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## COMMUNICATION

## Intramolecular monomer-on-monomer (MoM) Mitsunobu cyclization for the synthesis of benzofused thiadiazepine-dioxides†

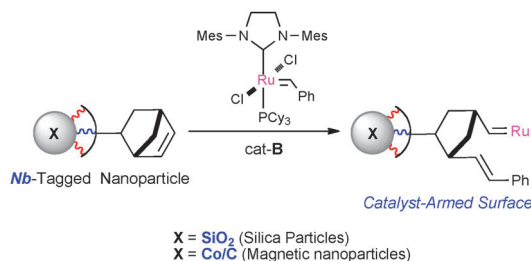
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The utilization of a monomer-on-monomer (MoM) intramolecular Mitsunobu cyclization reaction employing norbornenyl-tagged (Nb-tagged) reagents is reported for the synthesis of benzofused thiadiazepine-dioxides. Facile purification was achieved *via* ring-opening metathesis (ROM) polymerization initiated by one of three metathesis catalyst methods: (i) free metathesis catalyst, (ii) surface-initiated catalyst-armed silica, or (iii) surface-initiated catalyst-armed Co/C magnetic nanoparticles.

The ongoing effort in the search for new pharmacophores and small molecular probes is a key feature of modern drug discovery. The Mitsunobu reaction and its variants<sup>1</sup> represent versatile synthetic methods which are pivotal to accessing small molecules for drug discovery.<sup>2</sup> The Mitsunobu reaction is a mild and effective method for the conversion of alcohols into a variety of functionality through the formation of C–C, C–O, C–N and C–S bonds, including the ability to invert the stereochemistry of stereogenic carbinol-bearing centers. A formal “redox” reaction, the Mitsunobu reaction is promoted under relatively mild conditions by a combination of a tertiary phosphine, usually triphenylphosphine (PPh<sub>3</sub>) and an azodicarboxylate, usually diethyl or diisopropyl ester (DEAD or DIAD). Such is the scope of the Mitsunobu reaction, its application has played a pivotal role in the synthesis of natural products,<sup>3</sup> and bioactive small molecules.<sup>4</sup> Despite these powerful attributes, the Mitsunobu reaction suffers from the need for tedious purifications to isolate the desired product, an operational disadvantage in both high-throughput chemistry and natural product synthesis. Addressing this issue, several variants of the Mitsunobu reaction have been developed which include tagged, immobilized and water-soluble reagents that allow for facile



Scheme 1 Catalyst-armed Silica- and Co/C magnetic nanoparticles.

separation of the desired product from unwanted Mitsunobu by-products.<sup>5</sup>

Methods developed within our group for facile purification-free Mitsunobu protocols have focused on the application of a polymer-on-polymer (PoP) Mitsunobu protocol, employing ROMP-derived oligomeric triphenylphosphine (OTPP) and oligomeric benzylethyl azodicarboxylate (OBEAD) reagents,<sup>6</sup> as well as a monomer-on-monomer (MoM) Mitsunobu protocol, utilizing norbornenyl-tagged (Nb-tagged) PPh<sub>3</sub> and BEAD reagents.<sup>7</sup> In the latter case, facile sequestration of the excess and spent reagents was achieved *via* ring-opening metathesis (ROM) polymerization initiated by any one of three methods utilizing Grubbs catalyst [(IMesH<sub>2</sub>)(PCy<sub>3</sub>)(Cl)<sub>2</sub>Ru=CHPh, cat-B]:<sup>8</sup> (i) free catalyst in solution, (ii) surface-initiated catalyst-armed silica,<sup>9,10</sup> or (iii) surface-initiated catalyst-armed carbon-coated (Co/C) magnetic nanoparticles (Nps) (Scheme 1).<sup>7,11</sup>

The intramolecular Mitsunobu reaction has been widely utilized as a cyclization protocol for the synthesis of heterocyclic molecules.<sup>12</sup> Building on these reports, we herein report the synthesis of benzofused thiadiazepine-dioxides *via* an intramolecular 7-membered MoM Mitsunobu cyclization reaction, whereby facile purification was achieved utilizing ROMP sequestration initiated by free metathesis catalyst or catalyst-armed particle surfaces (Scheme 2).

The synthesis of benzofused thiadiazepine-dioxides **3a** and **3b** was investigated utilizing the intramolecular MoM Mitsunobu cyclization with the readily prepared Nb-tagged PPh<sub>3</sub> (Nb-TPP) and DEAD (Nb-BEAD) reagents.<sup>6</sup> The corresponding hydroxy-benzylsulfonamide starting materials **2a** and **2b** were rapidly generated *via* a microwave-assisted S<sub>N</sub>Ar protocol (Scheme 3).<sup>13</sup>

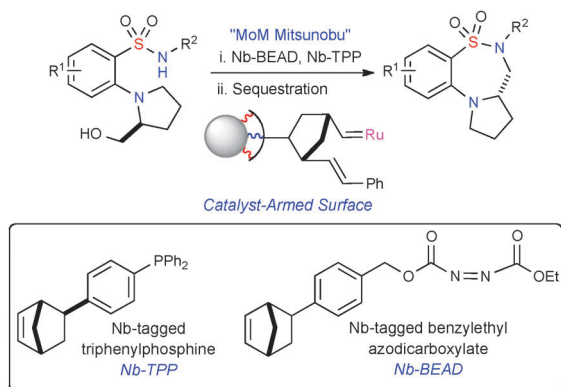
With sulfonamides **2a–b** in hand, the application of MoM cyclization reaction was investigated utilizing Nb-TPP and

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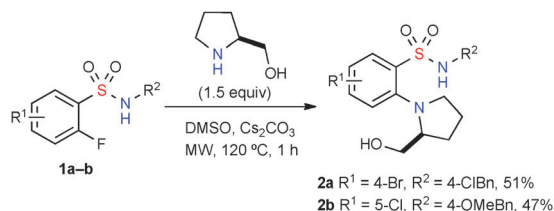
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**Scheme 2** Synthesis of benzofused thiadiazepine-dioxides *via* a intramolecular MoM Mitsunobu cyclization.



**Scheme 3** Synthesis of hydroxy-benzylsulfonamides **2a–b** *via* microwave-assisted  $S_NAr$ .

Nb-BEAD (Table 1). Initially, purification was achieved by phase switching of all Nb-tagged species in solution (monomeric reagents and spent reagents) by addition of free metathesis catalyst [(IMes)<sub>2</sub>(PCy<sub>3</sub>)(Cl)<sub>2</sub>Ru=CHPh, cat-B] (Method A) to induce ROM polymerization. The ROM polymerization event was followed by precipitation to produce the desired benzofused thiadiazepine-dioxides **3a** and **3b** in good yield and excellent

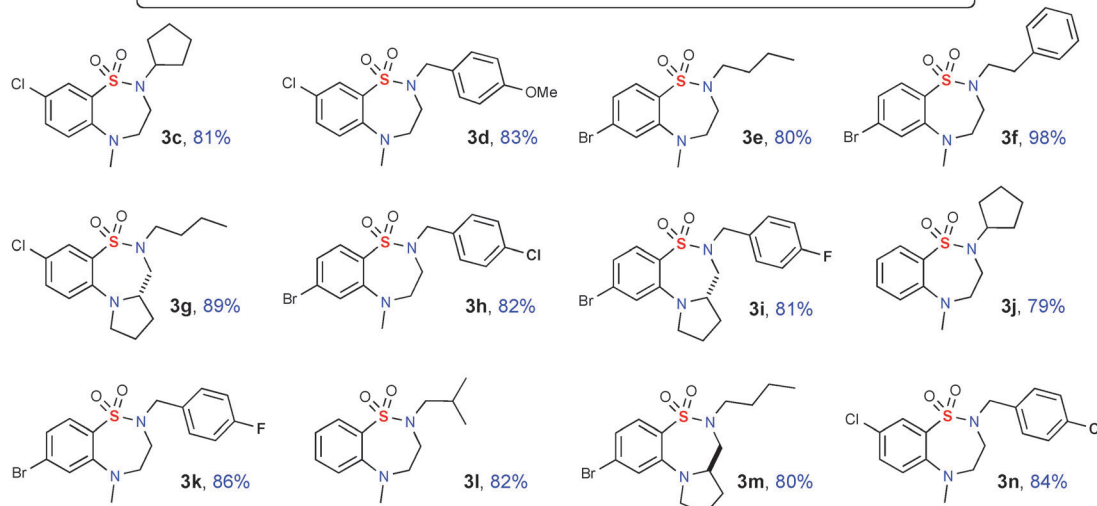
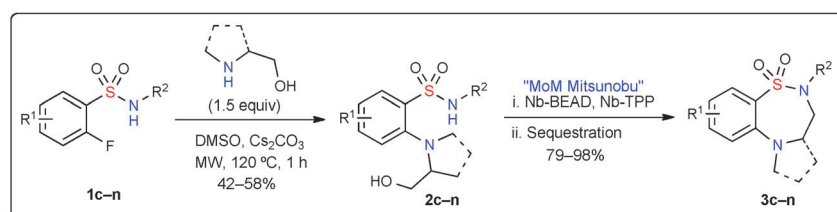
**Table 1** Intramolecular MoM Mitsunobu-Sequestration

Entry	Sequestration	Comp.	Method	Yield (%)	Crude Purity (%) <sup>a</sup>
1 <sup>b</sup>	Cat-B	<b>3a</b>	A	85	> 95%
2 <sup>b</sup>	Cat-B	<b>3b</b>	A	88	> 95%
3 <sup>c</sup>	Co/C Nb-tagged	<b>3a</b>	B	87	> 95%
4 <sup>c</sup>	Co/C Nb-tagged	<b>3b</b>	B	81	> 95%
5 <sup>d</sup>	Si Nb-tagged	<b>3a</b>	C	89	> 95%
6 <sup>d</sup>	Si Nb-tagged	<b>3b</b>	C	84	> 95%

<sup>a</sup> Purity determined by <sup>1</sup>H NMR. <sup>b</sup> Isolated *via* precipitation in Et<sub>2</sub>O. <sup>c</sup> Isolated *via* magnetic decantation and filtration through Silica SPE. <sup>d</sup> Isolated *via* filtration through Celite<sup>®</sup> SPE.

crude purity (Table 1, entries 1–2). Purification was followed by TLC analysis, whereby the typical Mitsunobu multispot crude reaction mixture was reduced to a single spot after utilizing this polymerization sequestration protocol. Despite this success, the need for precipitation of the crude reaction mixture to remove the polymerized reagents/spent reagents was deemed not ideal for a high-throughput approach. Therefore, alternative syntheses of benzofused thiadiazepine-dioxides **3a** and **3b** were investigated utilizing a catalyst-armed surface generated from either Nb-tagged Co/C magnetic particles, or Nb-tagged silica particles.

After polymerization sequestration of excess reagents/spent reagents on the surface of the magnetic Co/C beads [Method B], **3a** and **3b** could be obtained in reasonable crude purity by collecting the nanobeads with an external magnet, decanting the



**Scheme 4** Synthesis of benzofused thiadiazepine-dioxides. (**3c–3f**: Method A; **3g–3j**: Method B; **3k–3n**: Method C).

solution and evaporating the solvent (Table 1, entries 3–4). Noteworthy, this work-up procedure is carried out within a few seconds, being an operational advantage to conventional filtration techniques. However, to further improve the product purity the solution was filtered over a silica SPE. As an alternative method, the sequestration by Nb-tagged silica particles [Method C] was applied to generate **3a** and **3b** in comparable yields and purities with simple filtration through Celite® SPE to isolate the desired product, avoiding the need for precipitation (Table 1, entries 5–6). Building on these results, substrate scope was evaluated across all three purification sequestration protocols A–C for the synthesis of **3c–3n** via MoM Mitsunobu cyclization (Scheme 4). Thus, benzofused thiadiazepine-dioxides **3c–3f** were generated with free cat-B [Method A], compounds **3g–3j** via Nb-tagged Co/C magnetic particles [Method B] and benzofused thiadiazepine-dioxides **3k–3n** utilizing Nb-tagged SiO<sub>2</sub> particles [Method C].

In conclusion, we have demonstrated the application of a MoM intramolecular Mitsunobu cyclization for the synthesis of bi- and tri-cyclic benzofused thiadiazepine-dioxides. Facile purification of crude reaction mixtures was achieved via ROM polymerization sequestration of excess reagents/spent reagents. This was accomplished initially utilizing free metathesis catalyst Cat-B, followed by precipitation. The method was further optimized utilizing catalyst-armed surfaces generated from either Nb-tagged Si-particles or Nb-tagged Co/C magnetic nanoparticles.

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