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Masked 3-Aminoindan-1-ones by a Palladium-Catalyzed Three-Component Annulation Reaction

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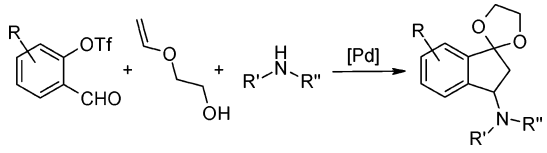

A new palladium(0)-catalyzed three-component reaction involving a set of salicylic aldehyde triflates, ethylene glycol vinyl ether, and various secondary nucleophilic amines has been developed. Through systematic optimization experiments using multivariate design, the conditions effecting robust and convenient one-pot generation of protected 3-aminoindan-1-ones were identified. A reaction route involving an initial internal Heck arylation of the hydroxyalkyl vinyl ether, iminium ion formation, and subsequent tandem cyclization is invoked to explain the selective formation of the isolated tertiary 3-aminoindan acetals. Hydrogenolysis of orthogonally blocked 3-aminoindan-1-ones delivered primary or secondary amines after 10−20 min of microwave heating.

Introduction

Indanones constitute an important class of compounds, and as a consequence thereof, several methods for their preparation have been developed. For instance, Larock has reported palladium-catalyzed carbonylative annulation reactions that frequently deliver very high yields of indanones from *o*-iodostyrenes.[1] Furthermore, Negishi observed *N*,*N*-diethylaminoindan-1-one as a byproduct in palladium-catalyzed carbonylative cyclizations starting from *o*-iodostyrenes when triethylamine was employed as the base.[1,2]

The indan skeleton is found in the P2 position in many potent aspartic protease inhibitors,[3] in particular encompassing an *N*-acylated 1-amino-2-hydroxyindan as in the HIV-inhibitor indinavir.[4] It was previously revealed by Lyle et al. that additional substituents at the 3-position of the bicyclic ring system were also well tolerated by the HIV-1 enzyme.[5] In our medicinal chemistry program,[6] we desired a method for chemoselective generation of substituted 3-aminoindan-1-ones and the corresponding glycol acetales since modeling suggested that these groups might be well accommodated in the S2 site of the protease. Previously, the preparation of 3-aminoindan-1-one was accomplished in a multistep procedure from benzaldehyde where an intramolecular Friedel−Crafts acylation of 3-amino-3-phenylpropanoic acid was a key reaction.[7,8] The corresponding *N*-substituted 3-aminoindan-1-ones were prepared via a five-step protocol involving α-bromination of 1-indanone, acetalization, dehydrobromination, removal of the protection group, and subsequent conjugate addition with various amines.

Multicomponent reactions have attracted increasing interest due to the significant preparative advantages over stepwise procedures.[9] We herein report a palladium-catalyzed three-component annulation reaction that delivers masked 3-aminoindan-1-ones in moderate to good yields. This noncarbonylative reaction sequence has the potential to smoothly provide a plethora of varied indan

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(4) Vacca, J. P.; Dorsey, B. D.; Schleif, W. A.; Levin, R. B.; McDaniel, S. L.; Darke, P. L.; Zugay, J.; Quintero, J. C.; Blahy, O. M.; Roth, E. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 4096−4100.
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(7) Dallemagne, P.; Rault, S.; Pilo, J. C.; Foloppe, M. P.; Robba, M. *Tetrahedron Lett.* **1991**, *32*, 6327−6328.
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TABLE 1. Optimization Study[a]

exp no.	[Pd] (μmol)	DPPP (μmol)	**3a** (mmol)	PMP (mmol)	resp[b] (%)
1	1	2	0.10	0.10	60
2	5	10	0.10	0.10	201
3	1	2	0.20	0.10	49
4	5	10	0.20	0.10	144
5	1	2	0.10	0.30	93
6	5	10	0.10	0.30	244
7	1	2	0.20	0.30	57
8	5	10	0.20	0.30	174
9	3	6	0.15	0.20	129
10	3	6	0.15	0.20	119
11	3	6	0.15	0.20	130

[a] Constant in all experiments: aryl triflate (**1a**) (0.10 mmol), vinyl ether (**2**) (0.30 mmol), 80 °C, 4 h (4.0 mg of naphthalene as internal standard). [b] Response = GC−MS peak area of **4a**/peak area of naphthalene × 100.

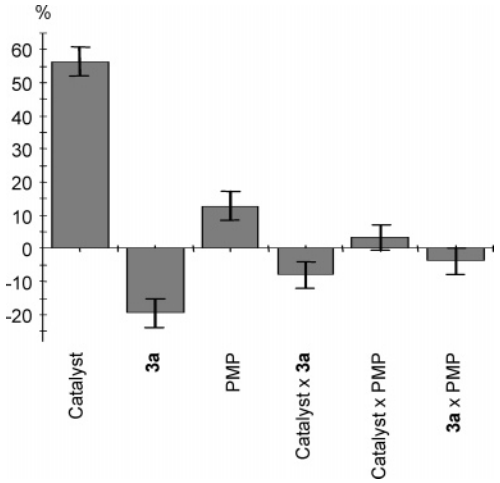
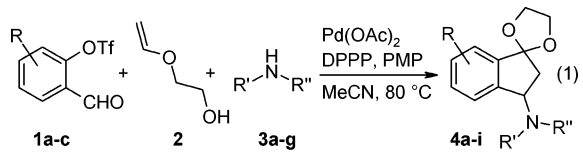


FIGURE 1. Scaled and centered coefficients (PLS, two components), $R^2 = 0.997$, $Q^2 = 0.649$, conf lev = 0.95.

structures that are not easily accessible by other synthetic methods and that should serve as useful building blocks in medicinal chemistry.

Results and Discussion

The primary aim of this study was to develop a general method for a one-pot reaction providing an entry to protected 3-aminoindan-1-one derivates (**4**) (eq 1). Salicylic aldehyde triflates (**1**), ethylene glycol vinyl ether (**2**), and various amines (**3**) constituted the reactants. Preferably this new method should be suitable for both the synthesis of primary, secondary, and tertiary amines. Unfortunately, initial attempts made with primary amines, e.g., butylamine, benzylamine, and valine methyl ester, were not successful despite manipulations of reaction temperatures as well as the relative amounts of reactants. Thus, we decided to focus our research efforts on secondary amines as starting materials with the ambition to employ benzylic derivatives as potential precursors for primary and secondary 3-aminoindanones. A model annulation reaction with aryl triflate **1a** and secondary amine **3a** (eq 1) was selected. The reaction optimization was performed using a full factorial design[10] with different concentrations of three reaction variables, the catalytic system ($Pd(OAc)_2$/DPPP (1,3-bis(diphenylphosphino)propane), 1:2), Bu_2NH, and PMP (1,2,2,6,6-pentamethylpiperidine), as outlined in Table 1 and Figure 1. To be able to compare the outcome of the reactions, naphthalene was added as internal standard. The reaction mixtures were analyzed with GC−MS, and the peak area ratio between product **4a** and naphthalene was used as the productivity response.

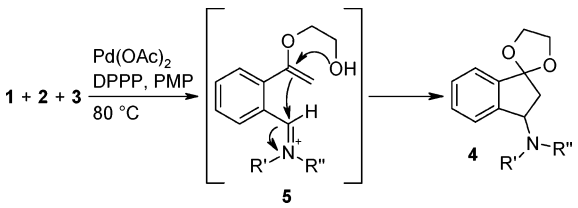


	R
1a	H
1b	3-methoxy
1c	4-methoxy

	R'	R"
3a	butyl	butyl
3b	isoamyl	isoamyl
3c	isobutyl	isobutyl
3d	isopropyl	isopropyl
3e	ethyl	cyclohexyl
3f	ethyl	benzyl
3g	benzyl	benzyl

All three varied factors were found to be of significance for the preparative outcome. The amount of palladium−phosphine catalyst had a big influence on the reaction rate, but in control experiments we could demonstrate that it did not have any effect on the yield if the reaction was heated at 80 °C for a longer time. However, the amount of PMP must be kept high, perhaps to facilitate the Pd(0) regeneration in the catalytic cycle and/or to suppress protonation of the reacting amines **3a**−**g**. The outcome of the reaction was also found to be favorable if the amount of the amine **3a** was lower than the amount of aryl triflate **1a**. There may be two primary reasons for this: First, nucleophilic amines are known to coordinate to palladium(II), consequently disturbing the catalytic cycle and making the Heck reaction less effective at high concentrations.[11,12] Second, if the amount of secondary amine in the reaction is too high the iminium ion **5** (Scheme 1) reacts further to form the corresponding

SCHEME 1. Proposed Reaction Pathway for the Formation of 4



aminal in an intermolecular process. If the aminal is formed no ring closure will occur. As demonstrated in Figure 1, it is more important to keep the concentration of the secondary amine low than to keep the amount of palladium catalyst high since the correlated cross-term between the catalyst and **3a** was found to be negative. After further experimental studies, a maximum limit of 3.0 equiv of PMP and 0.75 equiv of secondary amine (**3**)

(10) Box, G. E. P.; Hunter, W. G.; Hunter, J. S. Statistics for experimenters. *An introduction to design, data analysis, and model building*; John Wiley & Sons: New York, 1978.
(11) Olofsson, K.; Sahlin, H.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2001**, *66*, 544−549.
(12) Seligson, A. L.; Trogler, W. C. *J. Am. Chem. Soc.* **1991**, *113*, 2520−2527.

relative to the aryl triflate (**1**) was selected both to keep the amount of expensive reactants low and to accomplish an efficient workup procedure. The amount of catalyst was adjusted to 2.0 mol % securing that the reactions were completed overnight.

To evaluate the selected conditions a set of salicylic triflates and secondary amines were identified. Thus, a mixture of the salicylic triflate **1** (2.0 mmol), the secondary amine **3** (1.5 mmol), the vinyl ether **2** (6.0 mmol), palladium acetate/DPPP (0.040/0.080 mmol), PMP (6.0 mmol), and acetonitrile was heated overnight at 80 °C (eq 1). The results of the preparative reactions are outlined in Table 2.

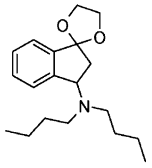
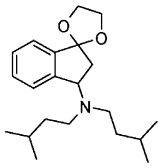
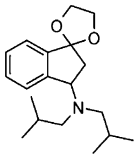
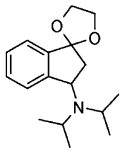
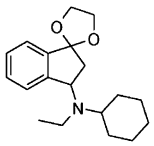
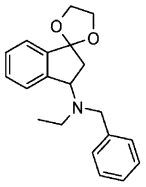
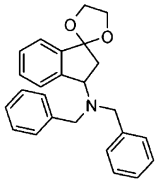
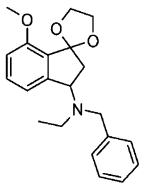
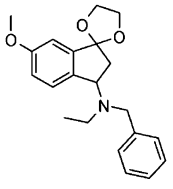
The effect of increasing sterical hindrance was studied with a selection of five different aliphatic secondary amines (**3a**−**e**). Interestingly, all products were obtained in good, comparable yields except **4d** wherein the highly hindered diisopropylamine (**3d**) was used as nucleophilic amine (entry 4). In this particular case, a considerable amount of the protected 3-hydroxy-indan-1-one was formed as a byproduct. Having a conformationally restrained tertiary carbon in the α-position in one of the *N*-alkyl groups, as in **3e**, turned out to slightly improve the yield (compare entries 1 and 5).

To investigate if the reaction was compatible with somewhat more electron-poor amines, two benzylic amines (**3f**,**g**) were examined. Our purpose when choosing benzylic amines was to explore whether benzylic amines could serve as equivalents for both primary amines and ammonia. Rewardingly, the annulation reaction worked as smoothly with benzylic amines as with aliphatic (entries 6 and 7).

We have previously reported that DPPP-controlled internal Heck reaction does not work with highly electron-withdrawing substituents on the salicylic aldehyde.[13,14] We therefore decided to include only electron-donating substituents in this study. Hence, the methoxy-substituted aryl triflates **1b**,**c** were reacted with the amine **3f**. The outcome was that compound **4h** was formed in slightly lower yield (51%) and **4i**, with the methoxy group para to the formyl group, in slightly higher yield (71%) than the corresponding parent compound **4f**. The disappointing yield of **4h** was a direct consequence of competing formation of 3-hydroxyindan-1-one acetal.

We suggest that **4** is formed by the reaction pathway presented in Scheme 1. The Heck arylation of vinyl ethers with aryl triflates and bidentate ligands is proposed to proceed via charged aryl palladium species.[15−17] Thus, the insertion process is electronically controlled leading to α-arylation of the electron-rich olefin **2**. During the reaction, the free aldehyde **1** and the corresponding iminium ion are in equilibrium. Since the iminium ion is very electron-deficient, thereby deactivating the system for internal vinylation,[14] the aldehyde form is probably more prone to undergo DPPP-controlled Heck coupling.

TABLE 2. One-Pot Synthesis of Protected 3-Aminoindan-1-ones (4)

Entry	Starting Materials		Product[a]		Isolated Yield (%)
1	**1a**	**3a**		**4a**	64
2	**1a**	**3b**		**4b**	57
3	**1a**	**3c**		**4c**	59
4	**1a**	**3d**		**4d**	17
5	**1a**	**3e**		**4e**	71
6	**1a**	**3f**		**4f**	64
7	**1a**	**3g**		**4g**	63
8	**1b**	**3f**		**4h**	51
9	**1c**	**3f**		**4i**	71

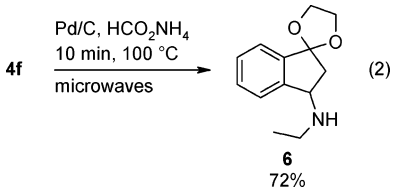
[a] All products were obtained as racemic mixtures.

(13) Bengtson, A.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 5854−5856.
(14) Larhed, M.; Andersson, C. M.; Hallberg, A. *Tetrahedron* **1994**, *50*, 285−304.
(15) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066.
(16) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2−7.
(17) Larhed, M.; Hallberg, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; John Wiley & Sons: New York, 2002; Vol. 1, pp 1133−1178.

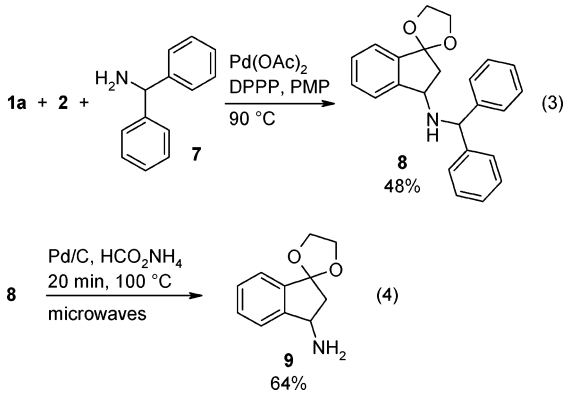
Once the iminium ion is formed on a vinylated substrate the ring closure is very fast.[18] With the methoxy group located in the para position to the formyl group (**1c**) the vinylated aldehyde is stabilized by resonance. The ring closure to the desired product **4i** via the iminium ion of type **5** is therefore a cleaner process, compared to that of the corresponding reaction with triflate **1b** where a substantial amount of 3-hydroxyindan-1-one acetal is generated after attack on the more activated aldehyde function (entries 8 and 9, Table 2). The cyclization of the charged intermediate **5** is believed to occur after initial activation of the vinyl ether by an intramolecular acetalization. Thus, the hydroxy function acts as a nucleophilic neighboring group in the annulation process.

As in the case of the previously reported one-pot synthesis of blocked 3-hydroxyindanones,[13] no monocyclized 2-aryl-2-methyl-1,3-dioxolane was detected even though the ethylene glycol vinyl ether has been successfully used previously for preparation of ketals of acetophenones from aryl triflates lacking an electrophilic group in the ortho position.[19−21]

To examine whether benzylamines could serve as equivalents for primary amines and ammonia, pure compounds **4f**,**g** were treated with Pd/C and ammonium-formiate to remove the benzyl groups. After 10 min of controlled microwave heating, compound **4f** was selectively cleaved into the desired secondary amine **6** (eq 2). Indeed, the benzylic C−N bond was cleaved rather than the benzylic indan C−N bond.



On the contrary, with the tertiary amine **4g**, carrying two benzyl groups, the indan C−N bond was cleaved preferentially, releasing dibenzylamine and carbonyl protected 1-indanon. Therefore, in the search for a more suitable ammonia equivalent we decided to revisit the use of primary amines. The sterically hindered and electron-poor α-phenylbenzylamine (**7**) was identified as a potential ammonia synthon. This compound was thought to coordinate weaker to palladium(II) than the previously studied aliphatic primary amines, at the same time as the corresponding imine should act as a reactive electrophile in the subsequent annulation.[22] Keeping the reaction conditions identical to those used for the secondary amines except for raising the temperature to 90 °C (sealed vessel), the desired *N*-protected product **8** was obtained in fair yield (eq 3). The diphenylmethyl protecting group could then be selectively cleaved into the primary amine **9** employing microwave-assisted hydrogenolysis (eq 4).



Conclusions

In conclusion, we have developed a novel one-pot method for the preparation of protected 3-aminoindan-1-ones from salicylic aldehyde triflates, ethylene glycol vinyl ether, and nucleophilic amines. Both primary, secondary, and tertiary amino products were produced and isolated in useful yields. The reaction sequence reported denotes a new type of palladium-catalyzed three-component annulation, which relies on a regioselective Heck arylation and subsequent intramolecular nucleophilic attack by the ethylene glycol vinyl ether. The protocol is expected to be useful in high-throughput synthesis of a range of 3-aminoindan derivatives.

Experimental Section

General Methods. The aryl triflates were prepared according to a fast microwave procedure.[23] All other chemicals used were commercially available.

General Procedure for the Synthesis of *N*,*N*-Disubstituted 3-Amino-1,1-(ethylenedioxy)indans (Table 2). The aryl triflate (2.0 mmol) was dissolved in MeCN (14 mL) in a reaction tube. Ethylene glycol vinyl ether (6.0 mmol, 540 μL), PMP (6.0 mmol, 1100 μL), $Pd(OAc)_2$ (40 μmol, 400 μL of 1 M stock solution in MeCN), DPPP (80 μmol, 400 μL of 1 M stock solution in MeCN), and the secondary amine (1.5 mmol) were added. The tube was flushed with N_2 and sealed with a screw cap. The reaction mixture was stirred at 80 °C for 18 h. After evaporation of the solvent the crude product was purified on basic Al_2O_3. The sample was applied to the column with a small volume of EtOAc and eluted with EtOAc, isohexane (1:4). The remaining PMP was removed in a vacuum (10 mbar, 70 °C).

3-(*N*,*N*-Dibutylamino)-1,1-(ethylenedioxy)indan (4a). The title compound was obtained in 64% yield (296 mg) as dark red, thick oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7.3, 6H), 1.20−1.30 (m, 2H), 1.30−1.39 (m, 2H), 1.40−1.49 (m, 4H), 2.19 (dd, J = 7.6, 13.4, 1H), 2.27−2.33 (m, 2H), 2.34 (dd, J = 7.1, 13.4, 1H), 2.37−2.44 (m, 2H), (4.02−4.24 (m, 4H), 4.56 (dd, J = 7.1, 7.6, 1H), 7.29−7.31 (m, 1H), 7.34−7.38 (m, 2H), 7.40−7.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 20.6, 31.1, 37.0, 50.5, 62.1, 64.8, 65.9, 115.1, 122.9, 125.1, 128.0, 129.8, 141.7, 145.7. Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.2; H, 9.6; N, 4.6. Found: C, 75.0; H, 9.4; N, 4.6.

3-(*N*-Ethylamino)-1,1-(ethylenedioxy)indan (6). Compound **4f** (124 mg, 0.40 mmol), Pd/C (10%) (43 mg, 40 μmol), ammonium formiate (250 mg, 4.0 mmol), and 4 mL of MeOH

(18) In case of sluggish amines, the intermediate vinyl-substituted salicylic aldehyde triflate was detected by LC/MS.

(19) McClelland, R. A.; Watada, B.; Lew, C. S. Q. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1723−1727.

(20) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 7858−7862.

(21) Vallin, K. S. A.; Larhed, M.; Johansson, K.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 4537−4542.

(22) Primary amines coordinate harder to palladium(II) than secondary amines, thereby retarding the catalytic cycle in the Heck reaction; see ref 12.

(23) Bengtson, A.; Hallberg, A.; Larhed, M. *Org. Lett.* **2002**, *4*, 1231−1233.

were mixed in a 5 mL process vial. The vial was sealed, and the reaction mixture was heated with microwaves to 100 °C for 10 min. After filtration, the solvent was removed in a vacuum and the crude product was extracted between EtOAc and 10% K_2CO_3(aq). The organic phase was dried with K_2CO_3(s) and evaporated to afford the title compound in 72% yield (63 mg) as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, J = 7.1, 3H), 1.73 (bs, 1H), 2.12 (dd, J = 4.9, 13.5, 1H), 2.62 (dd, J = 7.0, 13.5, 1H), 2.69−2.81 (m, 2H), 4.05−4.22 (m, 4H), 4.28 (dd, J = 4.9, 7.0, 1H), 7.27−7.41 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.6, 41.6, 45.5, 58.9, 65.3, 65.6, 115.2, 123.2, 124.8, 128.4, 129.8, 141.9, 145.3. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.2; H, 7.8; N, 6.4. Found: C, 71.0; H, 7.9; N, 6.2.

1,1-(Ethylenedioxy)-3-(α-phenylbenzylamino)indan (8). The aryl triflate (340 μL, 2.0 mmol) was dissolved in MeCN (14.0 mL) in a reaction tube. Ethylene glycol vinyl ether (6.0 mmol, 540 μL), PMP (6.0 mmol, 1100 μL), $Pd(OAc)_2$ (40 μmol, 400 μL of 1 M stock solution in MeCN), DPPP (80 μmol, 400 μL of 1 M stock solution in MeCN), and *C,C*-diphenylmethylamine (260 μL, 1.5 mmol) were added. The tube was flushed with N_2 and sealed with a screw cap. The reaction mixture was stirred at 90 °C for 18 h. After evaporation of the solvent, the crude product was purified on basic Al_2O_3. The sample was applied to the column with a small volume of EtOAc and eluted with EtOAc/isohexane (1:4). The product was further purified by recrystallization from MeOH. The title compound was obtained in 48% yield (260 mg) as pale orange crystals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (dd, J = 1.9, 11.3, 1H), 2.13 (dd, J = 5.3, 13.3, 1H), 2.65 (dd, J = 6.8, 13.3, 1H), 4.01−4.23 (m, 5H), 5.06−5.09 (m, 1H), 7.18−7.23 (m, 2H), 7.28−7.36 (m, 6H), 7.38−7.42 (m, 1H), 7.45−7.48 (m, 2H), 7.52−7.56 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.1, 56.7, 65.1, 65.4, 65.5, 115.2, 123.0, 124.9, 127.17, 127.19, 127.4, 127.5, 128.3, 128.62, 128.63, 129.8, 141.6, 143.7, 144.5, 145.9. Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.6; H, 6.5; N, 3.9. Found: C, 80.5; H, 6.6; N, 4.0.

3-Amino-1,1-(ethylenedioxy)indan (9). Compound **8** (143 mg, 0.40 mmol), Pd/C (10%) (43 mg, 40 μmol), ammonium formiate (250 mg, 4.0 mmol), and 4 mL of MeOH were mixed in a 5 mL process vial. The vial was sealed, and the reaction mixture was heated with microwaves to 100 °C for 20 min. After filtration, the solvent was removed in a vacuum and the crude product was extracted between MeCN, hexane, and an aqueous phase consisting of equal parts of brine and 10% K_2CO_3 (aq). The phases were separated, and the hexane phase was extracted three more times with MeCN. The combined MeCN phases were evaporated to afford the title compound in 64% yield (49 mg) as white crystals: ^{1}H NMR (400 MHz, CD_3OD) δ 1.95 (dd, J = 6.5, 13.4, 1H), 2.64 (dd, J = 7.1, 13.4, 1H), 4.00−4.20 (m, 4H), 4.28 (dd, J = 6.5, 7.1, 1H), 7.28−7.46 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ 48.6, 53.4, 65.9, 66.6, 115.8, 124.1, 124.9, 129.0, 131.0, 142.7, 148.2. Anal. Calcd for $C_{11}H_{13}NO_2 \cdot {}^1/_2H_2O$: C, 67.0; H, 7.0; N, 7.1. Found: C, 67.2; H, 6.9; N, 6.9.

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

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