



# Eu(fod)<sub>3</sub>-catalyzed solid-phase [4+2] heterocycloadditions: an efficient asymmetric process in catalyst-recycling conditions

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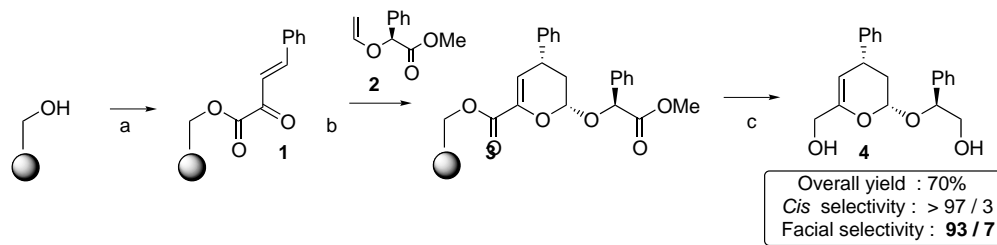
**Abstract**—Under Eu(fod)<sub>3</sub>-catalyzed conditions, the *endo*-selective hetero Diels–Alder reaction of (*S*)-(+)-*O*-vinyl mandelate with Wang-supported benzylidenepyruvate occurred with a 93/7 facial selectivity that compares well with those observed in solution. In addition, the solid-phase sequence allowed an unprecedented reuse of the catalyst in the presence of excess dienophile in solution. © 2001 Elsevier Science Ltd. All rights reserved.

In the last decade, the use of polymer-supported methodologies in carbon–carbon bond-forming asymmetric reactions has become a more and more attractive strategy.<sup>1–4</sup> Resin-immobilized chiral reagents or catalysts offer specific opportunities for the easy recovering and iterative use of expensive chiral sources.<sup>3,4</sup> A complementary approach, which avoids the prerequisite binding of the polymer to the chiral auxiliary or ligand, consists of supporting a prochiral substrate.

In the field of homogeneous liquid-phase asymmetric [4+2] heterocycloadditions, the use of Lewis acid catalysts (chiral or not) or promoters is typically required.<sup>5</sup> Therefore, compatibility of the carrier and the linker with the Lewis acid used is a main criterion for a successful application of such methodologies on solid support.<sup>6</sup> We recently reported the Eu(fod)<sub>3</sub>-catalyzed, *endo* selective, heterocycloaddition of vinyl ethers with

the Wang-supported benzylidene pyruvate **1**.<sup>7</sup> We now describe the successful asymmetric extension of this methodology using a chiral vinyl ether, (*S*)-(+)-methyl *O*-vinylmandelate **2**.

The cycloaddition process was easily monitored by FTIR spectroscopy (KBr disc). Indeed, characteristic stretches of the supported heterodiene **1** (1726, 1691 and 1662 cm<sup>−1</sup> for carboxylate, conjugate carbonyl and alkene groups, respectively) proved to be easily distinguishable from those of the supported heteroadduct **3** (1730–50 and 1649 cm<sup>−1</sup> for the esters and the enol, respectively). Contrary to previous results obtained with simple vinyl ethers,<sup>7</sup> the solid-supported cycloaddition of **1** with **2** gave only low conversions after 60 h with the quantities of lanthanide salt usually required in solution (5 mol%). With 20 mol% of Eu(fod)<sub>3</sub> the reaction was complete in less than 48 h. Reductive



**Scheme 1.** Reagents and conditions: (a) (*E*)-benzylidene pyruvic acid (3 equiv.), DIC, DMAP, DMF, 12 h, rt then filtration; (b) dienophile **2** (3 equiv.), 20% Eu(fod)<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 48 h, reflux then filtration; (c) LiAlH<sub>4</sub> (4 equiv.), 12 h, rt, THF/Et<sub>2</sub>O, then (i) aq. Na<sub>2</sub>SO<sub>4</sub> and (ii) filtration/Celite.

**Keywords:** hetero Diels–Alder reactions; solid-phase synthesis; chiral dienophile; reusable catalyst.

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cleavage by  $\text{LiAlH}_4$  under previous conditions afforded cleanly and in 70% overall yield the dihydropyranic diol **4** as a mixture of two *cis* isomers in a 93/7 ratio (Scheme 1).<sup>8</sup>  $^1\text{H}$  NMR comparison with the reduction product of the adduct obtained in our standard homogeneous liquid-phase conditions showed that the facial control in the solid-phase heterocycloaddition (86% diastereomeric excess in favor of *R,R*-isomer) has the same orientation as in solution<sup>9</sup> and compares well with that obtained in solution under the same catalytic conditions (84% d.e with methylene chloride as the solvent).<sup>10,11</sup>

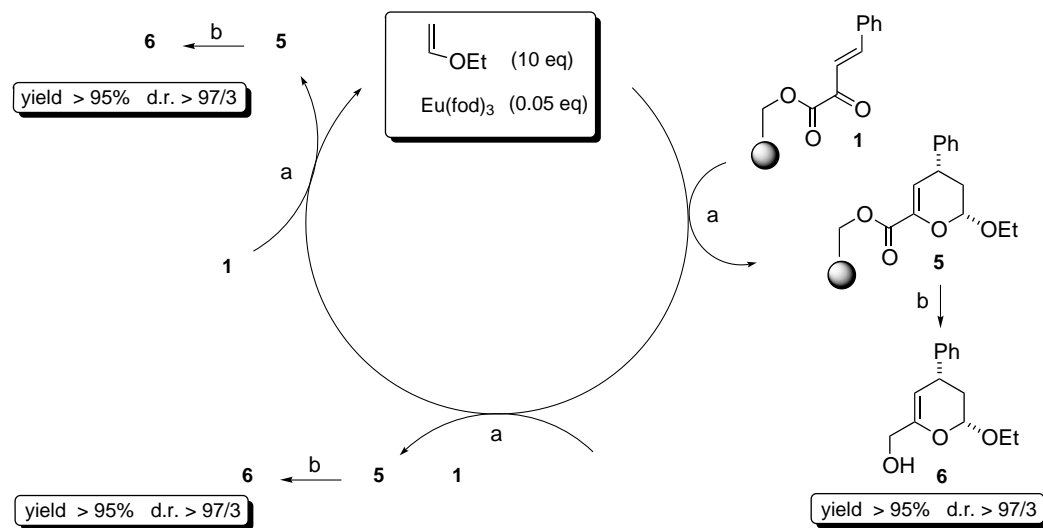
If we consider alternative strategies using a resin-supported chiral auxiliary,<sup>1–3,6</sup> this three-step asymmetric sequence on solid support has the potent advantage to allow access to enantiopure final product if the major diastereomer can be isolated before releasing the phenyl-ethanediol moiety. In fact, chromatographic separation of (4*R*,6*R*)-**4** gave only moderate yields (30–50% overall yield) because of the weak stability of this allylic alcohol over  $\text{SiO}_2$ , nevertheless such type of purification proved to be efficiently performed on stable tetrahydropyranic derivatives at a further stage.<sup>12</sup>

On the other hand, we had next to consider two main drawbacks to our approach, namely the use of a three-fold excess of the chiral dienophile together with appreciable quantities of high-cost catalyst during the cycloaddition step. We expected that both residual dienophile and catalyst would be cleanly removed from the resin-supported heteroadduct as a reusable homogeneous  $\text{CH}_2\text{Cl}_2$  solution at the end of this step.

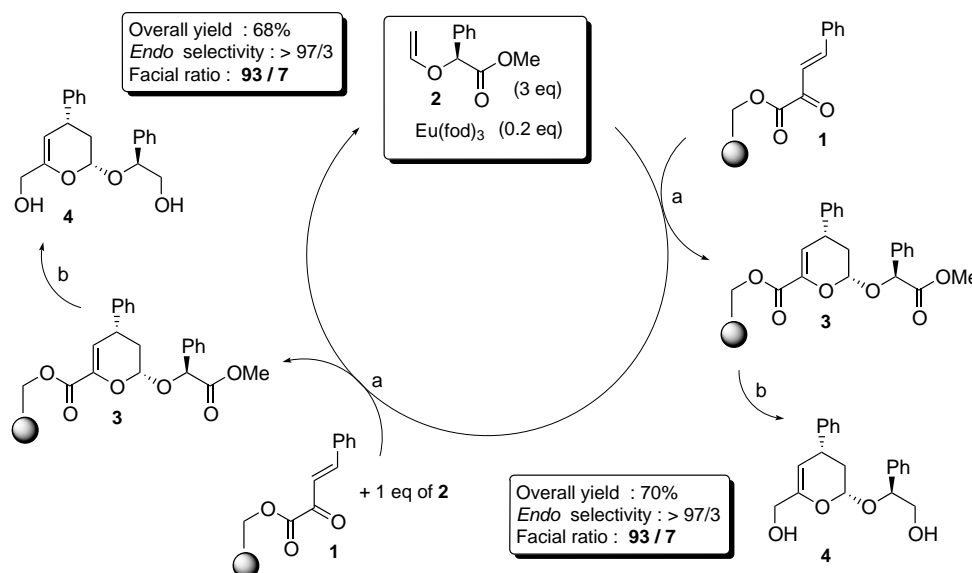
Preliminary attempts with ethyl vinyl ether as an achiral dienophile gave very positive results (Scheme 2). Thus, at the end of the solid-supported cycloaddition, the solution obtained by filtration of the reaction

medium and  $\text{CH}_2\text{Cl}_2$ -rinsing of the resin was successfully reused in two iterative sequences, without significant loss of yield and *cis*-selectivity.<sup>13</sup> The critical case of the chiral dienophile **2** was next studied. The supported heteroadduct **3** was filtered and carefully washed with anhydrous  $\text{CH}_2\text{Cl}_2$ .<sup>14</sup> The combined filtrate, after concentration and addition of both cycloreactants **1** and **2** (1 equiv. each), was submitted to a second heterocycloaddition using fresh immobilized heterodienophile **1**. Interestingly, after reductive cleavage, *cis* diol **4** was obtained with nearly the same yield and in the same diastereofacial ratio as in the first sequence (Scheme 3). The rate of recovered catalyst in the solution phase was deduced from Eu,F elementary analyses (ICP-MS) of the resin after the cycloaddition step: these measurements indicated that no more than 10% of the lanthanide salt initially used (nearly 0.02 equiv./1) remained complexed with the supported-adduct or trapped in the polymer matrix.<sup>15</sup>

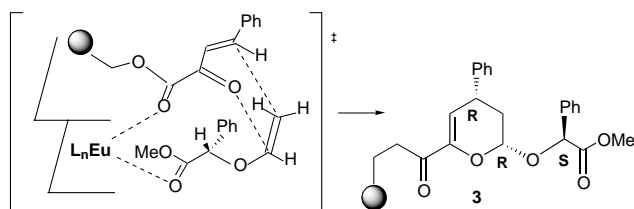
In conclusion, we demonstrated the usefulness of a Wang resin-bound heterodienophile for the stereoselective,  $\text{Eu}(\text{fod})_3$ -catalyzed, heterocycloaddition of a chiral vinyl ether: yields and diastereoselectivities compare well with those obtained in solution and for the first time, this catalyst can be simply recycled in the solution of the dienophile in excess. In the field of conventional homogeneous liquid phase chemistry, numerous reports have shown the great ability of hydrosoluble lanthanide catalysts—e.g. lanthanide triflates—to be recovered by final aqueous extraction.<sup>16</sup> Another efficient procedure involves the use of ionic solvents.<sup>17</sup> By contrast, to our knowledge no one reported any successful recovering of an organosoluble lanthanide catalyst such as  $\text{Eu}(\text{fod})_3$  (Siever's reagent). From a general point of view, our first results thus suggest that solid-supported chemistry can represent a positive context for an iterative recycling of such valuable catalysts.



**Scheme 2.** Reagents and conditions: (a)  $\text{CH}_2\text{Cl}_2$ , 48 h, reflux then filtration; (b)  $\text{LiAlH}_4$  (4 equiv.), 12 h, rt, THF/ $\text{Et}_2\text{O}$ , then (i) aq.  $\text{Na}_2\text{SO}_4$  and (ii) filtration/Celite.



**Scheme 3.** Reagents and conditions: (a)  $\text{CH}_2\text{Cl}_2$ , 48 h, reflux then filtration; (b)  $\text{LiAlH}_4$  (4 equiv.), 12 h, rt, THF/Et<sub>2</sub>O, then (i) aq.  $\text{Na}_2\text{SO}_4$  and (ii) filtration/Celite.



**Scheme 4.**

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- Dihydropyran **4**: thick colorless oil, IR (neat),  $\nu_{\text{max}}$ : 3378, 1681, 1674  $\text{cm}^{-1}$ . HRMS (LSIMS), calcd for  $[\text{M}-\text{H}]^+$  ( $\text{C}_{20}\text{H}_{21}\text{O}_4$ ): 325.1440. Found: 325.1438. Major *cis* isomer (4*R*,6*R*):  $R_f$  0.42 (cyclohexane/AcOEt 1/1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.06 (dt,  $J$  13.3, 7.8 Hz, 5-H), 2.32 (ddd,  $J$  13.3, 6.8, 1.8 Hz, 5-H), 3.58–3.66 (m, 3H), 3.79 (bs, 2H), 4.68 (dd,  $J$  8.2, 4.0 Hz, *O*-CH-Ph), 4.88 (d,  $J$  2.8 Hz, 3-H), 5.33 (dd,  $J$  7.3, 2.3 Hz, 6-H), 7.3–7.5 (m, 10H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  36.3, 36.4, 62.8, 66.7, 83.1, 100.2, 100.9, 126–128.6, 139.4, 144.4, 150.9. Minor *cis* isomer (4*S*,6*S*):  $R_f$  0.39 (cyclohexane/AcOEt 1/1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , characteristic signals):  $\delta$  4.13 (bs, 2H), 4.97 (dd,  $J$  7.0, 5.0 Hz, *O*-CH-Ph), 5.01 (d,  $J$  2.8 Hz, 3-H), 5.10 (dd,  $J$  7.2, 2.3 Hz, 6-H)  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.7, 36.2, 63.1, 67.1, 81.0, 97.3, 102.0, 126–128.6, 137.8, 144.5, 151.0.
- Absolute configuration of the major solid-supported adduct **3** agreed, as for its liquid-phase analog<sup>10</sup> with a favored Eu-chelated *endo* transition state in which the chiral dienophile would assume a well-stereodifferentiating conformation (Scheme 4).
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- It should be noticed that the facial discrimination increases significantly with the catalyst/substrate ratio. Indeed, the cycloaddition of (*R*)-(-)-**2** with (*E*)-methyl benzylidene pyruvate was previously reported with a 73% d.e. when using 5 mol% of  $\text{Eu}(\text{fod})_3$ .<sup>10</sup> With 20 mol% of  $\text{Eu}(\text{fod})_3$  80 and 84% d.e. were obtained in petrol ether and  $\text{CH}_2\text{Cl}_2$ , respectively.
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- No reaction occurred between **1** and ethyl vinyl ether under the same conditions without catalyst.<sup>7</sup>
- Typical solid-supported heterocycloaddition work-up is as follows: the reaction medium was filtered and the

resin was washed 8 times by equal volumes of  $\text{CH}_2\text{Cl}_2$  (20 mL per g of **1**). 8-Fold concentration of the combined organic layers furnished a stable, long-time storable dienophile/catalyst solution available for further hetero-cycloadditions.

15. This weak proportion was reduced to 5–7% with addi-

tional washing of the resin with a stoichiometric amount of fod-ligand in  $\text{CH}_2\text{Cl}_2$  solution.

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