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# An unexpected inversion of enantioselectivity in the proline catalyzed intramolecular Baylis–Hillman reaction

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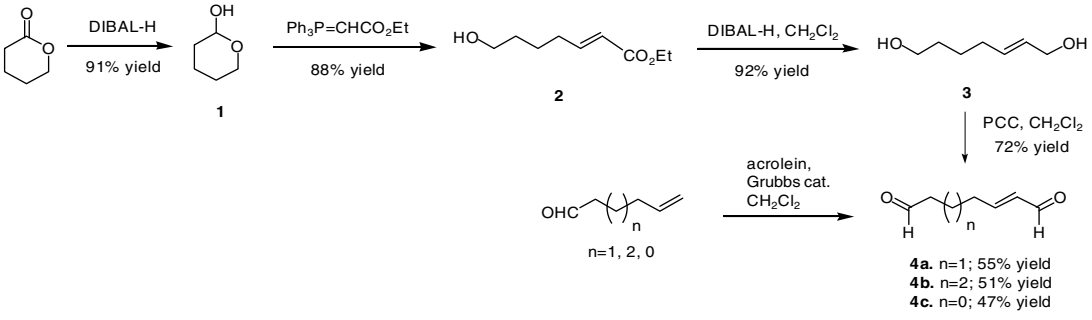
**Abstract**—A highly enantioselective proline catalyzed intramolecular Baylis–Hillman reaction of hept-2-enedial is reported. Addition of imidazole to the mixture results in an unusual inversion of enantioselectivity.


The recent advent of enantioselective organocatalysis has opened new doors in asymmetric chemistry.[1] These processes eliminate the need to carry out reactions under an inert atmosphere and do not require the use of anhydrous solvents or low temperatures. In certain instances, organocatalysis provides results that heretofore could not be achieved with the use of inorganic metals. Organocatalysts such as proline,[2] imidazolidinone[3] and their derivatives have found wide applications in asymmetric Mannich,[4] Michael,[5] aldol,[6] and Diels–Alder reactions,[7] as well as α-amination,[8] α-alkylations,[9] and α-selenenylation of aldehydes.[10]

The Baylis–Hillmann (B–H) reaction[11] allows the direct preparation of α-methylene-β-hydroxyl carbonyl compounds from the corresponding α,β-unsaturated carbonyls and aldehydes. Applications to total synthesis[12] and mechanistic studies[13] of this reaction are also well documented. Surprisingly, relatively few examples of the intramolecular B–H reaction have been reported so far.[14] Certain studies[15] revealed that the use of dual catalyst systems can increase the enantioselectivity of the asymmetric *intermolecular* B–H reaction.[16] Yet, to the best of our knowledge, there have been no reports of an *enantioselective intramolecular B–H reaction*. Herein, we disclose our recent attempts at achieving the first enantioselective intramolecular B–H reaction.

Hept-2-enedial (**4a**) was synthesized from tetrahydropyran-2-one in four steps and 53% total yield (Scheme 1). Reduction of tetrahydropyran-2-one with DIBAL-H afforded pyranol **1** in 91% yield. Wittig reaction of




**Scheme 1.** Synthesis of dialdehydes **4a**–**c**.

*Keywords*: Baylis–Hillman; Proline; Intramolecular; Inversion.
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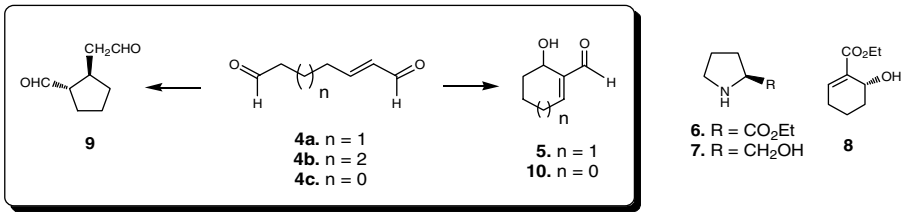
**1** with $Ph_3P{=}CHCO_2Et$ in $CH_2Cl_2$ afforded ester **2** (88% yield), which was reduced with DIBAL-H and oxidized with PCC to give dialdehyde **4a** in 92% and 72% yield, respectively. Alternatively, **4a–c** can be prepared by cross-metathesis of the corresponding olefinic aldehydes and acrolein in the presence of Grubbs' catalyst. The B–H reaction of **4a** with L-(*S*)-proline was examined in various solvents at ambient temperature (Table 1, entries 1–11). Most reactions gave rise to the corresponding (*S*)-6-hydroxy-cyclohex-1-enecarbaldehyde (**5**) albeit with variable yield and enantioselectivities. Reactions in DMF and $CH_3CN$ gave the highest yields, enantioselectivities and reaction rates. Reactions in non-polar solvents such as toluene were slower, and gave lower yield and ee values. No reaction took place in $Et_2O$, THF, or MeOH after two days at ambient temperature. Reaction with D-(*R*)-proline in DMF at 15 °C afforded (*R*)-**5** (entry 12). When the temperature increased to 70 °C, the reaction went to completion in 1 h and the ee value of the product increased from 45% to 60% (entries 11 and 13).

Recent reports have shown that the use of a Lewis base such as imidazole, quinuclidine, DABCO, or $Ph_3P$ facilitate the B–H reaction.[17] In our hands, addition of 0.1 equiv of imidazole to the reaction of **4a** and L-proline (0.1 equiv) resulted in an increased reaction rate and a higher yield of **5** at ambient temperature (entries 10, 11,

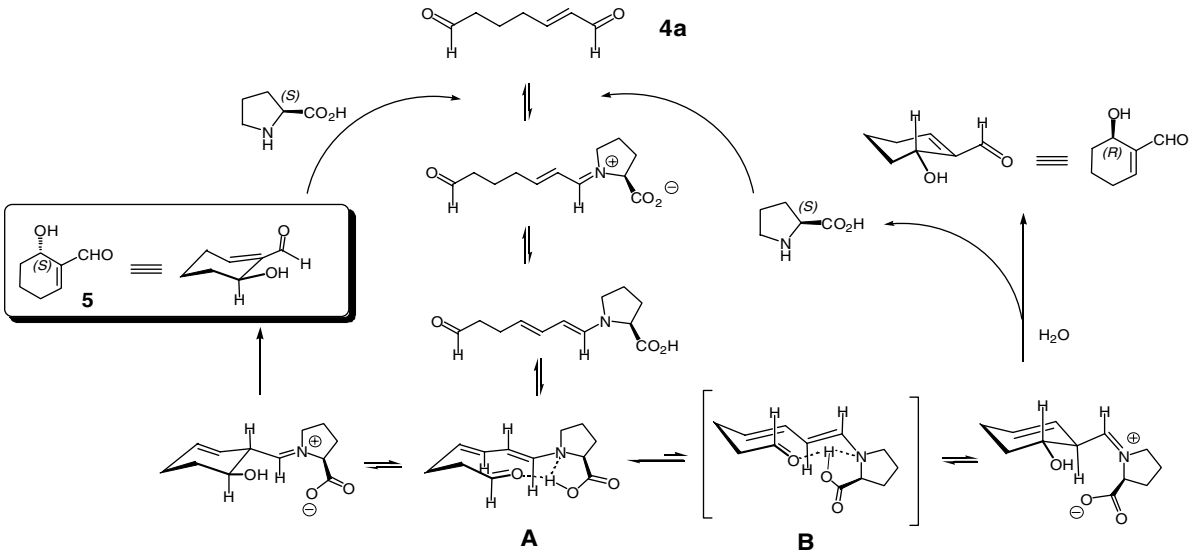
**Table 1.** Baylis–Hillman reaction of **4a–c**



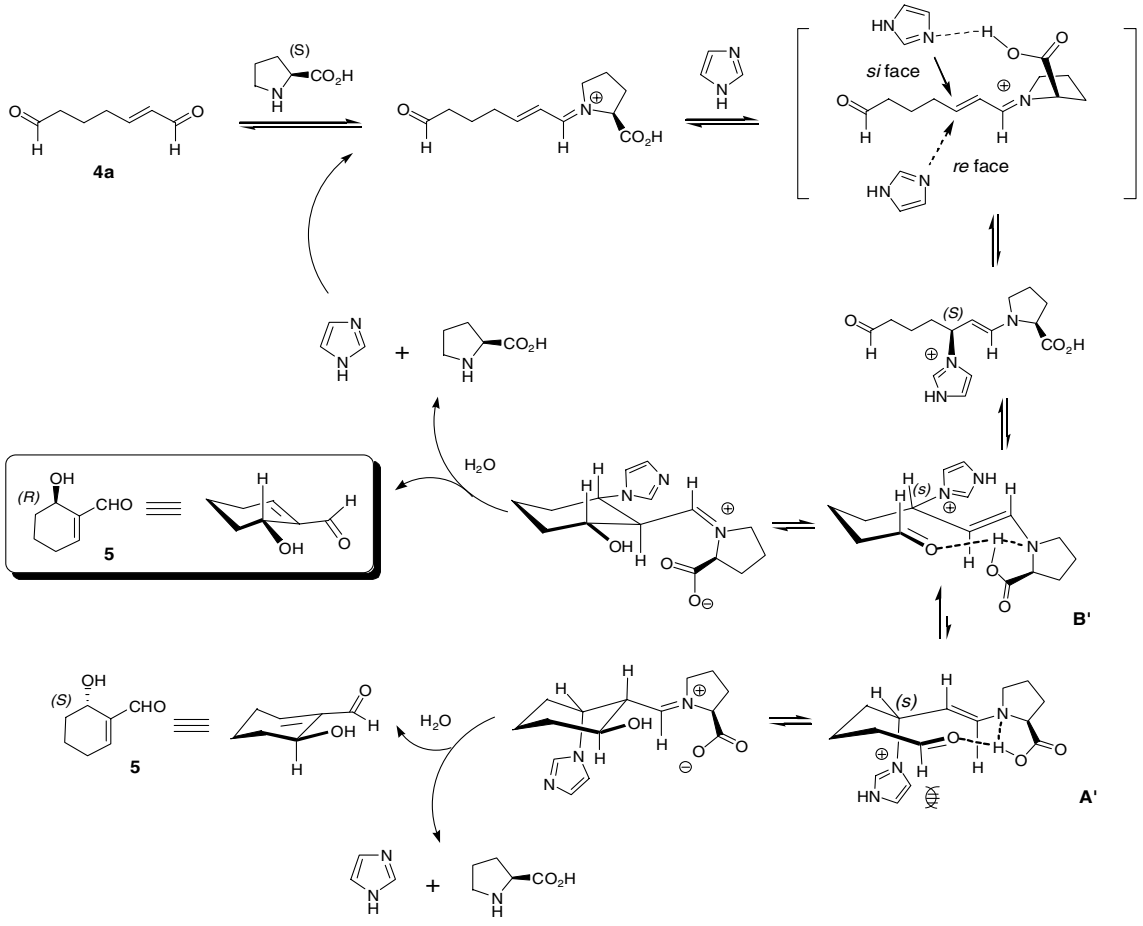

| Entry | Compound, Catalyst (equiv) | Additive (equiv) | *T* (°C) | Solvent | Time (h) | Product | Yield[a] (%) | ee[b] (%) | Conf.[c] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **4a**, L-Pro (0.1) | | 25 | $CH_2Cl_2$ | 8 | **5** | 47 | 10 | *S* |
| 2 | **4a**, L-Pro (0.1) | | 25 | Toluene | 96 | **5** | 31 | 5 | *S* |
| 3 | **4a**, L-Pro (0.1) | | 25 | $CHCl_3$ | 9 | **5** | 41 | 13 | *S* |
| 4 | **4a**, L-Pro (0.1) | | 25 | $Et_2O$ | 48 | **5** | ~0[d] | 0 | |
| 5 | **4a**, L-Pro (0.1) | | 25 | THF | 48 | **5** | ~0[d] | 0 | |
| 6 | **4a**, L-Pro (0.1) | | 25 | MeOH | 48 | **5** | ~0[d] | 0 | |
| 7 | **4a**, L-Pro (0.1) | | 25 | Dioxane | 6 | **5** | 5[e] | N.A | |
| 8 | **4a**, L-Pro (0.1) | | 25 | Dioxane–$H_2O$ | 48 | **5** | 68 | 30 | *S* |
| 9 | **4a**, L-Pro (0.1) | | 25 | DMSO | 6 | **5** | 54 | 7 | *S* |
| 10 | **4a**, L-Pro (0.1) | | 25 | $CH_3CN$ | 24 | **5** | 67 | 15 | *S* |
| 11 | **4a**, L-Pro (0.1) | | 25 | DMF | 5 | **5** | 73 | 45 | *S* |
| 12 | **4a**, D-Pro (0.1) | | 15 | DMF | 5 | **5** | 75 | 41 | *R* |
| 13 | **4a**, L-Pro (0.1) | | 70 | DMF | 1 | **5** | 69 | 60 | *S* |
| 14 | **4a**, L-Pro (0.1) | Imid. (0.1) | 25 | DMF | 4 | **5** | 79 | 24 | *R* |
| 15 | **4a**, L-Pro (0.1) | Imid. (0.1) | 25 | $CH_3CN$ | 6 | **5** | 71 | 59 | *R* |
| 16 | **4a**, L-Pro (0.1) | Imid. (0.1) | 0 | $CH_3CN$ | 14 | **5** | 73 | 80 | *R* |
| 17 | **4a**, L-Pro (1) | Imid. (1) | 0 | $CH_3CN$ | 7 | **5** | 72 | 93 | *R* |
| 18 | **4a**, D-Pro (0.1) | Imid. (0.1) | 15 | $CH_3CN$ | 5 | **5** | 76 | 77 | *S* |
| 19 | **4a**, D-Pro (0.1) | Imid. (0.1) | 0 | $CH_3CN$ | 15 | **5** | 77 | 96 | *S* |
| 20 | **4a**, D-Pro (1) | Imid. (1) | 0 | $CH_3CN$ | 8 | **5** | 74 | 98 | *S* |
| 21 | **4a**, L-Pro (1) | Imid. (1) | −30 | $CH_3CN$ | 72 | **5** | 68 | 82 | *R* |
| 22 | **4a** | Imid. (0.1) | 25 | $CH_3CN$ | 48 | **5** | ~0[d] | 0 | |
| 23 | **4a**, **6** (0.1) | | 25 | $CH_3CN$ | 48 | **5** | ~0[e] | 0 | |
| 24 | **4a**, **7** (0.1) | | 25 | $CH_3CN$ | 48 | **5** | ~0[e] | 0 | |
| 25 | **4a**, **7** (0.1) | HOAc (0.1) | 25 | $CH_3CN$ | 24 | **5** | 20[e] | 4 | *S* |
| 26 | **4a**, **7** (0.1) | HFIP (0.1) | 25 | $CH_3CN$ | 24 | **5** | 23[e] | 5 | *S* |
| 27 | **4b**, L-Pro (0.1) | Imid. (0.1) | 25 | $CH_3CN$ | 3 | **9** | ~0[e] | N.A | |
| 28 | **4b**, L-Pro (0.1) | | 25 | $CH_3CN$ | 5 | **9** | 20[e] | 31 | *anti*[f] |
| 29 | **4c**, L-Pro (0.1) | | 25 | DMF | 3 | **10** | 65[g] | 48 | *S* |
| 30 | **4c**, L-Pro (0.1) | Imid. (0.1) | 0 | $CH_3CN$ | 2 | **10** | 47[g] | 43 | *S* |
| 31 | **4c**, D-Pro (0.1) | | 25 | DMF | 3 | **10** | 62[g] | 54 | *R* |
| 32 | **4c**, D-Pro (0.1) | Imid. (0.1) | 0 | $CH_3CN$ | 2 | **10** | 46[g] | 24 | *R* |

[a] Isolated yield.
[b] Enantiomeric excesses (ee) were measured by GC–MS (Shimadzu QP 5000, chiral capillary column, gamma-cyclodextrin trifluoroacetyl, Astec Type G-TA, size 30 m × 0.25 mm, flow rate 24 mL/min, temperature range: 60–120 °C, gradient: 3 °C/min).
[c] Absolute configuration of the major isomer assigned by comparison of $[\alpha]_D$ values with the literature.[18]
[d] No reaction.
[e] Complex mixture of by-products.
[f] *anti:syn* > 99.5:1.
[g] **4c** was completely consumed.

14, and 15). Surprisingly, we found that in the presence of imidazole, the enantioselectivity of the reaction was completely reversed.[19] This selectivity is highly sensitive to the nature of the solvent and temperature. We found that the reaction in the presence of L-proline and imidazole was more selective in $CH_3CN$ than in DMF (entries 14 and 15). However, this was reversed in the absence of imidazole (entries 10 and 11). This unprecedented and striking inversion of selectivity is most likely due to the formation of a new reactive intermediate (Schemes 2 and 3).




**Scheme 2.** Proposed mechanism for the L-proline-catalyzed formation of (*S*)-**5**.




**Scheme 3.** Proposed mechanism for the L-proline-imidazole co-catalyzed formation of (*R*)-**5**.

Lowering the reaction temperature drastically increased the selectivity (entries 15–21). In fact, addition of D-proline and imidazole at 0 °C gave (*S*)-**5** in 98% ee (entry 20). However, lowering the temperature to −30 °C caused a slight loss of selectivity (entry 21). This is most likely due to the low solubility of proline in $CH_3CN$ at this temperature.

Enal **4a** is most likely activated by L-proline to give the corresponding iminium ion, which isomerizes to afford the enamine intermediate (Scheme 2). The enamine–aldol reaction proceeds preferentially through a Zimmerman–Traxler transition state (**A**), instead of transition state (**B**), to afford (*S*)-**5** and to regenerate the proline catalyst. The alternative transition state (**B**) is higher in energy and less favorable.[20]

Addition of imidazole facilitates the reaction and reverses the stereoselectivity (Scheme 3). It is likely that an intramolecular H-bond facilitates the addition of imidazole from the *Si*-face of the iminium ion[21] to afford the (*S*)-imidazolium. The resulting transition state **A′** suffers from an axial imidazonium group and would prefer to rearrange to the alternative transition state **B′** which would lead to the formation of (*R*)-**5**.

When compared to other amines, the pyrrolidine portion of proline displays enhanced nucleophilic activity in the B–H reaction. This can be contributed to the presence of the α-carboxyl group, which acts as a Brønsted co-catalyst during the formation of the enamine.[22] Such behavior is similar to the catalytic activity of an enzyme. In fact, the B–H reaction of **4a** in the presence of **6** or **7** gave none of the desired product **5** (entries 23 and 24). Product **5** was isolated, albeit in lower yield than with proline, when a Brønsted acid was added to the above mixtures (entries 25 and 26). Reaction of **4b** with proline gave the intramolecular Michael addition product **9** with high diastereoselectivity.[23] Addition of imidazole gave a complicated mixture (entries 27 and 28). Reaction of **4c** gave the Baylis–Hillman product **10**, albeit with lower enantioselectivity (entry 29). This erosion in selectivity may be a result of the small energy difference between the five-membered transition states (i.e., pseudo-axial vs pseudo-equatorial imidazole). Similarly, addition of imidazole in the reaction of **4c** did not invert the enantioselectivity (entry 30).

In summary, an efficient proline catalyzed enantioselective intramolecular Baylis–Hillman reaction is reported. Addition of imidazole to the mixture resulted in an inversion of selectivity. This unprecedented and novel inversion methodology provides an opportunity to explore a new concept in asymmetric synthesis. Further mechanistic studies and synthetic applications of this system are currently under active investigation in our laboratories.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.072.

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18. (a) The absolute configurations of (+)-**5** and (−)-**5** were assigned by comparison of their specific rotations with reported data for **8**. Compound **8** was prepared by oxidation of **5** with $NaClO_2$ ($NaClO_2$, *t*-BuOH, 2-methyl-2-butene, $NaH_2PO_4$, 23 °C) followed by esterification (cat. HCl, EtOH). $[\alpha]_D^{25}$ +57.4 (*c* 0.25, $CHCl_3$); lit. $[\alpha]_D^{28}$ +57.9 (*c* 0.99, $CHCl_3$), see: (a) Takano, S.; Yamane, T.; Takahashi, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1992**, *3*, 837; (b) The absolute configuration of (*S*)-**10** was assigned by comparison of its specific rotation with reported data for 2-hydroxymethyl-cyclopentanol (**12**). Compound **12** was prepared by reduction of (*S*)-**10**, 48% ee, with $NaBH_4$ followed by hydrogenation (cat. Pt/C, MeOH), see: (i) Buisson, D.; Azerad, R. *Tetrahedron Lett.* **1986**, *27*, 2631–2634; (ii) Weidner, J.; Theil, F.; Schick, H. *Tetrahedron: Asymmetry* **1994**, *5*, 751–754; (iii) Inoguchi, K.; Fujie, N.; Yoshikawa, K.; Achiwa, K. *Chem. Pharm. Bull.* **1992**, *40*, 2921–2926.
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