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C−H Activation under the Guise of Diels−Alder Reaction: Annulation toward the Synthesis of Benzo[*e*]isoindole-1,3-diones

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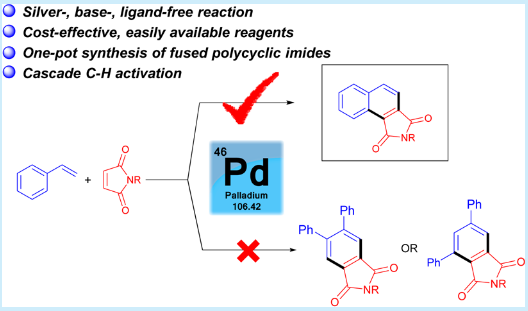
Supporting Information

ABSTRACT: A new paradigm in the coupling of external alkenes with internal electron-deficient alkenes has been investigated in which an unprecedented annulation of vinylarenes on maleimides takes place. The reaction is carried out via a tandem in situ activation of both olefinic and aromatic C−H bonds of styrenes driving the reaction in a pseudo-Diels−Alder mode.



π-Extended polycyclic compounds due to their salient properties are indispensable scaffolds which have been widely used both in industry and academia.[1] Regarding their growing applications, long-standing interest has been aroused for their construction.[2] In past decades, most efforts directed toward their synthesis comprised metal-catalyzed annulation of internal alkynes, which are a good deal more active than alkenes.[3] However, to the best of our knowledge, vinylarenes have been obscure in this field. Previously, a few Pd-catalyzed reactions emerged in which external alkenes were exploited as annulating reagents.[4] Nevertheless, the aforementioned reports, for the most part, were concerned with the involvement of only olefinic C−H bonds of vinylarenes. In our study, we managed to activate an aromatic C−H bond with a higher energy barrier together with an olefinic C−H bond. This startling discovery was achieved via an unexpected Pd-catalyzed C−H activation reaction of styrene with maleimide. Maleimides are among motifs that have been extensively used in ongoing research,[5] yet study of their reaction with vinylarenes has lagged behind. The major reason behind this scarcity might lie in the ease in the polymerization of both maleimides and styrenes which renders their reaction extremely arduous.[6]

Nevertheless, some compounds showed promise for hydrofunctionalization of maleimide through the reaction with alkenes.[7] In this context, Kiyooka took the first step in this direction and coupled styrene with *N*-benzylmaleimide with the aid of Ir.[7a] Another example was disclosed by Kim et al., who reacted maleimides with acrylamides using Rh as the catalyst.[7b] Rh-catalyzed reaction of maleimides with enol carbamates has been also reported.[7c] Taking the lead from prior work, Miura reported cross-coupling of maleimides with external alkenes bearing electron-deficient groups via a Ru-catalyzed reaction.[7d] Very recently, Zhang showed that cobalt was as effective as its counterparts having the aptitude to catalyze coupling of enamides with maleimides.[7e] However, the first report to couple maleimides with simple straight-chain olefins via a Pd-catalyzed reaction was released by White in which these entities could engage in a cycloaddition reaction.[7f] Despite all of their benefits, previous procedures unanimously demonstrated the preparation of functionalized *succinimides*, and to date, all endeavors to preserve the double bond of maleimide through its reaction with olefins have been in vain. To retrieve the double bond of maleimide, Stahl devised a protocol by which one could oxidize the cyclohexyl moiety installed on *N*-substituted maleimides to its arene counterpart.[8] Nonetheless, even this catalytic system fails for NH maleimides. Herein, we describe a method in which hydrofunctionalization, in contrast to the former work, did not occur but rather the maleimide core survived. This approach also provides a way by which one can preclude a stepwise reaction to make an aromatic ring on maleimides.

Initially, we commenced reacting maleimide with styrene with the aim of olefinating maleimide. Much to our surprise, the reaction proceeded further, and an unprecedented annulation occurred. Benzo[*e*]isoindole-1,3-diones, formed through this strategy, are efficient GSK-3β inhibitors that have been considered a powerful remedial pathway for treatment of diabetes,[9a−c] Alzheimer's disease,[9d−f] Down's syndrome,[9g] bipolar disorder,[9h] and colorectal cancer.[9i,j] Compared to traditional pathways to reach benzo[*e*]-isoindole-1,3-diones, which suffered from tedious several-step synthetic procedures and very low yields (overall yield <7%),[10] our procedure is operationally simple, *single step*, and catalytic and provides high yields.

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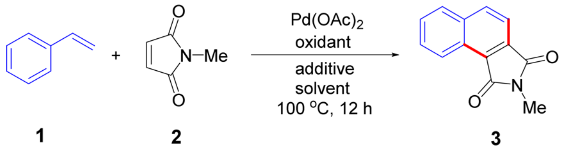
To start with, styrene **1a** was treated with *N*-methylmaleimide **2a** with 10 mol % of $Pd(OAc)_2$ and 1 equiv of $Cu(OAc)_2 \cdot H_2O$ as the oxidant in EtOAc to furnish the desired product **3a** in 21% yield (Table 1, entry 1). Switching from EtOAc to DMF increased the yield to 53% (entry 2). Further survey of solvents indicated that CH_3CN should be the solvent of choice (entries 3–6). Upon decreasing the oxidant loading to 10%, the yield diminished sharply (entry 7). Also, among different copper salts, CuCl seemed to be the most effective oxidant (entries 8–10). In the next step, control experiments showed that $Pd(OAc)_2$ was crucial for the viability of our reaction (entry 11). Moreover, utility of other oxidants in place of CuCl led to a drop in the yield (entries 12–16). Conducting the reaction in the presence of a base completely suppressed the reaction, whereas using HOAc improved the yield to 77% (entries 17 and 18). Using O_2 as the atmosphere of the reaction instead of air had a negligible effect on the yield (entry 19). Eventually, lowering the amount of styrene and the reaction temperature both resulted in lower yields (entries 20 and 21). In contrast, when the reaction time was decreased to 6 h, approximately the same yield was attained (entry 22).

Table 1. Screening Reaction Conditions in the Synthesis of Benzo[*e*]isoindole-1,3-diones 3[a]

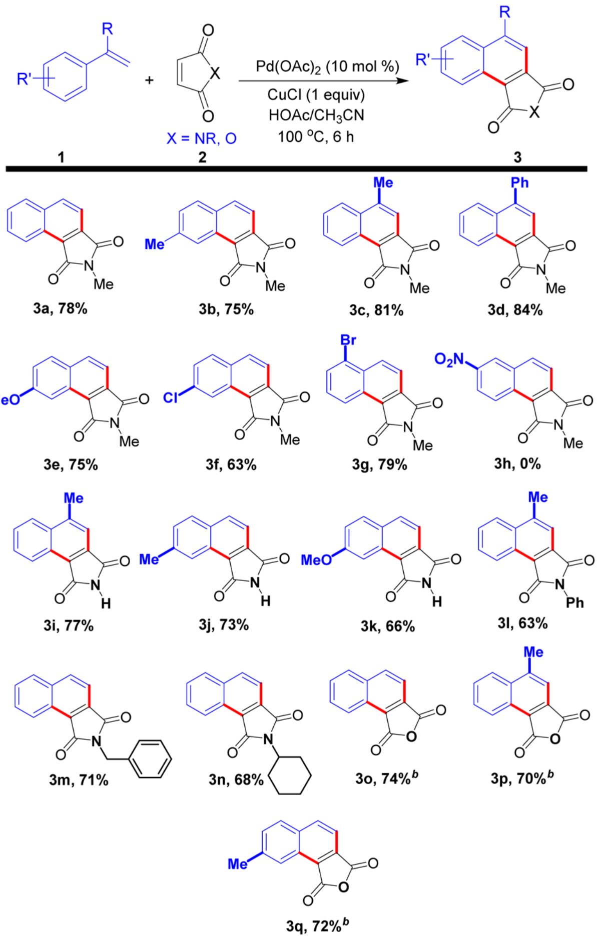


entry	oxidant	solvent	additive	yield (%)
1	$Cu(OAc)_2 \cdot H_2O$	EtOAc		21
2	$Cu(OAc)_2 \cdot H_2O$	DMF		53
3	$Cu(OAc)_2 \cdot H_2O$	DMSO		40
4	$Cu(OAc)_2 \cdot H_2O$	H_2O		trace
5	$Cu(OAc)_2 \cdot H_2O$	xylene		45
6	$Cu(OAc)_2 \cdot H_2O$	CH_3CN		58
7[b]	$Cu(OAc)_2 \cdot H_2O$	CH_3CN		trace
8	$Cu(NO_3)_2 \cdot 2.5H_2O$	CH_3CN		51
9	$CuCl_2$	CH_3CN		18
10	CuCl	CH_3CN		70
11[c]	CuCl	CH_3CN		NR
12	AgOAc	CH_3CN		68
13	TBHP	CH_3CN		N.R.
14	DTBP	CH_3CN		16
15	BP	CH_3CN		trace
16	$K_2S_2O_8$	CH_3CN		trace
17	CuCl	CH_3CN	K_2CO_3[d]	N.D.
18	CuCl	CH_3CN	AcOH[e]	77
19[f]	CuCl	CH_3CN	AcOH	75
20[g]	CuCl	CH_3CN	AcOH	trace
21[h]	CuCl	CH_3CN	AcOH	14
22[i]	CuCl	CH_3CN	AcOH	78

[a] Reactions were performed using styrene (0.3 mmol), *N*-metheylmaleimide (0.1 mmol), $Pd(OAc)_2$ (10 mol %), and oxidant (1 equiv) in 0.5 mL of solvent. [b] 10 mol % of oxidant was used. [c] Absence of $Pd(OAc)_2$. [d] 1 equiv. [e] 0.1 mL of acid was used. [f] Under O_2 balloon. [g] 0.1 mmol of styrene. [h] Reaction proceeded at 70 °C. [i] The reaction was run for 6 h.

Having found the optimal conditions, we then moved on to investigate the scope of the reaction (Scheme 1). To this end, different styrenes were exposed to the reaction conditions. As is shown in Scheme 1, styrenes containing a neutral methyl group served well under the reaction conditions (**3b**). Also, when α-substituted styrenes underwent the reaction, high yields were obtained (**3c**,**d**). Electron-rich *p*-methoxystyrene also afforded the corresponding product **3e** in 75% yield. Furthermore, halogen groups were well tolerated in this reaction, preparing the ground work for later functionalization (**3f**,**g**). Unfortunately, the reaction failed for styrene bearing nitro group (**3h**). It is noteworthy that this reaction was not limited to *N*-protected meleimides but could also be extended to a free NH maleimide (**3i**–**k**). *N*-Substituted maleimides also reacted successfully under the reaction conditions to give effective access to products **3l**–**n**.

Scheme 1. Scope of the Reaction[a]



[a] All reactions were run under the following conditions: styrene **1** (0.3 mmol, 3.0 equiv), maleimide **2** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), CuCl (1.0 equiv), and acetic acid (0.1 mL) in 0.5 mL of CH_3CN were heated at 100 °C for 6 h. [b] Maleic anhydride (3 mmol, 10 equiv) was used.

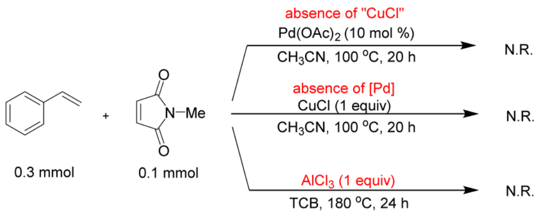
We then turned our attention to the reaction of maleic anhydride with styrene. Gratifyingly, keeping with our trend when maleic anhydride was used in lieu of maleimides, the anhydride segment remained intact despite its tendency to be cleaved under Pd catalyst,[11] and instead, its double bond took part in the reaction and culminated in derivatives **3o**–**q**. Naphtho[1,2-*c*]furan-1,3-dione derivatives are privileged structures due to their utility in the frameworks of numerous pharmaceuticals.[12a−g] They also benefited from luminescence properties,[12h] which allow them to be vastly used in industry.

Earlier, most of these products have been prepared from brominated styrenes.[13] It is also noteworthy that although compound **3o** is commercially available (available from Sigma-Aldrich, product ID T153397), it is highly expensive. Bear in mind that this reaction was previously conducted through a Diels−Alder mode; nonetheless, the aromatization product was only achievable at exceedingly high temperatures such as 220 °C.[14] This approach allows one to use an economical route to achieve naphtho[1,2-*c*]furan-1,3-dione and its derivatives. This promising result would also set the scene for further manipulation of the molecule to reach more complex all-carbon skeletons through a Pd-catalyzed reaction or naphthoisocoumarins via Ni-, Ru-, or Rh-catalyzed reaction with internal alkynes.[15]

Keeping in mind the aptitude of styrene in undergoing a Diels−Alder reaction, as a first step we set out to corroborate whether the reaction proceeded through a C−H activation or a Diels−Alder mechanism. After precise scrutiny, it was found that the presence of both Pd, which was needed to promote C−H activation, and the copper salt, which played the role of an oxidant, was vital to render the reaction feasible (Scheme 1).

In addition, when the reaction was exposed to Diels−Alder conditions, i.e., $AlCl_3$ (1 equiv) in refluxing 1,2,4-trichlorobenzene (TCB),[16] no product was observed even after a prolonged time at as temperatures as high as 180 °C (Scheme 2). As further evidence of this, when 1,4-benzoquinone and 1,4-naphthoquinone were subjected to the standard reaction conditions, no such an annulation occurred, verifying that the reaction proceeded through a mechanism that was perhaps a Diels−Alder reaction. Despite all investigations, we could not certainly rule out the probability of a Diels−Alder reaction. For further exploration in the mechanism, see the Supporting Information.

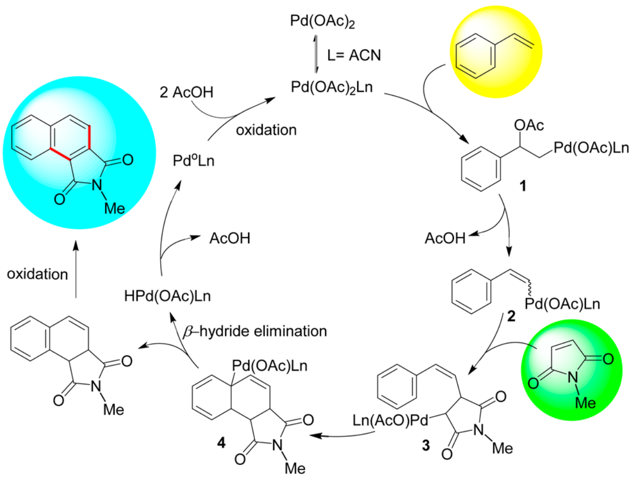
Scheme 2. Control Experiments



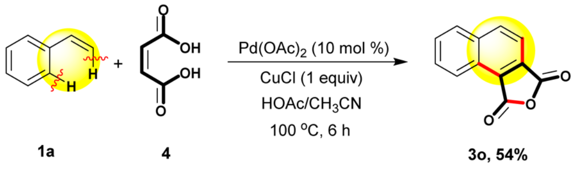
On the basis of the experimental data and precedents, a putative mechanism is depicted in Scheme 3. We envisaged that $Pd(OAc)_2$ was first added to the olefin to produce intermediate **1**. The following extrusion of AcOH would furnish an alkenyl-Pd-OAc intermediate **2**[17] whose carbopalladation with maleimide resulted in intermediate **3**. The catalytic cycle was not intercepted at this stage through a *β*-hydride eliminaton;[18] instead, a migratory insertion of Pd into the adjacent aryl ring occurred, which led to the cycloadduct **4**. Eventually, a *β*-hydride elimination and the subsequent oxidative aromatization gave rise to the formation of thus-formed product.

Finally, we are pleased to report our achievement involving a dicarboxylic acid as the second partner. When maleic anhydride was supplanted by maleic acid, a cyclization together with the dehydration occurred to afford **3o** in a moderate yield (Scheme 4). This is the first example of annulation of vinylarenes with an acid partner.

Scheme 3. Plausible Mechanism



Scheme 4. Annulation of Styrene on Maleic Acid Accompanied by a Spontaneous Condensation



In conclusion, we reported a method by which one is able to form two C−C bonds via consecutive activation of four C−H bonds in the reaction of maleimides/maleic anhydride with styrenes in a single step. This convenient strategy could also be applied to maleic acid, rendering the reaction intriguing by spanning the reaction conditions for another partner in place of its anhydride peers.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03757.

Experimental details, characterization data of all compounds, and ^{1}H and ^{13}CNMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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