Organic LETTERS

Letter

pubs.acs.org/OrgLett

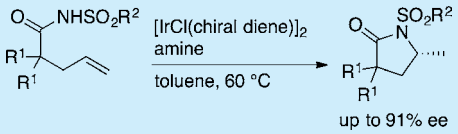
Asymmetric Cyclization of *N*-Sulfonyl Alkenyl Amides Catalyzed by Iridium/Chiral Diene Complexes

Midori Nagamoto, Tomoyuki Yanagi, Takahiro Nishimura,* and Hideki Yorimitsu

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

Supporting Information

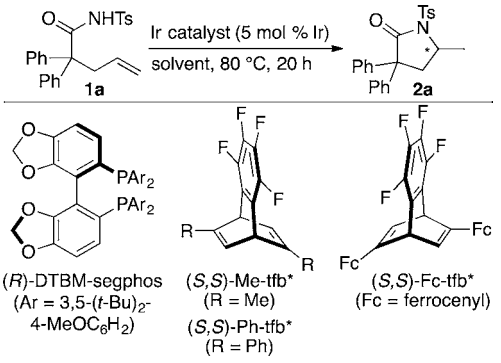
ABSTRACT: Iridium/chiral diene complexes efficiently catalyzed the asymmetric cyclization of *N*-sulfonyl alkenyl amides to give the corresponding 2-pyrrolidone derivatives with high enantioselectivity. A mechanistic study revealed that the reaction proceeds via nucleophilic attack of the amide on the alkene moiety.



Direct addition of N−H bonds to C−C unsaturated bonds, which is known as hydroamination, has attracted much attention, as it represents an atom-efficient approach to the synthesis of various nitrogen-containing compounds.[1] Primary and secondary amides have been often used as nucleophiles in the hydroamination reactions catalyzed by transition metal complexes. Although there have been many successful examples of the addition of amides to unactivated alkenes,[2] the asymmetric variant is still a challenging objective.[3−5] Widenhoefer and co-workers reported gold-catalyzed hydroamination reactions including the asymmetric addition of amides to alkenes.[3a,d] Hartwig and co-workers reported iridium-catalyzed asymmetric addition of benzamides to bicyclic alkenes.[3b] In this context, we recently reported iridium-catalyzed asymmetric cyclization of alkenoic acids leading to γ-lactones.[6] The reaction of 4-pentenoic acid derivatives in the presence of an iridium/chiral bisphosphine complex in an amide solvent gave the corresponding lactones with good enantioselectivity. We next focused on the asymmetric addition of amide nucleophiles toward the synthesis of chiral γ-lactams, which are often found in natural products and biologically active compounds.[7] Although various methodologies for the stereoselective synthesis of γ-lactams have been developed, there have been few reports on the catalytic enantioselective synthesis of 2-pyrrolidone derivatives in an intramolecular manner.[8] Herein we report the asymmetric cyclization of *N*-sulfonyl alkenyl amides catalyzed by iridium/chiral diene complexes.

It was found that the cyclization of an *N*-sulfonyl 4-pentenamide, which bears a highly acidic N−H bond, proceeded to give the corresponding 2-pyrrolidone under the same reaction conditions as the cyclization of 4-pentenoic acid. Treatment of *N*-tosyl-2,2-diphenyl-4-pentenamide (**1a**) in the presence of $[IrCl(coe)_2]_2$ (5 mol % of Ir, coe = cyclooctene) and (*R*)-DTBM-segphos in *N*-methylpyrrolidone (NMP) at 100 °C for 20 h gave **2a** in 91% yield albeit with 7% ee (Table 1, entry 1). An iridium complex $[IrCl(cod)]_2$ (cod = 1,5-cyclooctadiene), which has a chelating diene ligand, also displayed high catalytic activity at 80 °C (entry 2). These results encouraged us to examine chiral diene ligands to achieve the high enantioselectivity in the present reaction. Recently, we have developed chiral diene ligands based on a tetrafluorobenzobarrelene (tfb) framework, which have been successfully applied to Rh- and Ir-catalyzed asymmetric reactions.[9] The tfb ligand substituted with methyl groups was a promising one; the reaction in the presence of $[IrCl((S,S)\text{-Me-tfb}^*)]_2$ gave **2a** in 92% yield with 40% ee (entry 3). Other tfb ligands substituted

Table 1. Ir-Catalyzed Asymmetric Cyclization of 1a[a]



entry	Ir catalyst	solvent	yield (%)	ee (%)
1[b]	$[IrCl(coe)_2]_2$/(*R*)-DTBM-segphos	NMP	91	7
2	$[IrCl(cod)]_2$	NMP	92	–
3	$[IrCl((S,S)\text{-Me-tfb}^*)]_2$	NMP	92	40
4	$[IrCl((S,S)\text{-Ph-tfb}^*)]_2$	NMP	92	1
5	$[IrCl((S,S)\text{-Fc-tfb}^*)]_2$	NMP	83	25
6	$[IrCl((S,S)\text{-Me-tfb}^*)]_2$	TMU	99	35
7	$[IrCl((S,S)\text{-Me-tfb}^*)]_2$	DMA	98	41
8	$[IrCl((S,S)\text{-Me-tfb}^*)]_2$	toluene	0	–
9	$[IrCl((S,S)\text{-Me-tfb}^*)]_2$	1,4-dioxane	0	–

[a]Reaction conditions: Amide **1a** (0.10 mmol) and Ir catalyst (5 mol % of Ir) in solvent (0.40 mL) at 80 °C for 20 h. Isolated yields are shown. The ee was determined by chiral HPLC analysis. [b]At 100 °C. NMP = *N*-methylpyrrolidone. TMU = 1,1,3,3-tetramethylurea. DMA = *N*,*N*-dimethylacetamide.

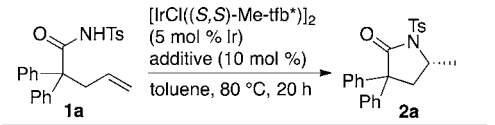
Received: July 6, 2016
Published: August 25, 2016

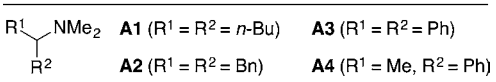
DOI: 10.1021/acs.orglett.6b01954
Org. Lett. 2016, 18, 4474−4477

with phenyl and ferrocenyl groups decreased the enantioselectivity (entries 4 and 5). The reactions in other amide solvents such as TMU and DMA proceeded to give **2a** in high yields with similar levels of ee to that obtained in the reaction in NMP (entries 6 and 7). In contrast, no reaction occurred in nonpolar solvents such as toluene and 1,4-dioxane (entries 8 and 9).

It is likely that the high catalytic activity in amide solvents might be derived from the coordination ability or the weak basicity of the amides. It was found that the reaction in nonpolar solvents proceeded with good enantioselectivity in the presence of an amine. Thus, the reaction in toluene in the presence of 10 mol % of triethylamine gave **2a** in 40% yield with 60% ee (Table 2, entry 1). The use of Hünig's base

Table 2. Effect of Amines[a]





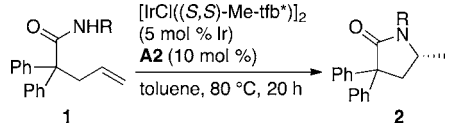
entry	additive	yield (%)	ee (%)
1	Et_3N	43	60
2	*i*-Pr_2NEt	12	11
3	Me_2NEt	96	26
4	Me_2NBn	95	51
5	Me_2N*i*-Pr	>99	53
6	**A1**	92	60
7	**A2**	89	68
8	**A3**	38	21
9	(*R*)-**A4**	92	64
10	(*S*)-**A4**	>99	65
11	pyridine	8	8
12	DBU	30	14
13	Na_2CO_3	0	–

[a]Reaction conditions: Amide **1a** (0.10 mmol), [IrCl((*S*,*S*)-Me-tfb*)]$_2$ (5 mol % of Ir), and additive (10 mol %) in toluene (0.40 mL) at 80 °C for 20 h. Isolated yields are shown. The ee was determined by chiral HPLC analysis. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

dramatically decreased the yield and enantioselectivity, whereas *N*,*N*-dimethylethylamine enhanced the reactivity to give **2a** in 96% yield with 26% ee (entries 2 and 3). Further screening of amines revealed that tertiary amines bearing dimethyl groups and a bulky alkyl group enhanced the enantioselectivity while maintaining the high yield. The reaction in the presence of *N*,*N*-dimethylbenzylamine and *N*,*N*-dimethylisopropylamine gave **2a** in high yields with moderate enantioselectivity (entries 4 and 5). Sterically bulkier **A1** and **A2**, having a 5-nonyl and a 1,3-diphenylpropan-2-yl group, increased the enantioselectivity to 60 and 68% ee, respectively (entries 6 and 7). However, a diphenylmethyl group of **A3** significantly decreased the yield and enantioselectivity (entry 8). The enantioselectivity was not influenced by the absolute configuration of chiral amine **A4**; the reactions in the presence of (*R*)- and (*S*)-**A4** gave (−)-**2a** with 64 and 65% ee, respectively (entries 9 and 10). Pyridine and DBU reduced both the yield and enantioselectivity (entries 11 and 12). An inorganic base was not effective for the present reaction (entry 13).

The enantioselectivity was further improved by modifying the arenesulfonyl groups on the amide (Table 3). In the

Table 3. Effect of Substituents on Nitrogen[a]



entry	R	yield (%)	ee (%)
1	SO_2(4-MeC_6H_4) (**1a**)	89 (**2a**)	68
2	SO_2(2-MeC_6H_4) (**1b**)	58 (**2b**)	77
3	SO_2(2-MeOC_6H_4) (**1c**)	75 (**2c**)	73
4	SO_2(2-EtOC_6H_4) (**1d**)	95 (**2d**)	84
5	SO_2(2-*i*-PrOC_6H_4) (**1e**)	95 (**2e**)	87
6	SO_2(2-CyOC_6H_4) (**1f**)	96 (**2f**)	84
7	SO_2Me (**1g**)	88 (**2g**)	1
8	CO_2*t*-Bu (**1h**)	60 (**2h**)	1
9[b]	**1e**	92 (**2e**)	89
10[b,c]	**1e**	95 (**2e**)	91

[a]Reaction conditions: Amide **1** (0.10 mmol), [IrCl((*S*,*S*)-Me-tfb*)]$_2$ (5 mol % of Ir), and **A2** (10 mol %) in toluene (0.40 mL) at 80 °C for 20 h. Isolated yields are shown. The ee was determined by HPLC analysis. [b]At 60 °C. [c]**A2** (5 mol %).

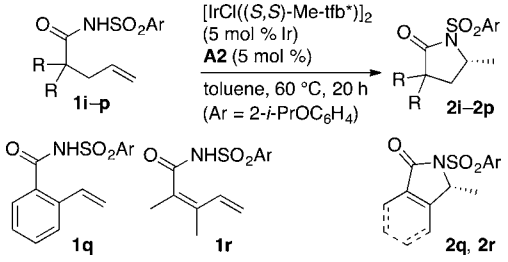
presence of amine **A2**, the reaction of **1b** having an *ortho*-toluenesulfonyl group gave **2b** with 77% ee (entry 2). We tested several *ortho*-alkoxybenzenesulfonyl groups, whose steric bulkiness can be changed by the alkyl groups. The reactions of amides **1c**−**f** having methoxy-, ethoxy-, isopropoxy-, and cyclohexyloxybenzenesulfonyl groups gave **2c**, **2d**, **2e**, and **2f** with 73, 84, 87, and 84% ee, respectively (entries 3−6). In contrast, the sterically less bulky methanesulfonyl group significantly decreased the enantioselectivity (1% ee, entry 7). Besides *N*-sulfonyl alkenyl amides, *N*-Boc alkenyl amide **1g** also reacted to give **2g** in 60% yield, albeit with a very low ee (entry 8).[10] The cyclization of **1e** smoothly proceeded at 60 °C to give **2e** in 92% yield with 89% ee (entry 9). The use of the same amount of the amine (5 mol %) as the Ir catalyst improved the enantioselectivity to 91% ee (entry 10).[11]

The results obtained for the iridium-catalyzed asymmetric cyclization of *N*-(2-isopropoxybenzenesulfonyl)alkenyl amides are summarized in Table 4. Several amides substituted at the 2-position underwent the cyclization in the presence of amine **A2** to give the corresponding lactams with good enantioselectivity. The reactions of the amides **1e**, **1i**−**l** bearing aryl groups gave the lactams **2e**, **2i**−**l** in 89−97% yield with 88−91% ee, regardless of electronic properties of the aryl groups (entries 1−5). The reactions of alkyl-substituted amides were relatively slow, but the cyclizations of **1m** and **1n**, having benzyl and *n*-hexyl groups at the 2-position, gave **2m** and **2n**, respectively, in good yields with high enantioselectivity (entries 6 and 7). The reactivity of **1o** and **1p**, having sterically less bulky cyclic pentamethylene and dimethyl groups, was not high even at 80 °C (entries 8 and 9), indicating that the strong Thorpe−Ingold effect is necessary for the present cyclization.[12] The amides **1q** and **1r** having a benzene ring and a diene moiety also participated in the reaction to give **2q** and **2r**, respectively, in high yields (entries 10 and 11).

The present catalyst system can also be applied to the cyclization of *N*-sulfonyl-*N*′-alkenyl urea **4** prepared from allylamine **3**, giving the corresponding 2-imidazolidinone derivative **5** (eq 1). Although the iridium/cod complex

DOI: 10.1021/acs.orglett.6b01954
Org. Lett. 2016, 18, 4474−4477

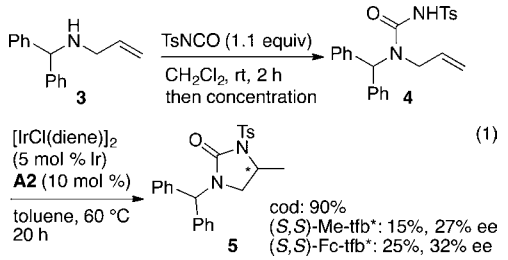
Table 4. Substrate Scope[a]



entry	R	yield (%)	ee (%)
1[b]	Ph (**1e**)	96 (**2e**)	88
2	4-MeC_6H_4 (**1i**)	89 (**2i**)	89
3	4-$MeOC_6H_4$ (**1j**)	97 (**2j**)	90
4	4-FC_6H_4 (**1k**)	89 (**2k**)	91
5	4-ClC_6H_4 (**1l**)	91 (**2l**)	90
6[c]	Bn (**1m**)	92 (**2m**)	86
7[d]	*n*-hexyl (**1n**)	90 (**2n**)	80
8[e]	$-(CH_2)_5-$ (**1o**)	38 (**2o**)	82
9[d]	Me (**1p**)	25 (**2p**)	74
10	**1q**	93 (**2q**)	81
11	**1r**	81 (**2r**)	23

[a]Reaction conditions: Amide **1** (0.20 mmol), $[IrCl((S,S)\text{-Me-tfb*})]_2$ (5 mol % of Ir), and **A2** (5 mol %) in toluene (0.80 mL) at 60 °C for 20 h. Isolated yields are shown. The ee was determined by HPLC analysis. [b]5-Fold scale reaction (1.0 mmol of **1e**). [c]For 48 h. [d]**A2** (10 mol %) at 80 °C for 48 h. [e]At 80 °C for 48 h.

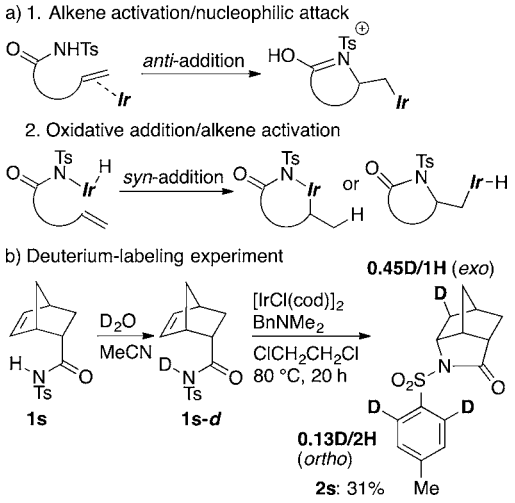
exhibited a high catalytic activity, iridium/chiral diene complexes displayed low catalytic activity and enantioselectivity.



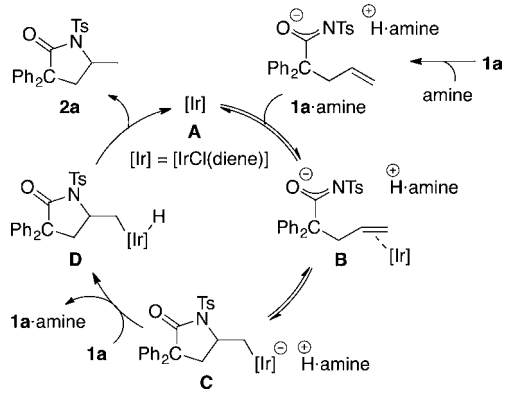
To gain some insight into the mechanism, we focused on the stereochemistry of the addition. The reaction involving alkene activation[13] leads to an *anti*-addition product, whereas a mechanism involving oxidative addition and alkene insertion[14] leads to a *syn*-addition product (Scheme 1a). We conducted a deuterium-labeling experiment to determine the stereochemistry by using norbornene carboxamide **1s** as a model substrate (Scheme 1b). The amide **1s** was treated with a large excess of D_2O to give deuterated amide **1s-*d***, which was directly subjected to the catalytic conditions after concentration under vacuum. The cyclization product was obtained in a moderate yield, where the deuterium was incorporated at the *exo*-position.[15] This result indicates that the reaction proceeds via nucleophilic attack of the amide to the alkene moiety, which is activated by coordination to the iridium.

The catalytic cycle is postulated as illustrated in Scheme 2. The amide **1a** reacts with the amine to generate an ammonium salt.[16] Iridium catalyst **A** activates an alkene moiety to generate complex **B**, and a nucleophilic attack of the nitrogen gave alkyliridium(I) intermediate **C**.[17] Protonation of intermediate **C** forms alkylhydridoiridium(III) intermediate **D**, which undergoes reductive elimination to give **2a** and regenerates catalyst **A**.[13] The presence of amines is crucial for the reaction, as they increase the nucleophilicity of the amide moiety to promote the cyclization of intermediate **B**.[18]

Scheme 1. Stereochemistry of the Addition



Scheme 2. Plausible Catalytic Cycle



In summary, we have developed the asymmetric cyclization of *N*-sulfonyl alkenyl amides using Ir/chiral diene complexes to give 2-pyrrolidones with good enantioselectivity. A mechanistic study revealed that the reaction proceeds via nucleophilic attack of the amide to the alkene moiety.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01954.

Experimental procedures and compound characterization (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tnishi@kuchem.kyoto-u.ac.jp.

Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.orglett.6b01954
Org. Lett. 2016, 18, 4474–4477

■ ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI Grant Number JP15H03810. M.N. thanks the JSPS for Research Fellowship for Young Scientists.

■ REFERENCES

(1) For recent reviews of transition-metal-catalyzed hydroamination of C−C unsaturated bonds, see: (a) Reznichenko, A. L.; Hultzsch, K. C. Hydroamination of Alkenes. In *Organic Reactions*; Denmark, S. E. et al., Eds.; Wiley & Sons: New York, 2015; Vol. *88*, Chapter 1, pp 1−554. (b) Bernoud, E.; Lepori, C.; Mellah, M.; Schulz, E.; Hannedouche, J. *Catal. Sci. Technol.* **2015**, *5*, 2017. (c) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. K. *Chem. Rev.* **2015**, *115*, 2596. (d) Hannedouche, J.; Schulz, E. *Chem. - Eur. J.* **2013**, *19*, 4972. (e) Patil, N. T.; Kavthe, R. D.; Shinde, V. S. *Tetrahedron* **2012**, *68*, 8079.

(2) For a pioneering report on the addition of amides to unactivated alkenes, see: (a) Wang, X.; Widenhoefer, R. A. *Organometallics* **2004**, *23*, 1649. For selected recent examples, see: (b) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798. (c) Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 4246. (d) Liu, X.-Y.; Li, C.-H.; Che, C.-M. *Org. Lett.* **2006**, *8*, 2707. (e) Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 5303. (f) Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747. (g) Bender, C. F.; Widenhoefer, R. A. *Chem. Commun.* **2006**, 4143. (h) Cochran, B. M.; Michael, F. E. *Org. Lett.* **2008**, *10*, 329. (i) Li, H.; Song, F.; Widenhoefer, R. A. *Adv. Synth. Catal.* **2011**, *353*, 955.

(3) For the asymmetric addition of amides to unactivated alkenes, see: (a) Zhang, Z.; Lee, S. D.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 5372. (b) Sevov, C. S.; Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 11960. (c) Kojima, M.; Mikami, K. *Synlett* **2012**, *2012*, 57. (d) Lee, S. D.; Timmerman, J. C.; Widenhoefer, R. A. *Adv. Synth. Catal.* **2014**, *356*, 3187.

(4) For the asymmetric addition of amides to allenes, see: (a) Lutete, L. M.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622. (b) Zhang, Z.; Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 2887. (c) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496. (d) LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452. (e) Zhang, Z.; Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 14148. (f) LaLonde, R. L.; Wang, Z. J.; Mba, M.; Lackner, A. D.; Toste, F. D. *Angew. Chem., Int. Ed.* **2010**, *49*, 598. (g) Li, H.; Lee, S. D.; Widenhoefer, R. A. *J. Organomet. Chem.* **2011**, *696*, 316. (h) Kim, H.; Rhee, Y. H. *J. Am. Chem. Soc.* **2012**, *134*, 4011. (i) Butler, K. L.; Tragni, M.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 5175. (j) Kim, H.; Lim, W.; Im, D.; Kim, G.; Rhee, Y. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 12055. (k) Li, C.; Kähny, M.; Breit, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 13780.

(5) For the asymmetric addition of amines to unactivated alkenes by late transition metal catalysts, see: (a) Dorta, R.; Egli, P.; Zürcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857. (b) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546. (c) Hu, A.; Ogasawara, M.; Sakamoto, T.; Okada, A.; Nakajima, K.; Takahashi, T.; Lin, W. *Adv. Synth. Catal.* **2006**, *348*, 2051. (d) Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 12220. (e) Shen, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 564. (f) Pan, S.; Endo, K.; Shibata, T. *Org. Lett.* **2012**, *14*, 780. (g) Otsuka, M.; Yokoyama, H.; Endo, K.; Shibata, T. *Org. Biomol. Chem.* **2012**, *10*, 3815. (h) Ickes, A. R.; Ensign, S. C.; Gupta, A. K.; Hull, K. L. *J. Am. Chem. Soc.* **2014**, *136*, 11256.

(6) Nagamoto, M.; Nishimura, T. *Chem. Commun.* **2015**, *51*, 13466.

(7) (a) Hartwig, W.; Born, L. *J. Org. Chem.* **1987**, *52*, 4352. (b) Corey, E. J.; Reichard, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 10677. (c) Mulzer, J.; Zuhse, R.; Schmiechen, R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 870. (d) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 36.

(8) For recent reviews of transition-metal-catalyzed synthesis of γ-lactams, see: (a) Ye, L.-W.; Shu, C.; Gagosz, F. *Org. Biomol. Chem.* **2014**, *12*, 1833. (b) Kammerer, C.; Prestat, G.; Madec, D.; Poli, G. *Acc. Chem. Res.* **2014**, *47*, 3439. For selected examples of other methodologies, see: (c) Saigo, K.; Shimada, S.; Hasegawa, M. *Chem. Lett.* **1990**, *19*, 905. (d) Hanessian, S.; MacKay, D. B.; Moitessier, N. *J. Med. Chem.* **2001**, *44*, 3074. (e) Combettes, L. E.; Schuler, M.; Patel, R.; Bonillo, B.; Odell, B.; Thompson, A. L.; Claridge, T. D. W.; Gouverneur, V. *Chem. - Eur. J.* **2012**, *18*, 13126. (f) Gesmundo, N. J.; Grandjean, J.-M. M.; Nicewicz, D. A. *Org. Lett.* **2015**, *17*, 1316.

(9) (a) Nishimura, T.; Kumamoto, H.; Nagaosa, M.; Hayashi, T. *Chem. Commun.* **2009**, 5713. (b) Nishimura, T.; Yasuhara, Y.; Nagaosa, M.; Hayashi, T. *Tetrahedron: Asymmetry* **2008**, *19*, 1778. (c) Nishimura, T.; Yasuhara, Y.; Sawano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 7872. (d) Nishimura, T.; Nagamoto, M.; Ebe, Y.; Hayashi, T. *Chem. Sci.* **2013**, *4*, 4499. (e) Hatano, M.; Nishimura, T. *Angew. Chem., Int. Ed.* **2015**, *54*, 10949. (f) Hatano, M.; Ebe, Y.; Nishimura, T.; Yorimitsu, H. *J. Am. Chem. Soc.* **2016**, *138*, 4010.

(10) The cyclization of 2,2-diphenylpent-4-enamide (R = H) did not proceed.

(11) The absolute configuration of **2e** was determined to be *R*, which was assigned by comparison of the specific rotation of 1,5-dimethyl-3,3-diphenyl-2-pyrrolidinone after detosylation and methylation. See the Supporting Information for details.

(12) The cyclization of nonsubstituted *N*-tosyl-4-pentenamide (R = H) did not proceed.

(13) For an example of iridium-catalyzed hydroamination *via* alkene activation, see: Hesp, K. D.; Tobisch, S.; Stradiotto, M. *J. Am. Chem. Soc.* **2010**, *132*, 413.

(14) For examples of iridium-catalyzed hydroamination *via* oxidative addition of a N−H bond, see refs 4b, 5d, and 5f.

(15) The reaction in the presence of additional D_2O (20 equiv) gave **2s** with 70% D (*exo*). See the Supporting Information for details.

(16) An NMR experiment showed that **1a** reacted with Et_3N to give an ammonium salt. See the Supporting Information for details.

(17) Another deuterium-labeling experiment indicates the reversibility of the C−N bond formation. See the Supporting Information for details.

(18) The enantioselectivity is influenced by the steric property of the amine probably because the ammonium salt forms a tight ion pair in the nonpolar solvent and remains in the vicinity of the amide moiety in the cyclization step.

DOI: 10.1021/acs.orglett.6b01954
Org. Lett. 2016, 18, 4474−4477