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Ruthenium- and rhodium-catalyzed cross-coupling reaction of acrylamides with alkenes: efficient access to (*Z*,*E*)-dienamides†

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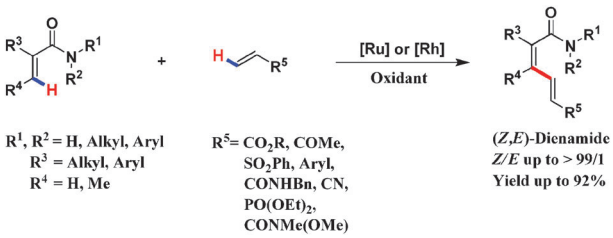
Ruthenium- and rhodium-catalyzed direct oxidative cross-coupling reactions of acrylamides with alkenes were developed. These methods provide an efficient route for the synthesis of (*Z*,*E*)-dienamides in excellent yields with good stereoselectivity. The catalytic systems allowed oxidative olefination of a wide range of alkenes bearing different functional groups, such as CO_2R, COMe, SO_2Ph, aryl, CONHBn, CN, $PO(OEt)_2$, as well as Weinreb amide.

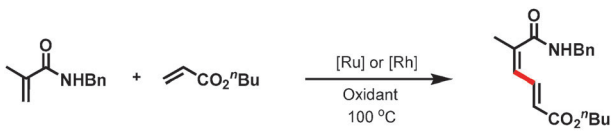
Butadiene is an important structural motif present in a large class of pharmaceutically active molecules and complex natural products,[1] such as naphthomycin A,[2] rifabutine,[3] (+)-dactylolide,[4] *etc*. Thus, development of efficient, selective and practical synthetic methodology would be highly desirable. To our knowledge, carbonyl olefination[5] such as Wittig reaction and cross-coupling reactions[6] such as Heck coupling reactions represents two general approaches for the synthesis of butadienes. However, direct alkenylation *via* vinylic C–H bond activation remains highly desirable as it minimizes waste formation and obviates pre-functionalization steps. To date, only several research groups, such as Ishii,[7] Loh,[8] Yu,[9] Glorius[10] and Liu[11] reported that certain classes of butadienes can be synthesized by Pd- or Rh-catalyzed olefination between simple alkenes, although the substrate scope is often limited. Recently, ruthenium has emerged as an efficient catalyst for C–H bond activation, olefination and alkynylation reaction.[12] However, to the best of our knowledge, the use of inexpensive ruthenium catalyst[12c] for direct cross-coupling reaction of olefins to form butadienes has not been reported. During our studies on oxidative olefination of vinylic C–H bond,[8] we developed a ruthenium-catalyzed direct cross-coupling reaction between acrylamides and electron-deficient alkenes to produce (*Z*,*E*)-dienamides in high efficiency.[13a] The same transformation also could be achieved by rhodium catalyst (Scheme 1).[13b] The catalytic systems allowed oxidative olefination of a wide range of alkenes bearing different functional groups, such as CO_2R, SO_2Ph, aryl, CONHBn, CN, $PO(OEt)_2$, as well as Weinreb amide, which opens up new possibilities for the synthesis of a series of complex natural products and drugs. At the outset of our studies, the reaction of methacrylamide with *n*-butyl acrylate was explored to screen the catalytic conditions, employing $[RuCl_2(p\text{-cymene})]_2$ as the catalyst[14] (Table 1).



Scheme 1 Direct cross-coupling reaction of acrylamides with alkenes providing (*Z*,*E*)-dienamides.

The cross-coupling reaction exhibited low conversion in the absence of additive (entry 1).[14] Usage of KPF_6 or $AgSbF_6$ as an additive led to the desired product in moderate yield

Table 1 Optimization of catalytic conditions[a]



Entry	Catalyst	Oxidant	Solvent	Yield (%)
1	[Ru]	$Cu(OAc)_2{\cdot}H_2O$	*t*-AmOH	28
2[b]	[Ru]	$Cu(OAc)_2{\cdot}H_2O$	Dioxane	50
3[c]	[Ru]	$Cu(OAc)_2{\cdot}H_2O$	Dioxane	44
4[b,d]	[Ru]	$Cu(OAc)_2{\cdot}H_2O$	Dioxane/H_2O	55
5[b,e]	**[Ru]**	**$Cu(OAc)_2{\cdot}H_2O$**	**Dioxane/H_2O/AcOH**	**83**
6[b,f]	[Ru]	$Cu(OAc)_2{\cdot}H_2O$	Dioxane/H_2O	57
7[b]	[Ru]	AgOAc	Dioxane/H_2O/AcOH	21
8	[Rh]	Ag_2CO_3	MeCN	0
9[b]	[Rh]	$Cu(OAc)_2{\cdot}H_2O$	DME	63
10	[Rh]	$Cu(OAc)_2{\cdot}H_2O$	*t*-AmOH	68
11	**[Rh]**	**$Cu(OAc)_2{\cdot}H_2O$**	**Acetone**	**85**
12[g]	[Rh]	$Cu(OAc)_2{\cdot}H_2O$	Acetone/H_2O	83

[a] Reaction conditions unless otherwise specified: **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.5 equiv.), Ru or Rh (5 mol%), and an oxidant (2.0 equiv.) in a specific solvent (0.6 mL), at 100 °C, under nitrogen, 18 h. The yields indicated in the table are isolated yields. [b] KPF_6 (20 mol%) was used as an additive. [c] $AgSbF_6$ (20 mol%) was used as an additive. [d] Dioxane/H_2O = 2/1(v/v). [e] Dioxane/H_2O/AcOH = 8/4/1(v/v/v). [f] 2.0 equiv. AcOH added. [g] Acetone/H_2O = 2/1 (v/v). [Ru] = $[RuCl_2(p\text{-cymene})]_2$; [Rh] = $[RhCp^*Cl_2]_2$.

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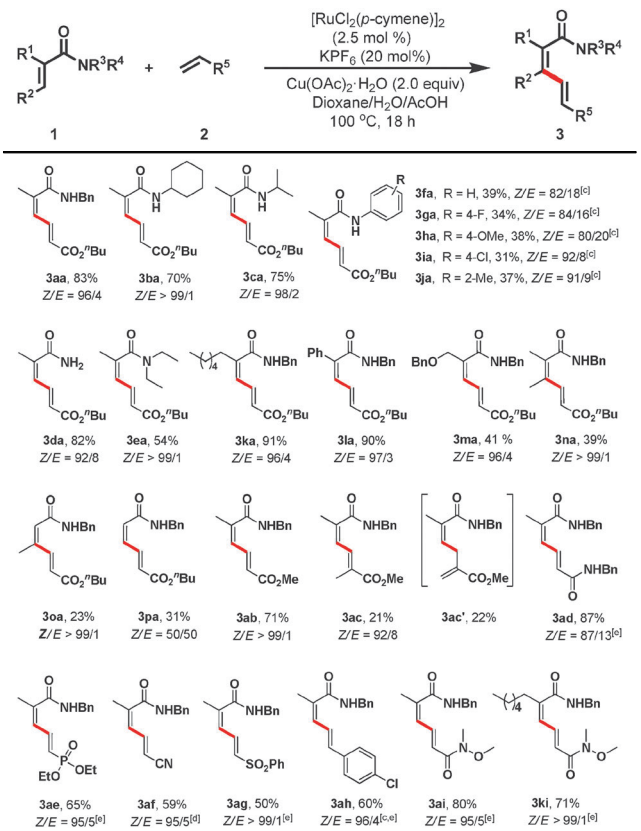
(entries 2 and 3).[15] To optimize the catalytic conditions, the effect of solvents was subsequently examined (see ESI†). To our delight, a mixed solvent system of dioxane/H_2O/AcOH (v/v/v = 8/4/1) dramatically improved the reaction, and the yield was increased to 83% with good stereoselectivity (Z/E = 96/4) (entry 5). The intramolecular cyclization reaction towards unsaturated lactam was not observed.[10,14a] Other oxidant, such as AgOAc, led to low yield. Simple ruthenium salts such as $RuCl_3$ were also examined but were ineffective (see ESI†). The same model reaction was chosen to screen the Rh-catalyzed olefination conditions. Different reaction parameters, such as solvent and oxidant, were explored (Table S2 in ESI†). Optimal yields of dienamide were obtained with $[RhCp^*Cl_2]_2$, along with $Cu(OAc)_2{\cdot}H_2O$ as an oxidant, and acetone as the solvent (entry 11).

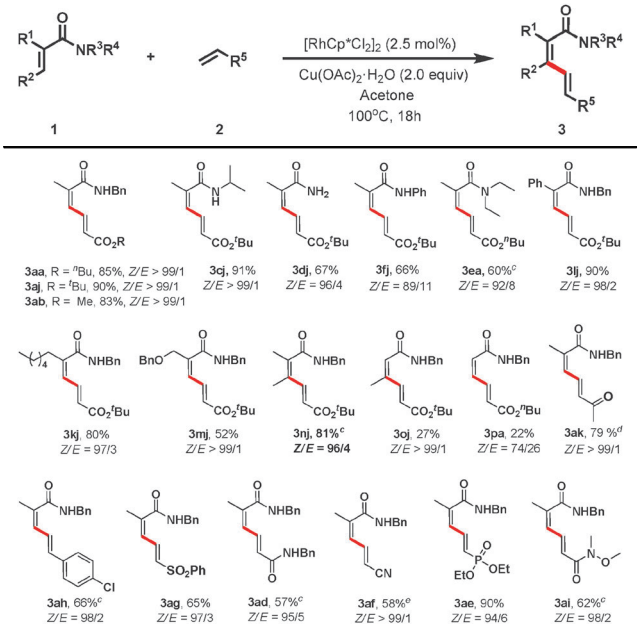
With the two optimised catalytic systems in hand, we firstly explored the scope of Ru-catalyzed oxidative olefination by employing differently substituted acrylamides and alkenes (Table 2). Acrylamides **1** bearing different alkyl groups or no substituent on the nitrogen atom were smoothly reacted. However, the cross-coupling reaction between *N*-aryl methacrylamides with acrylate showed low conversion even at elevated temperature, and the desired products were isolated in

Table 2 Exploration of the scope of various acrylamides towards direct cross-coupling with alkenes by ruthenium catalyst[ab]



[a] The reactions were carried out as follows: acrylamide **1** (0.1 mmol), acrylate **2a** (0.15 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), KPF_6 (20 mol%), $Cu(OAc)_2{\cdot}H_2O$ (0.2 mmol) in dioxane/H_2O/AcOH = 8/4/1 (0.6 mL) at 100 °C, 18 h. [b] The yields indicated in the table are isolated yields. [c] The reaction was performed at 120 °C. [d] 5.0 equiv. acrylonitrile used. [e] 1.2 equiv. alkene used.

Table 3 Exploration of the scope of acrylamides towards direct cross-coupling with various functionalized alkenes by rhodium[ab]

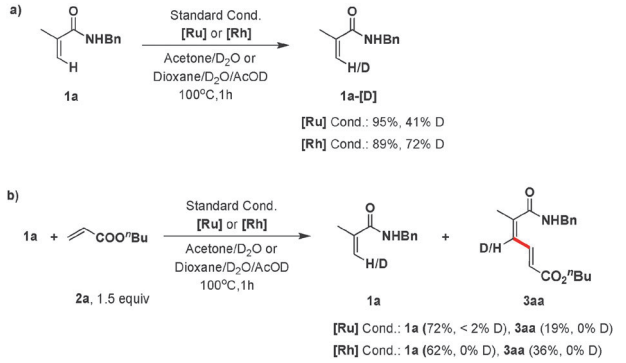


[a] The reactions were carried out as follows: acrylamide **1** (0.2 mmol), acrylate **2** (0.3 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol%), $Cu(OAc)_2{\cdot}H_2O$ (0.4 mmol) in acetone (0.6 mL) at 100 °C, 18 h. [b] The yields indicated in the table are isolated yields. [c] The reaction was performed at 120 °C, 12 h. [d] The reactions were performed at 80 °C for 6 h. [e] 5.0 equiv. acrylonitrile used.

31–39% yield (**3fa–3ja**).[12c] Further structural modifications at the α-position slightly influenced the catalytic process (**3ka**, **3la**, **3ma**).[16] It is worthy to note that *N*-benzyl-2,3-dimethylpropenamide also led to the *tetra*-substituted diene in low yield (**3na**). This is due to the degradation of the starting material under the acidic conditions. If a methyl group was introduced into the β-position of the acrylamide, the reaction was sluggish and the corresponding product was isolated in 23% yield (**3oa**).[14d,18b] Also, acrylamide with an un-substituted olefin unit reacted with low conversion, and a mixture of isomers (Z/E = 1/1) was obtained in only 31% yield (**3pa**).[14d] α-Methylacrylate also showed low conversion and a by-product (**3ac′**) was formed in 22% yield during the catalytic process.[17c] The catalytic system was not only restricted to the usage of acrylates, but also allowed for a series of differently functionalized alkenes, and the functional groups could be CONHBn (**3ad**), $PO(OEt)_2$ (**3ae**), CN (**3af**), SO_2Ph (**3ag**) and 4-Cl phenyl (**3ah**).[17] To our delight, Weinreb acrylamide was efficiently converted as well (**3ai** and **3ki**).

Next, we examined the scope of Rh-catalyzed cross-coupling reaction of acrylamides with alkenes. This catalytic system also proved to be tolerant of a series of functional groups (Table 3).

In addition, competition experiments between differently substituted styrenes with acrylamide as limiting reagent was performed, showing that electron-deficient styrene reacted preferentially.[10,17a] In contrast, intermolecular competition experiments between differently N-substituted and α-substituted acrylamides revealed that the electron-rich substrate was more efficiently converted, hence indicating an electrophilic C–H bond activation (see ESI†). To obtain some further mechanistic insight, we



Scheme 2 Isotopically labeled experiment.

performed some control experiments with isotopically labeled solvents. Both of the catalytic conditions led to *Z*-selective olefinic H/D exchange on methacrylamide **1a** in the absence of acrylate, thus indicating reversible cyclometallation modes (Scheme 2a).[19] In contrast, if the same reaction is performed in the presence of acrylate **2a**, no deuterium incorporation is observed in unreacted **1a**, and no H/D scrambling between the β-olefinic proton of the product **3aa** and the solvent was observed (Scheme 2b).

Based on these experiments we proposed the possible mechanism. The reaction is presumably initiated by cyclometalation of acrylamide **1** by amide-directing C–H bond activation. Coordination of alkene **2** to the metal center, and followed by insertion of the carbon–carbon double bond forms a 7-membered ruthacycle or rhodacycle species. Subsequent β-elimination occurs to afford the desired (*Z*,*E*)-dienamide **3**.

In summary, we have developed Ru- and Rh-catalytic systems for the direct cross-coupling of acrylamides with electron-deficient alkenes forming (*Z*,*E*)-dienamides. Both of the two transformations exhibit wide functional group compatibility and substrate flexibility, and thus would have potential broad application in organic synthesis.

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16 The electron-rich acrylamide was easier to be reacted, thus revealed an electrophilic activation manifold. This result is in agreement with intermolecular competition experiments (see ESI†).

17 For the two catalytic conditions: (*a*) Styrene and 4-methoxy styrene were also tested, but both of them led to low conversion, and the desired dienamide was obtained in <20% yield. Also, alkyl olefin, such as, 5-methoxy pentene, couldn't be well reacted, and only trace product was observed. These results indicated that electron-deficient alkene was reacted preferentially. (See competition experiment and ref. 14*b* and 18*a*); (*b*) moreover, alkenes with an internal olefin unit, such as methyl *trans*-2-hexenoate, was totally inactive, and the starting materials were mostly recovered; (*c*) homo-coupling by-product originated from acrylamide could be detected (<10% yield) when less reactive substrates were utilized.

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