## Deracemization of Baylis−Hillman Adducts

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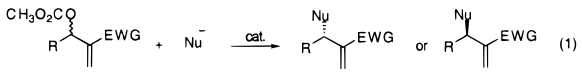
The Baylis−Hillman reaction provides a simple atom economic synthesis of $\beta$-hydroxy-α-methylene esters, ketones, nitriles, etc. The versatility of the functionality have made these adducts valuable synthetic intermediates.[1] An important objective becomes the availability of such adducts asymmetrically—a challenge that has proved formidable.[2,3] An alternative strategy envisions a dynamic kinetic asymmetric transformation (DYKAT) process as outlined in eq 1.

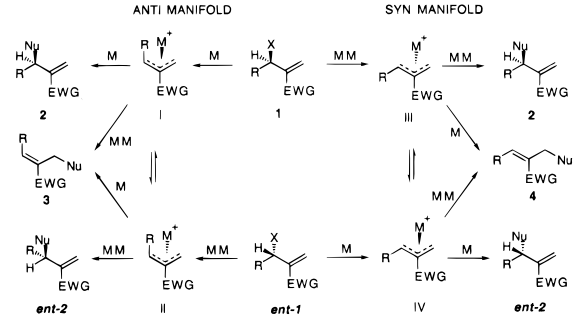


(1)

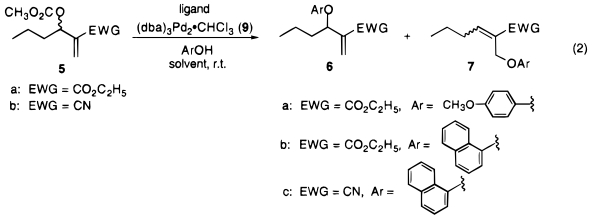
By using an oxygen nucleophile that can become a hydroxyl group, the process constitutes a deracemization. Scheme 1 outlines the magnitude of the challenge since only one out of a diversity of possible pathways must be selected. In contrast to monosubstituted $\pi$-allylmetal complexes wherein the *syn* manifold is normally strongly preferred, 1,2-disubstituted complexes increase the importance of the anti manifold (i.e., complexes I and II) due to destabilizing steric interactions in the *syn* complexes III and IV between R and EWG.[4] Furthermore, with one enantiomer of a chiral catalyst, there is a sequence of matched events leading from **1** to **2** as well as from ***ent-1*** to ***ent-2***. Thus, the chiral catalyst must contend with regioselectivity (i.e., **2** and ***ent-2*** vs **3** and **4**), *syn* vs *anti* manifolds, the relative rates of equilibration of diastereomeric complexes (I vs II and III vs IV), as well as the rate differential for the nucleophilic addition step leading to chiral products. Finally, the metal-catalyzed reaction must dominate any background reaction involving a conjugate addition of the nucleophile followed by elimination which generates products of type **3** and **4**.

The carbonate of the Baylis−Hillman adduct **5**, prepared in standard fashion with methyl chloroformate, was reacted with *p*-methoxyphenol (**8**)[5] in the presence of a chiral catalyst derived from the Pd(0) complex **9** and ligand **10** at ambient temperature.[6,7] As shown in Table 1, there is a significant solvent effect. Poor regioselectivity is observed with very nonpolar solvents (entries 1 and 2). Enhancing solvent polarity improved the regioselectivity (entries 3−8) with the best regioselectivity observed in chlorobenzene. The ee did not track the regioselectivity. For example, toluene gave good ee but poor regioselectivity. On the other hand, chlorobenzene did give the best ee as well as regioselectivity (entry 6). For simple laboratory scale, the greater ease of handling of dichloromethane, which gave an identical ee as chlorobenzene (entry 7) although somewhat poorer regioselectivity, became the solvent of choice.

**Scheme 1.** Complexities of Deracemization[a]



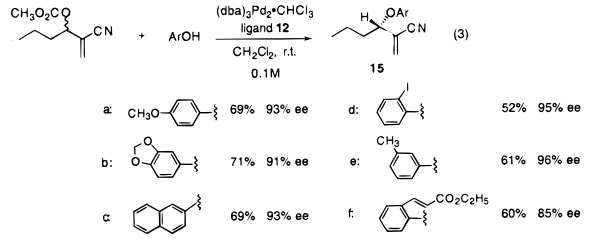

[a] The notation M (matched) or MM (mismatched) refers to whether that path is favored or disfavored by one particular enantiomer of a chiral catalyst. All of the labels will be reversed for the mirror image catalyst.



(2)

Variation of ligand[8] was examined in conjunction with α-naphthol (**11**) as the nucleophile (entries 9−12). The least rigid ligand **12** (entry 10) gave the best match of ee and regioselectivity. While the regioselectivity was slightly better with the more conformationally rigid ligand **14**,[8b] the ee was inferior. Changing the EWG to cyano saw the biggest improvement in both regioselectivity and ee (entries 13−16). Here too, the diphenyl ligand **12** (entry 14) gave the best results wherein a 75% yield of **6c**[9] of 93% ee was obtained. Reducing the concentration from 0.1 to 0.05 M increased the ee to 96% with no change in yield.

Equation 3 summarizes the results for obtaining the chiral products **15**[9] using a variety of additional phenols. With a diverse array of structures, excellent enantioselectivity can be obtained. Equation 4 illustrates a wide tolerance of variation of the Baylis−



(3)

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(9) New compounds have been fully characterized by spectroscopic methods and elemental composition established by high-resolution mass spectroscopy or combustion analysis.

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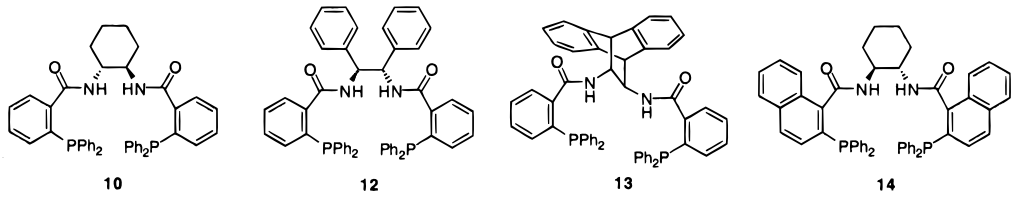
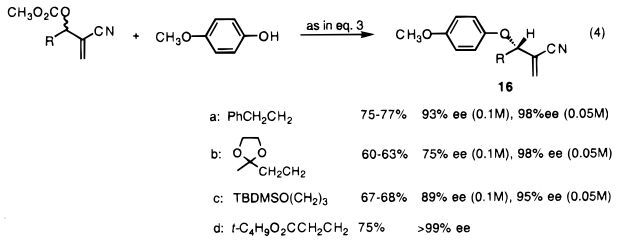
**Table 1**



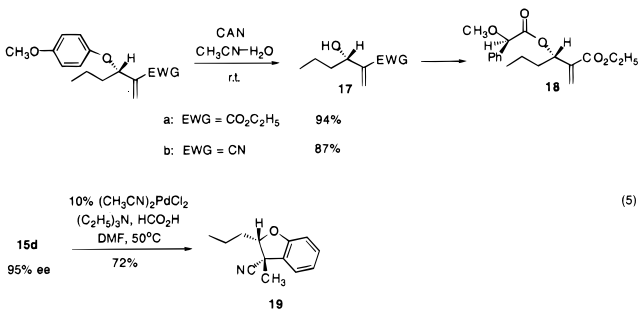

| entry | EWG | ligand | ArOH | solvent | ratio[b] **6:7** | **6** yield[c] | **6** ee[d] |
|---|---|---|---|---|---|---|---|
| 1 | $CO_2C_2H_5$ | **10** | **8** | dioxane | 1:2.5 | 21 | 67 |
| 2 | $CO_2C_2H_5$ | **10** | **8** | toluene | 1.1:1 | 54 | 86 |
| 3 | $CO_2C_2H_5$ | **10** | **8** | α,α,α-trifluorotoluene | 2.5:1 | 46 | 89 |
| 4 | $CO_2C_2H_5$ | **10** | **8** | DME | 1.8:1 | 48 | 70 |
| 5 | $CO_2C_2H_5$ | **10** | **8** | THF | 2.9:1 | 50 | 51 |
| 6 | $CO_2C_2H_5$ | **10** | **8** | chlorobenzene | 3.6:1 | 69 | 92 |
| 7 | $CO_2C_2H_5$ | **10** | **8** | dichloromethane | 2.7:1 | 64 | 92 |
| 8 | $CO_2C_2H_5$ | **10** | **8** | acetonitrile | 2.1:1 | 58 | 46 |
| 9 | $CO_2C_2H_5$ | **10** | **11** | dichloromethane | 3:1 | 69 | 87 |
| 10 | $CO_2C_2H_5$ | **12** | **11** | dichloromethane | 4.9:1 | 72 | 87[e] |
| 11 | $CO_2C_2H_5$ | **13** | **11** | dichloromethane | 3.6:1 | 78 | 75 |
| 12 | $CO_2C_2H_5$ | **14** | **11** | dichloromethane | 5.3:1 | 62 | 80[e] |
| 13 | CN | **10** | **11** | dichloromethane | 1.3:1 | 41 | 86 |
| 14 | CN | **12** | **11** | dichloromethane | 6.7:1 | 75 | 93[e] |
| 15 | CN | **13** | **11** | dichloromethane | 5.7:1 | 71 | 92 |
| 16 | CN | **14** | **11** | dichloromethane | 3.2:1 | 69 | 39[e] |

[a] Reactions performed at 0.1 M using 1 mol % $(dba)_3Pd_2{\cdot}CHCl_3$ and 3% ligand at rt. [b] The ratio determined by $^1H$ NMR spectroscopy on the crude products. [c] The quoted yields are for pure adduct **6**. [d] The ee's were determined by chiral HPLC. [e] The absolute configuration of the product is opposite to that obtained in runs using ligands **10** and **13**.




Hillman adducts in giving the corresponding alkylation product **16**[9] of high ee. The reactions are normally performed at 0.1 M, and the first set of ee's derive from these experiments. By performing the reaction at 0.05 M, the ee's (the second set) significantly increased in the first three cases, **16a**−**c**. In every case, the yields are for isolated pure products, **15** and **16** respectively, wherein the minor regioisomer has been separated during column chromatographic purification.[10]

For synthesis purposes, the *p*-methoxyphenyl ether serves as a convenient protecting group that can be readily removed oxidatively[11] when desired as illustrated in eq 5 for the initial adducts. Derivatizing the hydroxyester **17** with *R*-O-methylmandelic acid (DMAP, PCC, $CH_2Cl_2$, rt) to form **18** allows assignment[12] of the *S*-configuration to **17** derived from the *S*,*S*-ligand **12**. On the other hand, a reductive Heck-type cyclization[13] of adduct **15d** provides




entry to the dihydrobenzofuran derivative **19** as an 8.3:1 ratio of diastereomers (major one depicted) with control of absolute stereochemistry. This strategy constitutes a reasonable alternative strategy to access the versatile Baylis−Hillman derivatives in highly enantiomerically enriched form.

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**Supporting Information Available:** A sample experimental procedure for the asymmetric alkylation as well as characterization for **6a**−**c**, **15a**−**f**, **16a**−**d**, **17a**−**b**, **18**, **19** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For eq 3, the ratios of **15** to its regioisomer in the crude reactions are as follows: a. 93:7, b. 93:7, c. 87:13, d. 68:32, e. 86:14, f. 76:24. For eq 4, the ratios of **16** to its regioisomer in the crude reactions are as follows: a. 90:10, b. 87:13, c. 91:9, d. 86:14.

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