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Synthesis of epoxybenzo[d]isothiazole 1,1-dioxides *via* a reductive-Heck, metathesis-sequestration protocol^{†,‡}

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Abstract

An atom-economical purification protocol, using solution phase processing *via* ring-opening metathesis polymerization (ROMP) has been developed for the synthesis of tricyclic sultams. This chromatography-free method allows for convenient isolation of reductive-Heck products and reclamation of excess starting material *via* sequestration involving metathesis catalysts and a catalyst-armed Si-surface.

The growing need for new pharmaceutical leads has prompted advances in high-throughput screening and the development of emerging synthetic methods and technologies.¹ In this regard, access to novel heterocyclic scaffolds in a minimal number of steps is a key facet of drug discovery. Among these, the integration of synthesis and purification has enabled seminal advances in both combinatorial and parallel synthetic chemistry.² Conventionally, this goal has been achieved by operating on resin-bound substrates with excess reagents or treating solution phase substrates with excess immobilized reagents.³ Both scenarios, although not optimal in terms of atom economy, have been extensively represented in the literature. Though rarely used, a third scenario employs the use of excess substrate, normally considered the precious component. However, if excess substrate is warranted and can be further processed in a parallel reaction, *i.e.*, “reclaimed”, this unfavorable scenario can be advantageous. We herein report a new chromatography-free method in the context of complex sultam synthesis,^{4,5} which allows for convenient isolation of reductive-Heck products and reclamation of excess starting material *via* sequestration involving metathesis catalysts and catalyst-armed SiO₂ surface.

Previously, the synthesis of a diverse collection of sultams derived from a core intramolecular Diels–Alder (IMDA) scaffold **1** *via* a metathesis cascade protocol was reported.⁶ In this approach, the core scaffold that is readily synthesized on gram-scale utilizing a report by Metz and coworkers,⁷ undergoes a ring-opening, ring-closing, cross-metathesis (ROM-RC-CM) protocol with a variety of CM partners in a one-pot transformation. Building on this work, additional pathways for the diversification of this

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core scaffold were investigated. In this regard, sultam **1** was subjected to the reductive Heck reaction using Pd(OAc)₂, Zn and excess aryl coupling partner (1.5 equiv.) to push the reaction to completion.⁸ Despite the use of excess aryl iodide (4MeO-PhI), the reaction proceeded in good yield (60%) with excellent regio- and diastereoselectivity (>19: 1). However, it was found that purification of the crude reaction mixture *via* standard chromatographic purification was very tedious due to the close similarity in R_f between the desired product **2a** and the remaining starting material **1** (Scheme 1). Though markedly low product yield was easily improved through the use of excess scaffold **1** (1.5 equiv.), purification restricted the method's application to high-throughput generation of sultam derivatives **2**.⁹ To address this issue, it was envisioned that the remaining starting material **1**, possessing an oxa-norbor-nene motif ("armed scaffold"), could be removed *via* exposure to metathesis catalyst and phase-trafficking through ring-opening metathesis polymerization (ROMP) to generate the corresponding oligomeric scaffold **3**.^{10,11} Simple precipitation of the oligomer would allow for rapid isolation of desired product and recovery of oligomer in an atom economic approach (Scheme 2).

With the aforementioned goal in mind, initial investigation focused on sultam **1** (1.5 equiv.) which underwent reductive Heck reaction with 4-MeO-PhI (1 equiv.) in the presence of Pd(OAc)₂ and Zn in DMF at 60 °C. After completion of the reaction, the mixture was filtered through Celite (to remove Zn), concentrated, and subjected to ROM polymerization using Grubbs catalyst [(IMesH₂)(PCy₃)(Cl)₂Ru = CHPh, cat-**B**],¹² where simple precipitation and filtration afforded the corresponding reductive Heck sultam **2a** in 82% yield and >95% crude purity (Table 1, entry 1). With the successful application of this reductive-Heck, metathesis-sequestration protocol, nine aryl iodides were further successfully utilized (Table 1, entry 2–10).

Despite the success of this protocol, the required precipitation of each reaction was not ideal from a high throughput standpoint. In order to address this issue, the utilization of a catalyst-armed surface, generated from norbornenyl-tagged (Nb-tagged) silica particles,^{13,14} was investigated. Purification required simple filtration rather than the use of additional solvent to precipitate the spent oligomer. Sultam **4** was subjected to standard reductive-Heck conditions, and upon completion, the crude mixture was cannulated into a reaction vessel containing "pre-armed" Nb-tagged Si-particles. After heating for 30 min–1 h (TLC monitoring), the crude reaction mixture was filtered through a Celite[®] SPE to yield the desired product **5a–b** in good yield and crude purity (Scheme 3).

With the successful application of the reductive-Heck-metathesis sequestration protocol, we investigated the utilization of the reclaimed oligomerized scaffold **3** isolated after purification. To this effect, oligomer **3** was subjected to reductive ozonolysis¹⁵ generating diol intermediate **6**, which underwent cyclization with ROMP-derived oligomeric sulfonyl chloride (OSC)¹⁶ to yield the corresponding polyether **7** without the need for purification (Scheme 4).

Oligomer **3** could also be readily converted into oligomer **8** without the need for standard purification. Diversification and subsequent release off the oligomer *via* Barrett's vanishing support¹⁷ protocol was readily achieved in a 3-step Suzuki,¹⁸ reductive ozonolysis procedure to yield the corresponding diols **9a–d** in good overall yield and excellent purities. Overall, this approach offers several advantages, including: (i) atom economy, where the oligomer (*i.e.* reclaimed scaffold) is converted to alternative small molecules after degradation; (ii) elimination of the need for an additional linker (in contrast to traditional SPOC); and (iii) parallel processing with minimal waste stream.

In conclusion, an atom-economical protocol utilizing ROM polymerization has been developed. This chromatography-free method allows for convenient isolation of reductive-Heck products and reclamation of excess oligomeric sultam scaffold *via* precipitation. Using solution phase processing, the recovered oligomeric scaffold is readily transformed into an array of new, skeletally diverse sultam scaffolds *via* a vanishing support protocol.¹⁷ Application of this method to an array of norbor-nene-type scaffolds is in progress and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

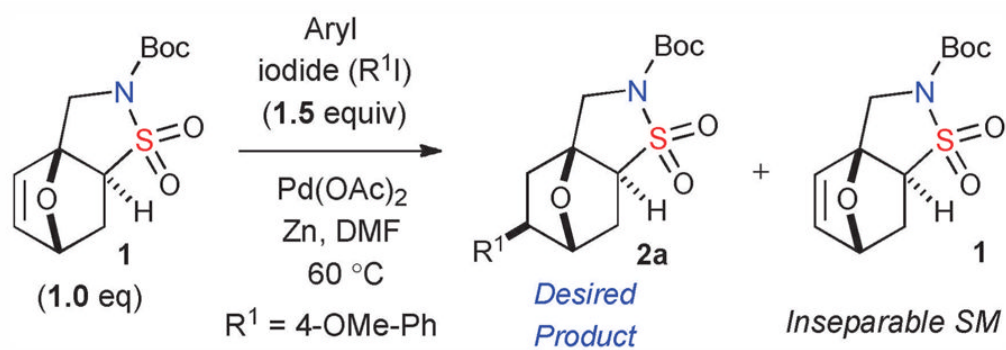
This work was supported by the National Institute of General Medical Sciences (Center in Chemical Methodologies and Library Development at the University of Kansas, KU-CMLD, NIH P50 GM069663, NIH P41-GM076302 and the NIH-STTR R41 GM076765). The authors acknowledge Dr Victor Day of the Molecular Structure Group (MSG) at the University of Kansas for X-ray analysis and Materia Inc. for providing metathesis catalyst.

Notes and references

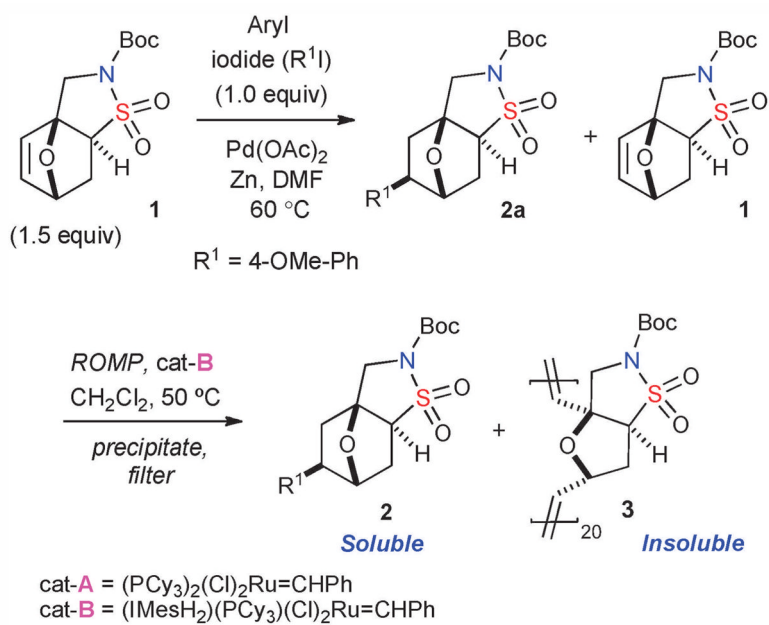
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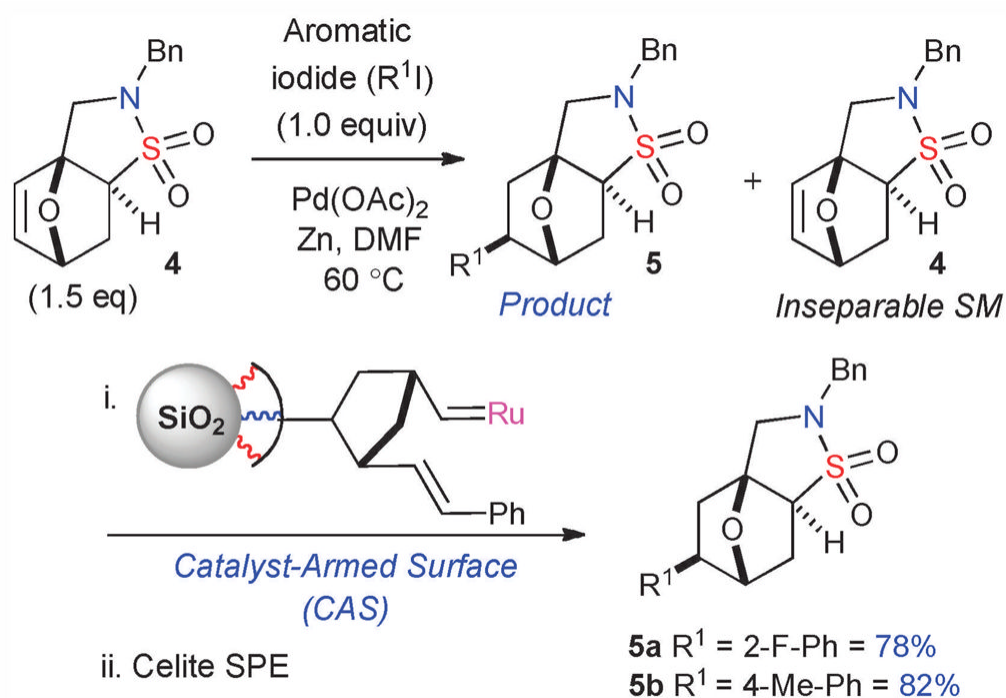
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18. It is worth noting that the Suzuki reaction of the corresponding monomer **6** afforded an inseparable mixture of products (Suzuki product as well as product resulting from the double Heck-addition across the double bond), thus further substantiating the use of the titled process.

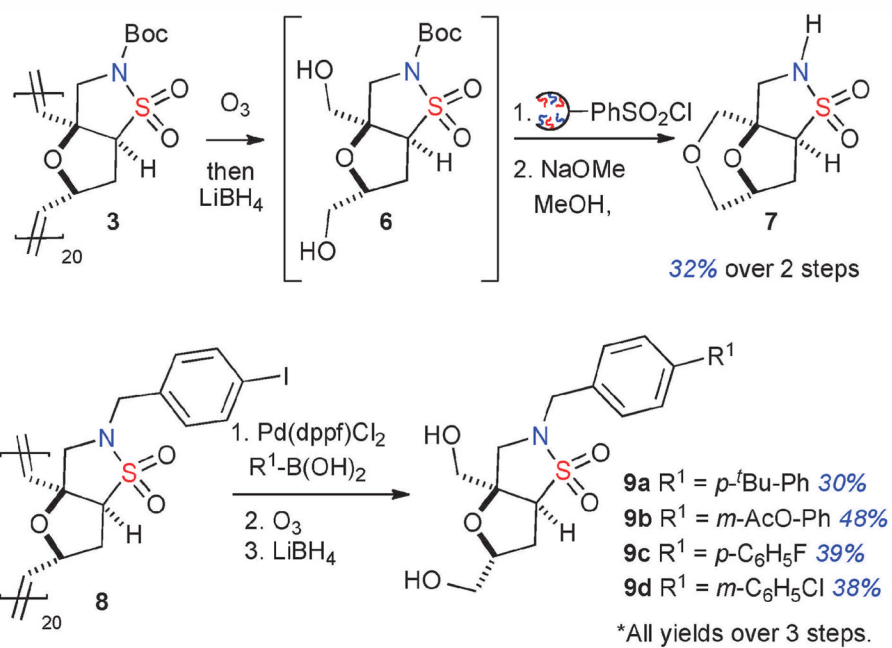


Scheme 1.
Reductive Heck diversification of **1** utilizing excess reagent.



Scheme 2.
Reductive Heck diversification of **1** utilizing excess scaffold **1**.

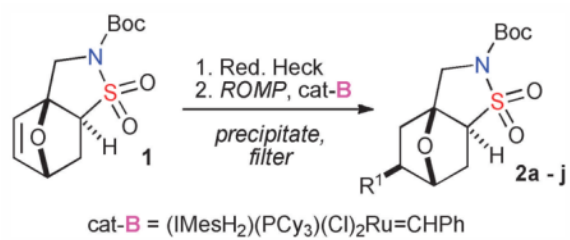
**Scheme 3.**Sequestration of excess SM **4** via catalyst-armed Si-particles.



Scheme 4. Diversification-release of corresponding derived-sultams from reclaimed oligomer 3.

Table 1

Reductive Heck, followed by ROMP sequestration



Entry	R ¹	Yield (%)	Purity % ^a	Comp.
1	<i>p</i> -CH ₃ O-Ph	82	>95	2a
2	<i>p</i> -F-Ph	77	>95	2b
3	<i>p</i> -CO ₂ CH ₃ -Ph	86	>95	2c
4	<i>p</i> -OH-Ph	89	>95	2d
5	<i>m</i> -F-Ph	82	>95	2e
6	3,5 di-CH ₃ -Ph	76	>95	2f
7	<i>p</i> -CH ₃ -Ph	75 ^b	>95	2g
8	2-thiophene-Ph	81 ^b	>95	2h
9	<i>p</i> -CF ₃ O-Ph	73 ^c	>95	2i
10	<i>p</i> -CN-Ph	65 ^c	>95	2j

^aPurity determined by ¹H NMR,^bdr = 3:1 determined by ¹H NMR,^cdr = 4:1 determined by ¹H NMR.