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# Favoring alkene insertion over β-hydride elimination: aqueous media and ligands enable a double Heck reaction on a substrate for which β-hydride elimination is possible

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**Abstract**

Under $Pd^0$ catalysis, the (iodoaryl)diene *N*-methyl-*N*-(1,5-hexadiene-3-yl)-2-iodobenzoic acid amide (**6**) would normally be expected to give monocyclized product from initial oxidative addition of the C–I bond, followed by insertion of one alkene function and β-hydride elimination. Conditions were sought to favor insertion of the second alkene unit over β-hydride elimination, so as to increase the yield of polycyclic products. In fact, the use of phenanthroline ligand and aqueous media in reactions of **6** increased the total yield of expected tricyclic products (**11–13**) to 52%. Three other products (**14–16**) appear to be derived from an unusual rearrangement. By a process of elimination, control experiments point to the possibility of a chelation-assisted Pd-catalyzed Cope rearrangement in the formation of these unexpected products.

*Keywords:* Aqueous organometallic chemistry; Cyclization; Selectivity; β-hydride elimination

Pioneering work by Beletskaya [1], followed by that of others [2–7], has shown that intermolecular Heck reactions [8] proceed readily under aqueous conditions. Beneficial effects of water added to Heck and related organopalladium reactions have been noted at various times [1–9], but such improvements have been in the rate of reaction rather than in significant changes in chemo- or stereoselectivity. The synthetic importance of the Heck reaction has increased in recent years as intramolecular variants [6,8,10] have been developed to produce complex polycyclic structures, as schematically illustrated by conversion of **A** to **D** (Scheme 1).

However, the successful formation of more than one ring in intramolecular Heck reactions of **A** has depended on substrate *structure* to prevent β-hydride elimination from intermediate(s) (e.g., **B**, $R \neq H$). Scattered exceptions to our knowledge are limited to a single Heck reaction [11] and two other related cyclizations of σ-alkyl-$Pd^{II}$ intermediates [12,13]. For **B** in which $R = H$, however, we wondered if aqueous media would favor further alkene coordination and/or insertion over β-hydride elimination in **B**, either because the alkene-bearing chain in an extended conformation would be poorly solvated by water (hydrophobic effect [14,15]) or because water would help to ionize the Pd–*X* bond. As to the latter point, we note the use of $Ag^I$ salts to speed reactions and

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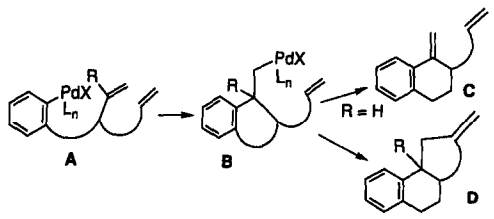



Scheme 1.

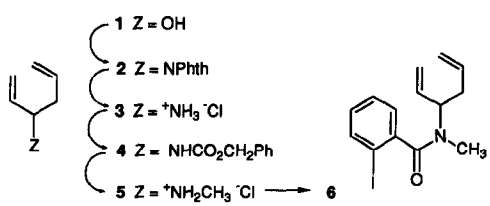
reduce alkene isomerizations [16]. Preliminary experiments reported here show the dramatic influences of solvent and ligands in the cyclization of **6**, a precursor to isoquinolone ring systems.

In order to prepare **6**, the alcohol function in 1,5-hexadien-2-ol **1** [17] was converted to an ammonium group in **3** by the Mitsunobu reaction with phthalimide in an $S_N2$ sense [18], giving **2**, followed by hydrazinolysis and salt formation. Introduction of the *N*-methyl substituent, deemed wise based on earlier difficulties with cyclizations of secondary amides [16], was achieved by carbamate formation (**4**) and subsequent reduction to the amine **5**. Finally, acylation provided cyclization substrate **6** (Scheme 2).

Initial evidence (Table 1) shows that solvent and ligands profoundly influence the cyclization of **6**. Cyclizations were performed at the same initial concentration of **6** (0.02 M), using 0.1 eq. $Pd(OAc)_2$ precatalyst (0.2 eq. for slower cases) and 2.5 eq. $K_2CO_3$ base; yields are unoptimized but are intended to provide comparative data. Based on literature precedents, **6** was expected to give **7** after insertion of the nearest alkene function. β-Hydride elimination from **7** would give **8**, whereas insertion of the remaining alkene and β-hydride elimination would give **11**. Isomerization of alkene functions [8,16] by addition and elimination of Pd–H species might be anticipated to produce **9** and **10** (from **8**) and **12** and **13** (from **11**). In fact, in acetonitrile (entry 1) **9** and small amounts of **12** were formed; this product distribution was not significantly altered by inclusion of $PPh_3$ and phase-transfer catalyst $Bu_4NBr$ (entry 2). Surprisingly, however, **14** and **16**, whose origins are discussed below, were major products in both entries. The connectivity of atoms in tricyclic products was elucidated by a combination of $^1H$-, COSY-, and NOESY-NMR experiments.

The effect of solvent on cyclizations of **6** was then investigated. Whereas **6** is not appreciably soluble in pure water, it dissolves in EtOH–$H_2O$ (1:1) at 0.02 M. Entries 3 and 4 show that the water solubility of the phosphine is of little significance, though with $PPh_3$ the switch to EtOH–$H_2O$ led to **14** as major product. The chelating diphosphine 1,3-bis(diphenylphosphino)propane (dppp) [19] did not improve selectivity (entry 5). Although phosphines may stabilize zero-valent Pd against precipitation, such large ligands $L_n$ in putative intermediate **7** might hinder approach of the alkene unit. When phosphine was omitted entirely (entry 6), the total yield of **12** and **13** rose to match that of **9**, apparently at the expense of **14–16**. Surprisingly, by comparing entries 6 and 7 it can be seen that the large $Bu_4N^+$ cation did not have an effect on either reaction rate [3] or the product distribution (no salting-in effect [14]). The advantage of EtOH–$H_2O$ over $CH_3CN$–$H_2O$ can be seen by comparing entries 6 and 8.

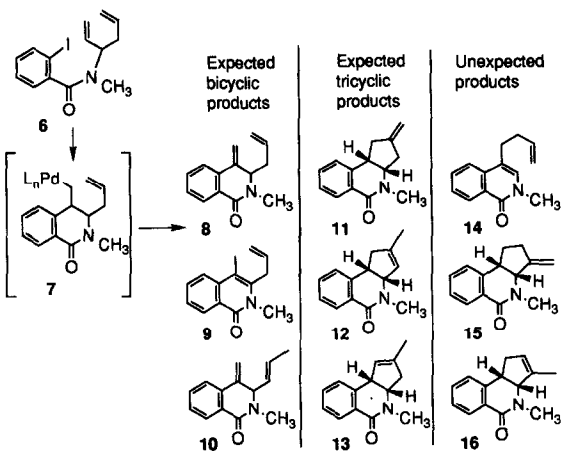
However, the most striking observation to date (entry 9) is that 1,10-phenanthroline [20] as ligand completely suppresses the formation of **8–10**, raising the total yield of **11–13** to 52%. The benefits of phenanthroline are entirely absent in $CH_3CN$ (entry 12), 73% of **6** being recovered after five times the reaction period in entry 9. The presence of methyl substituents adjacent to phenanthroline *N* (entry 11) is apparently deleterious. Though it is admittedly speculative at this point, as suggested in the




Scheme 2.

literature [20], the flat aromatic ligand may facilitate alkene approach to Pd because of reduced steric hindrance, increasing the amount of **11–13** in entry 9. Hydrophobic attraction of heterocycle and alkene may also play a role, as suggested by evidence for hydrophobic attraction of a terpyridine ligand and a hydrophobic residue in a glutathione–$Pt^{II}$ complex in aqueous media [21]. Experiments using phenanthrolines bearing electron-releasing, electron-donating [22,23] and hydrophilic substituents will be necessary to clarify the mechanistic uncertainties surrounding complete suppression of the formation of bicyclic products. Unfortunately, attempts at detailed analysis of reaction mixtures for intermediates by NMR spectroscopy have been unsuccessful. As noted by others [24], hindered, unsymmetrical amides such as **6** exhibit complex NMR spectra with broadened resonances consistent with the presence of several conformers, a problem absent in cyclized products **8–16**.

Table 1
Product distribution from cyclization of **6** under various conditions [a]




| Entry | Solvent(s) | Temp. (°C) | Time (h) | Additive(s) (eq.) | Yield of products [b] (%) | |
|---|---|---|---|---|---|---|
| | | | | | **8, 9, 10** | **11, 12, 13** | **14, 15, 16** |
| 1 | $CH_3CN$ | 80 | 48 | None | 0, 23, 0 | 0, 3, 0 | 17, 0, 32 |
| 2 | $CH_3CN$ | 80 | 24 | $Bu_4NBr$ (1.0), $PPh_3$ (0.2) | 0, 18, 0 | 0, tr, tr | 25, 0, 14 |
| 3 | EtOH–$H_2O$ (1:1) | 60 | 24 | $Bu_4NBr$ (1.0), $PPh_3$ (0.2) | 0, 0, 15 | 0, 0, 0 | 66, 0, 0 |
| 4 | EtOH–$H_2O$ (1:1) | 60 | 24 | $Na^+[3\text{-}(Ph_2Ph)C_6H_4SO_3]^-$ (0.2) | 0, 0, tr | 0, tr, tr | 68, 0, 0 |
| 5 | EtOH–$H_2O$ (1:1) | 60 | 24 | $Bu_4NBr$ (1.0), dppp (0.1) | 0, 9, 0 | 0, 13, 10 | 7, 13, 0 |
| 6 | EtOH–$H_2O$ (1:1) | 60 | 24 | $Bu_4NBr$ (1.0) | 0, 33, 0 | tr, 17, 15 | 3, 0, tr |
| 7 | EtOH–$H_2O$ (1:1) | 60 | 24 | None | 0, 31, 0 | tr, 9, 12 | 3, tr, tr |
| 8 [c] | $CH_3CN$–$H_2O$ (1:1) | 60 | 48 | $Bu_4NBr$ (1.0) | 0, 14, 0 | 0, 25, 14 | 7, 0, 13 |
| 9 [c] | EtOH–$H_2O$ (1:1) | 60 | 48 | $Bu_4NBr$ (1.0), 1,10-phenanthroline (0.2) | 0, 0, 0 | 8, 28, 16 | 0, 15, 0 |
| 10 [c] | EtOH–$H_2O$ (1:1) | 60 | 48 | $Bu_4NBr$ (1.0), 1,10-phenanthroline (0.2) 1,2-dinitrobenzene (1.0) | 0, 0, 0 | 9, 26, 10 | 0, 12, 0 |
| 11 [c] | EtOH–$H_2O$ (1:1) | 60 | 48 | $Bu_4NBr$ (1.0), 2,9-dimethyl-1,10-phenanthroline (0.2) | 0, 13, 0 | 0, 5, 2 | 32, 0, 0 |
| 12 [c,d] | $CH_3CN$ | 60 | 240 | $Bu_4NBr$ (1.0), 1,10-phenanthroline (0.2) | 0, 0, 0 | tr, 0, 0, | 4, 0, 0 |

[a] Unless otherwise specified, all reactions were run under nitrogen with $Pd(OAc)_2$ (0.1 eq.) and $K_2CO_3$ (2.5 eq.), the initial concentration of **6** being 0.02 M.

[b] Yields were determined by appropriate integration of $^1$H-NMR spectra of crude products containing added internal standard. '0' means compound was not detected; 'tr' means compound was detected, but in too small an amount to be determined. Products were separated by HPLC (completely in the case of **10–14**, and partially in the case of **9**, **15**, and **16**) and identified by a combination of HRMS, IR, $^1$H- and $^{13}$C-NMR spectra, and where necessary, NOESY and COSY spectra.

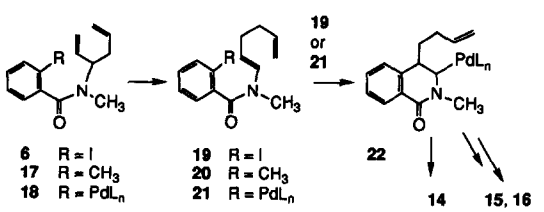
[c] In these cases 0.2 eq. of $Pd(OAc)_2$ was used.

[d] 73% of **1** was recovered.

Several control experiments were performed to clarify the product distributions. Attempted control experiments on **6** involving radical cyclization by atom-transfer were thwarted by decomposition, which in the case of closely related materials has been attributed to facile 1,5-hydrogen atom abstraction and subsequent reactions of the resulting radical [24]. However, as seen from entries 9 and 10, the radical inhibitor 1,2-dinitrobenzene [25–27] had virtually no effect on product distribution, which strongly argues against involvement of radical cyclization [24,28].

Initially, mechanistic considerations guided proposal of the origin of unexpected products **14–16**. Bicyclic isomer **14** may arise from Cope rearrangement of putative intermediate **8**, either thermally or in a Pd-catalyzed process [29]. However, the formation of **15** and **16** can not be explained by this pathway, but could occur in several steps, starting with Cope rearrangement of **6** to give **19**. From isomer **19**, standard single or double Heck reaction could produce **21**, then **22**, and ultimately **14–16** (Scheme 3).

A series of experiments were performed to address these questions. In a control experiment conducted in an NMR tube, iodide **6** was unchanged (NMR, TLC) after heating for 10 days at 60°C in $CD_3OD$–$D_2O$ (1:1) or $CD_3CN$. The sterically similar **17**, incapable of Heck reaction, was unchanged under the conditions of entry 3 or entry 9 in Table 1, as shown by NMR spectroscopic analysis of the mixture and high recovery (87%), suggesting that **6** would also be inert save for its carbon–iodine bond. Moreover, when **6** was subjected to the conditions of entry 3 in the presence of **17**, the spectator diene **17** was recovered unchanged. All results




Scheme 3.

point to the inertness of the 1,5-hexadiene unit to Cope rearrangement, either under the relatively mild heating or the influence of external Pd reagent. It should be noted that 1,5-hexadienes without a substituent at the 2-position (cf. **6**, **17**) appear to be inert to Cope rearrangement under Pd catalysis in organic solvents [29].

Based on all control experiments, by a process of elimination, we suggest that a Pd-catalyzed Cope rearrangement occurs at the stage of putative oxidative addition product **18**, aided by the proximity of the $Pd^{II}$ center to the diene unit. The new diene so formed (**21**) could give observed, unexpected products in either single (**14**) or double (**15**, **16**) Heck processes. The foregoing observations suggest that a wider range of 1,5-dienes may be induced to rearrange by metal-catalyzed Cope reactions with the assistance of suitably-placed coordinating groups on the diene framework, and experiments to test this are planned.

A potential complication offered by **6** as a substrate for the double Heck reaction is that it in principle may form two diastereomeric intermediates, *cis*- and *trans*-**7**. The variations in solvent and ligands presumably influence not only the partitioning of *cis*- and *trans*-**7** between **8** (and **9**, **10**) and **11** (and **12**, **13**), but also could influence the ratio of *cis*- and *trans*-**7** formed; for relatively minor influences of this sort, see [6]. Work in progress focusses on related achiral substrates, particularly (iodoaryl)enynes with racemic or achiral catalyst, which necessarily form a racemic mixture of enantiomeric intermediates after the initial alkene insertion. Nonetheless, the preliminary results presented in Table 1, particularly the favorable product distribution using phenanthroline and the drastic difference between reaction rates in polar protic and aprotic media, are of general interest, especially in light of the increasing use of bisoxazoline and diimine ligands in organopalladium chemistry [30,31], and the development of aqueous organometallic reactions [32].

## 1. Experimental

### 1.1. General

Solvents $CH_2Cl_2$, $CH_3CN$, hexane, petroleum ether (bp 35–60°C), and EtOAc were reagent grade and used as received, whereas THF and diethyl ether were freshly distilled from blue Na-benzophenone mixtures. Unless otherwise specified, all reactions were conducted under nitrogen atmosphere. Infrared spectra were acquired on samples prepared in KBr pellets or as a solution held in an NaCl cell. Either a Mattson Galaxy 2020 or a Nicolet 550 Magna FT–IR were used. NMR spectra were acquired at ambient probe temperature of ca. 25°C using either a Varian Gemini 300, Unity Plus 400, Bruker 400, or Varian 500 MHz spectrometer. $^1$H-NMR spectra are referenced to residual solvent peak, $CHCl_3 = \delta$ 7.24 ppm. $^{13}$C-NMR spectra are referenced to $CDCl_3$ solvent resonance at $\delta$ 77.0 ppm. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA, or at Arizona State University.

### 1.2. 3-N-Phthaloylamino-1,5-hexadiene (2)

To a solution of **1** (5.31 g, 54.2 mmol), triphenylphosphine (13.90 g, 53.0 mmol) and phthalimide (7.97 g, 54.2 mmol) in dry THF (150 ml) was added diethyl azodicarboxylate (9.91 g, 57.0 mmol) dropwise at 0°C. The resulting yellow solution was stirred at RT for 24 h. The solvent was removed in vacuo to afford a semisolid material, which was taken up in $Et_2O$ (140 ml) and filtered. Concentration of the filtrates afforded a yellow oil. This material was purified by flash chromatography (hexane–ethyl acetate, 10:1) to yield **2** (7.10 g, 59%). $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 7.63–7.78 (m, 4 H), 6.17 (ddd, $J$ = 7.1, 10.3, 17.3 Hz, 1 H), 5.60–5.73 (m, 1 H), 5.20 (d, $J$ = 17.2 Hz, 1 H), 5.15 (d, $J$ = 10.4 Hz, 1 H), 5.01 (d, $J$ = 17.1 Hz, 1 H), 4.93 (d, $J$ = 10.7 Hz, 1 H), 2.84 (dt, $J$ = 9.1, 14.3 Hz, 1 H), 2.54–2.63 (m, 1 H); $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ 36.3, 53.2, 117.5, 118.2, 123.2, 132.0, 134.0, 134.2, 135.5, 168.1; Anal. calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.76; N, 6.16%. Found: C, 73.96; H, 5.78; N, 6.08.

### 1.3. 1,5-Hexadiene-3-amine, hydrochloride salt (3)

A solution of **2** (5.32 g, 23.4 mmol) and hydrazine monohydrate (1.66 g, 33.2 mmol) in absolute EtOH (200 ml) was heated to reflux for 6 h, resulting in the formation of a white precipitate. The reaction mixture was cooled to room temperature, and concentrated HCl (10 ml) was added until pH < 2. The precipitate was removed by filtration and the filtrate was concentrated to a semisolid residue. This material was dissolved in 90 ml of EtOH–$H_2O$ (2:1). The insoluble portion was removed and the filtrate was concentrated in vacuo to afford **3** (3.05 g, 91%). The product (no detectable impurities found by NMR) was used directly without further purification. $^1$H-NMR (300 MHz, $D_2O$): $\delta$ 5.64–5.86 (m, 2 H), 5.14–5.34 (m, 4 H), 3.81 (q, $J$ = 6.7 Hz, 1 H), 2.31–2.46 (m, 2 H); $^{13}$C-NMR (75 MHz, $D_2O$): $\delta$ 43.6, 59.7, 126.9, 127.2, 138.9, 140.1.

### 1.4. 3-[(N-Benzyloxycarbonyl) amino]-1,5-hexadiene (4)

A solution of crude **3** (3.05 g, 22.8 mmol) in water (25 ml) was cooled in an ice-bath and stirred. Aqueous NaOH (5%) was added until the pH was about 10. Benzyl chloroformate (5.80 g, 34.0 mmol) was added to the stirred mixture during 30 min. The pH of the reaction mixture was maintained near 10 by adding additional 5% NaOH periodically. The reaction was complete within 10 h. The reaction mixture was extracted with EtOAc (3 × 50 ml). Combined extracts were washed with saturated NaCl (3 × 10 ml) and dried over anhydrous sodium sulfate. After filtering off drying agent, the filtrate was concentrated in vacuo to give a brown oil. This was chromatographed (8:1 petroleum ether–EtOAc) on a flash silica column (7.5 × 70

cm) to give **4** ($R_f$ 0.3, 8:1 petroleum ether–EtOAc) as a slightly yellow oil which solidified upon standing overnight. The product was recrystallized from MeOH–water to give needles (3.21 g, 62% based on **3**, 60% based on **2**), mp 56–58°C. $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 2.25–2.36 (m, 2 H), 4.21–4.33 (br, m, 1 H), 4.70 (br, s, 1 H), 5.06–5.18 (m, 6 H), 5.66–5.84 (m, 2 H), 7.32–7.34 (m, 5 H). $^{13}$C-NMR (75.28 MHz, $CDCl_3$): $\delta$ 39.0, 52.4, 66.4, 114.8, 118.1, 128.1, 128.3, 128.5, 134.0, 136.8, 138.2, 156.0. IR (KBr): 3210, 1660, 1605, 1499 cm$^{-1}$. Anal. calcd. for $C_{14}H_{17}NO_2$: C, 72.69; H, 7.41; N, 6.06. Found: C, 72.29; H, 7.22; N, 5.93.

### *1.5. N-Methyl-1,5-hexadiene-3-amine, hydrochloride salt (5)*

To a suspension of $LiAlH_4$ (2.45 g, 64.5 mmol) in THF (20 ml) chilled in an ice-bath was added **4** (2.01 g, 8.7 mmol) in THF (10 ml) dropwise. After stirring for 24 h at RT, the flask was put in an ice bath and the reaction mixture was quenched with water (10 ml), 5% NaOH (10 ml) and water (10 ml). The white insoluble portion was filtered off and thoroughly washed with diethyl ether (4 × 20 ml). The filtrates were acidified by concentrated HCl, concentrated in vacuo, and stored in the freezer overnight to give a solid product. The solid was washed by cooled diethyl ether (3 × 10 ml) to give **5** (0.81 g, 58%). Compound **5** was used directly without further purification, no detectable impurities being detectable by $^1$H-NMR (300 MHz, $D_2O$): $\delta$ 2.43–2.48 (m, 2 H), 2.56 (s, 3 H), 3.62 (dd, $J$ = 7.1, 15.0 Hz, 1 H), 5.13 (dm, $J \approx$ 10 Hz, 1 H), 5.15 (dm, $J \approx$ 17 Hz, 1 H), 5.34 (dm, $J \approx$ 16 Hz, 1 H), 5.44 (dm, $J \approx$ 9 Hz, 1 H), 5.60–5.75 (m, 2 H). $^{13}$C-NMR (75 MHz, $D_2O$): $\delta$ 37.0, 42.8, 68.4, 127.3, 130.9, 137.8, 138.5.

### *1.6. N-Methyl-N-(1,5-hexadiene-3-yl)-2-iodobenzoic acid amide (6)*

To a mixture of **5** (705.4 mg, 4.78 mmol) in $Et_2O$ (20 ml) was added $Et_3N$ (1.211 g, 11.98 mmol, predried over $CaH_2$, and distilled before use) dropwise, followed by 2-iodobenzoyl chloride (1.370 g, 5.11 mmol) in $Et_2O$ (10 ml) at 0°C. The reaction was followed by TLC (petroleum ether–EtOAc, 3:1), which indicated completion within 10 h. After the reaction was complete, 5% NaOH (20 ml) was added to the reaction mixture. The aqueous phase was extracted with $Et_2O$ (2 × 20 ml). The combined organic phases were washed with 1 M HCl (3 × 20 ml), saturated $NaHCO_3$ (2 × 20 ml), saturated NaCl (3 × 20 ml), and dried over $MgSO_4$. Filtration and concentration of the filtrate in vacuo afforded yellowish oil. The oily residue was flash chromatographed, using EtOAc–petroleum ether (1:3), to give **6** (1.163 g, 71%), mp 39.5–40°C. The signals could not be fully identified in the $^1$H-NMR spectrum (300 MHz, $CDCl_3$) because of the complexity of the spectrum, which was presumably due to the lack of free rotation of certain bond(s) in the molecule. $\delta$ 2.32–2.70 (m, 4.7 H), 2.94 (s, 0.7 H), 2.97 (s, 0.7 H), 2.43–2.48 (m, 2 H), 5.01–6.08 (m, 6.3 H), 7.00–7.16 (m, 1 H), 7.15–7.17 (m, 1 H), 7.28–7.38 (m, 1 H), 7.78–7.85 (m, 1 H); IR (KBr): 3077, 2927, 1695, 1628, 1584, 1478 cm$^{-1}$; Anal. calcd. for $C_{14}H_{16}NOI$: C, 49.28; H, 4.73; N, 4.09; Found: C, 49.33; H, 4.76; N, 4.09.

### *1.7. General procedure for the Heck reaction*

Smaller-scale reactions were performed in a Schlenk tube (12 mL capacity) with Teflon-lined screw cap. A mixture of $Pd(OAc)_2$ (0.1 eq., or stated in Table 1), base (2.5 eq. of $K_2CO_3$), compound **6**, additive(s), and solvent(s) was added. The contents of the tube were subjected to three cycles of freeze–pump–thaw and the tube was refilled with $N_2$ before immersion in an oil bath.

The larger scale reactions were performed in an oven-dried round-bottom two-neck flask. The flask was evacuated and refilled with $N_2$. Degassed solvents were transferred to this flask via

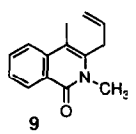
syringe, and solid(s) were added under positive $N_2$ pressure. The reaction was performed under an atmosphere of $N_2$.

The progress of the reaction was followed by TLC (petroleum ether–EtOAc, 3:1). After the reaction was complete the mixture was filtered through Celite 545. The filtrates were concentrated by rotary evaporation to one third of their original volume. The residue was extracted with EtOAc three times (twice as much as the volume of residue for each time). The organic extracts were washed with 1 M HCl, saturated $NaHCO_3$, and saturated NaCl (three times, same volume as the organic extract) and dried over $MgSO_4$. After removal of drying agent, concentration by rotary evaporation gave a brown oil. Using petroleum ether–EtOAc (1:1), desired products (with $R_f$ in the range of 0.4 to 0.6) were separated from polar unidentified impurities ($R_f = 0$) using flash chromatography (silica gel column 10 mm × 100 mm, 1:1 petroleum ether–EtOAc, UV detection) to give a crude mixture of products which was analyzed by $^1$H-NMR vs. the added internal standard $(CH_3)_3SiCH_2CH_2OH$, chosen because its $^1$H-NMR absorptions did not overlap with those of the products.

*1.8. Separation and identification of products from Heck cyclization*

Products from Heck cyclization were separated by HPLC (67% hexane and 33% EtOAc using an Alltech Silica 10 micron column (length: 250 mm, id 22 mm), and monitored by UV at 279 nm. Solvent flow 4.0 ml/min, AUFS = 2.5, injected volume 800 μl, concentration ca. 0.1 mg/μl.

*1.9. 3-Allyl-2,4-dimethyl-iso-quinolin-1-one (**9**)*



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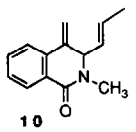
Obtained as a mixture with **16**. $^1$H-NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3 H), 3.53–3.56 (m, 2 H), 3.62 (s, 3 H), 4.97 (dm, $J \approx 17$ Hz, 1 H), 5.15 (dm, $J \approx 10$ Hz, 1 H), 5.90–6.01 (m, 1 H), 7.41–7.47 (m, overlapped with signal for compound **16**, ~ 1 H for compound **9**), 7.63–7.66 (m, overlapped with signal for compound **16**, ~ 2 H for compound **9**), 8.46 (dm, $J \approx 8.4$ Hz, 1 H). HRMS (EI) $m/z$ calcd. for $C_{14}H_{15}NO$ 213.1154, found 213.1155.

*1.10. 3,4-Dihydro-4-methylene-3-(trans-prop-1-enyl)-2-methyl-isoquinolin-1-one (**10**)*

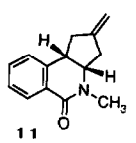


10

$^1$H-NMR (300 MHz, $CDCl_3$): δ 1.59 (dd, $J$ = 1.6, 7.0 Hz, 3 H), 3.09 (s, 3 H) 4.42 (sl br d, $J \approx 7$ Hz, 1 H), 5.20 (s, 1 H), 5.34 (qdd, $J$ = 1.6, 7.1, 15.2 Hz, 1 H), 5.55 (s, 1 H), 5.52–5.63 (m, 1 H), 7.35–7.52 (m, 3 H), 8.14 (d, $J$ = 8.2 Hz, 1 H).

Structure assignment was also secured by COSY spectra at 400 MHz.

*1.11. 4-Methyl-2-methylene-1,2,3,3a-cis,4,9b-cis-hexahydro-5H-cyclopent(c) iso-quinolin-5-one (**11**)*



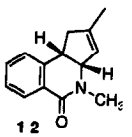
11

$^1$H-NMR (300 MHz, $CDCl_3$): δ 2.48 (ddd, $J$ = 2.9, 12.7, 15.7 Hz, 1 H), 2.56 (ddd, $J$ = 2.8, 12.2, 15.0 Hz, 1 H), 2.81 (dd, $J$ = 6.8, 15.0 Hz, 1 H), 2.96 (dd, $J$ = 7.3, 15.3 Hz, 1 H), 3.10 (s, 3 H), 3.14 (ddd, outer two lines assumed to be obscured by NC$H_3$, $J \approx 6$, 12, 12 Hz, 1 H), 3.49 (ddd, $J$ = 6.7, 12.1, 12.1 Hz, 1 H), 5.05–5.09 (m, 2 H), 7.10 (sl br d, $J$ = 7.4 Hz, 1 H), 7.34 (sl br t, $J \approx 8$ Hz, 1 H), 7.44 (dt, $J$ = 1.6,

7.4 Hz, 1 H), 8.08 (dd, $J = 1.5$, 7.7 Hz, 1 H); $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ 31.1, 33.0, 38.0, 45.2, 62.5, 110.4, 124.3, 127.6, 129.5, 130.3, 132.1, 141.2, 145.8, 167.3. HRMS (EI) $m/z$ calcd. for $C_{14}H_{15}NO$ 213.1154, found 213.1162. IR ($CHCl_3$): 1637 $cm^{-1}$.

Structure assignment was secured by COSY and NOESY spectra at 400 MHz.

*1.12. 2,4-Dimethyl-1,3a-cis,4,9b-cis-tetrahydro-5H-cyclopent(c) iso-quinolin-5-one (**12**)*

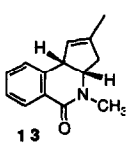


**12**

$^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 1.76 (sl br s, 3 H), 2.43 (sl br dd, $J \approx 7$, 16 Hz, 1 H), 2.68 (dd, $J = 8.6$, 16.3 Hz, 1 H), 3.06 (s, 3 H), 3.63 (dd, $J = 7.6$, 15.6 Hz, 1 H), 4.46 (d, $J = 6.5$ Hz, 1 H), 5.58–5.59 (m, 1 H), 7.14 (d, $J = 7.8$ Hz, 1 H), 7.25 (dt, $J = 1.4$, 7.7 Hz, 1 H), 7.36 (dt, $J = 1.5$, 7.5 Hz, 1 H), 8.09 (dd, $J = 1.6$, 7.8 Hz, 1 H); $^{13}$C-NMR (75 MHz, $CDCl_3$): 16.8, 32.3, 40.4, 45.7, 65.3, 124.6, 126.8, 127.3, 127.7, 128.9 132.2, 140.4, 146.0, carbonyl carbon is missing; IR ($CDCl_3$): 1640 (s) $cm^{-1}$. HRMS (EI) $m/z$ calcd. for $C_{14}H_{15}NO$ 213.1154, found 213.1156.

Structure assignment was also secured by COSY and NOESY spectra.

*1.13. 2,4-Dimethyl-3,3a-cis,4,9b-cis-tetrahydro-5H-cyclopent(c) iso-quinolin-5-one (**13**)*

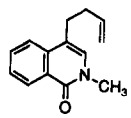


**13**

$^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 1.72 (br s, 3 H), 2.24 (sl br dd, $J \approx 8$, 16 Hz, 1 H), 2.61 (dd, $J = 7.4$, 15.4 Hz, 1 H), 3.14 (s, 3 H), 4.04–4.12 (m, 1 H), 4.22 (app q, $J \approx 8$ Hz, 1 H), 5.73 (sl br s, 1 H), 7.08 (d, $J = 7.7$ Hz, 1 H), 7.29 (dt, $J = 1.2$, 7.8 Hz, 1 H), 7.42 (dt, $J = 1.4$, 7.5 Hz, 1 H), 8.12 (dd, $J = 1.4$, 7.8 Hz, 1 H); $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ 16.9, 34.3, 42.5, 43.7, 61.4, 126.0, 126.9, 127.2, 128.4, 132.0, 132.4, 139.0, 140.7, 163.4; IR ($CHCl_3$): 1635 $cm^{-1}$; HRMS (EI) $m/z$ calcd. for $C_{14}H_{15}NO$ 213.1154, found 213.1162.

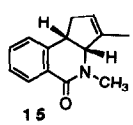
Structure assignment was secured by COSY and NOESY spectra at 500 MHz.

*1.14. 4-(But-3-enyl)-2-methyl-iso-quinolin-1-one (**14**)*




$^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 2.39 (sl br q, AA′ of AA′BB′ m, $J \approx 7$ Hz, 2 H), 2.75 ($\sim$ t appt BB′ of AA′BB′m, $J \approx 7$ Hz, 2 H), 3.57 (s, 3 H), 5.02 (dm, $J \approx 8$ Hz, 1 H), 5.06 (dm, $J \approx 16$ Hz, 1 H), 5.87 (tdd, $J = 6.7$, 10.4, 17.0 Hz, 1 H), 6.87 (s, 1 H), 7.48–7.51 (m, 1 H), 7.60–7.69 (m, 2 H), 8.48 (d, $J = 8.3$ Hz, 1 H); $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ 28.7, 33.5, 36.7, 115.7, 122.8 126.4, 126.8 128.5, 130.5, 132.1, 136.8, 137.8, 162.6, one $sp^2$ carbon signal is missing; IR ($CHCl_3$): 1644 $cm^{-1}$; HRMS (EI) $m/z$ calcd. for $C_{14}H_{15}NO$ 213.1154, found 213.1161.

*1.15. 4-Methyl-3-methylene-1,2,3,3a-cis,4,9b-cis-hexahydro-5H-cyclopent(c) iso-quinolin-5-one (**15**)*



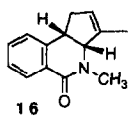
**15**

As a mixture with **12** (**15**:**12** = 2:3). $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 2.40–2.70 (partially

overlapped with signal for **12**, m, ~ 4 H), 3.11 (s, 3 H), 3.46 (dd, $J = 6.6$, 13.4 Hz, 1 H), 3.91 (dd, $J = 6.4$, 13.2 Hz, 1 H), 4.89 (m, 2 H), 7.12 (d, $J = 6.9$ Hz, 1 H), signals in region 7.15–7.45 overlap with those of **12**, 8.06 (dd, $J = 1.5$, 8.1 Hz, 1 H).

Structure elucidation was aided by COSY and NOESY spectra of the mixture.

*1.16. 3,4-Dimethyl-1,3a-cis,4,9b-cis-tetrahydro-5H-cyclopent(c) iso-quinolin-5-one (**16**)*



16

As a mixture with **9** (**16**:**9** = 2:5 or 5:4). $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 1.77 (sl br s, 3 H), 2.35–2.50 (m, 3 H), 3.03 (s, 3 H), 3.69–3.78 (m, 1 H), 5.84–5.95 (partially overlapped with signal for compound **9**, m, ~ 1 H), 7.41–7.66 (m, overlapped with signal for compound **9**, ~ 1 H for compound **16**), 7.63–7.66 (m, overlapped with for compound **9**, ~ 2 H for compound **16**), 7.98 (dd, $J = 1.4$, 7.8 Hz, 1 H). Structure was tentatively assigned based on these data and COSY spectra of the mixture.

## Acknowledgements

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