Stereoselective synthesis of highly substituted tetrahydrofurans by diverted carbene O–H insertion reaction

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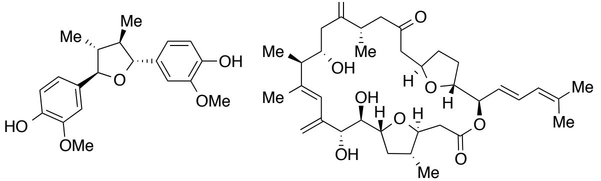
Dedicated to the memory of Adam David Przeslak (13 June 1985 – 18 March 2015)

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

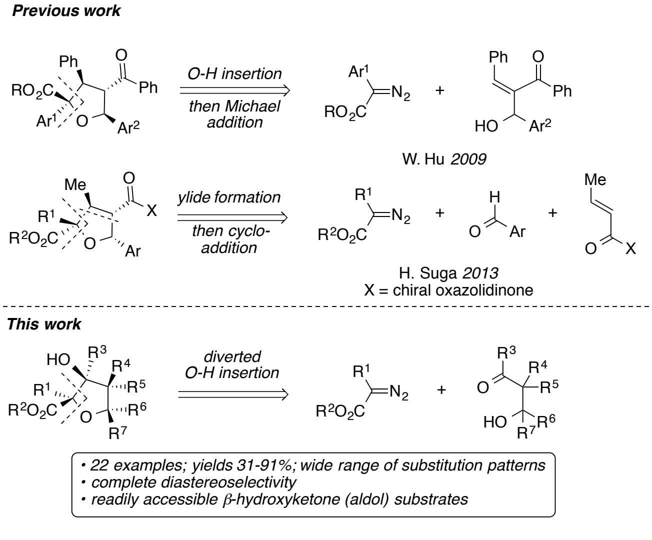
The tetrahydrofuran ring is a commonly found motif in naturally occurring bioactive compounds, and occurs in structural classes such as lignans,[1] acetogenins,[2] ionophores,[3] and macrolides.[4] Examples include (+)-fragransin A2[5] and amphidinolide F[6] (Figure 1). As a consequence, a number of strategies have been employed 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 novel process initiated by metallocarbene O–H insertion but diverted by intramolecular aldol reaction.



(+)-fragransin A2   amphidinolide F

Figure 1. Some naturally occurring tetrahydrofurans

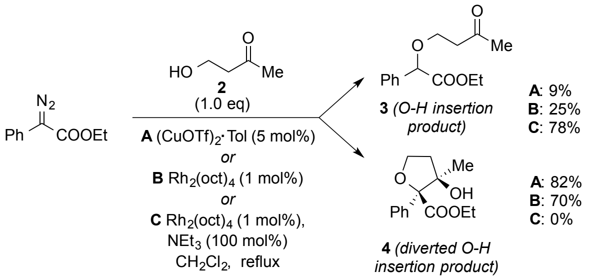
In continuation of our longstanding interest in O–H insertion reactions of metallocarbenes,[10,11] we now report that β-hydroxyketones and metallocarbenes derived from diazocarbonyl compounds can lead directly to substituted tetrahydrofurans by a process that we term *diverted carbene O–H insertion*. 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).



- 22 examples; yields 31-91%; wide range of substitution patterns
- complete diastereoselectivity
- readily accessible β-hydroxyketone (aldol) substrates

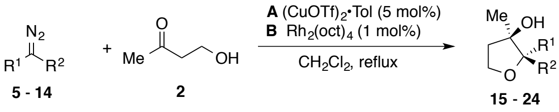
Scheme 1. Metallocarbene approaches towards tetrahydrofurans.

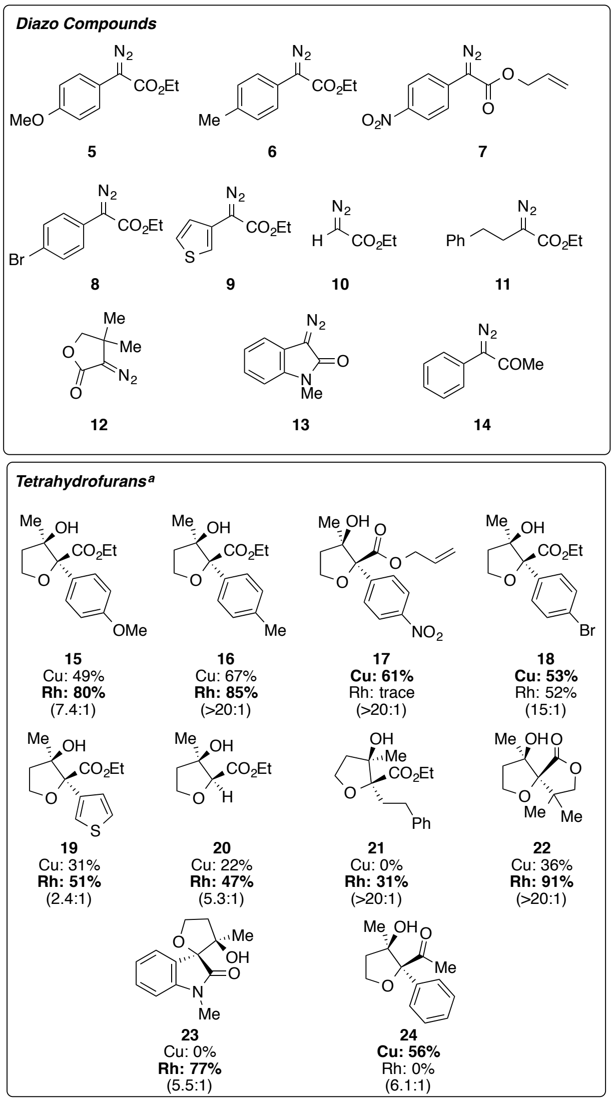
Our initial investigation focused on the reaction of ethyl phenyldiazoacetate **1** with 3-hydroxybutanone **2** under classical transition-metal catalyzed O–H insertion reaction conditions Although, the use of copper(I) iodide or copper(II) acetate as catalyst gave very slow reactions, copper(II) trifluoroacetate gave a mixture of the O–H insertion product **3** and the cyclized tetrahydrofuran **4**, in which O–H insertion has been diverted by intramolecular aldol reaction, in moderate yield. Several variations in the reaction parameters such as temperature, catalyst loading, addition of Lewis or Brønsted acid were carried out (Table S1, Supporting Information), but the key advance was the use of an increased stoichiometric ratio of diazo compound. This was further improved by switching to copper(I) triflate-toluene complex as catalyst that resulted in an isolated yield of 82% of the desired tetrahydrofuran **4** as a single diastereoisomer, with the yield of α-alkoxyester **3** below 10%. Rhodium octanoate dimer was also a competent catalyst (Scheme 2), although in this case a higher **3**:**4** ratio was obtained. 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 hydroxyl group and the carbonyl moiety in a *cis*-configuration as shown by ^{1}H-NOESY NMR spectroscopy.



Scheme 2. Synthesis of 3-hydroxytetrahydrofuran **4** by copper or rhodium catalyzed reaction of ethyl phenyldiazoacetate **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 only 49% yield of tetrahydrofuran **15** with copper(I) triflate as the catalyst, whilst the same reaction using rhodium octanoate dimer as the catalyst gave an improved 80% yield of **15** (Scheme 3). Similarly, the reaction of 4-methylphenyl diazoacetate **6** proceeded better under rhodium catalysis than copper catalysis. The inverse trend was observed with nitro substituted compound **7** which gave a 61% isolated yield of tetrahydrofuran **17** 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 catalysis for the diverted O–H insertion reaction. 4-Bromophenyl substituted diazo compound **8**, on the other hand, gave similar results under both catalytic systems, while thienyl diazo compound **9** gave tetrahydrofuran **19** in modest yield. Diazo compounds lacking the aryl group also participate: 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 α-to the diazo group gave tetrahydrofuran **21** in moderate yield due to competing 1,2-hydrogen shift.[14] When no α-C–H bond is present, as in diazo compound **12**, an excellent yield (91%) of spiro-tetrahydrofuran **22** was obtained. 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 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 sets of conditions **A** or **B**.





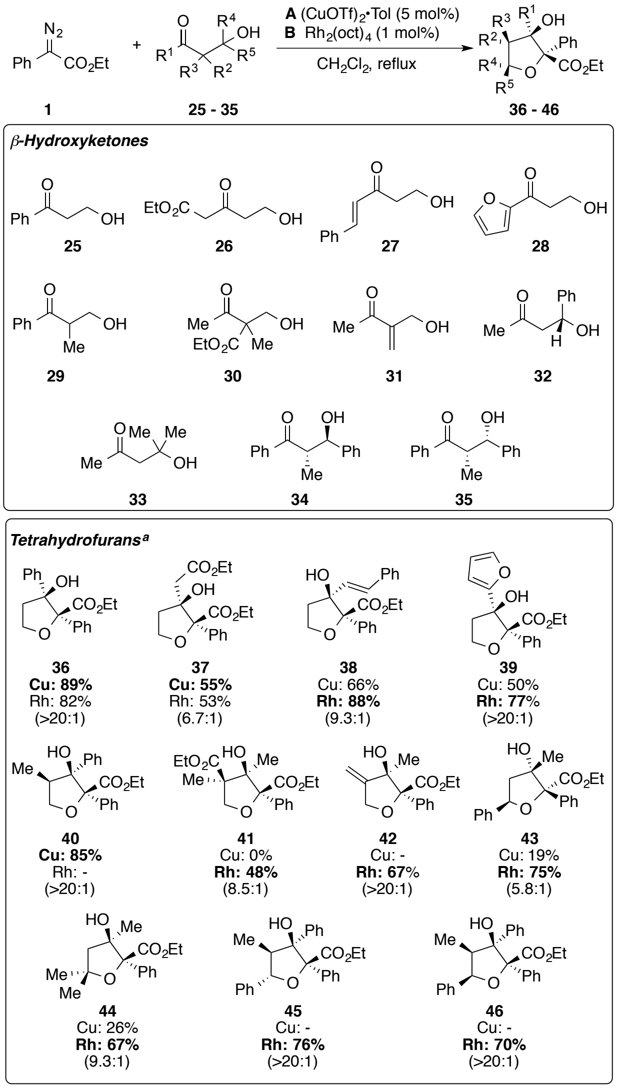
Scheme 3. Synthesis of 3-hydroxytetrahydrofurans by rhodium and copper catalyzed diverted O–H insertion reaction. [a]Ratio of tetrahydrofuran to O–H insertion product (for higher yielding reaction) as determined by NMR analysis of initial product shown in parentheses.

To extend the process, we surveyed the reaction of ethyl phenyldiazoacetate **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 53% yield 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** possessing an α-methyl-substituent underwent the reaction to give the *cis-cis* tetrahydrofuran **40** in 85% yield, thus showing that the stereoselectivity of the reaction could be extended to the substitutent on the 4-position of the cyclic ether ring. α-Disubstituted aldol **30** did not give the desired tetrahydrofuran **41** under copper(I) catalysis, whilst a 48% yield of a single diastereoisomer **41** was obtained under rhodium catalysis. When allylic alcohol **31** was submitted to rhodium catalysis, 67% yield of the desired tetrahydrofuran **42** with an exocyclic double bond was obtained.

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

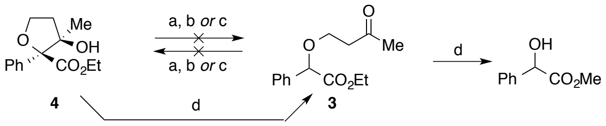
The reaction sequence was found to be relatively insensitive to steric bulk around the alcohol functionality, since tertiary alcohol **33** gave 67% yield of tetrahydrofuran **44**. Both α,β-disubstituted β-hydroxyketone diastereoisomers **34** and **35** were submitted to rhodium catalysis with diazo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



Scheme 4. Synthesis of poly-substituted tetrahydrofurans by rhodium and copper catalyzed diverted O–H insertion reaction. [a]Ratio of tetrahydrofuran to O–H insertion product (for higher yielding reaction) as determined by NMR analysis of initial product shown in parentheses.

The examples shown in Schemes 3 and 4 clearly establish the wide scope of this new 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. Firstly, to establish whether the tetrahydrofuran **4** was formed *via* 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 into 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 excess of triethylamine to encourage 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 due to retro-Michael elimination of methyl vinyl ketone and transesterification, and none of the tetrahydrofuran **4** was observed. In order to assess the reversibility of 5-membered ring formation, we exposed tetrahydrofuran **4** to the original reaction conditions (Scheme 5). Tetrahydrofuran **4** was found to be stable in the presence of the metal catalysts, and no retro-aldol product **3** was observed. Even with the addition of excess 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 *via* retro-aldol to give **3**, elimination of methyl vinyl ketone and transesterification.

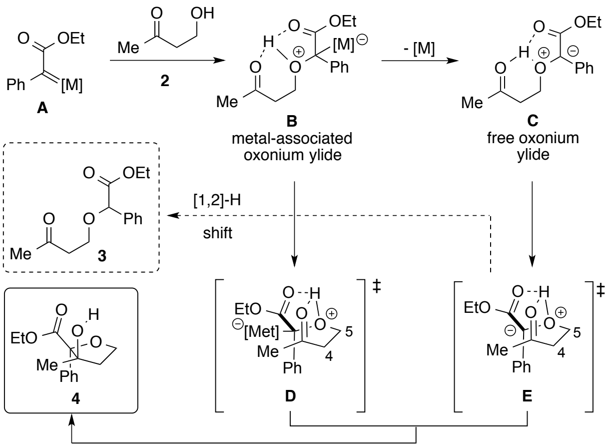


Scheme 5. Control experiments. *Reagents and conditions*: a, $Rh_2(oct)_4$ (1 mol%), CH_2Cl_2 at reflux; b, $Rh_2(oct)_4$ (1 mol%), NEt_3 excess, CH_2Cl_2 at reflux; c, $(CuOTf)_2$•Tol (5 mol%), CH_2Cl_2 at reflux; d, NaOMe, MeOH, 0 °C to rt.

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 *via* 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 attack of an alcohol (*e.g.* **2**) onto the electrophilic metallocarbene **A**, 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 by way of 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 diasterocontrol observed.

When chiral rhodium catalysts (Rh_2(*S*-DOSP)$_4$,[25] Rh_2(*S*-MEPY)$_4$,[26] Rh_2(*S*-TFPTTL)$_4$,[27] and Rh_2(*S*-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% (Supporting Information). This 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 **B** or **C** do predict the observed stereochemical outcome, and by placing C4 or C5 substituents in pseudoequatorial positions, also explains the diastereocontrol shown in the formation of **34** and **40**.

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 enantio-selective variants, and diazo compounds. The high stereoselectivities observed in the formation of tetrahydrofurans are rationalized by a mechanistic proposal involving an intramolecular aldol reaction of an intermediate (*E*)-enol.



Scheme 6. Proposed mechanism to rationalize the stereoselective formation of tetrahydrofurans via diverted O–H insertion reaction. [M] = Rh_2L_4 or CuL_n

Experimental Section

For full details of all experiments, see the Supporting Information.

Acknowledgements

We thank the University of Nottingham for support.

Keywords: oxygen heterocycles • diazo compounds • aldol reaction • transition-metal catalysis • carbenes

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