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Tetrahydrofurans *Very Important Paper*

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Stereoselective Synthesis of Highly Substituted Tetrahydrofurans through Diverted Carbene O–H Insertion Reaction**

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In memory of Adam David Przeslak

Abstract: *Copper- or rhodium-catalyzed reactions of diazocarbonyl compounds with β-hydroxyketones give highly substituted tetrahydrofurans with excellent diastereoselectivity. Under mild conditions, the single-step process starts as a carbene O–H insertion reaction, but is diverted by an intramolecular aldol reaction.*

The tetrahydrofuran ring is a commonly found motif in naturally occurring bioactive compounds, and occurs in structural classes such as lignans,[1] acetogenins,[2] ionophores,[3] and macrolides.[4] Examples include (+)-fragransin A2[5] and amphidinolide F[6] (Figure 1). As a consequence, a number of strategies have been developed for the stereoselective synthesis of tetrahydrofurans.[7–9] However, despite advances in synthetic methodology, highly substituted tetrahydrofurans remain difficult to access, and new approaches are needed. We now describe a new route to highly substituted tetrahydrofurans that proceeds with excellent diastereoselectivity under mild conditions in a single step (Scheme 1) by a process initiated by metallocarbene O–H insertion, but diverted by intramolecular aldol reaction.

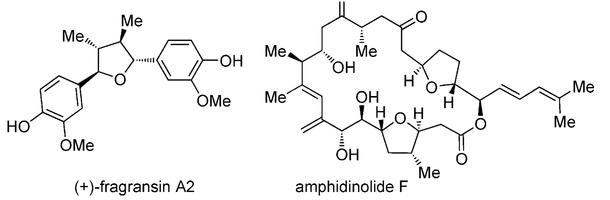
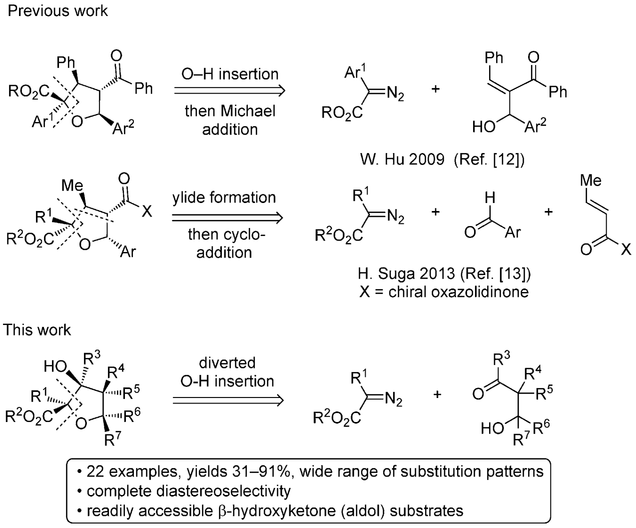


Figure 1. Some naturally occurring tetrahydrofurans.

In continuation of our longstanding interest in O–H insertion reactions of metallocarbenes,[10,11] we now report that β-hydroxyketones and metallocarbenes derived from diazocarbonyl compounds can lead directly to substituted tetrahydrofurans by a process that we term "diverted carbene O–H insertion". Recently, related methods based on metallocarbene O–H insertion/Michael addition,[12] and on carbonyl ylide cycloadditions,[13] have also been developed to prepare tetrahydrofurans (Scheme 1).



Scheme 1. Synthetic approaches toward tetrahydrofurans involving metallocarbenes.

Our initial investigation focused on the reaction of ethyl phenyl diazoacetate (**1**) with 4-hydroxybutanone (**2**) under the conditions of classical transition-metal-catalyzed O–H insertion reactions. Although the use of copper(I) iodide or copper(II) acetate as catalyst resulted in very slow reactions, copper(II) trifluoroacetate led to a mixture of the O–H insertion product **3** and the cyclized tetrahydrofuran **4**, for which O–H insertion was diverted by an intramolecular aldol reaction, in moderate yield. Several reaction parameters, such as temperature, catalyst loading, addition of Lewis or Brønsted acid, were varied (Table S1, Supporting Information), but the key advance was the use of an increased stoichiometric ratio of the diazo compound. This was further improved by switching to the copper(I) triflate/toluene complex as the catalyst, resulting in the desired isolated tetrahydrofuran **4** in 82 % yield as a single diastereoisomer, with the yield of α-alkoxyester **3** below 10 %. The rhodium octanoate dimer was also a competent catalyst (Scheme 2), although in this case the products were obtained in a higher ratio of **3**:**4**. Interestingly, the addition of triethylamine to this system led to the isolation of O–H insertion product **3** exclusively. In this tetrahydrofuran synthesis, two contiguous stereocenters are created in a highly stereoselective manner, with the hydroxy group and the carbonyl moiety in a *cis* configuration as shown by ^{1}H NOESY NMR spectroscopy.

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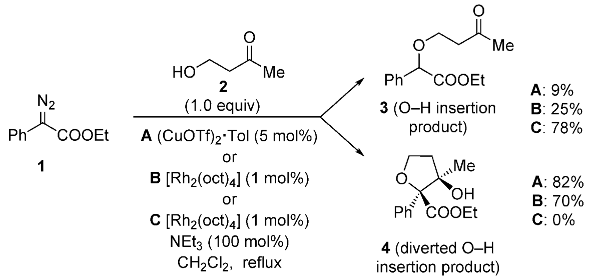
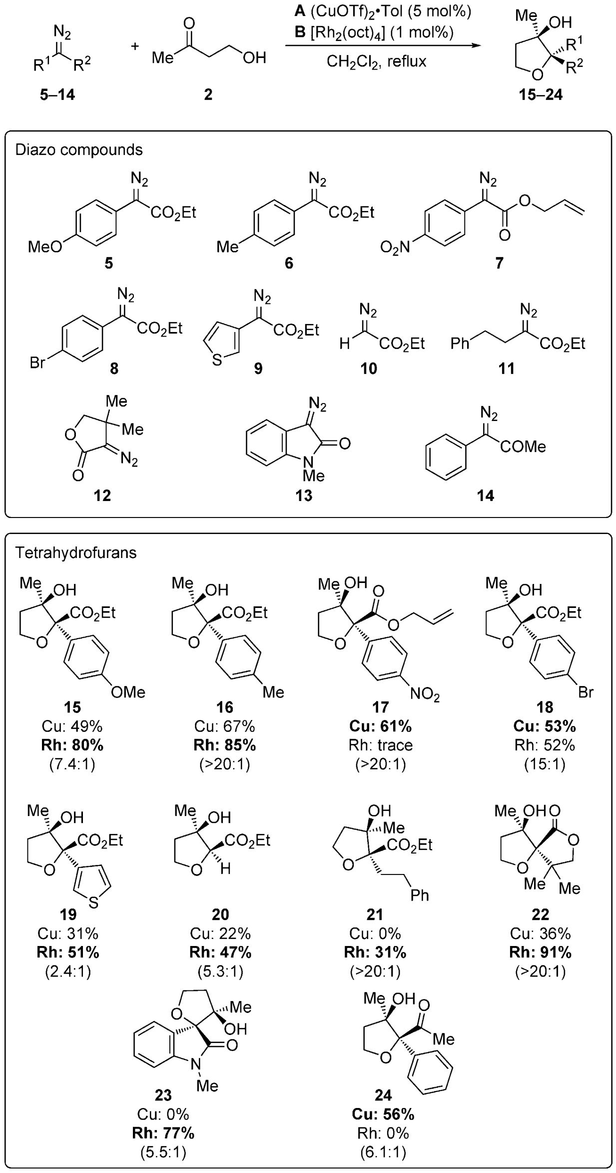


Scheme 2. Synthesis of 3-hydroxytetrahydrofuran **4** by the copper- or rhodium-catalyzed reaction of ethyl phenyl diazoacetate (**1**) with 4-hydroxybutan-2-one (**2**).

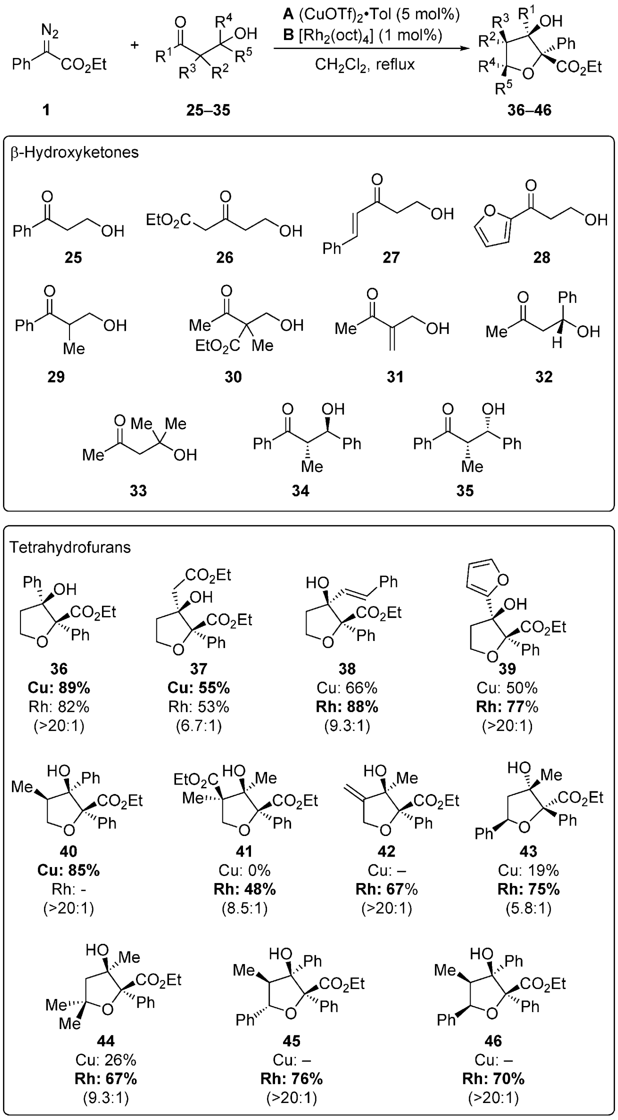
Having found the optimal conditions for tetrahydrofuran formation, we set out to determine the scope of the reaction. A wide range of highly substituted tetrahydrofurans was accessible in modest to excellent yield, accompanied in some cases by small amounts of the corresponding O–H insertion product (Schemes 3 and 4). Electron rich 4-methoxyphenyl diazoacetate **5** gave tetrahydrofuran **15** in only 49% yield with copper(I) triflate as the catalyst, while the same reaction using the rhodium octanoate dimer as the catalyst gave **15** in an improved yield of 80% (Scheme 3). Similarly, the reaction of 4-methylphenyl diazoacetate **6** proceeded better under rhodium catalysis than under copper catalysis. The opposite trend was observed with nitro-substituted compound **7**, which gave isolated tetrahydrofuran **17** in 61% yield with copper(I) catalyst, but only in trace quantities when the rhodium catalyst was used. It is noteworthy that no product resulting from intramolecular cyclopropanation was observed. The results obtained with diazo compounds **5–8** suggest that rhodium(II) and copper(I) are complementary catalysts for the diverted O–H insertion reaction. On the other hand, 4-bromophenyl-substituted diazo compound **8** gave similar results under both catalytic systems, while thienyl diazo compound **9** gave tetrahydrofuran **19** in modest yield. Diazo compounds that lack the aryl group also participated: for example, commercially available ethyl diazoacetate **10** gave tetrahydrofuran **20** under rhodium catalysis (along with carbene dimerization products). Diazo compound **11**, which possesses a C–H bond in α position to the diazo group, gave tetrahydrofuran **21** in moderate yield as a result of a competing 1,2-H shift.[14] When no α-C–H bond was present, as in diazo compound **12**, spiro-tetrahydrofuran **22** was obtained in an excellent yield (91%). Additionally, cyclic diazo compound **13** gave spiro compound **23** in good yield (77%), but only under rhodium catalysis. Finally, the complementary aspect of rhodium(II) and copper(I) catalysis was further illustrated by the reaction of diazoketone **14**, which gave predominantly the O–H insertion product under rhodium(II) catalysis, while the use of copper(I) triflate led to the isolation of tetrahydrofuran **24** in 56% yield. In the majority of cases, any traces of an O–H insertion product were readily removed by chromatography. The use of dimethyl diazomalonate under rhodium catalysis led to the isolation of the corresponding O–H insertion product exclusively, while diethyl α-phenyl diazophosphonate did not give any tetrahydrofuran product under conditions **A** or **B**.



Scheme 3. Synthesis of 3-hydroxytetrahydrofurans by rhodium- and copper-catalyzed diverted O–H insertion reaction. Ratios of tetrahydrofuran to O–H insertion products (for higher-yielding reactions) as determined by NMR analysis of the initial products are given in parentheses.

To extend the scope of the process, we surveyed the reaction of ethyl phenyl diazoacetate (**1**) with various β-hydroxyketones under both sets of catalytic conditions to give a diverse set of highly substituted tetrahydrofurans (Scheme 4). β-Hydroxyketone **25** behaved similarly to its methyl analogue **2** under copper(I) or rhodium(II) catalysis. Cyclization was also successful with hydroxyketoester **26**, and the tetrahydrofuran **37** was obtained in 55% yield under copper(I) catalysis and in a similar yield of 53% with rhodium(II) catalysis. Cyclization also occurred with cinnamyl hydroxyethyl ketone (**27**) and furylketone **28**. In both cases, the rhodium(II) catalyst was superior to the copper(I) catalyst.

Aldol **29**, which possesses an α-methyl substituent, underwent the reaction to give the *cis*/*cis* tetrahydrofuran **40** in



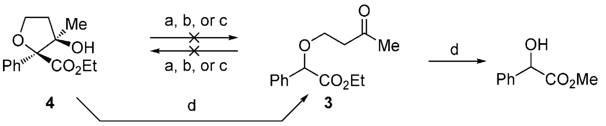
Scheme 4. Synthesis of polysubstituted tetrahydrofurans by rhodium- and copper-catalyzed diverted O–H insertion reaction. Ratios of tetrahydrofuran to O–H insertion products (for higher-yielding reactions) as determined by NMR analysis of initial products are given in parentheses.

85% yield, thus showing that the stereoselectivity of the reaction could be extended to the substituent at position 4 of the cyclic ether ring. α-Disubstituted aldol **30** did not give the desired tetrahydrofuran **41** under copper(I) catalysis, while single diastereoisomer **41** was obtained in 48% yield under rhodium catalysis. When allylic alcohol **31** was subjected to rhodium catalysis, the desired tetrahydrofuran **42** with an exocyclic double bond was obtained in 67% yield.

Secondary and tertiary alcohols also underwent the diverted O–H insertion/cyclization reaction, and in these cases, the rhodium catalyst was superior. Alcohol **32** gave a single diastereoisomer of tetrahydrofuran **43** in good yield, showing that the stereocontrol could be extended to the position 5 of the tetrahydrofuran product. When enantioenriched (*R*)-aldol **32** (77% *ee*) was used, no erosion of stereochemistry was observed, and the product tetrahydrofuran **43** was obtained with a similar enantiomeric excess of 84%, which could be readily improved to enantiopurity by crystallization.

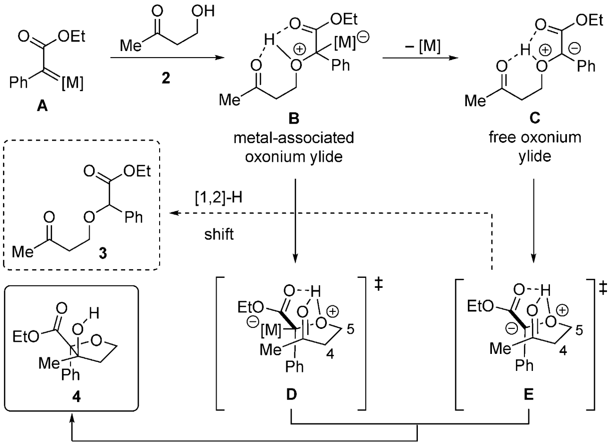
The reaction sequence was relatively insensitive to steric bulk around the alcohol functionality, for example, tertiary alcohol **33** gave tetrahydrofuran **44** in 67% yield. Both α,β-disubstituted β-hydroxyketone diastereoisomers **34** and **35** were subjected to rhodium catalysis with diazo compound **1** to give single diastereoisomers **45** and **46**, respectively. The latter results show that, when stereocontrol over positions 4 and 5 of the final tetrahydrofuran product can be achieved, the substituent at C4 has a greater effect on the stereocontrol than that at C5. Additionally, the structures of cyclic compounds **38** and **43** were confirmed by X-ray crystallography (Figures S1 and S2, Supporting Information).

The examples shown in Scheme 3 and 4 clearly establish the wide scope of this tetrahydrofuran synthesis. However, in order to rationalize the formation of tetrahydrofurans such as **4**, as opposed to O–H insertion (e.g. **3**) products, we performed a series of control experiments. First, in order to establish whether the tetrahydrofuran **4** was formed through an initial O–H insertion reaction and subsequent intramolecular aldol cyclization, the ketoester O–H insertion product **3** was exposed to the reaction conditions (i.e. rhodium octanoate or copper(I) triflate/toluene complex in CH_2Cl_2 at reflux; Scheme 5). Under these conditions, no conversion to the tetrahydrofuran **4** was observed, thus showing that the metal catalysts were not capable of mediating the intramolecular aldol reaction. The reaction was repeated, but this time in the presence of an excess of triethylamine to encourage the formation of a reactive aldol intermediate (enol/enolate), but once again, no tetrahydrofuran **4** was formed. Finally, we treated the ketoester **3** with a stronger base (NaOMe) in an attempt to force the aldol process, but under these conditions only methyl mandelate (44%) was formed as a result of a retro-Michael elimination of methyl vinyl ketone and transesterification, and no trace of the tetrahydrofuran **4** was observed. In order to assess the reversibility of the formation of the five-membered ring, we exposed tetrahydrofuran **4** to the original reaction conditions (Scheme 5). Tetrahydrofuran **4** was stable in the presence of the metal catalysts, and no retro-aldol product **3** was observed. Even with the addition of an excess of triethylamine, the tetrahydrofuran **4** was stable, and a stronger base (NaOMe) was required to cause decomposition of **4**. Under these conditions, methyl mandelate (73%) was formed, presumably through a retro-aldol reaction to give **3**, elimination of methyl vinyl ketone, and transesterification.



Scheme 5. Control experiments. Reagents and conditions: a) $[Rh_2(oct)_4]$ (1 mol%), CH_2Cl_2 at reflux; b) $[Rh_2(oct)_4]$ (1 mol%), NEt_3 excess, CH_2Cl_2 at reflux; c) $(CuOTf)_2$·Tol (5 mol%), CH_2Cl_2 at reflux; d) NaOMe, MeOH, 0°C→RT.

Having established that the O–H insertion product **3** is not on the reaction pathway to tetrahydrofuran **4**, we propose that the tetrahydrofurans result from a diversion from the O–H insertion reaction through an intramolecular aldol cyclization. This proposal is in line with the finding of Hu and others, who found that in a number of cases, transient oxonium and ammonium ylide intermediates in X–H insertion (X = O, N) pathways can be trapped by electrophiles.[15–18] The widely accepted mechanism for metallocarbene O–H insertion is a stepwise process initiated by the attack of an alcohol (e.g. **2**) onto the electrophilic metallocarbene **A**, which is generated by metal-catalyzed decomposition of the corresponding diazo compound, to give a metal-associated oxonium ylide **B** (Scheme 6).[19–24] The metal-associated oxonium ylide **B** can dissociate to give the corresponding free ylide **C**, which can undergo a 1,2-H shift to give the O–H insertion product **3**. However, we propose that both ylide intermediates **B** and **C** are susceptible to diversion by intramolecular reaction with the ketone via transition states **D** or **E** to form the observed tetrahydrofuran product **4**. Hydrogen bonding involving both ester and ketone carbonyl groups ensures a well-ordered transition state and helps to explain the high levels of diastereocontrol we observed.



Scheme 6. Proposed mechanism to rationalize the stereoselective formation of tetrahydrofurans through diverted O–H insertion reaction. [M] = $\mathrm{Rh_2L_4}$ or CuL_n.

When chiral rhodium catalysts ($[\mathrm{Rh_2}(S\text{-DOSP})_4]$,[25] $[\mathrm{Rh_2}(S\text{-MEPY})_4]$,[26] $[\mathrm{Rh_2}(S\text{-TFPTTL})_4]$,[27] and $[\mathrm{Rh_2}(S\text{-PTAD})_4]$[28]) were used in reaction of diazo compound **1** with hydroxyketone **25**, the tetrahydrofuran **36** was obtained in good yields but with no chiral induction (*ee* < 7%), whereas the use of copper(I) triflate in conjunction with chiral bisoxazoline ligand, 2,2-bis((4*S*)-(−)-4-isopropyloxazoline)-propane gave the product **36** (72%) in a low enantiomeric excess of 31% (see the Supporting Information). This result suggests that the rhodium-catalyzed process favors a metal-free intermediate, while the copper catalyst remains, at least to some extent, bound to the intermediate in accord with related work on metallocarbene asymmetric O–H insertion processes that are highly metal dependent, with copper being superior to rhodium.[22] Although further work is required to establish the details of the pathway, transition states **D** or **E** predict the observed stereochemical outcome, and by placing substituents at C4 or C5 in pseudoequatorial positions, also explains the diastereocontrol shown in the formation of **40** and **43**.

In conclusion, we have developed a strategy for the stereoselective construction of highly substituted tetrahydrofurans by a diverted metallocarbene O–H insertion/intramolecular aldol reaction process using both copper(I) and rhodium(II) catalysis. This convergent and highly selective approach tolerates a wide range of β-hydroxyketones, easily available by aldol reactions,[29] including diastereo- and enantioselective variants, and diazo compounds. The high stereoselectivities observed in the formation of tetrahydrofurans were rationalized by a mechanistic proposal involving an intramolecular aldol reaction.

Keywords: aldol reaction · carbenes · diazo compounds · tetrahydrofurans · transition-metal catalysis

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