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Platinum-Catalyzed Formal Markownikoff's Hydroamination/Hydroarylation Cascade of Terminal Alkynes Assisted by Tethered Hydroxyl Groups

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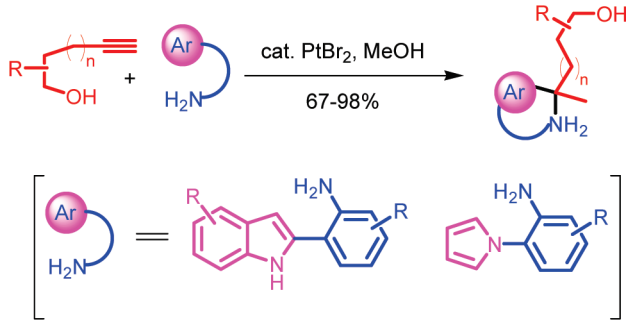

An efficient method for Markownikoff's hydroamination−hydroarylation of alkynols using $PtBr_2$ as catalyst has been developed. The platinum-catalyzed reactions of alkynols with amino group containing aromatics were achieved in methanol over a reaction time of 6−24 h and temperature ranging from rt to 80 °C. This method works well for a variety of alkynols and aromatic amino compounds to give substituted pyrrolo[1,2-*a*]quinoxalines and indolo[3,2-*c*]quinolines in good to excellent yields.

Transition-metal-catalyzed tandem carbon−carbon and carbon−heteroatom bond-forming reactions are powerful tools for the synthesis of a variety of building blocks.[1] Those processes are not only efficient but also have many other advantages such as they can directly construct complex molecules, without isolating any intermediates, from readily accessible starting materials under mild conditions and most importantly with high atom economy.[2] Out of the various metal-mediated reactions, the addition of N−H bonds, O−H bonds, and Ar−H bonds across alkynes generally called as hydroamination,[3] hydroalkoxylation,[4] and hydroarylation,[5] respectively, represents an efficient process to generate desired compounds (Figure 1, path A). Generally, this type of reaction relies on interaction of the metal catalyst with the π-bond of alkynes.[6] Nowadays, tandem processes involving more than one above-mentioned process are gaining much interest because of their elegancy. For example, hydroalkoxylation−hydroarylation,[7] double hydroalkoxylation,[8] double hydroamination,[9] and double hydroarylation[10] processes have recently been reported (Figure 1, path B). To our surprise, hydroamination−hydroarylation tandem reactions have remained overlooked so far. Recently, Dixon and co-workers reported gold-catalyzed cyclization of alkynoic acid with amino aromatics involving *N*-acyl iminium ion cascade.[11] Yi and Yun reported a cationic ruthenium hydride complex-catalyzed process of terminal alkynes, without having a hydroxyl group in the proximity.[12] Herein, we

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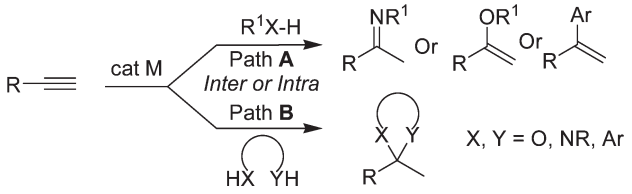

FIGURE 1. Various modes of addition of nucleophiles to alkynes.

report an efficient method for hydroamination−hydroarylation of alkynes, tethered with a hydroxyl group, by using $PtBr_2$ as catalyst for the synthesis of pharmacologically important heterocycles such as pyrrolo[1,2-*a*]quinoxalines[13] and indolo[3,2-*c*]quinolines.[14]

With the above background and keeping in mind some recent reports,[15] we hypothesized that a metal-catalyzed intramolecular hydroalkoxylation reaction of alkynol would form corresponding cyclic enol ether, which would react with amino aromatics **2** to form **3** (Figure 2). A proposed reaction might allow us to perform formal hydroamination−hydroarylation of alkynes and would give access to a wide range of heterocycles.

Our study began with commercially available 4-pentyn-1-ol **1a** and 2-aminophenyl pyrrole **2a**. On the basis of ample literature precedent on catalytic carbophilic activation, we studied the reaction of several transition-metal catalysts with these substrates. Various temperature, solvent, and catalysts, and a combination of two different catalysts (transition metal with either Brønsted acid or Lewis acid catalysts) resulted in either decomposition or complex mixture of products. We were pleased to find that $PtCl_2$-catalyzed reaction in DCE and toluene at room temperature afforded product **3a** in 40 and 60% yield, respectively (Table 1, entries 1 and 2). Interestingly, when polar protic solvent such as methanol was used, the yield of **3a** was substantially increased to 92% (entry 3). As shown in entry 4, the use of

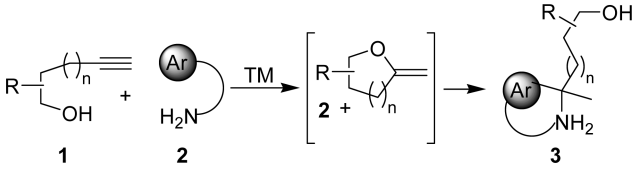

FIGURE 2. Concept of hydroamination−hydroarylation cascade.

TABLE 1. Catalyst Screening for Hydroamination−Hydroarylation of Alkynes

entry	catalyst	solvent	yield
1	$PtCl_2$	DCE	40%
2	$PtCl_2$	toluene	60%
3	$PtCl_2$	methanol	92%
4	$PtBr_2$	methanol	94%
5	$PtCl_4$	methanol	90%
6	$Au(PPh_3)Cl + AgSbF_6$	methanol	80%
7	$Au(PPh_3)Cl + AgBF_4$	methanol	75%
8	$Au(PPh_3)Cl$ + AgOTf	methanol	72%

[a]Reaction conditions: 0.6 mmol **1a**, 0.6 mmol **2a**, 5 mol % catalyst, solvent (0.4 M), rt, 6 h. [b]Isolated yields. [c]5 mol % of $Au(PPh_3)Cl$ and 10 mol % of silver salts were used.

$PtBr_2$ as a catalyst gave the product **3a** in 94% yield. When $PtCl_4$ was employed as a catalyst, the desired product **3a** was formed in 90% yield (entry 5). Not only platinum salts but also gold salts are effective. The cationic gold(I) complexes generated in situ from $Au(PPh_3)Cl$ and silver salts such as $AgSbF_6$, $AgBF_4$, and AgOTf give product in 80, 75, and 72% yield, respectively (entries 6−8).

After we optimized the reaction conditions (5 mol % of $PtBr_2$, MeOH), the scope of this process was evaluated for other alkynes and aromatic amino compounds (Table 2). Treatment of 4-pentyn-1-ol **1a** with 2-aminophenylpyrrole derivatives **2b** and **2c** under slightly elevated temperature gave the desired products **3b** and **3c** in 82 and 98% yield, respectively (entries 1 and 2). The reaction of 2-(1*H*-2-indolyl)aniline derivatives **2d**, **2e**, and **2f** with **1a** gave indolo-[3,2-*c*]quinoline derivatives **3d**, **3e**, and **3f**, respectively, in good yields (entries 3−5). The chloro substituent was also tolerated under present reaction conditions, and thus substrates **2g** and **2h** smoothly furnished **3g** and **3h** in 81 and 89% yield, respectively (entries 6 and 7). The alkynols bearing sterically demanding substituents in the tether such as **1b**, **1c**, and **1d** reacted well, giving corresponding products **3i**, **3j**, and **3k** in good yields (entries 8−10). A mixture of diastereomers **3l** + **3l′** and **3m** + **3m′** was obtained when **1e** and **1f** were employed as substrates (entries 11 and 12). Not only 4-pentyn-1-ols but also 5-hexyn-1-ols undergo reaction smoothly. Thus, substrate **1g** and **1h** underwent hydroamination−hydroarylation cascade to provide **3n** and **3o**, respectively (entries 13 and 14). It should be noted that this method is applicable to only terminal alkynes, and therefore, internal alkynes cannot be employed as substrates.

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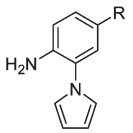
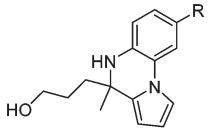
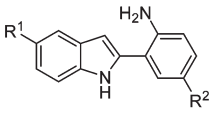
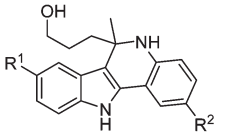
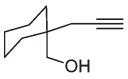
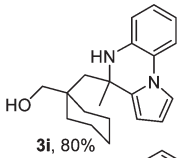
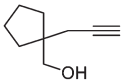
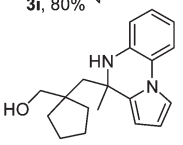
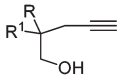
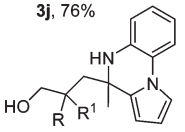
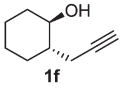
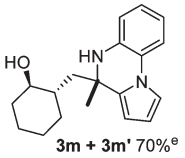
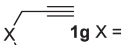
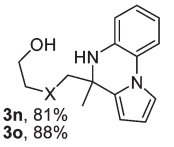
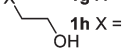
TABLE 2. $PtBr_2$-Catalyzed Hydroamination/Hydroarylation of Alkynes

entry	1	2	temp. (°C)	3, yield[b]
	 **1a**			
1	**1a**	**2b** R = Me	60	**3b**, 82%
2	**1a**	**2c** R = COOMe	60	**3c**, 98%
				
3	**1a**	**2d** $R^1 = R^2 = H$	rt	**3d**, 87%
4	**1a**	**2e** $R^1 = H$, $R^2 = Me$	80	**3e**, 68%
5	**1a**	**2f** $R^1 = R^2 = Me$	80	**3f**, 67%
6	**1a**	**2g** $R^1 = H$, $R^2 = Cl$	80	**3g**, 81%
7	**1a**	**2h** $R^1 = R^2 = Cl$	80	**3h**, 89%
8	 **1b**	**2a**	80	 **3i**, 80%
9[c]	 **1c**	**2a**	80	 **3j**, 76%
			80	
10[c]	**1d** $R = R^1 = Ph$	**2a**	80	**3k**, 76%
11	**1e** R = H, R^1 = Ph	**2a**	80	**3l + 3l'** 93%[d]
12	 **1f**	**2a**	80	 **3m + 3m'** 70%[e]
13	 **1g** X = CH_2	**2a**	80	 **3n**, 81% **3o**, 88%
14	 **1h** X = O	**2a**	80	

[a]Reaction conditions: **1** (0.5944 mmol), **2** (0.5944 mmol), 5 mol % of $PtBr_2$, MeOH (0.4 M), rt or heat, 12 h. [b]Isolated yields. [c]Reaction mixture was heated for 24 h. [d]Inseperable mixture of diastereomers in the ratio of 2:1 was obtained. [e]1:1 mixture of diastereomers obtained, which was separated by flash column chromatography.

The plausible mechanism is depicted in Figure 3. First, a $PtBr_2$-catalyzed intramolecular hydroalkoxylation of alkynol **1a** likely occurs to give 2-methylenetetrahydrofuran **6**

(16) One of the reviewers suggested that compound **6** may exist as 1-methoxy-1-methyltetrahydrofuran. However, the reaction between **1b** under standard Pt(II) catalysis, in the absence of **2a**, did not give anticipated product; decomposition occurred.

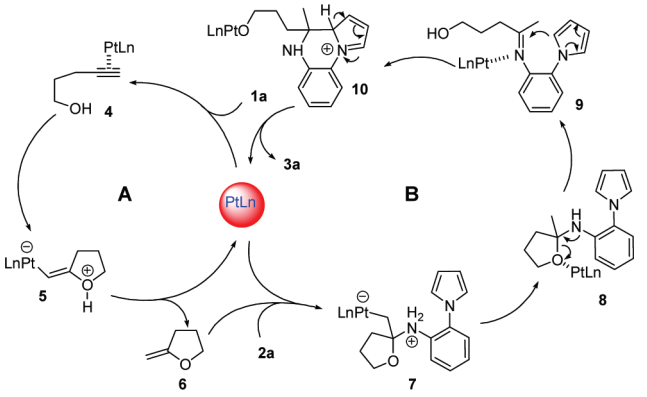
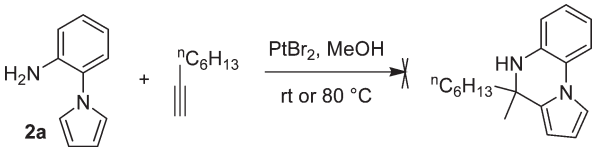


FIGURE 3. Plausible mechanism for Markownikoff's hydroamination/hydroarylation of alkynes.

SCHEME 1. $PtBr_2$-Catalyzed Reaction of 1-Octyne with 2a

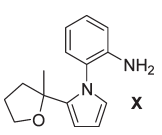


through intermediates **4** and **5** (cycle A).[16] Then, N−H bond addition of **2a** catalyzed by $PtBr_2$ again leads to the *N*, *O*-ketal **8** (cf. **7**). The coordination of the oxygen atom of *N*,*O*-ketal to $PtBr_2$ (cf. **8**) would form imine **9**, which on intramolecular nucleophilic addition of pyrrole gives **10**. Protonation of the resulting organoplatinum complex **10** affords final product **3a** and regenerates $PtBr_2$ (cycle B). The mechanism triggered by hydroarylation of **6** with the pyrrole moiety[17] in **2a** cannot be ruled out completely.[7b] It is noteworthy to emphasize that a single catalyst promotes all reactions, mentioned in catalytic cycles A and B.[18]

To confirm the role of the tethered hydroxyl group in alkynes, we have conducted an experiment presented in Scheme 1. 2-Aminophenylpyrrole **2a** and 1-octyne were subjected to platinum catalysis under previously established conditions. However, desired product was not obtained; at room temperature, starting material **2a** was recovered, and at 80 °C, a complex mixture was obtained as judged by TLC and ^{1}H NMR analysis.

Literature analysis on catalytic carbophilic activation revealed that most of the processes involve the use of alkyne as a trigger containing both nucleophile in the same

(17) In order to determine the existence of intermediate X in the reaction mixture, we have carefully examined the progress of reaction between **1a** and **2a** by TLC and ^{1}H NMR. However, the presence of X was not detected. The presence of starting materials and product **3a** was only the detectable species.



(18) The reaction of exocyclic enol ether **6**, prepared independently with **2a** in methanol at rt for 12 h, did not afford **3a**. However, 5 mol % of $PtBr_2$ **3a** was obtained in 90% yield. The possibility of Brønsted acid catalysis for the formation of **3i** from **1b** and **2a** was ruled out. The reaction between **1b** and **2a** in the presence of catalytic amounts of HCl in methanol did not give desired product **3i**.

molecule. Much more appealing strategies would involve the use of alkyne and nucleophiles present in two different substrates. In this regard, we have developed a formal hydroamination−hydroarylation cascade of terminal alkynes tethered with a hydroxyl group. The corresponding heterocycles were isolated in high yields, and this process constitutes an easy and efficient access to highly substituted pyrrolo[1,2-*a*]quinoxalines and indolo[3,2-*c*]quinolines; those, as such or their synthetically manipulated forms, may prove to be an important pharmacophore. Studies aimed at exploring the mechanistic aspects of this transformation and developing further uses of this concept to various heterocycles are ongoing.

Experimental Section

The preparation of **3a** is representative. To a methanol (1.5 mL, 0.4 M) solution of **1a** (50 mg, 0.5944 mmol) and **2a** (94 mg, 0.5944 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 room temperature with methanol as a solvent for 6 h. Then, the reaction mixture was filtered through a pad of silica gel with ethyl acetate, and the solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography using ethyl acetate/hexane (3:7) as eluent to obtain **3a** (135 mg, 94%) as a pure compound.

3-(4,5-Dihydro-4-methylpyrrolo[1,2-*a*]quinoxalin-4-yl)propan-1-ol (3a):. 94% yield, solid; mp 142−143 °C; R_f = 0.30 (hexane/EtOAc = 60/40); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.0 Hz, 1H), 7.15−7.05 (m,1H), 6.89 (t, J = 7.7 Hz, 1H), 6.75 (t, J=7.7 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 6.21 (t, J = 3.3 Hz, 1H), 5.90 (br d, J = 3.0 Hz, 1H), 3.50 (t, J = 6.2 Hz, 2H), 1.89−1.81 (m, 1H), 1.79−1.70 (m, 1H), 1.64−1.55 (m, 2H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 136.2, 133.0, 124.6, 123.8, 116.9, 114.7, 114.2, 113.8, 109.2, 102.7, 61.0, 53.0, 39.5, 28.0, 27.2; IR (KBr) ν_{max} 3246, 3188, 2974, 2941, 2909, 1608, 1516, 1489, 1336, 1288, 1026, 805, 706 cm^{-1}; HRMS calcd for $C_{15}H_{19}ON_2$ (M^+ + H) 243.1497, found 243.1507.

3-(4,5-Dihydro-4,8-dimethylpyrrolo[1,2-*a*]quinoxalin-4-yl)propan-1-ol (3b):. 82% yield, white solid; mp 152−154 °C; R_f 0.35 (hexane/EtOAc = 60/40); ^{1}H NMR (400 MHz DMSO-d_6 + D_2O) δ 7.41 (s, 1H), 7.04−7.01 (m, 1H), 6.67 (d, J = 7.8 Hz, 1H), 6.59 (d, J = 7.8 Hz, 1H), 6.17 (d, J = 2.9 Hz, 1H), 5.86 (d, J = 2.9 Hz, 1H), 3.44 (t, J = 6.4 Hz, 2H), 2.28 (s, 3H), 1.79−1.67 (m, 2H), 1.57−1.52 (m, 2H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 133.7, 133.2, 125.7, 124.9, 123.8, 114.8, 114.7, 113.6, 109.4, 102.4, 61.0, 53.0, 38.1, 27.8, 26.9, 20.3; IR (KBr) ν_{max} 3242, 3180, 2968, 2951, 2902, 1615, 1546, 1491, 1334, 1289, 807, 712 cm^{-1}; HRMS calcd for $C_{16}H_{20}N_2ONa$ (M^+ + Na) 279.1473, found 279.1466.

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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. This material is available free of charge via the Internet at http://pubs.acs.org.