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Chemoselectivities in the Platinum-Catalyzed Hydrative Carbocyclizations of Oxo-Alkyne-Nitrile Functionalities

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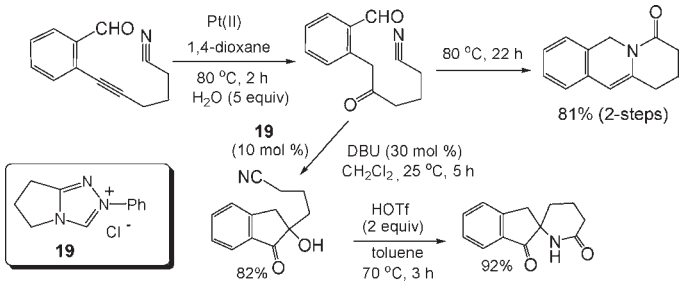
ABSTRACT



Two new hydrative carbocyclizations of oxa-alkyne-nitrile functionalities are reported to produce distinct nitrogen-containing heterocycles. Protracted heating of oxoalkynyl nitrile substrates with $PtCl_2/CO/H_2O$ in hot 1,4-dioxane gave 2,3-dihydro-1*H*-pyrido[1.2-*b*]-isoquinolin-4(6*H*)-ones. In this hydration reaction, dicarbonyl nitrile intermediates were isolated efficiently after a brief period, and they were subjected to an NHC-based crossed benzoin coupling to give spiro alcohols that further reacted with TfOH to give spiro[indene-2,2′-piperidine]-1,6′(3*H*)-diones.

Regiocontrolled metal-catalyzed hydrations of alkynes to form carbonyl derivatives are of prime interest in organic synthesis.[1,2] Hydrative coupling of an alkyne with another functionality is particularly interesting because it not only introduces a carbonyl group but also allows formation of a C−C bond. Metal-catalyzed three-component couplings are powerful tools to access complicated frameworks,[3] but hydrative carbocyclizations of alkynes are exclusively focused on two-component coupling reactions, including 1,*n*-diynes,[4] 1-yne-5-enones,[5] 1-en-5-ynes,[6] and 1-allen-*n*-ynes ($n = 5-7$),[7] with rare examples for three-component coupling reactions.[8] With $PtCl_2$ catalysts, we found that the neighboring ketone of 2-ketonyl-alkynylbenzenes **1** selectively controlled the hydration regioselectivity of the tethered alkyne to produce

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(3) (a) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095. (b) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439. (c) Cahiez, G.; Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435.

(4) (a) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 11516. (b) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2005**, *127*, 4763. (c) Odedra, A.; Wu, C.-J.; Pratap, T. B.; Huang, C.-W.; Ran, Y. F.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 3406. (d) Zhang, C.; Cui, D.-M.; Yao, L.-Y.; Wang, B.-S.; Hu, Y.-Z.; Hayashi, T. *J. Org. Chem.* **2008**, *73*, 7811. (e) Cui, D.-M.; Ke, Y.-N.; Zhaung, D.-W.; Wang, Q.; Zhang, C. *Tetrahedron Lett.* **2010**, *51*, 980.

(5) Trost, B. M.; Brown, R. E.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 5877.

(6) (a) Chen, Y.; Ho, D. M.; Lee, C. *J. Am. Chem. Soc.* **2000**, *127*, 12184. (b) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (c) Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 2056.

(7) Yang, C.-Y.; Lin, G.-Y.; Datta, S.; Liu, R.-S. *J. Org. Chem.* **2008**, *73*, 4907.

(8) (a) Chang, H.-K.; Datta, S.; Das, A.; Odedra, A.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2007**, *46*, 4744. (b) Das, A.; Chang, H.-K.; Yang, C.-H.; Liu, R.-S. *Org. Lett.* **2008**, *18*, 4061.

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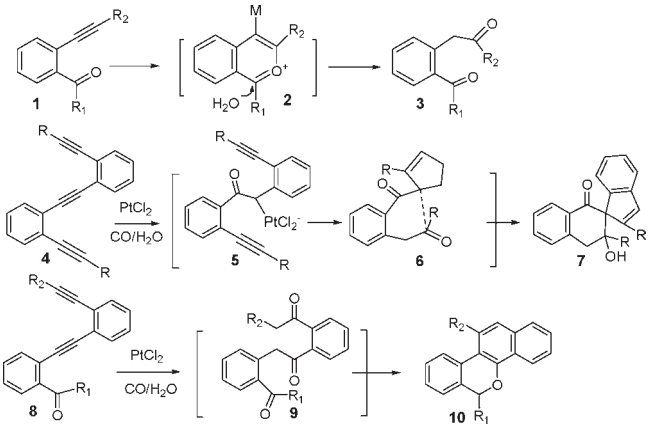
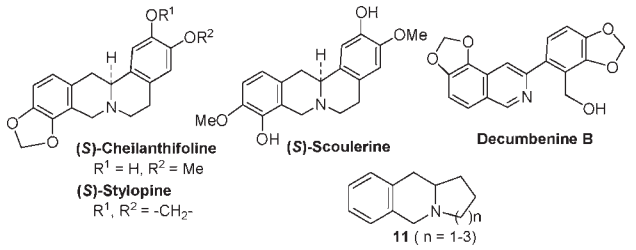
Scheme 1. Pt-Catalyzed Hydrative Carbocyclization



Scheme 2. Natural Azacyclic Compounds with Similar Skeleta



diketone **3**, via the formation of benzopyrilium species **2**.[8a] These novel findings prompted us to investigate the hydrative carbocyclizations of triynes **4**[8a] and oxodiynes **8**,[8b] giving spiroketones **7** and benzoisochromenes **10** respectively; their reaction pathways are outlined in Scheme 1. Despite intensive reports, there is no precedent on the synthesis of azacyclic compounds.

Nitrogen-containing polycyclic frameworks **11** are present in natural alkaloids including (*S*)-cheilanthifoline, (*S*)-stylopine, (*S*)-scoulerine, and decumbenine B (Scheme 2).[9] We report here a new platinum-catalyzed hydrative carbocyclization of oxoalkynyl nitriles (Scheme 3). During the course of this reaction, we also efficiently isolated dicarbonyl nitrile intermediates that were subjected to transformation, with an organocatalyst, into complicated spirolactams.[10]

Table 1 shows our efforts to realize the hydrative carbocyclization of starting nitrile **12a** using commonly employed gold and platinum catalysts. The use of $AuCl_3$ and $AuBr_3$ in wet 1,4-dioxane (80 °C), each at 10 mol % loading, only gave the dicarbonyl compound **13a** in 78−88% yields (entries 1−2), according to the mechanism in Scheme 1. With a $PtCl_2$/CO catalyst in hot 1,4-dioxane (80 °C), we obtained compound **13a** in 91% yield after 2 h (entry 3) but a mixture of **13a** (55%) and 2,3-dihydro-1*H*-pyrido[1.2-*b*]-isoquinolin-4(6*H*)-one **14a** (35%) over a protracted time (22 h, entry 4). A large loading (15 mol %) of $PtCl_2$/CO enabled a complete conversion of intermediate **13a** efficiently to azacyclic species **9a** (entry 5). The catalytic efficiency was further improved with $[PtCl_2(C_2H_4)]_2$ at a 5 mol % loading, giving the desired **14a** satisfactorily (81%).

We prepared various oxoalkynyl nitriles **12b**−**12m** to assess the generality of this hydrative carbocyclization (Table 2). Entries 1−2 show the applicability of this catalysis to substrates **12b** and **12c** bearing a ketone group; the corresponding products **14b** and **14c** were obtained in 81% and 71% yields respectively. The platinum-catalyzed hydrative carbocyclizations of substrates **12d**−**12f** bearing a $C(CO_2Et)_2$ unit gave the desired products **14d**−**14f** in 55−61% yields. The same reactions proceeded efficiently for substrates **12g** and **12h** bearing tosylamide and oxygen linkages respectively, giving **14g** and **14h** in 59−74% yields. We prepared oxoalkynyl nitriles **12i** and **12j** bearing an ethylene ($-C_2H_4-$) linkage; the resulting products **14i** and **14j** were obtained in 65−78% yields. The reactions worked well with substrate **12k** bearing a long butylene ($-C_4H_8-$)

Scheme 3. Deuterium Labeling Experiment

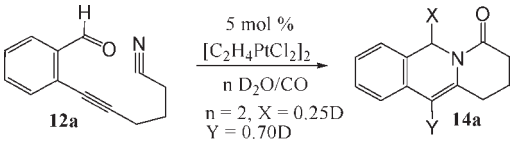
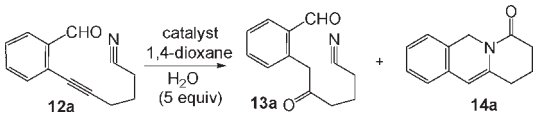


Table 1. Hydrative Carbocyclization of Oxoalkynyl Nitrile over Pt and Au Catalyst



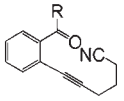
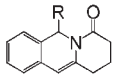
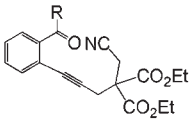
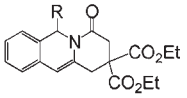
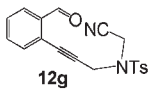
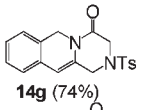
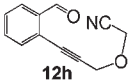
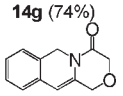
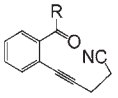
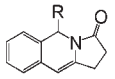
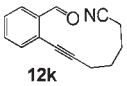
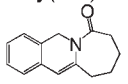
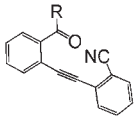
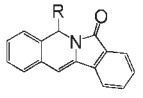
entry	catalyst (mol %)[a]	time, h (temp, °C)	products (yields, %)[b]
1	$AuCl_3$ (10)	15 (80)	**13a** (78%)
2	$AuBr_3$ (10)	15 (80)	**13a** (88%)
3	$PtCl_2$/CO (10)	2 (80)	**13a** (91%)
4	$PtCl_2$/CO (10)	22 (80)	**13a** (55%), **14a** (35%)
5	$PtCl_2$/CO (15)	22 (80)	**14a** (88%)
6	$[PtCl_2(C_2H_4)]_2$ (5)/CO	15 (80)	**14a** (81%)

[a] [Substrate] = 0.17 M; 80 °C. [b] Isolated yields are reported after silica chromatography.

(9) (a) Wada, Y.; Nishida, N.; Kurono, N.; Ohkuma, T.; Orito, K. *Eur. J. Org. Chem.* **2007**, 4320. (b) Yu, C. K.; MacLean, D. B.; Rodrigo, R. G. A.; Manske, R. H. F. *Can. J. Chem.* **1971**, *49*, 128. (c) Zenk, M. H. *Pure Appl. Chem.* **1994**, *66*, 2023. (d) Rueffer, M.; Zumstein, G.; Zenk, M. H. *Phytochemistry* **1990**, *29*, 3727. (e) Liscombe, D. K.; Facchini, P. J. *J. Biol. Chem.* **2007**, *282*, 14741.

(10) For the cycloisomerization of oxoalkynyl nitriles, see: Oh, C. H.; Reddy, K. V. *Bull. Korean Chem. Soc.* **2007**, *28*, 1927.

Table 2. Reaction Scopes of Substrates

entry	substrates[a]	time (h)	products (yields)[b]
1	 **12b** (R = Me)	12	 **14b** (81%)
2	**12c** (R = n-Bu)	15	**14c** (71%)
3	 **12d** (R = H)	12	 **14d** (61%)
4	**12e** (R = Me)	16	**14e** (55%)
5	**12f** (R = n-Bu)	20	**14f** (60%)
6	 **12g**	20	 **14g** (74%)
7	 **12h**	13	 **14h** (59%)
8	 **12i** (R = H)	7	 **14i** (78%)
9	**12j** (R = Me)	7	**14j** (65%)
10	 **12k**	16	 **14k** (83%)
11	 **12l** (R = H)	9	 **14l** (73%)
12	**12m** (R = Me)	11	**14m** (61%)

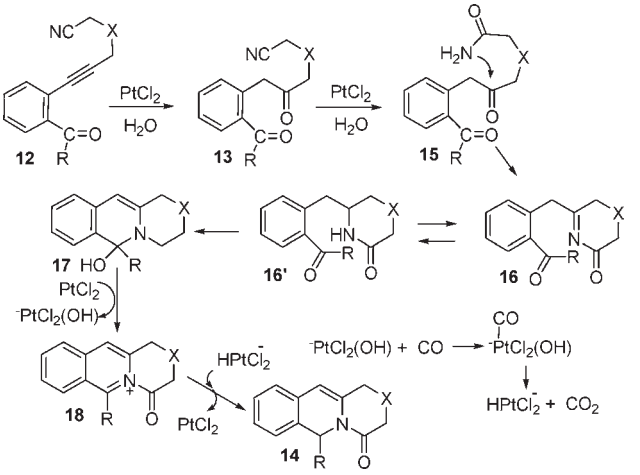
[a][Substrate] = 0.17 M. [b]Isolated yields are reported after silica chromatography.

linkage, giving compound **14k** in 83% yield. This catalysis was also applicable to nitriles **12l** and **12m** containing a benzene linkage, generating the desired products **14l** and **14m** in 73% and 61% yields respectively. This new method can be effected on substrates bearing alternative carbonyl groups and linkages.

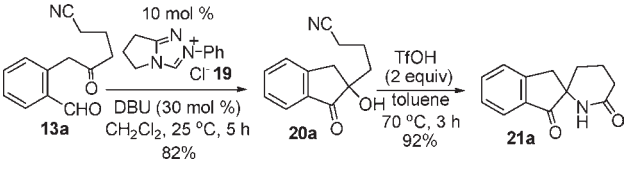
The transformation of nitrile **12a** into compound **14a** involved a reduction step, presumably caused by the $PtCl_2$/CO/H_2O mixture. As depicted in Scheme 3, the same platinum catalysis on compound **12a** with D_2O (2 equiv) in dry 1,4-dioxane gave desired compound **14a** with 25% deuterium content at one methylene proton together with 70% deuterium content at the olefin position. This observation confirms our hypothesis that $PtCl_2$/CO/H_2O serves as a reduction source.[11]

Scheme 4 depicts a plausible mechanism based on the intermediacy of dicarbonyl nitrile **13a**. We envisage that

Scheme 4. Proposed Reaction Mechanism



Scheme 5. Synthesis of Spiro Azacycles



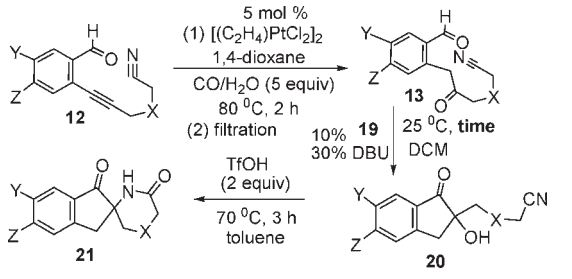
$PtCl_2$ is also active for the nitrile hydration to form dicarbonyl amide **15** that undergoes a subsequent amine/ketone condensation to give imine **16** or enamine **16′**. A second amine/aldehyde condensation provides acetal **17** which reacts with $PtCl_2$ to form pyridium **18**. The released Pt(OH)-Cl_2^- species reacted with coordinated CO to liberate $HPtCl_2^-$ and CO_2. A further reduction of the pyridinium ion by this hydride delivered the observed product **14**. This proposed mechanism is compatible with our deuterium labeling experiment because D_2O and acetal **17** are expected to undergo proton exchange rapidly under reaction conditions (80 °C, 1,4-dioxane).

The efficient isolation of dicarbonyl nitrile **13a** in the preceding reactions, as depicted in Table 1, enables alternative synthetic applications. Scheme 5 depicts the realization of a crossed benzoin reaction using a mixture of DBU (30 mol %) and 6,7-dihydro-5*H*-pyrrolo[2,1-*c*]-1,2,4-triazolium chloride (**19**, 10 mol %) in dry CH_2Cl_2. N-Heterocyclic carbenes (NHC) were reported to be effective catalysts to implement cross benzoin reactions.[12,13] Under these conditions, we obtained the condensation product **20a** in 82% yield. A subsequent treatment of alcohol **20a** with TfOH (2 equiv) in toluene afforded spiro[indene-2,2′-piperidine]-1,6′(3*H*)-dione (**21a**) in 92% yield.[14]

(11) Yoshida, T.; Ueda, Y.; Otsuka, S. *J. Am. Chem. Soc.* **1978**, *100*, 3941.

(12) Review: Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.

Table 3. Reaction Scope for Spiro Azacycles

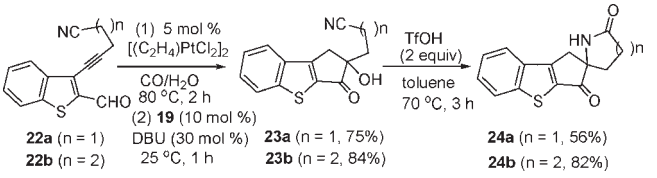


entry	substrates[a]	product (time, yields,%[b])	product (yields, %)
1	12h	20h (3h, 81%)	21h (98%)
2	12i	20i (3.5 h, 77%)	21i (83%)
3	12k	20k (3.5 h, 76%)	21k (54%)
4	12n (Y = F)	20n (3h, 78%)	21n (78%)
5	12o (Z = Cl)	20o (2h, 82%)	21o (52%)
6	12p (Z = F)	20p (2h, 76%)	21p (92%)
7	12q (Z = Cl)	20q (2h, 55%)	21q (75%)

[a] [Substrate] = 0.17 M. [b] Isolated yields are reported after silica gel column chromatography.

We evaluated additional aldehyde substrates to assess the scope of this spirolactam synthesis (Table 3). In a standard procedure, we awaited the complete conversion of oxoalkynyl nitrile **12** to dicarbonyl nitrile **13** in the initial alkyne hydration. We then filtered the resulting 1,4-dioxane solution through a short silica bed before evaporating it to dryness. The resulting crude product **13** was subsequently

Scheme 6. Application to Benzothiophene Substrates



treated with 10 mol % triazolium chloride (**19**) and 30 mol % DBU in CH_2Cl_2 to activate the benzoin coupling. This two-step synthesis worked well for aldehyde **12h** bearing an oxygen linkage, giving the desired **20h** in an 81% overall yield. The same reactions worked smoothly with aldehydes **12i** and **12k** bearing ethylene and butylene bridges respectively, giving the corresponding products **20i** and **20k** in 76−77% yields. These NHC-based coupling reactions were extendable to electron-deficient benzene derivatives **12n**−**12q**, providing products **20n**−**20q** in satisfactory yields in most cases. All these spiro alcohols **20** were transformed into the final spirolactam **21** with TfOH (2 equiv) in toluene (70 °C, 3 h); the yields were 52−98%.

Scheme 6 shows the use of benzothiophene substrates **22a** and **22b** in this spirolactam synthesis. We obtained the spiro alcohols **23a** and **23b** in useful yields through an initial isolation of dicarbonyl nitrile intermediates, followed by the same crossed benzoin coupling.[12] A final TfOH cyclization of these alcohols gave the desired lactams **24a** and **24b** in 56% and 82% yields respectively.

Before this work, metal-catalyzed hydrative carbocyclizations were strictly restricted to oxygen-containing carbocycles. We report here two hydrative carbocyclizations of oxa-alkyne-nitrile functionalities to produce distinct nitrogen-containing heterocycles. Protracted heating of these oxoalkynyl nitriles with $PtCl_2/CO/H_2O$ in 1,4-dioxane gave 2,3-dihydro-1*H*-pyrido[1.2-*b*]-isoquinolin-4(6*H*)-ones **14a** and related frameworks. In this hydration reaction, the dicarbonyl nitriles were isolated efficiently after a brief period and could be subjected to the NHC-based crossed benzoin coupling to give spiro alcohols. A subsequent treatment of this alcohol with TfOH provided the framework of spiro[indene-2,2′-piperidine]-1,6′(3*H*)-dione.

Acknowledgment. We thank the National Science Council, Taiwan, for financial support of this work.

Supporting Information Available. Spectral data, NMR spectra, and spectral data of new compounds are provided in the Supporting Information. This materials is available free of charge via the Internet at http://pubs.acs.org.

(13) Selected examples: (a) Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743. (b) Tachibana, Y.; Kihara, N.; Takata, T. *J. Am. Chem. Soc.* **2004**, *126*, 3438. (c) Enders, D.; Henseler, A. *Adv. Synth. Catal.* **2009**, *351*, 1749. (d) Takikawa, H.; Hachisu, Y.; Bode, J.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3492. (e) Li, Y.; Feng, Z.; You, S.-L. *Chem. Commun.* **2008**, 2263.

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