Solid-Phase Synthesis of Dihydropyrans by Heterocycloaddition of a Supported Vinyl Ether: Progress in Functional Diversity

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The carboxypolystyrene-bound vinyl ether of 1,4-butanediol smoothly underwent an efficient *endo*-selective hetero-Diels–Alder reaction, under Lewis-acid conditions, with heterodienes bearing methyl ester, trifluoromethyl and *para*-tolylsulfinylmethyl groups at the C-2 position. Reductive cleavage of the supported adducts afforded functionalized dihydropyrans, which are of particular interest for diversity-oriented parallel synthesis.

Methodological extension of hetero-Diels−Alder reactions on solid supports[1] is an important task owing to the potential of these convergent processes from a diversity-generating standpoint.[2] The first report concerning inverse-electron demand oxa-Diels−Alder reactions with vinyl and enol ethers described thermal heterocycloadditions involving solid-supported heterodienes bearing an ester linkage at the C-3 position.[3] Previous work in our laboratory,[4] performed with solid-supported heterodienes bearing an ester linkage at the C-2 position, demonstrated the compatibility between solid-phase conditions and the use of Lewis-acid catalysts such as $Eu(fod)_3$ in order to obtain dihydropyran adducts with high diastereoselectivities. These conditions also allowed an unprecedented degree of recycling of $Eu(fod)_3$.[5]

However, by this first approach, access to structurally and functionally diverse heteroadducts was restricted, and the alternative pathway involving the polymer-bound dienophile seemed more promising to us. We report here our results concerning the reactivity of the solid-supported vinyl ether **1** towards various attractive heterodienes — including previously undescribed (*E*)-2-oxo-1-sulfinyl-3-alkenes — that could generate new synthetic developments in the solid-phase sequence (Scheme 1). During our work, it should be noted that the enantioselective synthesis of an impressive encoded library of dihydropyrancarboxamides was reported by Schreiber's group,[6,7] using the Cu(BOX)X_2-catalyzed, asymmetric and *endo* selective hetero-Diels−Alder reaction[8−10] of solid-supported dienophiles as the key step.

4-Hydroxybutyl vinyl ether was anchored to carboxypolystyrene resin using Mitsunobu conditions (Scheme 2). Using $Eu(fod)_3$ as the catalyst in refluxing dichloromethane,[4] the resulting solid-supported vinyl ether **1** reacted smoothly with a range of activated heterodienes (Scheme 3, Table 1). Applied to methyl (*E*)-benzylidenepyruvates **2a−c**, the sequence involving a solid-supported HDA reaction followed by reductive cleavage of the benzoic ester linkage with Superhydride® led to allylic alcohols **4a−c** in good overall yields (60−84%). In all cases, *cis*/*trans* ratios reflected a high *endo* selectivity for the cycloaddition step (96:4 for **4a**, R = Ph), which compared well with those obtained both in the homogeneous liquid phase (96:4) and with the corresponding supported-heterodiene (94:6).[4] Thus, in this series, the lanthanide salt $Eu(fod)_3$ can be considered as an alternative catalyst to (tBuBOX)Cu$(OTf)_2$[6] for the stereoselective heterocycloaddition of supported vinyl ethers, when asymmetric control is not desired.

The same sequence applied to 4-alkoxy-substituted heterodienes **2d−e** led to the expected *cis* allylic alcohols **4d−e** with a fair *cis* selectivity (20:1 for **4d**) but in lower yields, especially in the case of the bulky heterodiene **2e**. However, the stereoselective access to allylic alcohol **4d** is of particular interest, suggesting that further selective manipulations of adduct **3d** could provide a valuable route for the solid-phase synthesis of (±)-2-deoxysugar derivatives. It should be noted that most of these sensitive allylic alcohols **4** were obtained with a fair purity after silica gel chromatography but they decomposed after a few days.

An interesting development of this solid-phase sequence concerned the reaction of (*E*)-4-benzyloxy-1,1,1-trifluoro-3-buten-2-one (**2f**). Regarding the cycloaddition of this heterodiene, reports of solution-phase conditions that would be easily transposable to solid-phase synthesis are few. Larsen's group has reported that $ZnCl_2$ efficiently promotes the heterocycloaddition of **2f** with ethyl vinyl ether at room temperature (three days, 76% yield) with a high

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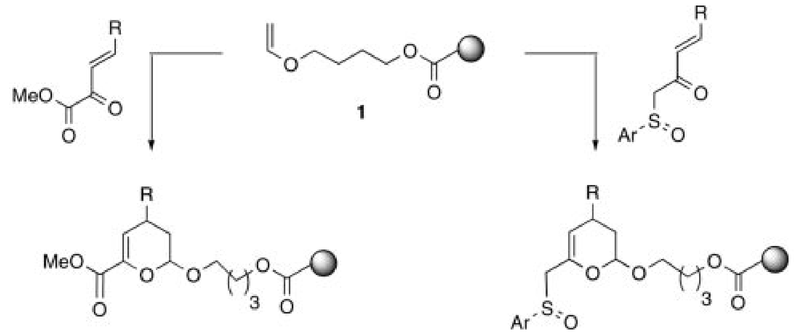
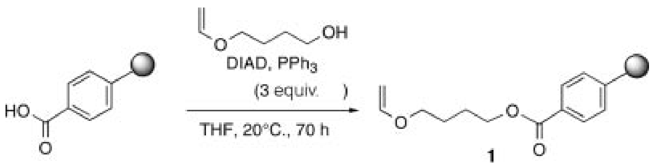
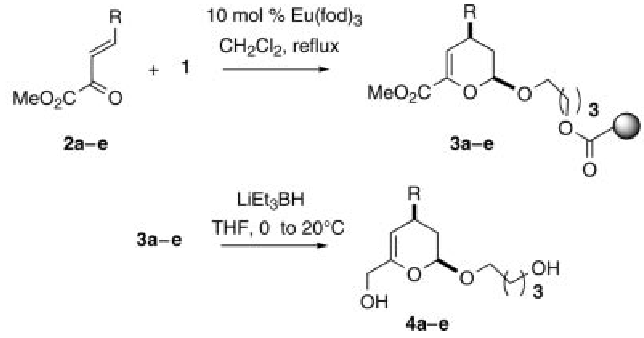


Scheme 1



Scheme 2



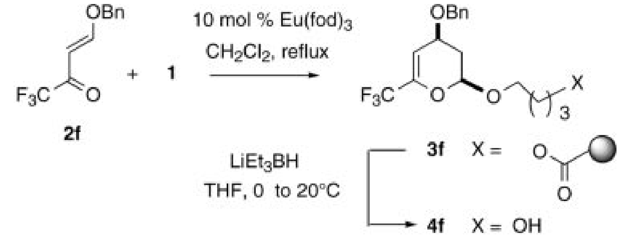
Scheme 3

Table 1. Solid-phase synthesis of allylic alcohols **4a−e**

Entry	Diene	R	Adduct	Yield[a]	*cis*/*trans*[b]
1	**2a** [11]	Ph	**4a**[4]	84	96:4
2	**2b** [11]	4-Cl-C_6H_4	**4b**	71	98:2
3	**2c** [11]	4-MeO-C_6H_4	**4c**	60 (54[c])	91:9
4	**2d** [12]	BnO	**4d**	45	95:5
5	**2e** [12]	*t*BuO	**4e**	10	91:9

[a] Isolated yield, purity > 97% otherwise noted. [b] Determined by 400MHz ^1H NMR spectroscopy. [c] Based on 90% purity of the chromatographed product.

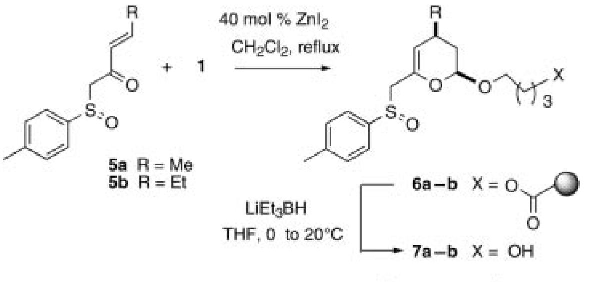
endo selectivity (> 95:5).[13] However, independent work in our laboratory demonstrated that the Eu(fod)$_3$-catalyzed heterocycloaddition of **2f** with ethyl vinyl ether proceeded quantitatively and with a high *endo* selectivity (> 97:3) under similar conditions (room temp., two days).[14] Thus, "Danishefsky's catalyst" was again selected. Although less reactive towards the supported dienophile **1** than its ester counterpart **2d**, under the same Eu(fod)$_3$-catalyzed conditions (CH_2Cl_2, reflux, four days), heterodiene **2f** led to the expected adduct, giving rise cleanly after cleavage to dihydropyran **4f** in 35% overall yield and with a 9:1 *cis* selectivity (Scheme 4).



35% yield, *cis* / *trans* ratio : 90 / 10

Scheme 4

In connection with our ongoing research on new sulfinyl heterodienes,[15,16] we next considered the sulfinylmethyl group as a potentially valuable functionality in place of the activating group of the heterodiene. Thus, the new heterodienes (±)-**5a**,**b**[17] were tested under various Lewis-acid conditions, with ZnI_2 [18] giving the best results. The supported dienophile **1** reacted with (±)-**5a** and (±)-**5b** (Scheme 5), leading to heteroadducts **6a**,**b** in good yields after reductive cleavage. The diastereomeric ratios observed for **7a**,**b** indicated that the cycloaddition occurred with moderate *endo* and facial selectivities.



7a : 61% yield, *cis* / *trans* ratio : 78 (75 : 25)* / 22 (73 : 27)*
7b : 66% yield, *cis* / *trans* ratio : 70 (83 : 17)* / 30 (74 : 26)* * : facial selectivity

Scheme 5

In summary, the solid-phase sequences reported here exemplify an efficient route to solid-supported heteroadducts bearing useful functionalities such as methyl ester, trifluoromethyl and sulfinylmethyl groups at the C-2 position. Solid-supported adducts **6** are substrates of choice for further experiments on the reactivity of allylic sulfoxides. In addition, we believe that the access to solid-supported analogs of allylic alcohols **4a−d** could lead to valuable extensions, provided that the internal linkage could tolerate the key reduction of the ester functionality within the adduct, by the use of an appropriate support. Further studies in this area are currently under investigation.

Experimental Section

Preparation and Characterization of the Solid-Supported Vinyl Ether 1: Triphenylphosphane (3 equiv.), 1,4-butanediol monovinyl ether (3 equiv.) and DIAD (3 equiv.) were added to a suspension of the commercial carboxy polystyrene resin [1 mmol (i) or 2 mmol (ii) CO_2H groups per gram; 1 equiv.] in dry THF [8 mL (i) or 16 mL (ii) per gram of resin]. After 3 days of shaking at room temperature, the mixture was filtered. The recovered resin was washed alternately with THF and Et_2O (three times each), then CH_2Cl_2 and petroleum ether (three times each) and was dried under reduced pressure. The capacity of the resin **1**, determined by reductive cleavage with Superhydride® ($LiEt_3BH$, 1 M in THF), was 0.75 mmol/g (i) and 1.5−1.6 mmol/g (ii) (approx. 80% functionalization rate in both cases).

General Procedure for Solid-Supported Heterocycloadditions Catalyzed by Eu(fod)$_3$: The vinyl ether resin **1** (1 equiv.) was suspended in a solution of the requisite heterodiene **2** (2 equiv. for **2a−c**, 4 equiv. for **2d−f**) and Eu(fod)$_3$ (0.1 equiv. for **2a−c**, 0.2 equiv. for **2d−f**) in dry CH_2Cl_2 (10 mL/300 mg resin). The resulting mixture was refluxed for 4 days (except for heterodiene **2e**, 7 days) with shaking and then filtered. The recovered resin was washed alternately with CH_2Cl_2 and Et_2O (4 times each) and dried under reduced pressure. A solution of $LiEt_3BH$ (1 M in THF, 8 equiv.) was added to a suspension of the supported adduct **3** in dry THF (30 mL/g) at 0 °C . After shaking for 30 minutes at 0 °C and overnight at 20 °C, the reaction medium was cooled to 0 °C, treated with saturated aqueous Na_2SO_4, shaken for 30 minutes and then filtered. The solid was washed several times alternately with THF and Et_2O and the combined filtrates were evaporated under reduced pressure. The oily residue was taken up in Et_2O and the resultant mixture filtered, the solvents evaporated under reduced pressure and purified by chromatography on silica gel (eluent Et_2O) to afford the dihydropyran **4**.

General Procedure for Solid-Supported Heterocycloadditions Catalysed by ZnI$_2$: ZnI_2 (0.4 equiv.) was added to a suspension of the vinyl ether resin **1** (1 equiv.) and the requisite heterodiene **5** (2 equiv.) in dry CH_2Cl_2 (8 mL/300 mg resin) at 0 °C . The resulting mixture was refluxed for 7 days with shaking and then filtered. The recovered resin was washed alternately with CH_2Cl_2 and Et_2O (4 times each) and dried under reduced pressure. Reductive cleavage of the supported adduct **6** was effected as described previously for **3**, with $LiEt_3BH$ (4 equiv.), and led to the 2-sulfinylmethyl dihydropyran **7**.

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[1] J. Yli-Kauhalauoma, *Tetrahedron* **2001**, *57*, 7053−7071.
[2] R. E. Dolle, *J. Comb. Chem.* **2002**, *4*, 369−418.
[3] L. F. Tietze, T. Hippe, A. Steinmetz, *Synlett* **1996**, 1043−1044.
[4] S. Leconte, G. Dujardin, E. Brown, *Eur. J. Org. Chem.* **2000**, 639−643.
[5] G. Dujardin, S. Leconte, L. Coutable, E. Brown, *Tetrahedron Lett.* **2001**, *42*, 8849−8852.
[6] R. A. Stavenger, S. L. Schreiber, *Angew. Chem. Int. Ed.* **2001**, *40*, 3417−3421.
[7] H. E. Blackwell, L. Perez, R. A. Stavenger, J. A. Tallarico, E. C. Eatough, M. A. Foley, S. L. Schreiber, *Chem. Biol.* **2001**, *8*, 1167−1182.
[8] J. Thorhauge, M. Johannsen, K. A Jorgensen, *Angew. Chem. Int. Ed.* **1998**, *37*, 2404−2406.
[9] D. A. Evans, E. J. Olhava, J. S. Johnson, J. M. Janey, *Angew. Chem. Int. Ed.* **1998**, *37*, 3372−3375.
[10] D. A. Evans, J. S. Johnson, E. J. Olhava, *J. Am. Chem. Soc.* **2000**, *122*, 1635−1649.
[11] G. Dujardin, S. Leconte, A. Bénard, E. Brown, *Synlett* **2001**, 147−149.
[12] G. Dujardin, S. Rossignol, E. Brown, *Synthesis* **1998**, 763−770.
[13] C. M. Hayman, D. S. Larsen, S. Brooker, *Aust. J. Chem.* **1998**, *51*, 545−553.
[14] S. Leconte, PhD Thesis, Le Mans, **2000**.
[15] P. Hayes, C. Maignan, *Tetrahedron: Asymmetry* **1999**, *10*, 1041−1050.
[16] P. Hayes, C. Maignan, *Synthesis* **1999**, 783−786.
[17] G. Solladié, G. Demailly, C. Greck, *J. Org. Chem.* **1985**, *50*, 1553−1554.
[18] E. Wada, W. Pei, H. Yasuoka, U. Chin, S. Kanesama, *Tetrahedron* **1996**, *52*, 1205−1208.

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