Catalytic Asymmetric Synthesis of α-Methylene-β-hydroxy-ketones

Anthony G. M. Barrett* and Akio Kamimura

Department of Chemistry, Imperial College of Science, Technology and Medicine, South Kensington, London, UK SW7 2AY

Condensation of an α,β-unsaturated ketone, an aldehyde and trimethylsilyl phenyl sulfide or selenide, catalysed by a chiral (acyloxy)borane, and subsequent oxidative elimination gives the title adducts in high enantiomeric excess.

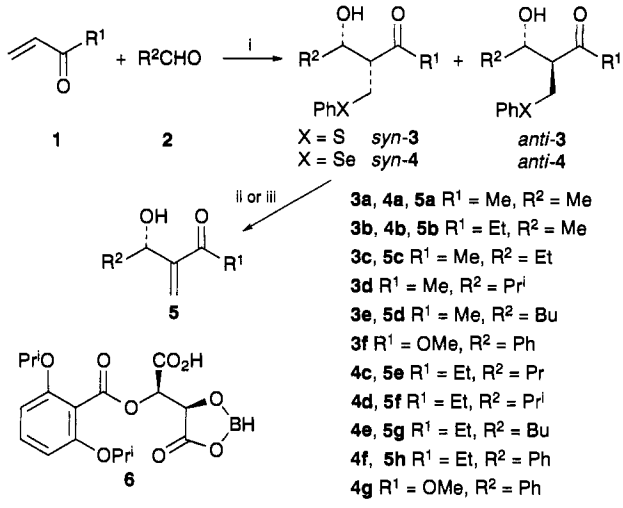
The use of asymmetric catalysis for the efficient synthesis of enantiomerically pure compounds is a topic of considerable current interest and importance.[1] The Baylis–Hillman reaction is a convenient process for the preparation of β-hydroxy-α-methylene-ketones, -nitriles and -esters.[2] In the process a vinyl ketone, acrylonitrile or an acrylic ester, is allowed to react with an aldehyde, under catalysis by diazabicyclo[2.2.2]octane (DABCO).[3] The resultant adducts are versatile synthetic intermediate and valuable building blocks for further synthetic transformations.[4] As a result, several groups have sought to adapt this chemistry for the synthesis of enantiomerically pure compounds.[5] Indeed, although both chiral Michael acceptors and chiral aldehydes have been used in the reaction, no effective asymmetric catalytic reactions have been reported. Herein, we report the catalytic[6] asymmetric synthesis of α-methylene-β-hydroxy-ketones using organosulfur (selenium) chemistry. This new process is preparatively equivalent to an asymmetric Baylis–Hillman reaction.

Reaction of methyl vinyl ketone, acetaldehyde and trimethylsilyl phenyl sulfide was catalysed by the chiral (acyloxy)borane **6** (20 mol%), generated *in situ* from (*R*,*R*)-2-*O*-(2,6-di-isopropyloxybenzoyl)-tartaric acid and BH_3–THF,[7] to give 4-hydroxy-3-(phenylthiomethyl)-2-pentanone **3a**† (50%) (Scheme 1). The adduct was obtained predominantly as the *syn* diastereoisomer (95 : 5)‡ and in high enantiomeric excess (e.e.) (93%).§ The reaction was extended to a range of aldehydes and to ethyl vinyl ketone and the results are summarized in Table 1. High diastereo- and enantio-selectivity were observed for the reaction in most cases, with the selectivity usually as high as 95/5. Both the chemical yield and diastereoselectivity in the reaction of methyl vinyl ketone with isobutyraldehyde (entry 4) were not as high as for other aldehydes. In addition, the reaction of methyl acrylate with benzaldehyde failed to provide the corresponding adduct **3f** (entry 6).

We also examined the use of trimethylsilyl phenyl selenide instead of the corresponding sulfide. This reaction also proceeded smoothly to give the adducts **4** in superior yields to the corresponding sulfides **3**. Again high *syn*-diastereoselectivity and high enantioselectivity were also observed. However, e.e.s were slightly lower than in the formation of sulfides **3**. Methyl acrylate was also inert under these reaction conditions and no condensation adduct were observed (entry 13).

Reaction of the sulfides **3** with *m*-chloroperbenzoic acid at −10 °C and subsequent thermolysis of the resultant sulfoxides at 130–150 °C gave the α-methylene-β-hydroxy-ketones **5** (entry 1–3 and 5) in moderate yields and with high e.e. It was found to be essential to directly distill the adducts **5** from the reaction vessel as formed to prevent partial racemisation and/or decomposition. The thermolysis of sulfoxides derived from sulfides **3** should only be useful for volatile enones **5**. In contrast, since the thermal *syn*-elimination of selenoxides is more facile than the corresponding sulfoxides, the selenides **4** are more generally useful. Thus, oxidation of the selenides **4** with aqueous hydrogen peroxide at room temp. gave the enones **5** in good yields and with minimal racemisation (entry 7–12).

The stereochemical assignments in this paper require substantiation. The absolute and relative configuration of adducts **3**, **4** and **5** were determined by comparison of their derivatives with known compounds in the literature. For example, the selenide **4b** was deselenylated using tributylstannane in the presence of

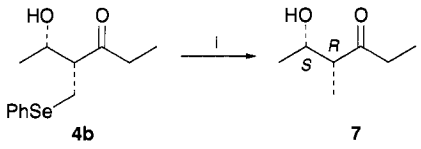


Scheme 1 *Reagents and conditions*: i, Me_3SiSPh or $Me_3SiSePh$, **6** (20 mol%), C_2H_5CN, −78 °C; ii, *m*-chloroperbenzoic acid, CH_2Cl_2, −10 °C then 130–150 °C; iii, H_2O_2, CH_2Cl_2, 25 °C

Table 1 Preparation of chiral Baylis–Hillman adducts **5**

Entry	Products	Yield (%)	*syn*/*anti*[a]	E.e.[a]	Method[b]	Products	Yield (%)	E.e.[c]
1	**3a**	50	95/5	93	A	**5a**	55	89[a]
2	**3b**	38	93/7	92	A	**5b**	71	87[a] (*S*)
3	**3c**	41	>98/2	>97	A	**5c**	46	96[a]
4	**3d**	9	84/16	89				
5	**3e**	39	98/2	91	A	**5d**	51	90[a]
6	**3f**	0	—	—				
7	**4a**	59	97/3	91	B	**5a**	88	87[a]
8	**4b**	49	93/7	84	B	**5b**	72	79[a] (*S*)
9	**4c**	53	97/3	85	B	**5e**	85	73[a] (*S*)
10	**4d**	37	97/3	63	B	**5f**	59	61[a]
11	**4e**	56	96/4	79	B	**5g**	72	83[a]
12	**4f**	50	87/13	69	B	**5h**	76	50[d]
13	**4g**	0	—	—				

[a] Determined by HPLC analyses (Chiralcel OD-H was used). [b] Method A: *m*-chloroperbenzoic acid, −10 °C, then 130–150 °C; Method B: H_2O_2, CH_2Cl_2, 25 °C. [c] Absolute configuration are in parentheses. [d] Determined by ^{1}H-NMR spectra in the presence of $Eu(tfc)_3$.



4b **7**

Scheme 2 *Reagents*: i, Bu_3SnH, azobisisobutyronitrile (34%).

AIBN (10 mol%) to give **7** (34%) (Scheme 2). ^1H and ^{13}C NMR spectra of this substance were identical to the data reported in the literature[8] and its sign of specific rotation was positive {$[\alpha]_D$ = +28.1 (*c* 1.33, $CHCl_3$)}, which clearly indicated that the absolute configuration was (4*R*, 5*S*). Consequently, the configuration of the chiral centre in **5b** was unambiguously determined to be *S*. The absolute and relative configurations of selenide **4e** were also confirmed to be (4*R*,5*S*) in the same way. Since these results are fully consistent with the known absolute stereochemical bias of the Yamamoto chiral (acyloxy)borane **6**[7b] in catalytic asymmetric aldol reactions, the absolute configuration of other adducts **5** were also assumed to be *S*.

Note added in proof: Recently, Hirama and co-workers report the use of chiral C_2-symmetric DABCO derivatives in catalytic asymmetric Baylis–Hillman reactions (e.e. ≤47%). T. Oishi, H. Oguri and M. Hirama, *Tetrahedron: Asymmetry*, 1995, **6**, 1241.

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Footnotes

† All new compounds were fully authenticated by spectroscopic data and microanalysis and/or HRMS.

‡ In each case the ratios of *syn* : *anti* diastereoisomers was determined from the ^1H NMR spectrum and by HPLC analysis.

§ In each case the enantiomeric excess was determined by chiral HPLC analysis.

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