1,3-Difunctionalization of Vinyl Diazo Esters Enabled by a Cobalt Catalyzed C–H Activation/Carbene Migratory Insertion: A One Pot Domino Approach in a Three Component Coupling

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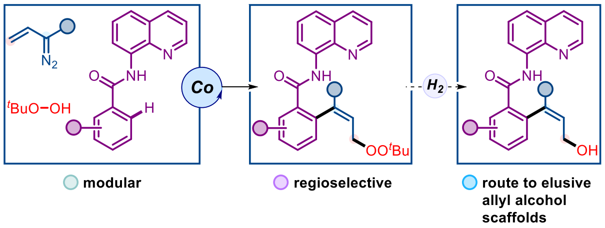
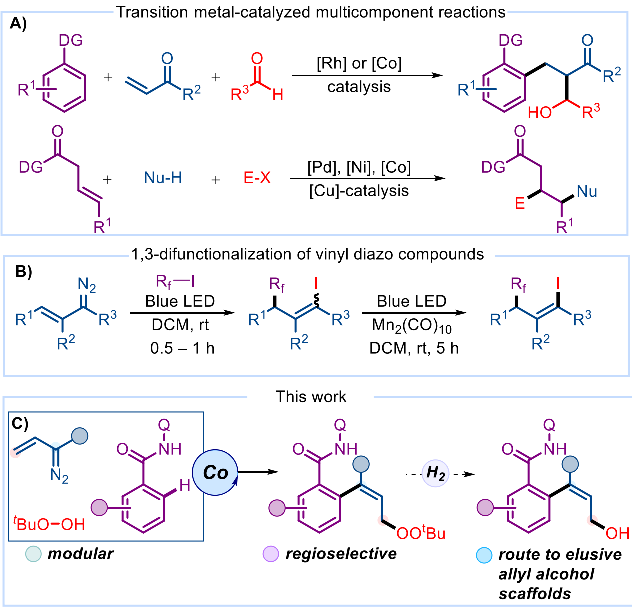


ABSTRACT: We report herein, a modular, regioselective 1,3-oxyarylation of vinyl diazo esters *via* a Co-catalyzed C–H activation/carbene migratory insertion cascade. The transformation involves the formation of C–C and C–O bonds in a one-pot fashion and displays a broad substrate scope with respect to both, vinyl diazo esters as well as benzamides. The coupled products were subjected to hydrogenation to access elusive allyl alcohol scaffolds. Mechanistic investigations reveal interesting insights on the mode of transformation, involving C–H activation, carbene migratory insertion of the diazo compound followed by a radical addition as the key steps of the transformation.

Owing to the rapid development in the molecular level understanding of transition metal-catalyzed C–H functionalization reactions, these have emerged as powerful tools for achieving molecular complexity, often in a step-economic fashion.[1] In this regard, extensive progress has been made in the area of two-component C−H bond additions to diverse coupling partners using transition metal catalysis, in which a C−H bond of the substrate and a transition-metal catalyst typically form a nucleophilic metallacycle intermediate which adds across a single coupling partner to create a functionalized product.[2] While this paradigm has proven to be successful for the C–C/C–heteroatom bond forming reactions, it has only been moderately efficient with respect to atom and step economy. At times, this limits the development of transformations possessing broad utility in organic synthesis.

To circumvent this challenge, multicomponent reactions (MCR) involving two or more different coupling partners can provide an alternative approach for the synthesis of complex organic scaffolds, often in a step and atom economical fashion.[3] In this regard, groups of Ellman,[4] Engle,[5] among others,[6] have demonstrated a variety of multicomponent transformations using diverse coupling partners, employing a variety of transition metals, and thereby proving the effectiveness of the multicomponent reactions (Scheme 1A). Despite the advances in the development of multicomponent reactions employing transition metal catalysis, future advancement to achieve regiodivergent products in such classes of reactions is still elusive due to the scarcity of coupling partners.

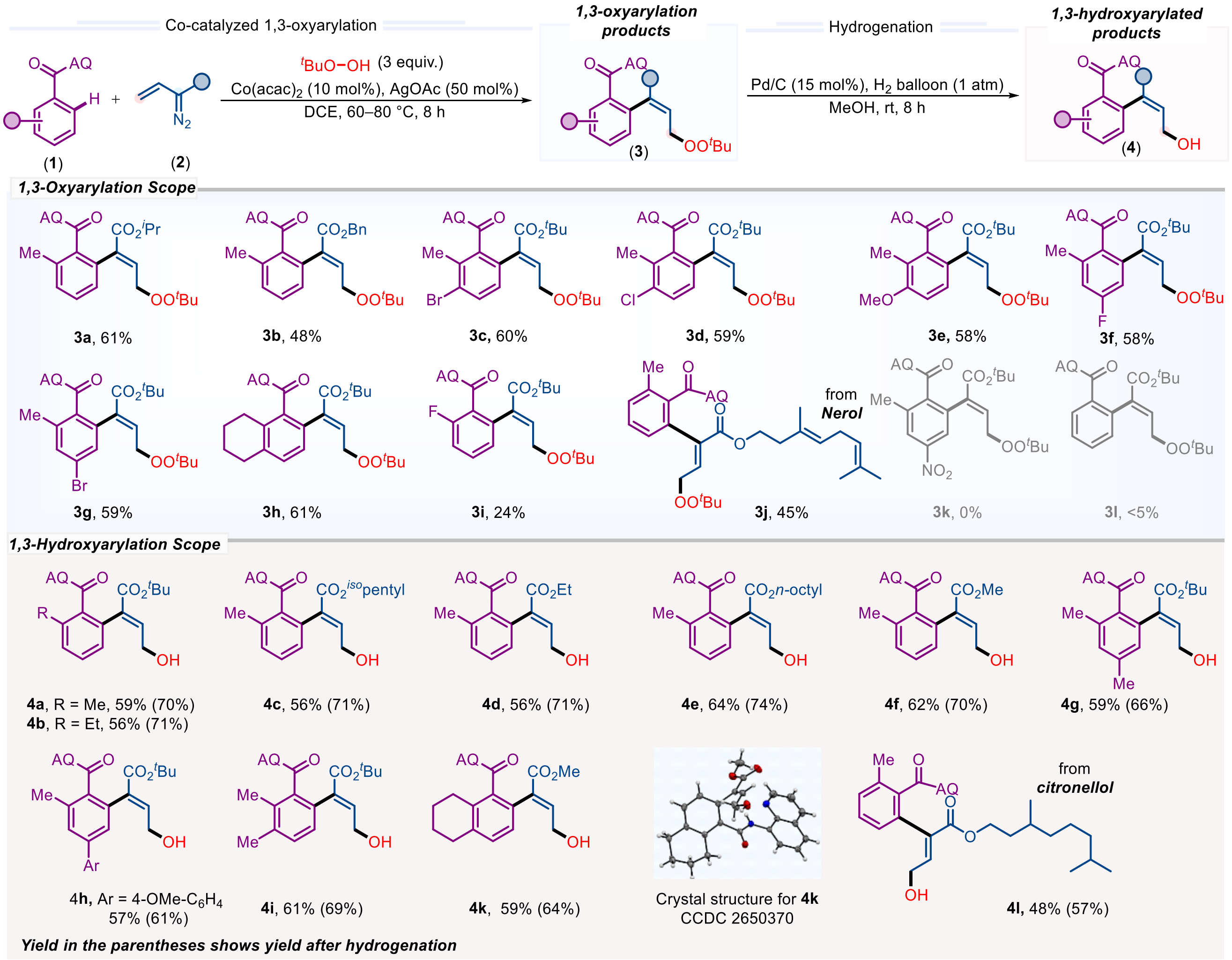


Scheme 1. (a) Transition metal-catalyzed multicomponent reactions; (b) 1,3-difunctionalizaiton of vinyl diazo compounds; (c) This work.

Diazo compounds are among the most frequently employed coupling partners in the TM-catalyzed carbene migratory insertion reactions.[7] In this regard, we envisioned that vinyl diazo compounds, a sub-class of diazo compounds, can be used for multicomponent reactions, as these show rich chemistry owing to the availability of two reaction centers, the alkene, and the diazo functional group.[8] Numerous synthetic transformations have been developed based on these vinyl diazo compounds, such as metal-catalyzed cycloadditions where they have been used as three-carbon building blocks to access various carbo- or heterocyclic frameworks. Very recently, these compounds have also been used in the radical addition reactions to achieve 1,3-difunctionalization using photoredox catalysis (Scheme 1B).[9] Despite these advancements, the 1,3-difunctionalization of vinyl diazo compounds employing a C–H activation/carbene migratory insertion cascade has not been explored yet.

With our continuing interest in diazo compounds,[10] we attempted to carry out the 1,3-difunctionalization of vinyl diazo esters using a C–H activation/carbene migratory insertion strategy. In this context, we report herein, a 1,3-oxyarylation of vinyl diazo compounds using a Co-catalyzed, one-pot, three-component coupling of benzamides with vinyl diazo esters and *tert*-butyl hydroperoxide (Scheme 1C). The notable features of this work are: (i) an effective use of a simple, non-expensive Co-catalyst as an efficient alternative to transition metal catalysis based on noble metals; (ii) one-pot, three component 1,3-oxyarylation of vinyl diazo compounds; (iii) a general route to synthesis of elusive 1,1-disubstituted allyl alcohols.

To probe the feasibility of the envisioned transformation, we chose 2-methyl-*N*-(quinolin-8-yl)benzamide (**1a**) and *tert*-butyl 2-diazobut-3-enoate (**2a**) as the benchmark substrates for the transformation Preliminary success was achieved with a simple catalytic system comprising of $Co(OAc)_2$ (10 mol%), TBHP (6M in decane, 2 equiv.), in DCE as the solvent at 60 °C for 8 h (for detailed optimization studies, see the Supporting Information). This afforded a mixture of 1,3-difunctionalized (**3a**) and allylated products (**3a'**) in 25% and 19% yields respectively (see the Supporting Information). We anticipated that a mixture of these products was formed owing to the competition between the two possible pathways *viz.*, 1,1-carbene migratory insertion and 1,3-allyl carbene migratory insertion. Therefore, to achieve the selective 1,3-difunctionalization as the major product, we first undertook the optimization of the Co-catalyst and to our delight $Co(acac)_2$ worked well giving the desired 1,3-difunctionalized product in 44% yield, and the allylated product was formed in 24% yield. Next, we screened other peroxide sources such as DTBP, TBBP, and Bz_2O_2 but these resulted in inferior results. Moreover, when we increased the stoichiometry of TBHP to 5 equiv. we observed a slight increase in the yield of the 1,3-difunctionalized product, to 51%. We wondered if the reactivity could be improved by using a catalytic amount of AgOAc as an additive and indeed, a significant result was observed.



Scheme 2. Substrate Scope

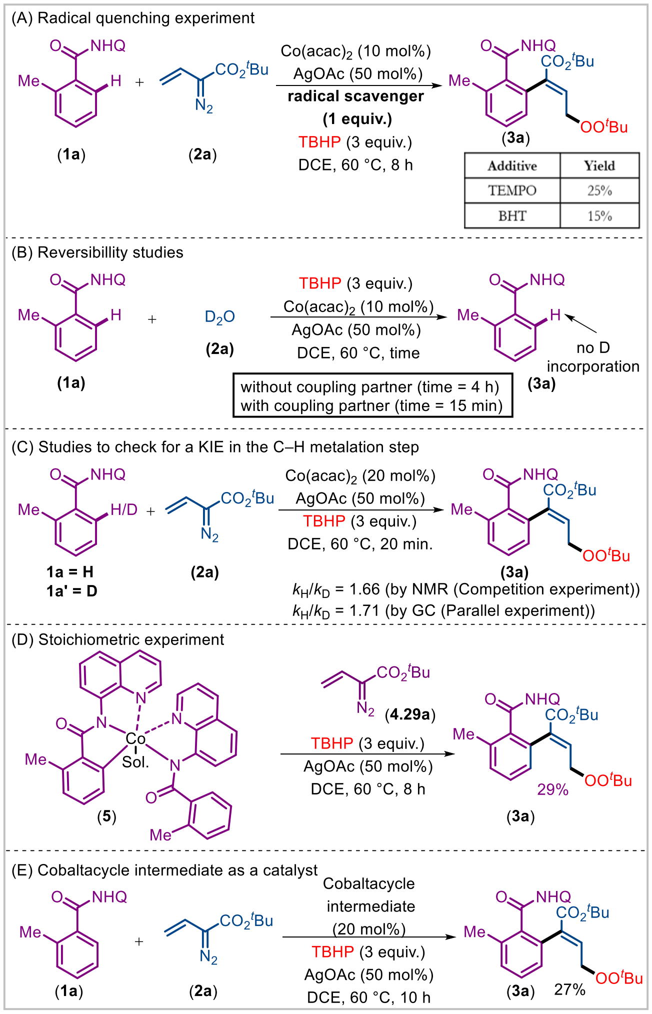
Other additives such as Et_3N, DBU failed to afford an improved yield. A short survey of solvents for this transformation indicated that DCE was the optimal solvent for this transformation. Control reactions were carried out in the absence of the Co-catalyst, these did not result in any desired product. In the absence of TBHP, the reaction did not work, and this indicated that both, the Co-catalyst as well as the peroxide source, are necessary for this transformation.

With these optimized conditions we sought to explore the versatility of the transformation. The three-component coupling to achieve the 1,3-oxyarylation of vinyl diazo esters worked well with all the vinyl diazo esters screened giving good to moderate yield (**3a–3b**, Scheme 2). We also checked the substrate scope for benzamides and to our delight, all the substituted benzamides that were screened worked well giving good to moderate yields (**3c–3i**, Scheme 2). The tetrahydronaphthalene derivative of benzamide also worked well giving a moderate yield (**3h**, Scheme 2). The reaction was also compatible with the bioactive molecule such as nerol (**3i**, Scheme 2).

Further, to show the synthetic utility of the protocol, we synthesized a series of 1,3-hydroxyarylated substrates, utilizing our Co-catalyzed 1,3-oxyarylation protocol, followed by hydrogenation of the coupled product (Scheme 2). First, we checked the substrate scope for vinyl diazo esters, to our delight a variety of long chain aliphatic vinyl diazo esters worked very well giving good to moderate yields for the 1,3-hydroxyarylated product (**4a–4f**, Scheme 2). Next, we also checked the substrate scope for benzamides, and we found that alkyl- as well as aryl-substituted benzamide derivatives worked quite well giving the 1,3-hydroxyarylated products in good to moderate yields (**4g–4l**, Scheme 2). It is noteworthy that we did not observe the reduction of olefinic bond, thus providing access to arylated allylic alcohols. The geometry of the olefin was confirmed by 2D NMR studies as well as the X-ray crystal structure analysis.

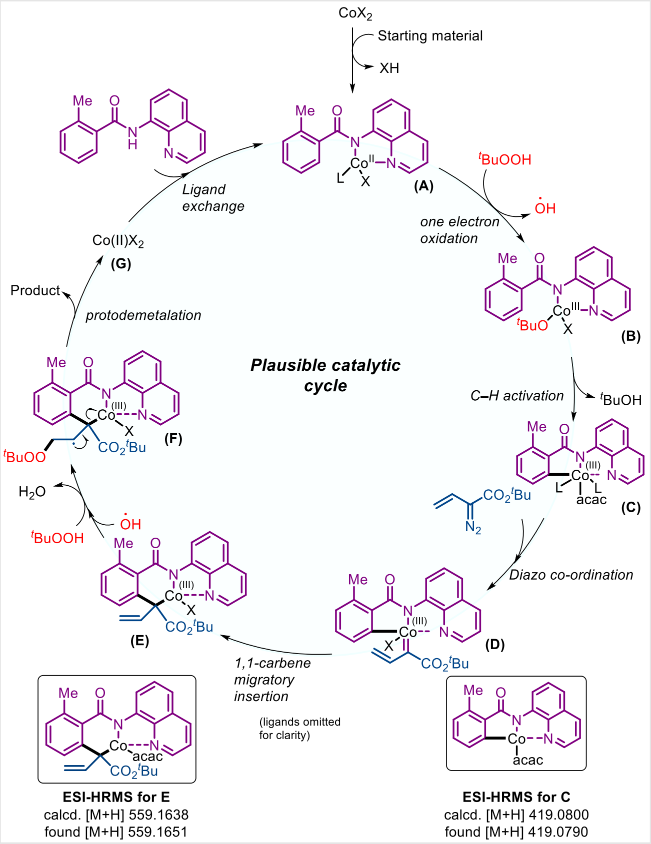
Given the versatile reactivity of this Co-catalyzed three-component 1,3-oxyarylation of vinyl diazo esters, we have performed experiments to gain insights into the mechanism. To find out whether the reaction proceeds through a single electron transfer/radical pathway, we performed the reaction in the presence of radical scavengers such as TEMPO and BHT under the optimized conditions (Scheme 3A). In both cases, the reaction was inhibited, with only 25% of the product being obtained with TEMPO and 15% yield of the product obtained in the presence of BHT. This implies that the reaction probably proceeds through a single electron transfer process/radical pathway.

Next, we performed experiments to check for reversibility of the metalation. No deuterium incorporation was observed when the reaction of the benzamide (**1a**) was performed with added D_2O and in the presence as well as the absence of the coupling partner (**2a**). This implies that, the C–H metalation step is irreversible in nature (Scheme 3B). To further investigate whether the C−H metalation step is rate-limiting, we carried out studies to check for a kinetic isotope effect. A value of 1.66 for k_H/k_D was obtained in the competition experiment (*via* NMR, average of 3 runs) and 1.71 by parallel experiments (*via* GC, average of 3 runs) which indicated that the C–H cleavage step is the rate-determining step (Scheme 3C). This also indicated that the carbene insertion step is comparatively the faster step in this transformation. Additionally, we performed a reaction with a stoichiometric amount of a pre-formed cobaltacycle[13] (**5**) under the optimized condition. This afforded the corresponding 1,3-difunctionalized product (**3a**) in 29% yield (Scheme 3D). This was followed by using this cobaltacycle (**5**) in a catalytic amount and this also yielded the 1,3-difunctionalized product (**3a**) in 27% yield. These results indicate that this type of Co(III) species may be present in the catalytic cycle (Scheme 3E).



Scheme 3. Mechanistic studies

Based on our studies and the previous literature reports,[6d] we have outlined a plausible mechanism for this transformation (Scheme 4). Initially, the Co(II) undergoes a ligand exchange with the benzamide to give intermediate (**A**). This is then oxidized by TBHP *via* a single electron transfer to give the Co(III) intermediate (**B**). This then undergoes a C–H activation *via* a concerted metalation deprotonation (CMD) pathway to afford the intermediate (**C**). This cobaltacycle Co(III)-intermediate undergoes diazo coordination to form the Co-carbene intermediate (**D**) which subsequently undergoes 1,1-carbene migratory insertion to form intermediate (**E**). Subsequently, ^{t}BuOO$^•$, which is generated *in situ* by the interaction with $^•$OH radical, undergoes radical addition to intermediate (**E**) to form the intermediate (**F**). This intermediate (**F**) then forms the olefin and *N*-coordinated Co(II) species, which subsequently undergoes protodemetalation to form the product with the liberation of Co(II) species (**G**). As mentioned earlier, the cobaltacycle intermediate (**C**) was detected by ESI-HRMS which indicates that this kind of cobaltacycle intermediate may be operative in the catalytic cycle. We are of the opinion that the cobaltacycle (**C**) is the one that may be the dominant species, as compared to **5**, which is a far more stable and isolable intermediate. The fact that low yields were obtained with **5** (Schemes 3(D) & (E)), may also indicate that the reactivity of the cobaltacycle **5** is probably lower than that of the cobaltacycle (**C**) (Scheme 4). The seven-membered cobaltacycle intermediate (**E**) was also detected by ESI-HRMS (Scheme 4).



Scheme 4. Plausible Mechanism

In summary, we have developed a cobalt-catalyzed, one-pot, three-component coupling for the 1,3-difunctionalization of vinyl diazo esters using benzamides and *tert*-butyl hydroperoxide. The methodology is distinguished by its mild conditions, readily available substrates, and a good functional group tolerance. Mechanistic investigations reveal key insights on the mode of the transformation involving irreversible, rate-limiting C–H activation, migratory insertion of vinyl diazo compounds and radical addition as the key steps. Further applications aimed at broadening the strategy for the synthesis of bioactive molecules and a detailed mechanistic understanding for the selectivity are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures, characterization data of all new compounds (PDF)

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Notes

The authors declare no competing financial interests.

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