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Enantioselective Synthesis of (+)-Estrone Exploiting a Hydrogen Bond-Promoted Diels−Alder Reaction

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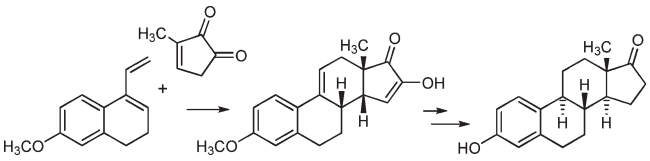

Starting from Dane's diene and methylcyclopentenedione, (+)-estrone is synthesized along the Quinkert−Dane route in 24% total yield. The key step is an enantioselective Diels−Alder reaction promoted by an amidinium catalyst as efficiently as by a traditional Ti-TADDOLate Lewis acid.

Estrone **7**, due to its relatively simple structure and its considerable pharmaceutical importance, has become—and still is—a most popular target compound for the development of novel synthetic methodologies.[1,2] This applies in particular to the Diels−Alder reaction:[3] numerous milestone achievements of constitutional and stereochemical control are closely associated with synthetic approaches toward estrone and related estrogens. Beginning with Dane's unsuccessful attempt to synthesize *rac*-**3** from diene **1** and diketone **2**,[4] Valenta's variant[5] of Johnson's synthesis[6]—both starting from diene **1**[7]—is among the early applications of Lewis acid catalyzed Diels−Alder reactions[8] in natural product synthesis. With the advent of effective chiral Lewis acids, Dane's concept regained attention. A TADDOL (α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol) based titanium Lewis acid[9] allowed Quinkert for the first time to implement Dane's original concept with high levels of constitutional control and enantioselection.[10] More recently Corey has demonstrated the utility of his oxazaborolidinium catalysts by synthesizing (+)-estrone from diene **1**.[7b,c]

Although the field of enantioselective catalysis was dominated in the past by metal containing catalysts, the past decade has seen an important number of highly selective reactions catalyzed by hydrogen bond donors such as chiral ureas and thioureas.[11] The acceleration of Diels−Alder reactions by hydrogen bonds was reported even prior to Lewis acid catalysis.[12] However, when compared to traditional strong Lewis acids, hydrogen bond donors are mostly considered to be rather weak electrophiles that are inferior at least in terms of rates. In contrast to this view, we will show below that a metal free catalyst forming up to three hydrogen bonds with diketone **2** promotes the Diels−Alder reaction with diene **1** as efficiently as the best titanium TADDOLates used earlier in this step, thus leading to a new organocatalytic variant of the Quinkert−Dane synthesis of (+)-estrone (Scheme 1).

In previous studies we demonstrated the hydrogen bond-mediated complexation of diketone **2** and lipophilic amidinium ions, resulting in a significant acceleration of the cycloaddition with Dane's diene **1**.[13] Axially chiral amidine **8a**[14] was intended to form three hydrogen bonds with dienophile **2**.[15] However,

(1) Selected classical syntheses: (a) Anner, G.; Miescher, K. *Helv. Chim. Acta* **1948**, *31*, 2173–2183. (b) Ananchenko, S. N.; Torgov, I. V. *Tetrahedron Lett.* **1963**, *4*, 1553–1558. (c) Rufer, C.; Schröder, E.; Gibian, H. *Justus Liebigs Ann. Chem.* **1967**, *701*, 206–216. (d) Cohen, N.; Banner, B. L.; Eichel, W. F.; Parrish, D. R.; Saucy, G.; Cassal, J.-M.; Meier, W.; Fürst, A. *J. Org. Chem.* **1975**, *40*, 681–685. (e) Eder, U.; Gibian, H.; Haffer, G.; Neef, G.; Sauer, G.; Wiechert, R. *Chem. Ber.* **1976**, *109*, 2948–2953. (f) Bartlett, P. A.; Johnson, W. S. *J. Am. Chem. Soc.* **1973**, *95*, 7501–7502.

(2) Selected recent syntheses: (a) Quellet, L.; Langlois, P.; Deslongchamps, P. *Synlett* **1997**, 689–690. (b) Tietze, L. F.; Nöbel, T.; Spescha, M. *J. Am. Chem. Soc.* **1998**, *120*, 8971–8977. (c) Pattenden, G.; Gonzales, M. A.; McCulloch, S.; Walter, A.; Woodhead, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12024–12029. (d) Lim, C.; Evenson, G. N.; Perrault, W. R.; Pearlman, B. A. *Tetrahedron Lett.* **2006**, *47*, 6417–6420. (e) Soorukram, D.; Knochel, P. *Org. Lett.* **2007**, *9*, 1021–1023. (f) Yeung, Y.-Y.; Chein, R. J.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 10346–10347. (g) Herrmann, P.; Buděšínský, M.; Kotora, M. *J. Org. Chem.* **2008**, *73*, 6202–6206.

(3) Synthesis of estrogens by intramolecular Diels−Alder reactions of *o*-quinodimethanes: (a) Kametani, T.; Matsumoto, H.; Nemoto, H.; Fukumoto, K. *J. Am. Chem. Soc.* **1978**, *100*, 6218–6220. (b) Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5253–5261. (c) Oppolzer, W.; Roberts, D. A. *Helv. Chim. Acta* **1980**, *63*, 1703–1705. (d) Grieco, P. A.; Takigawa, T.; Schillinger, W. J. *J. Org. Chem.* **1980**, *45*, 2247–2251. (e) Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1981**, *103*, 476–477. (f) Quinkert, G.; Schwartz, U.; Stark, H.; Weber, W.-D.; Adam, F.; Baier, H.; Frank, G.; Dürner, G. *Liebigs Ann. Chem.* **1982**, 1999–2040. (g) Hakuba, H.; Kitagaki, S.; Mukai, C. *Tetrahedron* **2007**, *63*, 12639–12645. (h) Djuric, S.; Sarkar, T.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 6885–6886. (i) Nicolaou, K. C.; Barnette, W. E.; Ma, P. *J. Org. Chem.* **1980**, *45*, 1463–1470.

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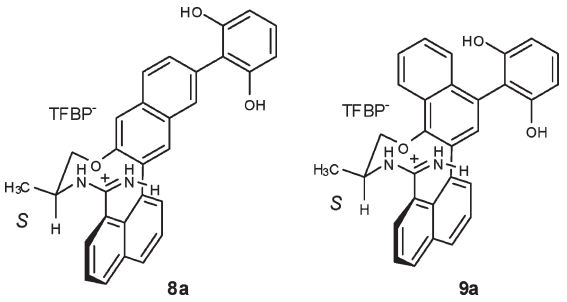
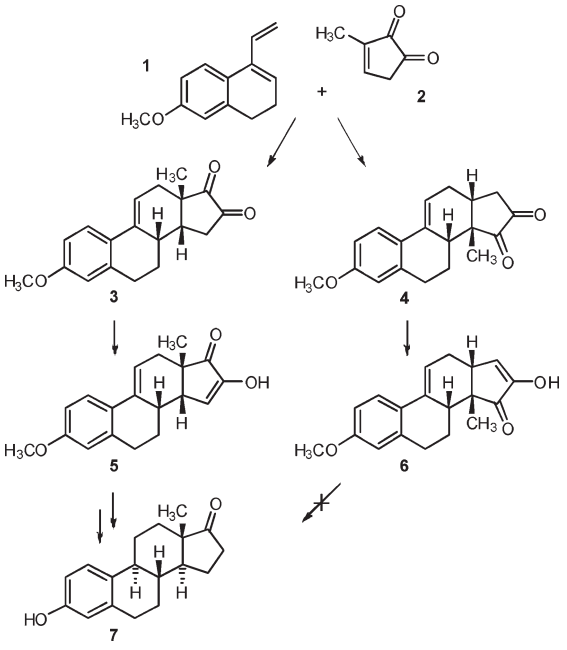


FIGURE 1. Structures of axially chiral amidinium salts used as catalysts in the cycloaddition step ($TFPB^- =$ tetrakis(3,5-bis(trifluoromethyl)phenyl)borate).

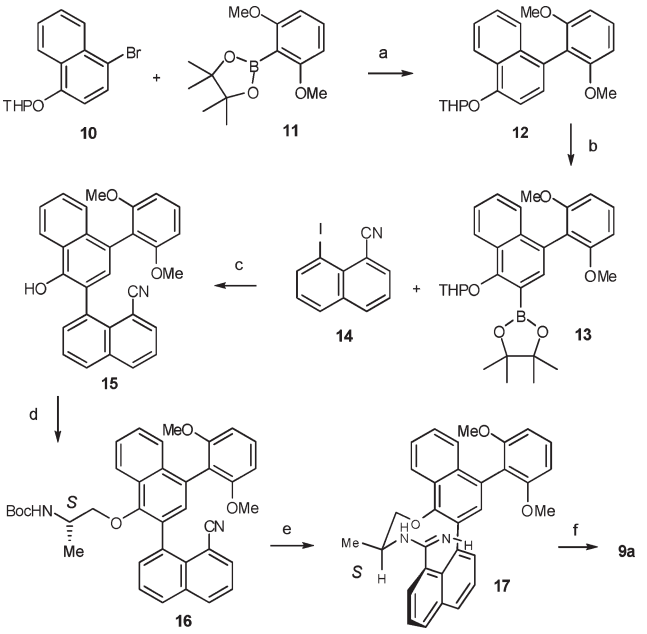
SCHEME 1. The Cycloaddition of Dane's Diene 1 Leading to Estrone 7 via Intermediates 3 and 5



reaction rates suggested that the resorcinol moiety of **8a** does not participate in substrate binding and activation. A crystal structure of a related compound later revealed a considerable distortion of the molecular framework displacing the hydroxy groups of **8a** thus preventing hydrogen bond formation with diketone **2** (Figure 1). In spite of this drawback, amidinium salt **8a**, like a Lewis acid catalyst, shifted the constitutional selectivity of the cycloaddition in favor of isomer **5** and induced up to 26% ee (43% ee when the methyl group of **2** was replaced by ethyl). The predominant configuration of product **5** is explained by an *endo* attack of the diene to the *Si*,*Si* face of dienophile **2** when bound to the chiral amidine.[15]

Having identified the reason for the moderate success of compound **8a**, we recently embarked on the synthesis of an optimized amidinium catalyst **9a** (Scheme 2). By changing the substitution pattern of the central naphthalene unit, the hydroxy groups are now closer to the amidinium ion and steric shielding around the substrate binding site is improved. Starting from 1-hydroxynaphthalene, resorcinol, and 8-iodo-1-naphthonitrile **14**, a sequence of bromination and cross coupling reactions afforded precursor molecule **15** as a racemic mixture of two conformers, slowly interconverting by rotation

SCHEME 2. Synthesis of Catalyst 9a[a]



[a]Conditions: (a) 1.1 equiv of **11**, 0.1 equiv of $Pd(PPh_3)_4$, DME, aqueous Na_2CO_3, 80 °C, 4 h, 91%; (b) (1) 1.1 equiv of *n*-BuLi, THF, −20 to −5 °C, (2) 1.1 equiv of 2-isopropoxy-4′4′5′5′-tetramethyl-1,3,2-dioxaborolane, 82%; (c) (1) 1.1 equiv of **13**, 0.1 equiv of Pd/C, DME, aqueous Na_2CO_3, 80 °C, 1 h, (2) PPTS, CH_2Cl_2, rt, 1.5 h, 77%; (d) 3 equiv of Cs_2CO_3, 2 equiv of *O*-mesylate of (*S*)-*N*-Boc-alaninol, DMF, 60 °C, 42 h, 97%;. (e) (1) TFA, CH_2Cl_2, rt, (2) 1 equiv of CuI, 2.1 equiv of LiHDMS, 1,4-dioxane + THF, Δ, 2 h, 33−46%; (f) (1) 5 equiv of BBr_3, CH_2Cl_2, rt, 2 h, (2) picric acid, (3) ion exchange, 61%.

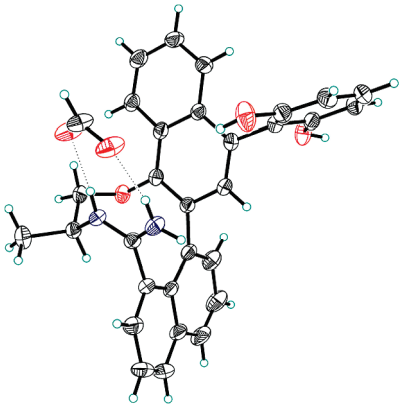


FIGURE 2. Crystal structure of amidine **9** as formic acid salt **9b**.

around the naphthalene−naphthalene axis (see the Supporting Information). Attachment of (*S*)-alaninol (→**16**), base induced stereoselective cyclization[14] (→**17**), and removal of protective groups led to amidine **9a** as a single isomer, accessible in gram amounts. A weakly coordinating counterion is crucial for the effective binding of neutral substrates and also increases catalyst solubility in nonpolar solvents at low temperatures.[13]

A crystal structure of amidinium salt **9b** (counterion: formate) reveals how hydrogen bond accepting guest molecules may bind to the cationic cleft (Figure 2). The formate oxygens sit on top of the amidinium NH with N···O distances of 2.80 and 2.82 Å, respectively. One of the resorcinol OH groups points toward a formate oxygen (O···O: 3.91 Å). Both

groups are well placed to form a third host−guest hydrogen bond in solution, which is prevented in the crystal by a competing OH···O bond from a neighbor molecule (O···O: 2.66 Å, see the Supporting Information).

The catalytic potential of amidinium salt **9a** was characterized by determining the cycloaddition kinetics of Dane's diene **1** (45 mM) and diketone **2** (30 mM) in CH_2Cl_2 at 4−5 °C. Reaction rates are calculated from the reduction of diene concentrations as detected by HPLC. When a minor correction term is introduced for the dimerization of **1**,[16] the reaction of **1** and **2** obeys a second order rate law. Compared to the uncatalyzed reaction (an upper limit for k_2 of 4×10^{-8} mM^{-1} s^{-1} can be estimated) 1 equiv of **9a** gives a roughly 550-fold acceleration ($k_2 = 2.2 \times 10^{-5}$ mM^{-1} s^{-1}), 4-fold above the rates seen with our previous catalyst **8a** ($k_2 = 5.3 \times 10^{-6}$ mM^{-1} s^{-1}). Thus, reaction kinetics supports the view of three hydrogen bonds involved in the catalyst−substrate complex. Further analysis is complicated by the fact that of the primary cycloadducts **3** and **4** only the latter tautomerizes readily to the keto enol stage.[13] Since we have observed quite different tautomerization rates for **3** and *ent*-**3** induced by chiral amidinium catalysts, a proper analysis of constitutional ratios and enantioselectivities requires complete tautomerization to the keto enols **5** and **6**. This can be enforced by addition of water prior to HPLC analysis. On the basis of HPLC, catalyst **9a** under these conditions gives 92% total yield of cycloadducts, a ratio of **5** and **6** of 4.7:1 and 60% ee favoring the non-natural enantiomer *ent*-**5**. Interestingly, amidinium salt **9a** directs the cycloaddition to the opposite face (*Re*,*Re*) of the diketone as catalyst **8a**. Lowering the reaction temperature to −30 °C increased the ee to 76% and the ratio of **5** and **6** to 7.5:1. Reduction of the catalyst load to 10 mol % just caused a minor loss of selectivity (73% ee). The absolute configuration of *ent*-**5**, established previously by chemical correlation,[15] could be confirmed by converting the compound into its TBDPS ether. Recrystallization led to an enantiomerically pure sample that allowed the determination of the stereochemistry by the anomalous X-ray dispersion effect of silicon (via Flack parameters, see the Supporting Information).

A simplistic approach to explain the antipodal influence of catalysts **8a** and **9a**, both exhibiting identical absolute configurations, is shown in Figure 3. While the OH groups of catalyst **8a** seem not to form hydrogen bonds with substrate **2** their steric influence will favor orientation b over a. Shielding of the backface by the naphthalene moiety should then direct diene **1** to the *Si*,*Si* face of **2**, leading to the observed natural configuration of product **5**. In catalyst **9a**, the OH group comes closer to the diketone. Thus by formation of bifurcated H-bonds the substrate may be tilted relative to the catalyst (bottom: c, d). Steric clashes with the amino ether and naphthalene moieties are reduced in orientation c, now exposing the *Re*,*Re* face of the diketone to Dane's diene. The Curtin−Hammet principle is respected insofar as stronger H-bonds will stabilize a complex while increasing at the same time its reactivity. It should be kept in mind, however, that additional attractive or repulsive interactions between catalyst and diene or the counterion, which are entirely neglected in Figure 3, may be decisive for the total transition state energies.

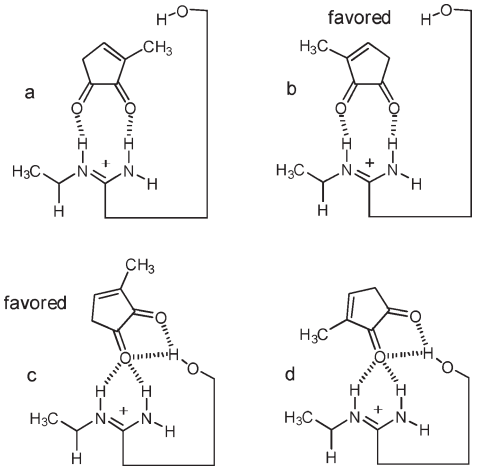


FIGURE 3. Schematic representation of host−guest orientations that may arise between diketone **2** and catalyst **8a** (top; a, b) or catalyst **9a** (bottom: c, d), respectively. The backface is shielded by the naphthalene moieties.

To synthesize naturally configurated (+)-estrone **7**, we prepared the amidinium salt *ent*-**9c** (TPPB salt, tetrakis(pentafluorophenyl)borate) from intermediate **15** and (*R*)-alaninol (Scheme 3). The preparative Diels−Alder reaction was then conducted in CH_2Cl_2 at −30 °C, using 15 mol % of catalyst *ent*-**9c**. After 2 d the reaction product—containing cycloadducts **3** and **5**—was isomerized by addition of HCl. High yields of ketoenols **18** + *ent*-**18** (91%) and only traces of constitutional isomers (resulting from cycloadduct **6**) could be isolated. Reduction of the enol triflates by published methods[10,17] led to the enones **19** + *ent*-**19** (71%). At this stage an enantiomeric excess of 81% ee was determined. It could be raised to 99.1% ee by a single recrystallization from MeOH (83%).[18] Torgov's diene **20**[1b] was obtained from **19** in a deprotonation/protonation sequence under kinetic control (74%). This compound could be stereoselectively reduced by a known two-step procedure consisting of catalytic hydrogenation followed by treatment with acid and Et_3SiH (→**21**, 82%).[2f,10] Ether cleavage finally led to (+)-estrone **7** (74%; ee > 99.9%). Thus, a total yield of 24% can be achieved from diketone **2** including all purification steps. Catalyst **9a** also promoted the cycloaddition of **1** and the ethyl analogue of diketone **2**. Replacing the methyl group of **2** by ethyl retarded the Diels−Alder reaction 3-fold and also lowered the enantiomeric excess to a still significant 58% ee (CH_2Cl_2, −30 °C, 20 mol % of **9a**).

How does catalyst *ent*-**9c** compare to titanium TADDOLates? To achieve high levels of enantioselectivities, sterically demanding TADDOL derivatives are required. For the best case (9-phenanthryl, 2 equiv of of catalyst, 1.5 equiv of **1**, 1 equiv of **2**, −80 °C, 2 d) 64% yield of ketoenols **18** + *ent*-**18** was reported with 93% ee.[10c] With use of substoichiometric amounts of Ti-TADDOLate (0.25 equiv, −80 °C) the ee

(16) Diels−Alder dimerization of Dane's diene: (a) Torgov, I. V.; Nazarov, I. N. *Zh. Obshch. Khim.* **1959**, *29*, 787. (b) Kuo, C. H.; Taub, D.; Wendler, N. L. *J. Org. Chem.* **1968**, *33*, 3126–2132.

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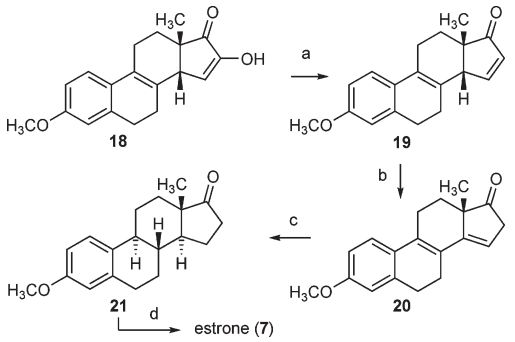
(18) A recrystallization yield of 83% requires the original enantiomeric excess to be higher than the reported value of 81% ee. This discrepancy may be explained by a nonhomogeneous distribution of enantiomers in the solid product of **19** + *ent*-**19** when the sample for ee determination was taken.

SCHEME 3. Synthesis of (+)-Estrone 7[a]



[a]Conditions: (a) (1) Tf_2O, 2,6-lutidine, (2) Et_3SiH, $PdCl_2$(dppf), DMF, 60 °C, 20 min, 71% (81% ee), (3) recrystallization from MeOH, 83% (99.1% ee); (b) LiHMDS, THF, −78 °C, then addition of AcOH, 74%; (c) (1) H_2, Pd/C, C_6H_6, 0 °C, 12 h, (2) TFA, Et_3SiH, rt, 13 h, 82%; (d) (1) BBr_3, CH_2Cl_2, 0 °C, 4 h, 85%, (2) purification by HPLC, 87% (ee >99.9%).

dropped to 85%. However, after prolonged reaction time (7 d) the yield improved to 78%.[10c] The total yield of recrystallized, enantiomerically pure intermediate **19** attainable by this method equals fairly well the results obtained with catalyst *ent*-**9c** (0.15 equiv of *ent*-**9c**, 1.5 equiv of **1**, 1 equiv of **2**, −30 °C, 2 d, 91%, 81% ee). Thus, axially chiral amidinium ions can compete in terms of rates and stereoselectivity with a well-established class of traditional chiral Lewis acids. The synthesis of *ent*-**9c**, undeniably, is more complex than the preparation of TADDOLs. It is also true that Lewis acids of the type $TiCl_2(OR)_2$ are milder than $TiCl_4$ or BF_3. The remaining challenge therefore is to identify simple cationic hydrogen bond donors that may rival the reactivity and selectivity of the most potent chiral Lewis acids. Toward this aim, we have already found chiral bisamidinium salts[19] that combine good synthetic accessibility with rate effects distinctly beyond that of axially chiral amidinium salts.[19a]

Experimental Section

Diels−Alder Reaction Yielding Cycloadducts 18 + *ent*-18. Diketone **2** (225 mg, 2.04 mmol) and catalyst *ent*-**9c** (TPPB salt, 400 mg, 0.30 mmol, 0.15 equiv) were dissolved in CH_2Cl_2 (24 mL), cooled to −30 °C in a polypropylene tube,[20] and then treated with a precooled solution of diene **1** (570 mg, 3.06 mmol, 1.5 equiv) in CH_2Cl_2 (10 mL). After 2 days at −30 °C, the mixture was warmed overnight to rt and concd HCl (5 drops) was added. It was intensively stirred for 30 min, filtered over $MgSO_4$, and evaporated to dryness. The residue was chromatographed on silica gel (*n*-hexane/EtOAc 4:1) to yield enol **18** + *ent*-**18** as an orange foam (550 mg, 91%). It was not further purified by recrystallization to allow a proper ee determination after the subsequent step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, J = 8.7 Hz, 1 H), 6.71 (dd, J = 8.7, 2.6 Hz, 1 H), 6.70 (s, 1 H), 6.54 (d, J = 3.1 Hz, 1 H), 5.36 (s, 1 H, O*H*), 3.80 (s, 3 H, OCH_3), 3.01 (br s, 1 H), 2.84−2.69 (m, 2 H), 2.47−2.36 (m, 2 H), 2.26−2.09 (m, 2 H), 1.94 (ddd, J = 13.1, 7.0, 4.5 Hz, 1 H), 1.64 (ddd, J = 13.1, 8.3, 4.5 Hz, 1 H), 1.24 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4, 158.3, 150.0, 136.7, 129.7, 128.72, 128.67, 128.4, 123.4, 113.5, 111.0, 55.3, 49.3, 45.7, 32.0, 28.6, 27.4, 22.8, 22.4. Anal. Calcd for $C_{19}H_{20}O_3 \cdot 0.3$ EtOAc: C, 75.16; H, 6.99. Found: C, 75.28; H, 6.86.

Reduction, Determination of ee, and Recrystallization To Obtain Enantiomerically Pure Enone 19.[10c] Enol **18** + *ent*-**18** (550 mg, 1.85 mmol) was dissolved in dry CH_2Cl_2 (27 mL) and treated simultaneously at 0 °C with Tf_2O (0.68 mL, 4.05 mmol, 2.2 equiv) and 2,6-lutidine (0.50 mL, 4.32 mmol, 2.3 equiv). After 1 h the solvent was evaporated and the residue purified on silica gel (*n*-hexane/EtOAc 4:1) to obtain an orange-brown oil that was dissolved in dry DMF (10 mL) along with $PdCl_2$(dppf) (32 mg, 0.039 mmol, 0.02 equiv). After heating to 60 °C, Et_3SiH (0.80 mL, 5.00 mmol, 2.7 equiv) was added and the solution was stirred for 20 min at this temperature. Then the reaction mixture was partitioned between Et_2O and H_2O, the aqueous phase was extracted with Et_2O, and the combined organic phase was washed with sat. $NaHCO_3$ and brine. After drying ($MgSO_4$) the solvent was removed in vacuo and the residue purified on silica gel (*n*-hexane/EtOAc 4:1) yielding enone (**19** + *ent*-**19**) as a slightly pink solid (370 mg, 71%), the ee of which was determined by chiral HPLC (DAICEL OJ, *n*-hexane/^{i}PrOH 10 + 4, 0.8 mL·min^{-1}, t_{major} = 12.4 min, t_{minor} = 21.7 min) to be 81%. Recrystallization from MeOH improved the ee to 99.1% (28 mL MeOH, reflux →4 °C; 370→307 mg, 83%). Recrystallized **19**: mp 156−158 °C (lit.[7a] mp 151−153 °C, lit.[10c] mp 160 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (dd, J = 5.6, 2.6 Hz, 1 H), 7.09 (d, J = 7.8, 0.8 Hz, 1 H), 6.72 (dd, J = 7.8, 2.7 Hz, 1 H), 6.70 (s, 1 H), 6.12 (dd, J = 5.8, 2.2 Hz, 1 H), 3.80 (s, 3 H, OCH_3), 3.15 (br s, 1 H), 2.90−2.70 (m, 2 H), 2.51−2.36 (m, 2 H), 2.30−2.21 (m, 1 H), 2.20−2.08 (m, 1 H), 1.92 (ddd, J = 13.0, 7.1, 4.6 Hz, 1 H), 1.60 (ddd, J = 13.0, 8.2, 4.6 Hz, 1 H), 1.20 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.4, 162.5, 158.3, 136.7, 130.6, 129.6, 128.7, 128.4, 123.4, 113.6, 111.0, 55.6, 55.3, 46.9, 31.6, 28.7, 27.5, 22.5, 22.3. Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.34; H, 7.19.

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Supporting Information Available: Experimental details for the syntheses of amidinium salt *ent*-**9c** and of (+)-estrone **7**, characterization data for all compounds, ^{1}H and ^{13}C NMR spectra, determination of ee values and of reaction kinetics, and crystal structure data for compounds *ent*-**5** and **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) (a) Tsogoeva, S. B.; Dürner, G.; Bolte, M.; Göbel, M. W. *Eur. J. Org. Chem.* **2003**, 1661–1664. (b) Akalay, D.; Dürner, G.; Bats, J. W.; Bolte, M.; Göbel, M. W. *J. Org. Chem.* **2007**, *72*, 5618–5624.

(20) Catalysis by glass surfaces (or by silica gel) is known to induce a nonselective background reaction; see ref 13.