J|A|C|S COMMUNICATIONS

Published on Web 03/25/2009

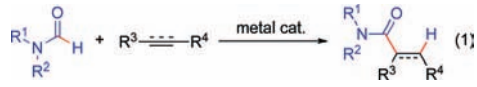
Hydrocarbamoylation of Unsaturated Bonds by Nickel/Lewis-Acid Catalysis

Yoshiaki Nakao,* Hiroaki Idei, Kyalo Stephen Kanyiva, and Tamejiro Hiyama*

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan

Received February 13, 2009; E-mail: yoshiakinakao@npc05.mbox.media.kyoto-u.ac.jp; thiyama@z06.mbox.media.kyoto-u.ac.jp

Selective introduction of an amide functionality into organic molecules is an important transformation in organic synthesis.[1] In this regard, manipulation of the formyl C−H bonds in formamides to form C−C bonds has great synthetic potential for the synthesis of amides with high atom efficiency.[2] Transition metal-catalyzed insertion of unsaturated bonds into the C−H bonds in formamides, namely hydrocarbamoylation reactions,[3,4] is one such transformation, and is a convenient alternative to aminocarbonylation reactions (eq 1),[5] which requires the use of poisonous carbon monoxide. Although there have been reported examples of the ruthenium- or rhodium-catalyzed hydrocarbamoylation reactions,[3] these methods suffer from relatively harsh reaction conditions or require a directing group to assist the oxidative addition of the C−H bonds to transition metals, that is less reactive than that in aldehydes[6] and formates.[7] Hydrocarbamoylation reactions that occur via homolytic cleavage of C−H bonds of formamides compete with reactions of C−H bonds α to the nitrogen.[4] Herein, we report that Lewis acid (LA) cocatalysts significantly promote stereo- and regioselective intermolecular hydrocarbamoylation reactions of alkynes and 1,3-dienes catalyzed by nickel under mild conditions to give variously substituted unsaturated amides. Examples of intramolecular hydrocarbamoylation of olefins are also performed, and these reactions create a novel route to lactams.

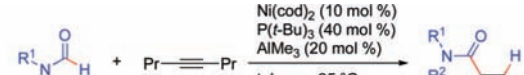


(1)

We recently reported C-2 alkenylation of pyridines and imidazoles by nickel/LA catalysis.[8] Pyridines coordinating to LA were expected to be responsible for the activation of C(2)−H bonds by nickel(0) through oxidative addition. We therefore envisioned that formamides coordinating to LA[9] (vide infra) might also exhibit similar reactivity to nickel(0), allowing the oxidative addition of their formyl C(sp^2)−H bonds located next to positively charged nitrogen. To test this hypothesis, we first examined the reaction of DMF (**1a**, 1.0 mmol) and 4-octyne (**2a**, 1.0 mmol) in the presence of $Ni(cod)_2$ (3 mol %), P(*t*-Bu)$_3$ (12 mol %), and $AlMe_3$ (6 mol %) in toluene at 35 °C, and found that (*E*)-*N*,*N*-dimethyl-2-propylhex-2-enamide (**3aa**) was obtained in 82% yield after 8 h (Table 1, entry 1).[10] The selective functionalization of the formyl C−H bond of abundant DMF for the hydrocarbamoylation reaction is noteworthy. The cis-stereochemisty of the addition reaction was ambiguously identified by NOE experiments of **3aa**.[10] Reactions conducted in the absence of LA catalysts gave no detectable amount of the adduct.[10] A range of *N*,*N*-dialkylformamides **1b**−**1g** also participated in the reaction under similar reaction conditions to give the corresponding α,β-unsaturated amides **3ba**−**3ga** with varying N-substituents (entries 2−7), whereas attempted addition reactions of *N*-aryl-substituted and primary formamides were unsuccessful.

With DMF as a formamide substrate, we next examined the scope of alkynes for the hydrocarbamoylation reaction (Table 2). Silylmethyl-subsituted acetylene **2b** participated in the reaction to give the corresponding cis-adduct **3ab** albeit in modest yield (entry 1), whereas the addition across diphenylacetylene gave trans-adduct (*Z*)-**3ac** as a major product (entry 2) likely via isomerization of the initially formed cis-adduct (*E*)-**3ac** under the reaction conditions (*E*/*Z* = 30:70 at 0.5 h). Indeed, an isolated sample of (*E*)-**3ac** isomerized to (*Z*)-**3ac** under the

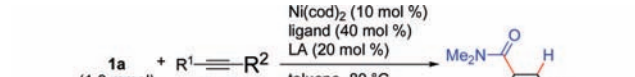
Table 1. Hydrocarbamoylation of **2a** Catalyzed by Nickel/$AlMe_3$

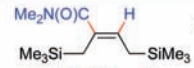
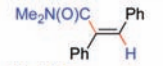
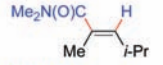
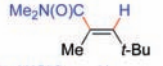
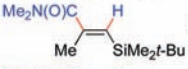
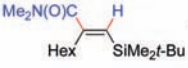
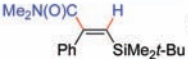


entry	formamide		time (h)	yield of **3** (%)[a]
1[b]	R = Me: **1a**		8	82 (**3aa**)
2	Et: **1b**		11	94 (**3ba**)
3	$PhCH_2$: **1c**		46	83 (**3ca**)[c]
4	*i*-Pr: **1d**		120	77 (**3da**)[d]
5	**1e**		48	86 (**3ea**)
6	X = CH_2: **1f**		9	84 (**3fa**)
7	O: **1g**		22	84 (**3ga**)

[a] Isolated yields. [b] Reaction run with a 3 mol % catalyst and 1.0 mmol of **2a**. [c] An amount of 8% of **1c** was recovered. [d] Conversion of **1d** was estimated to be 85% by GC.

Table 2. Hydrocarbamoylation of Alkynes with DMF

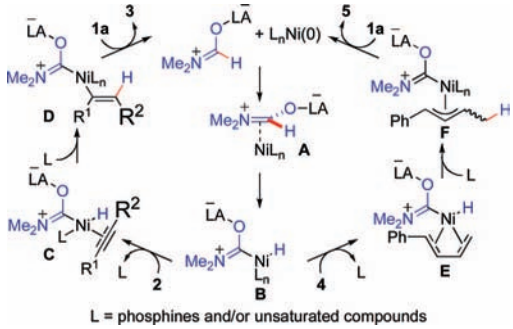


entry	R^1, R^2 in **2**	cond.[a]	time (h)	major product	yield (%)[b]
1[c]	CH_2SiMe_3 (**2b**)	B	3		55 (**3ab**)
2[d]	Ph (**2c**)	A	3		83 (**3ac**)[e]
3	Me, *i*-Pr (**2d**)	B	1		84 (**3ad**)[f]
4	Me, *t*-Bu (**2e**)	B	4		75 (**3ae**)
5	Me, $SiMe_2$*t*-Bu (**2f**)	A	15		58 (**3af**)
6	Hex, $SiMe_2$*t*-Bu (**2g**)	A	72		47 (**3ag**)
7[c]	Ph, $SiMe_2$*t*-Bu (**2h**)	A	26		68 (**3ah**)[g]

[a] Conditions A: P(*t*-Bu)$_3$ and $AlMe_3$. Conditions B: $PCyp_3$ and BPh_3. [b] Isolated yields based on **1a**. [c] Reaction run at 100 °C. [d] Reaction run with 1.0 mmol of the alkyne. [e] *E*/*Z* = 7:93. [f] Containing regioisomer **3′ae** (~3%). [g] *E*/*Z* = 96:4 (98:2 at 7 h).

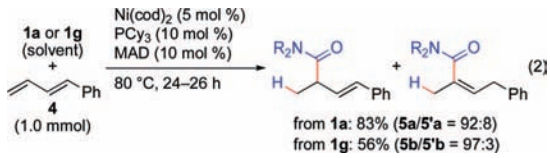
10.1021/ja901153s CCC: $40.75

Scheme 1. Plausible Mechanism



reaction conditions in the presence of **1b** and **2a**. This experiment gave no detectable amount of crossover products (e.g., **3aa**), suggesting that the hydrocarbamoylation reaction is irreversible. Alkynes with sterically biased substituents **2d**−**2h** reacted with excellent stereo- and regioselectivities to give adducts having a larger substituent trans to the dimethylcarbamoyl group (entries 3−7). Use of bulky *tert*-butyldimethylsilyl-substituted alkynes is important to obtain the cis-adducts selectively because adducts derived from trimethylsilyl-substituted ones isomerize relatively easily under the reaction conditions. In some cases, the combination of tricyclopentylphosphine ($PCyp_3$) and BPh_3 as a LA catalyst (conditions B) gave better yields.

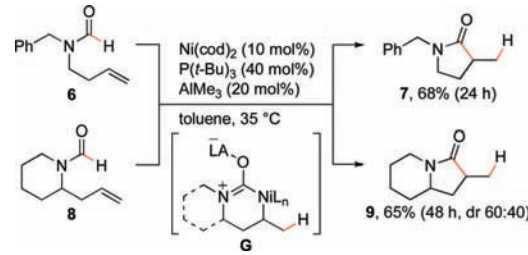
The hydrocarbamoylation of 1-phenyl-1,3-butadiene (**4**) proceeded by using (2,6-*t*-Bu_2-4-Me-$C_6H_2O)_2$AlMe (MAD)[11] as a LA catalyst to give (*E*)-β,γ-unsaturated amides **5** through exclusive hydrocarbamoylation of the terminal double bond of the 1,3-diene (eq 2). Partial isomerization of the double bond was observed, which slightly contaminated the products with α,β-unsaturated amides.



As mentioned above, initiation of the reaction appears to be activation of formamides by coordination to LA, making the formyl C(sp^2)-H bond reactive enough to undergo oxidative addition to nickel(0) species via η^2-coordination of the activated formamides as depicted in **A** (Scheme 1).[12] Coordination of alkynes to the nickel center in the direction to avoid a steric repulsion between the bulkier R^2 and the carbamoyl group followed by hydronickelation gives alkenylnickel intermediate **D**, which upon reductive elimination affords **3**. Coordination and subsequent migratory insertion of 1,3-dienes into the H−Ni bond at their terminal double bond would give π-allylnickel intermediate **F**.[13] Reductive elimination to form a C−C bond takes place selectively at the methyl-substituted carbon[13] of the allyl ligand in **F** to give **5**. No crossover was observed in the reaction of **1a**-d_1 and **1b** with **2a**, supporting the proposed catalytic cycle involving nickel hydride intermediate **B** rather than a carbamoylnickel intermediate with loss of a hydride ligand, that could lead to crossover products. An alternative mechanism through a nickeladihydrofuran intermediate can not be ruled out.[14]

Whereas 1-alkenes gave no intermolecular hydrocarbamoylation products under these reaction conditions, the intramolecular reaction proceeded at 35 °C in a 5-*exo*-*trig* fashion to give γ-lactam **7** (Scheme 2). Likewise, azabicycle **9** was obtained from formamide **8** derived from piperidine albeit with poor diastereoselectivity. The cyclization likely proceeds through oxidative addition of the C−H bond followed by hydronickelation of the double bond to give nickelacycle **G** and reductive elimination.

Scheme 2. γ-Lactam Synthesis by Intramolecular Hydrocarbamoylation



In conclusion, we have demonstrated that intermolecular hydrocarbamoylation reactions of alkynes and 1,3-dienes are efficiently catalyzed cooperatively by nickel and LA to allow direct and atom efficient access to a range of α,β- and β,γ-unsaturated amides. Intramolecular hydrocarbamoylation of olefins also proceeds by the binary catalysis to give lactam derivatives. Current efforts are directed toward expanding the scope of the hydrocarbamoylation reaction by cooperative metal/LA catalysis. A new strategy to activate otherwise inert C−H bonds by the cooperative catalysis is also being applied extensively to other catalytic C−C bond-forming reactions.

Acknowledgment. We thank James P. Stambuli for proofreading the manuscript and helpful comments. This work has been supported financially by a Grant-in-Aid for Creative Scientific Research and that for Priority Areas "Chemistry of Concerto Catalysis" from MEXT. K.S.K. acknowledges Honjo International Scholarship Foundation for generous financial support.

Supporting Information Available: Detailed experimental procedures including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Benz, G. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, p 381.
(2) For recent examples, see: (a) Hosoi, K.; Nozaki, K.; Hiyama, T. *Org. Lett.* **2002**, *4*, 2849. (b) Wan, Y. Q.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6232. (c) Ju, J.; Jeong, M.; Moon, J.; Jung, H.; Lee, S. *Org. Lett.* **2007**, *9*, 4615. For a review, see: (d) Morimoto, T.; Kakiuchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 5580.
(3) (a) Tsuji, Y.; Yoshii, S.; Ohsumi, T.; Kondo, T.; Watanabe, Y. *J. Organomet. Chem.* **1987**, *331*, 379. (b) Kondo, T.; Okada, T.; Mitsudo, T. *Organometallics* **1999**, *18*, 4123. (c) Ko, S.; Han, H.; Chang, S. *Org. Lett.* **2003**, *5*, 2687. (d) Kobayashi, Y.; Kamisaki, H.; Yanada, K.; Yanada, R.; Takemoto, Y. *Tetrahedron Lett.* **2005**, *46*, 7549.
(4) (a) Friedman, L.; Shechter, H. *Tetrahedron Lett.* **1961**, 238. (b) Gardini, G. P.; Minisci, F.; Palla, G.; Arnone, A.; Galli, R. *Tetrahedron Lett.* **1971**, 59. (c) Angioni, S.; Ravelli, D.; Emma, D.; Dondi, D.; Fagnoni, M.; Albini, A. *Adv. Synth. Catal.* **2008**, *350*, 2209.
(5) Park, J. H.; Kim, S. Y.; Kim, S. M.; Chung, Y. K. *Org. Lett.* **2007**, *9*, 2465, and references therein.
(6) For reviews of hydroacylation, see: (a) Jun, C. H.; Jo, E. A.; Park, J. W. Eur. J. Org. Chem. **2007**, 1869. (b) Fu, G. C. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005; p 79.
(7) For hydroesterification, see: Ko, S.; Na, Y.; Chang, S. *J. Am. Chem. Soc.* **2002**, *124*, 750, and references therein.
(8) (a) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448. (b) Kanyiva, K. S.; Löbermann, F.; Nakao, Y.; Hiyama, T. Tetrahedron Lett., doi:10.1016/j.tetlet.2009.02.195.
(9) Hanawa, H.; Abe, N.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 5365.
(10) See Supporting Information for details including optimization of reaction conditions.
(11) Saito, S.; Yamamoto, H. *Chem. Commun.* **1997**, 1585.
(12) Ogoshi, S.; Ikeda, H.; Kurosawa, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4930.
(13) For related nickel-catalyzed insertion reactions of 1,3-dienes into C−H bonds through hydronickelation, see: (a) Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* **2008**, *130*, 5410. (b) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 16170.
(14) (a) Moslin, R. M.; Miller-Moslin, K.; Jamison, T. F. *Chem. Commun.* **2007**, 4441. (b) Montgomery, J.; Sormunen, G. J. *Top. Curr. Chem.* **2007**, *279*, 1. (c) Ogoshi, S.; Arai, T.; Ohashi, M.; Kurosawa, H. *Chem. Commun.* **2008**, 1347.

JA901153S