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Tetrahedron Letters 47 (2006) 5581–5583
Tetrahedron Letters

Pseudoenzymatic catalyst–substrate interactions in ion-pair mediated chiral phase transfer catalysis

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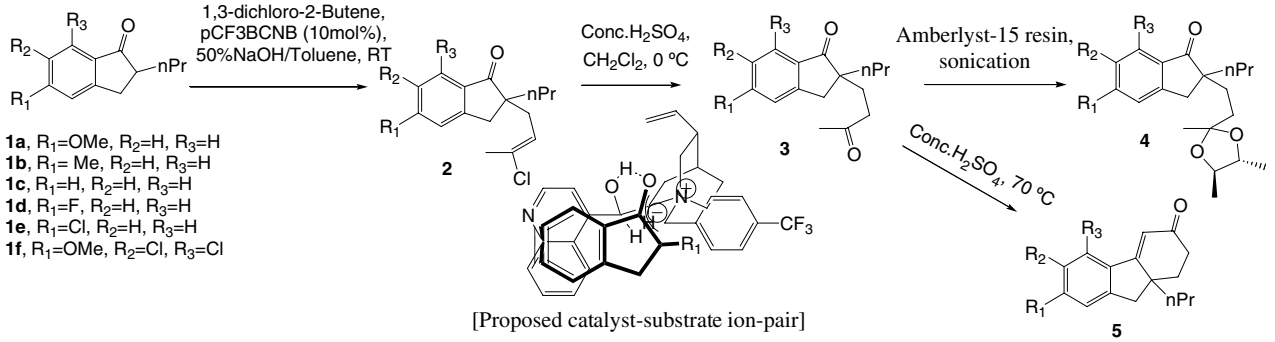
Received 8 December 2005; accepted 16 May 2006
Available online 15 June 2006

Abstract—Complementary electronic effects between the substrate and the cinchona-based catalyst in the pseudoenzymatic ion-pair mediated chiral phase transfer alkylations of indanone enolate anions were demonstrated.

Phase transfer-catalyzed (PTC) chiral alkylation, annulation, and oxidation of 2-substituted indanone enolate anions mediated by cinchona-based catalysts have been exploited to produce useful and predictable levels of asymmetric induction.[1] The stereochemistry was rationalized in terms of a tight ion-pair whereby the substrate indanone enolate anion is bound to the catalyst by a hydrogen bond as well as through pi-stacking and van der Waals attractions, with the quinuclidine ring lying behind the plane (Scheme 1).[1a–d] The seminal studies from Professor Corey's group and Professor Maruoka's group served as a milestone in this area that led chemists to think systematically about ion-pair mediated catalyst–substrate interactions and led to the rational design of second and eventually the third generation of conformationally rigidified improved catalysts.[2,3] We were intrigued by the paucity of similar rational catalyst design studies, especially in the versatile and useful arylcarbocycle fused model systems (indanone or tetralone type) involving mechanistic and geometrical factors responsible for enantioselection and subsequent attempts to design a better and highly effective new chiral PTC. Herein, we present the results of our studies directed to clarify the merits of the contact ion-pair hypothesis through complementary binding studies utilizing a number of carefully selected test substrate indanones with varied stereoelectronic demands.

Chiral PTC alkylation studies were conducted utilizing a series of electronically attenuated indanone enolate



Scheme 1. Chiral alkylation studies on electronically attenuated indanone substrates.

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doi:10.1016/j.tetlet.2006.05.099

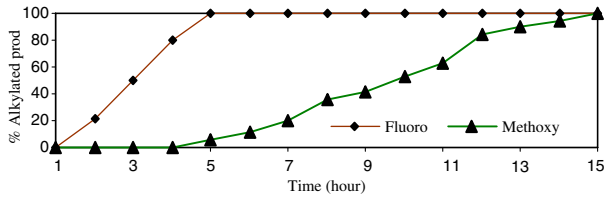
Table 1. Chiral alkylation of electronically attenuated indanones

Entry	Substrate (indanone)	Yield (%) 1 → 2	Yield (%) 2 → 3	Yield (%) 3 → 4	ee % 1 → 2
1	**1a**	86	82	76	0
2	**1b**	88	78	78	19.8
3	**1c**	92	84	80	25.2
4	**1d**	94	88	82	34.8
5	**1e**	90	76	74	48.6
6	**1f**	95	80	88	88.2

anions (**1a**–**f**) as substrates and 1,3-dichloro-2-butene (*Z*:*E* 4:1) as the alkylating agent in the presence of *N*-(*p*-trifluoromethyl) benzyl cinchoninium bromide (*p*-CF_3 BCNB) as the chiral PTC (10 mol %) under liquid–liquid conditions using 50% NaOH and toluene, analogous to the procedure described earlier.[1b] On the basis of the tight ion-pair theory proposed earlier, we anticipated that the products would be the (*S*)-enantiomer. The enantiomeric excess (ee) was determined by hydrolyzing each vinyl chloride product (**2a**–**f**) to the corresponding methyl ketone (**3a**–**f**) and ketalizing the enantiomeric ketone with 2*R*,3*R*-(-) 2,3-butanediol under acidic conditions (Amberlyst-15 resin, sonication, 1 h) followed by HPLC assay of the diastereomeric ketal (**4a**–**f**).[4] Compounds **3a**–**f** were cyclized with concentrated sulfuric acid (70 °C) to produce the corresponding annulation products **5a**–**f** (Scheme 1).[1b] Attempts to resolve the alkylated products (**2a**–**f**), the methyl ketones (**3a**–**f**), or the annulated products (**5a**–**f**) by chiral HPLC were unsuccessful.

Table 1 summarizes the results of the chiral alkylations with electron-rich and electron-poor test substrate indanones. The relative enantioselectivities appear to correlate with the electronic nature of the substituents, and higher enantioselectivities were obtained with indanones containing electron withdrawing groups (entries 4–6), whereas indanones with electron-releasing or neutral substituents (methyl, hydrogen, and methoxy) produce lower ee's. Such electronic correlation clearly points to an electronic complementarity arising out of a favorable binding interaction through extensive Π-contact, presumably between the quinoline moiety in the catalyst and the electron-poor aromatic ring of the indanone nucleus (matched pair).

In order to further investigate the indanone–catalyst interactions, a competitive chiral alkylation of a 1:1 mixture of 5-fluoroindanone, (**1d**), and 5-methoxyindanone, (**1a**), with 1,3-dichloro-2-butene in the presence of a low substoichiometric amount of the catalyst *p*-CF_3 BCNB (10 mol %) was conducted under conditions described above, and the reaction was monitored by quantitative HPLC analysis. The conversion of each substrate as a function of the total reaction (Scheme 2) showed a considerably faster reaction rate of the 5-fluoroindanone (**1d**) with respect to the corresponding 5-methoxyindanone (**1a**) during the initial stage; only a trace amount of **1a** reacted during the first 80% alkylation of **1d**. Only after all the 5-fluoro substrate was consumed did the 5-methoxy substrate begin to react at an appreciable rate. Independent control experiments showed that there was no induction period for the chiral alkylation of the 5-methoxyindanone (**1a**) when it was allowed to react in the absence of **1d** under otherwise identical conditions. These results are indicative of a favorable enzyme-like binding interaction of the electron-poor 5-fluoroindanone with the active site of the cinchona alkaloid catalyst over the electron-rich 5-methoxyindanone. During the initial stage of the reaction, almost all the catalyst active site is associated with the 5-fluoroindanone, resulting in competitive inhibition of the 5-methoxyindanone alkylation. After **1d** is totally consumed, the amount of available catalyst active site increases along with the reaction rate of **1a**.[5]



Scheme 2. Competitive chiral alkylations of 5-fluoro versus 5-methoxy indanones.

In summary, the correlation of enantioselectivity and the competitive catalyst inhibition as a function of the indanone structure provide further evidence to the proposed tight ion-pair, leading to a clearer understanding of the process. Successful use of the transition state model would allow one to modify the substrate as well as the catalysts, and enhance the predictive power and enantioselectivity in such pseudoenzymatic processes.

Selected NMR data. $CDCl_3$ with TMS, ^1H 600.1 MHz, ^{13}C 150.9 MHz, δ in ppm and J in Hz. Compound **5a**: ^1H NMR ($CDCl_3$, 600.1 MHz) δ 0.850 (t, 3H, $J = 7.2$ Hz, H_{16}), 1.192 (m, H_{15b}), 1.317 (m, H_{15a}), 1.433 (m, H_{14b}), 1.585 (m, H_{14a}), 1.954 (m, H_{1b}), 2.257 (m, H_{1a}), 2.362 (m, H_{9b}), 2.514 (m, H_{9a}), 2.707 (d, $J = 16.3$ Hz, H_{3b}), 3.021 (d, $J = 16.3$ Hz, H_{3a}), 3.839 (s, 3H, H_{19}), 6.067 (s, H_7), 6.841 (d, $J = 8.5$ Hz, H_{12}), 6.865 (s, H_{10}), 7.495 (d, $J = 8.5$ Hz, H_{13}). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 13.29 C_{16}, 17.19 C_{15}, 30.61 C_1, 32.48 C_9, 38.85 C_{14}, 41.84 C_3, 45.52 C_2, 54.09 C_{19}, 108.52 C_{10}, 113.24 C_{12}, 113.24 C_7, 122.76 C_{13}, 129.08 C_5, 148.45 C_4, 161.66 C_{11}, 171.58 C_6, 196.8 C_8. Compound **5b**: ^1H NMR ($CDCl_3$, 600.1 MHz) δ 0.846 (t, 3H, $J = 7.6$ Hz, H_{16}), 1.195 (m, H_{15b}), 1.316 (m, H_{15a}), 1.458 (m, H_{14b}), 1.590 (m, H_{14a}), 1.969 (m, H_{1b}), 2.271, (m, H_{1a}), 2.389 (s, 3H, H_{18}), 2.453 (m, H_{9b}), 2.575 (m, H_{9a}), 2.696 (d, $J = 16.3$ Hz, H_{3b}), 3.004 (d, $J = 16.3$ Hz, H_{3a}), 6.192 (s, H_7), 6.841 (d, $J = 8.5$ Hz, H_{12}), 7.100 (d, $J = 7.9$ Hz, H_{12}), 7.137 (s, H_{10}), 7.444 (d, $J = 7.9$ Hz, H_{13}). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 14.49 C_{16}, 18.62 C_{15}, 21.76 C_{18}, 32.03 C_1, 33.91 C_9, 40.02 C_{14}, 42.98 C_3, 46.67 C_2, 115.85 C_7, 122.57 C_{13}, 126.11 C_{10}, 128.3 C_{12}, 135.31 C_5, 142.37 C_4, 147.54 C_{11}, 173.32 C_6, 199.18 C_8. Compound **5c**: ^1H NMR ($CDCl_3$, 600.1 MHz) δ 0.855 (t, $J = 7.4$ Hz, H_{16}), 1.207 (m, H_{15b}), 1.327 (m, H_{15a}), 1.473 (m, H_{14b}), 1.603 (m, H_{14a}), 2.001 (m, H_{1b}), 2.299 (m, H_{1a}), 2.474 (m, H_{9b}), 2.594 (m, H_{9a}), 2.752 (d, $J = 16.3$ Hz, H_{3b}), 3.062 (d,

$J = 16.3$ Hz; H_{3a}), 6.246 (s, H_7), 7.297 (t, $J = 7.6$ Hz, H_{12}), 7.328 (d, $J = 7.6$ Hz, H_{10}), 7.401 (t, $J = 7.4$ Hz, H_{11}), 7.567 (d, $J = 7.9$ Hz, H_{13}). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 14.58 C_{16}, 18.73 C_{15}, 32.13 C_1, 34.02 C_9, 40.05 C_{14}, 43.24 C_3, 46.63 C_2, 116.76 C_7, 122.88 C_{13}, 125.65 C_{10}, 127.31 C_{12}, 131.71 C_{11}, 138.06 C_4, 147.24 C_5, 173.29 C_6, 199.35 C_8. Compound **5d**: ^{1}H NMR ($CDCl_3$, 600.1 MHz) δ 0.863 (t, 3H, $J = 7.2$ Hz, H_{16}), 1.196 (m, H_{15b}), 1.323 (m, H_{15a}), 1.470 (m, H_{14b}), 1.604 (m, H_{14a}), 1.999 (m, H_{1b}), 2.295 (m, H_{1a}), 2.467 (m, H_{9b}), 2.579 (m, H_{9a}), 2.746 (d, $J = 16.4$ Hz, H_{3b}), 3.053 (d, $J = 16.4$ Hz, H_{3a}), 6.184 (s, H_7), 6.996 (t, $J = 8.6$ Hz, H_{12}), 7.017 (d, $J = 8.7$ Hz, H_{10}), 7.534 (dd, $J = 5.1$ and 3.3 Hz, H_{13}). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 14.44 C_{16}, 18.55 C_{15}, 31.96 C_1, 33.68 C_9, 39.91 C_{14}, 43.13 C_3, 47.01 C_2, 112.46 and 112.61 ($^2J_{CF} = 22.5$ Hz) C_{10}, 114.92 and 115.08 ($^2J_{CF} = 23.6$ Hz) C_{12}, 116.3 C_7, 124.33 and 124.40 ($^3J_{CF} = 9.9$ Hz) C_{13}, 134.03 C_5, 149.70 and 149.76 ($^3J_{CF} = 9.1$ Hz) C_4, 164.27 and 165.94 ($^1J_{CF} = 251.9$ Hz) C_{11}, 171.67 C_6, 198.90 C_8. Compound **5e**: ^{1}H NMR ($CDCl_3$, 600.1 MHz) δ 0.854 (t, 3H, $J = 7.4$ Hz, H_{16}), 1.988 (m, H_{1b}), 2.292 (m, H_{1a}), 2.727 (d, $J = 16.3$ Hz, H_{3b}), 3.036 (d, $J = 16.3$ Hz, H_{3a}), 6.202 (s, H_7), 2.465 (m, H_9), 2.576 (m, H_{9a}), 7.306 (s, H_{10}), 7.253 (d, $J = 8.2$ Hz, H_{12}), 7.474 (d, $J = 8.2$ Hz, H_{13}), 1.455 (m, H_{14b}), 1.588 (m, H_{14a}), 1.183 (m, H_{15b}), 1.313 (m, H_{15a}). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 14.37 C_{16}, 18.46 C_{15}, 31.87 C_1, 33.65 C_9, 39.77 C_{14}, 42.38 C_3, 46.67 C_2, 116.88 C_7, 123.61 C_{13}, 125.7 C_{10}, 127.63 C_{12}, 136.42 C_{11}, 137.28 C_5, 148.62 C_4, 171.22 C_6, 198.62 C_8. Compound **5f**: ^{1}H NMR ($CDCl_3$, 600.1 MHz) δ 0.865 (t, 3H, $J = 7.4$ Hz, H_{16}), 1.182 (m, H_{15b}), 1.292 (m, H_{15a}), 1.477 (m, H_{14b}), 1.611 (m, H_{14a}), 2.004 (m, H_{1b}), 2.268 (m, H_{1a}), 2.458 (m, H_{9b}), 2.571 (m, H_{9a}), 2.753 (d, $J = 16.4$ Hz, H_{3b}), 3.009 (d, $J = 16.4$ Hz, H_{3a}), 3.959 (s, H_{19}), 6.820 (s, H_{10}), 6.838 (s, H_7). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 14.52 C_{16}, 18.69 C_{15}, 32.1 C_1, 33.44 C_9, 40.17 C_{14}, 43.7 C_3, 47.15 C_2, 56.65 C_{19}, 106.59 C_{10}, 119.95 C_7, 121.77 C_{12}, 128.45 C_{13}, 131.61 C_5, 148.46 C_4, 158.17 C_{11}, 169.6 C_6, 199.41 C_8. Compound **1d**: ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 13.97 C_{12}, 20.51 C_{11}, 32.72 C_{10}, 33.54 C_1, 47.46 C_2, 112.96 and 113.11 ($^2J_{CF} = 22.7$ Hz) C_6, 115.47 and 115.62 ($^2J_{CF} = 18.1$ Hz) C_8, 126.01 and 126.08 ($^3J_{CF} = 10.6$ Hz) C_9, 133.17 C_4, 156.54 and 156.61 ($^3J_{CF} = 10.6$ Hz) C_5, 165.28 and 167.97 ($^1J_{CF} = 255.2$ Hz) C_7, 207.06 C_3. Compound **2d**: ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 14.47 C_{12}, 17.59 C_{11}, 26.26 C_{19}, 36.31 C_{13}, 37.08 C_{10}, 53.14 C_2, 93.75 C_1, 112.90 and 113.04 ($^2J_{CF} = 22.0$ Hz) C_6, 115.57 and 115.73 ($^2J_{CF} = 23.9$ Hz) C_8, 126.08 and 126.15 ($^3J_{CF} = 10.6$ Hz) C_9, 132.8 C_{14}, 133.04 C_4, 133.04 C_{15}, 156.07 and 156.14 ($^3J_{CF} = 10.1$ Hz) C_5, 166.49 and 168.19 ($^1J_{CF} = 256.7$ Hz) C_7, 208.65 C_3. Compound **3d**: ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 14.5 C_{12}, 17.57 C_{11}, 29.93 C_{19}, 30.69 C_{13}, 37.95 C_{10}, 38.32 C_1, 39.29 C_{14}, 52.14 C_2, 112.95 and 113.09 ($^2J_{CF} = 22.0$ Hz) C_6, 115.78 and 115.94 ($^2J_{CF} = 23.9$ Hz) C_8, 126.19 and 126.26 ($^3J_{CF} = 10.4$ Hz) C_9, 133.16 C_4, 155.69 and 155.76 ($^3J_{CF} = 10.0$ Hz) C_5, 166.52 and 168.22 ($^1J_{CF} = 256.9$ Hz) C_7, 208.01 C_3, 208.69 C_{15}. Compound **4d**: ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 14.54 C_{22}, 16.42 and 16.38 C_{19}, 17.05 and 17.03 C_{18}, 17.53 C_{21}, 25.56 and 25.53 C_{17}, 31.34 C_7, 34.85 and 34.83 C_6, 37.69 and 37.66 C_{20}, 39.72 and 39.70 C_9, 53.4 C_8, 78.00 and 77.97 C_4, 78.79 and 78.77 C_5, 108.766 and 108.75 C_2, 112.83 and 112.97 ($^2J_{CF} = 22.0$ Hz) C_{13}, 115.55 and 115.70 ($^2J_{CF} = 23.9$ Hz) C_{15}, 126.05 and 126.12 ($^3J_{CF} = 10.4$ Hz) C_{16}, 133.5 C_{11}, 155.93 and 155.99 ($^3J_{CF} = 8.9$ Hz) C_{10}, 166.41 and 168.10 ($^1J_{CF} = 256.1$ Hz) C_{14}, 209.15 and 209.17 C_{12}.

Acknowledgements

Financial support provided by the Petroleum Research Fund (PRF), National Institute of Health (NIH), Welch Foundation, and Bristol Myers Squibb Corporation is gratefully acknowledged.

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4. Phenomenex Chirex *R*-phenylglycine 3,5-DNB normal phase, 88:12 hexane/chloroform, 2 ml/min. In each case, the *S*-isomer precedes the *R*-isomer in the chiral HPLC.[1b,c]
5. For analogous kinetic behavior in biological systems, see: Hackett, S. L.; Skye, G. E.; Burton, C.; Segel, I. H. *J. Biol. Chem.* **1970**, *245*, 4241.