Synthesis of optically active allenes using tandem enzyme and palladium-catalysed reactions

Pierre H. Dixneuf,[a] Thierry Guyot,[b] Mark D. Ness[b] and Stanley M. Roberts‡[b]

[a] *UMR 6505 CNRS, Université de Rennes I, Laboratoire de Chimie de Coordination et Catalyse, Campus de Beaulieu, 35042 Rennes, France*

[b] *Department of Chemistry, University of Liverpool, Liverpool, UK L69 7ZD*

The propargylic carbonates (*S*)-6 and (*R*)-9 are converted into the chiral allenes 10, 11, 13 and 14 (ee 82–85%) using organozinc reagents and tetrakis(triphenylphosphine)-palladium as catalyst.

The importance of allenes is well-established and the variety of chemical reactions that they undergo is documented.[1] Recently, methods have been reported for the construction of allenes of the type $R^1CH{=}C{=}CHR^2$, in optically active form.[2]

In this paper, we report the enzymatic resolution of secondary[3] and the classical resolution of tertiary propargylic alcohols, their conversion into chiral allenes of the type $R^1R^2C{=}C{=}CR^3R^4$ *via* the corresponding carbonates[4] and their activation with palladium catalysts[5] in the presence of a zinc derivative.[6]

The optically active compounds required as starting materials for this study were obtained by a variety of methods. The alcohols **1** and **2** were prepared in high enantiomeric purity using enzymatic resolution methods (Table 1), while the alcohol (*R*)-**3** (99% ee) was obtained from the racemate by fractional crystallisation of the brucine salt from acetone.[7] Treatment of alcohol (*R*)-**3** with bromobenzene, piperidine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0) in DMF at 80 °C furnished the alcohol (*S*)-**4** (86%).[8] Finally, the alcohol (*S*)-**5** (99% ee) was prepared by enzyme-catalysed acetylation of racemic material (Table 1),[9] while the alcohol (*R*)-**5** (92% ee) was prepared from 1-phenyl-3-(trimethylsilyl)prop-2-ynone by selective reduction using dipinanylborane,[10] followed by desilylation with potassium carbonate in methanol.

The alcohol (*S*)-**1** was converted quantitatively into the corresponding carbonate (*S*)-**6** using ethyl chloroformate in pyridine, in the presence of a catalytic amount of 4-*N*,*N*-dimethylaminopyridine (DMAP). Alcohols (*S*)-**2** and (*R*)-**5** afforded the carbonates (*S*)-**7** and (*R*)-**9** after similar treatment, while the alcohol (*S*)-**4** furnished the carbonate (*S*)-**8** (97%) on treatment with butyllithium for one hour followed by treatment with methyl chloroformate at low temperature.

The carbonate (*S*)-**6** was treated with phenylzinc bromide† and a catalytic amount of tetrakis(triphenylphosphine)palladium (TTPP) in THF to provide the (a*R*)-allene **10** in 84% yield and 83% ee (Scheme 1). This reaction is very similar to one

Table 1 Resolution of alcohols **1**, **2** and **5** using *Pseudomonas amano* sp. AK and *Candida antarctica* lipases[a]

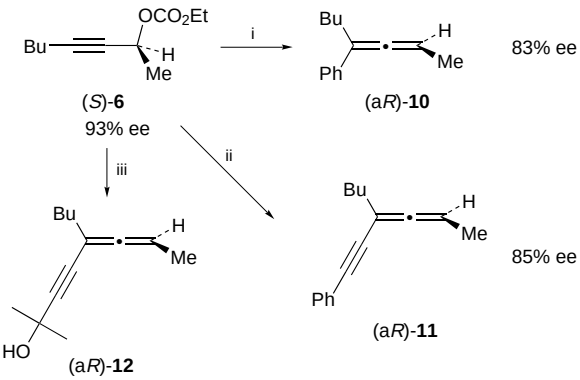
Substrate	Enzyme	*t*/h	Alcohol Yield (%) (ee) (%) configuration	Ester Yield (%) (ee) (%) configuration
1	*P. amano*	4	41 (93) *S*	41 (97) *R*
1	*C. antarctica*	2	39 (99) *S*	42 (94) *R*
2	*P. amano*	3	45 (86) *S*	42 (99) *R*
5	*C. antarctica*	3.5	46 (99) *S*	50 (98) *R*

[a] The substrate, enzyme and vinyl acetate were reacted for the specified time in hexane.

1 R^1 = Bu; R^2 = H; R^3 = Me; R^4 = Et **6**
2 R^1 = Ph; R^2 = H; R^3 = Me; R^4 = Et **7**
3 R^1 = H; R^2 = Bu^t; R^3 = Ph
4 R^1 = R^3 = Ph; R^2 = Bu^t; R^4 = Me **8**
5 R^1 = R^2 = H; R^3 = Ph; R^4 = Et **9**

performed by Vermeer *et al.*[6] The Dutch group reported a lower degree of stereocontrol, but these earlier studies were hampered by having a starting material of low optical purity (28% ee) and by having an uncertain amount of biphenyl in the product allene. Similarly, reaction of (*S*)-**6** with phenylacetylene in the presence of diisopropylamine, zinc chloride and catalytic amounts of copper(I) iodide and TTPP furnished the trisubstituted (a*R*)-allene **11** in 63% yield and 85% ee. The enantiomeric excesses of the products **10** and **11** were assessed by ^{1}H NMR spectroscopy using a mixture of a silver salt and a chiral ytterbium salt (ratio 1 : 1) as recommended previously.[11] The enantiomeric purity of the starting material and products suggests a high degree of control in the transfer from point to axial chirality. While the enantiomeric excess of the (a*R*)-dienynol **12**, obtained from the carbonate (*S*)-**6** and 2-methylbut-3-yn-2-ol, could not be assessed by physical methods, a high degree of stereocontrol in the reaction could be anticipated.

The absolute configuration of the allenes **10**–**12** has not been established conclusively but is assumed on the basis of the established mechanism of the reaction (Fig. 1). The palladium(0) is expected to activate the chiral carbonate by nucleophilic attack antiperiplanar to the leaving group, forming the chiral allenylpalladium intermediate (A). A cross-coupling on the intermediate (A) affords the chiral allene (B), regenerating the palladium(0) catalyst.



Scheme 1 *Reagents and conditions*: i, PhZnBr–Pd(PPh_3)$_4$, THF–Et_2O, 84%; ii, CuI–$ZnCl_2$–Pr^i_2NH–Pd(PPh_3)$_4$–THF–PhC≡CH, 63%; iii, CuI–$ZnCl_2$–Pr^i_2NH–Pd(PPh_3)$_4$–THF–$Me_2C(OH)C{\equiv}CH$, 59%

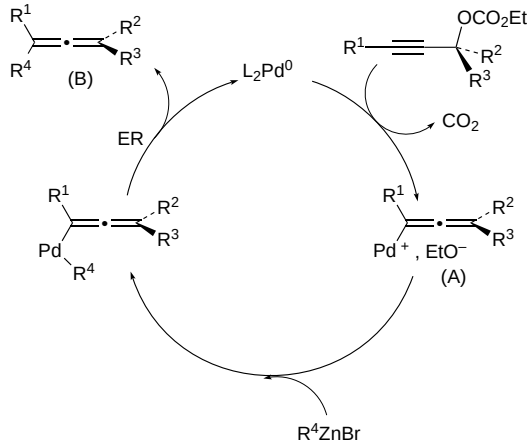
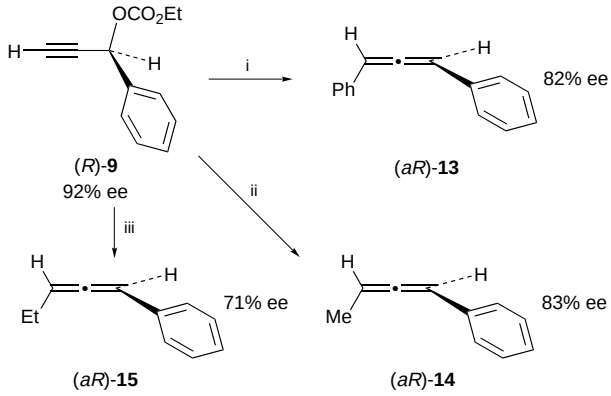


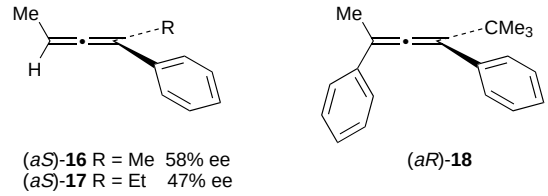
Fig. 1 Mechanism



Scheme 2 *Reagents and conditions*: i, $PhZnBr–Pd(PPh_3)_4–THF–Et_2O$, 65%; ii, $Me_2Zn–KBr–Pd(PPh_3)_4–THF$, 40%; iii, $EtZnBr–Pd(PPH_3)_4–THF–Et_2O$, 67%

In agreement with this proposal, the carbonate (*R*)-**9** (92% ee) reacts with phenylzinc bromide† in the presence of TTPP (Scheme 2) to furnish the (a*R*)-diphenylallene **13** (82% ee) {$[\alpha]_D^{22}$ −932 (*c* 1.0, $CHCl_3$); lit.[12] $[\alpha]_D$ +1137 ($CHCl_3$), for the (a*S*) enantiomer}. This carbonate (*R*)-**9** also reacts with dimethylzinc–potassium bromide or ethylzinc bromide in the presence of TTPP to give allenes **14** and **15** in 83 and 71% ee respectively (Scheme 2), as confirmed by ^{1}H NMR spectroscopy (Yb/Ag salts).

Incorporation of a phenyl group at the alkyne terminus, such as in compound (*S*)-**7**, leads to a poorer transfer of chirality on reaction with dimethylzinc–TTPP or diethylzinc–TTPP as shown with the allenes **16** and **17** being formed in 58 and 47% ee respectively. Thus, while the carbonate (*R*)-**8** reacts smoothly with dimethylzinc and TTPP in the presence of potassium bromide to give the allene **18** in 78% yield, the optical rotation of the product, $[\alpha]_D$ −250 (*c* 0.96, $CHCl_3$), may reflect only a moderate enantiomeric excess. (The optical purity of this tetrasubstituted allene could not be established by ^{1}H NMR spectroscopy using the silver–ytterbium chiral shift reagent.)



In summary, the preparation of highly substituted allenes of good to excellent optical purity can be accomplished by transformations involving secondary and tertiary propargylic carbonates.

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Footnotes and References

‡ E-mail: sj11@liverpool.ac.uk

† Made *in situ* from bromobenzene, magnesium turnings and zinc chloride.

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