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Ru (II)-Catalyzed C−H Activation: Ketone-Directed Novel 1,4-Addition of *Ortho* C−H Bond to Maleimides

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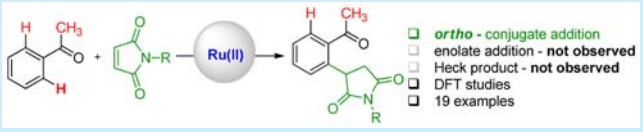
Supporting Information

ABSTRACT: A 1,4-addition with the nucleophilic center generated at the *ortho* carbon atom of an aromatic ketone in the presence of the highly reactive α-C−H bond, using a directing group strategy, is presented. The reaction yields pharmaceutically useful 3-arylated succinimide derivatives. In order to gain understanding of this redox neutral reaction, despite the presence of copper acetate, and to substantiate the lack of Heck-type products, DFT calculations have been carried out.

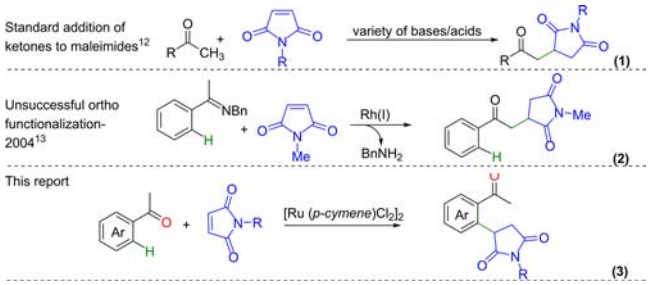


1,4-Addition of carbon nucleophiles to electron-deficient olefins is an advantageous and elegant strategy for the construction of carbon−carbon bonds.[1] Such conjugate additions are well-known for α,β-unsaturated ketones and similar systems.[2] In this direction, asymmetric conjugate additions using organometallic reagents have become increasingly popular in the last 10−15 years.[3] However, reports of conjugate additions for maleimide systems are still scarce, in spite of the pioneering work carried out by Hayashi et al. using phenylboronic acid.[4] Functionalization of arenes at the *ortho* position by employing a directing group is an attractive strategy.[5] Surprisingly, reports for such C−H activation followed by conjugate addition on to α,β-unsaturated systems are rare.[6,7a] Moreover, the recent reports that discuss such additions suggest the formation of a Ru−H species, followed by insertion of the olefin into Ru−H bond and subsequent reductive elimination of the metal.[7] Such processes do not provide an opportunity for β-hydride elimination and are generally addressed by the term hydroarylation and are carried out by using less stable (to moisture and air) and difficult to handle Ru(0) catalysts or precursors.[8]

Maleimide is a highly electrophilic olefin, which has attracted a lot of attention for 1,4-additions, as it readily provides a 5-membered ring, i.e., a succinimide ring, and functional groups which can be easily reduced to form pyrrolidine rings. Many natural products[9] and anticonvulsant[10] and antidepressant[11] drugs possess the succinimide moiety as a central scaffold. Simple methyl ketones are very good nucleophiles which have a good propensity to undergo Michael addition with maleimides in the presence of trace amounts of base and sometimes acid to furnish the corresponding Michael product (eq 1, Scheme 1).[12] Surprisingly, reports of 1,4-additions using C−H activation strategies on the maleimide system are, to the best of our knowledge, unknown. Notably, an attempt to accomplish such a reaction by Jun and co-workers using Rh(I) catalyst with maleimide as the partner was unsuccessful (eq 2, Scheme 1).[13]

In continuation of our work,[14] we chose to address this problem of selectively carrying out a C−H activation in the presence of a highly reactive enolizable ketone (eq 3). In this study, we have not detected any Michael addition (eqs 1 and 2) products despite the presence of acetic acid and the Lewis acidic copper acetate in the reaction medium. Further, we have carried out preliminary DFT studies to understand this reaction and also to provide a rationale for the lack of β-hydride elimination.

Scheme 1. Comparison of Previous Reports with Current Work



The first reaction using *p*-methoxyacetophenone (**1**) and *N*-benzylmaleimide (**2**,1.5 equiv) as the model substrates, in the presence of $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), and $Cu(OAc)_2{\cdot}H_2O$ (1 equiv) at 80 °C in DCE, yielded the required adduct (**3a**) in 15% yield (entry 1, Table 1). Increasing the amount of maleimide (**2**) and increasing the temperature was useful in improving the yields of **3a**. A similar trend was observed by increasing the amount of copper acetate and Ru catalyst. A significant improvement was achieved by employing 10 equiv of AcOH, leading to a jump in the yield of **3a** from 57% to 85% (entry 7). Further, to increase the dissociation of AcOH, 5 equiv of water was added, which led to the final optimal reaction conditions with the formation of **3a** in 96% yield (entry 8, isolated 90%). Further changes to the optimal conditions did not result in any improvement (entries 9−17).

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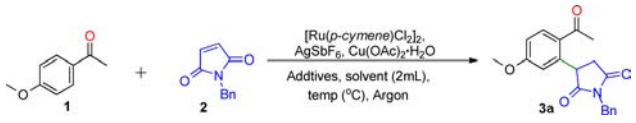
Table 1. Optimization Studies[a]

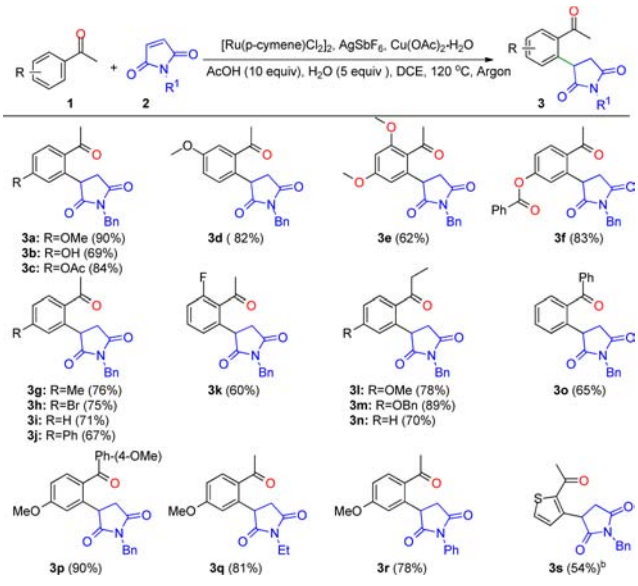


entry	2 (equiv)	Ru (mol %)	Cu (equiv)	temp (°C)	AcOH (equiv)	H_2O (equiv)	yield (%)[b]
1	1.5	5	1	80	—	—	15
2	2	5	1	80	—	—	26
3	2	5	1	100	—	—	38
4	2	5	1	120	—	—	45
5	2	5	1.5	120	—	—	49
6	2	7.5	1.5	120	—	—	57
7	2	7.5	1.5	120	10	—	85
8	**2**	**7.5**	**1.5**	**120**	**10**	**5**	**96 (90)**[c]
Deviations from the above Standard Conditions							
9	increase AcOH to 15 equiv						95
10	increase H_2O to 10 equiv						73
11	no AcOH						62
12	reduce $[Ru(p\text{-}cymene)Cl_2]_2$ to 5 mol %						87
13	No $Cu(OAc)_2 \cdot H_2O$						ND
14	3 equiv of NaOAc instead of $Cu(OAc)_2 \cdot H_2O$						ND
15	$CuSO_4$ instead of $Cu(OAc)_2 \cdot H_2O$						ND
16	KPF_6 or $NaPF_6$ or $AgNO_3$ instead of $AgSbF_6$						ND
17	$RuCl_3 \cdot 3H_2O$ instead of $[Ru(p\text{-}cymene)Cl_2]_2$						ND

[a]Conditions: **1** (0.3 mmol), DCE (2 mL), $AgSbF_6$ 4× the mol % of Ru used. [b]^{1}H NMR yield %, using terephthaldehyde as internal standard. [c]Isolated yield in parentheses. ND = not detected.

The reaction proceeded with great ease for electron-rich derivatives of acetophenone to furnish the products **3a**–**f** (Scheme 2). Even *meta*- and *ortho*-substituted acetophenone derivatives underwent a facile reaction (**3d** and **3e**). The electron-neutral derivatives also furnished the corresponding products in moderate to good yields (**3g**–**k**). As expected, the propiophenone and benzophenone derivatives reacted smoothly to afford the coupled products (**3l**–**p**) in good yields. Changing the coupling partner to *N*-ethyl maleimide and *N*-phenyl-maleimide also led to the formation of corresponding products (**3i** and **3j**) in excellent yields (81% and 78%, respectively). The heteroaromatic ketone, 2-acetylthiophene, was reacted with maleimide (**2**) in the absence of AcOH and water, and the requisite product (**3s**) was obtained in moderate yields (54%).

Scheme 2. Substrate Scope[a]

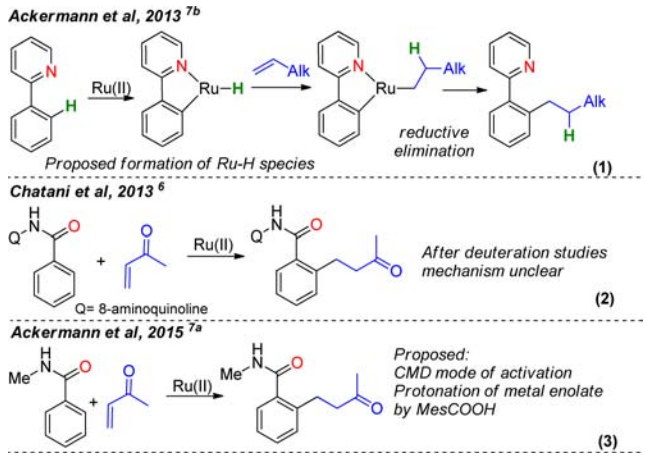


[a]Standard reaction conditions: Ru cat. (7.5 mol %), $AgSbF_6$ (30 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv), ketone (0.3 mmol), maleimide (0.6 mmol), AcOH (10 equiv), H_2O (5 equiv), DCE (2 mL), T = 120 °C. [b]In the absence of AcOH and H_2O.

Many classes of C–H activation to generate a metallacycle have been identified (see SI-Scheme 1 in the Supporting Information), namely oxidative addition (OA), electrophilic aromatic substitution (EAS), σ bond metathesis (SBM), and concerted metalation deprotonation (CMD).[15] For Ru(II)-catalyzed reactions, the mechanisms, in general, as proposed by various groups involve either an OA mode of C–H activation or the CMD mode.

Ackermann et al. used Ru(II) in the presence of KO_2CMes as an additive to achieve hydroarylation of unactivated alkenes and proposed the formation of a Ru–*H* species (Scheme 3, eq 1).[7b]

Scheme 3. Proposed Mechanisms by Others



Contemporaneously, Chatani et al. provided another hydroarylation method using Ru(II) catalyst, but they have reported the mechanism to be unclear in spite of well-designed deuterium-labeling studies (eq 2).[6] In light of these developments, we believed that it was imperative for us to justify the mechanism of our newfound reaction, and therefore, we carried out some basic DFT studies. However, during the preparation of this manuscript, Ackermann et al. reported yet another hydroarylation using a Ru(II) catalyst and proposed a different mechanism to justify the formation of the hydroarylated product (eq 3).[7a]

The discussion of theoretical calculations is presented in terms of the Gibbs free energies computed with the M06 density functional theory in 1,2-dichloroethane (DCE) as the continuum solvent (Scheme 4 and see the Supporting Information for a full description).[16−18] The catalytic cycle developed from computational studies is presented in Scheme 5. From the optimized structure for **Cat0** complex, we recognize that it is an 18-electron complex with benzene ligand acting as an η^6 ligand. Repeated efforts to obtain a TS for OA and EAS mechanisms were futile. Our calculation shows that the TS for the CMD process (**TS12a**, Scheme 4) is 20 kcal/mol lower than the TS generated for the SBM process (**TS12b**). The presence of a low energy CMD process safely rules out the possibility of an OA or EAS process for C–H activation. The C–H activation step leads to the formation of the key metallacycle (**Int2a**) followed by an

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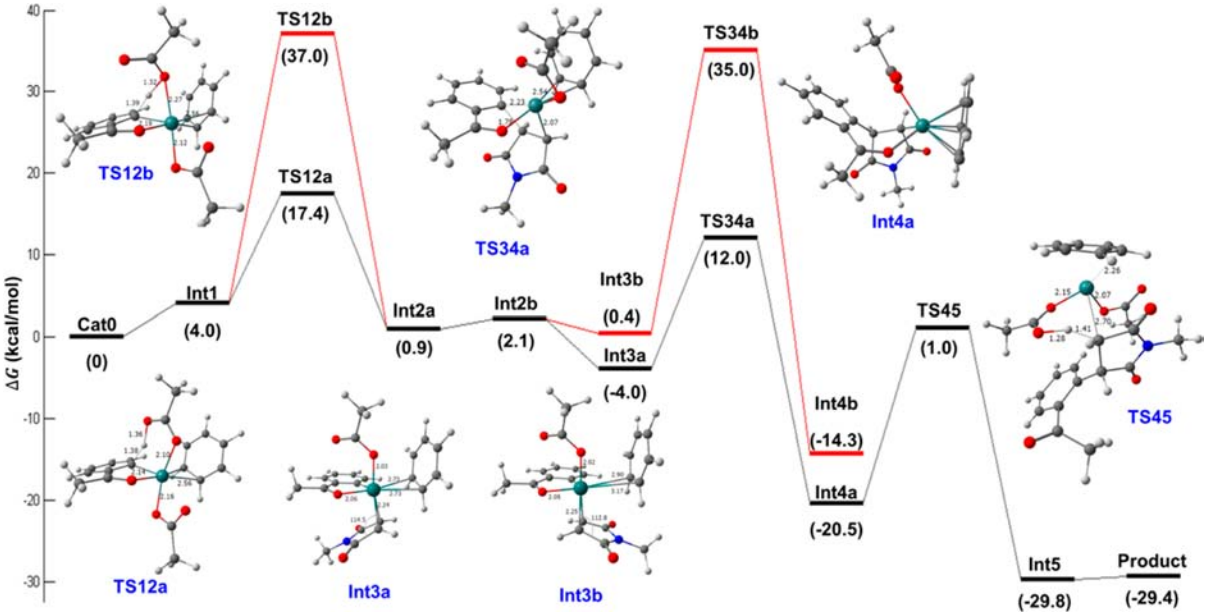
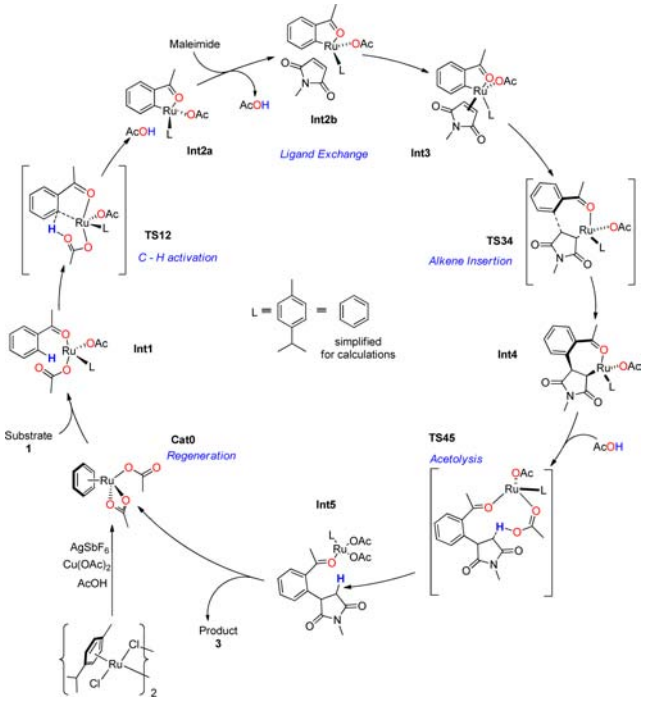
Scheme 4. Energy Diagram[a,b]



[a]Values in parentheses represent Gibb's free energies with respect to infinitely separated reactants (Cat0 + acetophenone + *N*-methylmaleimide). [b]For ease of calculation, the *p*-cymene ring and *N*-substituted maleimide have been reduced to a benzene ring and *N*-methylmaleimide, respectively. For enlarged structures, see the Supporting Information.

Scheme 5. Catalytic Cycle for Hydroarylation



exchange of acetic acid with maleimide (**Int2b**).The coordination of maleimide is possible only if the tetrahedral geometry of the complex changes to the trigonal bipyramidal (TBP) shaped intermediate (**Int3**). In this geometry, the orientation of the maleimide group can be visualized in two ways, inner or outer, in relation to the plane of the ruthenacycle (Scheme 4). The inner (or *endo*, **Int3a**) orientation was found to be more stable by about 4 kcal/mol than the outer (or *exo*, **Int3b**) orientation. The steric presence of the maleimide in **Int3b** leads to a decrease in the interaction between the π-electrons of the benzene ligand, and Ru and is characterized by the increase (6−16%) in distance between them and also the "twisting away" of the benzene ligand. Further, the transition-state calculations (**TS34a** and **TS34b**) for the insertion process showed an unexpectedly large difference (23 kcal/mol) in the activation energies starting from the two different intermediates (**Int3a** and **Int3b**). Clearly, the *endo*-transition state is kinetically preferred over the *exo*-TS, which could be due to secondary orbital interactions between the ruthenacycle and the maleimide (calculations have not been performed). The migratory insertion leads to the formation of a seven membered chelation stabilized Ru intermediate, with the aryl group and Ru present in a *cis* orientation (**Int4a** and **Int4b**, see the Supporting Information for structures). Our effort to generate a transition state to obtain a *trans*-substitution across the maleimide ring was unsuccessful, a process which would require a "twisted" maleimide ring in the transition state. Since formation of **Int4a** is more feasible, it was used for all further calculations.

From the structure of **Int4a**, one can recognize the absence of a *syn*-planar β-hydrogen atom with respect to the Ru atom, a necessity for the β-hydride elimination process. A *syn*-planar hydrogen would be available for elimination only if the "*trans*" addition occurred in the reaction. Moreover, we found that the "*trans*" intermediate (**Int4a trans**) was of higher energy (10 kcal/mol, see the Supporting Information for the structure) than the "*cis*" intermediate (**Int4a**), and any process that interconverts them would not be feasible (due to presence of the rigid bicyclic ring intermediate), leading to only one possible fate for the intermediate, i.e., a protonation by an external acid. Therefore, it can be clearly stated that the Heck-type product is not formed due to the inaccessibility of a *syn*-planar β-hydrogen atom with respect to the central metal atom, and such an access is also prohibited by the rigid nature of the bicyclic ring as depicted in the structure of **Int4a**. Acetic acid present in the medium, either generated in the first step or added in to the reaction, could lead to the protonation in the last step.[19] This step can be envisaged as a retro-CMD or a concerted demetalation protonation

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mechanism wherein the proton from the coordinated acetic acid quenches the Ru−C bond via a 6-membered ring (**TS45**). This leads to the formation of **Int5**, where the final product (**3**) remains coordinated to the **Cat0**, which on dissociation leads to the regeneration of **Cat0** and liberation of the product. Through all the structures in the catalytic cycle, the role of the ligand (i.e., *p*-cymene ring) is paramount in maintaining the electron count around the central ruthenium atom. The ring constantly shifts between η^6 to η^2 by slipping away from the central atom whenever the metal co-ordination sphere undergoes a change in geometry or during bond-making and -breaking processes. This ability of the *p*-cymene ring coupled with other factors probably make $[Ru(p\text{-cymene})Cl_2]_2$, an attractive catalyst for various C−H activation processes.

In conclusion, we have presented a novel Ru(II)-catalyzed C−H functionalization of acetophenone with maleimide using ketone as a directing group to obtain 3-arylated succinimides. Since ketones are known primarily to undergo Michael addition by formation of enolates, this present work enables one to synthesize 1,4-adducts with the *ortho* carbon of aromatic ketones. The DFT studies suggest that the C−H activation occurs by the concerted metalation−deprotonation process to yield the key ruthenacycle followed by an insertion of the olefin into the C−Ru bond. This olefin insertion occurs in an *endo* manner, and the organometallic species subsequently undergoes acetolysis leading to the formation of the required product and also regenerating the catalyst. The lack of *β*-hydride elimination is due to the inaccessibility of the *β*-hydrogen in a *syn*-periplanar fashion to the central ruthenium atom, and this is further restricted by the inability of the rigid bicyclic ring to undergo any rotation or flipping.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01810.

Experimental and computational procedures and data (PDF)

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Notes

The authors declare no competing financial interest.

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(16) All computations were performed using the Gaussian09 suite of programs: Frisch, M. J. et al. Gaussian 09, Revision D.01; Gaussian, Inc.: Wallingford, CT, 2009 (see the Supporting Information for the complete reference). The PCM_{DCE}/M06/6-31G(d), LANL2DZ(-Ru)//PCM_{DCE}/B3LYP/6-31G(d),LANL2DZ (Ru) level of theory has been used. See the computational methods in the Supporting Information for full details.

(17) The energies are computed with respect to the infinitely separated reactants. See: Anand, M.; Sunoj, R. B.; Schaefer, H. F. *J. Am. Chem. Soc.* **2014**, *136*, 5535 and references cited therein.

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