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Impurity Annihilation: Chromatography-Free Parallel Mitsunobu Reactions

Anthony G. M. Barrett,* Richard S. Roberts, and Jürgen Schröder

Department of Chemistry, Imperial College of Science, Technology and Medicine, London SW7 2AY, United Kingdom

agmb@ic.ac.uk

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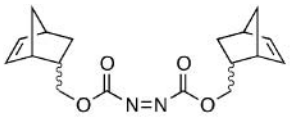
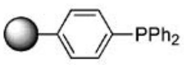
ABSTRACT



DNAD 4



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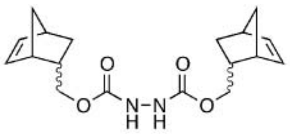
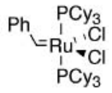


DNADH$_2$ 3



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Mitsunobu reaction of an alcohol ROH with a carboxylic acid, phthalimide, or *N*-hydroxyphthalimide (NuH) using DNAD (4) and (diphenylphosphino)polystyrene (11) gave the products RNu. Ring-opening metathetic polymerization of the side product DNADH$_2$ (3) using $Cl_2(Cy_3P)_2Ru{=}CHPh$ (13) and filtration, to remove poly(DNADH$_2$), (diphenylphosphino)polystyrene 11, its oxide, and its adduct with excess DNAD, gave RNu (43–100%, 86–96% purity) without recourse to chromatography.

Over the past few years combinatorial chemistry has enhanced the synthesis and discovery of pharmaceuticals, agrochemicals, catalysts, and other fine chemicals. Usually, parallel or combinatorial reactions are conducted on solid supports; however, solution-phase parallel synthesis, where reactions are easier to monitor and analyze, is becoming increasingly important. The removal of excess reagents or side products in a solution-phase reaction, however, can often be problematic, especially with an automated production of libraries of compounds. Some useful methods have already been developed, including automated chromatographic techniques, fluorous-phase chemistry,[1] polymer-supported reagents,[2] and scavenger chemistry.[3]

Recently, we reported a new strategy for solution-phase combinatorial chemistry, "impurity annihilation".[4] The approach is based upon the selective derivatization by polymerization of all contaminants, which are then removed by simple filtration as an insoluble product. This strategy was successfully applied to the synthesis of amides and sulfonamides. The excess of an acyl or sulfonyl chloride or of an amine reagent was removed by formation of an insoluble, highly cross-linked polymer by reaction with 1,4-benzenediisocyanate and pentaethylenehexamine. To extend the strategy, we investigated the use of a ruthenium alkylidene catalyzed ring-opening metathetic (ROM) polymerization[5] for the annihilation of the azodicarboxylate ester and/or the triarylphosphine reagents used in a Mitsunobu reaction.[6] In this venture we sought to use the Grubbs catalyst **13**, since it is known to tolerate diverse functionality, thereby making it ideal for the impurity annihilation protocol. In principle

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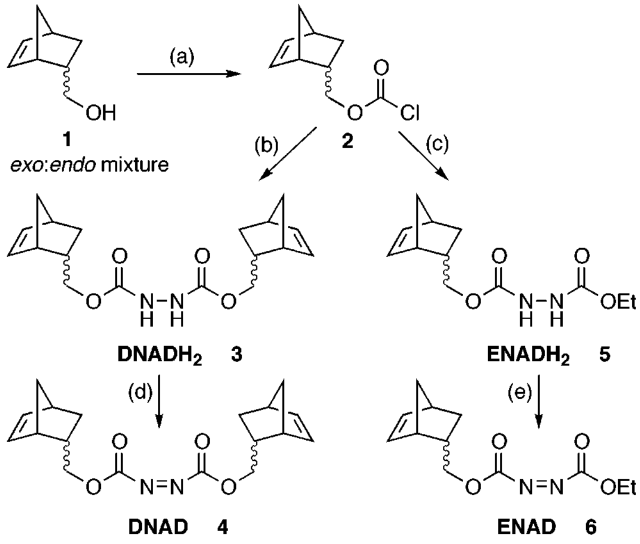
the Mitsunobu reaction is of value in parallel synthesis and combinatorial chemistry; however, the process is four-component, using an alcohol, acid (or nucleophilic equivalent), phosphine, and azodicarboxylate ester. Additionally, two side products, the phosphine oxide and the hydrazinedicarboxylate ester, are formed. As such, the reaction is not straightforward enough to simplify for library production either in the solution phase or on solid supports. Polystyrene-supported triphenylphosphine has been introduced for parallel Mitsunobu reactions, as has having acid labile phosphines and azodiesters.[7,8] Nonetheless, the method is still nonideal, since either chromatography and/or strongly acidic treatment is required for product isolation. We considered that ROM polymerization of the phosphine and/or azodicarboxylate reagents and their products should prove of value in simplified, mild, and chromatography-free Mitsunobu reactions.

Initially we sought to establish a completely homogeneous system for the solution-phase combinatorial Mitsunobu reaction. Instead of the traditionally used diethyl azodicarboxylate (DEAD), both bis(5-norbornenyl-2-methyl) azodicarboxylate (DNAD; **4**) and ethyl 5-norbornenyl-2-methyl azodicarboxylate (ENAD; **6**) were examined (Scheme 1).

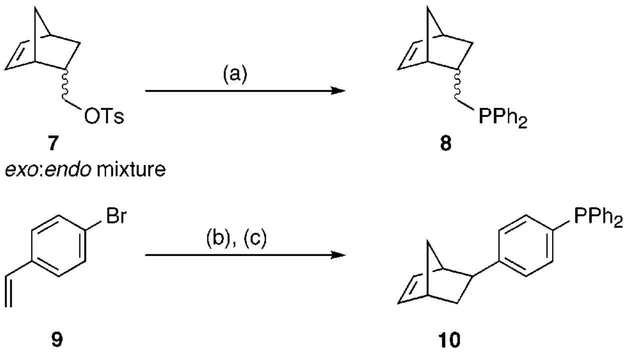
Scheme 1. Norbornene-Derived Azodicarboxylate Reagents



Reagents: (a) $COCl_2$, $PhNMe_2$, toluene (83%); (b) H_2NNH_2, Na_2CO_3, EtOH (88%); (c) EtO_2CNHNH_2, Na_2CO_3, EtOH (77%); (d) $PhI(OAc)_2$, CH_2Cl_2 (83%); (e) $PhI(OAc)_2$, CH_2Cl_2 (66%).

Phosphines **8** and **10** were also synthesized, in unoptimized yields, as shown in Scheme 2. The incorporation of the norbornene moiety was designed to allow for annihilation by ROM polymerization.

Scheme 2. Norbornene-Derived Phosphine Reagents

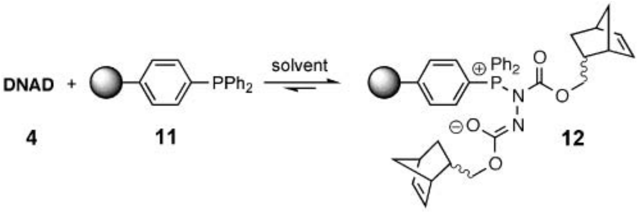


Reagents: (a) $NaPPh_2$, THF, dioxane, (78%); (b) cyclopentadiene, 150 °C (47%); (c) $LiPPh_2$, THF, reflux (19%).

Although Mitsunobu esterification reactions took place using DNAD (**4**) or ENAD (**6**) with phosphines **8** and **10**, attempted purification via ROM polymerization of all norbornene components was unsuccessful. Blank experiments showed that while $DNADH_2$ (**3**) underwent polymerization, neither azodiesters **4** and **6** nor the phosphines **8** and **10** gave ROMPs on treatment with Grubbs‘ catalyst **13** or alternative ruthenium carbenes. Since a key step in alkene metathesis is dissociation of one of the axial tricyclohexylphosphine ligands in catalyst **13**, inhibition of polymerization by phosphines **8** and **10** is hardly surprising. The azo entity in DNAD (**4**) and ENAD (**6**) may also act either as a ligand at ruthenium or by complexing the phosphine ligands around the ruthenium, causing catalyst decomposition.

In a second approach we examined the use of polystyrene-supported triphenylphosphine **11**, which has already been used in the Mitsunobu reaction.[8] The advantage of using supported triphenylphosphine **11** is 2-fold; excess phosphine **11** and its oxide can easily be removed by filtration. Second, excess DNAD (**4**) should form a complex such as **12** that can also be removed by filtration (Scheme 3), thus making the annihilation of $DNADH_2$ (**3**) by ROM polymerization more efficient.

Scheme 3



The general procedure for the Mitsunobu reaction including the impurity annihilation strategy is as follows.

Polystyrene-supported phosphine **11**[9] (50 mg, 0.15 mmol) was washed alternately with THF and MeOH five times

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under nitrogen, dried in vacuo, and resuspended in THF (1 mL). The alcohol (0.1 mmol) was added and the mixture stirred for 15 min. DNAD (**4**; 49 mg; 0.15 mmol) and the nucleophile (0.1 mmol) were added, and the reaction mixture was stirred overnight, filtered through charcoal and Celite, and washed with THF (3 × 1 mL). If the filtrate appeared yellow, an additional amount of phosphine **11** was added to capture the DNAD (**4**) still remaining, followed by a second filtration. Grubbs' catalyst **13** (4.1 mg, 5 μmol) was added to the filtrate, and the polymerization was monitored by TLC and GC. When the monomer could no longer be detected (15 min to 2 h), hexanes (2 mL) was added. The mixture was again filtered through charcoal and Celite and washed with THF–hexanes (1:1, 2 mL). Rotary evaporation gave the product esters or imides, the purities of which were assayed by GC-MS and both ^{1}H and ^{13}C NMR spectroscopy.

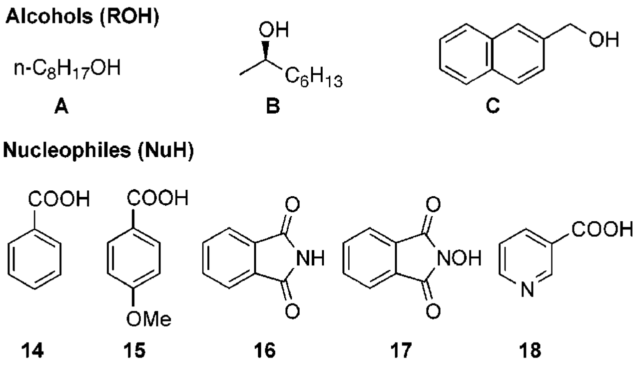
To show the utility of the developed method, a small library was prepared using alcohols **A**–**C** and nucleophiles **14**–**18**. The results obtained are shown in Table 1.

As can be seen from Table 1, the yields obtained range from moderate to excellent (43–100%) with GC purities greater than 95%. The NMR purities were slightly lower (86–96%), on account of the failure of GC-MS to detect trace amounts of tricyclohexylphosphine, its oxide, or any soluble ROM oligomers. The products **14A** to **17C** in Table 1 did not contain significant amounts of catalyst residues, starting alcohols, or starting nucleophiles. Presumably the ruthenium carbenes remain attached to the poly-DNADH$_2$, since the polymerization is living.[10] Since the yields of the products **14A** to **17C** are not quantitative, the mass balance of the alcohols and the nucleophiles must be bound either to poly-DNADH$_2$ or **11**. The formation of dialkyl *N*-acyl-[11] and dialkyl *N*-alkylhydrazinedicarboxylates[12] during Mitsunobu reactions are well-precedented. Clearly, ROM polymerization would remove these contaminants. Alternatively, P-alkylation of **11** and sequestration of the nucleophile conjugate base is an alternative scavenging pathway.

The amount of Grubbs' catalyst **13** used for the ROM polymerization could be reduced if the reaction was performed in dichloromethane, instead of THF, although the Mitsunobu reaction did not work as well in this solvent.

The impurity annihilation strategy by ROM-polymerization is limited to reagents that do not contain functional groups that are capable of coordinating to ruthenium. A functionality that suppresses alkene metathesis, such as the nicotinic acid derivatives from **18**, clearly are to be avoided. Nonetheless, the versatility and broad functional group tolerance of ruthenium-based metathesis catalysts are favorable auspices for the broad application of impurity annihilation Mitsunobu reactions.

Table 1[a]



	yield of alcohol, %		
nucleophile	**A**	**B**	**C**
14	100	94	73
	(92)	(95)	(95)
15	80	78	81
	(91)	(95)[b]	(91)[b]
16	100	73	62
	(96)	(90)[c]	(89)[b]
17	68	43	61
	(96)[b]	(86)[b,d]	(97)[b,d]
18	*e*	*e*	*e*

[a] Unless stated to the contrary, reactions were carried out using **11** (0.15 mmol), **4** (0.15 mmol), the alcohol (0.10 mmol), and the nucleophile component (0.10 mmol). The upper value refers to the isolated yield of the product RNu. Figures in parentheses are the purities of RNu as judged by ^{1}H NMR. Purities judged by GC/MS were $\geq$95% unless otherwise indicated. [b] DNAD **4** (2.5 equiv) and phosphine **11** (2.5 equiv) were used. [c] GC purity 86%. [d] Short filtration through silica. [e] The Mitsunobu reaction worked, but ROM polymerization did not.

In conclusion, we have developed a novel, very mild method to remove impurities in parallel solution-phase Mitsunobu reactions using ROM polymerization. We are currently extending the strategy to other reactions in our laboratory.

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(9) The supported phosphine **11** (3 mmol g^{-1}) is commercially available from Fluka. All norbornene reagents in this paper were *exo*:*endo* mixtures (approximately 1:2). DNAD, ENAD, and phosphine **8** were derived from commercial 5-norbornen-2-ylmethanol (Aldrich).

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