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Multipolymer Solution-Phase Reactions: Application to the Mitsunobu Reaction

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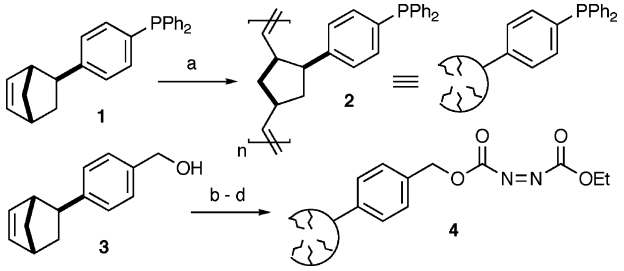
The development of polymer-supported reagents, and new strategies with which to employ them, is of continued interest for the facilitated synthesis of molecular libraries and natural products.[1,2] One strategy that has been deployed to a limited extent is the simultaneous use of multiple polymeric reagents in a single pot. There are three conceivable scenarios with which to employ more than one polymeric reagent. The first is through the use of polymeric reagents and a solution-phase substrate that is able to shuttle between the supported reagents. Typically the reagents employed have been of the insoluble, cross-linked variety, where the two reagents independently act upon a solution-phase substrate.[3,4] The second scenario involves the reaction of a solution-phase polymeric reagent on a solid-phase substrate, or vice versa. However, the same property that allows incompatible reagents to be present in the same reaction flask (i.e., heterogeneity) also keeps these insoluble reagents from being used in reactions that require the interaction of multiple reagents to carry out a single reaction step. There have been only a handful of reports describing the productive reaction between two polymers to generate a new functional group.[5] To the best of our knowledge, there are no reports describing the third scenario, in which multiple polymeric reagents interact to transform a solution-phase small molecule(s).[6] The Mitsunobu reaction is one such protocol that would benefit from this approach. However, not only has this reaction historically faced purification challenges[7] but also popular opinion asserts that a multipolymer, solid-on-solid approach is not feasible.[7b] We herein report the realization of polymer-on-polymer Mitsunobu reactions that employ the *simultaneous* use of a polymeric phosphine *and* a polymeric azodicarboxylate.[8] The literature void pertaining to polymer-on-polymer transformations of small molecules is not surprising when one realizes the complex kinetic and entropic factors associated with such processes. This problem is only compounded when one considers the decreased reactivity encountered with lightly loaded polymers, as well as when the reactive sites are lost as the reaction proceeds.[9] In addition, it is known that when two solutions of different polymers are mixed together, a biphasic system often results.[10] A possible solution to these problems includes the use of highly loaded, short and soluble oligomers.

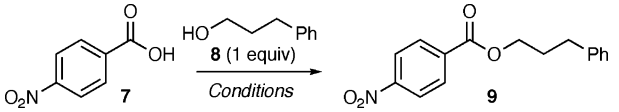
The synthesis of the required soluble ring-opening methathesis (ROM) oligomers is described in Scheme 1. The known monomeric phosphine, originally prepared by Barrett,[11] was polymerized with 3.3 mol % $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$ (**5**), affording soluble oligomeric triphenylphosphine (OTPP, **2**) as a free-flowing white solid.[12] Polymeric azodicarboxylate **4** was obtained from alcohol **3**, which was treated with phosgene, followed by ethyl carbazate.[13] The resulting hydrazine dicarboxylate was polymerized with 3.3 mol % $(IMesH_2)(PCy_3)(3\text{-}BrPyr)_2Ru{=}CHPh$ (**6**).[14] The olefin backbone of the resulting polymer was hydrogenated in situ[15] to avoid potential complications during the final Br_2 oxidation to hydrogenated oligomeric azodicarboxylate (HO-DEAD) **4**.[16] With the required polymers in hand, we then investigated their use in the Mitsunobu reaction of 4-nitrobenzoic acid (**7**) with 3-phenyl-1-propanol (**8**, Table 1). We found that by using 1.5 equiv of both **2** and **4**, ester **9** was produced with 74% conversion and 73% isolated yield. Simply increasing to 2 equiv of OTPP and HO-DEAD resulted in almost complete conversion and 88% isolated yield. Switching the phosphine source to linear polystyrene-bound tri-

Scheme 1. Synthesis of Required ROM Polymers[a]



[a] Reagents and conditions: (a) 3.3 mol % cat **5**, CH_2Cl_2, 50 °C, 96%; (b) (i) $COCl_2$, $PhCH_3$, 0 °C to room temperature, (ii) NH_2NHCO_2Et, Et_3N, DMAP, THF, 55%; (c) (i) 3.3 mol % cat **6**, THF, room temperature, (ii) 2 mol % $(PCy_3)_2(Cl)_2Ru{=}CHPh$, H_2 (1000 psi), 50 °C, 80%; (d) Br_2, Pyr, CH_2Cl_2, 86%.

Table 1. Mitsunobu Esterification with Multipolymer Systems



reaction conditions	conversion (%)[a]	yield (%)[b]
1.5 equiv OTPP, 1.5 equiv HO-DEAD, 0.25 M THF	74	73
2 equiv OTPP, 2 equiv HO-DEAD, 0.20 M THF	92	88
3 equiv OTPP, 3 equiv HO-DEAD, 0.12 M THF	>95	74
5 equiv OTPP, 5 equiv HO-DEAD, 0.25 M THF	>95	64
2 equiv LPS-PPh_3, 2 equiv HO-DEAD, 0.078 M THF	84[c]	49
2 equiv *JJ*-PPh_3, 2 equiv HO-DEAD, 0.085 M THF	50	51
2 equiv PS-PPh_3, 2 equiv HO-DEAD, 0.21 M THF	0	–
2 equiv OTPP, 2 equiv PS-DEAD, 0.1 M THF	0	–

[a] Determined by ^1H NMR of crude reaction following precipitation of polymers with EtOAc and filtration through a plug of silica gel. [b] Isolated yield after second filtration with 4:1 heptane/EtOAc. [c] Crude ^1H NMR showed 37% 3-phenylpropyl ether.

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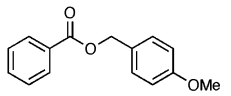
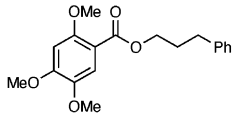
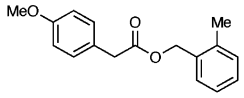
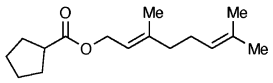
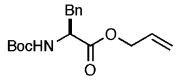
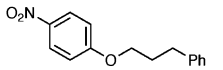
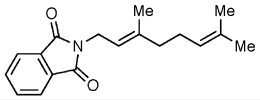
Table 2. Mitsunobu Products[a]

Entry	Product	Yield[b] (%)
1		84[c] (90)[d]
2		76[c]
3		70[c]
4		68[c] (84)[d]
5		73[d,e]
6		73[d,f]
7		69[d]

[a] Reactions performed with 1 equiv of ROH (0.1 mmol), 1.01−1.2 equiv of acid, 2 equiv of OTPP, and 2 equiv of HO-DEAD at 25 °C. [b] Isolated yield after second filtration with 4:1 heptane/EtOAc. [c] HO-DEAD with 1.5 mmol/g load. [d] HO-DEAD with 2.6 mmol/g load. [e] 1 equiv of acid and 1.02 equiv of alcohol. [f] ^{1}H NMR of isolated product showed 15% 3-phenylpropyl ether, which could not be separated.

phenylphosphine (LPS-PPh_3)[17] (2 equiv) resulted in only 47% conversion (49% yield).

In comparison studies, we employed the use of HO-DEAD in conjunction with *J*anda*J*el-PPh_3 (*JJ*-PPh_3)[18] and solid-supported PPh_3 (PS-PPh_3) as well as the implementation of OTPP with PS-DEAD (Table 1).[19] More dilute conditions were required in the reactions with *JJ*-PPh_3 and PS-DEAD because of the large amount of swelling associated with these insoluble resins. *JJ*-PPh_3, while successful in mediating the reaction, resulted in only 50% conversion to **9**. *However, both PS-PPh$_3$ and PS-DEAD failed to produce* ***9***.

Having found that the use of 2 equiv of both **2** and **4** were the optimal conditions, we investigated the use of these reagents in the Mitsunobu reaction between various nucleophiles and alcohols (Table 2). Overall, the Mitsunobu products were isolated in 69−90% yield, with the load of **4** having little effect on product yield.

In conclusion, we have demonstrated the viability of a multipolymer platform for transforming small molecules through the development of a Mitsunobu reaction system that simultaneously utilizes *two polymer-supported reagents*. This method allows for facile product isolation compared to traditional methods. We are currently examining additional details, expanding substrate scope, and investigating heretofore unrealized multipolymer reactions.

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Note Added after ASAP Publication. After this paper was published ASAP on December 13, 2004, the chemical notation in the Scheme 1 footnote, step (b), was changed. The corrected version was posted December 15, 2004.

Supporting Information Available: Experimental details and spectral characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) *JJ*-PPh_3 was prepared as described in ref 17 and had a loading of 1.54 mmol/g. PS-PPh_3 was obtained from Aldrich and had a loading of ∼3 mmol/g. PS-DEAD was obtained from Novabiochem and had a loading of 1.3 mmol/g.

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