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Application of an ephedrine chiral linker in a solid-phase, 'asymmetric catch-release' approach to γ-butyrolactones

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A Sm(II)-mediated, asymmetric, intermolecular ketyl-olefin addition employing α,β-unsaturated esters linked to resin through an ephedrine 'chiral link' has been applied in a direct 'asymmetric catch-release' approach to γ-butyrolactones.

Our interest in new solid-phase linker[1] technologies,[2] has led us to consider readily available and inexpensive ephedrine and pseudoephedrine derivatives as *'chiral linkers'* for solid phase synthesis. These linkers would allow substrates to be linked to resin and control the stereochemistry of reactions carried out on the substrate. Importantly, the 'one-step' attachment of the commercially available ephedrine or pseudoephedrine unit to resin through either oxygen or nitrogen is straightforward leading to robust ether or amine linkages (Fig. 1).

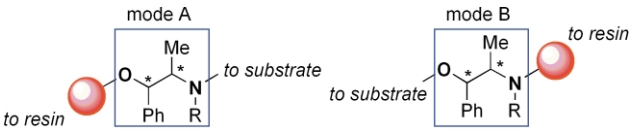
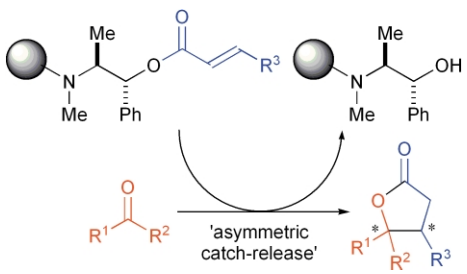


Fig. 1 Ephedrine and pseudoephedrine chiral linkers.

We have recently described the first application of this strategy in a pseudoephedrine linker approach (*linkage mode A*) for the asymmetric alkylation of amide enolates.[3] In this communication we describe the application of an ephedrine chiral link, using selective immobilisation through nitrogen (*mode B*), in intermolecular radical additions on solid-phase.[4]

Fukuzawa has described a highly enantioselective synthesis of γ-butyrolactones *via* the Sm(II)-mediated, intermolecular coupling of carbonyl compounds and α,β-unsaturated ephedrinyl esters.[5] We realised that adaptation of Fukuzawa's methodology would give rise to a solid phase 'asymmetric catch-release' approach to γ-butyrolactones. Thus the resin 'catches' a reactive intermediate, the ephedrine link controls the stereochemistry of addition, and the resulting product undergoes spontaneous, cyclative cleavage from the resin (Scheme 1).

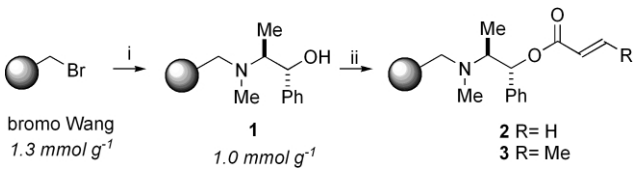
Hence, we envisaged that simply stirring a carbonyl compound with SmI_2 and a loaded ephedrine resin would give the enantiomerically enriched γ-butyrolactone directly. Lying somewhere between solid-phase chemistry and solid supported reagents, this methodology avoids the cleavage step traditionally associated with solid phase synthesis.[6] In addition, purification should be simpler as the ephedrine auxiliary



Scheme 1 An 'asymmetric catch-release' approach to γ-butyrolactones.

remains immobilised. Our approach also introduces the possibility of recovering the chiral resin by simple filtration, and recycling the support. The proposed methodology also points toward future applications in high-throughput asymmetric synthesis.

Inexpensive (1*R*, 2*S*)-ephedrine was immobilised on commercially available bromo Wang resin selectively through nitrogen and in one step, by adaptation of a literature procedure.[7] The loading of the resultant ephedrine resin **1** was found to be approximately 1 mmol g^{-1}.[8] Straightforward esterification of the resin with acryloyl chloride then gave the desired acrylate resin **2**, in which the ester moiety is bound to resin through an ephedrine chiral link (ν_{max}(C=O) 1724 cm^{-1}) (Scheme 2).



Scheme 2 *Reagents and conditions*: i, (1*R*, 2*S*)-ephedrine, DMF, 85 °C; ii, acryloyl chloride or crotonyl chloride, NEt_3, Et_2O, rt.

Using acetophenone and acrylate resin **2**, optimised conditions for the reaction were developed. Typically, ketyl-olefin couplings of this type are carried out by adding a mixture of the carbonyl compound and the acrylate to a solution of SmI_2.[9] Crucially, we found that changing the order of addition, *i.e.* adding SmI_2 to a mixture of the resin and the carbonyl compound, a prerequisite for a convenient solid-phase experimental procedure, did not significantly lower the enantioselectivities obtained.† Temperature was found to have a dramatic effect on the efficiency of the catch-release process. At −78 °C, only a trace of lactone **4** was detected, while at −40 °C, a disappointing 23% yield of **4** was isolated. Carrying out the reaction at −15 °C, however, gave a satisfactory isolated yield of lactone **4** (50%) in good enantiomeric excess (74% ee). Employing our optimised conditions (SmI_2, *tert*-butanol, THF, −15 °C), the asymmetric catch-release process with acrylate resin **2** and a range of ketones and aldehydes was investigated (Table 1). Significant ketyl-radical homo-coupling was not observed and few by-products were visible in the product mixtures. In general, the *isolated* yields obtained using **2** compare favourably with the GC yields of Fukuzawa.[5]

The analogous crotonate resin **3** was also prepared from ephedrine resin **1** (ν_{max}(C=O) 1734 cm^{-1}). Treatment of **3** with aldehydes under our optimised conditions gave the expected γ-butyrolactones in good yield and high enantiomeric excess. Only the *cis*-lactones were observed in the crude ^1H NMR of these reactions[5,10] (Table 2).

γ-Butyrolactone **8** is a moderate DNA-binding metabolite isolated from Streptomyces GT61115.[11] To illustrate the utility of our approach, we have undertaken a short synthesis of **8** (Scheme 3).

Diol **5** was prepared from δ-valerolactone according to a literature method.[12] Mono-protected diol **6** was prepared by bis-protection followed by cleavage of the primary TMS ether

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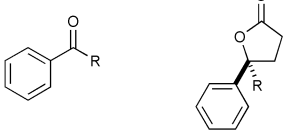
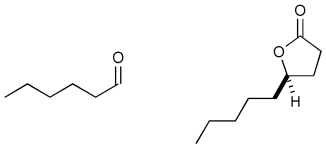
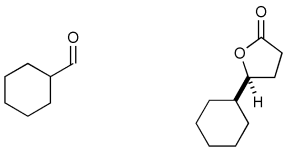
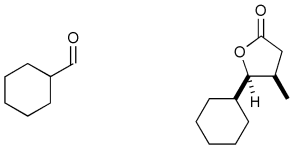
Table 1 γ-Butyrolactones formed using acrylate resin **2**[a]

	**4** R = Me, 50% (74%ee)[b] R = Et, 73% (70%ee)[b] R = Pr, 43% (74%ee)[b]
	37% (71%ee)[b]
	56% (70%ee)[c]
	56% (81%ee)[b]
	66% (76%ee)[b]

[a] Yields are isolated yields. [b] Enantiomeric excess determined by chiral GC (see ref. 14). [c] Enantiomeric excess determined by optical rotation.

Table 2 γ-Butyrolactones formed using crotonate resin **3**[a]

	56% (93%ee)[b]
	66% (96%ee)[c]
	55% (91%ee)[b]

[a] Yields are isolated yields. [b] Enantiomeric excess determined by chiral GC (see ref. 14). [c] Enantiomeric excess determined by optical rotation.

under basic conditions. Dess–Martin oxidation[13] of **6** then gave aldehyde **7** in excellent yield. On treatment with acrylate resin **2** and SmI_2 in the presence of *tert*-butanol, aldehyde **7** gave **8**, after loss of the TMS protection during work up, in 50% yield and 73% ee.[14] Our synthesis confirms the postulated absolute stereochemistry of **8**.[11]

In conclusion, we have described a solid-phase, asymmetric catch-release approach to γ-butyrolactones. In the process, a substrate immobilised through an ephedrine 'chiral link' undergoes asymmetric transformation through capture of a reactive intermediate from solution. Spontaneous, cyclative cleavage gives γ-butyrolactones in moderate yield and good enantiomeric excess. The development of methods for the efficient recycling of the chiral resin and the application of the methodology to the development of high-throughput asymmetric processes is currently under investigation.

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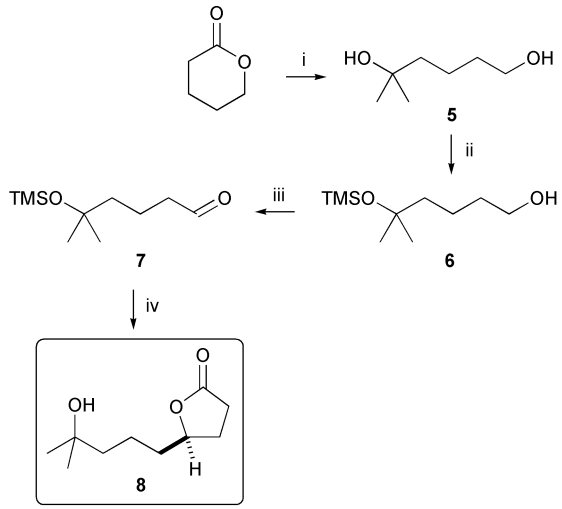

Scheme 3 *Reagents and conditions*: i, MeLi (1.5 M in Et_2O), THF, −78 °C to rt, 66%; ii, a) TMSCl, NEt_3, CH_2Cl_2, rt . b) K_2CO_3, MeOH, 0 °C, 96% for two steps; iii, Dess Martin periodinane, CH_2Cl_2, rt, 98%; iv, Acrylate resin **2**, SmI_2 (0.1 M in THF), −15 °C, THF, ^{t}BuOH, 50%.

Notes and references

† To investigate the effect of the order of addition on the enantioselectivity of the reaction we carried out solution phase model studies. For example, adding acetophenone, alcohol and acrylate to SmI_2 at 0 °C, gave lactone **4** in 73% ee, while adding SmI_2 to acetophenone, alcohol and acrylate, gave **4** in 68% ee. The yields obtained using both orders of addition were also similar.

1 For recent reviews on linkers for solid phase organic synthesis see: (*a*) I. W. James, *Tetrahedron*, 1999, **55**, 4855; (*b*) F. Guillier, D. Orain and M. Bradley, *Chem. Rev.*, 2000, **100**, 2091; (*c*) A. C. Comely and S. E. Gibson (née Thomas), *Angew. Chem. Int. Ed.*., 2001, **40**, 1012.
2 F. McKerlie, D. J. Procter and G. Wynne, *Chem. Commun.*, 2002, 584.
3 P. C. Hutchison, T. D. Heightman and D. J. Procter, *Org. Lett.*, 2002, **4**, 4583.
4 Relatively few intermolecular radical additions to immobilised acceptors have been reported. For selected examples see: (*a*) S. Caddick, D. Hamza and S. N. Wadman, *Tetrahedron Lett.*, 1999, **40**, 7285; (*b*) X. Zhu and A. Ganesan, *J. Comb. Chem.*, 1999, **1**, 157; (*c*) H. Miyabe, Y. Fujishima and T. Naito, *J. Org. Chem.*, 1999, **64**, 2174; (*d*) H. Miyabe, C. Konishi and T. Naito, *Org. Lett.*, 2000, **2**, 1443; (*e*) S. Caddick, D. Hamza, S. N. Wadman and J. D. Wilden, *Org. Lett.*, 2002, **4**, 1775; (*f*) D. C. Harrowven, P. J. May and M. Bradley, *Tetrahedron Lett.*, 2003, **44**, 503.
5 S. Fukuzawa, K. Seki, M. Tatsuzawa and K. Mutoh, *J. Am. Chem. Soc.*, 1997, **119**, 1482.
6 For a discussion of more conventional, two-step "resin-capture-release" processes, see: A. Kirschning, H. Monenschein and R. Wittenberg, *Chem. Eur. J.*, 2000, **6**, 4445.
7 J. M. J. Fréchet, E. Bald and P. Lecavalier, *J. Org. Chem.*, 1986, **51**, 3462.
8 The loading of **1** was determined by esterification with thiophene carbonyl chloride followed by sulfur elemental analysis of the resin. See ref 3.
9 S. Fukuzawa, A. Nakanishi, T. Fujinami and S. Sakai, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1669.See also ref. 5.
10 The diastereoselectivity was confirmed by comparison with Fukuzawa's ^{1}H NMR data (ref. 5) and by NOE studies.
11 C. Maul, I. Sattler, M. Zerlin, C. Hinze, C. Koch, A. Maier, S. Grabley and R. Thiericke, *J. Antiobiot.*, 1999, **52**, 1124.
12 A. S. Hernández and J. C. Hodges, *J. Org. Chem.*, 1997, **62**, 3153.
13 D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155.
14 The enantiomeric excess of lactones was determined by chiral GC (Supelco beta dex™ 120 fused silica capillary column —30 m) and comparison with authentic, racemic samples.