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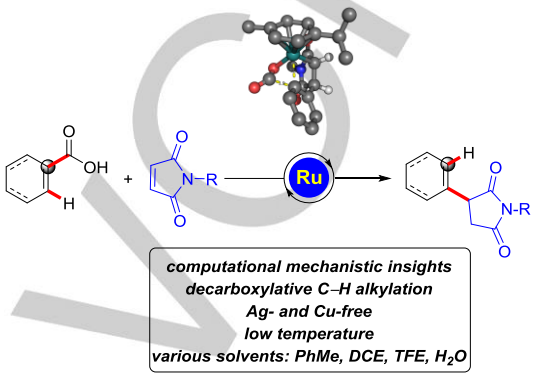
Mild Decarboxylative C–H Alkylation: Computational Insights for Solvent-Robust Ruthenium(II) Domino Manifold

N. Y. Phani Kumar,[a]† Torben Rogge,[a]† Santhivardhana Reddy Yetra,[a]† Alexander Bechtoldt,[a] Eric Clot,[b] and Lutz Ackermann*[a]

Abstract: Computational studies on decarboxylative C–H alkenylations provided key insights into the solvent-robust nature of C–H activation/decarboxylation domino reactions, which was exploited for ruthenium(II)-catalyzed C–H alkylations by decarboxylative ruthenium(II) catalysis with ample scope under copper- and silver-free reaction conditions.

Transition metal-catalyzed C–H functionalizations have emerged as a powerful tool for molecular syntheses, with transformative applications to medicinal chemistry, materials science and agrochemicals.[1] Carboxylic acids are particularly useful substrates, since they are readily accessible, inexpensive and can undergo a wealth of chemical transformations.[2] Thus, carboxylic acids have proven instrumental for the development of *inter alia* cross-couplings,[3] and C–H activation.[4, 2a] The last decade has witnessed major progress through the use of carboxylic acid as traceless directing groups in C–H functionalization.[5] Despite major advances, the practical utility of these methods is compromised by two-step operations, the use of more than one metal in (sub)stoichiometric amounts and high reaction temperatures. Very recently, single step transformations using monometallic systems have been concurrently discovered by Ackermann,[6] Zhao,[7] and Gooßen[8] using ruthenium(II)-catalysis, thereby achieving domino C–H alkenylation/decarboxylations.[9] A recent computational study on the mechanism of these ruthenium(II)-catalyzed decarboxylative C–H alkenylations of benzoic acids with alkynes proposed that the chemoselectivity of the reaction is fully controlled by the polarity of the reaction medium.[10] Within our own computational studies, we unraveled a solvent-robust decarboxylative C–H activation manifold, which enabled a unified strategy for domino C–H alkylation/decarboxylation to access succinimide derivatives which feature anticonvulsant[11] and anticancer activity.[12] Salient features of our approach include (*i*) computational and experimental mechanistic insights into decarboxylative C–H activation, (*ii*) carboxylic acids as traceless directing groups for positional selective C–H alkylation and (*iii*) a user-friendly single-component ruthenium catalyst for one step access to *meta*-substituted arenes.



Scheme 1. Ruthenium(II)-catalyzed decarboxylative C–H alkylation.

We initiated our studies by exploring the mechanism of our decarboxylative C–H alkenylation[6, 10] by means of DFT calculations. Our computational studies for decarboxylative C–H alkenylations with alkyne **M** at the PBE0-D3(BJ)/def2-QZVP*+SMD//PBE0/def2-SVP[13] level of theory revealed that the reaction proceeds *via* C–H ruthenation,[14] followed by migratory insertion, and decarboxylation for the final two-fold proto-demetallation (Figure 1). Moreover, we uncovered that the key activation barriers were not significantly altered by the nature of the reaction medium (see also Table S1 in the Supporting Information).

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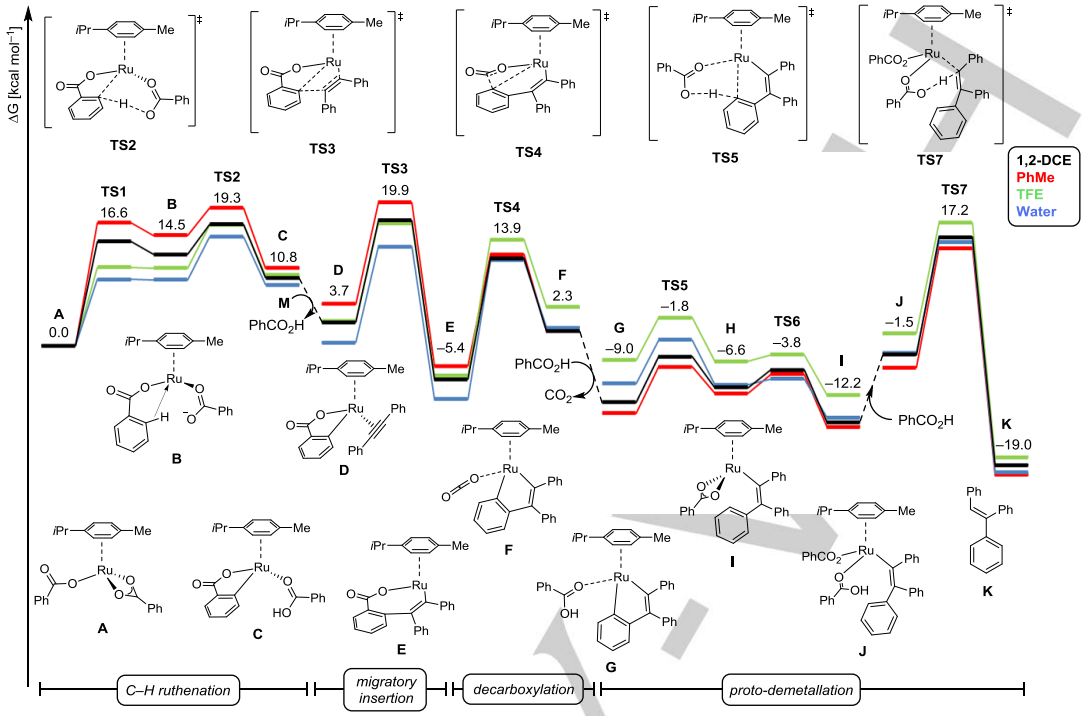

Figure 1. Relative Gibbs free energy diagram of the reaction path with alkyne **M** in different solvents; values are shown for 1,2-DCE.

With the solvent-robust chemo-selectivity of the domino C–H alkenylation/decarboxylation suggested, we computationally explored the envisioned decarboxylative transformation with maleimides **2** (Figure 2).[15] A potential annulation pathway was unfavorable, while the influence of the reaction medium on all activation energies was again found largely to be negligible (see also Table S2 in the SI).[13] Moreover, an analysis by Grimme's D3 dispersion correction[16] revealed that dispersion interactions significantly stabilize key intermediates and transition states, with differences of up to 27 kcal mol^{-1} for intermediate **J'** (Figure S2 in the SI). Based on our computational insights, we thereafter became attracted to probe the desired decarboxylative C–H alkylation by experiment. After considerable optimization (Table S5 in the SI),[13] we were pleased to identify the well-defined ruthenium(II) bis(carboxylate) complex [Ru(O_2CMes)$_2$(*p*-cymene)] (**4a**)[17] as a single-component catalyst for the desired domino decarboxylative C–H alkylation of benzoic acids **1**, thereby furnishing *meta*-decorated arenes **3**. As indicated by our computational analysis (*vide supra*), various solvents proved amenable, ranging from aprotic toluene and 1,2-dichloroethane (DCE) to polar protic 2,2,2-trifluoroethanol (TFE) and even H_2O. The outstanding chemo-selectivity of the versatile ruthenium(II) catalyst was reflected by fully tolerating valuable functional groups, such as iodo, bromo, hydroxyl, cyano, ester and nitro substituents (Scheme 2a). The high catalytic efficacy also enabled efficient catalysis even at a considerably lower reaction temperature of only 50 °C, and the step-economical synthesis of the anticonvulsant drug Phensuximide (**3he**) and its analogues **3ha**/**3hg**.[18]

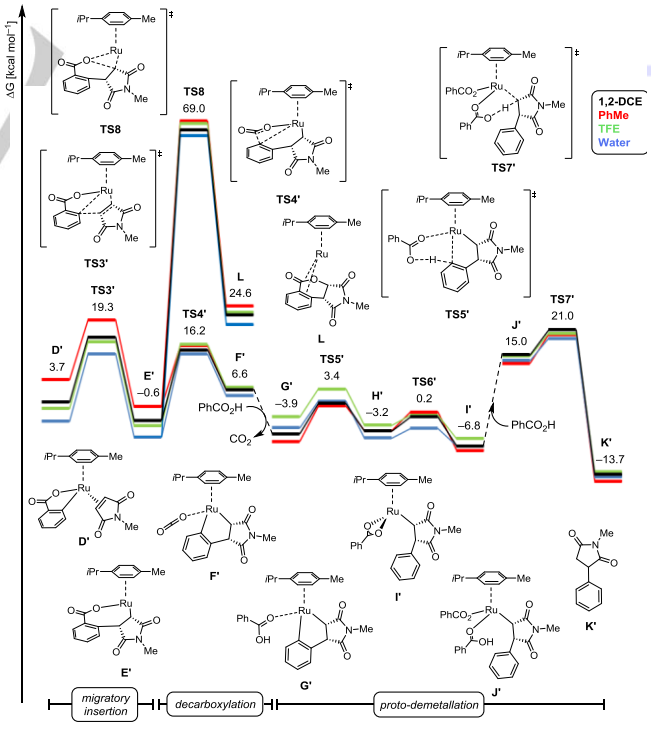

Figure 2. Relative Gibbs free energy diagram of the reaction with maleimides **2** in different solvents with respect to **A**; values are shown for 1,2-DCE.

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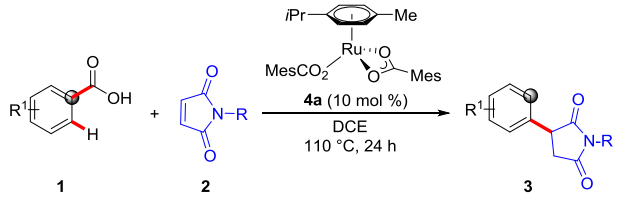
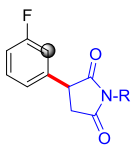
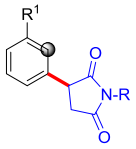


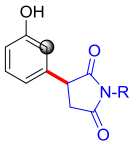
(a) ortho and meta-substituted benzoic acids



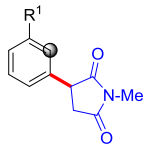
R = Bn (**3aa**): 72%[a], 82%[b] 89%
R = 4-MeC$_6$H$_4$ (**3ab**): 78%
R = 4-ClC$_6$H$_4$ (**3ac**): 66%
R = 4-MeOC$_6$H$_4$ (**3ad**): 78%



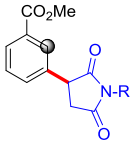
R^1 = I, R = Bn (**3ba**): 77%
R^1 = I, R = Me (**3be**): 81%
R^1 = Br, R = Bn (**3ca**): 79%
72%[a]



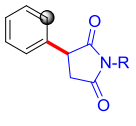
R = Me (**3de**): 82%
R = Cy (**3df**): 87%
R = Ph (**3dg**): 82%



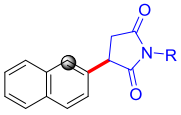
R^1 = CN (**3ee**): 75%
R^1 = CF$_3$ (**3fe**): 78%, 64%[a]



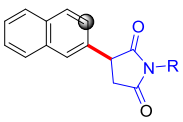
R = Me (**3ge**): 68%
R = Cy (**3gf**): 42%
R = Ph (**3gg**): 78%



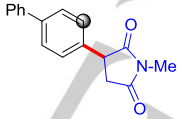
R = Bn (**3ha**): 69%
R = Me (**3he**): 76%, 72%[c]
Phensuximide
R = Ph (**3hg**): 72%
R = H (**3hh**): 59%



R = Me (**3ie**): 85%
R = Cy (**3if**): 91%, 75%[a]

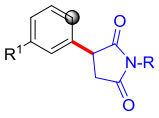


R = Me (**3je**): 85%
R = Cy (**3jf**): 94%

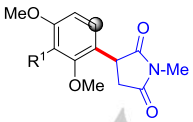


3ke: 95%

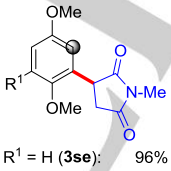
(b) para-substituted benzoic acids



R^1 = OH, R = Ph (**3lg**): 97%, 69%[a]
R^1 = CO$_2$Me, R = Ph (**3ng**): 83%
R^1 = F, R = Bn (**3oa**): 85%
R^1 = NO$_2$, R = Bn (**3ma**): 52%
R^1 = Cl, R = Bn (**3pa**): 75%

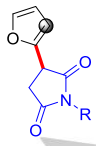


R^1 = OMe (**3qe**): 97%
R^1 = Me (**3re**): 85%

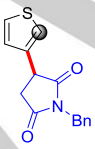


R^1 = H (**3se**): 96%
R^1 = OMe (**3te**): 93%

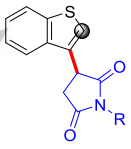
(c) heterocyclic carboxylic acids



R = Bn (**3ua**): 63%
R = Me (**3ue**): 67%
R = Cy (**3uf**): 57%
R = Ph (**3ug**): 58%



3va: 74%

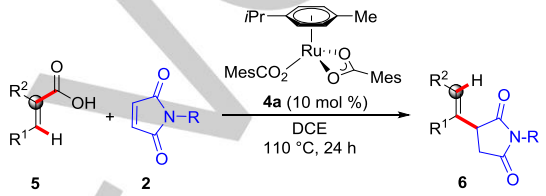


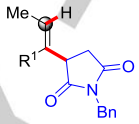
R = Me (**3we**): 85%
R = Cy (**3wf**): 89%
R = Ph (**3wg**): 91%
74%[a]

Scheme 2. Decarboxylative C–H alkylation with alkenes **2**. [a] In H_2O. [b] In TFE at 50 °C. [c] *t* = 30 min.

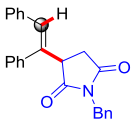
The remarkable reactivity of our ruthenium(II) catalyst was further illustrated by an extremely short reaction time of only 30 minutes. Notably, free (*NH*)-maleimide **2h** was also well tolerated. When using the *meta*-substituted benzoic acid **1k**, the *para*-alkylated product **3ke** was obtained. Considering the importance of heterocyclic motifs in medicinal chemistry and natural products,[19] we were pleased to identify heteroarenes as viable substrates under otherwise identical reaction conditions (Scheme 2c).

Furthermore, the user-friendly ruthenium(II) biscarboxylate complex **4a** was not limited to C–H functionalization of arenes **1**. Indeed, the versatile single-component catalyst **4a** likewise enabled alkenylic C–H activation on challenging acylic acids and cyclohexene carboxylic acid **5** (Scheme 3).[20]

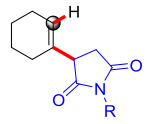




R^1 = H (**6aa**): 61%
R^1 = Me (**6ba**): 62%



6ca: 72%



R = Bn (**6da**): 74%
R = 4-ClC$_6$H$_4$ (**6dc**): 76%
R = 4-MeOC$_6$H$_4$ (**6dd**): 70%
R = Me (**6de**): 81%
R = Cy (**6df**): 77%
R = Ph (**6dg**): 75%

Scheme 3. Decarboxylative C–H alkylation of alkenyl carboxylic acids **5**.

Given the remarkably high efficiency of the domino C−H alkylation/decarboxylation, we performed experiments to gain further experimental insights into its *modus operandi*. To probe the decarboxylative nature of the domino C−H alkylation/decarboxylation regime, we first examined the CO_2 evolution during the course of the reaction, revealing a conversion of more than 50% in only 4 hours. (Figure 3).[13]

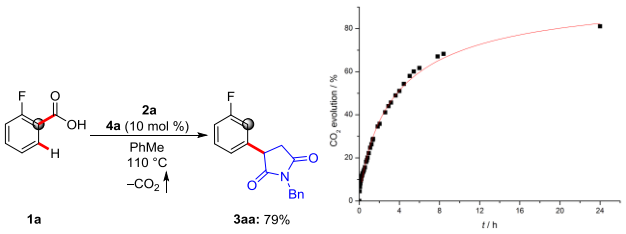
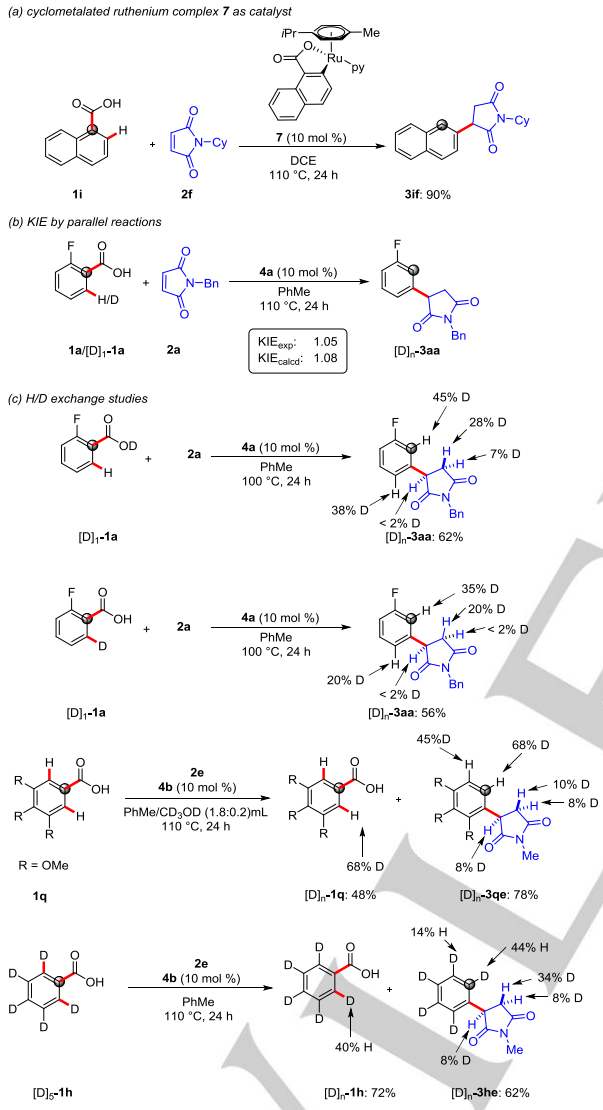


Figure 3. CO_2 evolution during ruthenium(II)-catalyzed C–H alkylation.

Given the importance of the cycloruthenated complexes as proposed intermediates in the ruthenium(II)-catalyzed domino C−H alkylation/decarboxylation reaction, we subsequently

performed successful reactions with the well-defined complex **7**, illustrating the organometallic mode of the C–H activation (Scheme 4a). A negligible kinetic isotope effect (KIE) of $k_H/k_D \approx 1.05$ was observed by *in situ* monitoring of the reaction by IR spectroscopy, which suggested that the C–H ruthenation is not the turnover-limiting step. This observation is in good agreement with a calculated KIE value of 1.08 (Scheme 4b).[13] In line with our KIE and computational studies, reactions performed with isotopically labeled compounds provided strong support for a facile C–H ruthenation event (Scheme 4c).



Scheme 4. Summary of key mechanistic findings.

In summary, we report on computational studies on ruthenium-catalyzed domino C−H activation/decarboxylations that highlight the solvent-robust nature of decarboxylative C−H alkenylations. These studies set the stage for the development of versatile ruthenium(II)-catalyzed decarboxylative C−H alkylations that provide step-economical access to *meta*- and *para*-alkylated arenes, heteroarenes and alkenes. Key to success was represented by carboxylate assistance, which allowed chemo- and site-selective domino C−H alkylation/decarboxylation with ample scope at reaction temperatures as low as 50 °C under copper- and silver-free reaction conditions. In contrast to previous catalytic systems, the robust single-component catalyst was operative under exceedingly mild reaction conditions in a large variety of solvents, ranging from apolar toluene and DCE to polar solvents, even including H_2O.

Acknowledgements

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Keywords: Density functional calculations • C–H activation • decarboxylation • ruthenium • reaction mechanism

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[20] Thus far, aliphatic carboxylic acids led to less satisfactory results.

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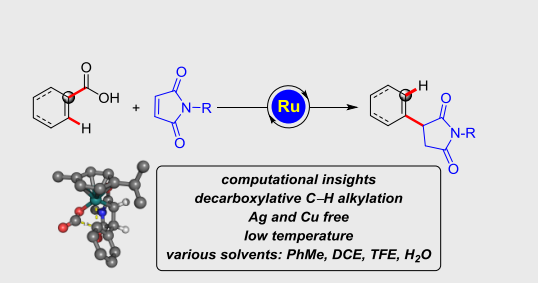

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Mild Decarboxylative C–H Alkylation: Computational Insights for Solvent-Robust Ruthenium(II) Domino Manifold

***Ex silico*:** Decarboxylative C–H alkylations were realized through key mechanistic insights, enabling ruthenium(II)-catalyzed domino C–H activation/decarboxylation under exceedingly mild condition.