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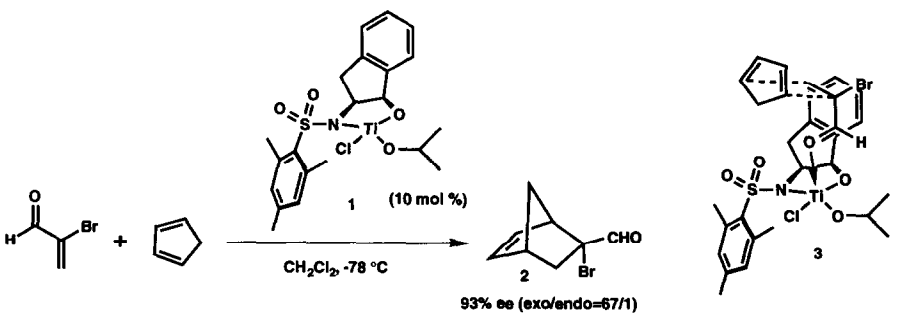
CATALYTIC ENANTIOSELECTIVE DIELS-ALDER REACTIONS USING TITANIUM COMPLEXES OF *CIS-N*-SULFONYL-2-AMINO-1-INDANOLS

E. J. Corey,* Thomas D. Roper, Kazuaki Ishihara and Georgios Sarakinos

Department of Chemistry, Harvard University, Cambridge, Massachusetts, 02138

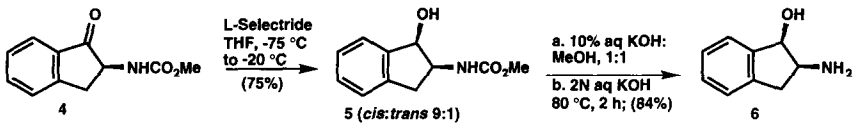
Summary: *A titanium complex derived from (1R, 2S)-N-(2,4,6-trimethylbenzenesulfonyl)-2-amino-1-indanol catalyzes the Diels-Alder reaction of 2-bromoacrolein and cyclopentadiene with 96.5:3.5 enantioselectivity. A new and efficient synthesis of 2-amino-1-indanol (**6**) contributes to the potential of this methodology.*

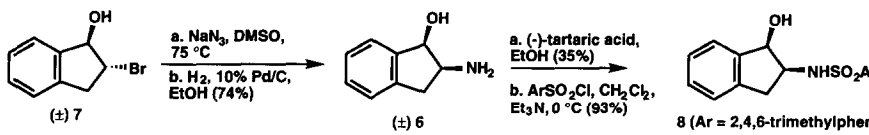
Recently we reported the highly enantioselective Diels-Alder reactions of 2-bromoacrolein and various dienes employing chiral 1,3,2-oxazaborolidines as catalysts.[1] The success of this class of catalysts which achieve selectivity through π-attractive interactions as well as the usual steric repulsions encouraged us to seek new catalytic systems which exploit π-neighboring group interactions and which in addition contain a Lewis acidic site that is capable of octahedral geometry about the metal. We envisioned the possibility that the 2-amino-1-indanol derived complex **1**, if obtainable, could provide a favorable reaction channel via the transition state assembly **3** which involves dienophile coordination at the axial site proximal to the indane aromatic moiety. In this complex the aldehyde assumes a parallel orientation to the indane ring system which is facilitated by the presence of the octahedral transition metal geometry[2] and in addition reacts preferentially through the *s-cis* conformation as has been noted in other catalytic systems.[1a,b]



Aminoindanol **6** was synthesized from (*S*)-2-[(methoxycarbonyl)amino]-1-indanone[3] (available from (*S*)-phenylalanine) by L-selectride reduction in THF (-75 °C for 4 h and -20 °C for 2 h; *cis*:*trans* 9:1) followed by basic hydrolysis (10% aqueous KOH:MeOH 1:1; then 2M KOH, 80 °C, 2 h) in 62% overall yield as a stable

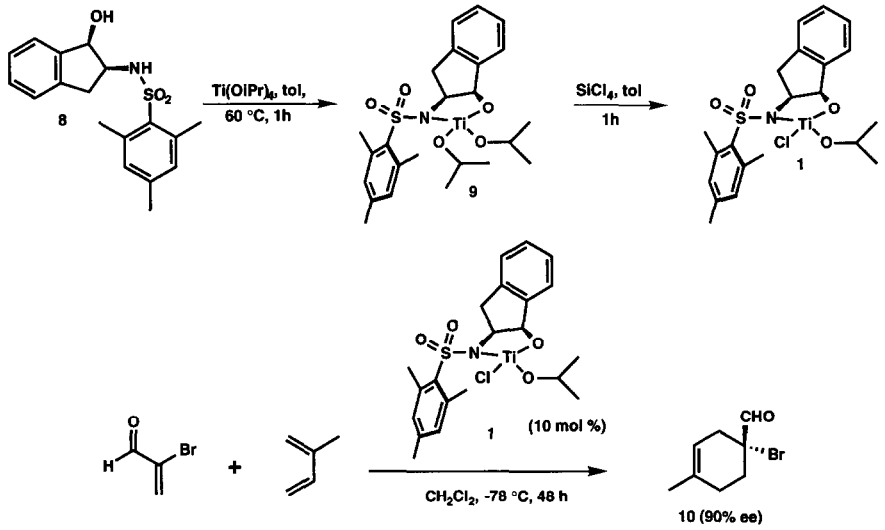
solid, mp 102-103 °C, $[\alpha]_D^{23}$ +53° (c=1.0, $CHCl_3$). While this route provided the necessary material for initial experiments, an improved synthesis of **6** was required for large scale operations. Hence racemic bromide **7**[4] was converted to the *cis*-azido alcohol[5] (NaN_3, DMSO, 75 °C, 3 h) and hydrogenated (10% Pd/C, H_2, EtOH, 3.5 h) to give (±)-amino alcohol **6** in 74% overall yield. Optically pure (1*R*, 2*S*)-2-amino-1-indanol was obtained by resolution[6] of racemic **6** (1 eq of (-)-tartaric acid in EtOH, 2 recrystallizations from 30% H_2O in EtOH and treatment of the salt with 1M NaOH) in 35% yield. The latter route provided large amounts of the desired ligand without the use of chromatographic techniques and has the advantage that both enantiomers are available through a single set of reactions. Finally, the desired sulfonamide **8**[7] was obtained by treatment of optically pure **6** with 2,4,6-trimethylbenzenesulfonyl chloride (CH_2Cl_2, Et_3N, 0 °C, 2 h). Although other sulfonamides were prepared and studied, **8** gave rise to the most useful catalyst.





Treatment of sulfonamide **8** with a variety of titanium reagents ($TiCl_4$, $Cl_2Ti(O\textit{i}\text{-}Pr)_2$, $Ti[OCH(CF_3)_2]_4$)[8] resulted in incomplete reaction, decomposition of the ligand, or formation of complicated mixtures of titanium complexes which induced low levels of enantioselectivity in Diels-Alder reactions. However, the reaction of **8** with 1 eq of $Ti(O\textit{i}\text{-}Pr)_4$ in toluene at 60 °C for 1 h, followed by removal of toluene and isopropanol at 0.2 mm Hg for 1 h, afforded a cyclic Ti complex from which a useful catalyst could be prepared. ^1H NMR analysis of this product indicated that it was not the simple monomer **9** but an aggregate thereof. Reaction of this complex with 1 eq of $SiCl_4$[9] in toluene at 23 °C for 1 h and removal of toluene and $Cl_3SiO\textit{i}\text{-}Pr$ at 0.2 mm Hg for 2 h gave an active catalyst as a yellow amorphous solid. This catalytic species contained a single isopropoxy ligand per Ti as determined by D_2O quenching and ^1H NMR determination of isopropyl alcohol. Replacement of this isopropoxy ligand with a second chloride to provide a more reactive catalyst was unsuccessful under a variety of conditions including excess $SiCl_4$. ^1H NMR analysis of the catalytically active yellow solid also revealed that the structure in $CDCl_3$ was not that of a simple monomer **1**

but an aggregate thereof, perhaps involving bridging oxygens (O*i*-Pr, indanyl-O or SO_2Ar). In the presence of 10 mol % of this catalyst, tentatively formulated as **1**, 2-bromoacrolein and cyclopentadiene (ca. 5 eq) underwent smooth Diels-Alder addition (CH_2Cl_2, -78 °C, 0.5 h) to give the (*R*)-bromoaldehyde **2** in 94% yield, 96.5:3.5 (*R/S*) enantioselectivity, and 67:1 (*exo*:*endo* CHO) diastereoselectivity.[10] Similar results were obtained from isoprene and 2-bromoacrolein which underwent Diels-Alder addition with 10 mol % of the catalyst (CH_2Cl_2, -78 °C, 48 h) to form aldehyde **10** in quantitative yield and 95:5 enantioselectivity.[11] 2-Bromoacrolein is an excellent dienophile in the catalytic Diels-Alder reaction both because of its high selectivity and for the synthetic versatility of the adducts.[1a]



The observed absolute stereochemical course of these Diels-Alder additions is consistent with reaction via a transition-state assembly such as **3**, although this must remain speculative because of lack of detailed information on the structure of the effective catalytic species and its complex with the dienophile. The structural complexity of Lewis acidic species containing titanium and the difficulty of assigning catalytic mechanisms in such systems is well known.[12,13]

Preparation of indane catalyst 1. To a suspension of 0.0317 g (0.0956 mmol) of the ligand (dried for 1 h at 90 °C, 0.2 mm Hg) in 2 mL of toluene was added 0.0285 mL (0.0957 mmol) of Ti(O*i*-Pr)$_4$, and the resulting solution was heated to 60 °C for 1 h. The solvent was removed in vacuo (0.2 mm Hg) and the residue was dried for 1 h (0.2 mm Hg). Toluene (2 mL) and freshly distilled $SiCl_4$ (0.0109 mL, 0.0951 mmol) were added, and the solution was stirred for 1 h at ambient temperature during which time the solution turned to a canary yellow color. The solvent was removed in vacuo (0.2 mm Hg), and the resulting yellow solid was dried for 2 h (0.2 mm Hg) before the addition of 4 mL of CH_2Cl_2.

Diels-Alder reaction catalyzed by 1. To a solution of 2 mL of the above catalyst solution at -78 °C was added 0.040 mL (0.50 mmol) of 2-bromoacrolein followed by 0.176 mL of cyclopentadiene. The mixture was stirred for 0.5 h at -78 °C, and then 0.05 mL each of triethylamine and saturated aqueous $NaHCO_3$ was added. The mixture was dried ($MgSO_4$), and the solvent was evaporated. Chromatography on silica gel (4:1 Hexane:Ethyl acetate) afforded 0.095 g (94%) of the product (*exo*:*endo* 67:1) and 0.011 g of recovered indanol.

References and Notes

1. (a) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966. (b) Corey, E. J.; Loh, T.-P.; Roper, T. D.; Azimioara, M. D.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290. (c) Corey, E. J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, *34*, 3979.
2. Molecular models indicate that metals with tetrahedral geometries (*i.e.* boron) would not allow for an optimum π–π interaction between the complexed dienophile and the benzenoid part of the indane ligand.
3. (a) McClure, D. E.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. *J. Org. Chem.* **1981**, *46*, 2431. (b) Dornhege, E. *Liebigs Ann. Chem.* **1971**, *743*, 42. (c) Rimek, H.-J.; Yupraphat, T.; Zymalkowski, F. *Liebigs Ann. Chem.* **1969**, *725*, 116.
4. Tamura, Y.; Kawasaki, T.; Yasuda, H.; Gohda, N.; Kita, Y. *J. Chem. Soc. Perkin Trans. 1*, **1981**, 1577.
5. Physical data for cis azidoalcohol: mp 129-130 °C; R_f = 0.50 (Ethyl acetate:Hexane 2:3); IR (film) 3263, 3149, 3026, 2960, 2913, 2888, 2700, 2135, 2112, 2062, 1478, 1273, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.25 (m, 4 H), 5.14 (d, 1 H, J = 5.1 Hz), 4.33 (m, 1 H), 3.20-3.10 (m, 2 H), 2.45 (bs, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.8, 139.0, 129.0, 127.6, 125.1, 124.7, 76.4, 65.7, 35.2; HRMS (CI, M+NH_3) *m/e* calc'd for $[C_9H_{12}N_4O]^+$: 193.1089, found: 193.1087.
6. Desimoni, G.; Faita, G.; Mellerio, G.; Righetti, P. P.; Zanelli, C. *Gazzetta Chimica Italiana* **1992**, *122*, 269.
7. Physical data for **8**: mp 133 °C; $[\alpha]_D^{23}$ + 22 ° (c = 1.0, $CHCl_3$); R_f = 0.57 (Ethyl acetate:Hexane 1:1); IR (film) 3457-3307 (br), 2926, 2855, 1461, 1153, 660 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, 1 H, J = 7.3 Hz), 7.27 (d, 1 H, J = 7.3 Hz), 7.23 (t, 1 H, J = 7.2 Hz), 7.17 (d, 1 H, J = 7.4 Hz), 6.98 (s, 2 H), 5.40 (d, 1 H, J = 8.7 Hz), 4.80 (d, 1 H J = 5.4 Hz), 3.93-3.87 (m, 1 H), 3.00 (dd, 1 H, J = 7.4, 15.8 Hz), 2.88 (dd, 1 H, J = 8.0, 15.8 Hz), 2.68 (s, 6 H), 2.32 (s, 3 H), 2.06 (bs, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4, 141.4, 140.6, 139.2, 134.2, 132.1, 129.5, 127.5, 125.3, 125.2, 74.2, 56.4, 36.8, 23.0, 21.0.
8. Prepared by heating a mixture of $TiCl_4$ and 6 eq $HOCH(CF_3)_2$ to reflux for 24 h, removal of the excess alcohol (20 mm Hg) and distillation of the product (0.2 mm Hg, 48-50 °C, 88% yield): ^1H NMR (300 MHz, C_6D_6) δ 4.04 (unresolved septet); ^{19}F NMR (282 MHz, C_6D_6, $CFCl_3$ ref) δ -76.2 (d, J = 22 Hz). See also Kapoor, P. N.; Kapoor, R. N.; Mehrotra, R. C. *Chemistry and Industry* **1968**, 1314.
9. It is imperative to maintain the purity of the $SiCl_4$ which is extremely moisture sensitive. The best results are obtained from freshly distilled HCl-free $SiCl_4$. For prior use of this method, see Corey, E. J.; Matsumura, Y. *Tetrahedron Lett.* **1991**, *32*, 6289.
10. Diastereoselectivity was determined by 300 MHz ^1H NMR analysis. Enantioselectivity was determined by reduction with $NaBH_4$ (wet THF, 23 °C), conversion to the Mosher MTPA ester (CH_2Cl_2, DMAP, 23 °C) and ^1H NMR measurement. The figure for enantioselectivity refers to the major diastereomer.
11. Enantioselectivity was determined by $NaBH_4$ reduction, benzoate formation, and chiral HPLC analysis on a Daicel OD column (0.1% *i*-PrOH/Hexane, 1 mL/min., major isomer 14.0 min, minor isomer 17.6 min).
12. See Duthholer, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807.
13. This research was supported by grants from the National Science Foundation and the National Institutes of Health.

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