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Gold- and Platinum-Catalyzed Formal Markownikoff's Double Hydroamination of Alkynes: A Rapid Access to Tetrahydroquinazolinones and Angularly-Fused Analogues Thereof

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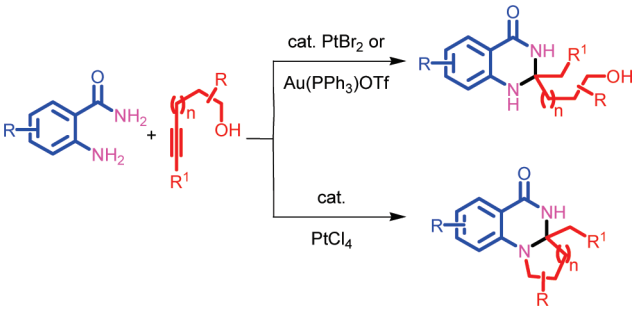

A highly efficient gold(I)- and platinum(II)-catalyzed process for formal Markownikoff's double hydroamination of alkynes tethered with hydroxyl group has been developed. The method was shown to be applicable to a broad range of 2-aminobenzamides and alkynols leading to the formation of multiply substituted tetrahydroquinazolinones. Interestingly, when Pt(IV)Cl_4 catalyst was employed, cyclic angularly fused compound was obtained.

Catalytic hydroamination of alkynes is a potentially powerful synthetic method by which valuable nitrogen-containing products can be obtained in an atom-economical manner.[1] Catalysts derived from both early and late transition metals[2] as well as lanthanides[3] have shown significant activity for the addition of N−H bonds across alkynes. In general, primary or secondary amines can undergo addition reactions with alkynes to give imines or enamines (Figure 1, path a). The imines or enamines thus obtained can be isolated or can be further used for various subsequent cascade transformations[4] without isolating them.[5] We sought to expand the alkyne hydroamination strategy beyond the example of imines/enamines formation and further develop a cascade reactions involving formal double hydroamination of alkynes as shown in Figure 1, path b.

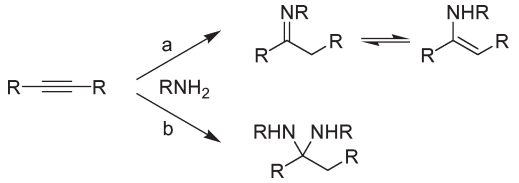

FIGURE 1. Hydroamination of alkynes.

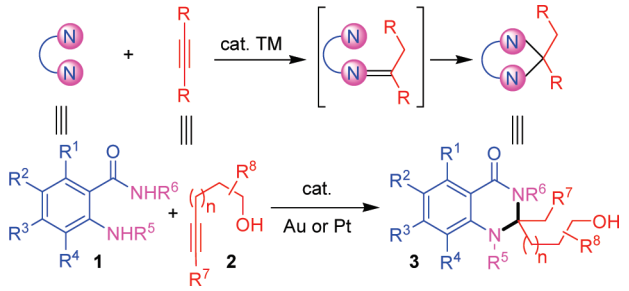

FIGURE 2. Formal double hydroamination of alkynes.

We recently described platinum-catalyzed hydroamination/hydroarylation of terminal alkynes assisted by tethered hydroxyl groups.[6] On the basis of this reactivity principle, we envisioned that imines could be generated from diamines **1** and alkynes **2** via a metal-catalyzed formal hydroamination, which would undergo trapping by tethered amines to form heterocycles **3** (Figure 2).

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(4) General reviews on cascade processes, see: (a) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993–3009. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. (c) de Meijere, A.; von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413–422. (d) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001–1020. (e) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302–312. (f) Ajamian, A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 3754–3760. (g) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.

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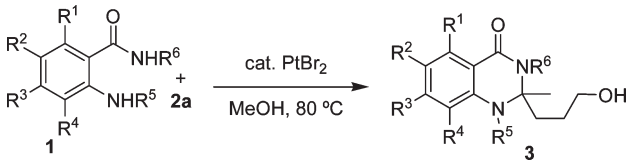
TABLE 1. Scope with 2-Aminobenzamides[a]



entry	1	3	time (h)	yield[b,c] (%)
1	**1a**, $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = H$	**3a**	12	96 (94)
2	**1b**, $R^3 = Me$, $R^1 = R^2 = R^4 = R^5 = R^6 = H$	**3b**	12	97
3	**1c**, $R^2 = Me$, $R^1 = R^3 = R^4 = R^5 = R^6 = H$	**3c**	12	94 (70)
4	**1d**, $R^2 = R^4 = Me$, $R^1 = R^3 = R^5 = R^6 = H$	**3d**	12	91 (85)
5	**1e**, $R^2 = OMe$, $R^1 = R^3 = R^4 = R^5 = R^6 = H$	**3e**	12	84
6	**1f**, $R^2 = R^3 = OMe$, $R^1 = R^4 = R^5 = R^6 = H$	**3f**	12	62
7	**1g**, $R^3 = Cl$, $R^1 = R^2 = R^4 = R^5 = R^6 = H$	**3g**	12	95
8	**1h**, $R^1 = Cl$, $R^2 = R^3 = R^4 = R^5 = R^6 = H$	**3h**	12	85
9	**1i**, $R^2 = Cl$, $R^4 = Me$, $R^1 = R^3 = R^5 = R^6 = H$	**3i**	12	89
10	**1j**, $R^2 = Br$, $R^1 = R^3 = R^4 = R^5 = R^6 = H$	**3j**	12	97
11	**1k**, $R^1 = F$, $R^2 = R^3 = R^4 = R^5 = R^6 = H$	**3k**	12	94 (85)
12	**1l**, $R^6 = Bn$, $R^1 = R^2 = R^3 = R^4 = R^5 = H$	**3l**	24	76
13	**1m**, $R^5 = Me$, $R^1 = R^2 = R^3 = R^4 = R^6 = H$	**3m**	30	69
14	**1n**, $R^5 = Bn$, $R^1 = R^2 = R^3 = R^4 = R^6 = H$	**3n**	30	60

[a]Reaction conditions: 0.59 mmol of **1**, 0.59 mmol of **2a**, 5 mol % of catalyst, MeOH (0.4 M), 80 °C. [b]Isolated yields. [c]Two catalysts were employed: (a) 5 mol % of $PtBr_2$, (b) 5 mol % of $Au(PPh_3)Cl$/10 mol % of AgOTf. Yields in parentheses refer to those obtained by Au catalyst.

Overall, the process can be referred to as formal Markownikoff's double hydroamination of alkynes. Although formal or direct hydroalkoxylation−hydroarylation,[7] double hydroalkoxylation,[8] hydroamination−hydroarylation,[9] double hydroarylation,[10] and hydroamination−hydroalkoxylation[11] of alkynes have recently been reported, to the best of our knowledge, there is no precedence for the analogues' double-hydroamination process[12] as described in Figure 2.

In order to explore the hypothesis, 2-aminobenzamide **1a** and 4-pentyn-1-ol **2a** ($n = 1$, $R^7 = R^8 = H$)[13] was treated with 5 mol % of alkynophilic catalysts[14] in various solvents at variable temperature. We were delighted to find[15] that $PtBr_2$ and $Au(PPh_3)Cl$/AgOTf catalysts in methanol gave product **3a** in 96 and 94% yields, respectively (Table 1, entry 1).[16] Treatment of methyl- and methoxy-substituted 2-aminobenzamide **1b**−**f** with **2a** under the platinum catalysis (or gold catalysis wherever specified) gave **3b**−**f** in high yields (entries 2−6). As can be judged from entries 7−11, halo-substituted amines can also be tolerated without affecting yields in the formal double-hydroamination of alkynes. Further investigations on the groups on the amines were then pursued. The substrate **1l** containing a benzyl group on amide nitrogen when reacted with **2a** in the presence of 5 mol % of $PtBr_2$ for 24 h, afforded tetrahydroquinazolinones **3l** in 76% yield (entries 12). However, the use of methyl and benzyl groups on the aromatic amine seems to hamper the reaction rate, and therefore, a longer reaction time was needed to obtain the products in acceptable yields (entries 13 and 14).

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(12) For reactions involving double hydroamination but differing conceptually, see: Zhang, Y.; Donahue, J. P.; Li, C.-J. *Org. Lett.* **2007**, *9*, 627–630.

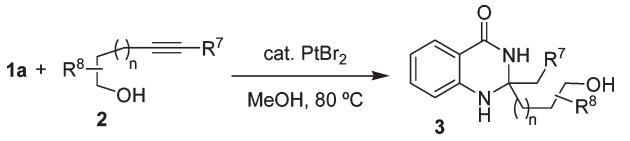
(13) A cascade process triggered by the cyclization of alkynols for entirely different transformations, see: (a) Barluenga, J.; Fernández, A.; Diéguez, A.; Rodríguez, F.; Fañanás, F. J. *Chem.—Eur. J.* **2009**, *15*, 11660–11667. (b) Barluenga, J.; Mendoza, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 1644–1647. (c) Barluenga, J.; Mendoza, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7044–7047. (d) Barluenga, J.; Mendoza, A.; Rodríguez, F.; Fañanás, F. J. *Chem.—Eur. J.* **2008**, *14*, 10892–10895.

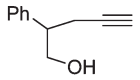
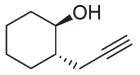
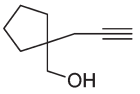
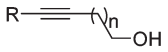
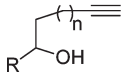
(14) Selected recent reviews on pi-activation chemistry: (a) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208–3221. (b) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395–3442. (c) Kirsch, S. F. *Synthesis* **2008**, 3183–3204. (d) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378. (e) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239–3265. (f) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266–3325. (g) Bongers, N.; Krause, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 2178–2181. (h) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449. (i) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (j) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403. (k) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333–346. (l) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896–7936. (m) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200–203. (n) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167–182.

(15) See the Supporting Information for details.

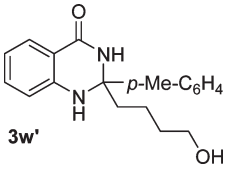
(16) Several diamines were reacted with **2a** with various catalysts; however, the desired product could not be obtained. Only 2-aminobenzamides worked well indicating that the special electronic nature of both the amines is responsible for this formal double-hydroamination reaction to occur.

TABLE 2. Scope with Alkynols[a]



entry	2		3	time	yield (%)[b,c]
1		**2b**	**3o**	12h	79[d]
2		**2c**	**3p**	12h	83[e]
3		**2d**	**3q**	24h	81
4		**2e** n = 1, X = CH_2	**3r**	12h	90 (70)
5		**2f** n = 1, X = O	**3s**	24h	87
6		**2g** n = 2, X = CH_2	**3t**	24h	72
					
7		**2h** n = 1, R = Me	**3a**	12h	92
8		**2i** n = 1, R = Et	**3u**	12h	80 (85)
9		**2j** n = 1, R = ^{n}Hex	**3v**	12h	85
10		**2k** n = 2, R = *p*-Me-C_6H_4	**3w**	36h	52[f]
11		**2l** n = 2, R = Me	**3x**	24h	66[d]
12		**2m** n = 1, R = Ph	**3y**	24h	74[d]

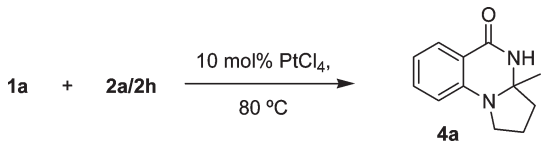
[a]Reaction conditions: 0.59 mmol **1a**, 0.59 mmol **2a**, 5 mol % catalyst, MeOH (0.4 M), 80 °C. [b]Isolated yields. [c]Two catalysts were employed; a) 5 mol % $PtBr_2$ b) 5 mol % $Au(PPh_3)Cl$/10 mol % AgOTf. Yields in parentheses refer to those obtained by Au catalyst. [d]1:1 mixture of diastereomers. [e]7:3 mixture of diastereomers. [f]8:2 mixture of regioisomers.



Next, scope of the reaction with various alkynols was studied. The alkynols bearing sterically demanding substituents in the tether such as **2b**, **2c**, and **2d** reacted well giving corresponding products **3o**, **3p**, and **3q** in high yields (Table 2, entries 1−3). As can be judged from entries 4−6 that 5-hexyn-1-ols and 6-heptyn-1-ols can also be used as substrates. Even internal alkynes such as **2h**, **2i**, and **2j** were tolerated giving the corresponding products in 92%, 80%, and 85% yields (entries 7−9). However, in the case of **2k**, a longer reaction time was required to get a regioisomeric mixture of products **3w** and **3w′** in 52% yield (entry 10). To further examine the scope of this process with secondary alcohols, the substrates **2l** and **2m** have been synthesized and their reactivity tested. The products **3x** and **3y** were obtained in 66% and 74% yields, respectively (entries 11 and 12).

Interestingly, when **1a** was allowed to react with **2a** and **2h** in the presence of 10 mol % of $PtCl_4$ in MeOH, double hydroamination−dehydrative cyclization reaction occurred

TABLE 3. $PtCl_4$-Catalyzed Double Hydroamination−Dehydrative Cyclization Cascade



entry	2	conditions	yield[a] (%)
1	**2a**	methanol, 48 h	91
2	**2h**	methanol, 48 h	80
3	**2a**	neat, 8 h	82
4	**2h**	neat, 8 h	85

[a]Isolated yields.

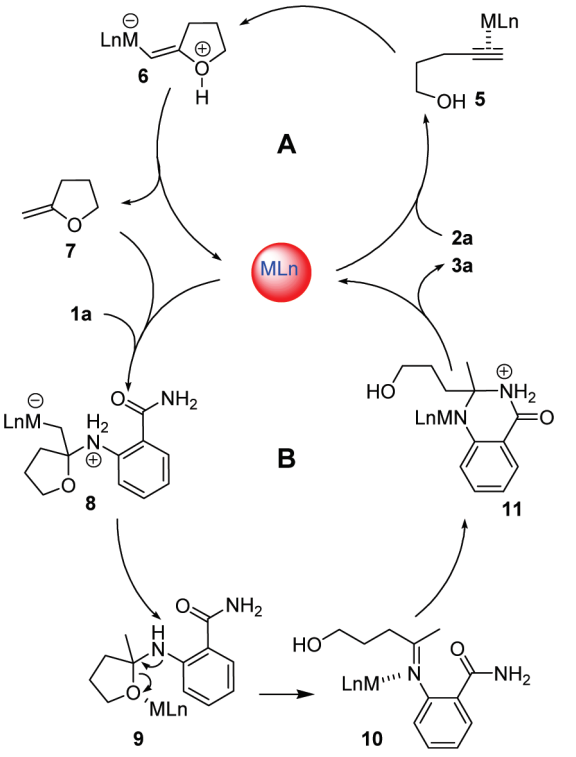


FIGURE 3. Plausible mechanism for double hydroamination of alkynes.

to give hexahydropyrrolo[1,2-*a*]quinazolin-5-one **4a** in high yields (Table 3, entries 1 and 2). The use of methanol as a solvent was not necessary; under neat conditions, **2a** and **2h** gave **4a** in 82% and 85% yields, respectively. The structure of **4a** was unequivocally determined by single-crystal X-ray structure analysis.[17]

A proposed mechanism, which is similar to that reported previously,[6a] is outlined in Figure 3. An intramolecular hydroalkoxylation of alkynol **2a** by metals likely occurs to give 2-methylenetetrahydrofuran **7** through intermediates **5** and **6**[18] (cycle **A**). Next, imine **10** would be generated from **7** and **1a** (cf. **8** and **9**) with assistance of the catalyst (cycle **B**).[19]

(17) X-Ray crystal structure of **4a** is given in Supporting Information.
(18) Hashmi, A. S. K.; Schuster, A. M.; Rominger, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 8247–8249.
(19) The product **3a** could not be obtained when **1a** and 1-octyne reacted under standard conditions, clearly indicating that tethered hydroxyl groups in alkyne is essential for the present reaction to occur.

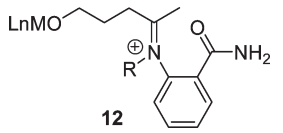


FIGURE 4. Possible involvement of iminium ions in the case of substrate **1m** and **1n**.

The activation of imine **10** by the co-ordination with metal catalyst would trigger the cyclization to form intermediate **11**. Protonation of the organometal complex **11** affords final product **3a** with the regeneration of metal catalyst. Since the formation of intermediate imine **10** would not be possible in the case of substrate **1m** and **1n**, an involvement of iminium ions **12** was proposed (Figure 4).[20] The iminium ions **12** would undergo intramolecular trapping by amide nitrogen followed by protonation to give **3m**/**3n** with regeneration of catalyst.

To understand the reaction mechanism for the formation of **4a**, the product **3a** was reacted under $PtCl_4$ and HCl catalysts independently. In the case of $PtCl_4$, dehydration proceeded smoothly to give product **4a** (MeOH, 95% and neat, 87%).[14,21] The reaction in the presence of catalytic amounts of HCl in methanol appeared to be sluggish, and only 20% of **4a** was isolated. Therefore, the involvement of Brønsted acid (HCl) as a catalyst, generated during the course of reaction, is unlikely.[14]

In conclusion, platinum and gold-catalyzed formal Markownikoff's double hydroamination of alkynes has been developed. This method employs 2-aminobenzamides and alkynols to provide efficient access to tetrahydroquinazolinones. We have also described the possibility toward the development of double hydroamination−dehydrative cyclization for the synthesis of angularly fused compounds. Owing to the importance of related compounds in medicinal chemistry,[22] the present method may prove applicable for generation of many compounds for biological evaluation.[23]

Experimental Section

Preparation of **3a** as a representative example.

Platinum Catalysis. To a methanol (1.5 mL, 0.40 M) solution of **2a** (50 mg, 0.59 mmol) and **1a** (77 mg, 0.59 mmol) in a 2.5 mL screw-cap vial was added $PtBr_2$ (11 mg, 5 mol %) under nitrogen atmosphere. The mixture was stirred at 80 °C for the specified time. Then, the reaction mixture was filtered through a pad of silica gel eluted with ethyl acetate and the solvent was evaporated under reduced pressure. The residue was purified by flash silica gel column chromatography using CH_2Cl_2/MeOH (95/5) as an eluent to obtain **3a** (125 mg, 96%) as a pure compound.

Gold Catalysis. To a methanol (1.5 mL, 0.40 M) solution of **2a** (50 mg, 0.59 mmol) and **1a** (77 mg, 0.59 mmol) in 2.5 mL screw-cap vial were added $Au(PPh_3)Cl$ (14 mg, 5 mol %) and AgOTf (15 mg, 10 mol %) under nitrogen atmosphere. The mixture was stirred at 80 °C for the specified time. Then, the reaction mixture filtered through a pad of silica gel eluted with ethyl acetate, and the solvent was evaporated under reduced pressure. The residue was purified by flash silica gel column chromatography using CH_2Cl_2/MeOH (95/5) as an eluent to obtain **3a** (122 mg, 94%) as a pure compound.

2-(3-Hydroxypropyl)-2-methyl-1,2,3,4-tetrahydro-4-quinazolinone (3a): thick liquid; R_f 0.23 (CH_2Cl_2/MeOH = 95/5); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.70 (brs, 1H, D_2O exchangeable), 7.58 (d, J = 7.8 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 6.62 (d, J = 7.8 Hz, 1H), 6.56 (t, J = 7.8 Hz, 1H), 3.42 (dd, J = 6.8, 5.8 Hz, 2H), 1.75−1.65 (m, 2H), 1.64−1.51 (m, 2H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.1, 147.2, 133.2, 127.0, 116.1, 114.0, 113.5, 69.0, 60.9, 38.1, 27.9, 27.1; IR (film) ν_{max} 3412, 3249, 2928, 1642, 1571, 1522, 1435, 1392, 1274, 1160, 1072, 760, 715, 655 cm^{-1}; HRMS calcd for $C_{12}H_{16}N_2O_2$-Na (M^+ + Na) 243.1109, found 243.1114.

2-(3-Hydroxypropyl)-2,7-dimethyl-1,2,3,4-tetrahydro-4-quinazolinone (3b): thick liquid; R_f 0.34 (CH_2Cl_2/MeOH = 95/5); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.78 (s, 1H, D_2O exchangeable), 7.50 (d, J = 7.7 Hz, 1H), 7.36 (brs, 1H), 6.41 - 6.39 (m, 2H), 5.90 (brs, 1H, D_2O exchangeable), 3.46 (t, J = 5.9 Hz, 2H), 2.24 (s, 3H), 1.73 (m, 2H), 1.64 −1.60 (m, 2H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.2, 147.2, 143.1, 127.2, 117.4, 114.0, 111.2, 69.0, 60.9, 38.1, 27.9, 27.2, 21.4; IR (film) ν_{max} 3420, 2924, 1645, 1531, 1457, 1282, 1025, 999, 825, 765, 627 cm^{-1}; HRMS calcd for $C_{13}H_{18}N_2O_2$ Na (M^+ + Na) 257.1265, found 257.1272.

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Supporting Information Available: All experimental procedures, analytical data, and copies of ^{1}H and ^{13}C NMR spectra of all newly synthesized products; X-ray structural data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

(20) We are thankful to one of the reviewers for pointing out this information.

(21) The fact that reaction of **3a** in methanol at 80 °C or under neat conditions for 24 h did not give **4a** clearly indicates that catalyst is essential for the reaction.

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