doi:10.1246/cl.2012.298
Published on the web February 25, 2012

Editor's Choice

Regioselective Hydrocarbamoylation of 1-Alkenes

Yosuke Miyazaki,[1] Yuuya Yamada,[1] Yoshiaki Nakao,*[1] and Tamejiro Hiyama*[2]
[1]*Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510*
[2]*Research & Development Initiative, Chuo University, Bunkyo-ku, Tokyo 112-8551*

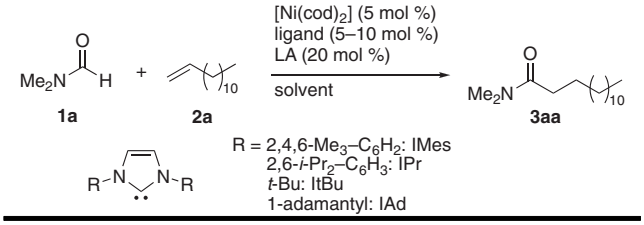
(Received November 29, 2011; CL-111150; E-mail: yoshiakinakao@npc05.mbox.media.kyoto-u.ac.jp)

Nickel/Lewis acid cooperative catalysis derived from [Ni(cod)$_2$], AlEt$_3$, and *N*-heterocyclic carbene (NHC) effects highly regioselective hydrocarbamoylation of 1-alkenes. Variously substituted formamides and 1-alkenes can be employed to give a range of linear alkanamides regioselectively.

Preparation of amides under neutral conditions without the need for toxic reagents and chemical wastes is still challenging in synthetic organic chemistry,[1] although a number of methods for the synthesis of amides are available.[2] Aminocarbonylation of unsaturated C–C bonds would offer an alternative and waste-free access to amides.[3] Insertion of unsaturated compounds into C–H bonds of formamides, namely, hydrocarbamoylation reaction, would allow such transformations without the need for toxic carbon monoxide. For example, ruthenium-catalyzed hydrocarbamoylation reactions of alkenes have been reported,[4] whereas we[5] and others[6] have recently developed the reaction across alkynes,[5,6] 1,3-dienes,[5] and norbornene[6b] catalyzed by such transition metals as nickel,[7] palladium, and rhodium. The ruthenium-catalyzed reactions across alkenes, however, require either harsh reaction conditions,[4a,4b] high-pressure carbon monoxide,[4a] or a pyridyl group as a directing group.[4c] In addition, regioselectivity of these ruthenium-catalyzed reactions is reportedly modest particularly with simple aliphatic 1-alkenes such as 1-hexene, giving linear alkanamides contaminated with a significant amount of branched amides as a minor component.[4] The regioselective hydrocarbamoylation of alkenes can be achieved via a radical pathway.[8] However, the addition reaction competes with alkylation of *N*-substituents. The hydrocarbamoylation of 1-alkenes with high linear selectivity and broad scope of substrates is highly desired as a novel transformation potentially applicable to industrial production of bulk chemicals without use of toxic carbon monoxide. Given the importance of such "*anti*-Markovnikov" functionalization of 1-alkenes,[9] we report herein that nickel/Lewis acid catalysis effects exclusively linear selective hydrocarbamoylation of 1-alkenes.

Our initial attempt to establish the regioselective hydrocarbamoylation was commenced with the reaction of DMF (**1a**) with 1-tridecene (**2a**) in the presence of [Ni(cod)$_2$] (5 mol %) various ligands, and 20 mol % of AlMe$_3$ as a cocatalayst in toluene at 130 °C (Table 1). Bulky phosphorus ligands such as P(*i*-Pr)$_3$ and P(*t*-Bu)$_3$, which were effective for the intramolecular hydrocarbamoylation of alkenes,[5] gave the corresponding linear alkanamide **3aa** exclusively albeit in low yield (Entries 1 and 2). Encouraged by the observed excellent regioselectivity, which was never achieved with the reported ruthenium catalysis with such simple aliphatic 1-alkenes as **2a**, we further explored other ligands to improve the yield of **3aa** and found that NHC ligands were highly effective (Entries 3–6). Particularly, IAd was found optimum to give **3aa** in 62% yield after 2 h (Entry 6).

Table 1. Hydrocarbamoylation of 1-tridecene[a]



Entry	Ligand	Solvent	LA	Temp /°C	Yield of **3aa**/%[b]
1	P(*i*-Pr)$_3$	toluene	AlMe$_3$	130	8
2	P(*t*-Bu)$_3$	toluene	AlMe$_3$	130	15
3	IMes	toluene	AlMe$_3$	130	36
4	IPr	toluene	AlMe$_3$	130	19
5	ItBu	toluene	AlMe$_3$	130	44
6	IAd	toluene	AlMe$_3$	130	62
7	IAd	CPME	AlMe$_3$	130	58
8	IAd	dioxane	AlMe$_3$	130	48
9	IAd	THF	AlMe$_3$	130	46
10	IAd	NMP	AlMe$_3$	130	2
11	IAd	DMF	AlMe$_3$	130	19
12	IAd	toluene	AlMe$_3$	100	81
13	IAd	toluene	AlEt$_3$	100	92 (84)[c]
14	IAd	toluene	Al(oct)$_3$	100	91

[a]The reactions were carried out using **1a** (0.50 mmol), **2a** (0.75 mmol), *n*-C$_{11}$H$_{24}$ (internal standard, 125 μmol), [Ni(cod)$_2$] (5.0 mol %), ligand (10 mol % for phosphines and 5.0 mol % for NHC), and Lewis acid (LA) (20 mol %) in a solvent (0.50 mL). [b]Determined by GC based on **1a** as the limiting reagent. [c]Isolated yield on a 1.0 mmol scale run for 3 h.

With IAd as a ligand, we next examined solvents for the reaction (Entries 7–11). Generally, nonpolar solvents were found to give yields of **3aa** better than with polar solvents, and, thus, the use of **1a** as a solvent was not effective (Entry 11). At this stage, we noted the formation of a significant amount of insoluble precipitates, which were tentatively ascribed to decomposition of either of the metal catalysts. Because this could cause the observed modest yields of **3aa**, we simply lowered the reaction temperature to 100 °C to find that the formation of the precipitates was slowed and the yield of **3aa** was improved (Entry 12). Whereas the reaction run at lower temperature slowed the reaction, the use of AlEt$_3$ and Al(oct)$_3$ instead of AlMe$_3$ showed improved homogeneity of the reaction mixture without the formation of such precipitates, and the yield of **3aa** was further increased (Entries 13 and 14). Under the reaction conditions thus optimized, alkanamide **3aa** was isolated in 84% yield from a reaction run on a 1.0 mmol-scale (Entry 13). Again,

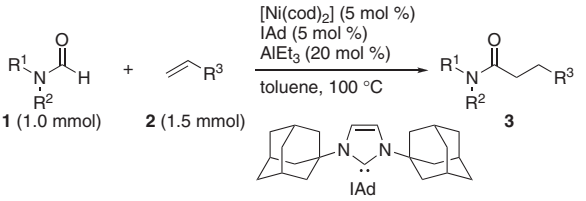
no trace amount of branched alkanamides was obtained under the preparative reaction conditions.

We next investigated the reaction of other formamides with **2a** under the optimized reaction conditions (Table 2). Various *N*-alkyl-substituted formamides gave the corresponding alkanamides in good yields (Entries 1–6), whereas the reaction of *N*-aryl-substituted one (**1h**) was sluggish (Entry 8). Notably, optically active formamide (*R*)- and (*S*)-**1e** gave enantiomerically pure alkanamide (*R*)- and (*S*)-**3ea** without any loss of stereochemical information (Entries 4 and 5). Formamides derived from primary amines did not give adducts at all under these reaction conditions due presumably to the presence of acidic hydrogen incompatible with the Lewis acid catalyst. The hydrocarbamoylation of other 1-alkenes also proceeded to give alkanamides having a range of functionalities including siloxy, alkoxycarbonyl, internal double bond, and silyl groups (Entries 9–14). All the reactions showed exclusive linear selectivity except for the reaction across styrene (**2h**), which gave a mixture of linear and branched alkanamides (Entry 15). The formation of a branched adduct in this particular case can be ascribed to the contribution of a stable benzylnickel intermediate in a catalytic cycle (vide infra).[9,10] On the other hand, the addition across 1,1- or 1,2-disubstituted alkenes was unsuccessful.

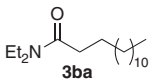
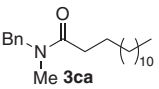
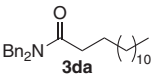
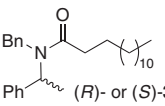
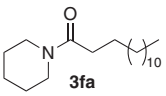
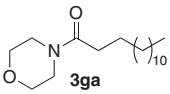
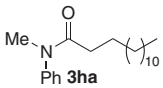
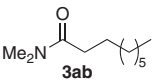
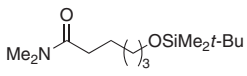
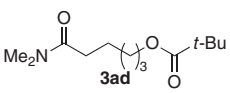
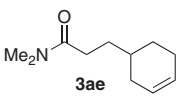
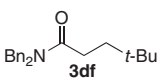
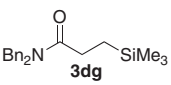
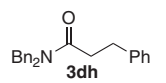
The reaction path is understood in terms of the catalytic cycle shown in Scheme 1. Formamides coordinating to the Lewis acid catalyst through their carbonyl oxygen would undergo the oxidative addition of the C(sp^2)–H bond to a nickel(0) species to give nickel hydride **B** via the formation of η^2-formamide–nickel intermediate **A** (Scheme 1).[11] Alkenes coordinate to the nickel center of **B** to form **C**, which undergoes migratory insertion to give alkylnickel **D**. Reductive elimination followed by ligand exchange reactions afford alkanamides and regenerate **A** to complete the catalytic cycle. The exclusive formation of the linear alkanamides results from regioselective migratory insertion, which favors sterically less hindered primary alkylnickel **D** rather than a secondary alkylnickel species. With vinylarenes, the corresponding *sec*-alkylnickel species could be stabilized by the aryl group[10] to give branched adducts to some extent (Entry 15 of Table 2). The reaction of **1d**-*d* with **2g** gave **3dg** with 4% and 26% deuteration at the methylenes α and β to the carbonyl group (eq 1). The yield of **3dg**-*d* was 47% as estimated by ^{1}H NMR. Unreacted **1d**-*d* and **2g** showed loss of deuterium and incorporation of deuterium, respectively. These results show that the elemental steps except for the reductive elimination in the proposed catalytic cycle are reversible. Partial incorporation of deuterium at the β-position of the silyl group in **3dg** and recovered **2g** can also be understood in terms of the reversible hydronickelation process to give a *sec*-alkylnickel species, which is reluctant to undergo the final reductive elimination. The use of highly bulky carbene ligands would be crucial to promote the reductive elimination from linear alkylnickel intermediate **D**.

In summary, we have developed regioselective hydrocarbamoylation of alkenes by nickel/Lewis acid cooperative catalysis.[12] The exceptionally high regioselectivity achieved with the present catalytic system would be highly useful as a method to access variously functionalized amides as well as a novel transformation of *anti*-Markovnikov selective functionalization of alkenes. Further efforts will be paid to understand the mechanism of the cooperative catalysis and its further application to functionalization of unreactive bonds.[13]

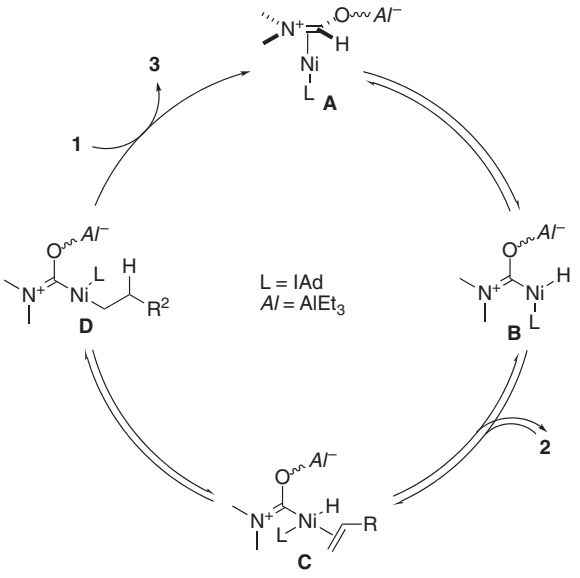
Table 2. Hydrocarbamoylation of 1-alkenes catalyzed by Ni/$AlEt_3$



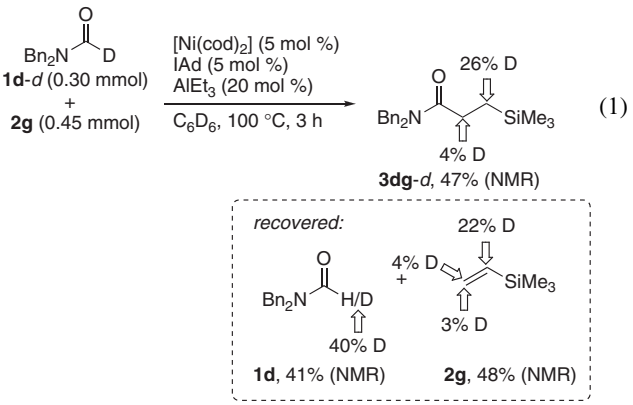
R^1, R^2 = Me, Me (**1a**); Et, Et (**1b**); Me, Bn (**1c**); Bn, Bn (**1d**); 1-phenylethyl, Bn (**1e**); –$(CH_2)_5$– (**1f**); –$(CH_2)_2O(CH_2)_2$– (**1g**); Me, Ph (**1h**)
R_3 = $C_{11}H_{23}$ (**2a**); C_6H_{13} (**2b**); $(CH_2)_3OSiMe_2t$-Bu (**2c**); $(CH_2)_3OPiv$ (**2d**); cyclohex-3-en-1-yl (**2e**); *t*-Bu (**2f**); $SiMe_3$ (**2g**); Ph (**2h**)

Entry	1	2	Time/h	Product	Yield/%[a]
1	**1b**	**2a**	12	 **3ba**	69
2	**1c**	**2a**	9	 Me **3ca**	68
3	**1d**	**2a**	9	 **3da**	75
4	(*R*)-**1e**[b]	**2a**	9	 (*R*)- or (*S*)-**3ea**	78[b]
5	(*S*)-**1e**[b]	**2a**	9		81[b]
6	**1f**	**2a**	9	 **3fa**	65
7	**1g**	**2a**	6	 **3ga**	53
8[c]	**1h**	**2a**	9	 Ph **3ha**	13
9	**1a**	**2b**	6	 **3ab**	81
10[c]	**1a**	**2c**	6	 **3ac**	77
11[c]	**1a**	**2d**	6	 **3ad**	59
12[d]	**1a**	**2e**	6	 **3ae**	90
13[d]	**1d**	**2f**	6	 **3df**	59
14	**1d**	**2g**	19	 **3dg**	83
15	**1d**	**2h**	19	 **3dh**	70[e]

[a]Isolated yields based on **1**. [b]>95% ee. [c]Run with [Ni(cod)$_2$] (10 mol %), IAd (10 mol %), and $AlEt_3$ (40 mol %). [d]Run with 3.0 mmol of **2**. [e]16% of a regioisomer was also obtained.



Scheme 1. Plausible catalytic cycle.



(1)

This work has been supported financially by a Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" (to Y.N., No. 22105003) and Scientific Research (S) (to T.H., No. 21225005) from MEXT and JSPS, respectively.

References and Notes

1 For some exceptional examples, see: a) T. Naota, S.-I. Murahashi, *Synlett* **1991**, 693. b) S. H. Cho, E. J. Yoo, I. Bae, S. Chang, *J. Am. Chem. Soc.* **2005**, *127*, 16046. c) J. W. Bode, R. M. Fox, K. D. Baucom, *Angew. Chem., Int. Ed.* **2006**, *45*, 1248. d) M. P. Cassidy, J. Raushel, V. V. Fokin, *Angew. Chem., Int. Ed.* **2006**, *45*, 3154. e) W.-K. Chan, C.-M. Ho, M.-K. Wong, C.-M. Che, *J. Am. Chem. Soc.* **2006**, *128*, 14796. f) C. Gunanathan, Y. Ben-David, D. Milstein, *Science* **2007**, *317*, 790.

2 a) R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, 2nd ed., Wiley-VCH, New York, **1999**. b) C. L. Allen, J. M. J. Williams, *Chem. Soc. Rev.* **2011**, *40*, 3405.

3 *Modern Carbonylation Methods*, ed. by L. Kollár, Wiley-VCH, Weinheim, **2008**.

4 a) Y. Tsuji, S. Yoshii, T. Ohsumi, T. Kondo, Y. Watanabe, *J. Organomet. Chem.* **1987**, *331*, 379. b) T. Kondo, T. Okada, T.-a. Mitsudo, *Organometallics* **1999**, *18*, 4123. c) S. Ko, H. Han, S. Chang, *Org. Lett.* **2003**, *5*, 2687.

5 Y. Nakao, H. Idei, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.* **2009**, *131*, 5070.

6 a) Y. Kobayashi, H. Kamisaki, K. Yanada, R. Yanada, Y. Takemoto, *Tetrahedron Lett.* **2005**, *46*, 7549. b) T. Fujihara, Y. Katafuchi, T. Iwai, J. Terao, Y. Tsuji, *J. Am. Chem. Soc.* **2010**, *132*, 2094.

7 For nickel-catalyzed arylation of formamides, see: J. Ju, M. Jeong, J. Moon, H. M. Jung, S. Lee, *Org. Lett.* **2007**, *9*, 4615.

8 For a review, see: H.-H. Vogel, *Synthesis* **1970**, 99.

9 M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem., Int. Ed.* **2004**, *43*, 3368.

10 a) A. L. Casalnuovo, T. V. RajanBabu, T. A. Ayers, T. H. Warren, *J. Am. Chem. Soc.* **1994**, *116*, 9869. b) Y. Nakao, N. Kashihara, K. S. Kanyiva, T. Hiyama, *Angew. Chem., Int. Ed.* **2010**, *49*, 4451.

11 S. Ogoshi, H. Ikeda, H. Kurosawa, *Angew. Chem., Int. Ed.* **2007**, *46*, 4930.

12 For our previous reports on nickel/Lewis acid-catalyzed functionalization of C–H bonds, see: a) Y. Nakao, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.* **2008**, *130*, 2448. b) K. S. Kanyiva, F. Löbermann, Y. Nakao, T. Hiyama, *Tetrahedron Lett.* **2009**, *50*, 3463. c) Y. Nakao, H. Idei, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.* **2009**, *131*, 15996. d) Y. Nakao, Y. Yamada, N. Kashihara, T. Hiyama, *J. Am. Chem. Soc.* **2010**, *132*, 13666.

13 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

