Highly Enantioselective Catalytic Ketone Allylation with $Sn(CH_2CH{=}CH_2)_4$/ $RSn(CH_2CH{=}CH_2)_3$ Mixtures (R = Et, Bu)

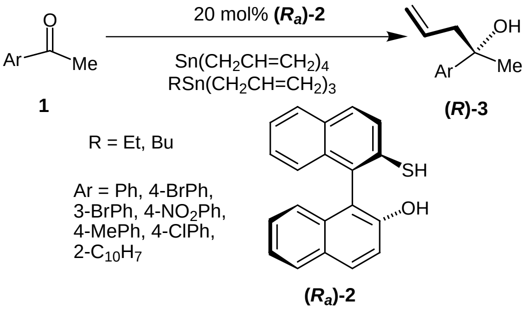
Anthony Cunningham, Simon Woodward*

School of Chemistry, The University of Nottingham, University Park, Nottingham NG7 2RD, United Kingdom
Fax +44(115)9513564; E-mail: simon.woodward@nottingham.ac.uk

Received 19 September 2001

Abstract: In the presence of the monothiobinaphthol (MTB) ligand aryl ketones are allylated by mixtures of $Sn(CH_2CH{=}CH_2)_4$/ $RSn(CH_2CH{=}CH_2)_3$ (R = Et, Bu) in high e.e. The presence of water suppresses racemic background allylation.

Key words: tin, asymmetric catalysis, ketones, allylation, thiols



Scheme

While numerous methods exist for catalytic enantioselective aldehyde allylation the equivalent chemistry for prochiral ketones is quiet underrepresented.[1,2] Including stoichiometric reagents, few systems have been reported that yield enantioselectivities of >80% for the ketones RC(=O)Me.[3–8] We report here a mechanistically interesting system for the allylation of aryl ketones **1** (Scheme) using mixtures of allylstannanes as the terminal allyl source. Tin-promoted carbonyl allylation is normally effected by either $Sn(CH_2CH{=}CH_2)_4$ or $Bu_3SnCH_2CH{=}CH_2$. Alternative tin allylating sources are rarely employed and, to the best of our knowledge, the use of mixtures of organometallics has never been reported.

When the literature preparation[9] of $Sn(CH_2CH{=}CH_2)_4$, is carried out using aged air-oxidised magnesium (to prepare the intermediate allyl Grignard in the presence of EtBr) the final product is appreciably contaminated by $EtSn(CH_2CH{=}CH_2)_3$ (0.15–0.30 mol fraction).[10] As a matter of course we tested this mixture in the allylation of acetophenone (**1a** R^1 = Ph) in the presence of monothiobinaphthol **2**[11] (20 mol%) as a chiral promoter (Scheme). To our delight this mixture showed potent efficacy: **3a** was formed in 67% e.e., in good yield, after 16 h at ambient temperature. Very surprisingly, reactions of the pure components alone were rather ineffective [e.e. values at 16 h: $Sn(CH_2CH{=}CH_2)_4$: 31% e.e.; $RSn(CH_2CH{=}CH_2)_3$ 26% e.e. (R = Et), 11% e.e. (R = Bu)]. The most efficient ketone allylation source is obtained from mixtures prepared by combining pure $Sn(CH_2CH{=}CH_2)_4$ (0.7 mol fraction)[9] and pure $RSn(CH_2CH{=}CH_2)_3$ (0.3 mol fraction; R = Et,[12] Bu[13]).[14] For technical simplicity the butyl compound is preferred, as it is easily prepared from commercially available $BuSnCl_3$.

Reaction of the ethyl mixture, under anhydrous conditions, with a range of aryl ketones **1** afforded the allylated products **3** in very high e.e. after 1 hour (Table). However, as the reaction conversion increased the enantioselectivity fell. This type of behaviour is common in asymmetric carbonyl allylation using organotin reagents.[1] Young has proposed that tin alkoxide products $Sn(OMe)_n(CH_2CH{=}CH_2)_{4-n}$ (mainly n = 4), formed in reactions carried out in methanol, using $Sn(CH_2CH{=}CH_2)_4$ lead to autocatalysis.[15] Similar behaviour, but involving product alkoxides, appears to be a common achiral background reaction in our 'dry' system and the catalysts described by Tagliavini[1] and Maruoka.[2] If this behaviour is not "switched off" then the e.e. of the alcohols **3** is compromised as the reaction proceeds to completion. Fortunately we noticed that, for our mixed allyl systems, the presence of small amounts of water inhibits these background reactions.[16] We are unaware of such an effect being noted before. The stereoselectivity of the 'wet' system can be marginally impaired compared to the 'dry' catalyst but the e.e. value is independent of the reaction conversion, even at reduced catalyst loadings (Table). If the ketone, solvent, or stannane mixture has not been rigorously dried an inadvertent water effect often results impairing the procedure's apparent reproducibility. Additionally, if too much water is present in the reaction mixture both the chemical yield and e.e. also suffer. For these reasons we recommend rigorous drying of all the reaction components so that the amounts of water present can be accurately quantified. Under these conditions the process is completely robust.

Compared to the predictable behaviour shown by aryl ketones, aliphatic ketones gave complex results depending on the substrate. For example, reaction of cyclohexyl methyl ketone **4** (Figure) with the 'dry' $EtSn(CH_2CH{=}CH_2)_3$/ $Sn(CH_2CH{=}CH_2)_4$ system led to a time dependent e.e. At low conversions only negligible e.e. values were realised

Synthesis 2002, No. 1, 28 12 2001. Article Identifier:
1437-2096,E;2002,0,01,0043,0044,ftx,en;D22301ST.pdf.

ISSN 0936-5214

Table Enantioselective Allylation of Ketones **1** by **2** (20 mol%) and Allyltin Mixtures [1.1 Equivalents of a 70:30 mol Fraction Mix of $Sn(CH_2CH{=}CH_2)_4/RSn(CH_2CH{=}CH_2)_3$; R = Et, Bu].

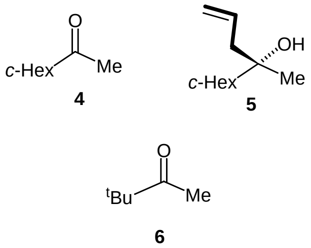
		'Dry' Method[a]		'Wet' Method[a]	
1	Ar	Yield [%]	e.e. [%]	Yield [%]	e.e. [%]
a	Ph	40–43	90–92	>98	86–89
a	Ph	–	–	71[b]	84[b]
b	4-BrPh	51	92	97	86
c	3-BrPh	53	85	>99	88
d	4-NO_2Ph	–	–	>98	86
e	4-MePh	32	90	78[c]	82
f	4-ClPh	–	-	94	87
g	2-$C_{10}H_7$	53	87	>98	84

[a] Yields and e.e. values at 1 h for 'dry' method using R = Et mix or 16 h for 'wet' method using R = Bu mix; see ref. 14 for details.

[b] At 9 mol% **2**,1.5 µL water and 16 h.

[c] 96% yield at 43 h, e.e. unaffected.

for product **5** (Figure) but this maximised at 59% e.e. at 19 h. With the 'wet' $BuSn(CH_2CH{=}CH_2)_3/Sn(CH_2CH{=}CH_2)_4$ system both the chemical yield and stereoselectivity were low [28% yield of **5** after 16 h, 41% e.e.]. Methyl *t*-butyl ketone **6** (Figure) did not participate in reaction with the 'wet' system.



Figure

In conclusion we have developed new catalytic systems for the allylation of aryl ketones in high e.e. The presence of $RSn(CH_2CH{=}CH_2)_3$ (R = Et, Bu) components in the terminal tetraallytin and a strong promotion effect by water are both highly beneficial. The variation of these components might also account for the non-reproducibility occasionally seen in other catalytic systems using tetraallytin as an allyl source. Further works on developing the utility of this new approach and in understanding its underlying mechanism are in hand.

Acknowledgement

We thank EPSRC for provision of a studentship (AC) and grant GR/R06205. We are also grateful to Mrs. Bridget K. Stein (EPSRC Mass Spectrometry Service) for GCMS advice and to Mrs. Nicola Bock for electron microscopy studies.

References

(1) Casolari, S.; D'Addario, D.; Tagliavini, E. *Org. Lett.* **1999**, *1*, 1061.

(2) Hanawa, H.; Kii, S.; Maruoka, K. *Adv. Synth. Catal.* **2001**, *343*, 57.

(3) (a) Titze, L. F.; Schiemann, K.; Wegner, C.; Wulf, C. *Chem. Eur. J.* **1998**, *4*, 1862. (b) Titze, L. F.; Völkel, L.; Wulff, C.; Weigand, B.; Bittner, C.; McGrath, P.; Johnson, K.; Schäfer, M. *Chem. Eur. J.* **2001**, *7*, 1304.

(4) Yasuda, M.; Kitahara, N.; Fujibayashi, T.; Baba, A. *Chem. Lett.* **1998**, 743.

(5) Loh, T.-P.; Zhou, J.-R.; Li, X.-R. *Tetrahedron Lett.* **1999**, *40*, 9333.

(6) Soderquist, J. A.; Prasad, K. G. *220th Meeting Am. Chem. Soc.-Abstr. Paper* **2000**, ORGN-508.

(7) Nakamura, M.; Hirai, A.; Sogi, M.; Nakamura, E. *J. Am. Chem. Soc.* **1998**, *120*, 5846.

(8) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432.

(9) O'Brien, S.; Fishwick, M.; McDermott, B.; Wallbridge, M. G. H.; Wright, G. A. *Inorg. Synth.* **1972**, *13*, 73.

(10) Other $Et_nSn(CH_2CH{=}CH_2)_{4-n}$, n = 2–4 species are also present as very minor contaminants in these preparations. Control reactions using d_5-EtBr confirm that the ethyl group arises from the EtBr used for magnesium activation in ref. 9. Fresh (silver-coloured) as opposed to aged (>2 years, black-coloured) magnesium leads only to pure $Sn(CH_2CH{=}CH_2)_4$. Electron microscopy in conjunction with EDS studies reveal that the surface of aged magnesium has an appreciable oxygen content (presumably MgO) and it appears to be this that favours production of EtMgBr over $CH_2{=}CHCH_2MgCl$.

(11) (a) Blake, A. J.; Cunningham, A.; Ford, A.; Teat, S. J.; Woodward, S. *Chem. Eur. J.* **2000**, *6*, 3586. (b) Azad, S. M.; Bennett, S. M. W.; Brown, S. M.; Green, J.; Sinn, E.; Topping, C. M.; Woodward, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 687.

(12) Kawakam, K.; Kuivila, H. G. *J. Org. Chem.* **1969**, *34*, 1502.

(13) Gambaro, A.; Peruzzo, V.; Plazzogna, G.; Tagliavini, G. *J. Organomet. Chem.* **1980**, *197*, 45.

(14) Experimental Procedure: All operations were performed under argon; toluene was distilled from sodium. A toluene solution of MTB **2** (24 mg, 0.08 mmol in 1.0 mL) was treated with a mixture of $Sn(CH_2CH{=}CH_2)_4/SnR(CH_2CH{=}CH_2)_3$ (0.7:0.3 mol fraction mix, 0.46 mmol total Sn content, R = Et, Bu). For the 'dry' catalyst this mixture (R = Et) was heated directly for 2 h at 52 °C. For the 'wet' catalyst water (3 µL, 0.16 mmol) was added to the mixture (R = Bu) prior to the heating period. The mixtures were cooled to ambient temperature, the ketone **1** (or **4**) (0.4 mmol) added and the mixture stirred whilst its composition was monitored by GC, HPLC, or $^1H/^{119}Sn$ NMR spectroscopy. Flash chromatography afforded the known alcohols **3** (or **5**) as essentially single products. Enantioselectivities were determined by GC (CYCLODEX-B for **3c**, *oktakis*(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin for **3a**, **3b**, **3e**, **3f**, **5**) or HPLC (Chiralcel AD for **3d**, Chiralcel OD for **3g**).

(15) (a) Cokley, T. M.; Marshall, R. L.; McCluskey, A.; Young, D. J. *Tetrahedron Lett.* **1996**, *37*, 1905. (b) Cokley, T. M.; Harvey, P. J.; Marshall, R. L.; McCluskey, A.; Young, D. J. *J. Org. Chem.* **1997**, *62*, 1961.

(16) We speculate that water co-ordination to mixed allyl-alkoxide species may limit their Lewis acidity preventing them acting as allylation promoters. For a review of water effects in asymmetric synthesis see: Ribe, S.; Wipf, P. *Chem. Commun.* **2001**, 299.