4	**8h**		68	14	**7** 	48	**10**		65

[a] Reaction conditions: substituted aniline (1 mmol), **9** (3 mmol), and $PdCl_2$ (10 mol%) in MeCN (5 mL) were heated in air at 80°C. [b] Yields were determined by HPLC. [c] Data for the formation of substituted *N*-propylaniline (side product) are shown in the Supporting Information.

donating or electron-withdrawing nature of the substituent on the aniline ring, to selectively provide substituted 2-ethyl-3-methylquinolines. The reaction with *para*-substituted anilines afforded 6-substituted 2-ethyl-3-methylquinolines in yields ranging from 55% to 72% (Table 3, entries 2, 5, 7, 10, 12, and 13). The reaction with *meta*-substituted anilines gave 7-substituted 2-ethyl-3-methylquinolines in yields ranging from 56% to 73% (Table 3, entries 3, 6, 8, and 11). Even the reaction with *ortho*-methylaniline (**2d**) and *ortho*-fluoroaniline (**2q**) gave 8-methyl-2-ethyl-3-methylquinoline (**8d**, 29%) and 8-fluoro-2-ethyl-3-methylquinoline (**8q**, 15%), respectively (Table 3, entries 4 and 9). The reaction of 1-naphthylamine (**7**) provided 2-ethyl-3-methylbenzo[*h*]quinoline (**10**) in 65% yield (Table 3, entry 14). Similar results were obtained by employing *n*-propenyl ether **11** in place of allyl ether **9** (Table 4), thus suggesting that **9** isomerizes to **11** under the reaction conditions.

Table 4: $PdCl_2$ catalyzed reaction of **2a** with allyl *n*-butyl ether (**9**) or 1-ethoxy-1-propene (**11**).[a]



Entry	Ether	Additive	Yield [%][b]
1	**9**	–	59
2	**11**	–	58
3	**11**	Pd/C (10 mg)	67
4	**11**	Pd/C (20 mg)	69

[a] Reaction conditions: **2a** (1 mmol), **9** or **10** (3 mmol), and $PdCl_2$ (5 mol%) in MeCN (5 mL) were heated in air at 80°C for 24 h. [b] Yields were determined by HPLC. [c] Data for the formation of substituted *N*-propylaniline (side product) are shown in the Supporting Information.

In conclusion, we have developed a new method based on a sequential $PdCl_2$-catalyzed process for the construction of functionalized alkyl quinolines from substituted anilines and alkenyl ethers. The efficiency and functional-group tolerance of this procedure have been fully demonstrated by synthesizing a number of substituted 2-alkylquinolines. The products are expected to be useful intermediates for preparing biologically active compounds as well as electronic and optoelectronic materials. Considering the relatively inexpensive catalytic system and the commercial availability of the starting materials, this method should find numerous applications, including in the industrial field.

Experimental Section

Typical procedure for the synthesis of 2-methylquinolines **1** and 2-ethyl-3-methylquinolines **8**: A 20 mL round-bottom flask equipped with a Dimroth condenser and a Teflon-coated stirrer bar was charged with a solution of **2** (1 mmol) in MeCN (5 mL). $PdCl_2$ (0.05 mmol for **1** or 0.10 mmol for **8**; finely powdered in an agate mortar) and vinyl ether **3** or allyl ether **9** (3 mmol) were added and the mixture was heated in air at 80°C for 24 h (for **1**) or 48 h (for **8**). The solvent was removed under reduced pressure, and the products were isolated by column chromatography on silica gel (hexane/benzene) to give **1** or **8**. The structures of the products were confirmed by comparison with reported spectroscopic data.

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