ChemPubSoc Europe

DOI: 10.1002/chem.201603126

CHEMISTRY
A European Journal
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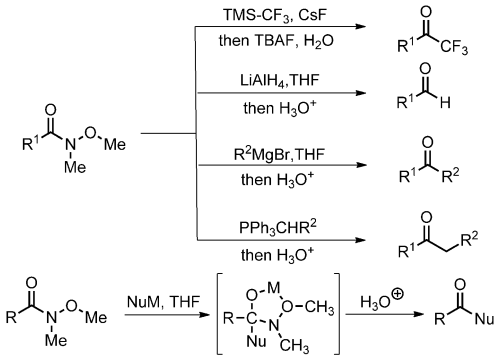
Product Control using Substrate Design: Ruthenium-Catalysed Oxidative C–H Olefinations of Cyclic Weinreb Amides

Riki Das and Manmohan Kapur*[a]

Abstract: A new class of Weinreb amides has been developed as directing groups for the ruthenium-catalysed regioselective oxidative C–H olefination. The new Weinreb amides successfully inhibit the N–O bond reductive cleavage usually associated with the cationic ruthenium system, thereby keeping intact the synthetic utility of Weinreb amides. Mechanistic studies reveal interesting aspects of the directing group capabilities of Weinreb amides when compared to simple amides of similar structures.

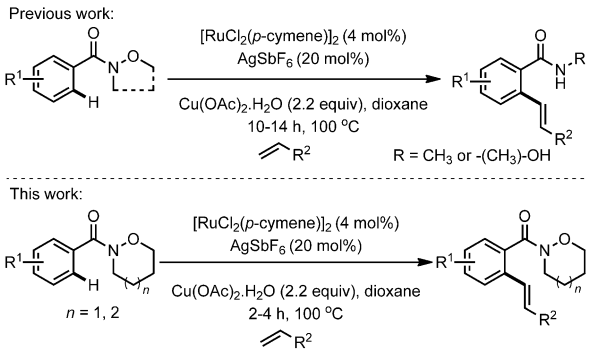
Introduction

Weinreb amides[1] are important building blocks in organic synthesis. Their versatile utilities are well reported in literature.[2] Nucleophilic addition to the Weinreb amides results in a unique and stable five membered cyclic tetrahedral intermediate which prevents the over-addition, leading to a selective transformation (Scheme 1).[3] The Mizoroki–Heck reaction[4] is one of the most remarkable discoveries in the field of C–C bond forming processes. An attractive improvisation of this reaction is the oxidative coupling of unactivated aryl C–H bonds with olefins, termed the Fujiwara–Moritani or the oxidative-Heck reaction.[5] Not limited only to palladium, other transition metals have been successfully incorporated to expand the synthetic utility of this transformation.[6]



Scheme 1. Synthetic utility of Weinreb amides.

Often, various directing groups are employed in this reaction to effect a site-selective C–H activation.[7] Recently, Weinreb amides have emerged as versatile directing groups, owing to their inherent synthetic utility. Further, the use of external oxidant could be avoided by utilising the sensitive N–O bond of the Weinreb amide as an internal oxidant.[8–10] However, the synthetic identity of Weinreb amides is lost if the *N*-alkoxyl group is missing and such a synthetic methodology may not be useful if further utility of the Weinreb amide is desirable after the C–H functionalisation reaction. In this regard, Wang and co-workers have reported a rhodium-catalysed oxidative-Heck of aryl Weinreb amides in which they used activated olefins like acrylates as coupling partners.[8c] Wang[9a] and Huang[9b] both reported palladium-catalysed double functionalisation in the synthesis of isoquinolines. In these reports as well as some other transformations, the sensitive N–O alkoxyl group survived the reaction conditions.[9] In continuation to our work in the area of C–H functionalisation,[11] we disclose herein, a new class of cyclic Weinreb amides which retain their synthetic utility upon ruthenium-catalysed oxidative Heck reaction. In a previously reported work, we had used simple Weinreb amides as substrates in the ruthenium-catalysed oxidative-Heck reaction (Scheme 2).[11f]



Scheme 2. Product control using substrate structure design.

[a] *R. Das, Dr. M. Kapur*
Department of Chemistry
Indian Institute of Science Education and Research Bhopal
Bhopal Bypass Road, Bhauri, Bhopal 462066, MP (India)
E-mail: mk@iiserb.ac.in

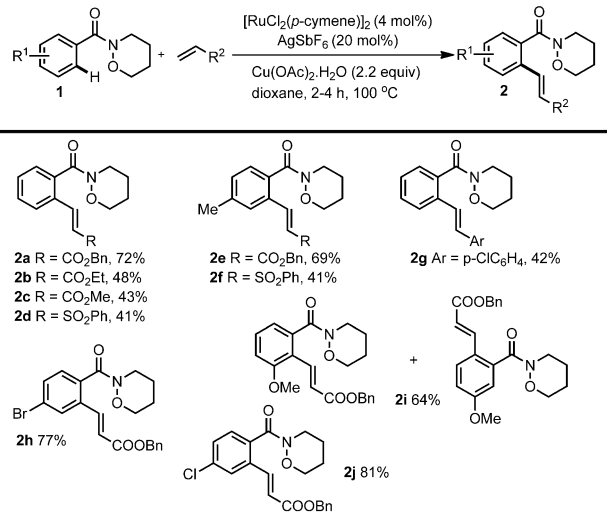
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201603126.

Although we had obtained very good transformation in the form of *ortho*-olefinated products, the Weinreb amide functionality was lost, with the *N*-alkoxyl group being reductively cleaved to result in products that were ordinary amides.

Results and Discussion

Our ultimate aim was to develop a substrate system where the Weinreb amide functionality would be unaffected at the end of the ruthenium-catalysed Fujiwara–Moritani reaction. In our previous work we had used five-membered cyclic Weinreb amides, along with simple ones. In almost all cases, we had obtained the ring-opened products. We postulated that the reason for this was the facile insertion of the metal into the N–O bond at the later stage of the reaction pathway. We therefore envisaged that inhibition of this insertion could lead us to the products, in which the Weinreb amide functionality would be retained at the end of the C–H functionalisation. One way to do this would be to make this insertion product relatively higher in energy and this would need a change in the structure of the substrate. To our delight, under our previously optimised reaction conditions,[11f] when the ring size was increased from five-membered isoxazolidine to higher ring sizes (six-membered oxazinane and seven membered oxazepane), it resulted in a clean conversion to the C–H olefination product without the destruction of the Weinreb amide functionality (Table 1 and Table 2).

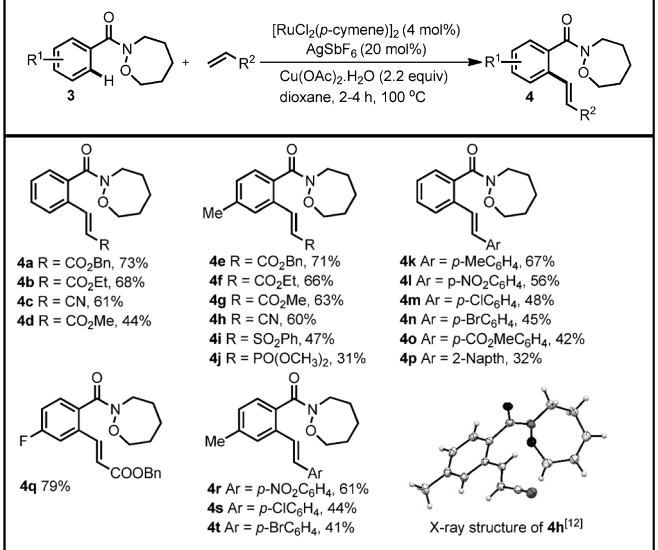
Table 1. Substrate scope for six-membered cyclic Weinreb amides.[a]



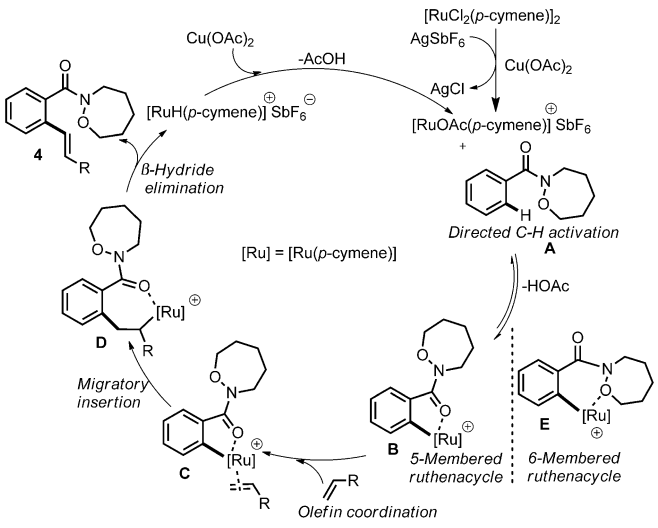
[a] All yields are isolated yields.

The substrate scope was excellent and in most cases good to moderate yield was observed. The regioselectivity was exclusive and unlike the previous case,[11f] no diolefinated product was observed. Electronic effects on both the coupling partners were well tolerated. The reaction worked well with styrenes and other activated olefins. Halogen functionalities on both the substrates were very well tolerated and were unaffected by the reaction conditions. Notably, the reaction did not work with electron-neutral olefins. It was not unexpected though, given the reactivity trend usually observed either for the Heck or the oxidative-Heck reactions. A plausible mechanism for this transformation is depicted in Scheme 3. The first step is usually the generation of the cationic ruthenium complex. Complexation of the metal to the more Lewis-basic amide carbonyl oxygen followed by the acetate-assisted C–H activation leads to the ruthenacycle. Interestingly, two different pathways are possible, one involving a 5-membered ruthenacycle arising out of coordination to the carbonyl oxygen (B in Scheme 3) and another pathway incorporating the 6-membered ruthenacycle arising out of coordination to the ring oxygen (E in Scheme 3).

Table 2. Substrate scope for seven-membered cyclic Weinreb amides.[a]



[a] All yields are isolated yields.



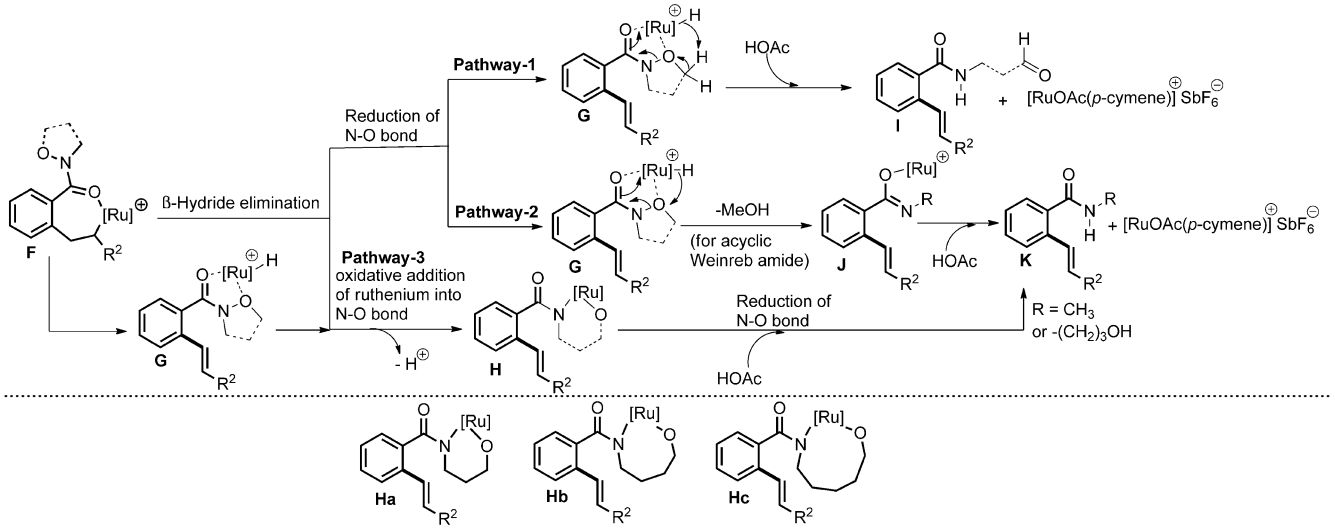
Scheme 3. Plausible mechanism and two different modes of coordination.

The first pathway is expected to dominate, due to the higher relative stability of the 5-membered ruthenacycle. This is followed by the coordination of the olefin, subsequent migratory insertion and then the β-hydride elimination.

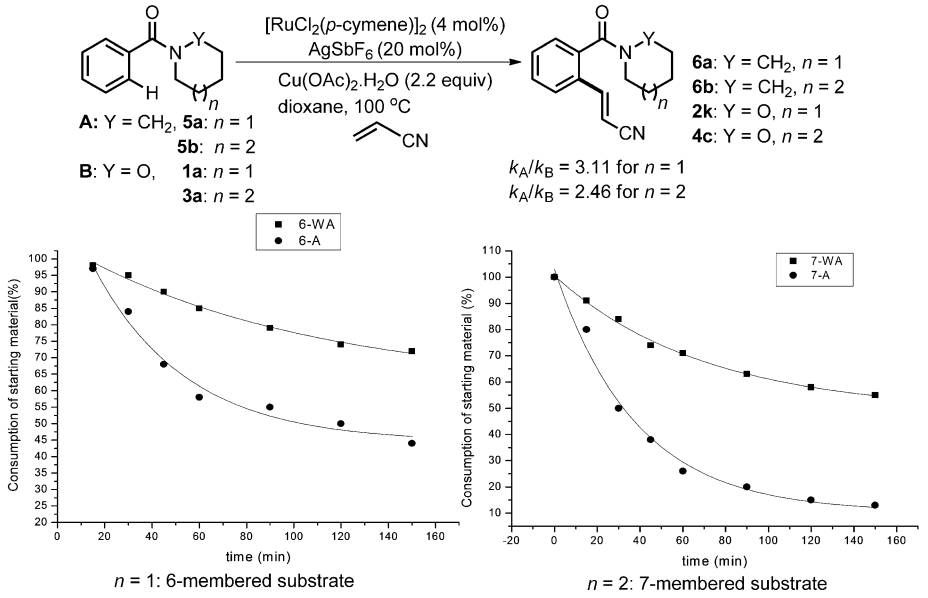
Release of AcOH followed by the oxidation of Ru^0 to Ru^{II} regenerates the active catalyst. Although there could be various postulated pathways for the N–O bond cleavage,[13a,b] we feel that three pathways could be proposed (Scheme 4). In the first pathway,[9b] an aldehyde by-product would be expected. Since we do not observe this product in our reactions, this pathway can be excluded. The second pathway,[9b] involving hydride-transfer, would be unlikely and is expected to be a rather high-energy pathway. The third pathway[13c–f] seems likely and can provide a plausible explanation for the fact that the higher ring-size Weinreb amides resist the N–O bond cleavage. In this mechanism, upon insertion into the N–O bond, the resulting ruthenacycle (**H**, Scheme 4) would be destabilised in higher ring systems and therefore this insertion would be disfavoured for the 6- and 7-membered Weinreb amides.

To check the effect of the ring oxygen on the rate of the reaction, a study of relative rates was conducted with the 6- and 7-membered cyclic amides (**5a**, **5b**). The rate of reaction (initial rates) of the 6- and 7-membered cyclic Weinreb amides (**1a**, **3a**) was found to be lower than the corresponding piperidine and azepane amides (**5a**,**b**, Scheme 5).

It is postulated that the ring-oxygen draws the electron density of the nitrogen towards itself, thus reducing the Lewis-basicity of the carbonyl oxygen. This would probably lead to



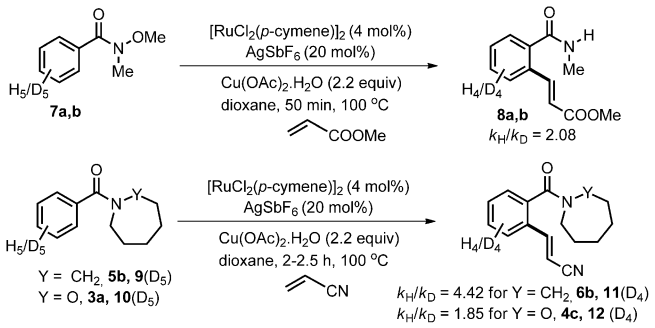
Scheme 4. Plausible pathways for the N–O bond cleavage.



Scheme 5. Study of relative rates of reactions for the cyclic Weinreb amide and corresponding cyclic amides.

a slightly weaker coordination of the carbonyl oxygen to the metal as against that for the substrate with azepane, in turn lowering the rate of the reaction. This also indicates that the carbonyl of the regular amides possess better coordinating ability than those of the Weinreb amides.

Study of the kinetic isotope effect provided a moderate KIE of 1.85 for the oxazepane amide and a value of 4.42 was obtained for the azepane amide (Scheme 6).[14]



Scheme 6. Kinetic isotope effect studies (parallel reactions).

The acyclic Weinreb amide also afforded a moderate value of 2.08 for the KIE. This indicated that the C–H activation step was probably proceeding through a concerted metalation deprotonation (CMD) process.[15] To check whether the metalation step was reversible, we carried out the reaction in the presence of D_2O (Scheme 7). In general, the reaction was retarded to some extent due to the presence of D_2O. When the reactions were carried out in the presence of the coupling partner, low levels of deuterium incorporation were observed in the recovered starting materials. The products were devoid of any deuterium incorporation in them. When the reactions were carried out in the absence of the coupling partner, deuterium incorporation was significant, clearly indicating that the next steps in the catalytic cycle were much faster than the reverse reaction. This also indicated that in both the cases, the metalation step was reversible.

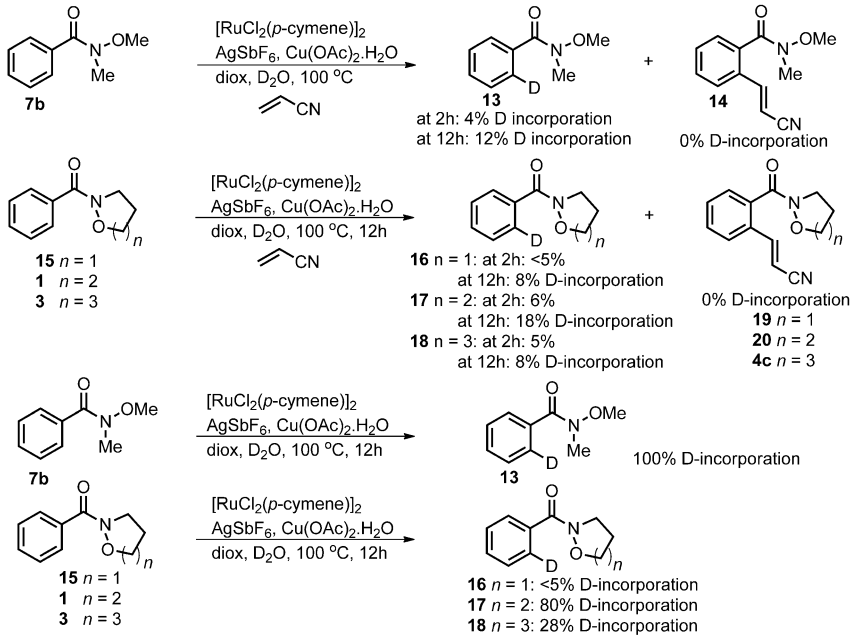
The synthetic utility of the cyclic Weinreb amides was demonstrated by converting the functionalised products to the corresponding aldehydes and ketones with reactions of excess lithium aluminium hydride and Grignard reagents, respectively, with high yields (Scheme 8). This indicated that the functionalised six- and seven-membered cyclic Weinreb amides possess the same synthetic potential as original Weinreb amides.

Conclusions

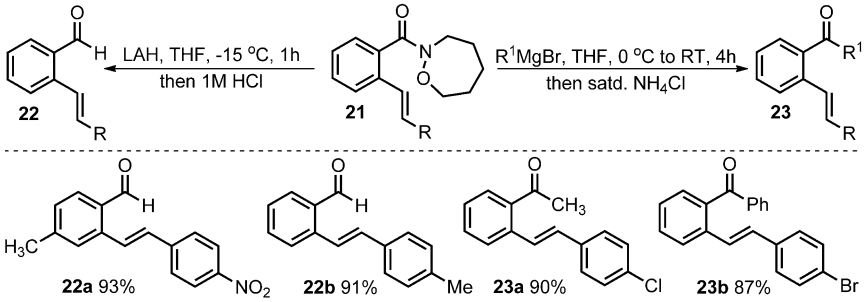
In summary, we have developed a new class of Weinreb amides which are not only excellent directing groups but also inhibit ruthenium-catalysed N–O bond reductive cleavage to provide C–H olefination products, retaining the important Weinreb amide functionality. The transformation is highly site-selective, provides good to moderate yields of monoolefinated products with a broad substrate scope and is expected to have important synthetic utility for organic chemists. The relative-rate studies as well as deuterium-incorporation studies provide insight into the pathway of the reaction and indicate that the ruthenacycle formation is reversible, with the subsequent steps being faster, thereby driving the reaction in the forward direction.

Acknowledgements

Funding from DST-India (SB/S1/OC-10/2014) and CSIR-India (02(205)/14/EMR-II) is gratefully acknowledged. R.D. thanks



Scheme 7. Reactions in the presence of D_2O.



Scheme 8. Retention of the synthetic utility of the Weinreb amides.

UGC-India for a Research Fellowship. We thank CIF, IISERB for the analytical data and Ms. Anusha Upadhyay, IISERB, for the X-ray data. We also thank the Director, IISERB, for funding and infrastructure facilities.

Keywords: C–H activation · C–H functionalization · oxidative-Heck · ruthenium · Weinreb amides

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[12] > CCDC 1043523 (**4h**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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Received: June 30, 2016
Published online on ■■ ■■, 0000

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Organic Chemistry

*R. Das, M. Kapur**

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Product Control using Substrate Design: Ruthenium-Catalysed Oxidative C–H Olefinations of Cyclic Weinreb Amides

In the right direction: A new class of Weinreb amides has been developed as directing group for the ruthenium-catalysed regioselective oxidative C–H olefination (see scheme). The new Weinreb amides successfully inhibit the N–O bond reductive cleavage usually associated with the cationic ruthenium system, thereby keeping intact the synthetic utility of Weinreb amides. Mechanistic studies reveal interesting aspects of the directing group capabilities of Weinreb amides when compared to simple amides of similar structures.