Heck Reactions of Quinoline-Derived Nonaflates

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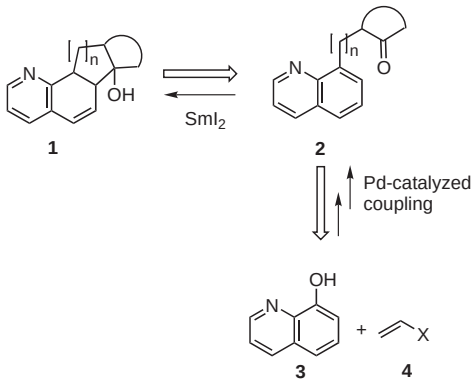
Dedicated to Professor Richard Heck

Abstract: An efficient synthesis of a series of quinolyl-substituted ketones or ketone precursors via the Heck reaction of 6- or 8-quinolyl nonaflates with an appropriate selection of olefins is presented. These ketones are useful building blocks for the diastereoselective construction of azapolycycles via SmI_2-induced intramolecular cyclization of (het)aryl-substituted ketones.

Key words: Heck coupling, Pd catalysis, nonaflate, samarium(II) iodide, quinoline

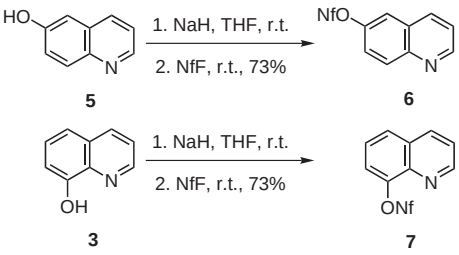
In continuation of our program focused on the synthesis of polycycles with steroid-like frameworks via SmI_2-induced cyclization of (het)aryl-substituted ketones,[1] we aimed at the construction of dihydroquinoline-containing tri- and tetracycles from quinolyl-substituted ketones. Azasteroids are receiving much attention,[2] due to the presence of the nitrogen atom which confers interesting biological properties. In order to achieve efficiently the synthesis of these azapolycyclic frameworks **1** (Scheme 1) a short and reliable synthesis of ketones **2** – used as substrate for the SmI_2-induced reductive coupling – was required. Suitable starting materials for precursors **2** should be quinoline derivative **3** and olefins **4**.



Scheme 1 Retrosynthetic analysis for the synthesis of azasteroids **1** via quinolyl-substituted ketones **2**.

As a method of choice, we decided to investigate the palladium-catalyzed arylation (Heck reaction)[3] of a series of selected olefins. This powerful carbon–carbon bond-forming process has the advantage of employing stable, low cost and less toxic olefins compared to the other cross-coupling reactions (Stille, Suzuki, Kumada, Negishi reactions) and therefore, explains for its exceptional utility.

Among possible quinolines, 6-hydroxyquinoline (**5**) and 8-hydroxyquinoline (**3**) have been selected because of their low cost, high stability and commercial availability. These compounds are readily transformed into the corresponding aryl nonaflates (nonafluorobutanesulfonates) **6** and **7**[4] (Scheme 2) by treating the sodium salt of the hydroxy quinolines with nonafluorobutanesulfonyl fluoride (2 equiv) in dry THF. Although not yet widely explored in cross-coupling reactions,[5] aryl nonaflates show similar reactivities compared to the corresponding triflates,[5f] but with the advantage of being rather stable and easily purifiable by crystallization or column chromatography. They can be smoothly prepared[6] using the commercially available, non-toxic and cost-effective nonafluorobutanesulfonyl fluoride.



Scheme 2 Synthesis of quinolyl nonaflates **6** and **7**.

With **6** and **7** in hand, the next step was to investigate and optimize the Heck reactions of these substrates. When electron-deficient olefins such as methyl acrylate **8** or methyl vinyl ketone **9** were employed in the presence of LiCl, triethylamine and 5 mol% of $Pd(OAc)_2$ in DMF, the couplings proceeded smoothly affording products **10** and **11** as single isomers in excellent yields (Scheme 3).

These encouraging results prompted us to test more challenging homoallylic alcohols (Table 1), in which the olefin moiety is not activated by an electron-withdrawing group. We expected that, under the coupling conditions, migration of the double bond would occur, leading (ultimately upon final work-up) to the desired quinolyl-substituted ketones.[7] With this goal in mind, nonaflate **7** and the acyclic homoallylic alcohol **12** were subjected to the conditions reported above. However, rather disappointingly, the reaction failed to afford any coupling

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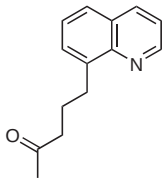
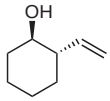
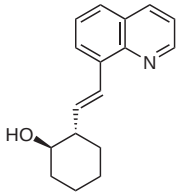
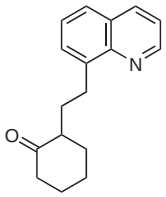
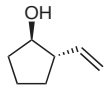
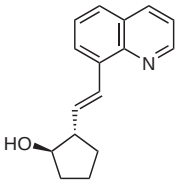
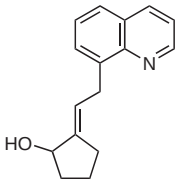
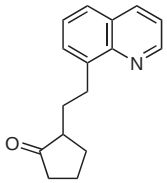
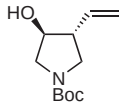
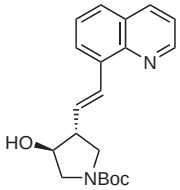
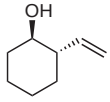
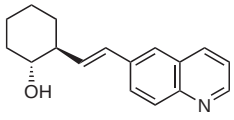
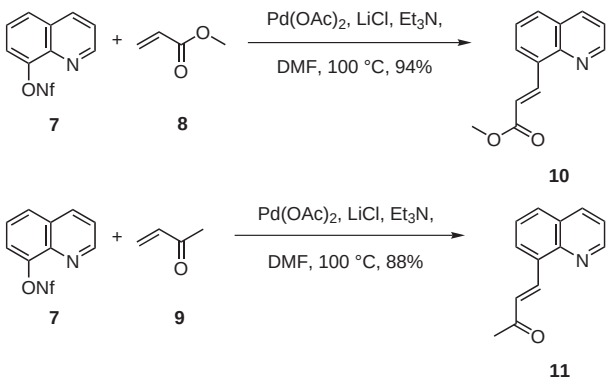
Table 1 Heck Reactions of the Quinolyl Nonaflates (QO-NF) **7** and **6** with Different Homoallylic Alcohols[a]

Entry	QO-Nf	Olefin (3–4 equiv)	Product		Yield (%)
1	**7**	 **12**	 **13**		30
2	**7**	 **14**	 **15**	 **16**	**15**: 75 **16**: 8
3	**7**	 **17**	 **18**	 **19**	**18** + **19**: 69
			 **20**		**20**: 8
4	**7**	 **21**	 **22**		89
5	**6**	 **14**	 **23**		95

[a] Conditions: DMF, $NaHCO_3$ (3–4 equiv), $BnEt_3N^+Cl^-$ (1.2–2 equiv), 6–20 mol% $Pd(OAc)_2$, 90 °C, 48 h.[7b]

product. Switching to modified Jeffery conditions[7b,8] and prolonging the reaction time, succeeded in delivering the desired ketone **13**, albeit in moderate 30% yield (entry 1).

The coupling of cyclic homoallylic alcohols **14** and **17** with nonaflate **7** under these optimized conditions, provided a mixture of allylic and homoallylic alcohols, as well as the corresponding ketones in good overall yields (entries 2,3). Formation of a mixture of products in the case of secondary allylic or homoallylic alcohols is due to poor regioselectivity in the β-hydride elimination step and similar results have already been reported by other authors.[9] However, in our case, the fact that a mixture of products was obtained did not represent a real problem, since the desired ketones were always easily separable by column chromatography from the alcohols. The two

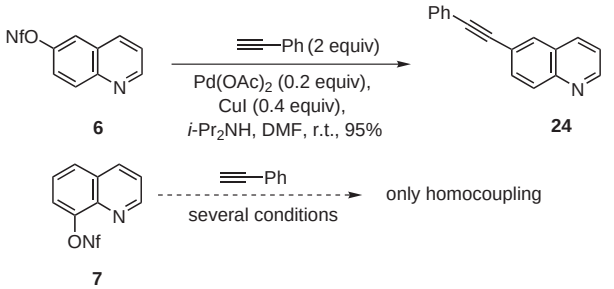


Scheme 3 Heck reactions leading to quinoline derivatives **10** and **11**.

regioisomeric alcohols were not separated, but conveniently converted into the corresponding ketones in a two-step procedure (as an example see Scheme 5). In the case of cyclic homoallylic alcohols, it is also plausible to assume that the presence of the cyclic framework may hinder the formation of the *syn*,*syn* conformation required in the β-hydride elimination step, which would lead to the double-bond isomerization. Such hypothesis might explain the very low yield obtained for ketones **16** and **20** and the complete lack of isomerization when olefin **21** was used. However, in this latter case, the yield of the coupled alcohol **22** was excellent.[10]

A very pleasing result was also obtained for the coupling of 6-quinolyl nonaflate **6** with alcohol **14** (entry 5). The reaction only afforded the homoallylic alcohol **23** in 95% yield.

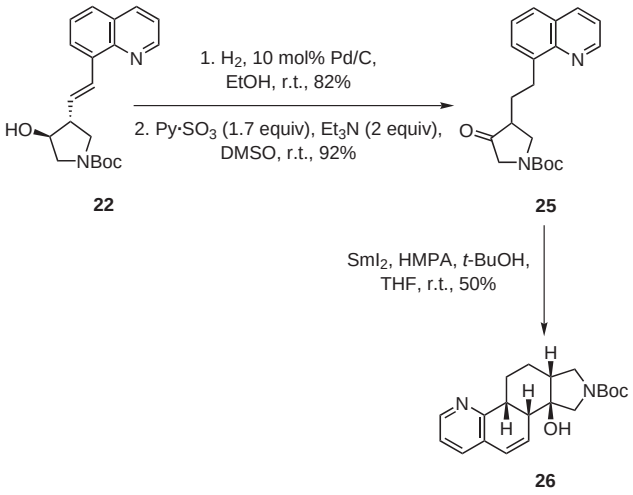
Led by the curiosity to establish whether these quinolyl nonaflates would also be good coupling substrates in other typical Pd-catalyzed cross-couplings such as the Sonogashira reaction, we treated **6** and **7** in the presence of phenylacetylene under several coupling conditions (Scheme 4). With great surprise, we observed that while nonaflate **6** afforded the expected coupling product **24** in excellent 95% yield, nonaflate **7** constantly failed to provide the expected disubstituted alkyne, affording instead only the homocoupled acetylene and unreacted starting material **7**. A plausible explanation to elucidate this result is that the oxidative insertion of Pd(0) would lead to a rather inert intermediate, in which the metal is strongly



Scheme 4 Attempted Sonogashira couplings of nonaflates **6** and **7** with phenylacetylene.

chelated to the nearby nitrogen and therefore, preventing the next step of the catalytic cycle.[11] On the contrary, in the case of the 6-substituted quinoline derivative **6** the nitrogen cannot interfere and the coupling reaction proceeds as expected. Complete lack of reactivity of nonaflate **7** was also observed when a Suzuki–Miyaura coupling was tried using an alkenyl boronic acid in the presence of $PdCl_2$, dppf, $BnEt_3NBr$ and K_3PO_4 as the base.[12]

With the range of alcohols and ketones obtained in a reliable and efficient fashion from Heck reactions, the synthesis of the desired aza-containing polycyclic skeletons was only few steps away. An example of the results obtained so far is described in Scheme 5. In the case of compound **22**, hydrogenation of the double bond in the presence of Pd/C in EtOH, followed by oxidation of the alcohol moiety by $Py{\cdot}SO_3$ in DMSO afforded the desired ketone **25** in 75% yield for the two steps. Precursor **25** was then subjected to the SmI_2-induced coupling reaction previously developed in our group.[1,13] Under standard conditions, ketone **25** furnished the expected cyclized product **26** in 50% yield as a single diastereomer. The relative configuration of this tetracyclic diazasteroid derivative **26** was confirmed by NOESY NMR analysis.



Scheme 5 Synthesis of diazasteroid derivative **26** from homoallylic alcohol **22** via SmI_2-induced cyclization of ketone **25**.

In conclusion, the use of quinolyl nonaflates as aryl components in Heck reactions proved to be an efficient, reliable and cost-effective method for the synthesis of a wide range of quinolyl-substituted homoallylic alcohols and ketones. Such compounds have found application in the diastereoselective synthesis of complex azapolycyclic skeletons, which resemble steroid structures with unnatural *cis*,*cis*-junction of rings B–C–D.

Acknowledgment

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(10) **Typical Procedure for the Heck Reaction of 7 and 21 Leading to 22.**
A high-pressure tube was loaded with $NaHCO_3$ (0.285 g, 3.40 mmol), triethylbenzylammonium chloride (0.389 g, 1.71 mmol), quinolin-8-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (**7**, 0.362 g, 0.85 mmol), $Pd(OAc)_2$ (39 mg, 0.17 mmol) and DMF (3 mL). The suspension was stirred at r.t. under argon for 10 min, then a solution of *rac*-*tert*-butyl (3*S*,4*R*)-3-hydroxy-4-vinylpyrrolidine-1-carboxylate (**21**, 0.729 g, 3.42 mmol) in DMF (1 mL) was added, the vessel was sealed and heated to 90 °C for 48 h. The vessel was then cooled to r.t., distilled H_2O was added and the phases were separated. The product was extracted in CH_2Cl_2 (3 × 5 mL), the combined organic layers were washed with brine (2 × 5 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure to leave the crude product, which was purified by column chromatography on silica gel (eluent: hexane–EtOAc from 4:1 to 1:1) to afford *tert*-butyl 3-hydroxy-4-[(*E*)-2-quinolin-8-ylvinyl]pyrrolidine-1-carboxylate (**22**) as a colorless oil (0.259 g, 89% yield). Two distinct rotamers were visible from NMR analysis at r.t. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, *t*-Bu), 3.01–3.07 (m, 1 H, 4-H), 3.30–3.36 (m, 2 H, 2-H, 5-H), 3.54 (br d, ^3J = 16.2 Hz, 1 H, OH), 3.72–3.80 (m, 2 H, 2-H, 5-H), 4.24–4.26 (m, 1 H, 3-H), 6.23 (m_c, 1 H, 1′-H), 7.37 (m_c, 1 H, Ar–H), 7.45–7.48 (m, 1 H, Ar–H), 7.67–7.70 (m, 1 H, Ar–H), 7.73–7.77 (m, 2 H, 2′-H, Ar-H), 8.10 (d, ^3J = 7.7 Hz, 1 H, Ar-H), 8.92 (m, 1 H, Ar-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 28.5 (q, *t*-Bu), 49.6, 49.8 (2 t, C-5), 50.3, 50.6 (2 d, C-4), 52.0, 52.2 (2 t, C-2), 70.4, 70.5 (2 d, C-3), 79.4 (s, *t*-Bu), 121.2 (d, C–Ar), 125.9 (s, C–Ar), 126.5 (d, C-2′), 127.4, 128.4 (2 d, C–Ar), 128.6 (s, C–Ar), 130.2, 135.4, 136.4 (3 d, C–Ar), 145.1 (s, C–Ar), 149.5 (d, C-1′), 154.6 (s, CO) ppm. IR (KBr): ν = 3380–3200 (OH), 3050–3005, 2970, 2940, 2880 (=CH, C–H), 1695 (C=O) cm^{-1}. MS (EI, 80 eV, 160 °C): *m/z* (%) = 340 (16) $[M]^+$, 283 (8) $[M - C_4H_9]^+$, 239 (8) $[M - C_5H_9O_2]^+$, 154 (46) $[M - C_8H_{15}O]^+$, 57 (100) $[C_4H_9]^+$. HRMS (80 eV, 160 °C): *m/z* calcd for $C_{20}H_{24}N_2O_3$: 340.17868; found: 340.17944.

(11) Formation of a stable dimeric complex would also be plausible.

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