Angewandte
International Edition Chemie

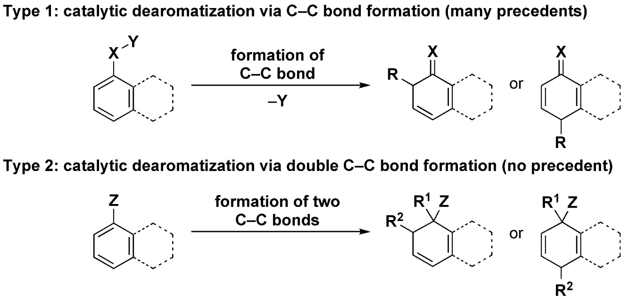
DOI: 10.1002/anie.201202165

Dearomatization Reaction

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

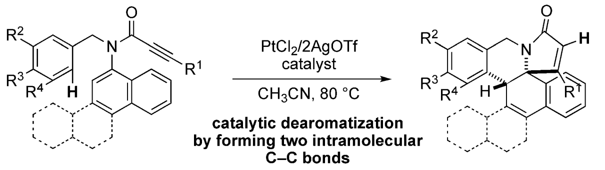
*Tetsuro Shibuya, Keiichi Noguchi, and Ken Tanaka**

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).

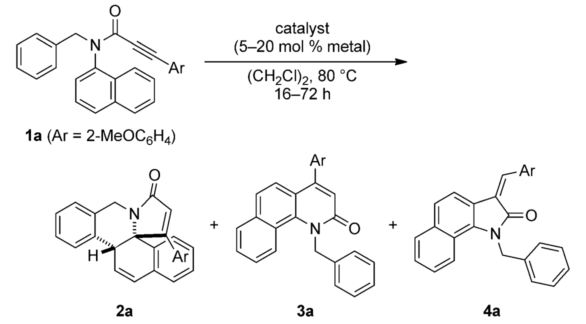
---

[*] T. Shibuya, Prof. Dr. K. Tanaka
Department of Applied Chemistry, Graduate School of Engineering
Tokyo University of Agriculture and Technology
Koganei, Tokyo 184-8588 (Japan)
E-mail: tanaka-k@cc.tuat.ac.jp
Homepage: http://www.tuat.ac.jp/-tanaka-k/
Prof. Dr. K. Noguchi
Instrumentation Analysis Center, Tokyo University of Agriculture and Technology
Koganei, Tokyo 184-8588 (Japan)

[**] This work was supported partly by Grants-in-Aid for Scientific Research (Nos. 23105512 and 20675002) from MEXT (Japan).

Supporting information for this article (experimental details) is available on the WWW under http://dx.doi.org/10.1002/anie.201202165.

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



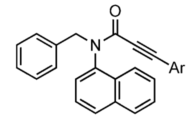
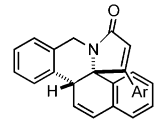
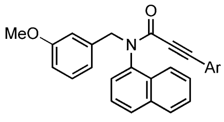
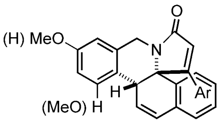
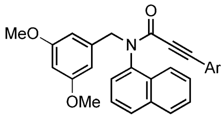
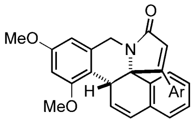
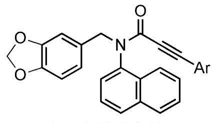
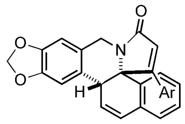
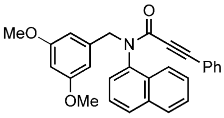
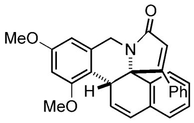
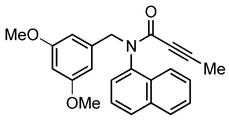
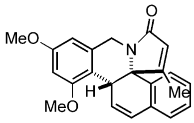
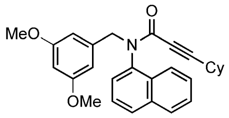
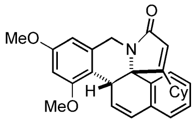
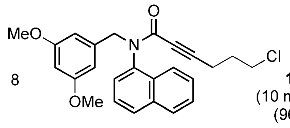
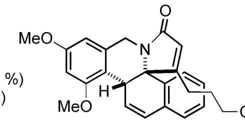
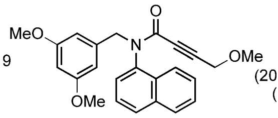
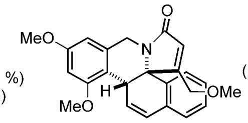
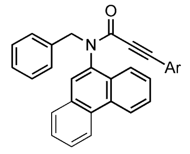
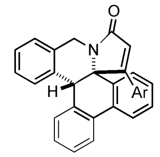
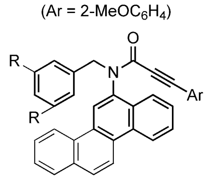
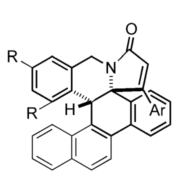
Entry	Ligand	Catalyst [mol %]	Time [h]	Conv. [%]	Yield [%][a]		
					2a	**3a**	**4a**
1	$[Pd(CH_3CN)_4](BF_4)_2$/ binap	20	16	92	0	0	70
2	$AuCl_3$/3 $AgBF_4$	20	16	100	11	13	77
3	$AuCl(SMe_2)/AgBF_4$	20	16	28	7	10	8
4	$AgBF_4$	20	16	19	5	4	5
5	$[Cp^*RhCl_2]_2$/4 $AgBF_4$	20	16	24	5	5	5
6	$PtCl_2$/2 $AgBF_4$	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.

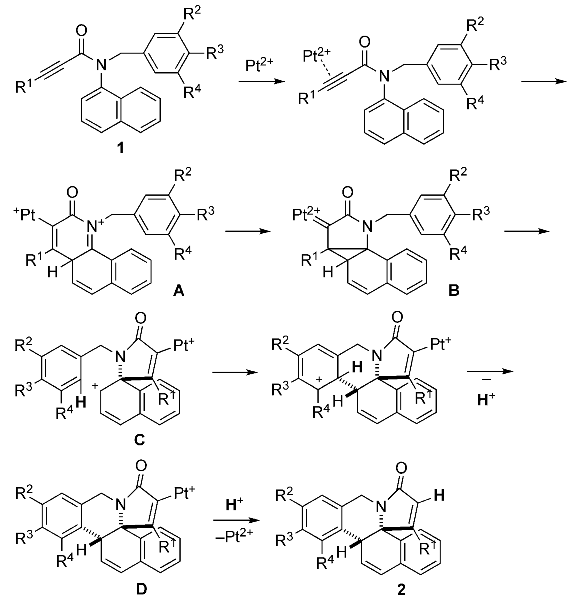
With the conditions optimized, the scope of the platinum(II)-catalyzed dearomatization reactions was examined (Table 2). The reactions of substrates **1b–d** possessing alkoxy-substituted electron-rich benzyl groups (entries 2–4) showed higher reactivity than **1a**, with a nonsubstituted benzyl group (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-aminophenathrene 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	 (Ar = 2-MeOC$_6$H$_4$)	**1a** (5 mol %) (72 h)		**2a** / 69%
2	 (Ar = 2-MeOC$_6$H$_4$)	**1b** (5 mol %) (40 h)		**2b** (**2b′**) / >99% (**2b**/**2b′** = 87:13)
3	 (Ar = 2-MeOC$_6$H$_4$)	**1c** (5 mol %) (40 h)		**2c** / 93%
4	 (Ar = 2-MeOC$_6$H$_4$)	**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	 (Ar = 2-MeOC$_6$H$_4$)	**1j** (5 mol %) (40 h)		**2j** / 56%
11	 (Ar = 2-MeOC$_6$H$_4$)	**1k** (R = H) (5 mol %) (40 h)		**2k** / 93%
12		**1l** (R = OMe) (5 mol %) (16 h)		**2l** / 88%

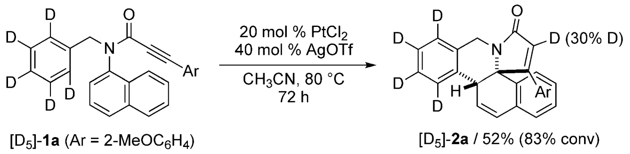
[a] Yield of isolated product. [b] Solvent: CH_3CN. Cp* = C_5Me_5.[a] Reactions were conducted using $PtCl_2$/2AgOTf as a catalyst in CH_3CN at 80 °C. [b] Yield of isolated product. Cy = cyclohexyl.



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.

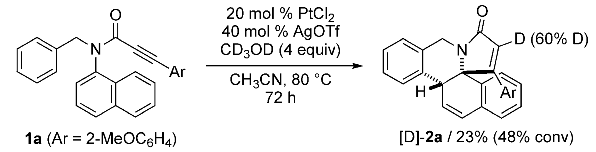
To confirm this deprotonation–protonation sequence, deuterium-labeling studies were conducted. The reaction of deuterated phenyl substituted *N*-(1-naphthyl)propiolamide $[D_5]$-**1a** produced partially deuterated product $[D_5]$-**2a** with selective incorporation of deuterium in the vinylic position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



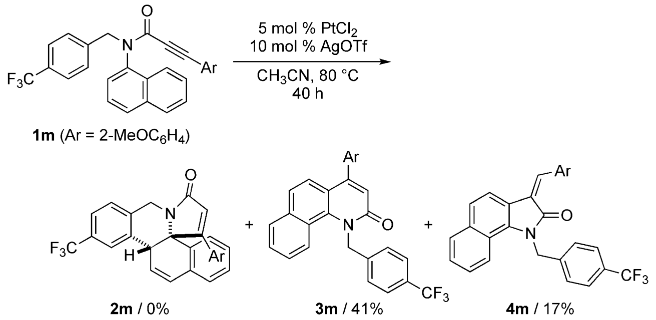
Scheme 4. Platinum-catalyzed reaction of $[D_5]$-**1a**.

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 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**.

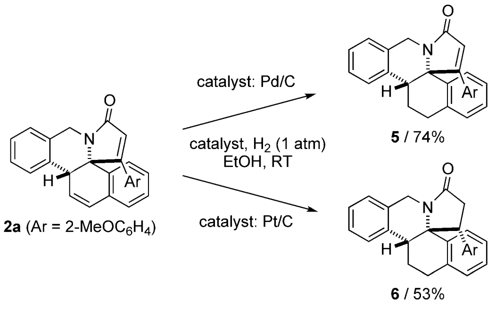


Scheme 5. Platinum-catalyzed reaction of **1a** in the presence of CD_3OD.



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.

Received: March 19, 2012

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.

[2] For selected examples, see: a) S. Wiegand, H. J. Schäfer, *Tetrahedron* **1995**, *51*, 5341; b) T. Nemoto, Y. Ishige, M. Yoshida, Y. Kohno, M. Kanematsu, Y. Hamada, *Org. Lett.* **2010**, *12*, 5020; c) Q.-F. Wu, W.-B. Liu, C.-X. Zhuo, Z.-Q. Rong, K.-Y. Ye, S.-L. You, *Angew. Chem.* **2011**, *123*, 4547; *Angew. Chem. Int. Ed.* **2011**, *50*, 4455.

[3] The chiral hypervalent iodine-mediated asymmetric oxidative dearomatization reactions of phenols and naphthols were reported; see: a) T. Dohi, A. Maruyama, N. Takenaga, K. Senami, Y. Minamitsuji, H. Fujioka, S. B. Caemmerer, Y. Kita, *Angew. Chem.* **2008**, *120*, 3847; *Angew. Chem. Int. Ed.* **2008**, *47*, 3787; b) S. Quideau, G. Lyvinec, M. Marguerit, K. Bathany, A. Ozanne-Beaudenon, T. Buffeteau, D. Cavagnat, A. Chénédé, *Angew. Chem.* **2009**, *121*, 4675; *Angew. Chem. Int. Ed.* **2009**, *48*, 4605; c) J. K. Boppisetti, V. B. Birman, *Org. Lett.* **2009**, *11*, 1221; d) M. Uyanik, T. Yasui, K. Ishihara, *Angew. Chem.* **2010**, *122*, 2221; *Angew. Chem. Int. Ed.* **2010**, *49*, 2175.

[4] J. Garci'a-Fortanet, F. Kessler, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 6676.

[5] a) M. Bao, H. Nakamura, Y. Yamamoto, *J. Am. Chem. Soc.* **2001**, *123*, 759; b) S. Lu, Z. Xu, M. Bao, Y. Yamamoto, *Angew. Chem.* **2008**, *120*, 4438; *Angew. Chem. Int. Ed.* **2008**, *47*, 4366; c) B. Peng, X. Feng, X. Zhang, L. Ji, M. Bao, *Tetrahedron* **2010**, *66*, 6013; d) B. Peng, X. Feng, X. Zhang, S. Zhang, M. Bao, *J. Org. Chem.* **2010**, *75*, 2619; e) B. Peng, S. Zhang, X. Yu, X. Feng, M. Bao, *Org. Lett.* **2011**, *13*, 5402.

[6] For other examples of transition-metal-catalyzed dearomatization reactions, see: a) M. Kimura, M. Futamata, R. Mukai, Y. Tamaru, *J. Am. Chem. Soc.* **2005**, *127*, 4592; b) B. M. Trost, J. Quancard, *J. Am. Chem. Soc.* **2006**, *128*, 6314; c) N. Kagawa, J. P. Malerich, V. H. Rawal, *Org. Lett.* **2008**, *10*, 2381; d) R. B. Bedford, C. P. Butts, M. F. Haddow, R. Osborne, R. F. Sankey, *Chem. Commun.* **2009**, 4832; e) Q.-F. Wu, H. He, W.-B. Liu, S.-L. You, *J. Am. Chem. Soc.* **2010**, *132*, 11418; f) R. B. Bedford, N. Fey, M. F. Haddow, R. F. Sankey, *Chem. Commun.* **2011**, *47*, 3649.

[7] Two non-catalytic examples have been reported. For the dearomatization–bis(alkylation) of naphthalenecarboxylates by way of a reductive generation of aldehyde metal enolates from ketenes, see: a) K. Tomioka, M. Shindo, K. Koga, *J. Org. Chem.* **1990**, *55*, 2276. For the dearomatization–bis(alkylation) of aromatic diesters promoted by Me$_3$SnLi by way of a Stanna–Brook rearrangement, see: b) P. Monje, P. Graña, M. R. Paleo, F. J. Sardina, *Org. Lett.* **2006**, *8*, 951.

[8] a) X. Zhang, R. C. Larock, *J. Am. Chem. Soc.* **2005**, *127*, 12230; b) B.-X. Tang, D.-J. Tang, S. Tang, Q.-F. Yu, Y.-H. Zhang, Y. Liang, P. Zhong, J.-H. Li, *Org. Lett.* **2008**, *10*, 1063; c) Q.-F. Yu, Y.-H. Zhang, Q. Yin, B.-X. Tang, R.-Y. Tang, P. Zhong, J.-H. Li, *J. Org. Chem.* **2008**, *73*, 3658; d) B.-X. Tang, Q. Yin, R.-Y. Tang, J.-H. Li, *J. Org. Chem.* **2008**, *73*, 9008; e) Z.-Q. Wang, B.-X. Tang, H.-P. Zhang, F. Wang, J.-H. Li, *Synthesis* **2009**, 891; f) T. Dohi, D. Kato, R. Hyodo, D. Yamashita, M. Shiro, Y. Kita, *Angew. Chem.* **2011**, *123*, 3868; *Angew. Chem. Int. Ed.* **2011**, *50*, 3784; g) P. R. Likhar, S. S. Racharlawar, M. V. Karkhelikar, M. S. Subhas, B. Sridhar, *Synthesis* **2011**, 2407; h) T. Dohi, T. Nakae, Y. Ishikado, D. Kato, Y. Kita, *Org. Biomol. Chem.* **2011**, *9*, 6899.

[9] T. Shibuya, Y. Shibata, K. Noguchi, K. Tanaka, *Angew. Chem.* **2011**, *123*, 4049; *Angew. Chem. Int. Ed.* **2011**, *50*, 3963.

[10] For our reports of the transition metal-catalyzed 6-*endo* hydroalkenylation of *N*-alkenylpropiolamides, which furnishes 4-aryl-2-pyridones, see: a) H. Imase, K. Tanaka, *Chem. Lett.* **2009**, *38*, 1152; b) H. Imase, T. Suda, Y. Shibata, K. Noguchi, M. Hirano, K. Tanaka, *Org. Lett.* **2009**, *11*, 1805.

[11] For reviews of the transition-metal-catalyzed hydroarylation of alkynes, see: a) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633; b) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077; c) C. Nevado, A. M. Echavarren, *Synthesis* **2005**, 167; d) M. Bandini, E. Emer, S. Tommasi, A. Umani-Ronchi, *Eur. J. Org. Chem.* **2006**, 3527; e) H. C. Shen, *Tetrahedron* **2008**, *64*, 3885; f) R. Skouta, C.-J. Li, *Tetrahedron* **2008**, *64*, 4917; g) T. Kitamura, *Eur. J. Org. Chem.* **2009**, 1111.

[12] The corresponding 6-*endo* hydroarylation product was generated in approximately 20% yield.

[13] CCDC 870055 (**2d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre www.ccdc.cam.ac.uk/data_request/cif.

[14] For reviews on the electrophilic activation of alkynes or alkenes with the platinum catalysts, see: a) S. I. Lee, N. Chatani, *Chem. Commun.* **2009**, 371; b) V. Michelet, P. Y. Toulec, J.-P. Genêt, *Angew. Chem.* **2008**, *120*, 4338; *Angew. Chem. Int. Ed.* **2008**, *47*, 4268; c) S. F. Kirsch, *Synthesis* **2008**, 3183; d) A. R. Chianese, S. J. Lee, M. R. Gagné, *Angew. Chem.* **2007**, *119*, 4118; *Angew. Chem. Int. Ed.* **2007**, *46*, 4042; e) Y. Yamamoto, *J. Org. Chem.* **2007**, *72*, 7817; f) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410; g) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271; h) C. Bruneau, *Angew. Chem.* **2005**, *117*, 2380; *Angew. Chem. Int. Ed.* **2005**, *44*, 2328; i) A. M. Echavarren, C. Nevado, *Chem. Soc. Rev.* **2004**, *33*, 431; j) L. Añorbe, G. Domínguez, J. Pérez-Castells, *Chem. Eur. J.* **2004**, *10*, 4938.

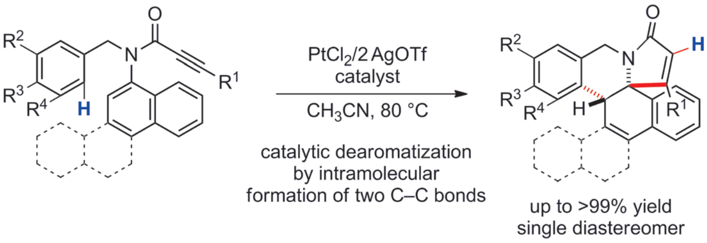
[15] For selected examples, see: a) D. Muroni, M. Mucedda, A. Saba, *Tetrahedron: Asymmetry* **2009**, *20*, 1154; b) L. F. Tietze, H. Braun, P. L. Steck, S. A. A. El Bialy, N. Toelle, A. Duefert, *Tetrahedron* **2007**, *63*, 6437; c) K. Kadlecikova, V. Dalla, S. Marchalin, B. Decroix, P. Baran, *Tetrahedron* **2005**, *61*, 4743; d) C. Bouaucheau, A. Parlier, H. Rudler, *J. Org. Chem.* **1997**, *62*, 7247.

Communications

Dearomatization Reaction

T. Shibuya, K. Noguchi,
K. Tanaka* ________ ■■■■–■■■■

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



The (de)aroma of success: A cationic platinum(II) complex generated in situ catalyzes dearomatization of fused arenes by forming two intramolecular C–C bonds (see scheme). Mechanistic studies reveal that this reaction could proceed through alkyne activation by the cationic platinum(II) complex followed by a Friedel–Crafts-type reaction.