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Ligand Effects in the Synthesis of *N*-Heterocycles by Intramolecular Heck Reactions

Emma L. Cropper, Andrew J. P. White, Agnes Ford,† and King Kuok (Mimi) Hii*

Department of Chemistry, Imperial College London, Exhibition Road, South Kensington SW7 2AZ, United Kingdom

mimi.hii@imperial.ac.uk

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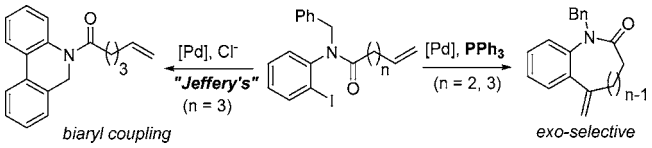
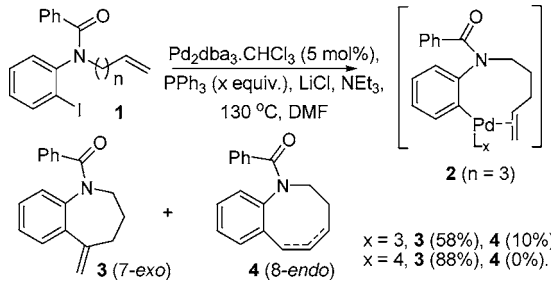


Chemo- and regioselectivity of intramolecular Heck reactions are dependent on the type of ligand employed. Six- to eight-membered benzolactams are produced in good yields using PPh_3 as ligand. In contrast, a biaryl coupling occurred preferentially under ligandless conditions to form a dihydrophenanthridine product. Conformations of the seven- and eight-membered benzolactams in the solid state were examined by X-ray crystallography.

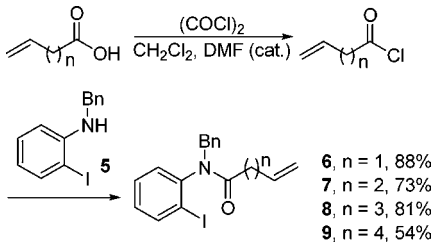
Among the many intramolecular processes provided by palladium catalysis in heterocyclic chemistry, the Heck reaction is particularly valuable for the formation of saturated rings and the creation of quaternary and/or stereogenic carbon centers.[1] Most often used for the formation of five- and six-membered rings, it is generally perceived to be selective for *exo* cyclizations. However, this regioselectivity can be altered in certain cases; for example, 6-*endo* ring closure may be favored by adopting "ligandless" (Jeffery's) conditions[2] or by conducting the reaction in an aqueous medium using water-soluble phosphines.[3,4]

There is a growing number of reports in recent years that demonstrate the synthetic utility of the intramolecular Heck reaction for the assembly of medium-sized rings (≥7). In most cases, the substrates contain a suitably placed substituent (e.g., an ester group) to effect arylation at the β-position, leading to exclusive formation of *exo*[5] or *endo*[6] products. In the absence of such stereodirecting groups, the outcome can be unpredictable, often leading to mixtures of products. Ways of controlling the regioselectivity of these cyclizations are rarely studied.[7]

SCHEME 1. Previous Synthesis of *N*-Heterocycles by Intramolecular Heck Reaction



SCHEME 2. Preparation of Acyclic Precursors



Previously, we described the synthesis of a benzazepine structure by an intramolecular Heck reaction, where the use of >3 equiv of PPh_3 suppressed *endo* cyclization, affording the 7-*exo* product **3** exclusively (Scheme 1).[8] Thus, the amount of ligand clearly dictates the nature of the transition state (**2**) and subsequent C−C formation. This peculiar result led us to initiate the current study to investigate the ligand effects on the regioselectivity of intramolecular Heck reactions, particularly in the formation of medium-sized benzolactams.

Acyclic precursors were prepared by amide coupling reactions between *N*-benzyl-2-iodoaniline **5** and the requisite acid chlorides, which were generated in situ from the corresponding ω-alkenoic acids (Scheme 2).

Reactions in the Presence of Monophosphine Ligands. Compounds **6**−**9** were subjected to the Heck reaction, under the conditions established previously. Employing a metal to ligand ratio of 1:4, cyclizations proceeded exclusively in an *exo* manner, furnishing quinolinone **10**, 1-benzazepinone **11**, and 1-benzazocinone **12** in good yields (Scheme 3).

The successful formation of the seven-membered benzazepinone **11** is a considerable improvement over previous cyclization strategies using radical[9] or nickel catalysts,[10] which furnished yields of less than 40% (in the latter case, with unspecified regiochemistry). The successful 8-*exo* cyclization is also worthy of note, as our earlier work showed that the

† AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH, U.K.

(1) (a) Link, J. T. *Org. React. (N.Y.)* **2002**, *60*, 157. (b) Dyker, G. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., de Meijere, A., Eds.; Wiley: New York, 2002; Vol. 1.

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(7) For example, see: (a) Santos, L. S.; Pilli, R. A. *Synthesis* **2002**, 87. (b) Tietze, L. F.; Sommer, K. M.; Schneider, G.; Tapolzsányi, P.; Wölfling, J.; Müller, P.; Noltemeyer, M.; Terlau, H. *Synlett* **2003**, 1494.

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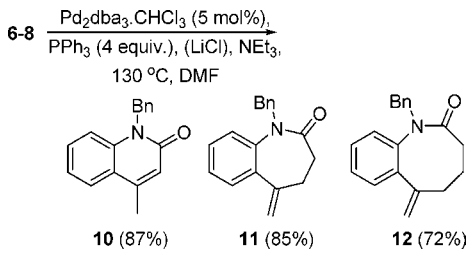
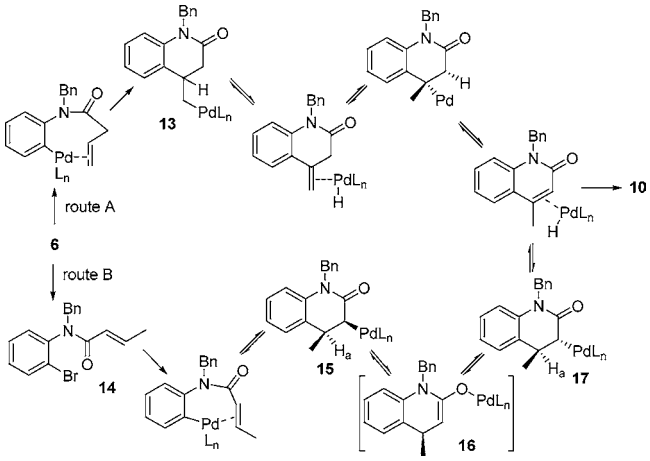
SCHEME 3. *N*-Heterocycles Obtained under "Standard" Heck Conditions



SCHEME 4. Possible Pathways for Formation of Quinoline 10



N-benzoyl precursor **1** ($n = 4$) failed to produce the corresponding eight-membered benzazocine ring under these exact reaction conditions. Hence, the comparative ease of formation of the benzazocinone **12** is attributed to greater rigidity of the acyclic chain imposed by the amide moiety, leading to a reduction in the entropy, which favors the formation of the eight-membered ring.[11] However, the formation of the nine-membered benzazoninone ring still proved to be difficult. In this case, only unreacted compound **9** was recovered at the end of the reaction. The addition of the LiCl salt was also later found to be unnecessary, as yields of **11** and **12** were unaffected in its absence (81% and 79% yields, respectively).

No double bond migration/isomerization occurs during the formation of the seven- and eight-membered benzolactams, as the exocyclic double bonds were formed exclusively in compounds **11** and **12**. For quinoline **10**, the formation of the endocyclic double bond may result from two possible pathways (Scheme 4). In the first (route A), an exocylic cyclization proceeds to generate the alkylpalladium intermediate **13**, which undergoes a series of β-hydride migrations, leading to the formation of the thermodynamically stable conjugate π-system. In the alternate pathway (route B), double bond isomerization of **6** occurs first to give the acyclic enone **14**. An endocyclic Heck cyclization will generate an intermediate **15**, which will undergo a formal *anti* β-hydride elimination to generate the product **10**. This process is well-documented for the intramolecular Heck addition of aryl halides to α,β-unsaturated carbonyl compounds, whereby a stereomutation to intermediate **17** is proposed to occur via the formation of an η^1-palladium enolate **16**.[12] Presently, it is difficult to determine whether one or both of the pathways operate(s) in the present system.[13]

FIGURE 1. Molecular structure of the benzazepinone **11** (left) and benzazocinone **12** (right) as determined by X-ray crystallography. Aromatic hydrogens omitted for clarity.

Molecular structures of **11** and **12** were established by single-crystal X-ray diffraction studies (Figure 1). The benzazepinone species **11** adopts a boat conformation for its seven-membered ring in the solid state, similar to that seen for the "parent" compound 4,5-dihydro-1,3-benzazepin-2-one.[14] Interestingly, the eight-membered ring in compound **12** displays a twist-boat-chair conformation, very similar to those seen for closely related heterocycles.[15]

Compounds **11** and **12** displayed different dynamic behavior in solution compared to their counterparts containing saturated heterocycles. In contrast to **3**,[16] benzazepinone **11** is conformationally labile. At ambient temperature, the benzylic and methylene protons of **11** give rise to time-averaged resonances in the ^{1}H NMR spectrum. For the eight-membered benzazocinone **12**, each diastereotopic methylene proton gives rise to a distinct resonance signal in the ^{1}H NMR spectrum, changing little even at 90 °C. This contrasts with the solution behavior of the corresponding benzazocine ring, which undergoes ring inversion at ambient temperature.[17] Thus, the incorporation of the amide moiety appears to *decrease* and *increase* the conformational rigidity of the seven- and eight-membered rings, respectively.

At this stage of the study, we also investigated the use of sterically bulky monophosphine ligands such as P(*t*-Bu)$_3$ and

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(13) The reversibility of β-hydride migration and the convergence of the intermediates rules out the determination of reaction pathways by isotopic (deuterium) labeling.

(14) CCDC reference code YUFFOU; see: Gupta, V. K.; Goswami, K. N.; Yadava, V. B. S.; Gupta, D. K.; Bhutani, K. K. *Z. Kristallogr.* **1995**, *210*, 154.

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(16) Conformational energy barrier of compound **3** is approximately $\Delta G^{\ddagger}$ 13.7 kcal mol^{-1} (ref 8).

(17) Partially and fully reduced 1-benzazocine conformers have energy barriers of approximately 17 kcal mol^{-1}: Qadir, M.; Cobb, J.; White, A. J. P.; Sheldrake, P. W.; Whittall, N.; Hii, K. K.; Horton, P. N.; Hursthouse, M. B. *J. Org. Chem.* **2005**, *70*, 1552.

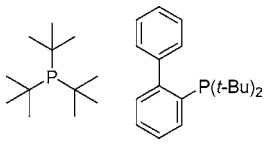


FIGURE 2. Sterically bulky monophosphine ligands employed in the intramolecular Heck reaction.

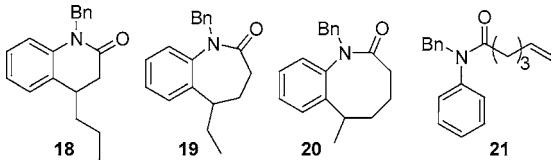


FIGURE 3. Reduced products (**18**−**20**) of the intramolecular Heck reaction using P(*t*-Bu)$_3$ as ligand: (i) **8**, Pd(dba)$_2$, P(*t*-Bu)$_3$, NEt$_3$, toluene, reflux, 24 h; (ii) H_2, Pd/C, EtOH.

2-(di-*tert*-butylphosphino)biphenyl (Figure 2). These ligands are known to stabilize coordinatively unsaturated monoligated [L-Pd] species,[18] which are highly active in many palladium-catalyzed processes, including the Heck reaction at room temperature.[19]

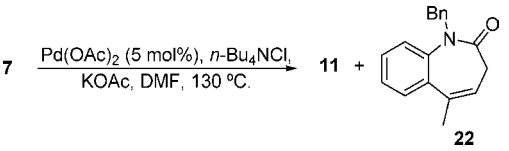
For the cyclization of substrate **8**, no product formation was observed with either ligand at room temperature. At higher temperatures, the reactions afforded complex mixtures of products. In the case of P(*t*-Bu)$_3$, at least five products with a combined yield of 82% was obtained, which converged upon hydrogenation (H_2, Pd/C) into three products, **18**, **19**, and **20**, in a ratio of 1:15:2 (Figure 3). Each of these compounds was isolated and easily identifiable by the observation of distinctive propyl, ethyl, and methyl signals in their ^{1}H NMR spectra (Supporting Information). Formation of the smaller heterocycles clearly indicates the operation of a competitive double bond isomerization, prior to the C−C bond-forming step (akin to route B, Scheme 4).

Conducting the reaction in a more polar DMF solvent, the isomerization process may be suppressed to a certain extent. The benzazocinone **12** may be isolated in ca. 50% yield (using the biphenylphosphine ligand), but the reaction mixture contains several side products. Postulating that the competitive process may be promoted by the formation of a hydridopalladium intermediate, we substituted triethylamine with an inorganic base (Cs_2CO_3).[20] However, the reaction again proved to be capricious, delivering a mixture of products from which the dehalogenated product **21** was isolated in 58% yield.

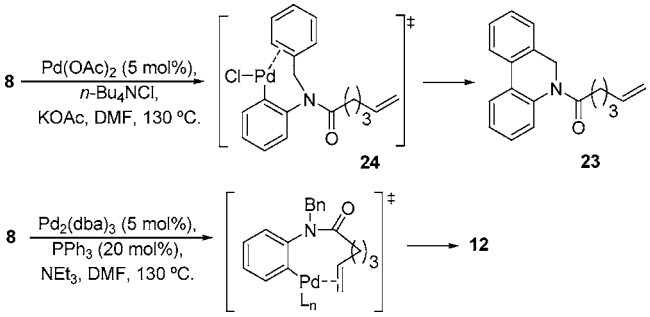
Reactions in the Absence of Phosphine Ligands. Jeffery's [Pd/Base/QX] catalyst system was also employed in the present study. It has been proposed that this "ligandless" protocol may offer a smaller metal coordination sphere, allowing the formation of sterically more demanding transition state structures for *endo* cyclizations.[3]

In the present study, 6- and 7-*exo* ring closures were again observed in the cyclization of **6** and **7** to give **10** (79%) and **11** (67%), respectively. In the latter case, an inseparable mixture of the benzazepinone **11** and its double bond isomer **22** was obtained in a 1: 1 ratio (Scheme 5).

SCHEME 5. Formation of Double-Bond Isomers under Ligandless Conditions



SCHEME 6. Chemoselective π-Activation under Different Reaction Conditions



Rather unexpectedly, compound **8** underwent biaryl coupling[21] to furnish the dihydrophenanthridine **23** in 68% yield (Scheme 6).[22] The structure was corroborated by the observation of eight aromatic proton resonances in the ^{1}H NMR spectrum, accompanied by a distinctive broadening and upfield shift of the benzylic carbon resonance from 51.5 to 45.2 ppm.[23] The formation of this tricyclic heterocycle presumably occurs via the putative intermediate **24**. Comparing this result with the 8-*exo* cyclization obtained earlier in the presence of triphenylphosphine ligands, it would suggest that for substrate **8** the activation of the *N*-benzyl moiety is favored under "ligandless" conditions.

As far as we are aware, this is the first example where arene or alkene is activated chemoselectively by adopting different Heck protocols. The result suggests that whereas olefin coordination (Heck reaction) is favored by phosphine-ligation (π-acceptor), the coordination of the aromatic π-system (biaryl coupling) occurs preferentially in the presence of anionic Cl^- ligand (σ-donor).

In summary, the regioselective formation of medium-sized benzolactams can be achieved using the intramolecular Heck reaction. The reaction is found to be highly dependent on the catalytic conditions, particularly the structure of the substrate, as well as the nature of the ligand employed. The latter is found to affect the chemoselectivity, regioselectivity, and competitive double bond migration processes. Whereas six- to eight-membered heterocycles were obtained exclusively using the PPh_3 ligand (4 equiv), biaryl coupling was preferred over 8-*exo* cyclization under "ligandless" conditions.

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(20) Palladium hydride can be generated through β-hydride elimination of a coordinated triethylamine. The choice of base has been found to affect the generation and stability of palladium hydride species; see: Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc*. **2004**, *126*, 13176.

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(22) Similar "Heck-type" biaryl coupling was effected by employing thallium and silver salts; see: (a) Grigg, R.; Savic, V.; Tambyrajah, V. *Tetrahedron Lett*. **2000**, *41*, 3003. (b) Harayama, T.; Akiyama, T.; Kawano, K. *Chem. Pharm. Bull*. **1996**, *44*, 1634. By adopting Jeffrey's conditions, see: (c) Garden, S. J.; Torres, J. C.; Pinto, A. C. *J. Braz. Chem. Soc*. **2000**, *11*, 441. (d) Gómez-Lor, B.; Echavarren, A. M. *Org. Lett*. **2004**, *6*, 2993.

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Experimental Section

General Procedure for Preparation of 10−12, under "Standard" Heck Reaction in the Presence of PPh_3. A Young's tube was charged with $Pd(dba)_2$ (14 mg, 0.025 mmol, 5 mol %), PPh_3 (26 mg, 0.099 mmol, 20 mol %), and LiCl (23 mg, 0.54 mmol, 1.1 equiv. *Note*: this is optional). To this was added Et_3N (0.137 mL, 0.98 mmol, 2.0 equiv), dry DMF (4 mL), and the appropriate amide (0.49 mmol, 1.0 equiv) as a solution in dry DMF (1 mL). The vessel was sealed by a PTFE tap and the reaction stirred at room temperature for 15 min, followed by heating at 130 °C for 22 h. After this time, the reaction mixture was cooled and filtered through Celite. The solution was then concentrated and purified by column chromatography.

1-Benzyl-4-methyl-1*H*-quinolin-2-one, 10. Recrystallized from hexane after column chromatography. Yield: 87% as a yellow crystalline solid; R_f = 0.16 (hexane/ethyl acetate, 2/1); mp 110−111 °C (lit.[24] 110.5−111.5 °C); ν_{max}(KBr)/cm^{-1} 1651 (C═O); δ_H (270 MHz, $CDCl_3$) 2.51 (3H, s), 5.56 (2H, s), 6.71 (1H, s), 7.20−7.31 (7H, m), 7.42 (1H, t, *J* 7.9), 7.72 (1H, d, *J* 7.9); δ_C (100 MHz, $CDCl_3$) 19.1, 45.7, 115.3, 121.0, 121.7, 122.0, 125.3, 126.5, 127.2, 128.8, 130.4, 136.5, 139.1, 147.1, 162.3; *m*/*z* (EI) 249 (M^+, 100%), 248 (72%), 143 (65%), 91 (72%).

1-Benzyl-5-methylene-1,3,4,5-tetrahydro-1-benzazepin-2-one, 11. Yield: 85% as a pale yellow solid; R_f = 0.28 (hexane/ethyl acetate, 2/1); mp 89−90 °C; ν_{max}(KBr)/cm^{-1} 1651 (C═O). Found: C, 81.94; H, 6.54; N, 5.22. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. δ_H (270 MHz, $CDCl_3$) 2.56 (2H, t, *J* 6.9), 2.98−3.01 (2H, m), 4.83 (1H, dt, *J* 1.6, 1.9), 5.01 (2H, s), 5.15 (1H, dt, *J* 1.6, 1.9), 7.12−7.27 (9H, m, ArH); δ_C (100 MHz, $CDCl_3$) 33.0, 36.3, 51.3, 115.5, 122.6, 126.4, 127.0, 127.7, 128.2, 128.5, 129.0, 137.5, 137.6, 140.8, 145.2, 173.0; *m*/*z* (EI) 263 (M^+, 63%), 172 (30%), 144 (33%), 130 (27%), 91 (100%).

1-Benzyl-6-methylene-3,4,5,6-tetrahydro-1*H*-benzazocin-2-one, 12. Yield: 72% as a pale yellow solid; R_f = 0.19 (hexane/ethyl acetate, 3/1); mp 65−66 °C; ν_{max}(KBr)/cm^{-1} 1658 (CO). Found: C, 82.16; H, 6.84; N, 4.96. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. δ_H (270 MHz, $CDCl_3$) 1.84−1.94 (2H, m), 2.00−2.21 (2H, m), 2.31−2.38 (1H, m), 2.54−2.62 (1H, m), 4.00 (1H, d, *J* 1.5), 4.83 (1H, d, *J* 14.3), 4.89 (1H, m), 4.99 (1H, d, *J* 14.3), 7.10−7.17 (2H, m) 7.19−7.28 (7H, m); δ_C (100 MHz, $CDCl_3$) 26.1, 33.1, 36.8, 52.7, 115.5, 125.6, 127.3, 127.3, 127.8, 128.1, 129.2, 129.3, 137.0, 139.6, 142.8, 145.9, 173.6; *m*/*z* (EI) 277 (M^+, 90%), 186 (61%), 91 (100%).

General Procedure for Cyclization under "Ligandless" Conditions. A Young's tube was charged with $Pd(OAc)_2$ (6 mg, 0.025 mmol, 5 mol %), *n*-Bu_4NCl (137 mg, 0.49 mmol, 1.0 equiv) and KOAc (121 mg, 1.23 mmol, 2.5 equiv). To this was added the appropriate amide (0.49 mmol, 1.0 equiv), followed by dry DMF (5 mL). The vessel was sealed with a PTFE tap and the reaction mixture was stirred at room temperature for 10 min, followed by heating at 130 °C for 22 h. After this time, the reaction mixture was cooled and filtered through Celite. The solvent was removed under vacuum, and the product purified by column chromatography.

1-Benzyl-5-methyl-1,3-dihydro-1-benzazepin-2-one, 22. Compound was not isolated but obtained as inseparable mixture with **11**. δ_H (270 MHz, $CDCl_3$) 2.10 (3H, s), 2.63−2.66 (1H, m), 3.06−3.14 (1H, m), 4.86 (1H, d, *J* 15.6), 5.33 (1H, d, *J* 15.6), 5.95 (1H, t, *J* 6.4), 7.04−7.40 (9H, m); δ_C (100 MHz, $CDCl_3$) 21.0, 35.6, 51.7, 123.2, 123.3, 124.9, 126.7, 126.9, 127.0, 127.8, 128.3, 135.1, 135.5, 140.3, 171.4; *m*/*z* (EI) 263 (M^+, 10%), 221 (100), 91 (28).

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Hex-5-1-(6*H*-phenanthridin-5-yl)-hex-5-en-1-one, 23. Yield: 68% as a yellow oil. ν_{max}(thin film)/cm^{-1} 1657 (CO). Found: C, 82.35; H, 6.98; N, 5.01. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. δ_H (270 MHz, $CDCl_3$) 1.65−1.76 (2H, m), 1.90−2.08 (2H, m), 2.48 (2H, t, *J* 7.4), 4.81−4.88 (4H, m), 5.60−5.67 (1H, m), 7.20−7.42 (6H, m), 7.76−7.81 (2H, m); δ_C (100 MHz, $CDCl_3$) 24.8, 33.1, 45.2, 114.9, 123.3, 124.5, 124.7, 126.2, 127.6, 128.0, 129.9, 131.9, 135.3, 137.8, 138.0, 172.2; *m*/*z* (EI) 277 (M^+, 28%), 180 (100%).

Hydrogenation of Double Bonds. A mixture of 10% Pd/C (190 mg, 0.5 equiv) and the appropriate benzolactam (0.36 mmol, 1.0 equiv) in ethanol (3.6 mL, 0.1 M) was stirred under a hydrogen atmosphere at room temperature for 18 h. Subsequently, the suspension was filtered through a short plug of silica and the solution was concentrated in vacuo to furnish the products.

1-Benzyl-4-propyl-3,4-dihydro-1*H*-quinolin-2-one, 18. δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.2), 1.25−1.39 (1H, m), 1.40−1.51 (1H, m), 1.53−1.75 (2H, m), 2.69−2.74 (1H, m), 2.88−2.95 (2H, m), 5.01 (1H, d, *J* 16.2), 5.35 (1H, d, *J* 16.2), 6.89 (1H, d, *J* 8.1), 6.98 (1H, t, *J* 7.4), 7.08−7.17 (2H, m), 7.21−7.32 (5H, m); δ_C (100 MHz, $CDCl_3$) 14.0, 20.1, 35.9, 36.0, 37.0, 46.0, 115.8, 122.8, 126.5, 127.0, 127.3, 127.8, 128.7, 130.1, 137.1, 138.9, 169.9; *m*/*z* (EI) 279 (M^+, 56%), 236 (39%), 91 (100%).

1-Benzyl-5-ethyl-1,3,4,5-tetrahydro-1-benzazepin-2-one, 19. δ_H (400 MHz, $CDCl_3$) 0.74 (3H, t, *J* 7.3), 1.47−1.58 (2H, m), 1.67−1.78 (1H, m), 2.15−2.32 (2H, m), 2.34−2.42 (2H, m), 4.74. (1H, d, *J* 14.6), 5.26 (1H, d, *J* 14.6), 7.14−7.29 (9H, m); δ_C (100 MHz, $CDCl_3$) 12.1, 24.7, 33.2, 35.8, 51.3, 123.2, 125.3,126.5, 126.9, 127.3, 128.3, 128.3, 137.7, 138.3, 142.6, 173.3; *m*/*z* (EI) 279 (M^+, 100%), 91 (80%).

Benzyl-6-methyl-3,4,5,6-tetrahyro-1*H*-1-benzazocin-2-one, 20. Obtained by hydrogenation of **12**. Yield: 95% as a white solid; mp 96−97 °C; ν_{max}(KBr)/cm^{-1} 1645 (CO). Found: C, 81.67; H, 7.55; N, 4.98. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. δ_H (270 MHz, $CDCl_3$): 0.88 (3H, d, *J* 7.0), 1.17−1.27 (1H, m), 1.66−1.74 (1H, m), 1.76−1.86 (2H, m), 1.87−1.96 (1H, m), 2.06−2.16 (1H, m), 2.22−2.27 (1H, m). 4.47 (1H, d, *J* 13.7), 5.45 (1H, d, *J* 13.7), 7.14−7.31 (9H, m); δ_C (100 MHz, $CDCl_3$): 21.9, 25.3, 32.3, 33.1, 37.8, 52.4, 125.6, 126.0, 126.6, 127.4, 128.2, 128.3, 129.3, 136.4, 140.0, 146.0, 174.2; *m*/*z* (EI) 279 (M^+, 100%), 91 (100%).

Hex-5-enoic Acid Benzyl-phenyl-amide, 21. A pure sample was obtained via an independent route by the amidation of hex-5-enoic acid by *N*-benzylaniline. Colorless oil. ν_{max}(thin film)/cm^{-1} 1657 (CO). Found: C, 81.80; H, 7.63; N, 5.00. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. δ_H (270 MHz, $CDCl_3$): 1.58−1.74 (2H, m), 1.95−2.11 (4H, m), 4.88−4.95 (4H, m), 5.63−5.71 (1H, m), 6.95−6.97 (2H, m), 7.14−7.41 (8H, m); δ_C (100 MHz, $CDCl_3$): 24.6, 33.1, 33.6, 33.6, 52.9, 114.8, 127.2, 127.8, 128.3, 128.4, 128.8, 129.4, 137.6, 138.1, 142.4, 172.7; *m*/*z* (EI) 279 (M^+,34%), 183 (88), 180 (55), 91 (100).

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Supporting Information Available: Description of general experimental procedures, preparation of precursors **6**−**9**, selected NMR spectra and X-ray crystallographic data, and CIF files for compounds **11** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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