## Transition-Metal Catalysis

## Platinum-Catalyzed Formation of Cyclic-Ketone-Fused Indoles from N-(2-Alkynylphenyl)lactams\*\*

Guotao Li, Xiaogen Huang, and Liming Zhang\*

ortho-Heterosubstituted aryl alkynes are excellent substrates for Au- and Pt-catalyzed cycloisomerization.<sup>[1]</sup> Substituted benzofurans, indoles, and benzothiophenes have been synthesized by intramolecular carboalkoxylation,<sup>[2]</sup> carboamination,<sup>[2a]</sup> acylamination,<sup>[3a]</sup> sulfonylamination, <sup>[3b]</sup> carbothiolation,<sup>[4a]</sup> and silylthiolation<sup>[4b]</sup> of the C–C triple bond. A common feature of this versatile chemistry is that the substituent (allyl, benzyl,  $\alpha$ -alkoxyalkyl, acyl, sulfonyl, or silyl) on the heteroatom undergoes selective 1,3-migration in the forming heteroaromatic ring via an alkenyl metal intermediate **A** (Scheme 1). A salient feature of gold and



Scheme 1. Pt/Au-catalyzed reactions of ortho-heterosubstituted aryl alkynes.

platinum chemistry is that alkenyl gold and alkenyl platinum species can react with electrophiles at the distal end of the C–C double bond to form metallocarbenoids.<sup>[5]</sup> We were surprised that no electrophilic migration of  $R^2$  in **A** to the 2-position had been reported, although a metallocarbenoid species **B** would be a plausible intermediate. Herein, we report the synthesis of substituted indoles fused to cyclic ketones by a Pt-catalyzed 1,2-acyl migration of this type.

We speculated that steric interactions may play a role in these highly selective 1,3-migrations, as internal alkynes had always been used (i.e.,  $R^1 \neq H$ ). Indeed, the treatment of 2-ethynyl-*N*-benzyl-*N*-methylaniline ( $R^1 = H$ ) with IPrAuNTf<sub>2</sub> (5 mol %; Tf = trifluoromethanesulfonyl) led to the formation of an inseparable mixture of 3-benzyl-1-methylindole and 2-benzyl-1-methylindole in a combined yield of 50% [Eq. (1); Bn = benzyl].<sup>[6]</sup> Although this initial result did suggest that

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



the 1,2-migration process could compete with 1,3-migration, it was apparent that controlling elements other than steric factors would be needed to favor substantially the desired 1,2migration. We reasoned that, in the case of 2-alkynyl anilines,

appropriate tethering of the two substituents on the nitrogen atom should abolish the 1,3-migration and promote the 1,2-migration. We selected lactams  $\mathbf{1}^{[3]}$  as  $\mathbf{P}_{\mathsf{R}^1}$  substrates and envisaged that Au/Pt-catalyzed sequential cyclization, 1,2-acyl migration, and 1,2-migration of R to the metallocarbenoid moiety<sup>[7]</sup> would result in the formation of highly substituted cyclic-ketone-fused indoles **2** (Scheme 2).<sup>[8]</sup> Alternatively, the 1,2-acyl migration could proceed stepwise via the acylium intermediate **C** (route b). Interestingly, this reaction can be viewed as an intramolecular insertion of one end of the C–C triple bond into the lactam amide bond with concurrent 1,2-migration of the substituent on the triple bond.

We examined the reaction of  $\gamma$ -lactam **3** in the presence of Au/Pt catalysts under a variety of conditions (Table 1). The anticipated cyclic-ketone-fused indole **4** was formed upon the treatment of **3** with IPrAuNTf<sub>2</sub> (5 mol%) in 1,2-dichloro-ethane at reflux (Table 1, entry 1). Two major side products were identified, one of which was inseparable from compound



**Scheme 2.** Proposed Pt/Au-catalyzed formation of highly substituted indoles fused to cyclic ketones.



<sup>[\*]</sup> Dr. G. Li, Dr. X. Huang, Prof. Dr. L. Zhang Department of Chemistry, University of Nevada, Reno 1664 North Virginia Street, Reno, NV 89557 (USA) Fax: (+1) 775-784-6804 E-mail: lzhang@chem.unr.edu Homepage: http://wolfweb.unr.edu/homepage/lzhang/
[\*\*] We thank the University of Nevada, Reno for support.

Table 1: Optimization of the reaction conditions for the Pt/Au-catalyzed synthesis of indoles fused to cyclic ketones.



[a] Substrate concentration: entries 1–9, 0.03 м; entries 10–12, 0.01 м. [b] Catalyst loading: 5 mol%. [c] Yield determined by NMR spectroscopy with diethyl phthalate as the internal reference. [d] The reaction was carried out in a capped vial. [e] Decomposition of the catalyst was observed. [f] The starting material remained unchanged. [g] No starting material remained. [h] Much of substrate 3 (80%) remained. [i] Much of substrate 3 (77%) remained. [j] The reaction was carried out under  $O_2$ (1 atm). [k] Yield of the isolated product. [l] A drying tube was mounted on the top of the condenser. [m] Catalyst loading: 10 mol%. DCE = 1,2dichloroethane, MS = molecular sieves, cod = 1,5-cyclooctadiene.

1



12

**4**. A singlet at  $\delta = 6.39$  ppm and an aromatic doublet at  $\delta =$ 7.95 ppm (shifted downfield relative to the aromatic signals for 4) in the <sup>1</sup>H NMR spectrum of the mixture led to the assignment of this by-product as the Friedel-Crafts product 5.<sup>[9]</sup> The other was the uncyclized carboxylic acid 6. The formation of 5 and 6 indicates that the 1,2-acyl migration is a stepwise process via the acylium intermediate C. In an attempt to limit the side reactions, we screened quickly various conditions in capped vials. Although the results with other Au catalysts, such as dichloro(pyridine-2carboxylato)gold(III)<sup>[10]</sup> (Table 1, entry 2), were disappointing, we observed much better selectivities for 4 over 5 with  $PtCl_2$  in 1,2-dichloroethane (Table 1, entry 4) or anisole<sup>[3]</sup> (Table 1, entry 5). The result in 1,2-dichloroethane was difficult to reproduce on a larger scale. Nevertheless, we continued our study with reactions in flasks, which allowed better control of the reaction conditions. The presence of additives known to improve PtCl2 catalysis (e.g., CO (1 atm),<sup>[11]</sup> 1,5-cyclooctadiene<sup>[12]</sup>) led to either low yield and selectivity (Table 1, entry 7) or no reaction (Table 1, entry 8). Surprisingly, compound 5 was not observed when the reaction was carried out in the presence of 4-Å molecular sieves under nitrogen (Table 1, entry 6), and the conversion of the substrate was low.<sup>[13]</sup>

These studies led us to suspect that  $O_2$  might play a role in the catalytic process.<sup>[14]</sup> Indeed, the reaction in the presence of PtCl<sub>2</sub> (5 mol%) was very slow under nitrogen: After 15 h, 77% of **3** remained (Table 1, entry 9). When this  $PtCl_2$ catalyzed reaction was carried out under an atmosphere of O<sub>2</sub> with a substrate concentration of 0.01m, the yield of 4 increased to 82% (Table 1, entry 10). However, the reaction took 42 h. The need to shorten the reaction time and the observed benefit of O<sub>2</sub> led us to test PtCl<sub>4</sub>.<sup>[15]</sup> To our delight, the desired indole 4 was formed in 72% yield in 1 h, and the excellent selectivity was preserved (Table 1, entry 11). This observation suggests that PtIV may be the real catalytic species even when PtCl<sub>2</sub> is used. Finally, the yield of 4 was increased to 83 % with 10 mol % of  $PtCl_4$  (Table 1, entry 12).

We set out to probe the scope of this chemistry under the optimized conditions described in Table 1, entry 12. The reaction worked well when alkyl groups were present at the alkyne terminus. For example, substrates with a methyl group (Table 2, entry 1) or a functionalized propyl group, such as 3bromopropyl (Table 2, entry 3) or 3-benzyloxypropyl (Table 2, entry 4), were transformed into the corresponding highly substituted indoles 8 in excellent yields. Surprisingly, the bromide product 8c was contaminated with the corresponding chloride in about 20% yield.<sup>[16]</sup> The chlorine atom

**Table 2:** Scope of the reaction with  $\gamma$ -lactam substrates.

R		PtCl <sub>4</sub> (10 mol CICH <sub>2</sub> CH	$(\%), O_2 (1 \text{ atm})$ $I_2 CI, \text{ reflux}$ R	R'		N R'
	7			8	9	
Entry <sup>[a]</sup>	7	R	R′	<i>t</i> [h]	Yield of <b>8</b> [%] <sup>[b]</sup>	8/9 <sup>[c]</sup>
1	7 a	Н	Me	1.5	83	28:1
2	7 b	Н	⊳ş	14	75 <sup>[d]</sup>	18:1
3	7 c	н	Br A.	11	88 <sup>[e]</sup>	29:1
4	7 d	н	BnO S	2	81	19:1
5	7 e	Н	Ph ,	23	70	14:1
6	7 f	н	MeO	11	73	8:1
7	7 g	Н	O H	34	70	10:1
8	7 h	н	C Z	14	60	> 30:1
9	7 i	н	<u></u>	48	52 <sup>[f]</sup>	> 30:1
10	7 j	Н	н	22	73/95 <sup>[g]</sup>	1:0
11	7 k	6-MeO <sup>[h]</sup>	nВu	1	89	1:0
12	71	4-Br <sup>[i]</sup>	nВu	1	71	> 30:1
13	7 m	4-EtO <sub>2</sub> C <sup>[i]</sup>	<i>n</i> Bu	1	65	> 30:1 <sup>[j]</sup>

[a] Substrate concentration: 0.01 м. [b] Yield of the isolated product. [c] The product ratio was determined by <sup>1</sup>H NMR spectroscopy or separation of the products by column chromatography. The uncyclized acid was present in less than 5% yield. [d] Value includes a 4% yield of the corresponding by-product 9. [e] Value includes a 20% yield of the corresponding chloride. [f] Some of substrate 7i (20%) remained. [g] PtCl<sub>2</sub> (5 mol%) was used as the catalyst (reaction time: 22 h). [h] The methoxy substituent is ortho to the nitrogen atom. [i] The substituent is para to the nitrogen atom. [j] The uncyclized acid was formed in 13% vield.

## Communications

probably comes from PtCl<sub>4</sub>, as the reaction of **7c** catalyzed by IPrAuNTf<sub>2</sub> (5 mol %) did not provide a detectable amount of the chloride. Remarkably, lactam 7b with a cyclopropyl substituent underwent smooth cyclopropyl migration to yield the 3-cyclopropylindole product 8b in 71% yield. The reactions of substrates with aryl groups having different electronic characteristics at the alkyne terminus led to the corresponding 3-aryl indoles in good yields (Table 2, entries 5-7). Even an aldehyde substituent on the aromatic ring was tolerated (Table 2, entry 7). Moreover, alkenyl groups, such as trans-\beta-styryl (Table 2, entry 8) and transhex-1-en-1-yl (Table 2, entry 9), were also suitable: the 3alkenyl indoles 8h and 8i were isolated in fairly good yields with retention of the trans geometry. The reaction of 7i was rather sluggish; 20% of the substrate remained after 2 days. Somewhat surprisingly, PtCl<sub>2</sub> was a better catalyst than PtCl<sub>4</sub> for the reaction of the ethynyl substrate 7j. The 3-unsubstituted indole 8j was formed in 95% yield in the presence of PtCl<sub>2</sub> (5 mol %; Table 2, entry 10).

Further studies revealed that substitution of the benzene ring of the substrate was generally allowed, regardless of the electronic nature of the substituent (Table 2, entries 11–13), and that the reaction was more efficient with an electrondonating substituent (Table 2, entry 11). The uncyclized acid was isolated from the reaction of **7m** in 13% yield (Table 2, entry 13), which is much higher than the yield of the acid in all other cases (<5%). Good to excellent selectivities were observed for the formation of the desired product 8 over the Friedel–Crafts acylation (i.e., the formation of compound 9) in most reactions described in Table 2. Moreover, in the case of substrate 7j ( $\mathbf{R}' = \mathbf{H}$ ; Table 2, entry 10) the by-product 9j was not detected, which indicates that the cyclization of the acylium species to the 2-position of 3-platinoindole C (M = Pt) is much faster than its cyclization to the 7-position when the steric environments of the two positions are similar. Not surprisingly, the formation of 9 was not observed when the 7position was substituted (Table 2, entry 11).

We attempted to extend this chemistry to lactams with different lactam-ring sizes. The  $\beta$ -lactam **10** with an ethynyl substituent on the aromatic ring reacted efficiently to yield selectively the benzene-fused pyrrolizinone **11** in 85% yield; the corresponding Friedel–Crafts acylation product was not observed [Eq. (2)]. PtCl<sub>2</sub> catalyzed this reaction better than



PtCl<sub>4</sub>, as observed for the γ-lactam substrate **7**j, to provide **11** in 99% yield. β-Lactams with either a phenyl or a cyclohexyl substituent at the alkyne terminus underwent smooth PtCl<sub>4</sub>catalyzed transformations. Although the combined yield of the desired product and the Friedels–Craft product was close to quantitative in each case, the desired products were favored only slightly [Eq. (3)]. In these cases the cyclization of the acylium species to the benzene ring becomes more



competitive, as it results in the formation of a 6-membered ring. Interestingly, the  $\delta$ -lactam **12** also underwent the desired reaction to afford the indole **13** with a fused seven-membered cyclic ketone, albeit in only 45% yield [Eq. (4)].



These experimental results support the general mechanism via a Pt-containing acylium intermediate C that is outlined in Scheme 2.<sup>[17]</sup> Our attempt to trap the Pt carbenoid (**D** in Scheme 2) with either Ph<sub>2</sub>SO<sup>[18]</sup> or styrene failed, presumably because the migration of R in **D** and subsequent rearomatization is facile.<sup>[19]</sup>

In conclusion, we have developed a PtCl<sub>4</sub>/PtCl<sub>2</sub>-catalyzed cycloisomerization of N-(2-alkynylphenyl)lactams to form substituted indoles fused to cyclic ketones. Various substituents at the alkyne terminus and on the benzene ring are tolerated, and lactams with different ring sizes are accommodated. This transformation, which is a net intramolecular insertion of one end of the alkyne into the lactam amide bond with concurrent migration of the substituent at the alkyne terminus, offers efficient access to ring-fused, highly substituted indoles.

## **Experimental Section**

 $PtCl_4$  (10 mol%) or  $PtCl_2$  (if specified; 10 mol%) was added to a 0.01M solution of the lactam in anhydrous 1,2-dichloroethane under an atmosphere of O<sub>2</sub>, and the resulting mixture was refluxed for the time indicated. Upon the completion of the reaction, the solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (eluent: hexanes/ethyl acetate 3:1) to yield the desired product.

Received: July 2, 2007 Revised: September 1, 2007 Published online: November 12, 2007

**Keywords:** carbenes · homogeneous catalysis · insertion · platinum · rearrangement

For selected reviews on Au and/or Pt catalysis, see: a) A. S. K. Hashmi, G. J. Hutchings, Angew. Chem. 2006, 118, 8064; Angew. Chem. Int. Ed. 2006, 45, 7896; b) L. Zhang, J. Sun, S. A. Kozmin, Adv. Synth. Catal. 2006, 348, 2271; c) R. A. Widenhoefer, X. Q. Han, Eur. J. Org. Chem. 2006, 4555; d) E. Jimenez-Nunez, A. M. Echavarren, Chem. Commun. 2007, 333; e) N. T. Patil, Y.

Yamamoto, ARKIVOC 2007, 5, 6; f) N. Marion, S. P. Nolan, Angew. Chem. 2007, 119, 2806; Angew. Chem. Int. Ed. 2007, 46, 2750; g) D. J. Gorin, F. D. Toste, Nature 2007, 446, 395; h) A. Fürstner, P. W. Davis, Angew. Chem. 2007, 119, 3478; Angew. Chem. Int. Ed. 2007, 46, 3410; i) A. S. K. Hashmi, Chem. Rev. 2007, 107, 3180.

- [2] a) A. Fürstner, P. W. Davies, J. Am. Chem. Soc. 2005, 127, 15024;
   b) I. Nakamura, Y. Mizushima, Y. Yamamoto, J. Am. Chem. Soc. 2005, 127, 15022.
- [3] a) T. Shimada, I. Nakamura, Y. Yamamoto, J. Am. Chem. Soc.
   2004, 126, 10546; b) I. Nakamura, U. Yamagishi, D. Song, S. Konta, Y. Yamamoto, Angew. Chem. 2007, 119, 2334; Angew. Chem. Int. Ed. 2007, 46, 2284.
- [4] a) I. Nakamura, T. Sato, Y. Yamamoto, *Angew. Chem.* 2006, *118*, 4585; *Angew. Chem. Int. Ed.* 2006, *45*, 4473; b) I. Nakamura, T. Sato, M. Terada, Y. Yamamoto, *Org. Lett.* 2007, *9*, 4081.
- [5] For selected examples, see: a) C. Nieto-Oberhuber, M. P. Munoz, E. Bunuel, C. Nevado, D. J. Cardenas, A. M. Echavarren, Angew. Chem. 2004, 116, 2456; Angew. Chem. Int. Ed. 2004, 43, 2402; b) K. Miki, K. Ohe, S. Uemura, J. Org. Chem. 2003, 68, 8505; c) M. J. Johansson, D. J. Gorin, S. T. Staben, F. D. Toste, J. Am. Chem. Soc. 2005, 127, 18002; d) N. Kim, Y. Kim, W. Park, D. Sung, A. K. Gupta, C. H. Oh, Org. Lett. 2005, 7, 5289; e) L. Peng, X. Zhang, S. Zhang, J. Wang, J. Org. Chem. 2007, 72, 1192; f) B. P. Taduri, S. M. A. Sohel, H.-M. Cheng, G.-Y. Lin, R.-S. Liu, Chem. Commun. 2007, 2530; g) G. Li, L. Zhang, Angew. Chem. 2007, 119, 5248; Angew. Chem. Int. Ed. 2007, 46, 5156; for a review, see Ref. [1h].
- [6] The formation of the known compound 3-benzyl-1-methylindole was ascertained by comparison of its <sup>1</sup>H and <sup>13</sup>C NMR spectra with reported data: Y. Jia, J. Zhu, J. Org. Chem. **2006**, 71, 7826. The existence of 2-benzyl-1-methylindole was assumed on the basis of the characteristic singlet at  $\delta = 6.27$  ppm in the <sup>1</sup>H NMR spectrum of the mixture, as well as the signal at  $\delta = 4.14$  ppm expected for the benzylic hydrogen atoms.
- [7] For examples of the migration of alkyl groups to Pt carbenoids, see: a) H. Kusama, Y. Miyashita, J. Takaya, N. Iwasawa, Org. Lett. 2006, 8, 289; b) J. Sun, M. P. Conley, L. Zhang, S. A. Kozmin, J. Am. Chem. Soc. 2006, 128, 9705; c) H. Funami, H. Kusama, N. Iwasawa, Angew. Chem. 2007, 119, 927; Angew. Chem. Int. Ed. 2007, 46, 909.
- [8] For selected examples of the Au/Pt-catalyzed preparation of indoles, see: a) A. Arcadi, G. Bianchi, F. Marinelli, *Synthesis* 2004, 610; b) K. Cariou, B. Ronan, S. Mignani, L. Fensterbank, M. Malacria, *Angew. Chem.* 2007, 119, 1913; *Angew. Chem. Int. Ed.* 2007, 46, 1881.

- [9] This structural assignment is supported by the isolation and characterization of the side product from the reaction of lactam 7a, in which a methyl group is at the alkyne terminus.
- [10] For the first use of the Au<sup>III</sup> complex as a precatalyst, see: A. S. K. Hashmi, J. P. Weyrauch, M. Rudolph, E. Kurpejovic, *Angew. Chem.* 2004, *116*, 6707; *Angew. Chem. Int. Ed.* 2004, *43*, 6545; for other reactions catalyzed by this complex, see: a) S. Wang, L. Zhang, *J. Am. Chem. Soc.* 2006, *128*, 8414; b) S. Wang, L. Zhang, *J. Am. Chem. Soc.* 2006, *128*, 14274.
- [11] A. Fürstner, P. W. Davies, T. Gress, J. Am. Chem. Soc. 2005, 127, 8244.
- [12] I. Nakamura, Y. Mizushima, Y. Yamamoto, J. Am. Chem. Soc. 2005, 127, 15022.
- [13] The reason for this decreased reactivity is not clear, but the molecular sieves may affect the Pt catalyst and partially trap the reactive acylium intermediate.
- [14] PtCl<sub>2</sub>-catalyzed reactions in vials have been observed previously to be more efficient than those in flasks under N<sub>2</sub>: B. A. Bhanu Prasad, F. K. Yoshimoto, R. Sarpong, *J. Am. Chem. Soc.* 2005, *127*, 12468.
- [15] For selected previous examples of the use of PtCl<sub>4</sub>, see: a) W. Baidossi, M. Lahav, J. Blum, J. Org. Chem. **1997**, 62, 669; b) C. H. Oh, S. Y. Bang, C. Y. Rhim, Bull. Korean Chem. Soc. **2003**, 24, 887; c) K. Hiroya, S. Matsumoto, M. Ashikawa, K. Ogiwara, T. Sakamoto, Org. Lett. **2006**, 8, 5349; d) J. Marco-Contelles, A. N. Arroyo, S. Anjum, E. Mainetti, N. Marion, K. Cariou, G. Lemière, V. Mouriès, L. Fensterbank, M. Malacria, Eur. J. Org. Chem. **2006**, 4618.
- [16] The structure of the chloride derivative was assigned on the basis of the close resemblance of the signals in its NMR spectra to those of the bromide product as well as the characteristic isotope pattern in its ESI<sup>+</sup> mass spectrum.
- [17] Additional evidence for the existence of the acylium intermediate **C** and/or the preceding spiro-zwitterionic intermediate is the formation of the ethyl ester of acid **6** in 30 % yield along with the product **4** (45 % yield) when EtOH (1.5 equiv) was added to the reaction mixture to trap the intermediates. Moreover, when EtOH (at reflux) was used as the solvent, the ethyl ester was isolated in 68 % yield, and the product **4** was observed (<2 %).
- [18] C. A. Witham, P. Mauleon, N. D. Shapiro, B. D. Sherry, F. D. Toste, J. Am. Chem. Soc. 2007, 129, 5838.
- [19] This result also suggests that the evolution of the Pt carbenoid D may not be the rate-limiting step, which would explain why substrates 7 with a primary alkyl group at the alkyne terminus reacted faster than those with an aryl group, although aryl groups usually show greater aptitude for nucleophilic migration.