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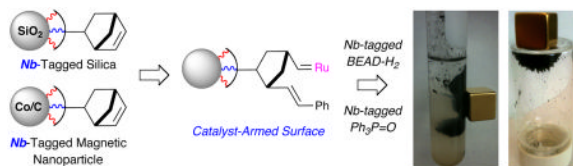
Monomer-on-Monomer (MoM) Mitsunobu Reaction: Facile Purification Utilizing Surface-Initiated Sequestration

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Abstract



A monomer-on-monomer (MoM) Mitsunobu reaction utilizing norbornenyl-tagged (Nb-tagged) reagents is reported, whereby purification was rapidly achieved by employing ring-opening metathesis polymerization which is initiated by any of three methods utilizing Grubbs catalyst (i) free catalyst in solution, (ii) surface-initiated catalyst-armed silica or (iii) surface-initiated catalyst-armed Co/C magnetic nanoparticles.

The Mitsunobu reaction and its variants are powerful tools for the synthesis of biologically active molecules and natural products in drug design.¹ The Mitsunobu reaction is a mild, but rapid method for the formation of C-C, C-S, C-N and C-O bonds including the capacity to invert the stereochemistry of stereogenic carbinol bearing centers.² The Mitsunobu reaction, formally a four-component “redox” condensation between an alcohol and an acidic pro-nucleophile, is promoted by a combination of a tertiary phosphine and an azodicarboxylate, usually triphenylphosphine (PPh₃) and diethyl or diisopropyl ester (DEAD or DIAD). Despite these attributes, the corresponding purification is a tedious and time-consuming process not desirable for parallel and high-throughput chemistry and several recent advances have been developed.³ Despite these recent innovations, continued development of facilitated chromatography-free Mitsunobu protocols for parallel synthesis is warranted.

Ring-opening metathesis polymerization (ROMP)-derived, high-load oligomeric reagents and scavengers have been utilized in many chromatography-free transformations, suited for

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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>.

parallel synthesis.^{4,5} Previously we reported the application of a polymer-on-polymer (PoP) Mitsunobu reaction employing both ROMP-derived oligomeric triphenylphosphine and oligomeric azodicarboxylate.⁶ This multi-polymer platform was successfully utilized to transform a variety of small molecules via an efficient Mitsunobu reaction. Facile purification was achieved via precipitation and filtration of now insoluble polymeric reagents and spent oligomers to yield the desired products in high purity. We herein report a new variant termed a monomer-on-monomer (MoM)⁷ Mitsunobu reaction which utilizes norbornenyl-tagged (Nb-tagged) reagents that are rapidly sequestered post reaction using ring-opening metathesis polymerization which is initiated by any of three methods utilizing Grubbs catalyst cat-**B**⁸, (i) free catalyst in solution, (ii) surface-initiated catalyst-armed silica or (iii) surface-initiated catalyst-armed Co/C magnetic nanoparticles (Nps) (Figure 1).

In comparison to solid-phase immobilized reagents, the utilization of norbornenyl-tagged (Nb) reagents allows for reactions to be carried out in solution phase with small monomeric reagents. This is an important feature, which allows reactions to be carried out without the need of excess reagents, reaction times (heterogeneous kinetics) or harsher conditions to name a few classic properties when utilizing immobilized reagents. With the norbornenyl-tagged PPh₃ (Nb-TPP) and DEAD (Nb-BEAD)^{6a} readily accessed, we investigated their application in the Mitsunobu reaction utilizing a variety of benzoic acids and benzyl alcohols (Table 1, entry 1–6). Utilizing 1.3 equivalents of both reagents, the desired esters were synthesized in good yield and purity without the need for standard chromatography.

Key to this efficient purification was the phase switching of the Nb-tagged monomeric reagents/spent reagents by the utilization of ROM polymerization. This process transforms the Nb-monomeric reagents into a soluble oligomeric polymer, possessing a differential solubility profile to the desired products. Precipitation of the spent oligomer in Et₂O or MeOH, followed by filtration via a silica SPE yields the desired products in high crude purity. This purification protocol can be observed via TLC analysis, whereby a multi-spot crude reaction is purified to a single product spot utilizing the polymerization sequestration protocol. Building on these results, the MoM protocol was utilized efficiently for the esterification and stereoinversion of chiral, non-racemic secondary alcohols (Table 1, entries 9–12).

Despite success in this protocol, precipitation of each reaction containing catalyst was deemed not ideal for a parallel high-throughput approach. Therefore, investigations were directed toward sequestration of the functionalized Nb-monomers by polymerizing off a catalyst-armed immobilized surface. Sequestration in this manner would further optimize the MoM protocol by removing the need for precipitation and ultimately result in an overall more cost efficient and environmental friendly protocol. To this effect, the use of silica⁹ or carbon-coated cobalt (Co/C)¹⁰ nanoparticles bearing a norbornene moiety, was envisioned for the sequestration of excess/spent Nb-tagged reagents via surface-initiated ROM polymerization.^{11,12} Magnetic nanoparticles are increasingly being utilized as supports for immobilized catalysts in chromatography-free protocols,¹³ whereas Nb-tagged silica particles have been utilized to synthesize silica surface grafted polymer supports.^{9,11} Key to this approach was the arming of the nanoparticle surface (1 equiv.) with cat-**B**⁸ (0.6–0.8 equiv.) for 30 minutes before the addition of the crude reaction mixture.¹⁴

With the corresponding Nb-tagged silica and Nb-tagged Co/C in hand, the employment of the MoM Mitsunobu reaction utilizing catalyst-armed Si-particles (Table 2, entries 1–5) and Co/C Nps (Table 2, entries 6–11) was successfully achieved yielding the desired products in high crude purity. Purification when utilizing Si-armed particles was minimized to a simple filtration of the crude reaction via a Celite[®] SPE. The utilization of Co/C magnetic Nps

required simple application of an external magnet to the reaction vessel and decantation of the crude mixture (Figure 2).

In conclusion, we have demonstrated the utilization of Nb-tagged PPh₃ and Nb-tagged BEAD reagents in a new MoM Mitsunobu reaction. Purification of the excess and spent monomeric reagents was initially achieved via a polymerization-precipitation-filtration protocol utilizing Grubbs cat-B. Purification was further optimized and streamlined for parallel application utilizing catalyst-armed immobilized surfaces to polymerize any Nb-tagged species via simple filtration of the Nb-tagged Si-particles or magnetization-decantation when utilizing Nb-tagged Co/C magnetic Nps.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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 14. The order of addition of reagents in the sequestration protocol is critical to minimize polymerization occurring due to free catalyst in solution.

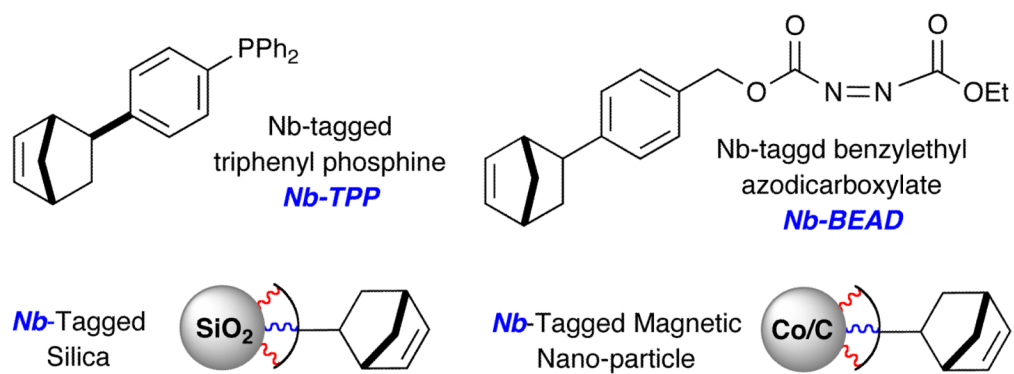


Figure 1. Norbornenyl-tagged reagents and Co/C Nps for MoM Mitsunobu Reactions.



Figure 2.
(a) Sequestration utilizing catalyst-activated Nb-tagged Co/C, (b) spent magnetic oligomer and (c) Nb-tagged Si-particles.

Table 1

Mitsunobu esterification utilizing Nb-TPP and Nb-DEAD



entry	R ¹	R ² -OH	yield (%)	purity (%)
1	4-NO ₂	2-MeBnOH	75	>95
2	4-NO ₂	3,5-OMeBnOH	77	>95
3	4-NO ₂	3-Me-2-butene-1-ol	78	>95
4	2,4-Cl	2-MeBnOH	79	>95
5	4-NO ₂	4-ClBnOH	84	>95
6	4-NO ₂	4-BrBnOH	81	>95
7	2-Me	3-NMe ₂ BnOH	81	>95
8	3,4-Cl	3-OMeBnOH	91	>95
9	4-NO ₂	(<i>R</i>)-MeCH(OH) CO ₂ Et	74	>95
10	2,6-Cl	(<i>R</i>)-MeCH(OH) CO ₂ Et	71	>95
11	3-NMe ₂	(<i>R</i>)-MeCH(OH) CO ₂ Et	73	>95
12	4-Cl	(<i>R</i>)-MeCH(OH) CO ₂ Et	76	>95

^aCrude purity determined by ¹H NMR following precipitation of polymers with EtOAc and filtration through silica SPE.

Table 2

MoM Mitsunobu reaction utilizing silica and Co/C nano-particle sequestration



entry	R ¹	R ²	yield (%)	crude purity (%) ^a
1 ^b	4-NO ₂	2-MeBn	84	>95
2 ^b	4-NO ₂	3,5-OMeBn	88	>95
3 ^b	4-NO ₂	4-BrBn	82	>95
4 ^b	4-NO ₂	3-NMe ₂ Bn	83	>95
5 ^b	2-Me	3,5-NMe ₂ Bn	87	>95
6 ^c	4-NO ₂	4-ClBn	84	>95
7 ^c	4-NO ₂	3,5-OMeBn	88	>95
8 ^c	4-NO ₂	4-BrBn	82	>95
9 ^c	4-Cl	3-NMe ₂ Bn	83	>95
10 ^c	2-Me	3-NMe ₂ Bn	87	>95
11 ^c	3,4-Cl	3,5-OMeBn	93	>95

^aCrude purity determined by ¹H NMR following precipitation of polymers with EtOAc and filtration through silica SPE.

^bCrude reactions sequestered with catalyst-activated Si-Nb-tagged Nps.

^cCrude reactions sequestered with catalyst-activated Nb-tagged Co/C-Nps.