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Cross-Coupling of Acrylamides and Maleimides under Rhodium Catalysis: Controlled Olefin Migration

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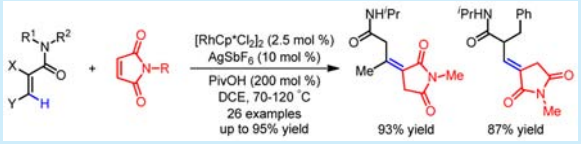
Supporting Information

ABSTRACT: The rhodium(III)-catalyzed direct cross-coupling reaction of electron-deficient acrylamides with maleimides is described. This protocol displays broad functional group tolerance and high efficiency, which offers a new opportunity to access highly substituted succinimides. Dependent on the substituent positions of acrylamides and reaction conditions, olefin migrated products were obtained with high regio- and stereoselectivity.



The directing group-assisted transition-metal-catalyzed C−H bond functionalization has evolved into a powerful tool for facile access to biologically relevant molecules.[1] In particular, the amide directing groups have been widely explored under rhodium catalysis due to the excellent directing ability as well as potential C−N bond precursors.[2] In this context, the Rh-catalyzed C−H functionalization of electron-deficient olefins has been less investigated and is more challenging.[3] For example, Tanaka, Glorius, and Loh described the formation of conjugated dienamides from acrylamides and various π-unsaturates such as alkenes, alkynes, and allenes under rhodium catalysis.[4] Glorius and Loh independently reported the Rh-catalyzed vinylic C−H alkynylation of acrylamides using TIPS-EBX as an electrophilic alkynylation reagent leading to 1,3-enynes.[5] In addition, acrylamides have been used for the preparation of pyridones via tandem Rh-catalyzed annulations reactions with alkynes.[6] Moreover, arylation,[7] allylation,[8] and halogenation[9] of acrylamides have been also reported under rhodium catalysis.

The succinimide motif is among the most interesting discoveries in the field of organic and medicinal chemistry. In particular, this scaffold is found to be a central pharmacophore of many pharmaceuticals such as phensuximide, ethosuximide, apremilast, thalidomide, and lurasidone (Figure 1).[10] Furthermore, succinimide frameworks could be readily transformed into biologically relevant pyrrolidines and γ-lactams.[11] Thus, the synthesis of succinimides has been an important area for drug development. Traditional methods for the preparation of succinimides include the dehydrative condensation of dicarboxylic acids or anhydrides with amines and the cyclization of amic acids under acidic conditions.[12]

Recently, maleimides have been applied to the synthesis of functionalized succinimides via the conjugated addition strategy using various nucleophiles under metal catalysis, organocatalysis, and acid/base conditions.[13] With the advance of catalytic C−H functionalization, maleimides have been used for the construction of succinimides (Scheme 1). In 2011, Li demonstrated

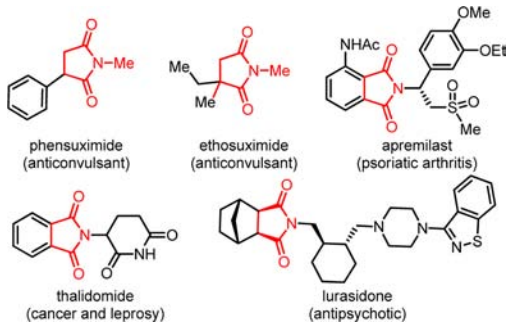


Figure 1. Pharmaceuticals with succinimide scaffold.

a single example of the Rh(III)-catalyzed oxidative coupling of (NH)-isoquinolones and maleimides.[14a] Zhu also disclosed a single example of the formation of spirosuccinimides from maleimides and *N*-benzoylsulfonamides under Rh catalysis.[14b] In addition, Hirano and Miura described the Cu-mediated synthetic protocol for the formation of spiro adducts.[14c] Recently, Prabhu reported the C−H alkylation reactions of acetophenones[15a] and *N*-benzoyl indoles[15b] with maleimides under Ru(II) catalysis.

In contrast to previous studies on the formation of spirosuccinimides using secondary benzamides under Rh(III) catalysis, we found that the cross-coupling of both electron-deficient acrylamides and maleimides did not furnish any corresponding spiro compounds. In addition, Loh reported the allylation reaction of acrylamides with allylic acetates under Rh(III) catalysis affording the allylated products without olefin migration.[8a] Herein, we described the cross-coupling of acrylamides and maleimides with controlled olefin migration under Rh(III) catalysis. Notably, olefin migration was observed in all cases of both α- and β-substituted acrylamides to give

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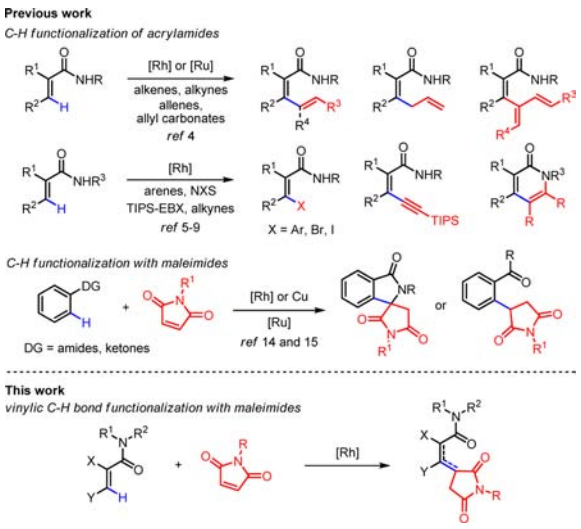
Scheme 1. C−H Functionalization of Acrylamides with Maleimides

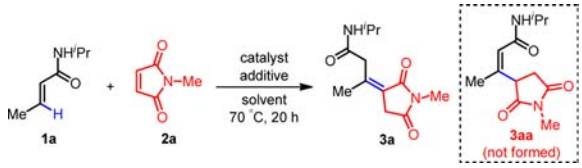


thermodynamically stable olefins with high diasteroselectivity, which were confirmed by NOE experiments.

Our initial investigation was commenced by coupling (*E*)-*N*-isopropylbut-2-enamide (**1a**) and *N*-methyl maleimide (**2a**) under rhodium catalysis (Table 1). Surprisingly, the coupling reaction afforded tetrasubstituted olefin **3a** in 7% yield instead of the expected trisubstituted compound **3aa** or intramolecular cyclization compound, as reported by Zhu.[14b] This outcome could be reasoned due to the higher stability of tetrasubstituted olefin product **3a**. Based on this interesting result, further optimization was performed using different additives. As shown in entries 2−7, pivalic acid (PivOH) and acetic acid (AcOH) were found to be highly effective for this transformation. In addition, the decreased amount (100 mol %) of PivOH provided a comparatively lower yield of **3a** as shown in entry 8. Further screening of solvents revealed that DCE is an optimal solvent for the formation of our desired product **3a** (Table 1, entries 9−11). However, other metal catalysts such as $[CoCp^*(CO)I_2]$ and $[Ru(p\text{-cymene})Cl_2]_2$ were found to be less effective under otherwise identical reaction conditions (Table 1, entries 12 and 13). Further study showed that a cationic rhodium complex in the presence of PivOH is very crucial to promote the coupling of **1a** and **2a** (Table 1, entries 14 and 15). Moreover, an almost similar yield was obtained under a N_2 atmosphere (Table 1, entry 16).

To examine the substrate scope and limitations, a broad range of *β*-substituted acrylamides were screened to couple with maleimide **2a**, as shown in Scheme 2. First, we screened different *N*-protection groups on crotyl amide under the optimal reaction conditions. To our delight, crotonamide **1b** underwent the coupling reaction to give our desired product **3b** in moderate yield. However, secondary acrylamides **1c** and **1d** smoothly participated in the alkylation and migration process to give the corresponding products **3c** and **3d** in high yields. Interestingly, *N*-phenyl acrylamide **1e** was found to undergo the coupling reaction at both olefinic and aromatic C−H bonds affording **3e** and **3e′** in 55% combined yields. In sharp contrast to primary and secondary acrylamides, tertiary amides **1f**−**1h** provided corresponding products as a mixture of *Z*- and *E*-isomers in high yields, presumably due to increasing steric interaction between tertiary amides and the carbonyl group on succinimides. In

Table 1. Selected Optimization for Reaction Conditions[a]



entry	catalyst	additive (mol %)	solvent	yield (%)[b]
1	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10)	DCE	7
2	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), $Cu(OAc)_2$ (200)	DCE	60
3	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), AgOAc (200)	DCE	40
4	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), NaOAc (200)	DCE	24
5	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), CsOAc (200)	DCE	N.R.
6	**$[RhCp^*Cl_2]_2$**	**$AgSbF_6$ (10), PivOH (200)**	**DCE**	**93**
7	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), AcOH (200)	DCE	89
8	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), PivOH (100)	DCE	81
9	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), PivOH (200)	THF	36
10	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), PivOH (200)	MeOH	N.R.
11	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), PivOH (200)	DMSO	N.R.
12	$[CoCp^*(CO)I_2]$	$AgSbF_6$ (10), PivOH (200)	DCE	10
13	$[Ru(p\text{-Cy})Cl_2]_2$	$AgSbF_6$ (10), PivOH (200)	DCE	21
14	$[RhCp^*Cl_2]_2$	PivOH (200)	DCE	trace
15		$AgSbF_6$ (10), PivOH (200)	DCE	N.R.
16[c]	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), PivOH (200)	DCE	90

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (2.5 mol %), additive (quantity noted), and solvent (1 mL) under air at 70 °C for 20 h in pressure tubes. [b]Isolated yield by flash column chromatography. [c]The reaction was carried out under N_2.

addition, *β*-alkyl substituted acrylamides showed high (*Z*)-selectivity under the current reaction conditions to furnish **3i** in 62% yield. Furthermore, this method could be applied to cinnamides **1j**−**1m** and heteroaryl substituted acrylamide **1n** to provide the corresponding products at elevated temperature (120 °C). It should be noted that *β*-aryl substituted acrylamides show the same orientation as in the case of *β*-alkyl substituted compounds to provide *E*-isomers **3j**−**3n** with high diastereoselectivity.

To further evaluate the scope of this process, the coupling of a range of maleimides **2b**−**2k** with acrylamide **1a** was screened under the optimal reaction conditions (Scheme 3). Gratifyingly, unprotected maleimide **2b** was found to deliver tetrasubstituted olefin **4b** in 57% yield. Additionally, *N*-alkyl and *N*-aryl **2c**−**2g** were found to be good substrates in this coupling reaction to afford our desired products **4c**−**4g** in high yields. However, *N*-allyl maleimide (**2h**) showed low reactivity toward the coupling reaction under the standard reaction conditions. Notably, maleimide **2i** derived from the L-alanine amino acid furnished **4i** in 71% yield. Moreover, we found that this reaction proceeded readily with bis-maleimide **2j** to afford **4j** with high monoselectivity. It should be mentioned that the remaining

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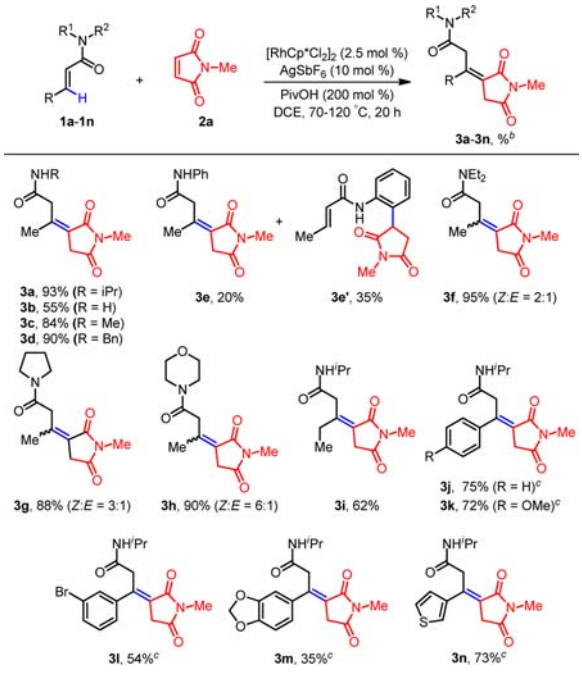
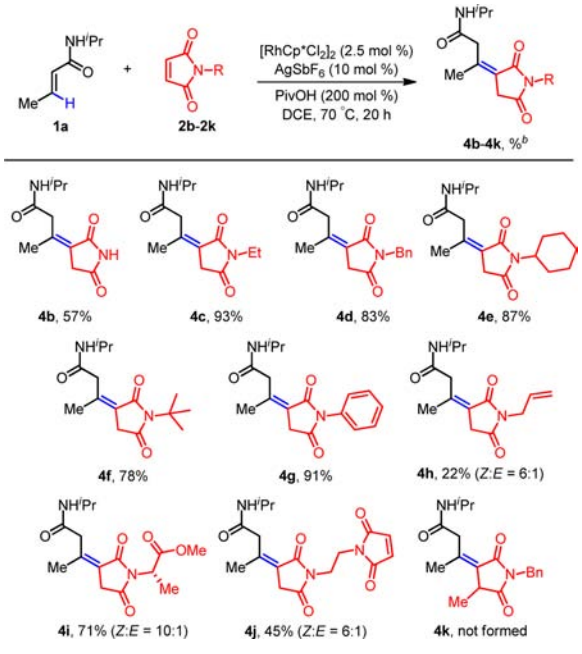
Scheme 2. Scope of β-Substituted Acrylamides[a]



[a]Reaction conditions: **1a−1n** (0.2 mmol), **2a** (0.4 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), PivOH (200 mol %), DCE (1 mL) under air at 70 °C for 20 h in pressure tubes. [b]Isolated yield by flash column chromatography. [c]The reaction was carried out at 120 °C.

Scheme 3. Scope of Maleimides[a]

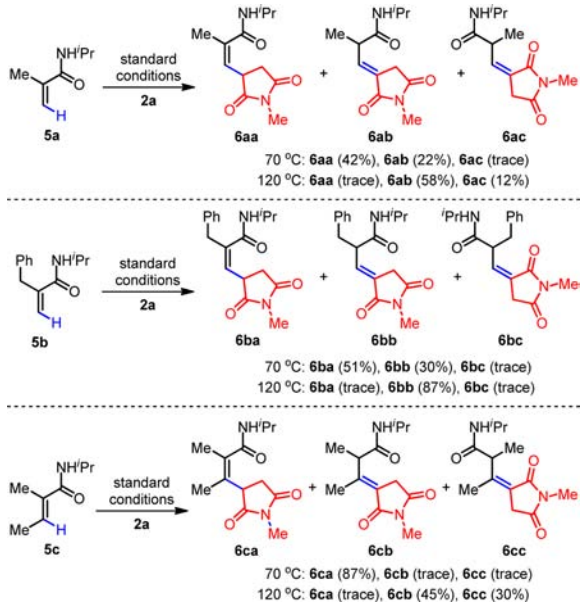


[a]Reaction conditions: **1a** (0.2 mmol), **2b−2k** (0.4 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), PivOH (200 mol %), DCE (1 mL) under air at 70 °C for 20 h in pressure tubes. [b]Isolated yield by flash column chromatography.

maleimide moiety on **4j** offers versatile synthetic functionality for further transformation. Unfortunately, C2-substituted maleimide **2k** was found to be unreactive in this transformation.

Next, we expanded the substrate scope of acrylamides to α-substituted analogues **5a−5c** (Scheme 4). The reaction of

Scheme 4. Scope of α-Substituted Acrylamides[a,b]

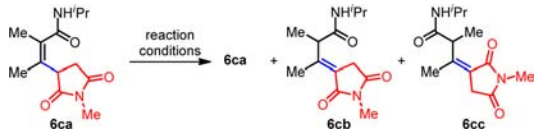


[a]Reaction conditions: **5a−5c** (0.2 mmol), **2a** (0.4 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), PivOH (200 mol %), DCE (1 mL) under air at 70 and 120 °C for 20 h in pressure tubes. [b]Isolated yield by flash column chromatography.

methacrylamide **5a** with **2a** provided an inseparable mixture of nonmigrated compound **6aa** and migration product **6ab** in 66% combined yield. Interestingly, at elevated temperature, this reaction afforded predominantly the migrated compound **6ab** (*E*-isomer) and **6ac** (*Z*-isomer) as a separable mixture with a ratio of ab. 5:1. In addition, α-benzyl acrylamide **5b** provided similar results with **2a** at 70 °C. However, only the *E*-isomer product **6bb** was exclusively obtained at 120 °C in 87% yield with a trace amount of nonmigrated compound **6ba** and *Z*-isomer **6bc**. In the case of α,β-disubstituted acrylamides **5c** at 70 °C, nonmigrated compound **6ca** was formed in 87% yield. In contrast, increasing temperature to 120 °C resulted in the olefin migration of **6ca** to give a separable *E*/*Z* mixture of **6cb** and **6cc**, respectively.

To understand the olefin migration process, four parallel reactions using **6ca** were performed, as shown in Table 2. First,

Table 2. Control Experiments for Olefin Migration[a]



entry	reaction conditions	ratio of 6ca:6cb:6cc[b]
1	DCE	100:0:0
2	PivOH, DCE	80:12:8
3	$[RhCp^*Cl_2]_2$, $AgSbF_6$, DCE	65:25:10
4	$[RhCp^*Cl_2]_2$, $AgSbF_6$, PivOH, DCE	0:75:25

[a]Reaction conditions: **6ca** (0.1 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), PivOH (200 mol %), DCE (0.5 mL) under air at 120 °C for 16 h. [b]Ratio was determined by crude ^1H NMR analysis.

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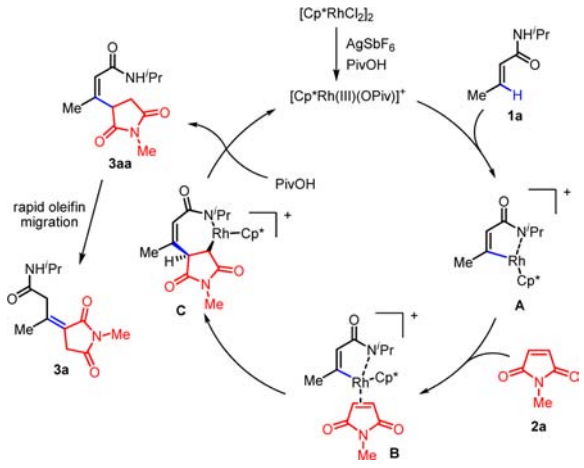
Scheme 5. Plausible Reaction Mechanism



6ca was employed in the absence of the Rh catalyst and additives at 120 °C, but no olefin migration was detected and starting compound **6ca** was almost recovered. Then, treatment of **6ca** with PivOH in DCE provided approximately 20% conversion to migration products **6cb** and **6cc**. In addition, a cationic Rh complex without PivOH afforded an increase in olefin migration. Finally, olefin migration was completely observed under the standard reaction conditions to give **6cb** and **6cc** with an *E*/*Z* ratio of 3:1. These results indicate that both the Rh complex and PivOH might be necessary for complete olefin migration at high reaction temperature. Thus, we believe that alkylation on acrylamides first takes place to give nonmigrated compounds, which can further undergo the migration reaction under the current reaction conditions leading to our desired olefin migration products.

Based on the above experimental results and previous literature,[4,15] a plausible reaction mechanism is depicted in Scheme 5. A cationic Rh(III) complex undergoes vinylic C−H activation with acrylamide **1a** to afford rhodacycle intermediate **A**. Further coordination of complex **A** with maleimide **2a** followed by migratory insertion delivers intermediate **C**. Finally, protonation with PivOH may lead to the formation of **3aa**, which undergoes rapid olefin migration providing thermodynamically stable olefin **3a**.

In conclusion, we have described the rhodium(III)-catalyzed direct C−H alkylation and migration reaction of various acrylamides with maleimides to afford biologically important succinimide-containing amides. These transformations proceed with good levels of stereoselectivity for olefins as well as with high functional group tolerance. The biological application of the synthesized succinimides is underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00909.

1D NOE data, experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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