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Microwave-Enhanced Carbonylative Generation of Indanones and 3-Acylaminoindanones

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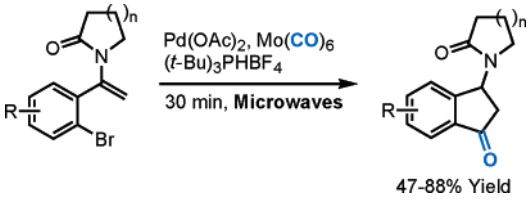


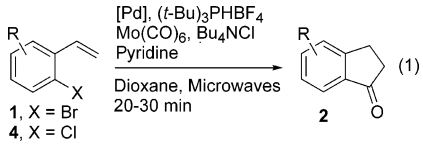
The development of microwave-accelerated protocols for palladium(0)-catalyzed carbonylative cyclization of unsaturated aryl bromides and chlorides is described. By employing *o*-bromostyryl derivatives lacking substituents on the vinylic bond, molybdenum hexacarbonyl-mediated in situ carbonylation delivered a set of indan-1-one products in high yield after only 20 min of heating. Without the addition of the tri-*tert*-butylphosphine releasing Fu-salt ((*t*-Bu)$_3$PHBF$_4$), only incomplete conversions of sluggish *o*-styryl bromides and chlorides were realized. Internal and chemoselective palladium(0)-catalyzed Heck arylations of enamides afforded suitable starting materials for subsequent rapid ring-closing reactions. Microwave-heated intramolecular in situ carbonylation of these electron-rich and sterically congested olefins conveniently afforded eight functionalized 3-acylaminoindanone derivatives in a novel synthetic process. Attempted carbonylative annulation of electron-poor *o*-bromocinnamic acid derivatives furnished only the corresponding lactones via a competing hydroxycarbonylation−Michael addition reaction sequence.

In a lead-optimization program toward the identification of improved linear HIV-1 protease[1] and plasmepsin I and II inhibitors[2] we required access to novel 1,3-difunctionalized indan structures. These structures should ideally have the potential to serve as both unique P2/P2′ residues and as precursors for further modifications. Derivatives of indanones have previously been prepared via various types of palladium-catalyzed carbonylative cyclizations.[3,4] Recently, Larock and co-workers managed to use *o*-iodostyrenes as starting materials, synthesizing five different indan-1-ones under a carbon monoxide atmosphere in modest to excellent yields.[5] Under these reaction conditions they were able to carboannulate not only monosubstituted olefins but also two examples of internally alkylated *o*-iodostyrenes. Inspired by this elegant approach, we decided to further investigate the scope of the methodology starting from the more readily available *o*-styryl bromides (**1**) and chlorides (**4**). Utilizing presynthesized 1-acylamino-*o*-bromostyrenes (**7**), we aimed to develop a novel route to 3-acylaminoindan-1-ones (**8**).

Over the past few years, the applications of controlled microwave heating[6−8] and solid-phase reagents[9] have been two areas of rapid growth, and their importance in today's chemistry is now beyond question. Despite the power these tools offer, there is still a considerable degree of effort required in setting up and performing high-speed reactions with gases. To address this issue in carbonylation chemistry, we previously identified molybdenum hexacarbonyl as an easily handled solid reagent for in situ release of carbon monoxide upon heating in sealed vessels.[10−13]

As a part of our interest in developing new, rapid, and robust chemistry suitable for medicinal chemistry applications,[7,14] we now wish to report a microwave method to prepare indan-1-ones (**2**) and 3-amidoindan-1-ones (**8**) by carbonylative cyclizations, using molybdenum hexacarbonyl as a solid source of carbon monoxide.

In our initial cyclization experiments we focused our attempts on *o*-bromostyrenes (**1**) as starting precursors (eq 1). For the preparation of styrenes **1b**−**f**, we started



from readily available *o*-bromobenzaldehydes and employed classical Wittig reactions following high-yielding literature procedures.[5] Parent compound **1a** was instead purchased from a commercial supplier. Palladium-catalyzed intramolecular carbocyclizations of **1a**−**f** were thereafter carried out with a catalytic system composed of 5% palladium acetate and 10% of the tri-*tert*-butylphosphine precursor (*t*-Bu)$_3$PHBF$_4$[15] in 2 mL of dioxane or DMF. Microwave heating at 150 °C for 20 min with 0.5 equiv of molybdenum hexacarbonyl, 1.0 equiv of Bu$_4$NCl, and 2.0 of equiv pyridine generally afforded good yields of cyclized indan-1-ones **2a**−**e** (59−82%), with the exception of the methylated **2f** (34%, entry 6, Table

(1) Alterman, M.; Björsne, M.; Mühlman, A.; Classon, B.; Kvarnström, I.; Danielson, H.; Markgren, P. O.; Nillroth, U.; Unge, T.; Hallberg, A.; Samuelsson, B. *J. Med. Chem.* **1998**, *41*, 3782−3792.
(2) Ersmark, K.; Feierberg, I.; Bjelic, S.; Hamelink, E.; Hackett, F.; Blackman, M. J.; Hultén, J.; Samuelsson, B.; Åqvist, J.; Hallberg, A. *J. Med. Chem.* **2004**, *47*, 110−122.
(3) Negishi, E.-i.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365−93.
(4) Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4089−4092.
(5) Gagnier, S. V.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 4804−4807.
(6) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283.
(7) Larhed, M.; Hallberg, A. *Drug Discov. Today* **2001**, *6*, 406−416.
(8) Kappe, C. O. *Curr. Opin. Chem. Biol.* **2002**, *6*, 314−320.
(9) Ley, S. V.; Baxendale, I. R. *Nat. Rev. Drug Discov.* **2002**, *1*, 573−586.
(10) Kaiser, N. F. K.; Hallberg, A.; Larhed, M. *J. Comb. Chem.* **2002**, *4*, 109−111.
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(12) Wannberg, J.; Larhed, M. *J. Org. Chem.* **2003**, *68*, 5750−5753.
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(14) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717−727.
(15) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295−4298.

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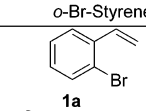
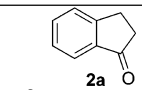
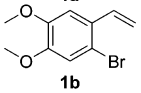
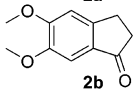
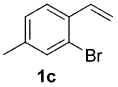
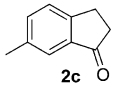
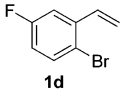
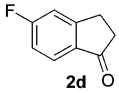
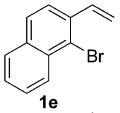
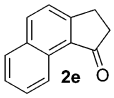
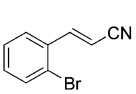
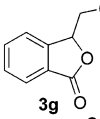
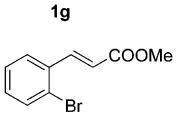
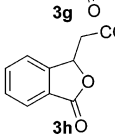
TABLE 1. Palladium-Catalyzed and Microwave-Heated Carbonylative Cyclization of *o*-Bromostyrenes

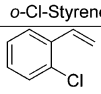
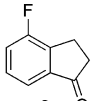
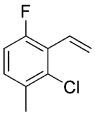
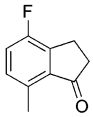
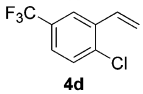
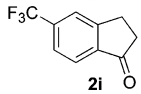
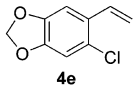
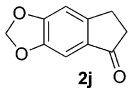
Entry	*o*-Br-Styrene	Indanone	Isolated Yield (%)[a]
1	 **1a**	 **2a**	75 70[b]
2	 **1b**	 **2b**	59 67[b]
3	 **1c**	 **2c**	77
4	 **1d**	 **2d**	79
5	 **1e**	 **2e**	82
6	 **1f**	 **2f**	34 62[c]
7	 **1g**	 **3g**	31
8	 **1h**	 **3h**	30

[a] Reaction conditions: 1.0 mmol of **1**, 5 mol % of $Pd(OAc)_2$, 10 mol % of $(t\text{-Bu})_3PHBF_4$, 0.5 equiv of $Mo(CO)_6$, 1.0 equiv of $n\text{-Bu}_4NCl$, 2.0 equiv of pyridine, and 2.0 mL of dioxane at 150 °C; microwave heating for 20 min in a sealed vessel. [b] Reaction conditions: 2.0 mL of DMF as solvent at 130 °C for 20 min. [c] Reaction conditions: 0.7 equiv of $Mo(CO)_6$ and 1.5 equiv of $n\text{-Bu}_4NCl$ without pyridine at 150 °C for 40 min.

1). In the latter case, a short series of optimization reactions provided improved conditions using 40 min of microwave heating. The highest yield of **2f** (62%, Table 1) was surprisingly experienced employing an increased amount of $Mo(CO)_6$ and Bu_4NCl, but in complete absence of the pyridine base. The pyridine-free protocol furnished only inferior yields with monosubstituted olefins **1a**−**e**, as did reactions with the alternative bases diisopropylethylamine and 4-(dimethylamino)pyridine. In all investigated cases, the use of $(t\text{-Bu})_3PHBF_4$ was essential for reaching full consumption of **1**. Thus, the released $(t\text{-Bu})_3P$ ligand produced a much superior carbonylation catalyst compared to all investigated arylphosphine ligands. With styryl derivatives that were substituted in the terminal vinylic position with electron-withdrawing groups the anticipated acylpalladium intermediate did not insert into the C−C double bond. Instead, **1g** and **1h** underwent hydroxycarbonylation and subsequent 1,4-addition to deliver the corresponding lactones **3g**,**h**[16] in relatively low yields (30−31%).

To increase the substrate scope of this in situ carbonylation, we decided to investigate challenging *o*-chlorostyrenes (**4**) as starting materials. In fact, the catalytic system employed in Table 1 with *o*-bromostyrenes (**1**) was originally developed by Fu's research group for activation

TABLE 2. Palladium-Catalyzed and Microwave Heated Carbonylative Cyclization of *o*-Chlorostyrenes

Entry	*o*-Cl-Styrene	Indanone	Isolated Yield (%)[a]
1	 **4a**	 **2a**	51 25[b]
2	 **4b**	 **2g**	43
3	 **4c**	 **2h**	34
4	 **4d**	 **2i**	30
5	 **4e**	 **2j**	26

[a] Reaction conditions: 1.0 mmol of **4**, 5 mol % of palladacycle, 10 mol % of $(t\text{-Bu})_3PHBF_4$, 0.5 equiv of $Mo(CO)_6$, 1.0 equiv of $n\text{-Bu}_4NCl$, 2.0 equiv of pyridine, and 2.0 mL of dioxane at 170 °C; microwave heating for 30 min in a sealed vessel. [b] DMF as solvent.

of sluggish aryl chlorides in related, but non-carbonylative, palladium(0)-catalyzed coupling reactions.[15] To increase the thermal stability of the catalytic system, the palladium source was switched to Herrmann's palladacycle,[17] and it was discovered that this small modification was sufficiently general to afford complete conversion of **4a**−**e** after 30 min at 170 °C in dioxane. The yields of the isolated products **2** were unfortunately low (25−51%, Table 2). GC−MS and ^1H NMR analysis on the reaction mixtures proved that dehalogenated starting materials were always formed, but only in small amounts. We therefore suspect that the moderate yields obtained were a consequence of competing polymerization of the starting styrenes **4** at the high reaction temperature (170 °C).[18]

Having established the principle of carbonylative ring closing with $Mo(CO)_6$ and *o*-halostyrenes under high temperature we turned our attention to prepare the desired 3-acylaminoindan-1-ones (**8**). Regarding the preparation of the *o*-haloaryl enamide starting materials, it has been known for some time that enamides can be regioselectively arylated at the internal α-carbon using bidentate ligands and aryl triflates following a cationic reaction route.[19] In addition, Cabri has demonstrated the high reactivity of the triflate leaving group under these cationic Heck conditions.[20] Prompted by these literature preferences, we decided to investigate *o*-bromoaryl triflates (**5**) as starting materials for the preparation of electron-rich carboannulation precursors **7a**−**h**. Using in principle the reported standard method for dppp (1,3-bis(diphenylphosphino)propane)-controlled α-arylations,[20] sluggish but very chemo- and regioselective reactions

(16) Larock, R. C.; Varaprath, S.; Lau, H. H.; Fellows, C. A. *J. Am. Chem. Soc.* **1984**, *106*, 5274−5284.
(17) *trans*-Di(μ-acetato)bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium-(II); CAS registry no. 172418-32-5.
(18) Kacker, S.; Sissano, J. A.; Schulz, D. N. *J. Polym. Sci. Part A−Polymer Chem.* **2000**, *38*, 752−757.
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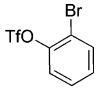
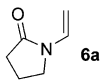
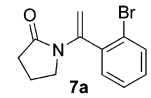
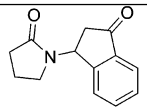
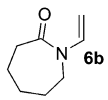
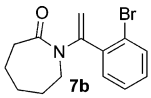
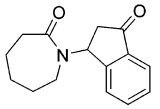
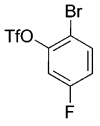
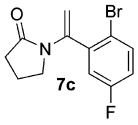
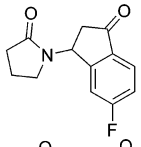
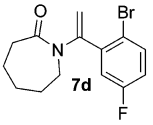
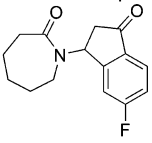
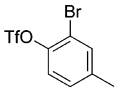
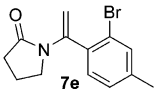
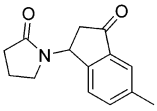
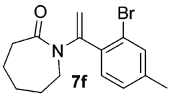
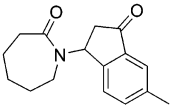
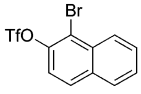
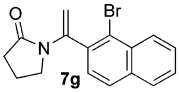
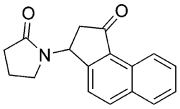
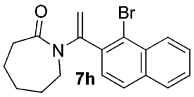
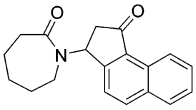
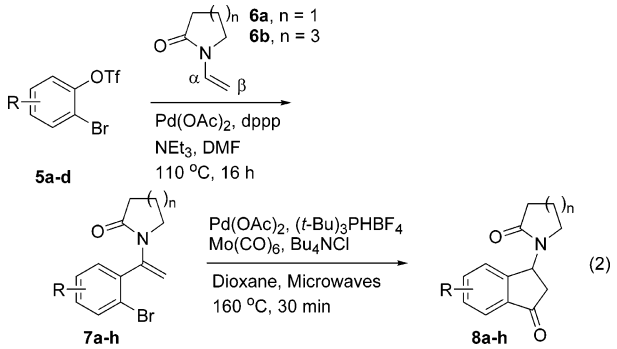
TABLE 3. Two-Step Synthesis of 3-Acylamino-1-indanones by Internal Heck Arylation and Subsequent Microwave-Heated in Situ Carboannulation

Entry	Triflate	Enamide	*o*-Bromostyrene	Isolated Yield (%)[a]	Indanone	Isolated Yield (%)[b]
1	 **5a**	 **6a**	 **7a**	44		**8a** 58 / 51[c] / 43[d] / 47[e]
2	**5a**	 **6b**	 **7b**	48		**8b** 47
3	 **5b**	**6a**	 **7c**	26		**8c** 48
4	**5b**	**6b**	 **7d**	33		**8d** 52
5	 **5c**	**6a**	 **7e**	63		**8e** 51
6	**5c**	**6b**	 **7f**	53		**8f** 55
7	 **5d**	**6a**	 **7g**	59		**8g** 84
8	**5d**	**6b**	 **7h**	78		**8h** 88

[a] Reaction conditions: 3.0 mmol of **5**, 7.5 mol % of $Pd(OAc)_2$, 15 mol % of dppp, 3.0 equiv of enamide **6a** or **6b**, 1.1 equiv of NEt_3, and 12.0 mL of DMF at 110 °C; classical heating for 16 h. [b] Reaction conditions: 0.50−0.82 mmol of **7**, 5 mol % of $Pd(OAc)_2$, 10 mol % of $(t\text{-}Bu)_3PHBF_4$, 0.5 equiv of $Mo(CO)_6$, 1.0 equiv of $n\text{-}Bu_4NCl$, 2.0 equiv of pyridine, and 2.0 mL of dioxane at 160 °C; microwave heating for 30 min. [c] Reaction conditions: 0.75 equiv of $Mo(CO)_6$. [d] Reaction conditions: 0.8 equiv of $Mo(CO)_6$ and without pyridine. [e] Cyclization according to condition b but product mixture subsequently reduced with Pd/C and HCO_2NH_4.[21]

were realized with both enamides **6a** and **6b**. Although detriflatation of starting materials **5a**−**d** were always detected, the fact that no substitution of the bromine atoms occurred simplified the purification such that this shortcoming did not compromise the viability of the reaction, except for the low yields of electron-poor **7c**,**d** (eq 2, Table 3, entries 3 and 4). Thus, the *o*-bromoaryl substituted enamides **7a**−**h** were isolated in 26−78% yield after standard silica column purification (Table 3). Higher reaction temperature furnished reduced regioselectivity and lower yields.

To produce the target compounds **8a**−**h**, electron-rich **7a**−**h** were microwave heated for 30 min on a 0.5−0.8 mmol scale using identical in situ carbonylation conditions as in the syntesis of **2a**−**e** in Table 1 except at a slightly higher reaction temperature (160 °C). Hence, products **8a**−**h** could be isolated in 47−88% yield (Table 3). In the synthesis of vinylpyrrolidinones **8a**,**c**,**e**,**g**, 5−20% of the corresponding unsaturated 3-acylaminoindenones were formed as side products, while debromination was the most pronounced side reaction with the remaining caprolactams **8b**,**d**,**f**,**h**. Different modifications of the reaction protocol were therefore investigated to improve the outcome of entry 1. However, it was experienced that the original protocol remained the best, delivering 58% of parent **8a** (Table 3). Subsequent transfer hydrogenation[21] of **8a**/3-acylamino-2-indenone reaction mixtures did not result in an improved final yield of purified **8a**. Notably no traces of acetophenones,



(2)

(20) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1992**, *57*, 3558−3563.

the hydrolysis products from α-arylated enamides **7**, were detected in any of the annulations reactions despite the high reaction temperature (160 °C).[22]

Larock has rationalized the closely related carbonylative ring closure of unsaturated aryl iodides under classical conditions in terms of a Pd(0)-catalyzed oxidative addition−carbon monoxide insertion−acylpalladium−protonation pathway.[5] In this highly plausible scenario, the released Pd(II) salt is subsequently reduced back to Pd(0) under the reductive pressure of carbon monoxide. We currently find no reason to question the validity of this mechanistic hypothesis also for the presented $Mo(CO)_6$-mediated carboannulation of *o*-styryl bromides and chlorides. Regarding the required proton/water source, we suggest that hygroscopic Bu_4NCl provides the essential water.

We have demonstrated for the first time that the combination of a thermostable catalytic system and carbon monoxide releasing $Mo(CO)_6$ with controlled microwave heating can be utilized in high-speed annulation chemistry for the production of novel indanones from either *o*-bromostyrenes or *o*-chlorostyrenes. Both neutral and electron-rich *o*-halostyrene derivatives underwent rapid and robust carbonylative cyclization without the need for an external carbon monoxide source. The ability to conduct internal Heck arylations of enamides with *o*-bromoaryl triflates without affecting the bromo group enabled easy access to annulation precursors for the rapid synthesis of valuable 3-amidoindan-1-ones. Finally, we believe that the use of microwave-assisted in situ carbonylation protocols will markedly increase the preparative convenience of carbonylative transformations in organic synthesis.

Experimental Section

General Procedure for Carboannulation of *o*-Bromostyrenes 1a−h and Isolation of Indanones 2a−2f and Lactones 3 g,h, Table 1. A 5 mL process vial was flushed with N_2 and then charged with **1** (1.0 mmol), $Mo(CO)_6$ (132.0 mg, 0.5 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), $(t\text{-}Bu)_3PHBF_4$ (29.0 mg, 0.10 mmol), $n\text{-}Bu_4NCl$ (277.9 mg, 1.0 mmol), pyridine (158 mg, 2.0 mmol), and dioxane 2.0 mL. The reaction mixture was flushed with nitrogen again and the cap was tightened thoroughly. The vessel was exposed to microwave heating for 20 min at 150 °C. The reaction tube was thereafter cooled to room temperature, and the mixture was diluted with ethyl acetate and then filtered. The precipitate was washed with ethyl acetate. The organic layer was concentrated and dissolved in 3 mL of dichloromethane. The crude product was thereafter purified on silica gel using diethyl ether and pentane as eluents to give pure indanones **2a**−**f** or lactones **3g**,**h**.

General Procedure for Formation and Isolation of Indanones 2a,g−j from *o*-Chlorostyrenes 4a−e, Table 2. A 5 mL process vial was flushed with N_2 and then charged with **4** (1.0 mmol), $Mo(CO)_6$ (132 mg, 0.5 mmol), Herrmann's palladacycle (47 mg, 0.05 mmol), $(t\text{-}Bu)_3PHBF_4$ (29 mg, 0.10 mmol), $n\text{-}Bu_4NCl$ (278 mg, 1.0 mmol), pyridine (158 mg, 2.0 mmol), and dioxane 2.0 mL. The reaction mixture was flushed with nitrogen again, and the cap was tightened thoroughly. The vessel was exposed to microwave heating for 30 min at 170 °C. The reaction tube was thereafter cooled to room temperature, and the mixture was diluted with ethyl acetate and then filtered. The precipitate was washed with ethyl acetate. The organic layer was concentrated and dissolved in 3 mL of dichloromethane. The crude product was thereafter purified on silica gel using diethyl ether and pentane to give pure indanones **2a**,**g**−**j**.

General Procedure for Internal Arylation and Isolation of Enamides 7a−h from 5a−d,[20] Table 3. A mixture of $Pd(OAc)_2$ (51 mg, 0.23 mmol), dppp (186 mg, 0.45 mmol), aryl triflate **5** (3.0 mmol),[23] NEt_3 (334 mg, 3.3 mmol), *N*-vinylpyrrolidinone **6a** (1.000 g, 9.0 mmol), or *N*-vinylcaprolactam **6b** (1.253 g, 9.0 mmol) and 12 mL of DMF was stirred at 110 °C under nitrogen for 16 h using a heating block. The crude product was concentrated with bulb-to-bulb distillation at 65 °C/1−2 mmHg. Thereafter, the residue was diluted with 5 mL of dichloromethane and purified on silica gel with a mixture of diethyl ether, hexane, and triethylamine as eluent to give pure bromo arylenamides **7**.

1-[1-(2-Bromo-4-methylphenyl)vinyl]pyrrolidin-2-one (7e). The residue was purified over silica gel with 35:65:5 diethyl ether/hexane/triethylamine as eluent to give 531 mg, yield 63%: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96−2.08 (m, 2H), 2.13 (s, 3H), 2.47 (dd, J = 8.2, 7.9 Hz, 2H), 3.48 (dd, J = 7.1, 6.9 Hz, 2H), 4.84 (s, 1H), 5.30 (s, 1H), 7.07−7.12 (m, 1H), 7.20 (d, J = 7.7 Hz, 1H), 7.34 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 20.8, 32.0, 48.6, 106.3, 121.5, 128.1, 130.8, 133.0, 135.5, 140.0, 143.0, 173.6; IR 1708 cm^{-1}; MS (*m*/*z*, relative intensity) 282 ((M^+ + 2) + H), 25), 280 ((M^+ + H), 25), 200 (100); HRMS (FAB+) calcd for $C_{13}H_{15}BrNO$ (M^+ + H) 280.0337, found 280.0323. Anal. Calcd for $C_{13}H_{14}BrNO$: C, 55.73; H, 5.04; N, 5.00. Found: C, 55.79; H, 5.09; N, 5.12.

General Procedure for Formation and Isolation of 3-Acylaminoindanones 8a−h from *o*-Bromoaryl Enamides (7a−h). A 5 mL process vial was flushed with N_2 and then charged with **7** (0.50−0.82 mmol, 1.0 equiv), $Mo(CO)_6$ (0.5 equiv), $Pd(OAc)_2$ (0.05 equiv), $(t\text{-}Bu)_3PHBF_4$ (0.1 equiv), Bu_4NCl (1.0 equiv), pyridine (2.0 equiv), and dioxane 2.0 mL. The reaction mixture was flushed with nitrogen again, and the cap was tightened thoroughly. The vessel was exposed to microwave heating for 30 min at 160 °C. The reaction tube was thereafter cooled to room temperature, and the mixture was diluted with ethyl acetate and then filtered. The precipitate was washed with ethyl acetate, and the crude product mixture was concentrated. The residue was dissolved in 3 mL of dichloromethane and purified over silica gel with petroleum ether−ethyl acetate or CH_2Cl_2−MeOH as eluent to afford pure products **8a**−**h**.

1-(5-Methyl-3-oxoindan-1-yl)pyrrolidin-2-one (8e). The reaction was run at a 0.80 mmol scale and the residue was purified on silica gel with ethyl acetate to give a colorless solid (94 mg, yield 51%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85−2.10 (m, 2H), 2.40 (s, 3H), 2.46 (t, J = 8.4 Hz, 2H), 2.51 (dd, J = 19.2, 3.2 Hz, 1H), 2.81−2.90 (m, 1H), 3.00 (dd, J = 19.2, 7.6 Hz, 1H), 3.05−3.14 (m, 1H), 5.94 (dd, J = 7.6, 3.2 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 20.8, 30.8, 40.3, 41.8, 48.3, 123.1, 125.2, 136.2, 137.0, 139.1, 149.0, 174.9, 202.6; IR 1716, 1686 cm^{-1}; MS (*m*/*z*, relative intensity) 229 (M^+, 100). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.34; H, 6.56; N, 6.17.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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