Synthetic Methods

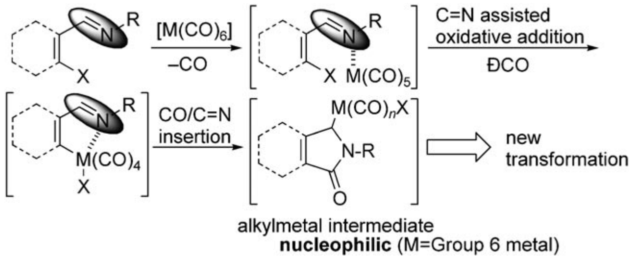
DOI: 10.1002/anie.200902884

Molybdenum(0)-Promoted Carbonylative Cyclization of *o*-Haloaryl- and β-Haloalkenylimine Derivatives by Oxidative Addition of a Carbon(sp^2)–Halogen Bond: Preparation of Two Types of γ-Lactams**

*Jun Takaya, Kenichiro Sangu, and Nobuharu Iwasawa**

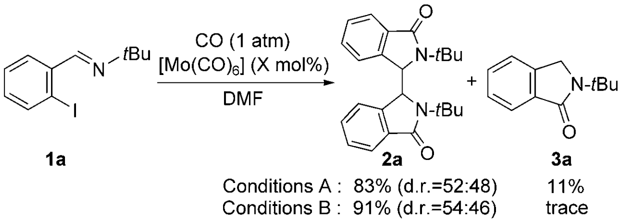
In contrast to the widespread use of late-transition-metal catalysts for the activation and transformation of a carbon-(sp^2)–halogen bond by oxidative addition,[1] related reactions promoted by early-transition-metal complexes have scarcely been reported owing to their low activity to oxidative addition and difficulty in regenerating the catalytic species.[2–4] Nevertheless, it is highly desirable to develop such reactions as the carbon–metal bond of early-transition-metals formed by the oxidative addition is expected to show characteristic reactivity resulting from the high polarity of this bond. Our research group has recently reported a reaction involving the stoichiometric intermolecular addition to alkenes of acylmolybdenum species generated by oxidative addition of aryl- or alkenylhalides to a molybdenum(0) carbonyl complex.[5] Herein, we report that by utilizing chelation-assisted oxidative addition of *o*-haloaryl- and β-haloalkenylimines to [Mo(CO)$_6$], two types of synthetically useful γ-lactam derivatives can be obtained selectively by the appropriate choice of reaction conditions.

We chose a Group 6 metal carbonyl species to promote the carbonylative cyclization reaction of aryl- or alkenylhalides bearing an aldimine moiety at a neighboring position, with the expectation that coordination of the imine nitrogen atom to the metal would assist oxidative addition of the carbon(sp^2)–halogen bond to initiate the reaction (Scheme 1).[6] The focus of this study involves the investigation of reaction pathways that follow this oxidative addition step, also the usefulness of Group 6 metal carbonyl species will be compared to the well-known palladium-catalyzed reactions.[7,8]



Scheme 1. Carbonylative cyclization promoted by a Group 6 metal carbonyl species.

Based on these considerations, we examined the reaction of (*N*-*tert*-butyl)-*o*-iodobenzylideneamine **1a** as a model substrate. After extensive screening of reaction conditions, it was found that when the aldimine **1a** was treated with a stoichiometric amount of [Mo(CO)$_6$] in DMF at 100 °C in a CO atmosphere, bis(isoindolinone) **2a** was obtained in 83 % yield as a mixture of diastereomers and was accompanied by 11 % yield of a monomeric isoindolinone **3a** (Scheme 2).[9] The structure of the dimer **2a** was determined by ^{1}H and ^{13}C NMR spectroscopy, high-resolution mass spectrometry, elemental analysis, and X-ray analysis of its analogue.[10] Further investigation of various additives disclosed that the addition of 1,8-bis(dimethylamino)naphthalene (the proton sponge) realized a semi-catalytic version of this carbonylative cyclization with perfect selectivity of products. Thus, treatment of **1a** with 30 mol % of [Mo(CO)$_6$] and 200 mol % of proton sponge in DMF at 120 °C in a CO atmosphere afforded **2a** as the exclusive product in 93 % yield. Among the Group 6 metals examined, only [Mo(CO)$_6$] showed activity while Cr(CO)$_6$ or W(CO)$_6$ did not afford the products.



Scheme 2. Formation of bis(isoindolinone) **2a** by the carbonylative cyclization of **1a** with [Mo(CO)$_6$] in the presence of the proton sponge. Conditions A: X = 100, 100 °C, 1.5 h. Conditions B: X = 30, proton sponge (200 mol %), 120 °C, 10 h. DMF = *N*,*N*-dimethylformamide.

A proposed reaction mechanism is depicted in Scheme 3. First, (*N*-*tert*-butyl)-aldimine-assisted oxidative addition of aryl iodide to coordinatively unsaturated Mo(CO)$_n$, which is generated by the dissociation of carbonyl ligands under the reaction conditions, occurs to afford an arylmolybdenum(II) intermediate **A**.[11] The successive insertion of a carbonyl

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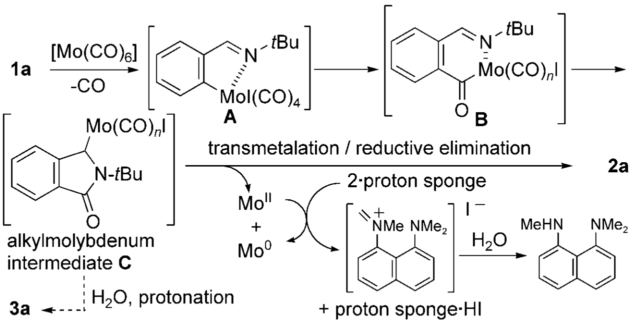
[**] This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200902884.



Scheme 3. Proposed reaction mechanism.

ligand generates an acyl molybdenum complex **B** and insertion of the C=N bond occurs to afford an alkyl molybdenum intermediate **C**. Finally, transmetalation and reductive elimination of intermediate **C** gives the dimeric isoindolinone **2a**, whereas protonation of intermediate **C** by the water present in DMF affords the monomer **3a** as a minor product. The generated Mo^{II} species is reduced to the catalytically active Mo^{0} by the proton sponge.[12,13] These two reaction pathways (of alkylmolybdenum intermediate **C**) are characteristic of the molybdenum-mediated reaction and are in striking contrast to palladium-promoted carbonylative cyclization of similar haloimines: in which alkylpalladium intermediates corresponding to **C** react with nucleophiles to give coupling products instead of undergoing dimerization or protonation.[14,15] This behavior strongly reflects the nucleophilic character of alkylmolybdenum species, which favor transmetalation and protonation. Although the efficiency of the current catalytic reaction is still inadequate compared to the well-developed palladium-catalyzed reactions, this reaction is a rare example of a carbon–carbon bond-forming reaction (including oxidative addition of an carbon(sp^2)–halogen bond) catalyzed by a Group 6 metal.

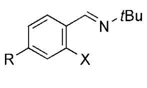
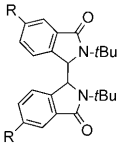
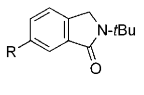
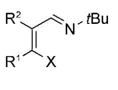
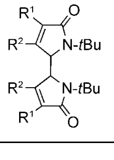
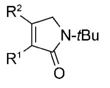
Table 1 shows the generality of our $[Mo(CO)_6]$-catalyzed synthesis of bis(γ-lactam) derivatives under the reaction conditions described above (30 mol% of $[Mo(CO)_6]$). Aryl iodides **1b** and **1c** with an electron-donating substituent on their aromatic rings smoothly reacted to afford the corresponding bis(isoindolinone) derivatives **2b** and **2c** in good yields (Table 1, entries 1 and 2). A chloride atom on the benzene ring was also tolerated and selective activation of the carbon–iodine bond was realized (Table 1, entry 3). Furthermore, not only aryl halides but also alkenyl halides containing cyclic (**1f**, **1g**: Table 1, entries 5 and 6) or acyclic backbones (**1h**, **1i**: Table 1, entries 7 and 8) smoothly underwent this carbonylative cyclization with and gave bis(γ-lactam) derivatives in good to high yields: although the production of monomeric lactams increased slightly. The successful application of this methodology to less reactive aryl- or alkenyl-bromides disclosed the high activity of $Mo(CO)_n$ toward oxidative addition (Table 1, entries 4–6). Thus, this protocol is general and provides easy access to bis(γ-lactam) derivatives, which are difficult to synthesize by previously reported processes catalyzed by late-transition-metals. This dimeric skeleton is observed in the structure of β-isoindigo derivatives and is also potentially useful as a precursor to diimine-type bidentate ligands.

Based on the observation that monomeric lactam **3** was formed by protonation of intermediate **C** even with a trace amount of water present in DMF, we developed a general protonation protocol leading to monomeric lactam **3** in the presence of a proton donor. After examination of the reaction of **1h**, it was found that the addition of 3 equivalents of water dramatically changed the course of the reaction and only monomeric γ-lactam **3f** was obtained in 90% yield using a stoichiometric amount of $[Mo(CO)_6]$ at 160 °C (Scheme 4).[16] This ease of protonation is thought to result from the high nucleophilicity of alkylmolybdenum intermediate **D** and has rarely been observed in related palladium-promoted reactions.[17]

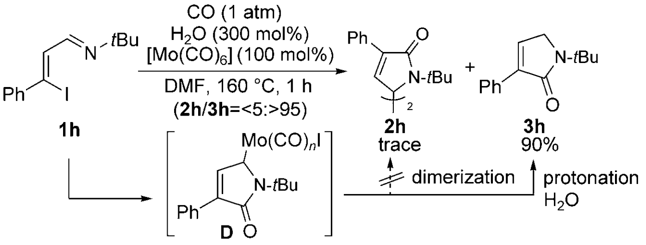
This protonation protocol also showed generality as summarized in Table 2. Other alkenyl- or arylhalides bearing various substituents were also applicable to this protocol and

Table 1: General scope of the $[Mo(CO)_6]$-catalyzed synthesis of bis(γ-lactam) derivatives.

$$\underset{\mathbf{1}}{\text{aldimine}} \xrightarrow[\text{DMF, 120 °C, 3–6 h}]{\text{CO (1 atm)},\ [Mo(CO)_6]\ (30\ \text{mol\%}),\ \text{proton sponge (200 mol\%)}} \underset{\mathbf{2}}{\text{bis(γ-lactam)}} + \underset{\mathbf{3}}{\text{γ-lactam}}$$

Entry	Aldimine		Products				Ratio of **2**/**3**
			Yield of bis(γ-lactam) [%] (d.r.)		Yield of γ-lactam [%]		
1		**1b** R = CH_3, X = I		**2b** 86 (61:39)		**3b** trace	>95:<5
2		**1c** R = OMe, X = I		**2c** 72 (53:47)		**3c** trace	>95:<5
3		**1d** R = Cl, X = I		**2d** 55 (58:42)		**3d** 2	>95:<5
4[a]		**1e** R = H, X = Br		**2a** 75 (69:31)		**3a** trace	>95:<5
5		**1f** $R^1 = R^2 = CH_2CH_2CH_2$, X = Br		**2f** 90 (83:17)		**3f** trace	>95:<5
6		**1g** $R^1 = R^2 = CH_2(CH_2)_2CH_2$, X = Br		**2g** 91 (79:21)		**3g** trace	>95:<5
7		**1h** R^1 = Ph, R^2 = H, X = I		**2h** 58 (95:5)		**3h** 21	73:27
8		**1i** R^1 = Ph, $R^2 = CH_3$, X = I		**2i** 60 (77:23)		**3i** 13	82:18

[a] Reaction temperature at 160 °C.

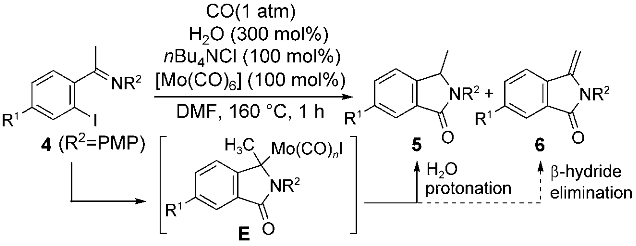


Scheme 4. Selective formation of γ-lactam **3** by protonation of intermediate **D**.

selectively afforded monomeric γ-lactams by the appropriate choice of the proton source (water or PPTS) and the substituent on the nitrogen center (*t*Bu or PMP; Table 2). Furthermore, the uniqueness of the alkylmolybdenum intermediate is highlighted by the reaction of ketimine derivatives, in which similar alkyl transition-metal intermediates bearing a β hydrogen are known to undergo rapid β-hydride elimination to afford enamine derivatives.[18] Various ketimines derived from acetophenones bearing an electron-donating or -accepting substituent gave protonation products **5** with high selectivity under slightly modified reaction conditions (100 mol% of $n\mathrm{Bu_4NCl}$ and 3 equiv of water as additives; Table 3). Interestingly, no formation of dimerized bis(isoindolinone) derivatives was observed, probably owing to strong steric repulsion between *tert*-alkylmolybdenum intermediates in the transmetalation step. Even though this protonation protocol needs a stoichiometric amount of molybdenum at present, it is a facile method for the construction of synthetically useful γ-lactam and isoindolinone derivatives.

In conclusion, we have established a unique molybdenum-promoted carbonylative cyclization of *o*-haloaryl- and β-haloalkenylimines leading to γ-lactam derivatives. By utilizing the characteristic property of the molybdenum complex, two kinds of products (both of which have rarely been obtained by reactions catalyzed by late-transition-metals) were obtained selectively simply by changing the reaction conditions.

Table 3: Selective protonation over β-hydride elimination.



Entry	Ketimine	Yield of **5** + **6** [%]	Ratio of **5**/**6**
1	**4a** R^1 = H	73	**5a**/**6a** = 92:8
2	**4b** R^1 = Cl	59	**5b**/**6b** = 92:8
3	**4c** R^1 = $\mathrm{CF_3}$	52	**5c**/**6c** = >95:<5
4	**4d** R^1 = Me	79	**5d**/**6d** = 71:29
5	**4e** R^1 = OMe	81	**5e**/**6e** = 86:14

Experimental Section

General procedure for $[\mathrm{Mo(CO)_6}]$-promoted carbonylative cyclization of (*N-tert*-butyl)-2-iodobenzylideneamine **1a** in the presence of the proton sponge: A mixture of aldimine **1a** (41 mg, 0.14 mmol), $[\mathrm{Mo(CO)_6}]$ (11 mg, 0.042 mmol), and proton sponge (60 mg, 0.28 mmol) in DMF (5.6 mL) was heated at 120 °C for 10 h in a CO atmosphere. After **1a** was completely consumed (as evident by TLC) the reaction was quenched at room temperature with 1 M HCl solution, and then the mixture was neutralized with a phosphate buffer at pH 7. The mixture was extracted four times with diethyl ether and the combined organic extracts were washed with brine and dried over $\mathrm{MgSO_4}$. The solvent was removed under reduced pressure and the residue was purified by preparative TLC (silica gel, eluent: 1:1 hexanes:ethyl acetate) to afford the bis(isoindolinone) **2a** (24.1 mg, 0.064 mmol, 91% yield).

Received: May 29, 2009
Published online: August 24, 2009

Keywords: carbonylation · lactams · molybdenum · oxidative addition · synthetic methods

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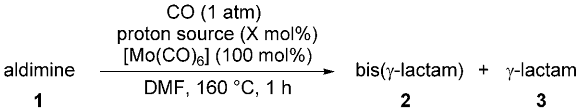
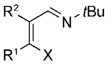
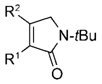
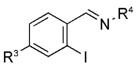
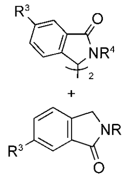
[1] a) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; b) *Handbook*

Table 2: General scope of protonation protocol.



Entry	Aldimine			Yield of **2** + **3** [%]	Ratio of **2**/**3**
1[a]		**1f** R^1 = R^2 = $\mathrm{CH_2CH_2CH_2}$, X = Br		68	**2f**/**3f** = 32:68
2[b]		**1g** R^1 = R^2 = $\mathrm{CH_2(CH_2)_2CH_2}$, X = Br		86	**2g**/**3g** = 2:98
3[b]		**1i** R^1 = Ph, R^2 = $\mathrm{CH_3}$, X = I		94	**2i**/**3i** = <5:>95
4[c]		**1j** R^3 = H, R^4 = PMP		82	**2j**/**3j** = 20:80
5[c]		**1k** R^3 = $\mathrm{CH_3}$, R^4 = PMP		76	**2k**/**3k** = 21:79
6[c]		**1l** R^3 = OMe, R^4 = PMP		65	**2l**/**3l** = 15:85
7[c]		**1d** R^3 = Cl, R^4 = *t*Bu		61	**2d**/**3d** = 20:80

[a] 200 mol% PPTS. [b] 300 mol% $\mathrm{H_2O}$. [c] 500 mol% PPTS. PMP = *p*-methoxyphenyl, PPTS = pyridinium *p*-toluenesulfonate.

of Organopalladium Chemistry for Organic Synthesis (Ed.: E. I. Negishi), Wiley, New York, **2002**; c) A. Leitner in *Iron Catalysis in Organic Chemistry* (Ed.: B. Plietker), Wiley-VCH, Weinheim, **2008**, p. 147.

[2] For the well-developed area of molybdenum- or tungsten-catalyzed allylic substitution reactions by oxidative addition of allylic halide equivalents, see: a) B. M. Trost, M. Lautens, *J. Am. Chem. Soc.* **1982**, *104*, 5543; b) B. M. Trost, M.-H. Hung, *J. Am. Chem. Soc.* **1983**, *105*, 7757; c) O. Belda, C. Moberg, *Acc. Chem. Res.* **2004**, *37*, 159, and references therein.

[3] Richmond and co-workers established that a bidentate or tridentate chelating lignd assisted oxidative addition of Ar−X to tungsten or molybdenum carbonyl complexes to give air-stable, seven coordinate W^{II} or Mo^{II} complexes. However, the high stability of the resulting complexes and specificity of substrates limited their application to synthetic chemistry, see: a) T. G. Richmond, M. A. King, E. P. Kelson, A. M. Arif, *Organometallics* **1987**, *6*, 1995; b) B. P. Buffin, A. M. Arif, T. G. Richmond, *J. Chem. Soc. Chem. Commun.* **1993**, 1432; c) J. L. Kiplinger, T. G. Richmond, *Polyhedron* **1997**, *16*, 409.

[4] a) H. Guo, F. Kong, K.-i. Kanno, J. He, K. Nakajima, T. Takahashi, *Organometallics* **2006**, *25*, 2045; b) A. Aballay, R. Arancibia, G. E. Buono-Core, T. Cautivo, F. Godoy, A. H. Klahn, B. Oelckers, *J. Organomet. Chem.* **2006**, *691*, 2563; c) G.-q. Chen, S.-t. Wang, X.-j. Zhou, *Transition Met. Chem.* **1990**, *15*, 236.

[5] K. Sangu, T. Watanabe, J. Takaya, N. Iwasawa, *Synlett* **2007**, 929.

[6] Palladium-catalyzed carbonylative cyclization utilizing $[Mo(CO)_6]$ as a carbonyl source has been reported: a) X. Wu, A. K. Mahalingam, Y. Wan, M. Alterman, *Tetrahedron Lett.* **2004**, *45*, 4635; b) X. Wu, P. Nilsson, M. Larhed, *J. Org. Chem.* **2005**, *70*, 346.

[7] For catalytic carbonylative cyclization reactions of *o*-halophenylimines, see: a) C. S. Cho, L. H. Jiang, D. Y. Lee, S. C. Shim, H. S. Lee, S.-D. Cho, *J. Heterocycl. Chem.* **1997**, *34*, 1371; b) C. S. Cho, D. Y. Chu, D. Y. Lee, S. C. Shim, T. J. Kim, W. T. Lim, N. H. Heo, *Synth. Commun.* **1997**, *27*, 4141; c) C. S. Cho, H. S. Shim, H.-J. Choi, T.-J. Kim, S. C. Shim, *Synth. Commun.* **2002**, *32*, 1821; for stoichiometric reactions, see: d) J. M. Thompson, R. F. Heck, *J. Org. Chem.* **1975**, *40*, 2667; e) P. W. Clark, S. F. Dyke, G. Smith, C. H. L. Kennard, *J. Organomet. Chem.* **1987**, *330*, 447; f) A. D. Ryabov, *Synthesis* **1985**, 233; g) R. Cao, H. Sun, X. Li, *Organometallics* **2008**, *27*, 1944.

[8] For carbonylative cyclization reactions of *o*-halobenzaldehyde, *o*-halophenylketones, or related compounds, see: a) I. Shimoyama, Y. Zhang, G. Wu, E.-i. Negishi, *Tetrahedron Lett.* **1990**, *31*, 2841; b) P. G. Ciattini, G. Mastropietro, E. Morera, G. Ortar, *Tetrahedron Lett.* **1993**, *34*, 3763; c) W. Tully, L. Main, B. K. Nicholson, *J. Organomet. Chem.* **1995**, *503*, 75; d) S. C. Shim, D. Y. Lee, L. H. Jiang, T. J. Kim, S.-D. Cho, *J. Heterocycl. Chem.* **1995**, *32*, 363; e) C. S. Cho, J. U. Kim, H.-J. Choi, *J. Organomet. Chem.* **2008**, *693*, 3677, and references therein; f) G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644.

[9] The reaction with a stoichiometric amount of $[Mo(CO)_6]$ in a nitrogen atmosphere afforded the products in slightly lower yield (by ≈10%).

[10] The structures of both stereoisomers of **2d**, derived from (*N-tert*-butyl)-2-iodo-4-chloro-benzylideneamine **1d**, were confirmed by X-ray analysis (see the Supporting Information).

[11] The fact that the *N*-tosyl analogue, in which coordinating ability of its imino nitrogen atom is decreased because of the strong electron-withdrawing nature of the tosyl group, failed to afford any carbonylation products. This result strongly supports the crucial role of the (*N-tert*-butyl)-aldimine moiety as a directing group (see the Supporting Information).

[12] The role of the proton sponge as a reductant is confirmed by the observation of *N*,*N*,*N*′-trimethylnaphthalene-1,8-diamine after work-up.

[13] The complete suppression of the formation of **3a** in the presence of the proton sponge can be explained by considering the role of the proton sponge as a proton scavenger.

[14] The formation of dimer as a minor product has been observed in a palladium-catalyzed reaction of a similar haloimine, see Ref. [7a].

[15] Recently, Li and co-workers reported nickel-promoted carbonylative cyclization and dimerization of *o*-halophenylimines to give bis(isoindolinone)in low yields, see Ref. [7g].

[16] The reaction of **1i** in the presence of 3.0 equivalents of D_2O afforded **3i** with 81% incorporation of deuterium at the γ-position, thus supporting the concept of protonation of the alkylmolybdenum intermediate by added water (see the Supporting Information).

[17] a) During the preparation of this manuscript, Cho and Ren reported the palladium-catalyzed synthesis of isoindolinone through the hydrogenolysis of an alkylpalladium intermediate generated by carbonylative cyclization of *o*-halophenylimines. The hydrogenolysis was proposed to proceed with H_2 generated by the reaction of DMF and/or CO with H_2O, see: C. S. Cho, W. X. Ren, *Tetrahedron Lett.* **2009**, *50*, 2097; b) See Ref. [8e].

[18] See Ref. [7c, 8a, 8b].