Dearomatization Reaction

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Dearomatization of Fused Arenes Using Platinum-Catalyzed Intramolecular Formation of Two C–C Bonds**

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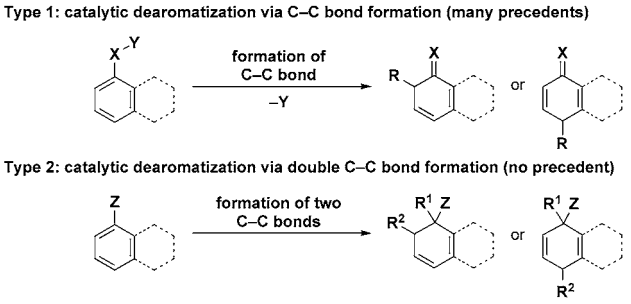
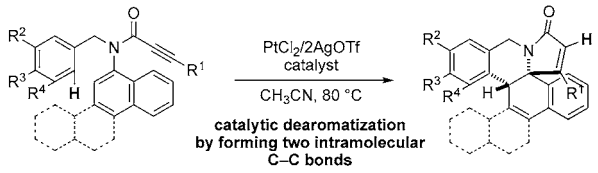
The dearomatization of arenes has been extensively studied to make simple aromatic compounds useful for the preparation of complex aliphatic compounds.[1] The catalytic dearomatization by way of C–C bond formation is particularly attractive. As shown in Scheme 1, previous reports have focused on C–C bond formation at the *ortho* or *para* position of the substituent (X–Y) through the elimination of the leaving group (Y) to produce substituted cyclohexadienes (Scheme 1, type 1).[2–6] Three π-bonds still remain after the dearomatization in this transformation, which stabilizes the dearomatization products. For example, a number of metal-catalyzed C–C bond-forming dearomatization reactions of phenol (X–Y = O–H)[2,3] or aniline derivatives (X–Y = NR′–H)[4] to produce cyclohexadienones or iminocyclohexadienes have been reported. The palladium-catalyzed allylative dearomatization reactions of substituted benzyl or cinnamyl chlorides (X–Y = CH(R′)–Cl or CH=CHCH$_2$–Cl) to produce methylenecyclohexadienes have also been reported.[5] However, the catalytic formation of two C–C bonds at the *ipso* and *ortho* or *para* positions of the substituent Z to produce cyclohexadienes has not been reported to date (Scheme 1, type 2).[7]



Scheme 1. Catalytic dearomatization by forming either one or two C–C bonds.

Herein, we present the platinum(II)-catalyzed dearomatization of *N*-benzyl-*N*-(1-naphthyl)propiolamide derivatives through the formation of two intramolecular C–C bonds at the *ipso* and *ortho* positions of the acylamino group (Scheme 2). Several intramolecular C–C bond-forming *ipso* iodocyclizations of *N*-arylpropiolamides have been reported;[8] however, these reactions are not catalytic and did not involve the formation of two C–C bonds.



Scheme 2. Platinum-catalyzed dearomatization by way of the formation of two C–C bonds.

Our research group recently reported the enantioselective intramolecular 6-*endo* hydroarylation of *N*-arylpropiolamides, which was catalyzed by palladium(II)/xyl-H$_8$-binap (xyl-H$_8$-binap = 2,2′-bis[di(3,5-xylyl)phosphine]-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl). This system furnishes axially chiral 4-aryl-2-quinolinones with good yields and *ee* values.[9–11] In this reaction, *N*-(2-naphthyl)propiolamides showed high reactivity. Consequently, we also investigated the reaction of *N*-(1-naphthyl)propiolamide **1a** in the presence of a cationic palladium(II)/binap complex (binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl). Although the corresponding 6-*endo* hydroarylation product **3a** was not obtained, the corresponding 5-*exo* hydroarylation product **4a** was obtained in good yield (Table 1, entry 1). Interestingly, the use of cationic gold(III), gold(I), silver(I), rhodium(III), and platinum(II) complexes as catalysts produced dearomatization product **2a** in low yields along with 6-*endo* and 5-*exo* hydroarylation products **3a** and **4a** (entries 2–6). As the cationic platinum(II) complex showed the highest yield and selectivity for the formation of **2a** (entry 6), further optimization was conducted to improve the yield of **2a**. Prolonged reaction time gave 73% conversion of **1a** (entry 7), and screening of silver salts (entries 7–10) revealed that the use of AgOTf showed the highest selectivity for the formation of **2a** (entry 10). The use of CH$_3$CN as a solvent significantly increased the yield of **2a** (entry 11) and could reduce the required catalyst loading to 5 mol% (entry 12).

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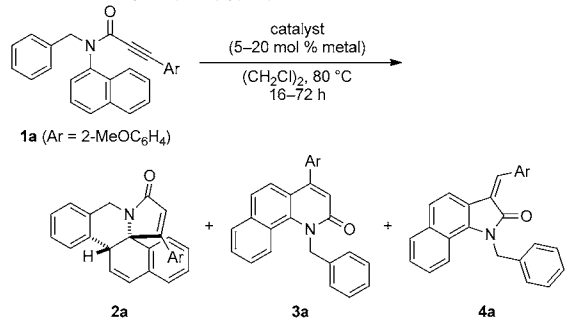
Table 1: Optimization of reaction conditions for the formation of two C–C bonds on *N*-(1-naphthyl)propiolamide **1a**.



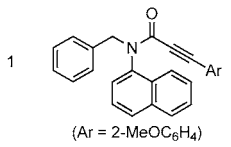
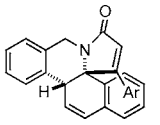
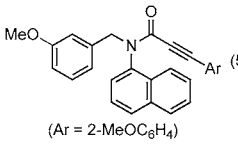
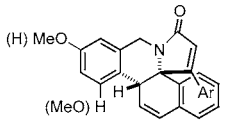
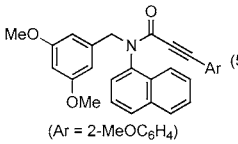
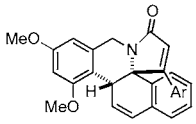
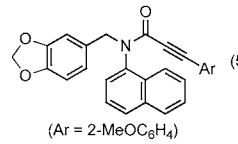
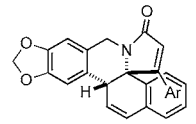
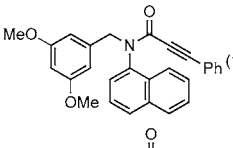
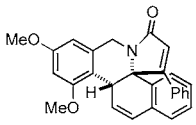
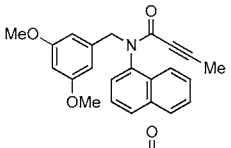
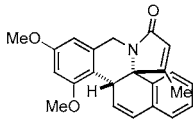
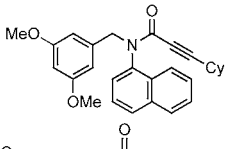
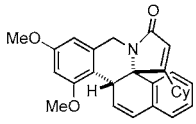
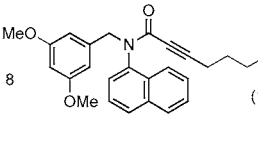
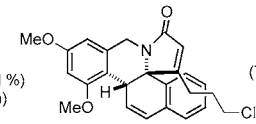
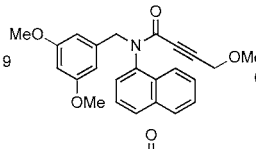
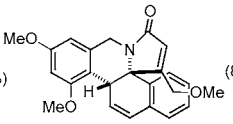
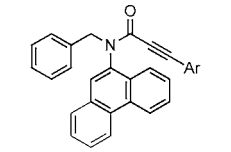
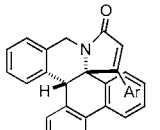
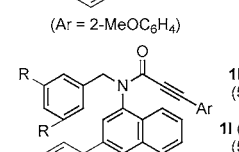
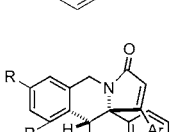
Entry	Ligand	Catalyst [mol%]	Time [h]	Conv. [%]	Yield [%][a]		
					2a	**3a**	**4a**
1	$[Pd(CH_3CN)_4](BF_4)_2$/binap	20	16	92	0	0	70
2	$AuCl_3$/3 $AgBF_4$	20	16	100	11	13	77
3	$AuCl(SMe_2)/AgBF_4$	20	16	28	7	10	8
4	$AgBF_4$	20	16	19	5	4	5
5	$[Cp^*RhCl_2]_2$/4 $AgBF_4$	20	16	24	5	5	5
6	$PtCl_2$/2 $AgBF_4$	20	16	55	13	13	15
7	$PtCl_2$/2 $AgBF_4$	20	72	73	26	18	21
8	$PtCl_2$/2 $AgSbF_6$	20	72	100	14	44	28
9	$PtCl_2$/2 $AgPF_6$	20	72	80	21	22	26
10	$PtCl_2$/2 AgOTf	20	72	100	36	25	20
11[b]	$PtCl_2$/2 AgOTf	20	72	100	63	15	13
12[b]	$PtCl_2$/2 AgOTf	5	72	96	69	12	9

[a] Yield of isolated product. [b] Solvent: CH_3CN. $Cp^* = C_5Me_5$.

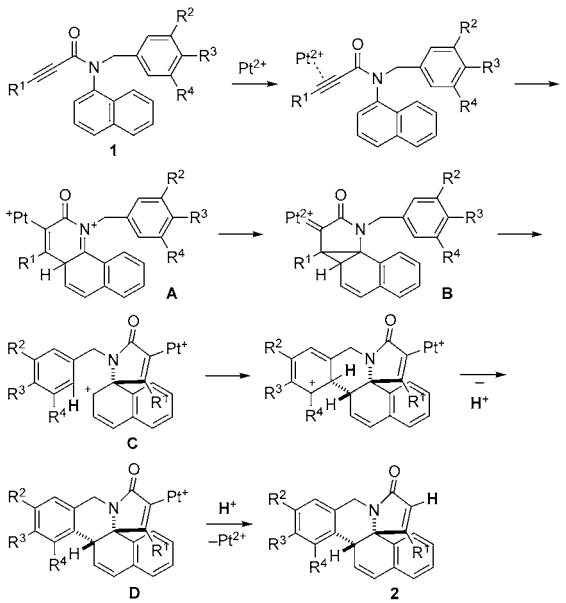
With the conditions optimized, the scope of the platinum(II)-catalyzed dearomatization reactions was examined (Table 2). The reactions of substrates **1b–d** possessing alkoxy-substituted electron-rich benzyl groups (entries 2–4) showed higher reactivity than **1a**, with a nonsubstituted benzyl group (entry 1). In the reaction of **1b**, the sterically less-demanding regioisomer **2b** was obtained as a major product along with the minor regioisomer **2b′** (entry 2). The substrate **1c** possessing the 2-methoxyphenyl group at the alkyne terminus showed higher reactivity than **1e** with a nonsubstituted phenyl group (entry 3 versus 5). Not only aryl groups but also alkyl groups could be incorporated at the alkyne terminus, although high catalyst loadings and/or long reaction times were required (**1f-i**, entries 6–9). Other fused arenes were also examined, which revealed that 9-aminophenanthrene derivative **1j** produced the corresponding dearomatization product **2j** in moderate yield owing to the formation of a 6-*endo* hydroarylation product as a byproduct (entry 10).[12] 6-Aminochrysene derivatives **1k,l** were particularly suitable substrates for this process, and the desired dearomatization products **2k,l** were obtained in high yields (entries 11 and 12). In all cases, the reaction products **2a–l** were obtained as a single diastereomer. The structure of the dearomatization product was unambiguously confirmed by X-ray crystallographic analysis of the crystalline compound **2d**.[13]

Scheme 3 depicts a possible mechanism for the present dearomatization reactions. We believe that the coordination of the cationic platinum(II) complex to the alkyne triple bond of *N*-(1-naphthyl)propiolamide **1** would induce the *endo*

Table 2: Dearomatization of fused arenes **1a–l** by way of platinum-catalyzed intramolecular formation of two C–C bonds.[a]

Entry	Substrate **1** (Catalyst Loading, Time)	Product **2** / Yield[b]
1	 **1a** (5 mol %) (72 h)	 **2a** / 69%
2	 **1b** (5 mol %) (40 h)	 **2b (2b′)** / >99% (**2b/2b′** = 87:13)
3	 **1c** (5 mol %) (40 h)	 **2c** / 93%
4	 **1d** (5 mol %) (40 h)	 **2d** / 92%
5	 **1e** (10 mol %) (96 h)	 **2e** / 71% (84% conv)
6	 **1f** (5 mol %) (72 h)	 **2f** / 79%
7	 **1g** (10 mol %) (96 h)	 **2g** / 46% (69% conv)
8	 **1h** (10 mol %) (96 h)	 **2h** / 56% (77% conv)
9	 **1i** (20 mol %) (96 h)	 **2i** / 80% (86% conv)
10	 **1j** (5 mol %) (40 h)	 **2j** / 56%
11	 **1k** (R = H) (5 mol %) (40 h)	 **2k** / 93%
12	**1l** (R = OMe) (5 mol %) (16 h)	**2l** / 88%

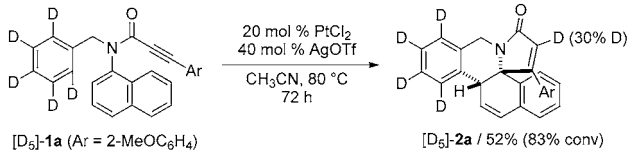
[a] Yield of isolated product. [b] Solvent: CH_3CN.
$Cp^* = C_5Me_5$.[a] Reactions were conducted using $PtCl_2$/2AgOTf as a catalyst in CH_3CN at 80 °C. [b] Yield of isolated product. Cy = cyclohexyl.



Scheme 3. Possible mechanism for the formation of **2** from **1**.

cyclization to generate intermediate **A**.[14] Subsequent skeletal rearrangement through intermediate **B** would afford intermediate **C**, although direct formation of **C** from **1** through *ipso* cyclization cannot be excluded at the present stage. Friedel–Crafts-type reaction followed by deprotonation gives intermediate **D**. Protonation of **D** affords the dearomatization product **2** and regenerates the platinum catalyst.

To confirm this deprotonation–protonation sequence, deuterium-labeling studies were conducted. The reaction of deuterated phenyl substituted *N*-(1-naphthyl)propiolamide [D_5]-**1a** produced partially deuterated product [D_5]-**2a** with selective incorporation of deuterium in the vinylic position (Scheme 4).



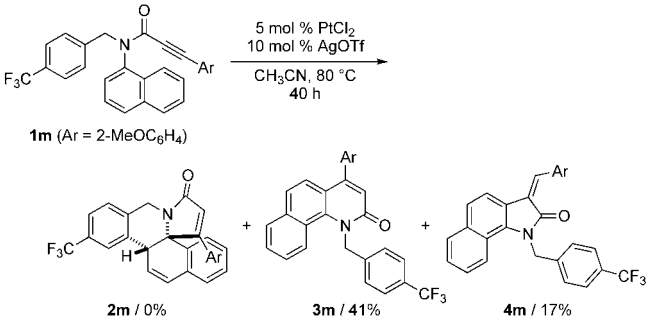
Scheme 4. Platinum-catalyzed reaction of [D_5]-**1a**.

Furthermore, the reaction of nondeuterated phenyl substituted *N*-(1-naphthyl)propiolamide **1a** in the presence of a large excess of external deuterium source (CD_3OD) also gave partially deuterated product [D]-**2a** with selective incorporation of deuterium in the vinylic position (Scheme 5). These results are consistent with the formation of **2** by way of the proposed deprotonation–protonation mechanism.

To confirm the Friedel–Crafts-type reaction of the benzyl group with the naphthyl group, the electronic effect of the benzyl group was examined. As shown in Table 2, the reactions of substrates **1b–d** possessing alkoxy-substituted electron-rich benzyl groups produced the corresponding

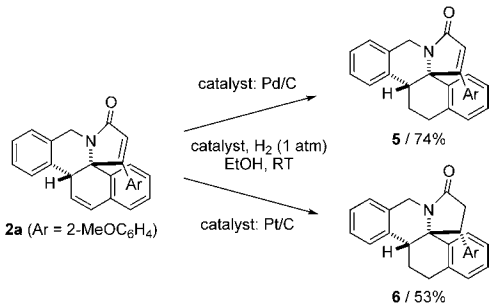
Scheme 5. Platinum-catalyzed reaction of **1a** in the presence of CD_3OD.

dearomatization product **2b–d** in excellent yields (entries 2–4). However, the reaction of substrate **1m** with a trifluoromethyl substituted electron-deficient benzyl group did not give the corresponding dearomatization product **2m**, but hydroarylation products **3m** and **4m** (Scheme 6). These results suggest that the initial formation of intermediate **C** is reversible and the Friedel–Crafts-type reaction of the electron-rich benzyl group proceeds through intermediate **C** to form dearomatization product **2**.



Scheme 6. Platinum-catalyzed reaction of **1m** with a trifluoromethyl substituted electron-deficient benzyl group.

Finally, hydrogenation of dearomatized product **2a** was examined as shown in Scheme 7. Chemoselective hydrogenation of the 1,2-dihydronaphthalene moiety of **2a** proceeded by using Pd/C as a catalyst to give dihydropyrroloisoquinoline derivative **5** in good yield. On the other hand, hydrogenation of both the 1,2-dihydronaphthalene and α,β-unsaturated γ-lactam moieties of **2a** occurred when Pt/C was used as the catalyst to give tetrahydropyrroloisoquinoline derivative **6** in moderate yield as a single diastereomer. From a synthetic point of view, various biologically active multicyclic alkaloids contain hydropyrroloisoquinoline structures.[15] The dearomatization–hydrogenation sequence that forms two C–C



Scheme 7. Hydrogenation of dearomatized product **2a**.

bonds presented herein enables the facile synthesis of interesting new analogues.

In conclusion, we have established that a cationic platinum(II) complex generated in situ catalyzes dearomatization of fused arenes using intramolecular formation of two C–C bonds. The results of the deuterium-labeling studies were consistent with a mechanism involving alkyne activation by the cationic platinum(II) complex, followed by a Friedel–Crafts-type reaction. Future work will focus on asymmetric and/or intermolecular variants of this reaction.

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Keywords: alkynes · arenes · C–C bond formation · dearomatization · platinum

[1] For selected reviews, see: a) L. N. Mander, *Synlett* **1991**, 134; b) A. Pelter, R. S. Ward, *Tetrahedron* **2001**, *57*, 273; c) E. P. Kündig, A. Pape, *Top. Organomet. Chem.* **2004**, *7*, 71; d) W. D. Harman, *Top. Organomet. Chem.* **2004**, *7*, 95; e) S. Quideau, L. Pouységu, D. Deffieux, *Curr. Org. Chem.* **2004**, *8*, 113; f) F. López-Ortiz, M. J. Iglesias, I. Fernández, C. M. Andújar-Sánchez, G. Ruiz-Gómez, *Chem. Rev.* **2007**, *107*, 1580; g) S. Quideau, L. Pouységu, D. Deffieux, *Synlett* **2008**, 467; h) S. P. Roche, J. A. Porco, Jr., *Angew. Chem.* **2011**, *123*, 4154; *Angew. Chem. Int. Ed.* **2011**, *50*, 4068.

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