

Regiocontrolled Coupling of Aromatic and Vinylic Amides with α -Allenols To Form γ -Lactams via Rhodium(III)-Catalyzed C–H Activation

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S Supporting Information

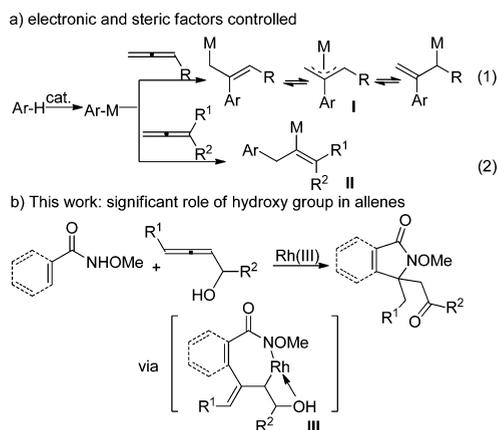
ABSTRACT: A mild, regiocontrolled coupling of aromatic and vinylic amides with α -allenols to form γ -lactams via rhodium(III)-catalyzed C–H activation has been demonstrated. This [4 + 1] annulation reaction provides an efficient method for the synthesis of isoindolinones and 1,5-dihydro-pyrrol-2-ones bearing a tetrasubstituted carbon atom α to the nitrogen atom with good functional group tolerance. The hydroxyl group in the allene substrate is essential in controlling the chemo- and regioselectivity of the reaction probably by coordination interaction with the rhodium catalyst.



The construction of heterocyclic scaffolds from simple and readily available starting materials is important in view of their prevalence in bioactive molecules.¹ Among a broad range of synthetic methods, the heteroannulation of allenes² has proven to be a versatile strategy.³ In recent years, allenes have been used as the coupling partners in transition metal catalyzed C–H functionalization,⁴ which provides a step- and atom-economical route to various heterocycles from less functionalized substrates.^{5,6} A variety of heterocycles can be accessed through this protocol to furnish dihydroisoquinolinone,^{5a,d,i} dihydropyridone,⁵ⁱ indolo[2,3-*c*]pyrane-1-one,^{5b} dihydrofuran,^{5c} eight-membered lactam,^{5e} chromane,^{5f,h} and phthalide.^{5g} Despite impressive progress, the development of new types of reactions between C–H and allenes affording privileged heterocycles is still in demand.

Compared with alkynes and alkenes,⁷ allenes are less explored in C–H functionalization. A major challenge existed in the C–H functionalization with allenes arises from the difficulty to achieve high chemo- and regioselectivity, which is usually controlled by electronic and steric effects of allenes. Normally, carbometalation of allenes forms a new C–C bond at the central carbon atom of the allene moiety to produce a π -allyl metal species I (Scheme 1a, eq 1), which potentially enables the subsequent reaction occurring at either side of the allylic carbon.^{5a,d,f–h} The regioselectivity can be switched in some cases, in which carbometalation takes place at the less substituted C=C bond giving vinyl metal species II (Scheme 1a, eq 2).^{6a,d,e,i} Taking advantage of different substituted allenes, diversified reaction modes of C–H functionalization can be achieved. Herein, we present a regiocontrolled [4 + 1] annulation^{5f–h} of *N*-methoxybenzamides or *N*-methoxyacrylamides with α -allenols (Scheme 1b), in which the hydroxyl group in the allene is crucial for the chemo- and regioselectivity probably by coordination with rhodium catalyst to form a regioselective η^1 -allyl rhodium species III. In this transformation, allenes act as the one-carbon

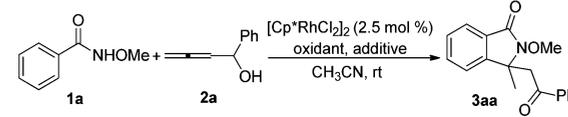
Scheme 1. Diversified Reaction Modes of C–H Functionalization Tuned by Different Substituted Allenes



component^{5f–h} to construct isoindolinones and 1,5-dihydropyrrol-2-ones bearing a tetrasubstituted carbon atom. Since both isoindolinones⁸ and pyrrol-2-ones⁹ contain the γ -lactam skeleton and present in many bioactive natural products and drug candidates, this transformation should have profound potential in synthetic chemistry.

At the outset of our investigation, we tested the reactions of *N*-methoxybenzamide (1a) with 1-phenylbuta-2,3-dien-1-ol (2a) under rhodium(III) catalyzed conditions (Table 1). The 3,3-disubstituted isoindolin-1-one product 3aa could be obtained via a [4 + 1] annulation, in which a stoichiometric amount of silver acetate was inevitable (Table 1, entries 1 and 2). Preliminary experiments indicated that acetonitrile was an optimal solvent.¹⁰

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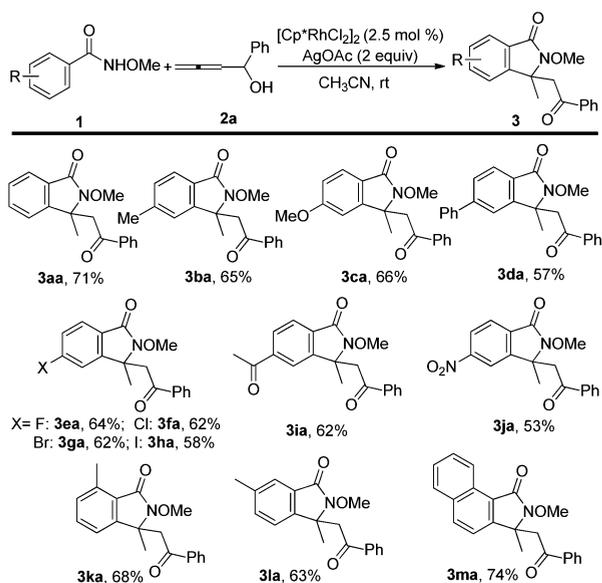
Table 1. Reaction Conditions Screening^a


entry	oxidant (equiv)	additive (equiv)	yield (%) ^b
1	—	CsOAc (0.5)	<5
2	AgOAc (1)	—	48
3 ^c	AgOAc (1)	—	53
4 ^{c,d}	AgOAc (2)	—	73
5 ^{c,d}	Cu(OAc) ₂ (2)	—	13
6 ^{c,d}	Ag ₂ CO ₃ (2)	—	44
7 ^{c,d}	(PhCO ₂) ₂ (2)	CsOAc (0.5)	52
8 ^{c,d}	PhI(OAc) ₂ (2)	—	49
9 ^{c,d}	AgOAc (2)	K ₂ CO ₃ (1)	65
10 ^{c,d}	AgOAc (2)	HOAc (1)	57

^aReaction conditions: **1a** (0.1 mmol), **2a** (0.14 mmol), [Cp*RhCl₂]₂ (2.5 mol %), oxidant and additives in solvent (0.2 M) at room temperature for 24 h under air. ^b¹H NMR yield based on **1a**. ^cCH₃CN (0.1 M). ^d**2a** (0.3 mmol).

Increasing the amounts of the external oxidant and α -allenol **2a** significantly improved the yield to 73% (Table 1, entry 4). Other external oxidants were also examined but gave inferior results compared with AgOAc (Table 1, entries 5–8). Moreover, the addition of K₂CO₃ or acetic acid decreased the yield of the desired product (Table 1, entries 9 and 10). A control experiment showed that the absence of a rhodium catalyst resulted in no reaction.¹¹

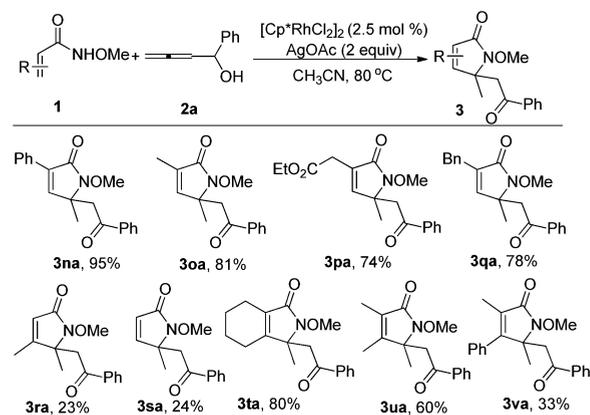
Further exploration of the scope of *N*-methoxybenzamides was next conducted under the optimized reaction conditions. By using **2a** as the coupling partner, a variety of isoindolinone derivatives were constructed effectively (Scheme 2). Fortunately, various commonly encountered functional groups, such as

Scheme 2. Reaction Scope for Aromatic C–H Functionalization with α -Allenol **2a**^a

^aReaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol), [Cp*RhCl₂]₂ (2.5 mol %), AgOAc (2 equiv) in CH₃CN (0.1 M) at room temperature for 24 h under air; isolated yield was reported.

methyl (**3ba**), methoxyl (**3ca**), phenyl (**3da**), and halogens (**3ea–3ha**), were well tolerated in this transformation, furnishing the corresponding products in moderate to good yields. The reaction was also compatible with *N*-methoxybenzamides bearing electron-withdrawing groups (**3ia** and **3ja**), which reacted smoothly to give the desired products in moderate yields. In addition, *ortho* methyl-substituted *N*-methoxybenzamide was also a good reactant for this transformation affording **3ka** in a yield of 68%. When *meta*-substituted *N*-methoxybenzamide was employed, selective C–H functionalization at the less hindered site was observed (**3la**). Of note, *N*-methoxy-1-naphthamide resulted in a good yield of the desired isoindolinone derivative under standard conditions (**3ma**, 74%).

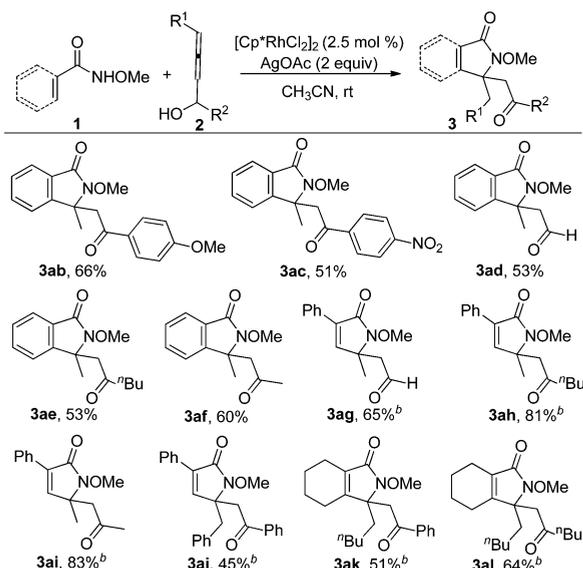
Having developed a rhodium(III)-catalyzed coupling reaction of *N*-methoxybenzamides for the synthesis of isoindolinones, we were next intrigued to explore the feasibility of an olefinic C–H functionalization for the construction of the pyrrol-2-one skeleton. To our delight, this transformation proceeded smoothly to afford the desired products with a lower loading of α -allenol **2a** at 80 °C.¹² It is noteworthy that a substituent at the α position of *N*-methoxyacrylamide was helpful for this olefinic C–H functionalization (**3na–3qa**), while the acrylamides without an α -substituent (**3ra** and **3sa**) seemed to be less effective (Scheme 3).¹³ Moreover, the cyclic olefinic substrate

Scheme 3. Reaction Scope for Olefinic C–H Functionalization with Allenyl Alcohol **2a**^a

^aReaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), [Cp*RhCl₂]₂ (2.5 mol %), AgOAc (2 equiv) in CH₃CN (0.1 M) at 80 °C for 24 h under air; isolated yield was reported.

(**3ta**) and α,β -dimethyl *N*-methoxyacrylamide (**3ua**) readily participated in this annulation, leading to the corresponding products in good yields. However, when α -methyl- β -phenyl *N*-methoxyacrylamide was subjected to the reaction conditions, only a 33% yield of desired product **3va** was obtained. The electronic property of the phenyl substituent close to the vinylic C–H bond might result in the low reactivity of **1v**.

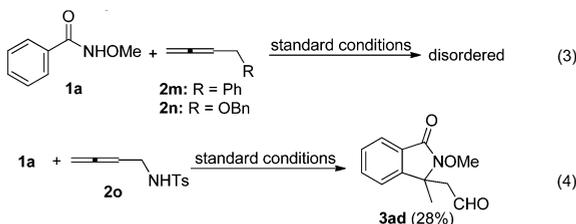
We subsequently extended the scope of this transformation by employing a variety of substituted α -allenols **2** (Scheme 4). The reaction is compatible with both electron-donating and -withdrawing group substituted 1-phenylbuta-2,3-dien-1-ols (**3ab** and **3ac**). Buta-2,3-dien-1-ol and 1-alkyl-substituted buta-2,3-dien-1-ols were also tolerated to deliver the corresponding isoindolinones and pyrrol-2-ones in moderate yields (**3ad–3ai**). Notably, when 4-alkyl substituted buta-2,3-dien-1-ols were employed, the specific regioselectivity¹⁴ was also observed furnishing the expected pyrrol-2-ones with a carbonyl group (**3ak** and **3al**).

Scheme 4. Reaction Scope for α -Allenols^a

^aReaction conditions: 1 (0.2 mmol), 2 (0.6 mmol), [Cp*RhCl₂]₂ (2.5 mol %), AgOAc (2 equiv) in CH₃CN (0.1 M) at room temperature for 24 h under air; isolated yield was reported. ^bReaction was conducted at 80 °C with 1.5 equiv of α -allenol 2.

We suspected the coordination of the hydroxyl group to rhodium was mostly involved in controlling the regioselectivity.

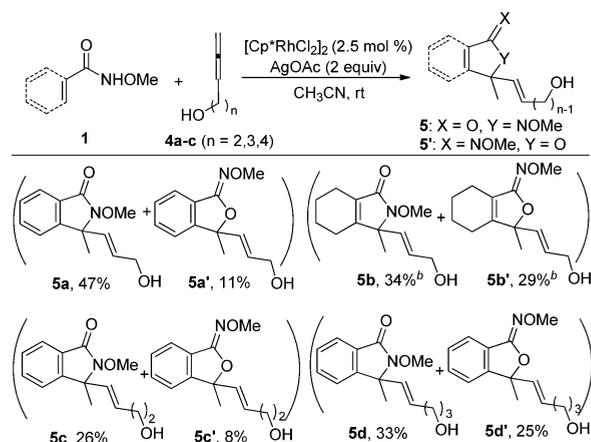
To gain more insight into the effect of the hydroxyl group in α -allenol, a series of controlled experiments were then carried out. When benzyl substituted allene 2m or benzyl protected buta-2,3-dien-1-ol 2n was subjected to the reaction with 1a under standard conditions, the reaction turned out to be complicated, resulting in an inseparable mixture of complex products (eq 3). These



results indicate that the free hydroxyl group is essential for the [4 + 1] annulation. Considering that an amide group could also potentially chelate with the Rh center, substrate 2o was subjected to the reaction. The expected product 3ad could be constructed in a relatively low yield (eq 4), which proves the importance of a coordinating substituent in the allene substrate.

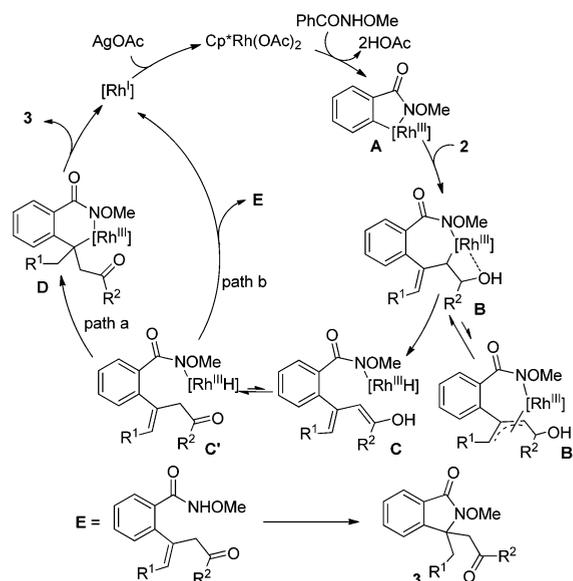
To further test our hypothesis that the hydroxyl group greatly influenced regio- and chemo-selectivity control by chelating the Rh, various allenes bearing a hydroxyl group at different positions (4a–c) were synthesized and subjected to the reaction (Scheme 5). Delightfully, under the standard conditions, the [4 + 1] annulation proceeded smoothly to yield the mixture of γ -lactam (5a–5d) and iminolactone (5a'–5d'). The formation of iminolactone was probably due to the attack of the oxygen atom rather than the nitrogen atom from the directing group during the annulation step.¹⁵

On the basis of our experimental results and the previous literature,^{5,6} a plausible catalytic cycle is proposed for this transformation (Scheme 6). Initially, an active catalyst Cp*Rh-

Scheme 5. Further Investigation on the Effect of Hydroxy Group in the Allenes^{a,b}

^aReaction conditions: 1 (0.2 mmol), 4 (0.4 mmol), [Cp*RhCl₂]₂ (2.5 mol %), AgOAc (2 equiv) in CH₃CN (0.1 M) at room temperature for 24 h under air; isolated yield was reported. ^bReaction was conducted at 80 °C.

Scheme 6. Proposed Mechanism



(OAc)₂ is likely generated by anion exchange in the presence of AgOAc, followed by a facile amide directed C–H activation to afford intermediate A. The regioselective insertion of an allene double bond into the C–Rh bond provides a seven-membered rhodacycle intermediate B. We envisioned that hydroxyl group in the allene may provide the binding affinity to Rh,¹⁶ which would guide the regioselective migratory insertion to form the η^1 -allylic rhodium intermediate B⁶⁸ and disfavor the formation of the π -allyl rhodium species B'. Next, β -H elimination followed by enol–keto tautomerism gives intermediate C', from which two possible mechanistic pathways are envisioned. In path a, the double bond in intermediate C' might insert into the Rh–H bond leading to intermediate D, which undergoes reductive elimination to yield product 3 together with Rh^I species. Alternatively, intermediate C' undergoes reductive elimination to deliver Rh^I species and *o*-alkenyl benzamide intermediate E. Subsequently, intramolecular hydroamination of an alkene might take place to deliver the desired product 3.¹⁷ Finally, the Rh^I

species could be oxidized by AgOAc to regenerate the Rh^{III} active catalyst.

In summary, by using α -allenols as the coupling partners, we have developed an efficient Rh^{III}-catalyzed C–H functionalization of aromatic and vinylic amides for the synthesis of isoindolinone and 1,5-dihydro-pyrrol-2-one skeletons. The hydroxyl group in the allene substrate is essential in controlling the chemo- and regioselectivity of the reaction probably by coordination interaction with the rhodium catalyst. Further investigations on the synthetic application of this transformation are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02903.

Experimental procedures and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Wiley-VCH: Weinheim, 2003. (b) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395.
- (2) (a) *Morden Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004. (b) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (c) Ma, S. *Pure Appl. Chem.* **2006**, *78*, 197. (c1) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994.
- (3) (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (b) Lechel, T.; Reissig, H.-U. *Pure Appl. Chem.* **2010**, *82*, 1835. (c) Alcaide, B.; Almendros, P. *Chem. Record* **2011**, *11*, 311. (d) Pinho e Melo, T. M. V. D. *Monatsh. Chem.* **2011**, *142*, 681.
- (4) For some recent reviews on transition metal catalyzed C–H functionalization, see: (a) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (b) Li, B.; Dixneuf, P. H. *Chem. Soc. Rev.* **2013**, *42*, 5744. (c) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. (d) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281. (e) Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Chem. Sci.* **2014**, *5*, 2146. (f) Ros, A.; Fernández, R.; Lassaletta, J. M. *Chem. Soc. Rev.* **2014**, *43*, 3229. (g) Shi, G.; Zhang, Y. *Adv. Synth. Catal.* **2014**, *356*, 1419. (h) Kuhl, N.; Schröder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443. (i) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. *Chem. Rev.* **2015**, *115*, 1622.
- (5) For C–H functionalization with allenes for the synthesis of heterocycles, see: (a) Wang, H.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 7318. (b) Suresh, R. R.; Swamy, K. C. K. *J. Org. Chem.* **2012**, *77*, 6959. (c) Zeng, R.; Ye, J.; Fu, C.; Ma, S. *Adv. Synth. Catal.* **2013**, *355*, 1963. (d) Xia, X.-F.; Wang, Y.-Q.; Zhang, L.-L.; Song, X.-R.; Liu, X.-Y.; Liang, Y.-M. *Chem. - Eur. J.* **2014**, *20*, 5087. (e) Wu, S.; Zeng, R.; Fu, C.; Yu, Y.; Zhang, X.; Ma, S. *Chem. Sci.* **2015**, *6*, 2275. (f) Casanova, N.; Seoane, A.; Mascareñas, J. L.; Gullías, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 2374. (g) Gandeepan, P.; Rajamalli, P.; Cheng, C.-H. *Chem. - Eur. J.* **2015**, *21*, 9198. (h) Kuppusamy, R.; Muralirajan, K.; Cheng, C.-H. *ACS Catal.* **2016**, *6*, 3909. (i) Thrimurtulu, N.; Dey, A.; Maiti, D.; Volla, C. M. R. *Angew. Chem., Int. Ed.* **2016**, *55*, 12361.

(6) For other catalytic C–H functionalizations with allenes as the coupling partner, see: (a) Zhang, Y. J.; Skucas, E.; Krische, M. J. *Org. Lett.* **2009**, *11*, 4248. (b) Tran, D. N.; Cramer, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 8181. (c) Kuninobu, Y.; Yu, P.; Takai, K. *Org. Lett.* **2010**, *12*, 4274. (d) Zeng, R.; Fu, C.; Ma, S. *J. Am. Chem. Soc.* **2012**, *134*, 9597. (e) Zeng, R.; Wu, S.; Fu, C.; Ma, S. *J. Am. Chem. Soc.* **2013**, *135*, 18284. (f) Ye, B.; Cramer, N. *J. Am. Chem. Soc.* **2013**, *135*, 636. (g) Wang, H.; Beiring, B.; Yu, D.-G.; Collins, K. D.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 12430. (h) Gong, T.-J.; Su, W.; Liu, Z.-J.; Cheng, W.-M.; Xiao, B.; Fu, Y. *Org. Lett.* **2014**, *16*, 330. (i) Nakanowatari, S.; Ackermann, L. *Chem. - Eur. J.* **2015**, *21*, 16246.

(7) (a) Satoh, T.; Miura, M. *Chem. - Eur. J.* **2010**, *16*, 11212. (b) Patureau, F. W.; Wencel-Delord, J.; Glorius, F. *Aldrichimica Acta* **2012**, *45*, 31. (c) Mesganaw, T.; Ellman, J. A. *Org. Process Res. Dev.* **2014**, *18*, 1097. (d) Zhou, L.; Lu, W. *Chem. - Eur. J.* **2014**, *20*, 634. (e) Muzart, J.; Le Bras, J. *Synthesis* **2014**, *46*, 1555. (f) Gandeepan, P.; Cheng, C.-H. *Chem. - Asian J.* **2015**, *10*, 824.

(8) (a) Bjoere, A.; Bostrom, J.; Davidsson, O.; Emtenaes, H.; Gran, U.; Iliofski, T.; Kajanus, J.; Olsson, R.; Sandberg, L.; Strandlund, G.; et al. PCT Int. Appl. WO 2008008022, 2008. (b) Baldwin, J. J.; Cacatian, S.; Claremon, D. A.; Dillard, L. W.; Flaherty, P. T.; Ishchenko, A. V.; Jia, L.; McGeehan, G.; Simpson, R. D.; Singh, S. B.; et al. PCT Int. Appl. WO 2008156816, 2008.

(9) (a) Floch, L.; Nydegger, F.; Gossauer, A. *Helv. Chim. Acta* **1994**, *77*, 445. (b) Ito, M.; Okui, H.; Nakagawa, H.; Mio, S.; Iwasaki, T.; Iwabuchi, J. *Heterocycles* **2002**, *57*, 881. (c) Chatzimpaloglou, A.; Yavropoulou, M. P.; Rooij, K. E.; Biedermann, R.; Mueller, U.; Kaskel, S.; Sarli, V. *J. Org. Chem.* **2012**, *77*, 9659. (d) Shionozaki, N.; Yamaguchi, T.; Kitano, H.; Tomizawa, M.; Makino, K.; Uchiro, H. *Tetrahedron Lett.* **2012**, *53*, 5167. (e) Nicolaou, K. C.; Shi, L.; Lu, M.; Pattanayak, M. R.; Shah, A. A.; Ioannidou, H. A.; Lamani, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 10970. (f) Chatzimpaloglou, A.; Kolosov, M.; Eckols, T. K.; Tweardy, D. J.; Sarli, V. *J. Org. Chem.* **2014**, *79*, 4043.

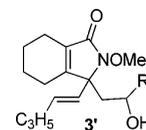
(10) For detailed optimization studies, see Table S1 in the Supporting Information.

(11) The following benzamides bearing different substituents on the amide group were also tested, but no reaction was observed: PhCONHR (R = Me, Ph, Bn, Ts).

(12) An elevated temperature was necessary for *N*-methoxyacrylamides since most of the starting materials were recovered at room temperature. In contrast, the reaction of *N*-methoxybenzamides can proceed smoothly at room temperature and increasing the reaction temperature could not improve the yield. These results indicate *N*-methoxyacrylamides have lower reactivity compared with *N*-methoxybenzamides in this [4 + 1] annulation.

(13) (a) Xu, Y.-H.; Lu, J.; Loh, T.-P. *J. Am. Chem. Soc.* **2009**, *131*, 1372. (b) Wen, Z.-K.; Xu, Y.-H.; Loh, T.-P. *Chem. - Eur. J.* **2012**, *18*, 13284. (c) Hu, X.-H.; Zhang, J.; Yang, X.-F.; Xu, Y.-H.; Loh, T.-P. *J. Am. Chem. Soc.* **2015**, *137*, 3169.

(14) The possible regioisomeric product 3' was not observed.



(15) (a) Zhao, J.-F.; Duan, X.-H.; Yang, H.; Guo, L.-N. *J. Org. Chem.* **2015**, *80*, 11149. (b) Zhang, Z.-Q.; Liu, F. *Org. Biomol. Chem.* **2015**, *13*, 6690. (c) Su, B.; Wei, J.-B.; Wu, W.-L.; Shi, Z.-J. *ChemCatChem* **2015**, *7*, 2986.

(16) Shimp, H. L.; Hare, A.; McLaughlin, M.; Micalizio, G. C. *Tetrahedron* **2008**, *64*, 3437.

(17) (a) Ding, D.; Mou, T.; Feng, M.; Jiang, X. *J. Am. Chem. Soc.* **2016**, *138*, 5218. (b) Ma, W.; Ackermann, L. *ACS Catal.* **2015**, *5*, 2822.