Cationic Ir(I)-Catalyzed sp³ C—H Bond Alkenylation of Amides with Alkynes

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A cationic Ir(I)-BINAP catalyst cleaved sp³ C–H bonds of arylamides rather than sp² C–H bonds, which was followed by alkenylation with alkynes to give allylamides. Several types of amides and alkynes were suitable as substrates, and the corresponding allylamides were obtained in moderate to good yield. We also demonstrated that carbonyl-directed sp³ C–H bond cleavage would be an initial step in the present reaction by a deuterium-labeling experiment.

The direct functionalization of unactivated carbon-hydrogen bonds has attracted much attention in both academic and industrial fields over the past decade. Especially, transition metal catalysts have been comprehensively investigated as a powerful tool in C–H activation/carbon–carbon or carbon-heteroatom bond-forming processes.¹ However, transformation at sp³ C–H bonds is still a challenging topic due to the lack of a π -electron system which would facilitate the interaction between catalyst and substrate. Recently, the coupling of sp³ C–H bonds with several functionalities such as alkenes,^{2a–d} aryl halides,^{2e–g} and boronic acids^{2h,i} has been developed using a directing group or α -quaternary carbon.³ To the best of our knowledge, however, there have been only limited examples of sp³ C–H bond functionalization in which alkynes were used as a coupling partner.⁴ In this study, we found that a cationic Ir(I)–BINAP complex showed high catalytic activity in the sp³ C–H bond alkenylation of amides with alkynes through carbonyl-directed C–H bond activation, which prevailed over aromatic sp² C–H bond activation.^{2d}

We previously reported that a cationic Ir(I)-BINAP complex can act as an effective catalyst in the *ortho*-alkenylation of arylketones with alkynes via carbonyl-directed sp² C-H bond activation.⁵ During our investigation of substrates, we found that the alkenylation of arylamides

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⁽³⁾ For selected examples of sp³ C-H bond activation without assisting groups, see: (a) Murphy, J. M.; Lawrence, J. D.; Kawamura, K.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 13684. (b) Ishiyama, T.; Ishida, K.; Takagi, J.; Miyaura, N. *Chem. Lett.* **2001**, *30*, 1082. (c) Shimada, S.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2168. (d) Dong, C.-G.; Hu, Q.-S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2289. (e) Ren, H.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3462.

proceeded with unexpected chemoselectivity: in the presence of cationic Ir(I)–BINAP catalyst in chlorobenzene, the addition of *N*,*N*-dimethylbenzamide (**1a**) to diphenylacetylene (**2a**) occurred at the sp³ C–H bond to provide allylamide **3aa** as an (*E*)-isomer, albeit in low yield (eq 1). In contrast, only trace amounts of adduct **3aa'** derived from alkenylation at the sp² C–H bond was detected by ¹H NMR.⁶



We further screened several reaction conditions using benzamide **1a** and alkyne **2a** as model substrates (Table 1).

Table 1. Optimization of the Reaction Conditions $1a + 2a$ $\frac{[Ir(cod)_2]X}{+ ligand (10 mol \%)}$ $3aa + 3aa$ $(2 equiv)$ PhCl, 135 °C, 24 h				
entry	ligand	Х	yield of 3aa $(\%)^a$	yield of 3aa ' (%) ^a
1	rac-BINAP	SbF_6	31	6
2	rac-BINAP	PF_6	41	5
3	rac-BINAP	OTf	$80 \ (75)^b$	$5 (4)^b$
4^c	rac-BINAP	OTf	$(78)^{b}$	5
5^d	rac-BINAP	OTf	91	6
6	BIPHEP	OTf	53	<5
7	DPPBenzene	OTf	ND	11
8	PPh_3	OTf	ND	ND

^{*a*} Yield was determined by ¹H NMR integration relative to 1,1,2,2-tetrachloroethane as an internal standard. ^{*b*} Isolated yield. ^{*c*} **1a/2a** = 2:1. ^{*d*} **1a/2a** = 1:5. BIPHEP, 2,2'-bis(diphenylphosphino)-1,1'-biphenyl. DPP-Benzene, 1,2-bis(diphenylphosphino)benzene. ND, not detected.

The counteranion of the cationic iridium complex was found to be an important factor in the product yield and the chemoselectivity: high conversion was achieved when trifluoromethanesulfonate anion (OTf) was used as a counteranion for the iridium complex, and the adduct at the sp³ C–H bond of benzamide **1a** was formed predominantly (eq 1 and entries 1–3 in Table 1).⁷ A decrease in the amount of alkyne **2a** did not affect the reaction rate (entry 4). Moreover, an excess amount of the alkyne improved the yield without the formation of multialkenylated adducts (entry 5). Moderate yield was achieved with BIPHEP, whereas ligands without a biaryl scaffold were ineffective (entries 6–8).

To survey the substrate scope, several amides and alkynes were subjected to catalytic addition by using the best catalyst ($[Ir(cod)_2]OTf + rac$ -BINAP) (Table 2). Alkylamides were







found to be good substrates in the present reaction: benzylamide, pivalamide, acetamide, and *N*-methyl-2-pyrrolidinone (NMP) were cleanly converted to the corresponding allylamides in good yields (entries 1-4). *N*,*N*-Dimethylformamide (DMF) also participated in the reaction with alkyne **2a** to give allylamide **3fa**, albeit in low yield (entry 5). In addition, *N*-methylacetamide also afforded allylamide **3ga** in moderate yield without the formation of enamides derived from hydroamidation (entry 6).⁸ In contrast, *N*-ethyl-2-pyrrolidinone and *N*-benzyl-2-pyrrolidinone did not give any adducts, which indicates that alkenylation at secondary sp³ C–H bonds did not proceed under the present reaction conditions. Both electron-rich and electron-deficient diarylacetylenes were tolerable as coupling partners (entries 7–9). Dinaphthylacetylene also underwent the reaction despite of its bulkiness (entry 10). Moreover, the reaction of 1-phenyl-1hexyne with amide **1a** proceeded regioselectively to give adduct **3af** as the sole regioisomer in moderate yield (entry 11). However, dialkylacetylenes such as 4-octyne were inactive, which illustrates that at least one aryl substituent on the alkyne terminus should be required.

Next, several experiments were conducted to elucidate the reaction mechanism. First, the reaction of deuterated NMP **1e**- d_3 with alkyne **2a** was examined. As a result, the corresponding allylamide **3ea**- d_3 was obtained along with almost the complete incorporation of deuterium at the vinylic position and partial protonation at the allylic position (Scheme 1). Second, the reaction of *N*,*N*-dimethybenzylamine



was examined under the same reaction conditions; however, no adducts were detected. On the basis of these results, we assume that carbonyl-directed sp^3 C–H bond cleavage of amides is an initial step to afford intermediate **A**. Subsequent

alkyne insertion would give allylamides.⁹ There may be successive C–H bond cleavage of the allylamides at the allylic position, resulting in partial protonation by an external proton source such as water.¹⁰

In summary, we developed a cationic Ir(I)-BINAP complexcatalyzed alkenylation of amides with alkynes via carbonyldirected sp³ C–H bond activation. This transformation allowed for a straightforward construction of highly substituted allylamides. Further studies on modification of the catalyst and elucidation of the detailed reaction mechanism are in progress.

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Supporting Information Available: Experimental procedures and spectral data for new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) The corresponding Rh catalyst ($[Rh(cod)_2]BF_4 + rac-BINAP$) did not give adduct **3aa** at all, but gave a trace amount of adduct **3aa'**. The cationic Rh(I)-catalyzed sp² C-H bond alkenylation of pyrrolidine amides with alkynes was recently reported, see: Shibata, Y.; Otake, Y.; Hirano, M.; Tanaka, K. *Org. Lett.* **2009**, *11*, 689.

(7) A typical experimental procedure (entry 3 in Table 1): $[Ir(cod)_2]OTf$ (5.7 mg, 10 μ mol) and *rac*-BINAP (6.8 mg, 11 μ mol) were placed in a Schlenk tube, which was then evacuated and backfilled with argon (×3). To the reaction vessel were added *N*,*N*-dimethylbenzamide (**1a**) (15.0 mg, 0.1 mmol), diphenylacetylene (**2a**) (36.6 mg, 0.2 mmol), and PhCl (0.2 mL). The solution was then stirred at 135 °C for 24 h. After completion of the reaction, the solvent was evaporated. The crude products were purified by thin-layer chromatography (hexane/AcOEt = 1/1) to give analytically pure **3aa** (75%) and **3aa'** (4%).

(8) Togni and co-workers reported that neutral iridium-bis(diphenylphosphino)biaryl complexes catalyzed the hydroamidation of benzamide to norbornene, see: Aufdenblatten, R.; Diezi, S.; Togni, A. *Monatsh. Chem.* **2000**, *131*, 1345.

(9) At present, we cannot rule out an alternative mechanism, which includes nucleophilic addition of the vinyliridium to the iminium ion intermediate generated from **A**. For a recent report on the oxidative cyanation of sp³ C-H bonds via an iminium intermediate, see: Murahashi, S.-I.; Nakae, T.; Terai, H.; Komiya, N. J. Am. Chem. Soc. **2008**, *130*, 11005.

(10) When allylamide **3ea**- d_3 and H₂O (3 equiv) were heated in the presence of Ir(I)–BINAP catalyst, the deuteration ratio at the allylic position decreased to 37%-D.

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