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Diastereoselective Synthesis of Indanes via a Domino Stetter−Michael Reaction

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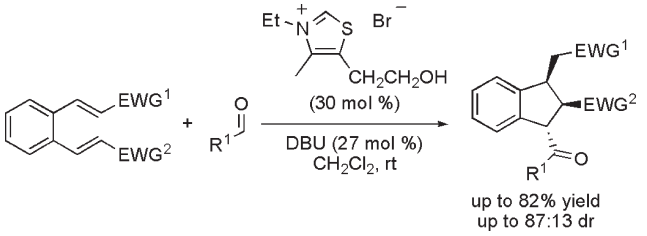
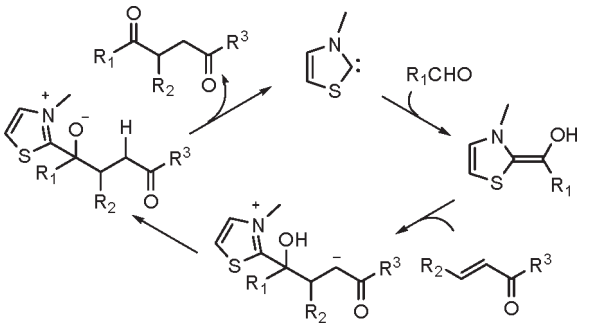


N-Heterocyclic carbenes were found to catalyze a domino Stetter−Michael reaction for the synthesis of indanes. The products were obtained in good yield and diastereomeric ratio, allowing access to highly functionalized indanes under mild conditions. In addition, the functional groups present on the indanes could be used for the synthesis of polycyclic pyrroles.

In recent years, *N*-heterocyclic carbene (NHC)-catalyzed carbon−carbon bond forming reactions have become a very intense area of research in organic chemistry.[1] One such reaction, discovered by Stetter and co-workers in the 1970s, effects the addition of aldehydes onto electron-poor olefins.[2] Thiazolium-derived NHCs were employed to reverse the typical mode of reactivity (*umpolung*[3]) of aldehydes, thus obtaining 1,4-dicarbonyl compounds containing one new stereogenic center (Scheme 1). Mechanistically, the reaction is believed to proceed through the addition of an acyl anion equivalent onto the electron-poor olefin to generate an enolate intermediate. Subsequent proton transfer and elimination of the NHC catalyst complete the catalytic cycle.[4]

Despite the formation of an enolate intermediate in this reaction, no domino process has been described that employs this synthetically useful handle. We hypothesized that this enolate intermediate could perform a nucleophilic attack onto an appropriate electrophile, such as a second electron-poor olefin. If the two olefin acceptors are linked by a tether,

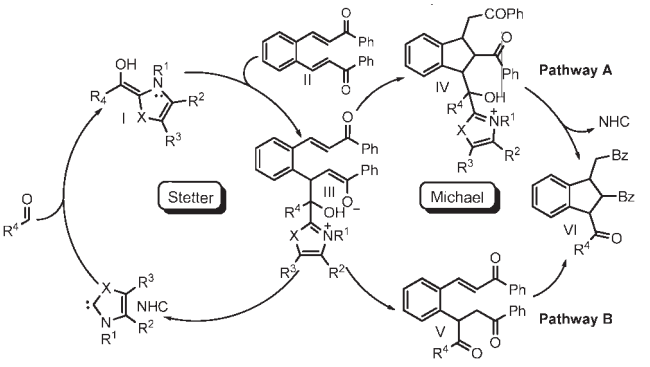
SCHEME 1. Catalytic Cycle for the Stetter Reaction



the resulting domino Stetter−Michael reaction would proceed with concomitant cyclization.[5] In the case of a phenyl derivative bearing two acceptors, the domino process would provide highly functionalized indanes, which represent an important pharmaceutical scaffold.[6]

As illustrated in Scheme 2, we envisioned that an aldehyde would react with an NHC to form a "Breslow intermediate" **I**,[7] which would then attack the Michael acceptor **II** to yield an enolate intermediate (**III**). Subsequently, this intermediate can undergo two possible cyclization pathways. In pathway A, the enolate would directly cyclize to **IV** and the catalyst would then be released to generate an indane (**VI**). In pathway B, proton transfer and ejection of the catalyst would form a simple Stetter

SCHEME 2. Domino Stetter−Michael for the Synthesis of Indanes



(1) For reviews, see: (a) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988–3000. (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655.

(2) (a) Stetter, H.; Schreckenberg, M. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 81. (b) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639–712. (c) Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, *40*, 407–496.

(3) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239–258.

(4) Hawkes, K. J.; Yates, B. F. *Eur. J. Org. Chem.* **2008**, 5563–5570.

(5) For reviews on domino reactions, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. (b) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365–2379. (c) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006. (d) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1–21. (e) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581.

(6) For examples of 1,2,3-trisubstituted indanes in medicinal chemistry, see: (a) Ho, H.; Hollinshead, S. P.; Hall, S. E.; Kalter, K.; Ballas, L. M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 973–978. (b) Ulmschneider, S.; Müller-Vieira, U.; Klein, C. D.; Antes, I.; Lengauer, T.; Hartmann, R. W. J. *J. Med. Chem.* **2005**, *48*, 1563–1575. (c) Gross, M. F.; Beaudoin, S.; McNaughton-Smith, G.; Amato, G. S.; Castle, N. A.; Huang, C.; Zou, A.; Yu, W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2849–2853. (d) Hudson, S.; Kiankarimi, M.; Eccles, W.; Mostofi, Y. S.; Genicot, M. J.; Dwight, W.; Fleck, B. A.; Gogas, K.; Wade, W. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4495–4498. (e) Camps, P.; Formosa, X.; Galdeano, C.; Gómez, T.; Muñoz-Torrero, D.; Scarpellini, M.; Viayna, E.; Badia, A.; Clos, M. V.; Camins, A.; Pallàs, M.; Bartolini, M.; Mancini, F.; Andrisano, V.; Estelrich, J.; Lizondo, M.; Bidon-Chanal, A.; Luque, F. J. *J. Med. Chem.* **2008**, *51*, 3588–3598.

(7) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726.

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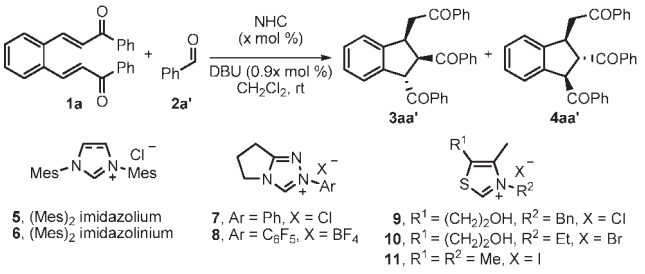
TABLE 1. Optimization of the Reaction Conditions[a]



entry	NHC	catalytic loading (×)	time (h)	yield[b] (%)	dr[c,d] **3aa′**:**4aa′**
1	**5**	50	1.5	0	
2	**6**	50	1.5	5	80:20
3	**7**	50	1.5	0	
4	**8**	50	1.5	0	
5	**9**	50	1.5	15	82:18
6	**10**	50	1.5	32	83:17
7	**11**	50	1.5	27	80:20
8[e]	**10**	30	48	64	80:20

[a]Unless otherwise noted, all reactions were performed by addition of DBU to a solution of **1a**, **2a′** (2 equiv), and precatalyst in CH_2Cl_2 (0.5 M) at room temperature. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [b]Combined yield of pure isolated **3aa′** and **4aa′**. [c]Diastereomeric ratios were determined by ^{1}H NMR on the crude reaction mixture. [d]Relative configurations of **3aa′** and **4aa′** were determined by NOE experiments (see the Supporting Information). [e]Reaction concentration = 1.0 M.

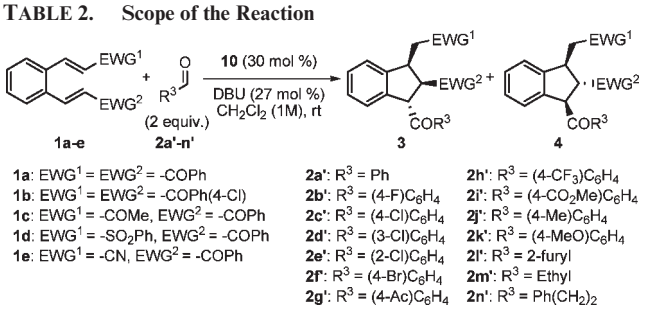
product (**V**). Under basic reaction conditions, this resulting diketone could then regenerate the required enolate to afford the indane (**VI**) following cyclization. Overall, two carbon−carbon bonds and three new contiguous stereogenic centers would be generated in the formation of the indane.

We began our studies by screening some of the main families of commercially available NHCs (Table 1). The use of commonly employed NHC precursors, such as imidazolium **5** (entry 1), imidazolinium **6** (entry 2), or triazoliums salts **7** and **8** (entries 3 and 4), led to poor conversions or no reaction. Thiazolium salts **9**, **10**, and **11** all catalyzed the reaction with superior efficiency (entries 5−7), with **10** giving the best results (entry 6). Increasing the concentration and the reaction time allowed us to reduce the catalytic loading, providing the desired indane in good yield and diastereoselectivity (entry 8). Further reduction of the catalytic loading resulted in low conversions (not shown).

Under these optimized conditions, we examined a variety of functionalized aldehydes and Michael acceptors to assess the scope of this reaction (Table 2). The use of electron-poor aldehydes usually led to good yields and diastereoselectivities (entries 2−9). On the other hand, 3- and 2-chlorobenzaldehyde (entries 4 and 5) proved to be much less reactive than 4-chlorobenzaldehyde (entry 3). We attribute the lack of reactivity for 2-chlorobenzaldehyde to steric factors.[8] The absence of a benzoin dimerization product usually observed during the course of these reactions supports this rationale.[9]

(8) The presence of ortho substituents, including Cl, was also found to decrease the rate of the benzoin reaction: (a) Miyashita, A.; Suzuki, Y.; Iwamoto, K.-i.; Igashino, T. *Chem. Pharm. Bull.* **1994**, *42*, 2633–2635. (b) Dünkelmann, P.; Kolter-Jung, D.; Nitsche, A.; Demir, A. S.; Siegert, P. *J. Am. Chem. Soc.* **2002**, *124*, 12084–12085. (c) Bag, S.; Vaze, V. V.; Degani, M. S. *J. Chem. Res.* **2006**, 267–269. (d) Iwamoto, K.-i.; Hamaya, M.; Hashimoto, N.; Kimura, H. *Tetrahedron Lett.* **2006**, *47*, 7175–7177.

TABLE 2. Scope of the Reaction



entry	acceptor	aldehyde	time (h)	yield[a] (%)	dr[b] **3**:**4**
1	**1a**	**2a′**	48	64	80:20
2	**1a**	**2b′**	10	63	80:20
3	**1a**	**2c′**	30	69	75:25
4	**1a**	**2d′**	24	18	82:18
5	**1a**	**2e′**	24	< 5	
6	**1a**	**2f′**	10	77	77:23
7	**1a**	**2g′**	18	82	80:20
8[c]	**1a**	**2h′**	4	81	80:20
9[c]	**1a**	**2i′**	0.5	74	87:13
10	**1a**	**2j′**	48	34	86:14
11	**1a**	**2k′**	48	17	83:17
12	**1a**	**2l′**	5	74	80:20
13[d]	**1a**	**2m′**	72	15 (42)[e]	52:48
14[d]	**1a**	**2n′**	24	33 (44)[e]	52:48
15[f]	**1b**	**2f′**	6	72	80:20
16[f]	**1b**	**2l′**	2	72	76:24
17[c]	**1c**	**2i′**	6	52	74:26
18[g]	**1d**	**2i′**	5	65	48:52
19[g]	**1e**	**2i′**	24	37	25:75

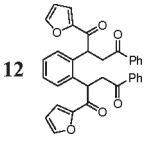
[a]Combined yield of pure isolated product diastereomers. [b]Diastereomeric ratios were determined by ^{1}H NMR on the crude reaction mixture. [c]Reaction performed at 0 °C. [d]Thiazolium **9** was used as precatalyst. [e]The number in parentheses represents the total yield of indanes (**3** + **4**) following treatment of the uncyclized side product (**V**) with DBU (27 mol %). The dr for the combined products is 25:75. [f]Reaction performed at 0.2 M. [g]1 equiv of DBU was employed.

For aldehydes bearing strong electron-withdrawing groups (entries 8 and 9), the reaction times were drastically reduced, thereby allowing the reaction to be performed at a lower temperature. As a result, when aldehydes **2h′** and **2i′** were subjected to the reaction conditions at 0 °C, noticeable improvements in the diastereomeric ratios were observed (from 57:43 to 80:20 and 67:33 to 87:13, respectively). On the other hand, electron-rich aldehydes displayed a tremendous decrease in reactivity, but still provided the indane product in good diastereoselectivity (entries 10 and 11). 2-Furaldehyde was also very reactive, affording the corresponding indane in 74% yield (entry 12).

(9) As noted previously by others, the aldehydes are consumed to generate benzoin products prior to their conversion into Stetter adducts: (a) Enders, D.; Han, J.; Henseler, A. *Chem. Commun.* **2008**, 3989–3991. (b) Liu, Q.; Perreault, S.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14066–14067.

(10) The following is the structure of the isolated product from a double Stetter addition:

12



Interestingly, we were able to isolate a side product resulting from the addition of 2-furaldehyde onto each olefin of the acceptor.[10] This side product appears to be the result of a second "Breslow intermediate" **I** attacking the simple Stetter intermediate **V**, suggesting that the major product is formed through pathway B (Scheme 2).

Aliphatic aldehydes reacted slowly at room temperature and resulted in significant amounts of Stetter product (**V**), which could be cyclized to the desired indane by using catalytic DBU (entries 13 and 14). As noted previously by Stetter and co-workers, the use of the *N*-benzyl-substituted thiazolium salt proved superior to its *N*-ethyl-substituted counterpart when using aliphatic aldehydes.[2b]

Different Michael acceptors were studied as well (entries 15−19). When the benzoyl groups on the electron-deficient olefins were replaced by 4-chlorobenzoyl groups, a slight increase in the rate was observed (entries 15 and 16). To assess the chemoselectivity in the intermolecular conjugate addition (Stetter) step, unsymmetrical acceptors containing different electron-poor olefins were employed (entries 17−19). In all cases, benzoyl-substituted olefins proved to be more reactive than acetyl-, benzenesulfonyl-, or cyano-substituted olefins, delivering the indanes as single regioisomers. When **1d** and **1e** were used, it was necessary to employ 1 equiv of base to cyclize the Stetter intermediate (entries 18 and 19).

Taken together, these results clearly show that the substitution pattern on the aldehyde plays a determinant role in the rate of the domino Stetter−Michael reaction. Indeed, electron-deficient aldehydes react very rapidly to afford the desired indanes in good yield, whereas a much more sluggish reaction is observed with electron-rich aldehydes.

When a solution of diastereomerically pure indane **3aa′** in dichloromethane was treated with catalytic DBU at room temperature, an equilibrium mixture favoring diastereomer **4aa′** was obtained after several hours (dr = 15:85). This result indicates that the domino reaction proceeds under kinetic control, with **3aa′** being favored. Therefore, the predominant formation of **3aa′** arises from a diastereoselective Michael reaction rather than a subsequent equilibration. A possible explanation for this selectivity is the stabilization of the enolate intermediate via π-stacking, leading to the cis−trans indane (Figure 1). The cis selectivity observed at C1−C2 is in sharp contrast to the trans selectivity observed in related processes in which indanes are formed from a Michael cyclization.[11] Thus, the present approach allows access to indanes that are diastereomerically and structurally distinct from previously disclosed domino methods. To confirm the relative configuration obtained from NOE experiments for **3aa′**, we obtained crystals suitable for X-ray diffraction analysis (see the Supporting Information).[12]

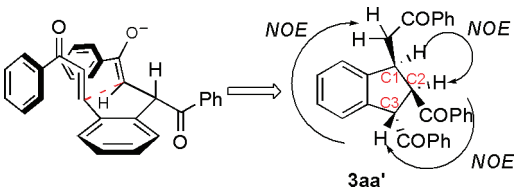
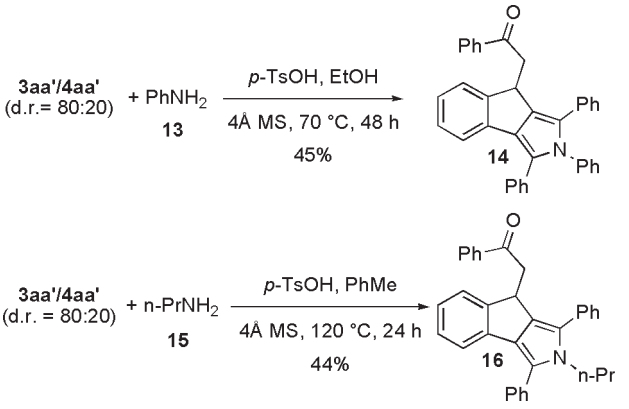


FIGURE 1. Proposed transition state for the formation of kinetic diastereomer **3aa′**.

All the indanes prepared in this study feature a 1,4-dicarbonyl pattern, which allows the elaboration of complex heterocycles via the Paal−Knorr synthesis.[13] As shown in Scheme 3, fused pyrrole-containing polycyclic structures can be generated in a straightforward manner from the indanes obtained in the domino Stetter−Michael reaction.

SCHEME 3. Paal−Knorr Synthesis of Polycyclic Pyrroles



In summary, we have developed a new NHC-catalyzed domino Stetter−Michael reaction. Aliphatic, aromatic, and heteroaromatic aldehydes were successfully employed and highly substituted indanes were synthesized with good diastereoselectivity. This process represents the first example of a domino reaction involving the enolate intermediate generated from a Stetter reaction. This new domino method for the construction of indanes is complementary to other domino reactions, providing access to a different diastereomer than the ones obtained previously. The presence of multiple functional groups on the resulting indane framework allows further derivatization, as demonstrated through the construction of polycyclic pyrroles. Enantioselective variants and synthetic applications of this reaction are currently under investigation and will be reported in due course.

Experimental Section

General Procedure for the Synthesis of Indanes: 3-(2-Oxo-2-phenylethyl)-2,3-dihydro-1*H*-indene-1,2-diyl)bis(phenylmethanone) (3aa′/4aa′). In a Schlenk flask fitted with a septum, DBU (6.1 μL, 0.04 mmol) was added to a stirred solution of **1a**[11c] (50 mg, 0.15 mmol), 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (**10**) (11.4 mg, 0.045 mmol), and benzaldehyde (**2a′**) (30.4 μL, 0.3 mmol) in CH_2Cl_2 (0.15 mL). Following the addition of DBU, the septum was replaced with a reflux condenser to avoid evaporation of solvent. The mixture was stirred for 48 h at ambient

(11) (a) Voigt, K.; Lansky, A.; Noltemeyerb, M.; de Meijere, A. *Liebigs Ann.* **1996**, 899–911. (b) Suwa, T.; Nishino, K.; Miyatake, M.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **2000**, *41*, 3403–3406. (c) Bull, S. D.; Davies, S. G.; Smith, A. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2931–2938. (d) Yang, J. W.; Fonseca, M. T. H.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036–15037. (e) Navarro, C.; Csáky, A. G. *Org. Lett.* **2008**, *10*, 217–219. (f) Navarro, C.; Csáky, A. G. *Synthesis* **2009**, 860–863. (g) For a rare example of cis-selective formation of *1,2-disubstituted* indanes from a Michael cyclization, see: Phillips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3107–3110.

(12) Crystallographic data for compound **3aa′** have been deposited with the Cambridge Crystallographic Data Centre (deposition no. CCDC 736059). Copies of the data can be obtained, free of charge, on application to the director, CCDC 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

(13) (a) Knorr, L. *Chem. Ber.* **1884**, *17*, 1635–1642. (b) Paal, C. *Chem. Ber.* **1885**, *18*, 367–371.

temperature. The reaction was then quenched with a saturated aqueous solution of ammonium chloride (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate, and the solvent was removed in vacuo. The crude product was purified by flash column chromatography on silica gel (40% hexanes/CH_2Cl_2), yielding 34.1 mg of **3aa′** and 8.4 mg of **4aa′** (64% combined yield). **3aa′** was obtained as white crystals (recrystallized from CH_2Cl_2/2-propanol): mp 115−116 °C; R_f 0.35 (100% CH_2Cl_2); FTIR (KBr film) 3064, 1680, 1596, 1579, 1448, 1217 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, J = 7.7 Hz, 2H), 8.07 (d, J = 7.7 Hz, 2H), 7.74 (d, J = 7.7 Hz, 2H), 7.66 (dd, J = 7.4, 7.4 Hz, 1H), 7.61−7.55 (m, 3H), 7.51−7.47 (m, 3H), 7.36 (dd, J = 7.3, 7.3 Hz, 2H), 7.29 (d, J = 7.5 Hz, 1H), 7.16 (t, J = 7.4 Hz, 1H), 7.08 (dd, J = 7.4 Hz, 1H), 6.89 (d, J = 7.5 Hz, 1H), 5.90 (d, J = 9.6 Hz, 1H), 5.30 (dd, J = 8.8, 8.8 Hz, 1H), 4.56 (ddd, J = 7.8, 7.8, 6.2 Hz, 1H), 3.14 (dd, J = 17.2, 8.6 Hz, 1H), 3.10 (dd, J = 17.2, 5.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3, 199.2, 198.1, 145.5, 140.3, 137.9, 137.1, 136.8, 133.9, 133.9, 133.3, 129.5, 129.2, 129.1, 128.8, 128.7, 128.2, 128.1, 127.8, 125.6, 124.4, 54.1, 52.4, 42.5, 41.1; HRMS (EI^+) m/z calcd for $C_{31}H_{24}O_3$ [M^+] 444.1725, found 444.1726. **4aa′** was obtained as a pale yellow foam: mp 48−49 °C; R_f 0.28 (100% CH_2Cl_2); FTIR (KBr film) 3342, 3065, 2928, 1681, 1596, 1580, 1480 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J = 7.3 Hz, 2H), 7.95 (d, J = 7.3 Hz, 2H), 7.92 (d, J = 7.3 Hz, 2H), 7.62 (dd, J = 7.4, 7.4 Hz, 1H), 7.55 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.6 Hz, 3H), 7.43 (dd, J = 7.8, 7.8 Hz, 2H), 7.38 (dd, J = 7.6, 7.6 Hz, 2H), 7.25 (d, J = 7.5 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.08 (t, J = 7.4 Hz, 1H), 6.89 (d, J = 7.7 Hz, 1H), 5.46 (d, J = 5.5 Hz, 1H), 4.74 (dd, J = 5.5, 5.5 Hz, 1H), 4.46 (ddd, J = 6.7, 6.4, 6.4 Hz, 1H), 3.61 (dd, J = 17.6, 6.0 Hz, 1H), 3.60 (dd, J = 17.7, 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.1, 199.4, 198.8, 145.7, 139.8, 137.2, 137.1, 136.9, 133.9, 133.4, 133.3, 129.5, 129.1, 128.9, 128.9, 128.8, 128.3, 127.6, 124.8, 124.8, 56.3, 54.3, 45.2, 43.8; HRMS (EI^+) m/z calcd for $C_{31}H_{24}O_3$ [M^+] 444.1725, found 444.1708.

Synthesis of 1-Phenyl-2-(1,2,3-triphenyl-2,8-dihydroindeno-[1,2-*c*]pyrrol-8-yl)ethanone (14). In a Schlenk flask fitted with a septum, a stirred solution of 3-(2-oxo-2-phenylethyl)-2,3-dihydro-1*H*-indene-1,2-diyl)bis(phenylmethanone) (**3aa′**:**4aa′**, dr = 80:20) (100 mg, 0.225 mmol) in THF/MeOH (2:3, 0.5 mL, 0.5 M) containing powdered 4 Å molecular sieves (25 mg) was heated to 70 °C. Aniline (**13**) (61.5 μL, 0.675 mmol) was then added, followed by *p*-toluenesulfonic acid monohydrate (42.8 mg, 0.225 mmol). The flask was fitted with a reflux condenser and the mixture was stirred at 70 °C for 48 h. The resulting mixture was then diluted with ethyl acetate (3 mL) and saturated aqueous ammonium chloride (5 mL). The organic layer was washed with brine, and then dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the crude mixture was purified by flash column chromatography on silica gel (10% ethyl acetate/hexanes) yielding a white−yellow solid (50.4 mg, 45%), mp 216−217 °C: R_f 0.45 (30/70 ethyl acetate/hexanes); FTIR (KBr film) 3055, 1682, 1597, 1495, 1443, 1355 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 7.3 Hz, 2H), 7.51−7.48 (m, 2H), 7.41 (d, J = 7.5 Hz, 1H), 7.37 (dd, J = 7.8, 7.5 Hz, 2H), 7.30−7.25 (m, 5H), 7.24−7.19 (m, 3H), 7.17−7.15 (m, 5H), 7.11−7.03 (m, 4H), 5.08 (dd, J = 9.3, 3.5 Hz, 1H), 3.33 (dd, J = 17.3, 3.7 Hz, 1H), 3.24 (dd, J = 17.3, 9.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.8, 151.3, 139.1, 137.4, 133.1, 132.8, 132.5, 132.1, 130.2, 129.3, 129.2, 129.0, 128.8, 128.6, 128.4, 128.3, 128.2, 127.6, 127.2, 127.1, 127.0, 126.6, 126.1, 125.7, 125.5, 119.7, 42.4, 38.3. HRMS (EI^+) m/z calcd for $C_{37}H_{27}NO$ [M^+] 501.2092, found 501.2084.

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Supporting Information Available: Experimental procedures, characterization data, NMR spectra for all new compounds, ORTEP representation, and a CIF file for **3aa′**. This material is available free of charge via the Internet at http://pubs.acs.org.