Rapid Assembly of Stereochemically Rich Polycyclic Tetrahydrofurans by a Conjugate Addition-Rh(II) Catalysis Sequence

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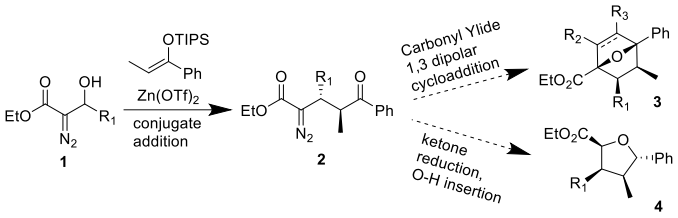
Supporting Information Placeholder

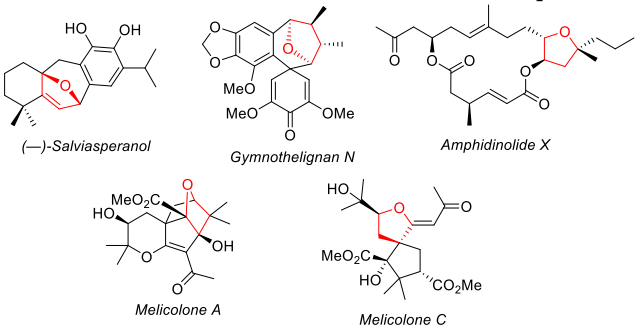


Key Words: Diazo, vinyl diazonium, dipolar cycloaddition, furan

ABSTRACT: An efficient reaction sequence that gives stereochemically rich, polycyclic tetrahydrofurans is described. A highly diastereoselective conjugate addition of enoxy silanes to vinyl diazonium salts gives 2-diazo-1,5-dicarbonyl compounds in yields up to 99%. The diazo functional group can then be taken advantage of in subsequent Rh catalyzed carbonyl ylide 1,3-dipolar cycloaddition or OH insertion reactions to give tetrahydrofuran products that contain up to 6 contiguous stereocenters in yields up to 89%.

Tetrahydrofurans are common subunits in biologically active natural products and medicinal agents. Important classes of these compounds include complex polyketides,[1] polyether ionophore antibiotics,[2] macrodiolides,[3] and lignans.[4–7] Selected examples are shown in Figure 1.

Figure 1. Examples of tetrahydrofuran-containing natural products

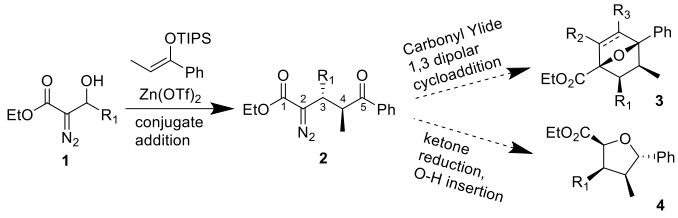


These families of natural products have diverse bioactivities including antibiotic, cytotoxic, anti-HIV, and anticancer properties. The lignans are an especially broad class of bioactive natural products, and many lignans contain mono- or bicyclic tetrahydrofuran cores with multiple stereogenic centers about the ring. Methodologies which allow for the rapid construction of these types of scaffolds are especially useful, and 1,3-dipolar cycloaddition reactions hold special advantage in this regard. Since the seminal work by Büchner in 1893,[8] and thorough studies by Huisgen in the 1960s,[9–11] 1,3-dipolar cycloaddition reactions have garnered significant attention from the organic synthesis community and a variety of different synthetically useful 1,3-dipoles have since been reported, including organic azides, azomethine ylides, and carbonyl ylides.[12] Because they are atom economical and construct complex heterocycles in a single step,[13] these cycloadditions have been used in many total syntheses.[14–17] Padwa and coworkers have done extensive research on the catalytic generation of carbonyl ylides from carbonyl-tethered diazo compounds and have studied their use in dipolar cycloaddition reactions to give tetrahydrofuran scaffolds. [18–28] Rhodium complexes are typically used as catalysts in these transformations, giving ylides by intramolecular capture of a pendant carbonyl onto a rhodium metallocarbene intermediate that is generated by the reaction of a diazo compound with the rhodium catalyst. Rhodium metallocarbenes are also known to participate in O-H insertion reactions,[29] providing another route to tetrahydrofuran products.

We recently discovered a Lewis acid-catalyzed conjugate addition reaction of enoxysilanes to vinyl diazonium salts, which gives 2-diazo-1,5-dicarbonyl products diastereoselectively and in high yield (Scheme 1).[30] This reaction proved to be general, and using 10 mol% of $Zn(OTf)_2$ as a Lewis acid catalyst we were able to produce a broad scope of diversely functionalized 2-diazo-1,5-dicarbonyls including those containing common protecting groups. Because these types of diazo dicarbonyl compounds are progenitors to carbonyl ylides, we reasoned that a reaction sequence involving this conjugate addition reaction followed by a Rh(II)-catalyzed 1,3-dipolar cycloaddition would enable

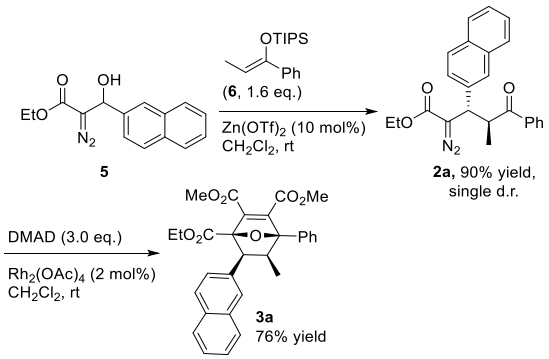
facile and rapid construction of structurally complex tetrahydrofurans with up to 6 stereogenic centers (Scheme 1). This sequence would begin with simple starting materials and would result in a rapid increase in structural complexity.

Scheme 1. Conjugate addition reaction and proposed use of diazo products as THF precursors



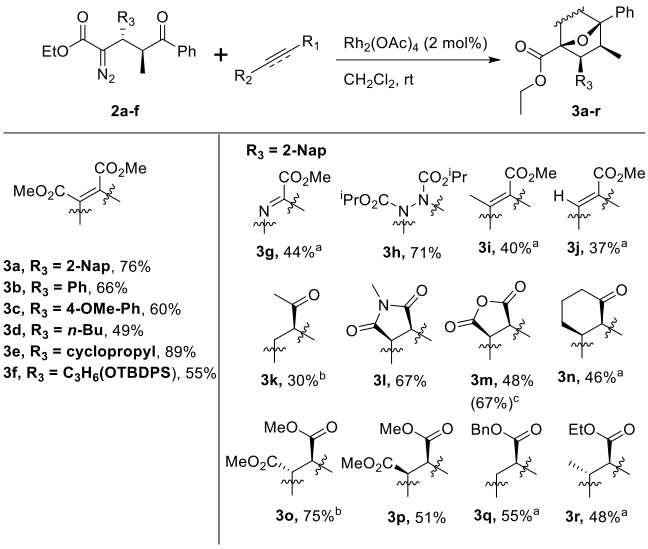
We began our studies on diazo dicarbonyl **2a**, which is readily prepared on gram scale as a single diastereomer from **5** and **6** in 90% yield (Scheme 2). Exposing **2a** to 2 mol% of $Rh_2(OAc)_4$ in the presence of dimethyl acetylenedicarboxylate (DMAD) at room temperature gave bicyclic tetrahydrofuran **3a** in 76% yield as a single diastereomer (Scheme 2). An interesting feature of this cycloaddition is that the carbonyl adjacent to the diazo group is exocyclic in the product, which is relatively uncommon in these types of reactions.

Scheme 2. Preparation of 2a and 3a



We selected some diastereomerically pure conjugate addition products bearing different substituents adjacent to the diazo moiety and exposed them to the same reaction conditions used to synthesize 3a (Table 1, left panel). The bicyclic tetrahydrofuran products 3b-3f were formed in good yield as single diastereomers. When R_3 was phenyl (3b) or 4-methoxyphenyl (3c) the yield was slightly diminished, presumably due to the ability of these substrates to undergo undesired side reactions including hydride migration and the reactions shown in Scheme 3. The yield was lowered when R_3 was a primary alkyl group (3d and 3f), although it is not clear why because we did not observe major side-products in these reactions, and the yield of the dipolar cycloaddition increased to 89% when R_3 was a cyclopropyl ring (3e). Presumably, the bulk of the cyclopropane compared to the *n*-butyl promoted ring formation.

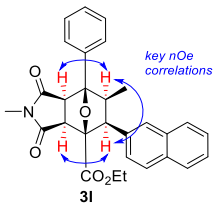
Table 1. Scope of 1,3-dipolar cycloaddition.



[a]Single regioisomer observed. [b]Isolated as a 4:1 mixture of diastereomers. [c]Determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

We next exposed **2a** to a variety of dipolarophiles under $Rh_2(OAc)_4$ catalysis (Table 1, right panel). Doubly activated dipolarophiles such as N-methylmaleimide, diisopropyl azodicarboxylate, and dimethyl fumarate (entries **3l**, **3h**, and **3o**) gave higher yields than singly activated dipolarophiles such as methyl vinyl ketone, cyclohex-2-en-1-one, and methyl propiolate (entries **3k**, **3n**, and **3j**). The reaction of **2a** with maleic anhydride gave tetrahydrofuran **3m** in 67% yield as determined by ^1H NMR, although the isolated yield was lower (48% isolated) due to the instability of the anhydride moiety towards chromatography. Electron rich or neutral dipolarophiles such as 3,4-dihydropyran and 4-octyne failed to react, which suggests a normal electron demand cycloaddition. In almost all cases, the tetrahydrofurans were formed as single diastereomers and regioisomers as confirmed by NOESY NMR analysis (see Supporting Information). This is noteworthy because in most cases the dipolar cycloaddition could in principle produce four or more isomers. NOESY NMR analysis of tricyclic product **3l** revealed the stereochemical configuration as shown in Figure 2. From these data we concluded that this dipolar cycloaddition proceeds with exclusively *exo* selectivity. However, the *endo* product was observed as a minor diastereomer in the case of **3k**.

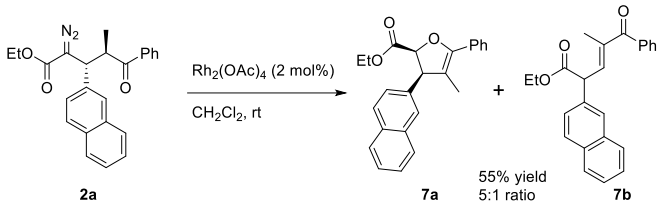
Figure 2. Relative stereochemistry of 3l as determined by nOe correlation.



The remaining mass balance of these reaction was determined to be a mixture of the dihydrofuran **7a** and the aryl migration product **7b**. Compound **7a** is formed from the carbonyl ylide intermediate by a proton transfer event, while **7b** comes from the carbene by 1,2-migration of the

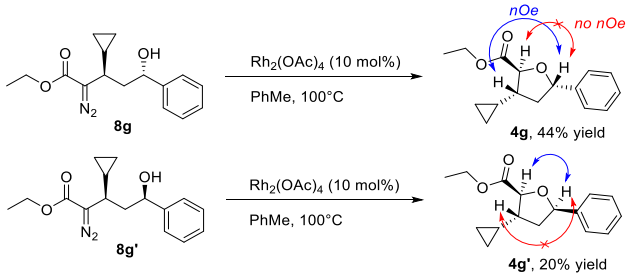
naphthyl substituent followed by alkene isomerization.[31,32] Indeed, when **2a** was subjected to $Rh_2(OAc)_4$ in the absences of a dipolarophile, a 5:1 mixture of **7a** and **7b** was isolated in 55% yield (Scheme 3). In the reactions shown in Table 1, the amount of **7a** and **7b** seemed to increase as the reactivity of the dipolarophile decreased, suggesting that as the rate of dipolar cycloaddition decreases, these alternative pathways become more prominent. Since furans such as **7a** could be synthetically useful targets, we attempted to optimize their formation. Unfortunately, these attempts were not productive and consistently returned mixtures of the dihydrofuran and the rearranged product (**7b**) in mediocre yields.

Scheme 3. Formation of side-products 7a and 7b.



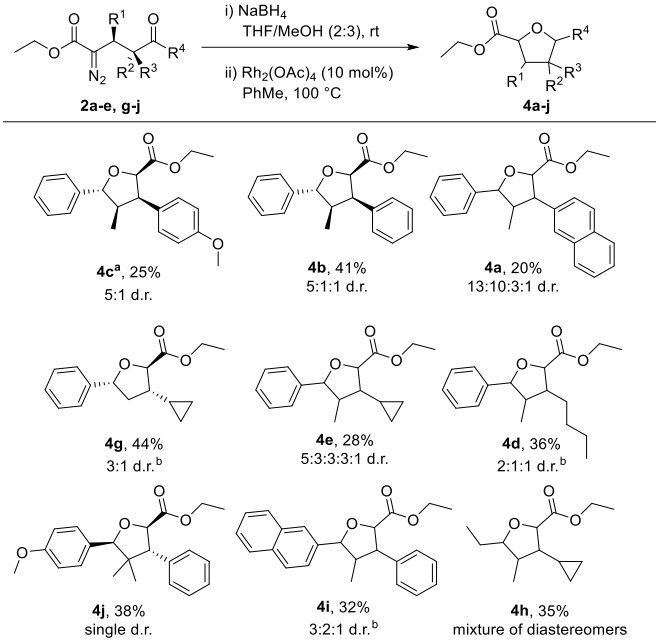
As an alternative route to monocyclic furans, we considered the possibility of taking advantage of the conjugate addition products in an O-H insertion reaction. To that end, reduction of the C5 ketone could be accomplished easily and in high yield using $NaBH_4$ in a THF:MeOH solvent mixture to give diazo alcohol products such as **8g** (Scheme 4). Although the conjugate addition step usually gives good diastereoselectivity at the C3 and C4 positions (see **2**, Scheme 1 for position labels), reduction of the C5 ketone typically gave a mixture of alcohol diastereomers that were difficult to separate. We were able to separate diastereomeric alcohols **8g** and **8g'** and conduct the O-H insertion on them separately (Scheme 4). Although Rh-catalyzed OH insertion reactions are well-described on simpler systems, the reaction proved to be capricious on these substrates and gave tetrahydrofurans **4g** and **4g'** in 44% and 20% yield respectively. Subjecting the diazo alcohols to 10 mol% $Rh_2(OAc)_4$ in toluene at 100 °C gave the best yields with reaction times of less than one hour. $Rh_2(TFA)_4$ and $Rh_2(Oct)_4$ were also tested as catalysts but offered no improvement over $Rh_2(OAc)_4$ (see supporting information for details). The large difference in yield of these diastereomeric furanes indicates that the efficiency of the O-H insertion depends on the stereochemistry of the alcohol starting material.

Scheme 4. Dependence of C5 Stereochemistry on O-H Insertion



While the $NaBH_4$ mediated carbonyl reduction gave good yields of a variety of diazo alcohols, these reductions were not stereoselective and in many cases the resulting diastereomeric alcohols were inseparable. Carrying these mixtures through the OH insertion led to complex mixtures of diastereomeric tetrahydrofuranes (Table 2). In some cases, it was possible to identify the major diastereomer (e.g. **4b**, **4c**, **4g**, **4j**), but in other cases, the mixtures were too complex to be of practical use. A stereoselective carbonyl reduction would help to simplify these mixtures.

Table 2. Scope of Reduction/O-H Insertion Sequence.



[a]Relative stereochemistry of **4c** confirmed by x-ray crystallography. [b]Additional diastereomers were detected in trace amounts.

In summary, we have developed a pair of short reaction sequences which allow for the rapid construction of stereochemically complex tetrahydrofuran scaffolds containing up to 6 stereocenters. The conjugate addition of enoxysilanes to vinyl diazonium salts provides 2-diazo-1,5-dicarbonyls in a highly diastereoselective fashion, which can then easily be transformed into either bridged bicylic or monocylic tetrahydrofuran derivatives under $Rh_2(OAc)_4$ catalysis. We consider the overall divergent nature of these reactions advantageous, because it allows for the synthesis of two complementary series of tetrahydrofuran derivatives from common starting materials.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. / ‡These authors contributed equally. (match statement to author names with a symbol)

Notes

Any additional relevant notes should be placed here.

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