ORGANIC LETTERS
2011
Vol. 13, No. 1
8−10

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

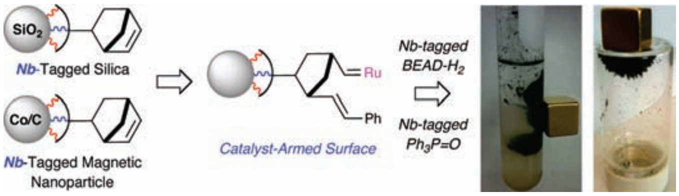
Pradip K. Maity,[†] Alan Rolfe,[†] Thiwanka B. Samarakoon,[†] Saqib Faisal,[†]
Ryan D. Kurtz,[†] Toby R. Long,[†] Alexander Schätz,[‡] Daniel L. Flynn,[†]
Robert N. Grass,[||] Wendelin J. Stark,[||] Oliver Reiser,*[,‡] and Paul R. Hanson*[,†]

Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045, United States and The University of Kansas Center for Chemical Methodologies and Library Development (KU-CMLD), 2034 Becker Drive, Delbert M. Shankel Structural Biology Center, Lawrence, Kansas 66047, United States, Institute for Organic Chemistry, University of Regensburg, Universitätsstr. 31, D-93053 Regensburg, Germany, Deciphera Pharmaceuticals LLC, 1505 Wakarusa Drive, Lawrence, Kansas 66047, and Institute for Chemical and Bioengineering, Department of Chemistry and Applied Biosciences, ETH Zurich, Wolfang-Pauli-Strasse 10, CH-8093 Zurich, Switzerland

phanson@ku.edu

Received September 18, 2010

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 was 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] Formally a four-component "redox" condensation between an unactivated alcohol and an acidic pro-nucleophile, the Mitsunobu reaction, is promoted under relatively mild conditions by a combination of a tertiary phosphine and an azodicarboxylate, usually triphenylphosphine (PPh_3) and diethyl or diisopropyl ester (DEAD or DIAD). Despite these attributes, the corresponding purification is a tedious and time-consuming process that is not desirable for parallel and high-throughput chemistry, and several recent advances have been developed.[3] Even with these recent innovations,

---

[†] University of Kansas.
[‡] University of Regensburg.
[†] Deciphera Pharmaceuticals LLC.
[||] ETH Zurich.

(1) (a) Abero, M. A.; Lin, N.-H.; Garvey, D. S.; Gunn, D. E.; Hettinger, A.-M.; Wasicak, J. T.; Pavlik, P. A.; Martin, Y. C.; Donnelly-Roberts, D. l.; Sullivan, J. P.; Williams, M.; Arneric, S. P.; Holladay, M. W. *J. Med. Chem.* **1996**, *39*, 817–825. (b) Park, A.-Y.; Moon Hyung, R.; Kim Kyung, R.; Chun Moon, W.; Jeong Lak, S. *Org. Biomol. Chem.* **2006**, *22*, 4065–4067. (c) Azzouz, R.; Fruit, C.; Bischoff, l.; Marsais, F. *J. Org. Chem.* **2008**, *73*, 1154–1157. (d) Zapf, C. W.; Del Valle, J. R.; Goodman, M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4033–4036.

(2) For comprehensive reviews, see: (a) Mitsunobu, O. *Synthesis* **1981**, 1–28. (b) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127–164.

10.1021/ol1022382

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 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 multipolymer 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 that utilizes norbornenyl-tagged (Nb-tagged) reagents that are rapidly sequestered post reaction using ring-opening metathesis polymerization that 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 (Np's) (Figure 1).

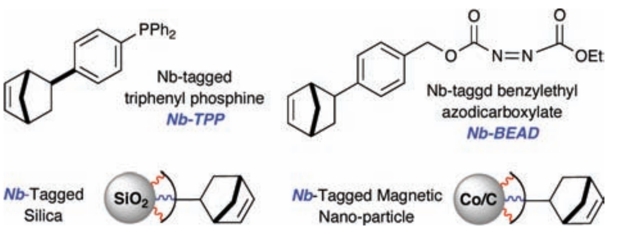


Figure 1. Norbornenyl-tagged reagents and Co/C Np's for MoM Mitsunobu Reactions.

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 that enables reactions to be performed 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 PPh_3 (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 equiv of both reagents, the desired esters were synthesized in good yield and purity without the need for standard chromatography.

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_2BnOH	81	>95
8	3,4-Cl	3-OMeBnOH	91	>95
9	4-NO_2	(*R*)-MeCH(OH) CO_2Et	74	>95
10	2,6-Cl	(*R*)-MeCH(OH)CO_2Et	71	>95
11	3-NMe_2	(*R*)-MeCH(OH) CO_2Et	73	>95
12	4-Cl	(*R*)-MeCH(OH) CO_2Et	76	>95

[a] Crude purity determined by ^1H NMR following precipitation of polymers with EtOAc and filtration though silica SPE.

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 Et_2O 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 multispot crude reaction is purified to a single product spot utilizing the polymerization sequestration protocol. Building

---

(3) (a) Dembinski, R. *Eur. J. Org. Chem.* **2004**, 2763–2772. (b) Reynolds, A. J.; Kassiou, M. *Curr. Org. Chem* **2009**, *13*, 1610–1632, and references therein. (c) Chu, Q.; Henry, C.; Curran, D. P. *Org. Lett.* **2008**, *10*, 2453–2456. (d) Lan, P.; Porco, Jr, J. A.; South, M. S.; Parlow, J. J. *J. Com. Chem* **2003**, *5*, 660–669. (e) Starkey, G. W.; Parlow, J. J.; Flynn, D. L. *Bioorg. Med. Chem. Let* **1998**, *8*, 2385–2390. (f) Danapani, S.; Newsome, J. J.; Curran, D. P. *Tetrahedron Lett.* **2004**, *45*, 6653–6656. (g) But, T. Y. S.; Toy, P. H. *J. Am. Chem. Soc.* **2006**, *128*, 9636–9637. (h) Taft, B. R.; Swift, E. C.; Lipshutz, B. H. *Synthesis* **2009**, *2*, 322–334.

(4) For reviews concerning ROMP reagents, see: (a) Barrett, A. G. M.; Hopkins, B. T.; Köbberling, J. *Chem. Rev.* **2002**, *102*, 3301–3324. (b) Flynn, D. L.; Hanson, P. R.; Berk, S. C.; Makara, G. M. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 571–579. (c) Harned, A. M.; Probst, D. A.; Hanson, P. R. The Use of Olefin Metathesis in Combinatorial Chemistry: Supported and Chromatography-Free Syntheses. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; pp 361−402. (d) Harned, A. M.; Zhang, M.; Vedantham, P.; Mukherjee, S.; Herpel, R. H.; Flynn, D. L.; Hanson, P. R. *Aldrichimica Acta* **2005**, *38*, 3–16.

(5) (a) Long, T.; Maity, P. K.; Samarakoon, T. B.; Hanson, P. R. *Org. Lett.* **2010**, *12*, 2904–2907. (b) Rolfe, A.; Probst, D.; Volp, K.; Omar, I.; Flynn, D.; Hanson, P. R. *J. Org. Chem.* **2008**, *73*, 8785–8790. (c) Stoianova, D. S.; Yao, L.; Rolfe, A.; Samarakoon, T.; Hanson, P. R. *Tetrahedron Lett.* **2008**, *49*, 4553–4555. (d) Barrett, A. G. M.; Hopkins, B. T.; Love, A. C.; Tedeschi, L. *Org. Lett.* **2004**, *6*, 835–837. (e) Arstad, E.; Barrett, A. G. M.; Tedeschi, L. *Tetrahedron Lett.* **2003**, *44*, 2703–2707. (f) Mukherjee, S.; Poon, K. W. C.; Flynn, D. L.; Hanson, P. R. *Tetrahedron Lett.* **2003**, *44*, 7187–7190.

(6) (a) Harned, A. M.; Song He, H. S.; Toy, P. H.; Flynn, D. L.; Hanson, P. R. *Org. Lett.* **2005**, *127*, 52–53. (b) Of notable importance is the seminal advances made by Barrett and co-workers demonstrating the concept of reagent annihilation (norbornenyl-tagged DEAD); see: (c) Barrett, A. G. M.; Roberts, R. S.; Schröder, J. *Org. Lett.* **2000**, *2*, 2999–3002. For additional examples of in situ scavenging, see: (d) Moore, J. D.; Harned, A. M.; Henle, J.; Flynn, D. L.; Hanson, P. R. *Org. Lett.* **2002**, *4*, 1847–1849.

(7) MoM is an acronym for reactions that utilize two monomeric species ("monomer-on-monomer") to carry out a transformation, in which upon completion these monomers are sequestered via polymerization. This acronym correlates to our previous use of "polymer-on-polymer" (PoP), for reactions employing the simultaneous use of two polymeric species that react together in a transformation; see ref 6a.

(8) Cat-**B**: (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956. It should be noted that the Grubbs first generation catalyst $(PCy_3)_2(Cl)_2Ru{=}CHPh$ [Cat-**A**] is deactivated in the presence of $Ph_3P{=}O$. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110. (c) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039–2041.

on these results, the MoM protocol was utilized efficiently for the esterification and stereoinversion of chiral, nonracemic 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 environment-friendly protocol. To this effect, the use of silica[9] 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 min 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 Np's (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 Np's required simple application of an external magnet to the reaction vessel and decantation of the crude mixture (Figure 2).

Table 2. MoM Mitsunobu Reaction Utilizing Silica and Co/C Nanoparticle 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_2Bn	83	>95
5[b]	2-Me	3,5-NMe_2Bn	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_2Bn	83	>95
10[c]	2-Me	3-NMe_2Bn	87	>95
11[c]	3,4-Cl	3,5-OMeBn	93	>95

[a] Crude purity determined by ^{1}H NMR following precipitation of polymers with EtOAc and filtration though silica SPE. [b] Crude reactions sequestered with catalyst-activated Si−Nb-tagged Np's. [c] Crude reactions sequestered with catalyst-activated Nb-tagged Co/C- Np's.

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

In conclusion, we have demonstrated the utilization of Nb-tagged PPh_3 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 Np's.

Acknowledgment. This work was supported by the National Institute of General Medical Science (Center in Chemical Methodologies and Library Development at the University of Kansas, KU-CMLD, NIH P50 GM069663 and NIH-STTR R41 GM076765) with additional funds from the State of Kansas, the International Doktorandenkolleg NANOCAT (Elitenetzwerk Bayern), the Deutsche Forschungsgemeinschaft (Re 948/8-1, "GLOBUCAT"), and the EU-Atlantis program CPTUSA-2006-4560. We thank Materia Inc. for providing metathesis catalyst.

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.

OL1022382

---

(9) (a) Buchmeiser, M. R.; Sinner, F.; Mupa, M.; Wurst, K. *Macromolecules* **2000**, *33*, 32–39. (b) Krause, J. O.; Lubbad, S.; Nuyken, O.; Buchmeiser, M. R. *Adv. Synth. Catal.* **2003**, *345*, 996–1004. (c) Kim, N. Y.; Jeon, N. L.; Choi, I. S.; Takami, S.; Harada, Y.; Finnie, K. R.; Girolami, G. S.; Nuzzo, R. G.; Whitesides, G. S.; Laibinis, P. E. *Macromolecules* **2000**, *33*, 2793–2795.

(10) (a) Grass, R. N.; Athanassiou, E. K.; Stark, W. J. *Angew. Chem.* **2007**, *119*, 4996. (b) Schätz, A.; Grass, R. N.; Stark, W. J.; Reiser, O. *Chem.—Eur. J.* **2008**, *14*, 8262–8266. (c) Schätz, A.; Grass, R. N.; Kainz, Q.; Stark, W. J.; Reiser, O. *Chem. Mater.* **2010**, *22*, 305–310. (d) Wittmann, S.; Schätz, A.; Grass, R. N.; Stark, W. J.; Reiser, O. *Angew. Chem., Int. Ed. Engl.* **2010**, *49*, 1867–1870.

(11) (a) Mayr, M.; Mayr, B.; Buchmeiser, M. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 3839–3842. (b) Weck, M.; Jackiw, J. J.; Rossi, R. R.; Weiss, P. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1999**, *121*, 4088–4089. (c) Schätz, A.; Long, T. R.; Grass, R. N.; Stark, W. J.; Hanson, P. R.; Reiser, O. *Adv. Func. Mater.* **2010**, published online ahead of print; DOI:, 10.1002/adfm.201000959.

(12) For examples of ROM polymerization off of polymeric beads, see: (a) Fuchter, M. J.; Hoffman, B. M.; Barrett, A. G. M. *J. Org. Chem.* **2006**, *71*, 724–729. (b) Barrett, A. G. M.; Cramp, S. M.; Roberts, R. S. *Org. Lett.* **1999**, *1*, 1083–1086.

(13) (a) Abu-Reziq, R.; Wang, D.; Post, M. L. *J. Am. Chem. Soc.* **2006**, *128*, 5279. (b) Lee, D.; Lee, J.; Lee, H.; Jim, S.; Hyeon, T.; Kim, B. M. *Adv. Syn. Catal.* **2006**, *348*, 41–46. (c) Dalaigh, C. A.; Corr, S. A.; Gun'ko, Y.; Connon, S. J. *Angew. Chem.* **2007**, *119*, 4407–4410.

(14) The order of addition of reagents in the sequestration protocol is critical to minimize polymerization occurring as a result of free catalyst in solution.