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Separation tagging with cyclodextrin-binding groups: Mitsunobu reactions with bis-(2-(1-adamantyl)ethyl) azodicarboxylate (BadEAD) and bis-(1-adamantylmethyl) azodicarboxylate (BadMAD)

Sivaraman Dandapani, Jeffery J. Newsome and Dennis P. Curran*

Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA

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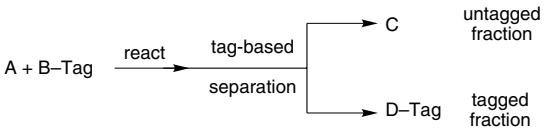
Abstract—A new method for separation tagging with cyclodextrin-binding groups is introduced and is exemplified in the context of the Mitsunobu reaction with adamantyl tags. HPLC experiments showed that molecules containing adamantyl groups were especially well retained on Sumichiral OA7500 β-methylated cyclodextrin bonded silica columns relative to many other types of molecules. Two new Mitsunobu reagents, bis-(1-adamantylmethyl) azodicarboxylate (BadMAD) and bis-(2-(1-adamantyl)ethyl) azodicarboxylate (BadEAD), were prepared, used in typical Mitsunobu reactions and separated with both β-methylated cyclodextrin bonded silica and standard silica.

Modern strategy level separations are often designed based on concepts of separation tagging.[1] A selected reaction component (substrate, reactant, reagent, catalyst, etc.) bearing a separation tag is reacted with one or more other reaction components lacking the tag. Following the reaction, a tag-complementary 'workup-level' separation technique is applied to bifurcate the reaction mixture into fractions containing tagged and untagged reaction components (Fig. 1). Separation tags in common use or actively being developed include soluble and insoluble polymers, fluorous tags, ionic tags, lipophilic tags, polymerizable tags, and precipitons, among others.[1]



A,B = substrates, reactants, reagents, catalysts, etc.
C,D = products derived from A,B
Tag = separation tag
This work: the tag is a cyclodextrin binding group; the tag-based separation media is silica gel with a cyclodextrin bonded phase

Figure 1. A schematic illustration of separation tagging.

Many demands are placed on separation tags. Among other things, they should be easy to introduce, exhibit broad control during tag-complementary separations, be chemically stable to diverse reaction conditions, be recyclable, and be as small, as inexpensive and as readily available as possible. They should not be toxic, interfere with or limit reactions, or complicate spectroscopic characterization or chromatographic analysis, and ideally they should not require extra reactions after the target reaction to effect separation. Just as there is no 'universal' protecting group, there is no tag that can meet all of the requirements all of the time, so a diverse assortment of tags is needed.

The broad fields of molecular recognition and supramolecular chemistry provide a gold mine of potential separation tags (guests) and tag-complementary separation techniques (hosts). Unfortunately, hydrogen bond interactions often contribute significantly to host/guest binding. The functional groups responsible for hydrogen bonding—carbonyl groups, OH groups, NH groups, and the like—are generally not attractive as

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* Corresponding author. Tel.: +1-412-624-8240; fax: +1-412-624-9861; e-mail: curran@pitt.edu

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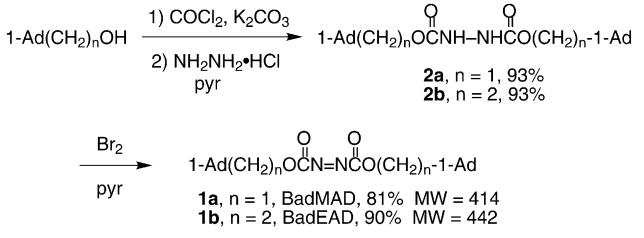
tag components because their reactivity limits potential chemical transformations.

An important exception to this generalization is cyclodextrin chemistry, where binding of relatively unfunctionalized guests is primarily driven by hydrophobic interactions and shape complementarity.[2] Among the molecular sub-units that bind to cyclodextrin (halo-, nitro-, and alkyl-substituted phenols and derivatives, substituted benzoic acids, naphthalenes, biaryls, to name a few), we selected the adamantyl group for study as a cyclodextrin-binding tag because of its strong interactions with cyclodextrins,[3] its inertness, its ready availability and its low cost. To demonstrate the use of adamantyl tagging with cyclodextrin separation, we selected the Mitsunobu reaction,[4] which has become a focal point of strategy separation methods because of the difficulties of separating target products from reagents and derived byproducts.[5] We report herein two new adamantyl-tagged Mitsunobu reagents and we use the reagents in Mitsunobu reactions followed by cyclodextrin and standard silica separations. Concurrently, Blodgett and Li introduce the 4-*tert*-butylphenyl group as a tag for cyclodextrin-based separation.[6]

The two new Mitsunobu reagents, bis-(1-adamantylmethyl) azodicarboxylate (BadMAD) **1a** and bis-(2-(1-adamantyl)ethyl) azodicarboxylate (BadEAD) **1b**, were prepared in the manner shown in Eq. 1.[7] Reaction of the appropriate alcohol with phosgene followed by addition of hydrazine hydrochloride and pyridine provided the dicarbonyl hydrazides **2a**,**b**. These in turn were oxidized with bromine to provide the Mitsunobu reagents **1a**,**b** as yellow solids.



(1)

Following Mitsunobu reactions with these reagents, target products must be separated from the dicarbonyl hydrazides **2a**,**b**, so we initially explored the HPLC retention behavior of these compounds in comparison with assorted controls. Preliminary experiments showed that the adamantyl hydrazides were much better retained on a Sumichiral OA7500[8] column than on a Cyclobond I-2000 (Astec) column, so we focused our efforts on the former.

Retention times on a Sumichiral OA7500 column of a series of dicarboxy hydrazides ($R^1OCONHNHCOOR^2$) including **2a** and **2b** are summarized in Table 1. The column was eluted under isocratic conditions with 100% acetonitrile. Hydrazides bearing lipophilic alkyl groups like *t*-butyl, menthyl, benzyl, octyl, and cyclohexyl all emerge at or near the solvent front (3.7 min) under these powerfully eluting conditions. Fluorous hydrazides are not retained either.[9] In contrast, **2a** is retained for 23.5 min and **2b** is retained for 26.5 min.

Table 1. Retention times of adamantyl and control carbonyl hydrazides $R^1OCONHNHCOOR^2$ on a Sumichiral OA7500 column eluting with 100% acetonitrile

Entry	R^1	R^2	t_R (min)[a]
1	Oct	Oct	4.8
2	^{t}Bu	$PhCH_2$	5.4
3	^{t}Bu	^{i}Bu	5.0
4	*c*-C_6H_{11}	*c*-C_6H_{11}	5.7
5	^{t}Bu	Menthyl	5.9
6[b]	1-$AdCH_2$	1-$AdCH_2$	23.5
7[c]	1-$AdCH_2CH_2$	1-$AdCH_2CH_2$	26.5

[a] The solvent front is at about 3.7 min.
[b] Hydrazide **2a**.
[c] Hydrazide **2b**.

These results show that bis-adamantyl-tagged compounds are strongly retained by Sumichiral OA7500 columns, even under powerfully eluting conditions. To further show that they are selectively retained, we injected members of a series of representative organic compounds, many of which were made by Mitsunobu reactions. The structures and retention times for these compounds are shown in Figure 2. All compounds elute at or near the solvent front except bis-(2(1-adamantyl)ethyl)carbonate, which was strongly retained as expected (40.5 min).

While the reverse phase nature of the methylated β-cyclodextrin media could contribute to the retention of **2a**,**b**, the lack of retention of other nonpolar compounds suggests that this is not the only factor. Accordingly, we hypothesize that the complexation of the adamantyl groups to the cyclodextrin on the stationary phase is important. Regardless of the mechanism, the results suggest that the cyclodextrin-based separation of adamantyl-tagged hydrazides **2a**,**b** from typical Mitsunobu reaction products will have considerable generality.

To complement the separation studies, we conducted Mitsunobu reactions with reagents **1a** and **1b** to show that they couple alcohols and acidic pronucleophiles in the expected fashion. Eq. 2 shows the coupling of 3,5-dinitrobenzoic acid with methanol. After standard reaction of the alcohol and pronucleophile with triphenylphosphine and **1b**, a part of the reaction mixture was purified by repeated injection onto the Sumichiral OA7500 analytical column. Triphenylphosphine oxide ($t_R = 11$ min) emerged after 3,5-dinitrobenzoic acid methyl ester ($t_R = 4.0$ min), so we were able to obtain the pure ester product by collecting the solvent front peak. In 'overload' injections designed to mimic flash chromatographic or solid phase extraction separations, the ester and the triphenylphosphine oxide peaks merged together, but this merged peak was still very easily separated from the hydrazide peak of **2b**. This proof-of-principle experiment demonstrates the viability of the proposed cyclodextrin separation. A separate reaction mixture was purified by standard flash chromatography, and the Mitsunobu product was isolated in 97% yield.

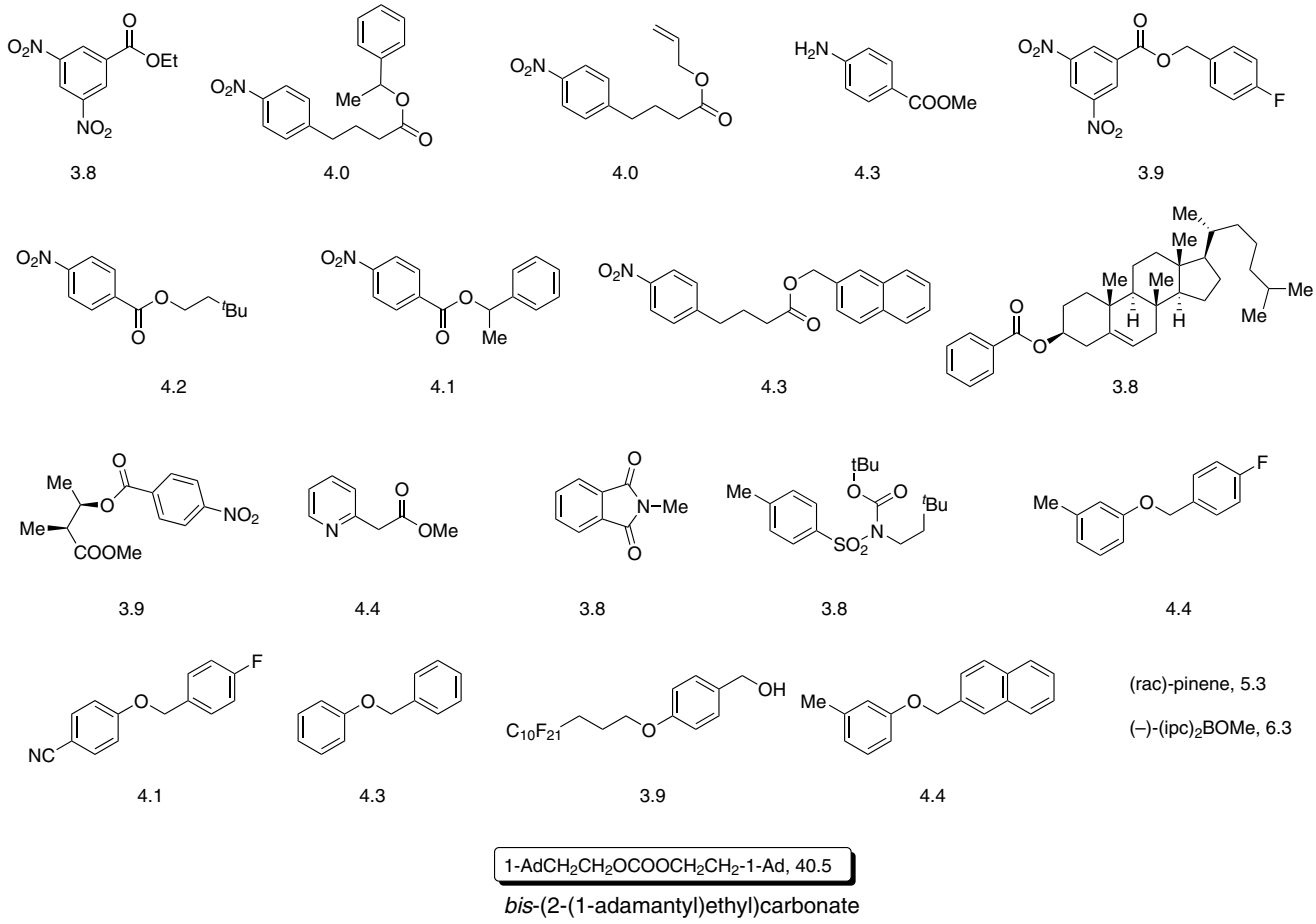
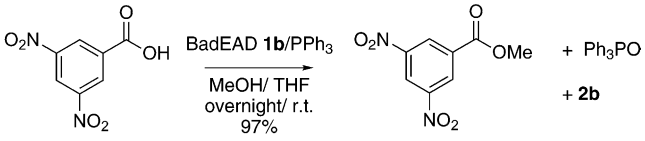


Figure 2. Retention times (min) of assorted esters, ether, and other compound on a Sumichiral OA7500 column eluting with 100% acetonitrile.



(2)

The scope of the BadEAD reagent **1b** was briefly probed by reacting a series of four nucleophiles (3,5-dinitrobenzoic acid, phthalimide, 4-(4-nitrophenyl)butyric acid, and 4-cyanophenol) with four alcohols (methanol, 3,3-dimethyl-1-butanol, isopropanol, and 4-fluorobenzyl alcohol). The degree of difficulty of the pairings ranges from very easy (reactions with methanol) to quite difficult (less acidic nucleophiles and hindered alcohols). The coupled products shown in Figure 2 were isolated by standard flash chromatography. Eight pairings gave good to excellent yields of coupled products, while four did not. Among these failures are three of the four alcohol couplings with phthalimide; only methanol coupled with this nucleophile. Two successful couplings were also conducted with BadMAD reagent **1a**. No effort was made to vary the Mitsunobu procedure, so these results should not be viewed as optimized. Even so, they suggest that reagents **1a**,**b** should exhibit a good scope in the Mitsunobu reaction.

New Mitsunobu reagents BadMAD **1a** and BadEAD **1b** show excellent promise as practical alternatives to existing classes of reagents. While methylated β-cyclodextrin is well known, it is not widely available in bonded formats suitable for large scale separation, and we hope that this work will spur further commercialization efforts. In the meantime, small scale separation with commercial Sumichiral OA7500 columns is a technique that is immediately accessible. And the new Mitsunobu reagents have different separation properties from the standard DEAD and DIAD reagents,[10] so they will find use in combination with traditional separation techniques such as chromatography over standard silica gel (Fig. 3).

Clearly, the use of adamantyl tags will extend beyond the Mitsunobu reaction, and the selective retention of molecules with adamantyl groups on methylated β-cyclodextrin silica gel makes this an especially attractive tag/separation media pair. The adamantyl group is stable, and has a relatively low molecular weight compared to many existing separation tags.[1] A range of simple adamantane-containing molecules are available at modest price, and this constitutes a starting point for fashioning tags, reagents, protecting groups, catalysts, scavengers, etc., by using standard reactions.

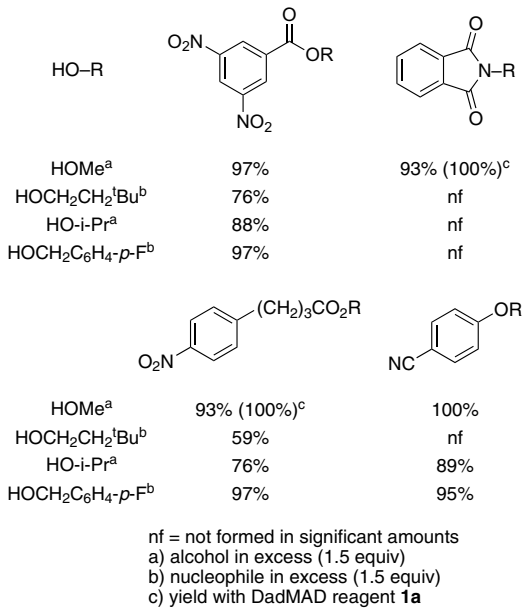


Figure 3. Isolated yields of Mitsunobu products in couplings promoted by BadEAD **1b** and triphenylphosphine.

More generally, this work and that of Blodgett and Li[6] set the stage for a broad strategy of separation tagging with cyclodextrin-binding tags. Such tags will be applicable in all the usual substrate-, reagent-, and catalyst-tagging applications as well as in phase switching techniques such as scavenging and product capture.[1b] Attachments of cyclodextrin tags to resin-bound products will provide a useful adjunct to solid phase synthesis.[11] The large amount of literature on the host–guest chemistry of cyclodextrins provides the foundation for selecting cyclodextrin-binding tags and appropriate cyclodextrin-based separation media. The ready availability of cyclodextrins, and the small size and lack of reactive functionality of many cyclodextrin-binding groups conspire with other factors to make this new separation tagging strategy useful and appealing.

Acknowledgements

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Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.07.009. Contains characterization data for **1a**,**b** and **2a**,**b** along with experimental procedures for reagent synthesis and Mitsunobu reactions (5 pages).

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8. Sumichiral QA7500 is methylated β-cyclodextrin bonded to silica with an alkylene spacer. It is available from Sumika at http://www002.upp.so-net.ne.jp/sas/oa_column.html.
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