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ARTICLE TYPE

Direct Cross-Coupling Reaction of Electron-Deficient Alkenes Using an Oxidizing Directing Group†

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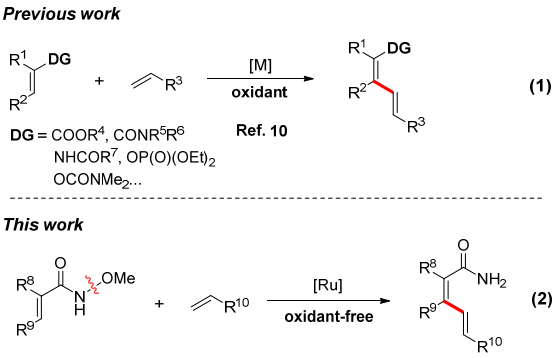
An oxidant-free cross-coupling reaction of electron-deficient alkenes using inexpensive ruthenium catalyst is reported. With the assistance of the oxidizing directing group CONH(OMe), this protocol provides a mild, straightforward and efficient method for the preparation of valuable 1,3-butadiene skeletons with excellent *Z,E* selectivities.

Over the past decades, transition-metal-catalyzed direct C-H bond functionalizations have attracted significant interest, because these transformations realize the activation of inert C-H bonds, thus allowing the use of cheaper and readily available starting materials with increased sustainability.[1] One of the most popular strategies to obtain a chemo- and regioselective C-H activation is the introduction of a directing group (DG) that directs functionalization to the desired position.[2] However, such C-H bond transformations generally require external metal or non-metal oxidants to regenerate the active catalytic species and complete the catalytic cycle, and most of which are usually performed under rather harsh oxidative conditions and provide stoichiometric amounts of the reduced oxidant as waste, reducing the overall "greenness" of the process. Recently, Ackermann group reported a ruthenium(II)-catalyzed oxidative alkenylation reactions with ambient oxygen as the sole oxidant.[3] Jeganmohan and co-workers also disclosed a ruthenium-catalyzed alkenylation of arenes at room temperature with hydrogen evolution.[4] These examples represent two strategies to overcome those drawbacks by reducing waste formation from oxidant. Another emerging strategy in the realm of C-H activation chemistry is the application of an internal oxidizing directing group (DG^{Ox}) that acts as both a directing group and an internal oxidant for redox-neutral coupling reactions.[5] Recently, several N-O containing directing groups such as *N*-methoxy, *N*-oxide, *N*-acyloxy, nitroso and even hydrazine groups are demonstrated to be popular and useful oxidizing directing groups.[6] These results have numerous advantages: the reaction proceeds under mild conditions, is very practical and completely regio- and *mono*-selective, and most importantly, results in improved yields and substrate scope.

Butadiene derivatives are valuable building blocks in synthetic organic chemistry and represent key structural motifs in naturally occurring products as well as in various bioactive molecules.[7] From the viewpoint of atom and step economy, direct cross-coupling of unactivated alkenes *via* a double C-H bond activation pathway would undoubtedly be an extremely attractive process for the preparation of 1,3-butadienes.[8-10] Very recently, Loh group reported a stereo- and chemo-selective cross-coupling between simple acrylates, providing an efficient route to (*Z,E*)-muconate derivatives, but the reaction should be performed at 135 °C and 2.0 equiv. $Cu(OAc)_2$ was required as oxidant.[10e] Meanwhile, a selective alkenylation of enol phosphates *via* direct C-H functionalization was reported by the same group, also using quantitative amount of metal oxidant (Scheme 1, eq 1).[10f] Herein, we describe a novel redox-neutral (2*Z*,4*E*)-dienamide synthesis employing oxidizing directing group under very simple and mild reaction conditions (Scheme 1, eq 2).



Scheme 1 Directed cross-coupling of alkenes.

The first step of the present work was the installation of suitable directing group to an alkene. Concerning the subsequent cross-coupling step, the initial optimization experiments were performed with *N*-methoxy-2-methyl-2-propenamide (**1a**) derived from methacrylic acid and *n*-butyl acrylate (**2a**), in the presence of inexpensive $[Ru(p\text{-cymene})Cl_2]_2$[11] (5.0 mol%) and NaOAc (30 mol%) in DCE at 60 °C as the catalytic conditions, but the reaction afforded desired 1,3-dienamide **3a** in only 19% yield (Table 1, entry 1). After screening a series of representative solvents, we were pleased to find that the yield was increased to 49% when the reaction was performed in *N*,*N*-dimethyl formamide (DMF) (Table 1, entry 2). In contrast, it is worthy to note that other polar solvents such as DMSO and THF even afforded no desired product (Table 1, entries 4 and 5). Considering that basicity may influence the reaction, then acetates with different alkali metals were tested, but all of them could not greatly improve the reaction (Table 1, entries 7-9). It is worth noting that addition of $AgSbF_6$ even totally retarded the cross-coupling, indicating that acetate is crucial for the

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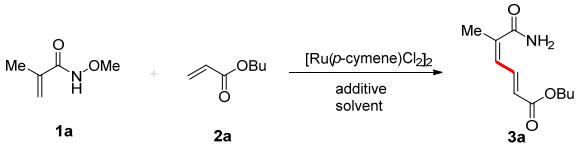
ruthenium-based cyclometalation and the regeneration of the catalyst (Table 1, entry10).[6p,11] Subsequently, we turned to examine sterically hindered carboxylate additives including KO_2CMes and KOPiv.[11d] To our delight, both of the carboxylates gave better yields. If KOPiv was employed, the product yield increased to 82% with 99/1 *Z*/*E* ratio (Table 1, entries 11 and 12). The *Z*-configuration of product **3a** was determined by a NOESY NMR spectrum experiment, indicating a directed vinylic C-H bond functionalization event.[6,10] Changing the amount of additive or reaction temperature led to decreased yields. Moreover, the reaction provided no product in the absence of [Ru(*p*-cymene)Cl_2]$_2$ (see the SI for details).

Table 1 Optimization of catalytic conditions[a]



1a **2a** **3a**

Entry	Additive	Solvent	Yield (%)[b]	*Z*/*E*[c]
1	NaOAc	DCE	19	99/1
2	NaOAc	DMF	49	99/1
3	NaOAc	CH_3CN	37	93/7
4	NaOAc	THF	0	-
5	NaOAc	DMSO	0	-
6	NaOAc	*t*-AmOH	20	99/1
7	CsOAc	DMF	32	99/1
8	LiOAc	DMF	58	94/6
9	KOAc	DMF	55	99/1
10	$AgSbF_6$	DMF	0	-
11	KO_2CMes	DMF	63	99/1
12	**KOPiv**	**DMF**	**82**	**99/1**

[a] Unless otherwise noted, the reactions were carried out using acrylamide (**1a**) (0.20 mmol), acrylate **2a** (0.36 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5.0 mol%), additive (30 mol%) in a solvent (0.2 M, 1.0 mL) at 60 °C for 16 h under an argon atmosphere (1 atm). [b] The yields indicated in the table are isolated yields. [c] *Z*/*E* ratios were determined by ^{1}H NMR. DCE = 1,2-dichloroethane; DMSO = dimethyl sulphoxide; DMF = *N*,*N*-dimethyl formamide.

With the optimized reaction conditions in hand, we next examined the scope and limitation of differently substituted *N*-methoxyacrylamide (**1**) by employing butyl acrylate (**2a**) as coupling partner (Table 2). Subjecting acrylamide (**1**) tethering a hexyl, decyl or 2-phenylethyl substituent at the *α*-position of acrylamide to acrylate **2a** delivered the corresponding 1,3-butadiene in moderate to good yields with excellent *Z*/*E* stereoselectivity. However, introduction of aromatic rings to the *α*-position of acrylamide (**1**) decreased the product yields remarkably even at elevated temperature (80 °C) due to low conversion, and obvious electronic effect was observed, showing that electron-donating groups accelerated the reaction while electron-withdrawing groups gave opposite results (Table 2, **3e-j**). Moreover, this catalytic protocol is not only limited to *α*-monosubstituted acrylamide but also is applicable to *α*,*β*-disubstituted acrylamide derivatives (**3l** and **3m**), albeit with decreased yields. Other *β*-substituted acrylamide, as exemplified with *N*-methoxy-2-butenamide, was also investigated, but only 15% yield was obtained (**3n**).[12]

The scope of the different alkenes as coupling partners was also investigated (Table 2). Various acrylates, such as methyl acrylate, ethyl acrylate, *tert*-butyl acrylate, hexyl acrylate, and phenyl acrylate were all efficiently reacted with acrylamide **1a** to produce the corresponding butadienes in good yields with excellent stereo-selectivities (Table 2, **3o-t**). Intriguingly, acrylamide **1a** also reacted with 2,2,2-trifluoroethyl acrylate to give the cross-coupling product **3t** in 45% yield without a decrease in *Z*/*E* ratio selectivity. Although electron-rich alkenes and styrene are inactive in such cross-coupling reactions,[13] other electron-deficient alkenes,[14] such as *α*,*β*-unsaturated ketone, 2,3,4,5,6-penta-fluorostyrene and vinyl phosphonate, all reacted well and gave the corresponding butadiene products in moderate to good yields with excellent *Z*/*E* stereo-selectivity (Table 2, **3u-w**).

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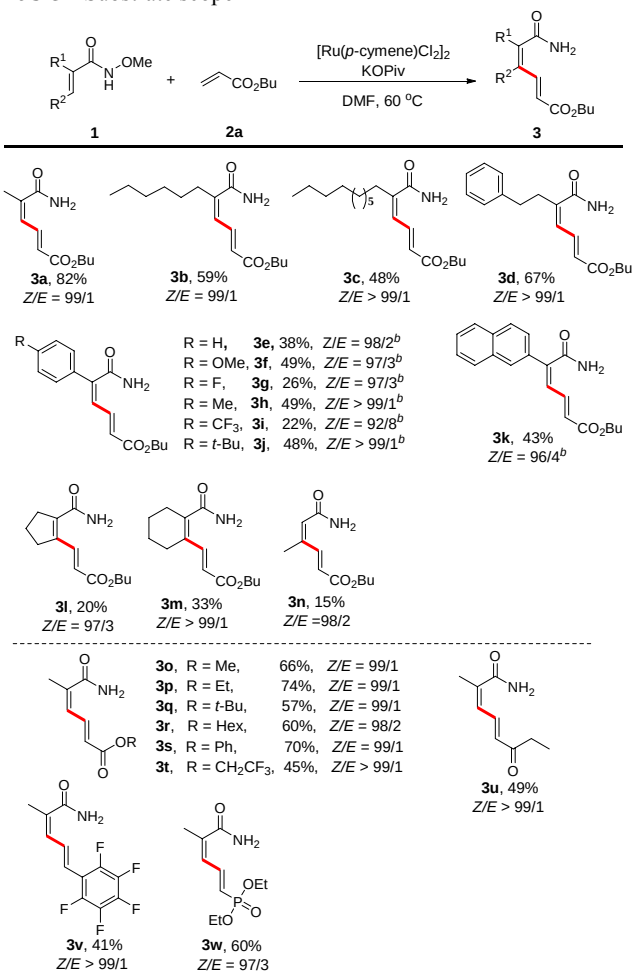
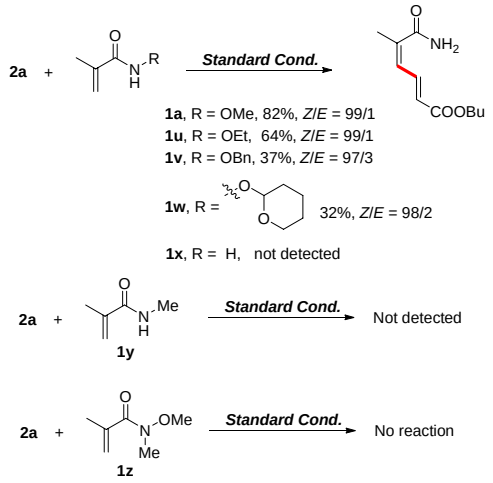
Table 2 Substrate scope[a]



[a] Unless otherwise noted, the reactions were carried out using amide **1** (0.2 mmol), acrylate **2a** (0.36 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5.0 mol%), KOPiv (30 mol%) in DMF (1.0 mL) at 60 °C for 16 h under an argon atmosphere (1 atm). The yields indicated in the table are isolated yields; *Z*/*E* ratios were determined by ^{1}H NMR. [b] The reaction was performed at 80 °C.

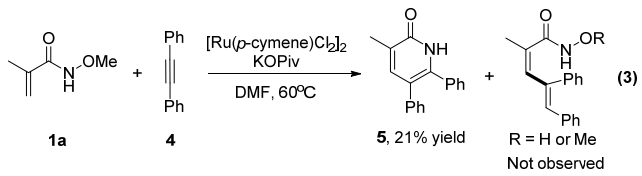
The versatility of the reaction is also exemplified by the tolerance of varied *O*-substituents (Scheme 2). *N*-Ethoxy-2-methyl-2-propenamide (**1u**) reacted well with acrylate. However, installation of more bulky groups, such as Bn (**1v**) and tetrahydropyrane (**1w**), to oxygen atom led to decreased yields. Moreover, methacrylamide (**1x**) and *N*-methyl methacrylamide

(**1y**) without *N*-methoxy group were also tested as precursors, but neither of them afforded desired butadiene product. Furthermore, Weinreb amide **1z** did not show any reactivity, exhibiting a Ru-N bond based five-membered ruthenacycle intermediate.[6]

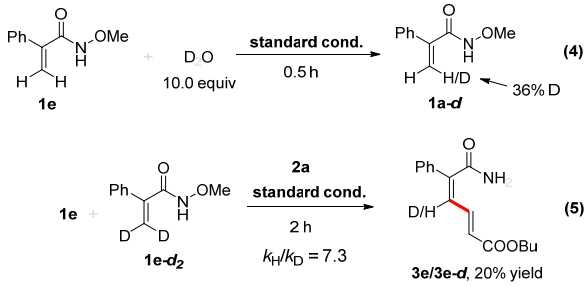


Scheme 2 Variation of the differently *N*- and/or *O*-substituted acrylamides.

Moreover, if diphenyl acetylene **4** was subjected to acrylamide **1a** under the optimal conditions, a valuable pyridone **5** *via* cyclization was obtained in 21% yield without the formation of desired 1,3-butadiene (eq 3).[6d,p,q]



Finally, we pursued some mechanistic studies of the catalytic process. Exposure of acrylamide **1e** to optimal conditions without acrylate in the presence of deuterated water led to an exclusively *Z*-selective vinyl H/D exchange, suggesting a reversible cyclometalation event (Scheme 3, eq 4).[6,10] Moreover, a KIE value of 7.3 reveals that the vinylic C-H bond cleavage might be involved in the rate-determining step (Scheme 3, eq 5).[6r,10e-f]



Scheme 3 Isotopic labeling experiments.

On the basis of the above results and previous reports,[6] we propose that the reaction proceeds *via* reversible C-H bond activation process, yielding a five-membered ruthenacycle **II**, with concomitant liberation of pivalic acid. Then, the alkene **2** inserts into the Ru-C bond to form seven-membered ruthenacycle intermediate **III**. Subsequently, *β*-H elimination followed by reductive elimination furnishes ruthenium(0) intermediate. Next, insertion of ruthenium(0) to N-O bond takes place to afford ruthenium(II) amide intermediate **IV**. Finally, protonation of **IV** by pivalic acid releases the desired product **3** while at the same time regenerating the active ruthenium(II) biscarboxylate catalyst **I** to facilitate the next catalytic cycle (Scheme 4).

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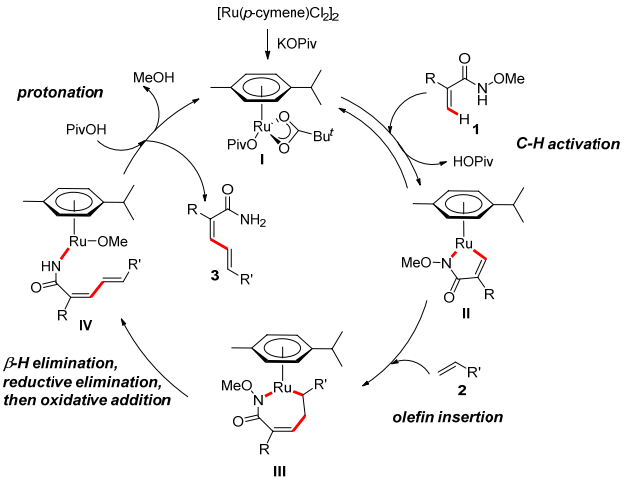

Scheme 4 Proposed mechanism.

Conclusions

In conclusion, we have developed an inexpensive ruthenium-catalyzed direct cross-coupling reaction of electron-deficient alkenes. With the assistance of the oxidizing directing group, this protocol provides a mild, oxidant-free, straightforward method for the preparation of valuable 1,3-dienamide with excellent *Z*,*E* selectivities.

Acknowledgement

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12 Generally, the poor or moderate yields are caused by decreased conversions comparing to **3a**, especially in the examples of **3e**, **3l** and **3n**. Moreover, N-O bond cleavage also occurred in the examples of **1f**, **1g**, **1h**, **1i**,**1j** and **1k**, leading to primary acrylamides as side products which could not react as cross-coupling precursors.

13 Increased catalyst concentration (10 mol%) still did not improve the reaction yield.

13 Styrene derivatives and electron-rich alkenes were proved to be inactive and no diene or dihydropyridone product was formed (ref. 6f, 6p-q).

14 Branched and linear acrylates, such as methyl methacrylate and methyl crotonate, led to trace amount of product.