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# Exploring Functional and Molecular Diversity with Polymer-Bound *p*-Alkoxybenzyl Ethers – Scope and Applications of Preparatively Useful Organic Reactions

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***Abstract:*** *Alcohols immobilized as p-alkoxybenzyl ethers on Wang resins have been subjected to a variety of chemical transformations based on existing functionality (enolate chemistry, carbonyl group reactivity, Mitsunobu inversion, ozonolysis, Heck reactions, etc.), in an effort to test the suitability of this novel resin-bound ether linkage. The modified substrate was released from the resin by mild acid treatment.* 

The ability to immobilize organic molecules on a solid-support directly through a functional group or through a tether, and subsequent single or multiple stage chemical transformations on remaining functionality, ultimately detaching the chemically modified substrate is presently an area of renewed interest.[1] Solid-phase organic synthesis, popularized in the wake of landmark contributions by Merrifield[2] in the field of peptide synthesis, remained as a specialized and untapped area of research activity until the advent of combinatorial techniques for drug discovery and lead optimization.[3] A current trend is to expand the repertoire of known organic reactions on solid phase with the objective of achieving as much functional diversity as possible in the released substrates, thus avoiding tedious workup procedures which are inevitable in solution phase chemistry.

In the previous letter[4] we reported on the mild and efficient protection of alcohol functions in a variety of molecules as p-alkoxybenzyl ethers, utilizing the Wang and PEG-HMP trichloroacetimidate resins as solid-phase benzylating agents. In this letter, we demonstrate the scope and applications, in most cases for the first time, of a variety of organic chemical transformations that can be effected on such resin-bound ethers. We describe in addition, the release of the chemically modified substrates under mild conditions.

## Carbonyl Group Chemistry

Scheme 1A illustrates sequences of reactions in which resin-bound methyl 2-(R)-hydroxy-3-phenyl butyrate[4] (85% ee) was subjected to an ester interchange reaction via a) hydrolysis with lithium hydroxide (0.1 N in 4:1 mixture of THF/$H_2O$, 7 h, 25 °C), b) acidification (1 N HCl in 9:1 mixture of THF/$H_2O$); c. treatment with diazomethane; d. cleavage (10% TFA in $CH_2Cl_2$, 15 min); e. isolation of methyl 2-(R)-hydroxy-3-phenylbutyrate; $[\alpha]_D$ (+6.3° (c 1.6, $CHCl_3$) (95% pure by HPLC);[5] reported[6]: +7.6° (c 2.0, $CHCl_3$)).

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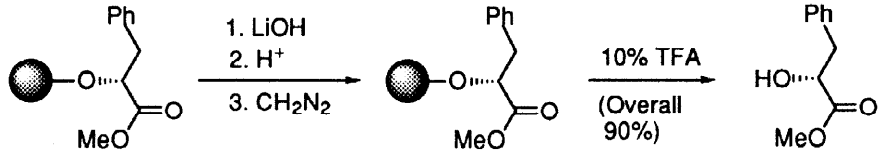
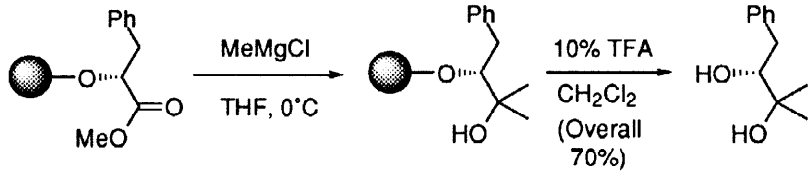
Scheme 1 A



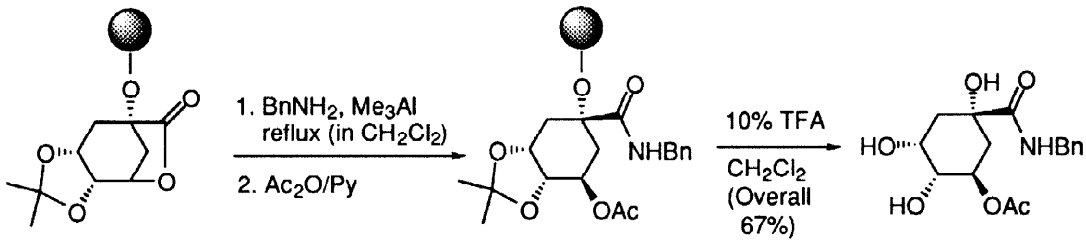

Treatment of the resin bound methyl ester (85% ee, 100 mg) with methylmagnesium chloride (0.3 mmol, THF, 0 °C), followed by cleavage (10% TFA in $CH_2Cl_2$, 15 min) gave 2-(R)-1,2-dihydroxy-1,1-dimethyl-3-phenylpropane without loss of optical purity compared to the starting ester; $[\alpha]_D$ 52.0° (c 0.7, $CHCl_3$); reported[7]: +58.9° (c 0.91, $CHCl_3$)); (Scheme 1B).[8]

Scheme 1B




Application of the Weinreb amide bond formation reaction is shown in Scheme 1C. Resin-bound 3,4-O-isopropylidene-quinic acid lactone[4] (100 mg) was treated with benzylamine-trimethylaluminum (0.5 mmol, reflux in $CH_2Cl_2$, 1 h), the liberated hydroxy group on the resulting amide was acetylated, and the latter subjected to acidic cleavage (1% TFA in $CH_2Cl_2$, 6 h) to afford 5-O-acetyl quinic acid N-benzyl amide in 67% overall yield.[9] Attempts to cleave the product without affecting the O-isopropylidene group failed even with 1% TFA in $CH_2Cl_2$. Treatment with NaOMe gave quinic acid N-benzylamide, the structure of which was ascertained by an independent synthesis from quinic acid following a standard protocol.[10]

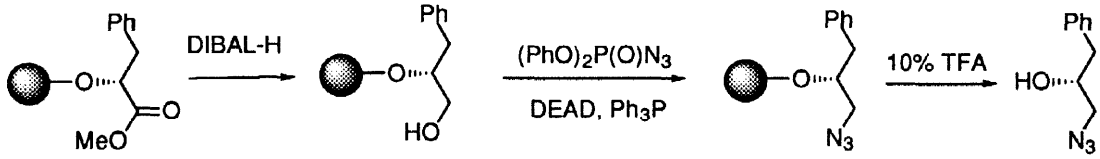
Scheme 1C




## Mitsunobu Chemistry

Reduction of the ester group in resin-bound methyl 2-(R)-hydroxy-3-phenylbutyrate (85% ee, 100 mg) with Dibal-H (0.3 mmol) led to the corresponding alcohol which was smoothly converted to the corresponding azide under the general conditions of the Mitsunobu reaction[11,12] ($Ph_3P$/DEAD/$(PhO)_2P(O)N_3$/THF, overnight). Acid cleavage (10% TFA in $CH_2Cl_2$, 10 min) gave 1-azido-2-(R)-hydroxy-3-phenylbutane in 60% overall yield (Scheme 2).

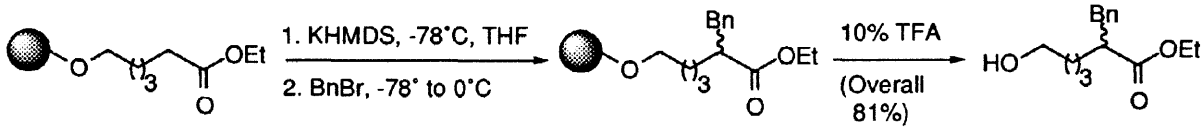
Scheme 2




## Enolate Chemistry

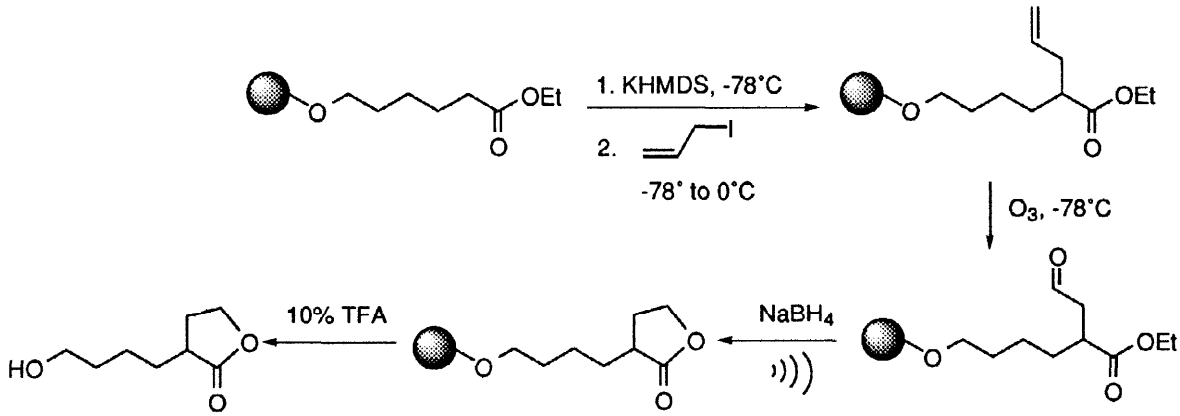
Applications of enolate alkylation[13] was demonstrated on resin-bound ethyl 6-hydroxy hexanoate (100 mg). Thus, treatment with KHMDS (0.1 mmol, THF, -78 °C), followed by addition of benzyl bromide (0.3 mmol, -78 °C to 0 °C, 1.5 h) led to the corresponding α-benzyl derivative, which upon acidic cleavage gave the expected racemic ethyl 2-benzyl-6-hydroxy hexanoate in 77% yield as illustrated in Scheme 3A.

Scheme 3A




The versatility of the p-methoxybenzyl ether linkage on solid phase is shown in Scheme 3B where the α-allyl ester (100 mg), prepared via enolate alkylation was ozonolytically cleaved ($O_3$, $Py/CH_2Cl_2$, -78 °C, 6 min, IR monitoring).[14] The resulting aldehyde was reduced with sodium borohydride ($MeOH/CH_2Cl_2$) under sonication,[15] and the lactonized product was released from the resin upon acid cleavage.[16] This demonstrates a rare and useful example of ozonolysis of olefinic bonds on solid-support.[15]

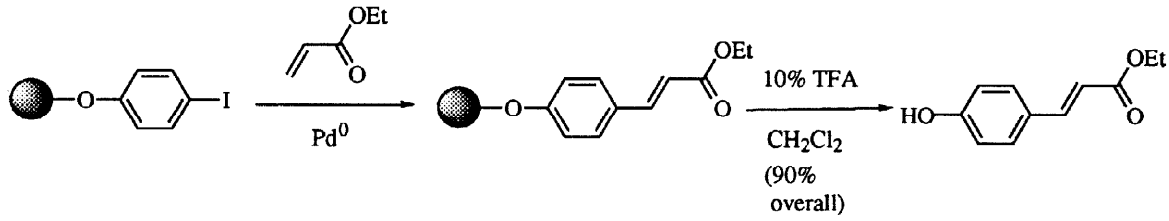
Scheme 3B




## Heck Reaction

The application of the Heck reaction,[17] already known to take place on solid supports[18,19] to a phenolic iodide bound to the Wang resin is shown in Scheme 4. Thus, treatment of the iodo compound with ethyl acrylate in the presence of $Pd_2(dba)_3/(o\text{-tolyl})_3P$ (10%) in DMF (110 °C, 24 h) led to the corresponding coupling product, which was cleaved to afford ethyl p-hydroxy cinnamate (>90% yield). It should be noted that conversion was poor in the presence of $Pd(OAc)_2$.[18]

Scheme 4




We have shown that a variety of organic molecules containing an alcohol group and immobilized on a Wang resin as the p-alkoxybenzyl ether, can be subjected to preparatively useful organic transformations in single or multiple steps. Acid-catalyzed cleavage of the ether linkage releases the chemically modified alcohols.[20] This technology is presently being used to generate libraries of diversely functionalized polyfunctional molecules deployed with potentially interesting pharmacological probes. Results pertaining to these and related motifs of interest in the general area of combinatorial methods will be reported in due course.

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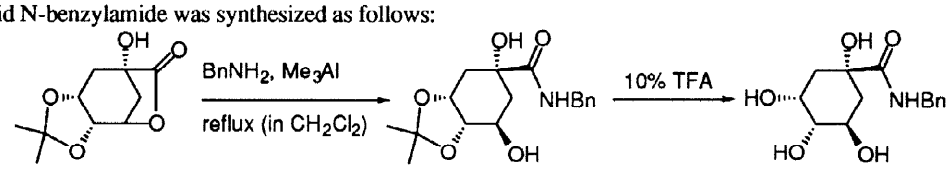
9. For an amidation reaction of an ester-bound substrate, see ref. 8.
10. Quinic acid N-benzylamide was synthesized as follows:

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20. The purity of the products was ascertained by HPLC (>90%) as well as by comparison with authentic samples.