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SOLID PHASE APPROACH TO MUSCONE SYNTHESIS: Rh(I)-CATALYZED HYDROFORMYLATION OF A 1,1-DISUBSTITUTED ALKENE ON THE MULTIPIN™ SYSTEM

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Abstract: *Rh(I)-catalyzed hydroformylation of a polymer-supported 1,1-disubstituted alkene was carried out on the Multipin™ system. The reaction proceeded under 75 atm of syngas (H_2 : CO = 1 : 1) providing the corresponding aldehyde on the solid support. Optimization of the reaction conditions is described.*

Solid phase organic synthesis is a useful tool for preparing large sets of diverse chemical compounds for drug lead discovery and optimization.[1] Although many organic reactions have been reported,[2] there are few solid phase reactions performed using gaseous reagents.[3-5] If homogeneous catalyzed reactions of solid-supported compounds can proceed under high pressure, this technique would be useful in parallel synthesis. We have been interested in employing hydroformylation as a means of efficiently constructing a carbonyl unit from an alkene in the presence of various functional groups. In particular, the hydroformylation of 1,1-disubstituted alkenes is attractive as an equivalent to nucleophilic 1,4-addition to 2-alkenals.[6] As part of an overall strategy designed to exploit solid-supported aldehydes as versatile reaction intermediates for combinatorial organic synthesis, we were initially intrigued by the potential of applying hydroformylation on a solid support. This provides an attractive route for the synthesis of macrocyclic ketones as shown in Figure 1.[6]

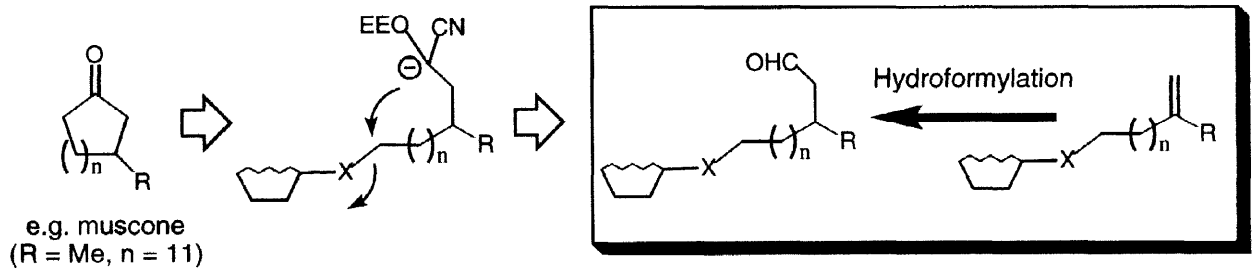

Figure 1.

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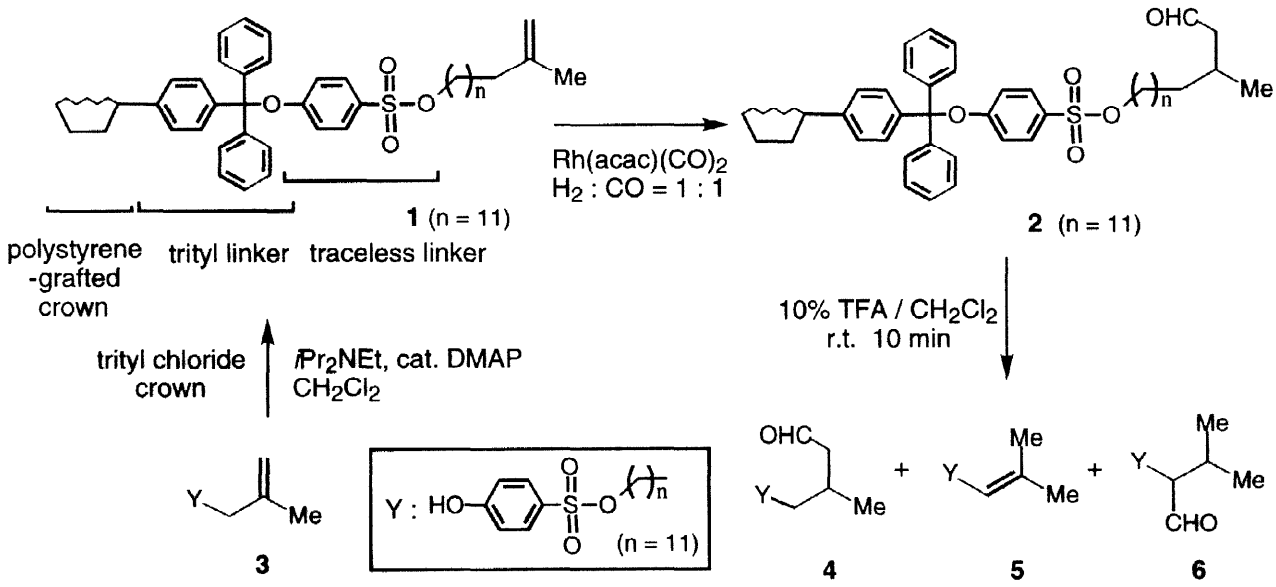
The Multipin™ system has been successfully used in the synthesis of a chemical library.[7] As we recently reported that rhodium-catalyzed hydroformylation of 1,1-disubstituted alkenes proceeded efficiently in toluene,[6] we decided to adapt this chemistry to polystyrene-grafted SynphaseTM crowns (Scheme 1). We planned to use a "traceless" linker[8] that would act as a leaving group X in the intramolecular alkylation step shown in Figure 1. The traceless linker selected was based on 4-hydroxyphenylsulfonate,[9,10] as the tosyl group is a well known leaving group in alkylation reactions, furthermore, we recently reported that the tosyl group is compatible with Rh(I)-catalyzed hydroformylation of 1,1-disubstituted alkenes.[6] In order to allow for the assessment of conversions and quality of the supported-bound intermediates throughout the synthesis, system **1** was built up on crowns derivatized with the trityl linker[11,12] as this linker is stable to cyanohydrin formation and intramolecular alkylation strategies, but can be cleaved with 10% TFA / CH_2Cl_2.



Scheme 1.

The polystyrene-grafted crowns with a trityl chloride linker were treated with a 0.1 M solution of the substrate **3**, diisopropylethylamine, and catalytic amount of DMAP in CH_2Cl_2 for 2 h providing the crown alkenyl tosylate **1**. Hydroformylation of **1** was carried out in a toluene solution of $Rh(acac)(CO)_2$ under pressured syngas (H_2 / CO = 1) to give **2**. The crude products were analyzed after cleavage from the crowns (10% TFA / CH_2Cl_2). Effect of solvent, temperature and the concentration of the rhodium catalyst on this reaction was examined (Table 1). From these experiments,[13] the following results were obtained. 1) The concentration of the rhodium catalyst was found to be optimal: $Rh(acac)(CO)_2$ 30 mM (Entry 4). The lower concentration of the catalyst resulted in lower conversions of **1** and alkene isomerization to **5** (Entries 1-3). 2) Reactions at 40 °C gave better purity of the product (Entry 4) whereas those at 60 °C resulted in poor purity due to isomerized alkene, which underwent hydroformylation leading to **6** (Entries 5-7).[14] 3) Pressure of syngas

Table 1. Rh(I)-Catalyzed Hydroformylation of Alkenyl Tosylate Crown 1[a]

Entry	Temp / °C	Press[b] / atm	Solvent	Conc of Cat / mM	Convn[c] / %	Selectivity[d] / % 4	5	6
1	40	75	toluene	1	18	34	66	-
2	40	75	toluene	10	53	84	16	-
3	40	75	toluene	20	70	90	10	-
4	40	75	toluene	30	83	98	2	-
5	60	75	toluene	5	98	66	-	34
6	60	75	toluene	10	99	55	-	45
7	60	75	toluene	20	99	72	-	28
8	40	40	toluene	30	55	51	46	3
9	40	40	toluene	40	89	34	13	53
10	40	75	THF	30	16	49	51	-
11	40	75	DMF	30	83	3	87	10
12	40	75	DCE	30	95	16	84	-

[a] All reactions were carried out in the presence of $Rh(acac)(CO)_2$ as a catalyst for 40 h. [b] Synthetic gas H_2 : CO = 1 : 1. [c] Conversion was determined by HPLC with integration of peak area of **3** in the crude products after TFA cleavage from crowns. [d] HPLC purity of **4** in the products determined by refractive index and UV (260 nm) after TFA cleavage from crowns.

(H_2 : CO = 1, 75 atm) was important to provide the product with high purity avoiding from the isomerization of alkenes as described in our previous report in solution phase[6] (Entries 4 and 8 or 9). It is noteworthy that the reaction on the crowns worked well under relatively high pressure. 4) Toluene was effective solvent rather than other polar solvents. Reactions in THF gave low conversion of **1** and those in DMF or 1,2-dichloroethane (DCE) resulted in poor purity of the product due to isomerization to an internal alkene (Entries 10-12). Alternatively, the best result was obtained when the reaction was carried out at 40 °C for 40 h in a 30 mM toluene solution of $Rh(acac)(CO)_2$ under 75 atm of syngas (H_2 / CO = 1) providing **2** with 98% purity in 83% conversion of **1**.

In summary, it is demonstrated that the Rh(I)-catalyzed hydroformylation on solid supported 1,1-disubstituted alkene gave exclusive formation of versatile aldehyde, which can be utilized for a solid-phase synthesis toward the construction of combinatorial libraries.

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REFERENCES AND NOTES

1. For a review, see: Gordon, E. M.; Barrett. R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A., *J. Med. Chem.* **1994**, *37*, 1385-1401.
2. Reviews for solid-phase organic reactions, see: James, I. W.: A Compendium of Solid-Phase Chemistry

Publications. In *Annual Reports in Combinatorial Chemistry and Molecular Diversity*; Moos, W. H.; Pavia, M. R.; Ellington, A. D.; Kay, B. K., Eds.; ESCOM: Leiden, The Netherlands, 1997; Vol. 1, pp. 326-344; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C., *Tetrahedron* **1997**, *53*, 5643-5678; Thompson, L. A.; Ellman, J. A., *Chem. Rev.* **1996**, *96*, 555-600.

3. For hydrogenation and hydroformylation catalyzed by polymer-supported Rh(I)-phosphine complexes, see: Dumont, W.; Poulin, J.-C.; Dang, T.-P.; Kagan, H. B., *J. Am. Chem. Soc.* **1973**, *95*, 8295-8299; Takaishi, N.; Imai, H.; Bertelo, C. A.; Stille, J. K., *J. Am. Chem. Soc.* **1978**, *100*, 264-268; Bayer, E.; Schurig, V., *Chemtech* **1976**, 212-214.

4. For the rhodium-catalyzed asymmetric hydrogenation of polymer supported dehydropeptides, see: Ojima, I.; Tsai, C.-Y.; Zhang, Z., *Tetrahedron Lett.* **1994**, *35*, 5785-5788.

5. For an example of asymmetric hydrogenation using chiral phosphine ligands loaded on Multipin system, see: Gilbertson, S. R.; Wang, X., *Tetrahedron Lett.* **1996**, *37*, 6475-6478.

6. Takahashi, T.; Machida, K.; Kido, Y.; Nagashima, K.; Ebata, S.; Doi, T., *Chem. Lett.* **1997**, 1291-1292.

7. For Multipin approach, see: Valerio, R. M.; Bray, A. M.; Maeji, N. J., *Int. J. Peptide Protein Res.* **1994**, *44*, 158-165; Virgilio, A. A.; Ellman, J. A., *J. Am. Chem. Soc.* **1994**, *116*, 11580-11581; Valerio, R. M.; Bray, A. M.; Patsiouras, H., *Tetrahedron Lett.* **1996**, *37*, 3019-3022; Rodebaugh, R.; Joshi, S.; Fraser-Reid, B.; Geysen, H. M., *J. Org. Chem.* **1997**, *62*, 5660-5661.

8. Plunkett, M. J.; Ellman, J. A., *J. Org. Chem.* **1995**, *60*, 6006.

9. Takahashi, T.; Tomida, S.; Inoue, H.; Doi, T., unpublished results.

10. For alkylsulfonate linker, see: Hunt, J. A.; Roush, W. R., *J. Am. Chem. Soc.* **1996**, *118*, 9998-9999.

11. Fréchet, J. M. J.; Nuyens, L. J., *Can. J. Chem.* **1976**, *54*, 926-934; Barlos, K.; Gatos, D.; Kallitsis, J.; Papaphotiu, G.; Sotiriu, P.; Wenqing, Y.; Schäfer, W., *Tetrahedron Lett.* **1989**, *30*, 3943-3946.

12. Trityl chloride crown was prepared from trityl alcohol crown with acetyl chloride before use. See ref 13; $HOC(Ph)_2C_6H_4CONHCH_2$-Polystyrene, Batch no. 810-1. Loading = 9.5 μmol per crown, Chiron Technologies Pty. Ltd., 11 Duerdin St., Clayton, Victoria 3168, Australia.

13. *Experimental*: The freezed-dry trityl alcohol crowns were treated with acetyl chloride (2.5 mL) and methylene chloride (2.5 mL) at room temperature under argon. After being left for 12 h, the crowns were washed five times with dry methylene chloride (5 mL) for 2 min in each time in a globe bag filled with nitrogen. The obtained trityl chloride linked crowns were subsequently treated with a 0.1 M solution of 13-methyl-13-tetradecenyl 4-hydroxyphenylsulfonate (**3**) in dry methylene chloride in the presence of catalytic amount of 4-dimethylaminopyridine and 5 equiv. of *N,N*-diisopropylethylamine. After being left for 2 h at room temperature, the crowns were consecutively washed with methylene chloride (3 min x 5), methanol (3 min x 5), methylene chloride (2 min x 5), and toluene (2 min x 5). Then, the **3**-loaded crowns **1** were dried *in vacuo* and were placed in a sample tube with a toluene solution of $Rh(acac)(CO)_2$. The tubes were placed in an auto crave, which was purged with syngas (H_2 : CO = 1) for three times before pressed under 75 atm. After being left at 40 °C for 40 h, the hydroformylated crowns **2** were washed with methylene chloride (2 min x 5) and dried *in vacuo*. The cleavage of **2** was performed by treatment with a 10% trifluoroacetic acid (TFA) solution in methylene chloride for 10 min providing the crude products, which were isolated by HPLC and analyzed by ^1H NMR: 8 x 300 mm Senshu Pak, Silica-3301-N, elution 20% ethyl acetate / hexane, flow rate 3.0 mL /min, **3**: Rt = 9.5-11.6 min; **4**: 20.8-25.0 min; **5**: 12.5-13.9 min; **6**: 16.5-19.3 min.

14. The partial cleavage (30-45%) was observed by TLC analysis of the solution of the reaction mixture. The concentrated residue of the reaction solution and washed solvents was analyzed by HPLC in the same concentration as that of the crude products shown in Table 1. This partial cleavage was less than 5% when the reaction was carried out at 40 °C for 40 h.