Pergamon

Tetrahedron 57 (2001) 2507–2514

TETRAHEDRON

Syntheses of acetylquinolines and acetylisoquinolines via palladium-catalyzed coupling reactions

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Received 30 July 2000; revised 11 September 2000; accepted 15 September 2000

Abstract—Acetylquinolines and acetylisoquinolines were obtained from the corresponding chloro-, bromo- or trifluoromethylsulfonyloxy-heteroaromatics via four different palladium-catalyzed coupling reactions: (i) Stille coupling with tri(*n*-butyl)-1-ethoxyvinylstannane; (ii) Negishi coupling with 1-ethoxyvinylzinc chloride; (iii) cross-coupling with tri(1-ethoxyvinyl)indium; (iv) Heck arylation of *n*-butyl vinyl ether.

1. Introduction

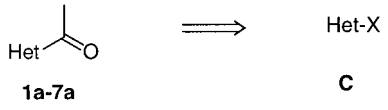
In the past decade, we have described the palladium-catalyzed nucleophilic substitution of naphthylmethyl and 1-(1- or 2-naphthyl)ethyl esters (acetates and methyl carbonates) by carbon[1–3] or nitrogen[4] nucleophiles. This reaction was recently applied to the development of a new protecting group for carboxylic acids, namely the 4-quinolylmethyl (4-QUI) group.[5,6] The deprotection step consist in a homogeneous palladium-catalyzed hydrogenolysis by formate anion of the 4-QUI ester of the acid, which is more reactive than the 1- or 2-naphthylmethyl analogue.

The palladium-catalyzed nucleophilic substitution of quinolylmethyl, 1-isoquinolylethyl and 1-quinolylethyl acetates by dimethylmalonate anion was recently studied.[7] In contrast to 1-(1- and 2-naphthyl)ethanols, the heteroaryl methyl carbinols of type **B**, precursors of secondary heteroaromatic substrates of type **A** by acetylation (Scheme 1), are not commercially available. So we needed a convenient preparative method of these compounds from easily available precursors.

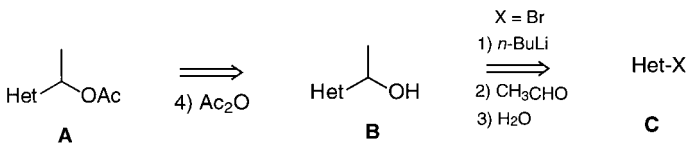
The shortest described procedure[8] for compounds of type **A** is not straightforward. For example (Scheme 1), lithium–halogen exchange (excess *n*-BuLi, −80°C) on 3-bromoquinoline (**C**, X=Br), followed by treatment with an excess of acetaldehyde and direct acetylation of the crude mixture obtained after hydrolysis and work-up leads to 1-(3-quinolyl)ethyl acetate in 7.5% yield.[8] We tried to improve this reaction, but we observed that compound of type **B** (i.e. 1-(3-quinolyl)ethanol) was obtained in moderate (<50%) yield and was difficult to purify. So we decided to investigate a new route to compounds **B** (and hence to compounds **A**) by reduction of acetylquinolines and acetylisoquinolines **1a**–**7a** (Scheme 2).

Acetylquinolines and acetylisoquinolines were prepared in the litterature by different ways. The main general routes developed are:

(a) reaction of a methylmagnesium halide on a nitrile **C** (X=CN).[9–12] This method is not applicable for all isomeric substrates: for example, 4-acetylisoquinoline is



Scheme 2. Het=quinolyl, isoquinolyl.



Scheme 1. Het=quinolyl, isoquinolyl.

Keywords: isoquinolines; quinolines; Heck reaction; Stille reaction.

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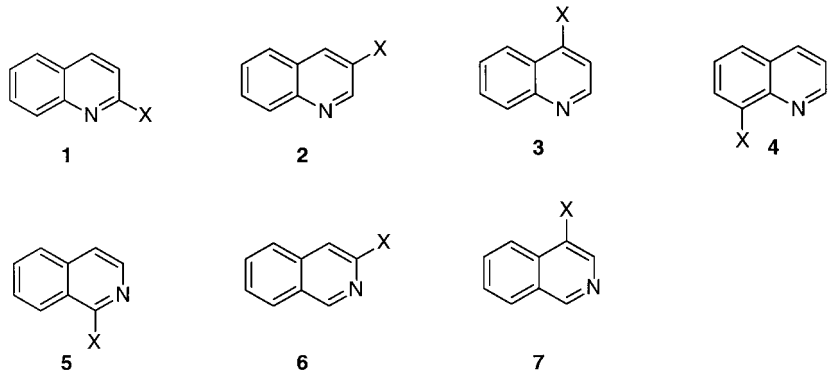


Figure 1. a: X=$COCH_3$; **b**: X=Br; **c**: X=Cl; **d**: X=OSO_2CF_3; **d′**: X=OH.

not obtained from 4-cyanoisoquinoline and methylmagnesium iodide;[11]
(b) mixed Claisen condensation between ethyl acetate and an ester **C** (X=CO_2Et), followed by hydrolysis and decarboxylation of the resulting β-ketoester; [8,11,13]
(c) palladium-catalyzed Stille coupling between acetyl chloride and a trimethylstannyl derivative **C** (X=$SnMe_3$); [14]
(d) palladium-catalyzed Sonogashira coupling between trimethylsilylacetylene and a halogenoheteroaromatic **C** (X=Br, Cl), followed by desilylation and hydratation of the carbon–carbon triple bond.[15,16]

These four methods suffers from at least of the two following drawbacks:

- all the isomeric precursors **C** are not commercially available (a, b and c),
- the preparations are multi-step syntheses (b, d).

In this paper, we report on the syntheses of acetylquinolines and acetylisoquinolines **1a**–**7a** (see Fig. 1) via palladium-catalyzed Stille and Heck coupling reactions. In addition, we discuss on the regioselectivity of the Stille reaction on three dichloroheteroaromatic substrates and some preliminary results concerning the palladium-catalyzed coupling reactions with organozinc **8b** and organoindium **8c** reagents are added. All the isomers with the acetyl group on the heterocycle are obtained and we prepared also 8-acetylquinoline **4a**. The precursors of these ketones are commercially available (chloro- or bromo-heteroaromatics) or easily prepared from commercially available products (triflates). These syntheses are based on the use of 1-ethoxyvinyltri(*n*-butyl)stannane **8a** in palladium-catalyzed Stille reaction,[17,18] the use of 1-ethoxyvinylzinc chloride **8b** in palladium-catalyzed Negishi coupling,[19,20] and on the results of Cabri et al. concerning the palladium-catalyzed arylation of *n*-butylvinylether **8d** (Heck reaction).[21,22] To the best of our knowlegde, **8c** was not already reported in the literature. Compounds **8** could be considered as acetyl equivalents (Scheme 3).

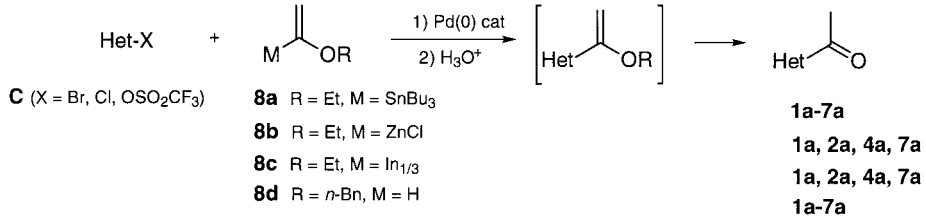
2. Results and discussion

2.1. Substrates for coupling reactions

As mentioned above, we prepared the six ketones **1a**–**3a**, **5a**–**7a** with the acetyl group on the heterocycle together with 8-acetylquinoline **4a**. Direct available precursors for these compounds via palladium-catalyzed reactions are 2-chloroquinoline **1c**, 3-bromoquinoline **2b**, 4-chloroquinoline **3c** and 4-bromoisoquinoline **7b**. For the other substituted positions, hydroxy derivatives **4d′**, **5d′** and **6d′** were reacted with triflic anhydride in the presence of pyridine according to the procedure described by Echavarren and Stille[23] to give trifluoromethanesulfonates **4d**, **5d** and **6d**. In addition, **3d** was prepared by the same method to allow the comparison between two substrates, chloride **3c** and triflate **3d**. **4d**[23] and **5d**[24] were already prepared and engaged in Stille coupling reactions with various organostannanes.

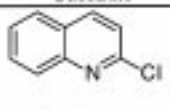
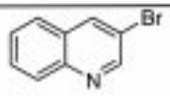
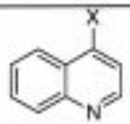
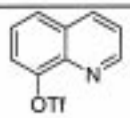
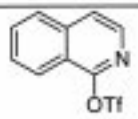
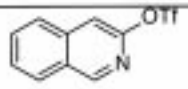
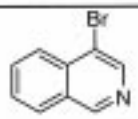
2.2. Stille coupling reactions

(1-Ethoxyvinyl)tri(*n*-butyl)stannane **8a** was prepared as described in the literature for the methoxy analogue.[25] The coupling reactions were conducted in refluxing toluene (for chlorides and bromides) or dioxane (for triflates) in the presence of 4 mol% of a palladium catalyst prepared by adding 2 equiv. of triphenylphosphine to bis(dibenzylideneacetone)palladium(0), denoted $Pd(dba)_2$. For the triflates, addition of 3 equiv. of lithium chloride was necessary.[23] After completion of the reaction, the intermediate ethyl enol ether was hydrolyzed by a HCl solution



Scheme 3.

Table 1. Stille cross-coupling reactions

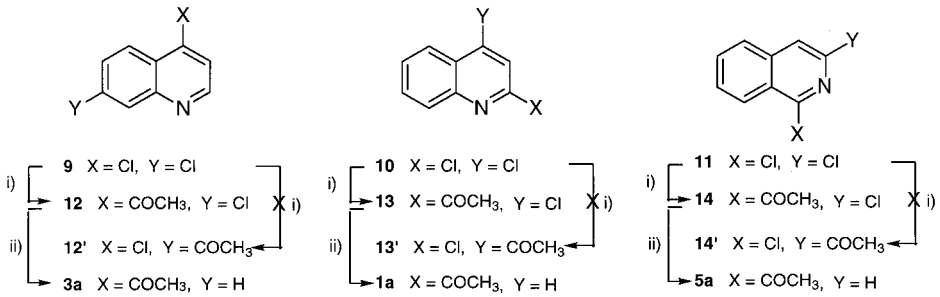
Entry	Substrate		t (h)	LiCl	Product	Isolated Yield (%)
1[a,b]	**1c**		12	no	**1a**	68
2[a]	**2b**		1	no	**2a**	88
3[a]	**3c**	 X = Cl	24	no	**3a**	60
4[c]	**3d**	X = OTf	24	yes		32
5[c]	**4d**		18	yes	**4a**	40
6[c]	**5d**		24	yes	**5a**	52
7[c]	**6d**		24	yes	**6a**	53
8[a]	**7b**		24	no	**7a**	64

[a] Solvent=toluene.
[b] Hydrolysis was performed with 4N HCl.
[c] Solvent=dioxane.
Unless otherwise noted, all reactions were conducted onto 1 mmol substrate, with 4 mol% $Pd(dba)_2$ and 8 mol% PPh_3 at solvent reflux for the time indicated. Hydrolyses were carried out at room temperature with 1N HCl for 24 h.

(Scheme 3). Results are collected in Table 1. All reactions were conducted on 1 mmol of substrate.

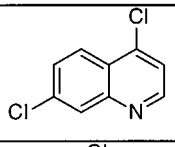
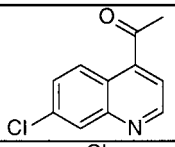
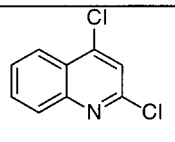
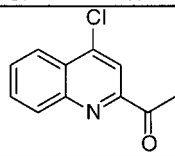
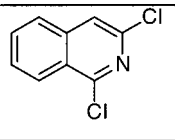
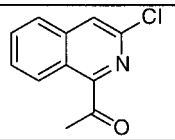
All the compounds **1a**–**7a** were obtained in moderate to good (40–88%) yield. The employed conditions required a reaction time of 12–24 h to reach completion except for substrate **2b**, which reacted much faster, to give 88% of ketone **2a** in less than 1 h (entry 1). Triflate **3d** gave **3a** albeit in low yield (32%, entry 4), a much better yield (60%, entry 3) being obtained from chloro compound **3c**.

We next investigated the regioselectivity of the Stille reaction of **8a** with three different dichloro derivatives, 4,7-dichloroquinoline **9**, 2,4-dichloroquinoline **10** and 1,3-dichloroisoquinoline **11** (Scheme 4). In each case, utilizing the same reaction conditions as above, only one product **12**,



Scheme 4. (i) **8a**, 4 mol% $Pd(dba)_2$, 8 mol% PPh_3, toluene, reflux. (ii) $HCOOH/Et_3N$, 0.26 equiv. $Pd(OAc)_2$, 0.5 equiv. dppf, DMF, 80°C.

Table 2. Stille cross-coupling reactions on dichloroheteroaromatic substrates

Entry	Substrate	Product	Isolated Yield (%)
1	**9** 	**12** 	40
2	**10** 	**13** 	44
3	**11** 	**14** 	65

Unless otherwise noted, all reactions were conducted onto 1 mmol substrate, with 4 mol% $Pd(dba)_2$ and 8 mol% PPh_3 at toluene reflux (110°C) for the time indicated. Hydrolyses were carried out at room temperature with 1N HCl for 12 h.

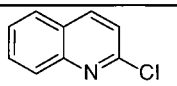
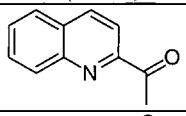
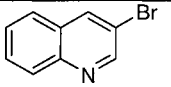
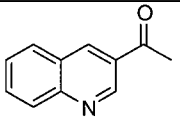
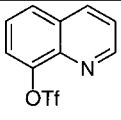
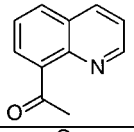
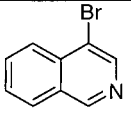
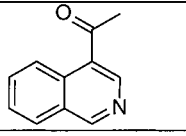
13 or **14**, respectively, was isolated in moderate yield (Table 2). Neither the regioisomer (**12′**, **13′**, **14′**) nor the diacetylated compound was detected by NMR analysis of the crude reaction mixture.

The structures of compounds **12**, **13** and **14** were confirmed by comparison of the reduced (HCO_2H/NEt_3, $Pd(OAc)_2$/dppf cat.)[26] product with an authentic sample of **3a**, **1a** and **5a**, respectively (Scheme 4).

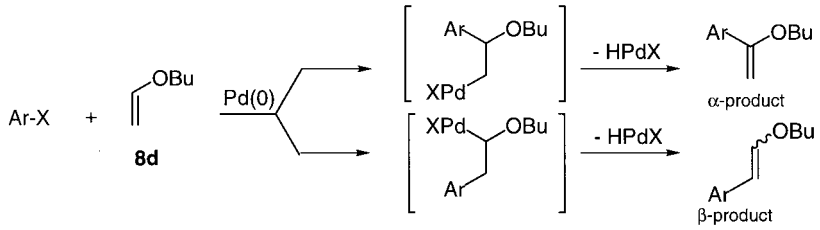
The selectivity of the substitution on 4,7-dichloroquinoline **9** is not surprising since the regiodetermining step is oxidative addition, i.e. insertion of a palladium(0) complex into a carbon–chlorine bond: the exclusive formation of **12** results from the higher reactivity of a chloropyridine compared to chlorobenzene. Some precedents are reported in the literature: palladium-catalyzed Suzuki reactions on **9** is initiated by the same oxidative addition and leads exclusively to 4-aryl-7-chloroquinolines.[27,28]

Palladium-catalyzed coupling reactions on 2,4-dichloroquinoline **10** are also precedented and our result is in agreement with the selectivity described.[29] In this case, the regioselectivity is attributed to a coordination of the

Table 3. Palladium-catalyzed cross-coupling reactions with organozinc **8b** and organoindium **8c** reagents

Entry	Substrate	Reactant	Cat. [a]	Product (Het-Ac)	Yield (%) [b]	Het-Het (%) [c]
1	**1c** 	**8b**	A	**1a** 	58	-
2		**8c**	A		62	-
3	**2b** 	**8b**	B	**2a** 	72	< 5
4		"	A		65	< 5
5 [d]		**8c**	B		24 [c]	12
6 [d]		"	A		35	28
7		"	A		56	6
8	**4d** 	**8b**	A	**4a** 	47	-
9		**8c**	A		35 [c]	-
10	**7b** 	**8b**	A	**7a** 	68	-
11		**8c**	A		58	-

[a] Catalyst A=[$Pd(dba)_2$+2PPh_3]; catalyst B=$PdCl_2(PPh_3)_2$.
[b] Isolated yield unless otherwise noted.
[c] NMR yield.
[d] In this entry, organoindium **8c** was prepared by addition of a 1-ethoxyvinyllithium solution to $InCl_3$.
Reactions were performed at refluxing THF for 24 h, using 4 mol% palladium catalyst; hydrolysis step was carried out stirring with 1N HCl solution for 24 h.



Scheme 5.

quinoline nitrogen atom to the palladium, directing the oxidative addition in the α position of the heteroatom.

Finally, the observed regioselectivity on 1,3-dichloroisoquinoline **11** illustrates the greater reactivity of the 1-chloro substituent compared to its 3-chloro counterpart. Here again, the obtained result is in accord with the reported palladium-catalyzed Suzuki reactions of **11**.[30]

The Stille reaction requires to prepare the stannane coupling partner **8a**, and the elimination of tin by-products during purification of the product is often problematic. Furthermore, considering the well-known toxicity of tin, we envisaged another preparation of ketones **1a**–**7a** from the same precursors.

2.3. Cross-coupling reactions with organozinc and organoindium compounds

In order to avoid the presence of tin compounds in the reaction medium, we envisaged two other acetyl synthetic equivalents, namely 1-ethoxyvinylzinc chloride **8b** and tri(1-ethoxyvinyl)indium **8c**. The former was already employed in Negishi palladium-catalyzed cross-coupling reactions.[19,20] The recently described palladium-catalyzed cross-coupling reaction of triorganoindium compounds with aryl triflates and iodides[31] prompted us to prepare **8c** and to evaluate its behaviour as nucleophilic partner towards some of heteroaromatic electrophiles studied in this article. Our preliminary results are presented in Table 3.

The reaction conditions were briefly optimized on 3-bromoquinoline **2b** (entries 3–7). The preparation and coupling reaction of organozinc **8b** were conducted as recently described.[32] A 72% isolated yield of **2a** was obtained (entry 3). We detected on the NMR spectrum the presence of a small amount of homocoupling product, 3,3′-bisquinoline. Replacement of $PdCl_2(PPh_3)_2$ for the combination of $Pd(dba)_2$ and 2 equiv. of PPh_3 gave essentially the same result (entry 4).

For cross-coupling of organoindium **8c**, application of the reported procedure[31] was unsatisfactory. Even with a double amount of **8c** (0.7 equiv. instead of 0.34), the reaction was very slow and the conversion was only 47% (from NMR) after 48 h (entry 5). Utilisation of $Pd(dba)_2$ in presence of PPh_3 gave a faster reaction (86% conversion in the same time) but a considerable amount of 3,3′-bisquinoline was produced (entry 6). Finally, we found that a modification in the procedure of preparation of **8c** (addition of indium trichloride to a THF solution of 1-ethoxyvinyllithium instead of the reverse sequence, see Section 4) led to a better result (entry 7).

The above conditions could be apply to a chloro (**1c**), a triflate (**4d**) and another bromo (**7b**) derivatives and the corresponding methyl ketones **1a**, **4a** and **7a** were isolated in reasonable yields (entries 1–2, 8–11), except in the case of coupling of triflate **4d** with organoindium **8c** (only 46% conversion, entry 9). Homocoupling reaction was not detected on these substrates in contrast to **2b**.

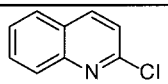
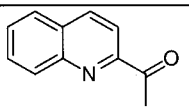
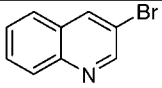
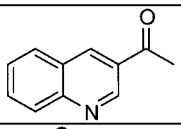
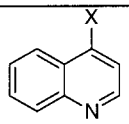
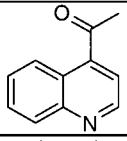
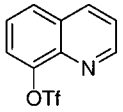
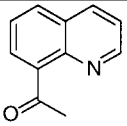
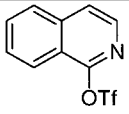
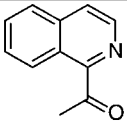
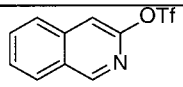
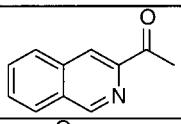
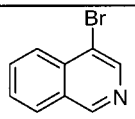
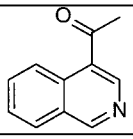
2.4. Heck reactions

The regioselectivity of the palladium-catalyzed arylation of *n*-butyl vinyl ether **8d** is affected by many factors.[33] Hence **8d** could be regarded as an acyl anion or an acetaldehyde enolate synthetic equivalent, after hydrolysis of the α- or the β-arylation product, respectively (Scheme 5). The coupling of 3-bromoquinoline **2b** as well as some 3-bromopyridines with **8d** was recently described,[34] afforded a mixture of the α-, (*E*) β- and (*Z*) β-arylation products in which the formed was predominant.

Cabri and coworkers developed conditions for exclusive α-arylation of acyclic enol ethers.[21] For aryl triflates, a bidentate phosphine (and especially 1,3-bis(diphenylphosphino)propane dppp) was the ligand of choice for palladium in combination with triethylamine as added stoichiometric base for regenerating the Pd(0) catalyst from the HPd(II)X species. However, in the case of aryl halides, substitution of Et_3N by a silver(I) or thallium(I) salt was necessary for a good catalytic activity and a total α-regioselectivity. We initially applied both sets of conditions on quinolyl and isoquinolyl substrates, with some modifications after optimisation (vide infra) and the results are presented in Table 4. All reactions were conducted on 1 mmol of substrate.

The described procedure for α-arylation of **8d** (conditions B) was unsatisfactory for some substrates, for example **2b** (entry 3). If the product of β-arylation was not detected after reaction, only a poor yield of **2a** (36%) was obtained. A much better yield resulted from the replacement of $Pd(OAc)_2$ for $Pd(dba)_2$ as catalyst precursor and the conditions A were successfully applied to halide substrates **1c**, **2b** and **7b** (entries 1, 2 and 10). However, 4-chloroquinoline **3c** was recovered unchanged under these conditions (entry 4). Presently, we have no explanation for the inertness of **3c**, but the oxidative addition of Pd(0) could not be the reason since this substrate was not reluctant to the Stille reaction.

Table 4. Heck coupling reactions

Entry	Substrate		Reaction conditions [a]	t (h)	T(°C)	Product	Isolated Yield (%)
1	**1c**		A	24	80	**1a** 	68
2	**2b**		A	24	80	**2a** 	81
3			B	24	80		36
4	**3c**		X = Cl	A	24	80	**3a** 	0
5	**3d**		X = OTf	C	24	100		36
6	**4d**			D	24	80	**4a** 	68
7	**5d**			C	24	100	**5a** 	64
8	**6d**			D	24	80	**6a** 	72
9				E	48	80		75
10	**7b**			A	48	80	**7a** 	69

[a] Conditions A: 5 mol% $Pd(dba)_2$, 5.5 mol% dppp, 1.1 equiv. TlOAc, DMF. Conditions B: id. A, $Pd(OAc)_2$ instead $Pd(dba)_2$. Conditions C: 5 mol% $Pd(dba)_2$, 5.5 mol% dppp, 3 equiv. Et_3N, dioxane. Conditions D: id. C, DMF instead dioxane. Conditions E: id. D, $Pd(OAc)_2$ instead $Pd(dba)_2$; an equal amount of catalyst was added after 24 h reaction.

With triflate derivatives, use of DMF as solvent (conditions D) was possible only for **4d** (entry 6) and **6d** (entry 8). Here again, $Pd(dba)_2$ was superior to $Pd(OAc)_2$ since the latter gave only a partial conversion after 24 h of reaction (entry 9). Applying conditions D to triflates **3d** and **5d** did not give methyl ketones **3a** and **5a** but led only to substrate decomposition (results not shown). This behaviour could be attributed at least partially to the presence of DMF: switching the solvent to dioxane (conditions C) restored the course of the reaction (entries 5 and 7). The yield was modest in the case of **3d** (36%), but it should be noticed that approximatively the same yield of **3a** resulted from the Stille reaction on the same substrate (32%).

If we compare the results of Tables 1 and 4, the Heck method gave comparable or superior yields of acetylquinolines and acetylisoquinolines, excepted for 4-acetylquinoline **3a** from chloride **3c**. Moreover, it was not necessary to prepare the coupling partner in this case, since *n*-butyl vinyl ether **8d** is a commercially available product. The Stille reaction suffers also from the toxicity of tin-containing compounds. So, although the use of toxic heavy metals was not completly avoided (presence of thallium acetate for halide substrates), the Heck reaction was prefered for reactions on a preparative scale, especially from triflates.

3. Conclusion

In summary, various acetylquinolines (2-, 3-, 4-, 8-acetyl) and acetylisoquinolines (1-, 3-, 4-acetyl) have been synthesized from easily available substrates through palladium-catalyzed reactions: Stille couplings between the corresponding chloro-, bromo- or trifluoromethylsulfonyloxy-substituted substrates and (1-ethoxyvinyl)tri(*n*-butyl)stannane, or Heck reactions involving *n*-butyl vinyl ether as a partner. Comparison of these two methods indicates that in many cases the second method was higher yielding. In addition, it could avoid the use of tin reagent and is particularly advantageous on triflates since the presence of thallium salt is not required.

The Stille procedure was carried out onto some dichloroheteroaromatic substrates and proved to be regioselective affording a monoacetyl product.

Organozinc and organoindium reagents were as efficient

in cross-coupling although some homocoupling of the substrate was observed.

4. Experimental

4.1. General

^1H and ^{13}C NMR were recorded on a Bruker AC-250 MHz spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard.

All reactions involving palladium catalysis were carried out using Schlenk techniques under an argon atmosphere. Tetrahydrofuran (THF) was distilled under argon from sodium benzophenone ketyl immediatly before use. Dioxane, toluene and *N*,*N*-dimethylformamide (DMF) were dried over CaH_2 and distilled prior to use.

$Pd(dba)_2$ (dba denotes dibenzylideneacetone) was prepared according to a reported procedure.[35] The following materials were obtained from commercial sources and used as purchased: $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, 2-chloroquinoline **1c**, 3-bromoquinoline **2b**, 4-chloroquinoline **3c**, 4-hydroxyquinoline **3d′**, 8-hydroxyquinoline **4d′**, 1-hydroxyisoquinoline **5d′**, 3-hydroxyisoquinoline **6d′**, 4-bromoisoquinoline **7b**, 4,7-dichloroquinoline **9**, 1,3-dichloroisoquinoline **11**. 2,4-Dichloroquinoline **10**,[36] (1-ethoxyvinyl)tri(*n*-butyl)stannane **8a**,[25] and triflates **3d**–**6d**[23] were prepared as reported in the literature.

4.1.1. Palladium-catalyzed Stille cross-coupling reactions with (1-ethoxyvinyl)tri(*n*-butyl)stannane 8a. A typical procedure for heteroaryl halides is as follows (Table 1, entry 2): a toluene (3 mL) solution of $Pd(dba)_2$ (23 mg, 0.04 mmol), PPh_3 (21 mg, 0.08 mmol) and 2-bromoquinoline **2b** (208 mg, 1 mmol) was stirred at room temperature under argon for 0.25 h. (1-Ethoxyvinyl)tri(*n*-butyl)stannane **8a** (363 mg, 1 mmol) in toluene (2 mL) was added and the resulting reaction mixture was stirred at 110°C for 1 h, cooled to room temperature, then 10 mL of 1 M HCl were added. After 24 h stirring, the reaction mixture was neutralized with 1 M NaOH and extracted with 3×10 mL of diethyl ether. The combined ethereal phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (silica, heptane/ethyl acetate 8:2) to give **2a** (150 mg, 0.88 mmol, 88%).

The procedure for heteroaryltriflates was modified as follows: LiCl (127 mg, 3 mmol) was added to the catalyst — substrate solution and dioxane was substituted for toluene.

Spectral data of compounds **1a**–**3a**,[16] **5a**–**7a**,[16] and **13**[37] were in satisfactory agreement with the reported values.

4.1.2. 8-Acetylquinoline 4a. Mp 42°C (lit:[8] 42–43.5°C). IR (KBr) ν_{max}: 1683 cm^{-1}. ^1H NMR: 2.92 (3H, s), 7.44 (1H, dd, *J*=8 and 4 Hz), 7.56 (1H, t, *J*=8 Hz), 7.90–7.94 (2H, m), 8.18 (1H, dd, *J*=8 and 2 Hz), 8.96 (1H, dd, *J*=4 and 2 Hz). ^{13}C NMR 32.6, 121.3, 125.9, 128.2, 129.1, 131.2, 136.2, 139.5, 145.4, 150.3, 203.8. HRMS calculated for $C_{11}H_9NO$: 171.068420. Found: 171.0690.

4.1.3. 4-Acetyl-7-chloroquinoline 12. Mp 75–76°C. IR (KBr) ν_{max}: 1690 cm^{-1}. ^1H NMR: 2.74 (3H, s), 7.57 (1H, dd, *J*=9 and 2 Hz), 7.63 (1H, d, *J*=4 Hz), 8.13 (1H, d, *J*=2 Hz), 8.47 (1H, d, *J*=9 Hz), 9.03 (1H, d, *J*=4 Hz). ^{13}C NMR: 29.8, 120.2, 122.1, 127.1, 128.8, 129.3, 136.0, 142.1, 149.7, 150.0, 200.6. HRMS calculated for $C_{11}H_8ClNO$: 205.029442. Found: 205.0290.

4.1.4. 1-Acetyl-3-chloroisoquinoline 14. Mp 83–85°C. IR (KBr) ν_{max}: 1690 cm^{-1}. ^1H NMR 2.83 (3H, s), 7.64–7.77 (3H, m), 7.86 (1H, s), 8.92 (1H, dd, *J*=8 and 1.5 Hz). ^{13}C NMR 28.4, 124.1, 124.6, 126.3, 127.2, 129.5, 131.3, 139.5, 143.7, 152.7, 201.1. HRMS calculated for $C_{11}H_8ClNO$: 205.029442. Found: 205.0295.

4.1.5. Palladium-catalyzed Negishi cross-coupling reaction with 1-ethoxyvinylzinc chloride 8b. A typical procedure is as follows (Table 4, entry 4): a 3 mL solution of ethyl vinyl ether (0.3 mL, 3 mmol) in THF was cooled to −78°C under argon and 1.3 mL of a 1.5 M commercial solution of *t*-butyllithium in pentane (2 mmol) was added dropwise. The reaction mixture was warmed to 0°C, stirred for 1 h, then cooled back to −78°C and a 3 mL solution of anhydrous zinc dichloride (272 mg, 2 mmol) in THF was added. The resulting mixture was warmed to room temperature and stirred for 0.5 h.

A THF (3 mL) solution of $Pd(dba)_2$ (23 mg, 0.04 mmol), PPh_3 (21 mg, 0.08 mmol), 2-bromoquinoline **2b** (208 mg, 1 mmol) was stirred at room temperature under argon for 0.25 h and then added to the previously prepared organozinc **8b** solution. The resulting reaction mixture was stirred at 70°C for 48 h, cooled to room temperature, then 10 mL of 1 M HCl were added. After 24 h stirring, the reaction mixture was neutralized with 1 M NaOH and extracted with 3×10 mL of diethyl ether. The combined ethereal phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (silica, heptane/ethyl acetate 8:2) to give 2a (111 mg, 0.65 mmol, 65%).

4.1.6. Palladium-catalyzed cross-coupling with tri(1-ethoxyvinyl)indium 8c. A typical procedure is as follows (Table 4, entry 7): a 3 mL solution of ethyl vinyl ether (0.3 mL, 3 mmol) in THF was cooled to −78°C under argon and 1.3 mL of a 1.5 M commercial solution of *t*-butyllithium in pentane (2 mmol) was added dropwise. The reaction mixture was warmed to 0°C, stirred for 1 h, then cooled back to −78°C and a 3 mL solution of anhydrous indium trichloride (160 mg, 0.7 mmol) in THF was added. The resulting mixture was warmed to room temperature and stirred for 0.5 h.

A THF (3 mL) solution of $Pd(dba)_2$ (23 mg, 0.04 mmol), PPh_3 (21 mg, 0.08 mmol), 2-bromoquinoline **2b** (208 mg, 1 mmol) was stirred at room temperature under argon for 0.25 h and then added to the previously prepared organoindium **8c** solution. The resulting reaction mixture was stirred at 70°C for 48 h, cooled to room temperature, then 10 mL of 1 M HCl were added. After 24 h stirring, the reaction mixture was neutralized with 1 M NaOH and extracted with 3×10 mL of diethyl ether. The combined ethereal phases were dried ($MgSO_4$) and concentrated. The crude

product was purified by flash chromatography (silica, heptane/ethyl acetate 8:2) to give **2a** (96 mg, 0.56 mmol, 56%).

4.1.7. Palladium-catalyzed Heck reactions with *n*-butyl vinyl ether 8d. A typical procedure for heteroaryl halides is as follows (Table 3, entry 2): a DMF (3 mL) solution of $Pd(dba)_2$ (29 mg, 0.05 mmol), dppp (23 mg, 0.055 mmol), 2-bromoquinoline **2b** (208 mg, 1 mmol) and TlOAc (288 mg, 1.1 mmol) was stirred at room temperature under argon for 0.25 h. *n*-Butyl vinyl ether **8d** (500 mg, 5 mmol) in DMF (2 mL) was added and the resulting reaction mixture was stirred at 80°C for 24 h, cooled to room temperature, then 10 mL of 1 M HCl were added. After 24 h stirring, the reaction mixture was neutralized with 1 M NaOH and extracted with 3×10 mL of diethyl ether. The combined ethereal phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (silica, heptane/ethyl acetate 8:2) to give **2a** (139 mg, 0.81 mmol, 81%).

The procedure for heteroaryltriflates was modified as follows: Et_3N (300 mg, 3 mmol) was substituted for TlOAc and (eventually, see Table 3) dioxane was substituted for DMF.

References

1. Legros, J. Y.; Fiaud, J. C. *Tetrahedron Lett.* **1992**, *33*, 2509–2512.
2. Legros, J. Y.; Toffano, M.; Fiaud, J. C. *Tetrahedron* **1995**, *51*, 3235–3246.
3. Legros, J. Y.; Toffano, M.; Fiaud, J. C. *Tetrahedron: Asymmetry* **1995**, *6*, 1899–1902.
4. Toffano, M.; Legros, J. Y.; Fiaud, J. C. *Tetrahedron Lett.* **1997**, *38*, 77–80.
5. Boutros, A.; Legros, J. Y.; Fiaud, J. C. *Tetrahedron Lett.* **1999**, *40*, 7329–7332.
6. Boutros, A.; Legros, J. Y.; Fiaud, J. C. *Tetrahedron* **2000**, *56*, 2239–2246.
7. Legros, J. Y.; Primault, G.; Toffano, M.; Rivière, M. A.; Fiaud, J. C. *Org. Lett.* **2000**, *2*, 433–436.
8. Taylor, R. *J. Chem. Soc. B* **1971**, 2382–2387.
9. Kaufmann, A.; Peyer, H.; Kunkler, M. *Chem. Ber.* **1912**, *45*, 3090–3098.
10. Kaufmann, A.; Dändliker, P. *Chem. Ber.* **1913**, *46*, 2929–2935.
11. Padbury, J. J.; Lindwall, H. G. *J. Am. Chem. Soc.* **1945**, *67*, 1268–1270.
12. Crowne, F. R.; Breckenridge, J. G. *Can. J. Chem.* **1954**, *32*, 641–645.
13. Jones, R. G.; Soper, Q. F.; Behrens, O. K.; Corse, J. W. *J. Am. Chem. Soc.* **1948**, *70*, 2843–2848.
14. Yamamoto, Y.; Yanagi, A. *Chem. Pharm. Bull.* **1982**, *30*, 2003–2010.
15. Sakamoto, T.; Shiraiwa, M.; Kondo, Y.; Yamanaka, H. *Synthesis* **1983**, 312–314.
16. Sakamoto, T.; Kondo, Y.; Shiraiwa, M.; Yamanaka, H. *Synthesis* **1984**, 245–247.
17. Kosugi, M.; Sumiya, T.; Obara, Y.; Suzuki, M.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 767–768.
18. Kwon, H. B.; McKee, B. H.; Stille, J. K. *J. Org. Chem.* **1990**, *55*, 3114–3118.
19. Russell, C. E.; Hegedus, L. S. *J. Am. Chem. Soc.* **1983**, *105*, 943–949.
20. Negishi, E.; Luo, F. T. *J. Org. Chem.* **1983**, *48*, 1560–1562.
21. Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi, R. *J. Org. Chem.* **1992**, *57*, 1481–1486.
22. Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1992**, *57*, 3558–3563.
23. Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478–5486.
24. Crisp, G. T.; Papadopoulos, S. *Aust. J. Chem.* **1989**, *42*, 279–285.
25. Soderquist, J. A.; Hsu, G. J. H. *Organometallics* **1982**, *1*, 830–833.
26. Kitahara, Y.; Nagatsu, M.; Shibano, Y.; Kubo, A. *Chem. Pharm. Bull.* **1997**, *45*, 1697–1701.
27. Ali, N. M.; McKillop, A.; Mitchell, M. B.; Rebelo, R. A.; Wallbank, P. J. *Tetrahedron* **1992**, *48*, 8117–8126.
28. Dubé, D.; Blouin, M.; Brideau, C.; Chan, C. C.; Desmarais, S.; Ethier, D.; Falgueyret, J. P.; Friesen, R. W.; Girard, M.; Girard, Y.; Guay, J.; Riendeau, D.; Tagari, P.; Young, R. N. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1255–1260.
29. Shiota, T.; Yamamori, T. *J. Org. Chem.* **1999**, *64*, 453–457.
30. Ford, A.; Sinn, E.; Woodward, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 927–934.
31. Pérez, I.; Pérez Sestelo, J.; Sarandeses, L. A. *Org. Lett.* **1999**, *1*, 1267–1269.
32. Smith III, A. B.; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Duan, J. W.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Spoors, P. G.; Salvatore, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 10478–10486.
33. Daves Jr, G. D.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433–1445.
34. Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Heterocycl. Chem.* **1998**, *35*, 719–723.
35. Rettig, M. F.; Maitlis, P. M. *Inorg. Synth.* **1977**, *17*, 134–137.
36. Osborne, A. G.; Buley, J. M.; Clarke, H.; Dakin, R. C. H.; Price, P. I. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2747–2754.
37. Sashida, H.; Kaname, M.; Tsuchiya, T. *Chem. Pharm. Bull.* **1990**, *38*, 2919–2925.