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Intramolecular Cyclization Using Palladium-Catalyzed Arylation toward Formyl and Nitro Groups

Hideaki Muratake [a]* and Hiroshi Nakai [b]

[a] *Research Foundation Itsuu Laboratory, 2-28-10 Tamagawa, Setagaya-ku, Tokyo 158-0094, Japan*
[b] *Shionogi Research Laboratories, Shionogi & Co., Ltd., 5-12-4, Sagisu, Fukushima-ku, Osaka 553-0002, Japan*

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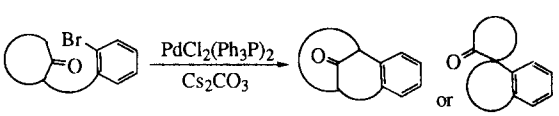
Abstract

Intramolecular arylation of properly designed substrates bearing a formyl or nitro terminating group was achieved employing a $PdCl_2(Ph_3P)_2$—Cs_2CO_3 catalyst system to form various carbocyclic compounds. Arylation toward the formyl group occurred at the α-position (*α-arylation*) or at the carbonyl carbon (*carbonyl-arylation*) depending on the structure of the substrates and on the reaction solvent. The α-arylated secondary nitro group was partially transformed to ketone, whereas the tertiary nitro group was partially eliminated to a styrene type of olefin.

Keywords: Aldehydes; Arylation; Nitro compounds; Palladium and compounds

While a great number of palladium-catalyzed arylation and vinylation reactions have been investigated, most of which involve olefins (Heck reaction [1]), organo-tin compounds (Stille reaction [2]), or organo-borane compounds (Suzuki reaction [3]) as terminators. Exploitation of other functional groups as the terminator is expected to enable expanded application. Recently, intermolecular palladium-catalyzed α-arylation reactions of ketone were reported by several groups [4–6]. Independently, we also reported its intramolecular version to form benzene-annulated bridged- and spirocycloalkanones employing a $PdCl_2(Ph_3P)_2$–Cs_2CO_3 catalyst system (**1**→**2**, **3**) (Scheme 1) [7].



1 Scheme 1 2 3

In this communication, we describe an extension of the above intramolecular $PdCl_2(Ph_3P)_2$–Cs_2CO_3 catalyzed arylation reaction to formyl and nitro terminating groups, constructing various types of carbocyclic compounds which are anticipated to serve as useful intermediates for the synthesis of natural products, including terpenes. Related γ-arylation of α,β-unsaturated aldehyde and benzylic arylation of 4-alkylnitrobenzene were reported by Miura *et al.* [8]. Pinhey *et al.* reported an α-arylation reaction of nitroalkanes with aryllead triacetate [9].

At the outset, several substrates bearing a formyl terminating group (**4a,b**; **7a,b**; **10**; **13** and **16**) were prepared,[1] and were subjected to the cyclization employing 10 mol% of $PdCl_2(Ph_3P)_2$ [2] and 3 eq. of Cs_2CO_3 [3] (Scheme 2). The following points were clarified.

(1) Arylation toward the formyl group took place at the α-position (*α-arylation*) to form **5**; **8a,b**; **11a,b**; **14** and **17** or at the carbonyl carbon (*carbonyl-arylation*) to form **6a,b**; **9a,b**; **12a,b** and

[1] Preparation of the substrates will be reported in due course in a full paper.

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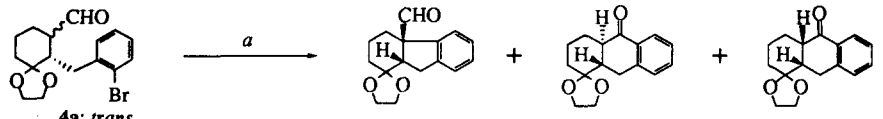
(Entry 1–4)

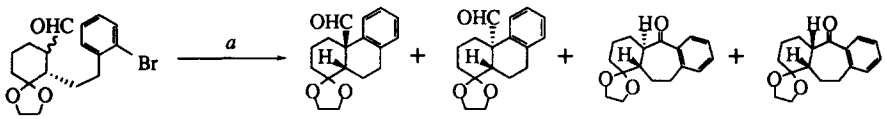


4a: *trans*
4b: *cis*

5 **6a** **6b**

Entry	Substrate	Solvent	Temp.	Time (h)	Products (yield %)		
1	**4a**	toluene	reflux	5	—	76	11
2	**4a**	THF	100°C [b]	24	**5+6a** [c] (46, 1:1.7)		9
3	**4b**	toluene	reflux	6	**5+6a** [c] (45, 1:2.5)		17
4	**4b**	THF	100°C [b]	22	**5+6a** [c] (50, 1:1.6)		10

(Entry 5–8)

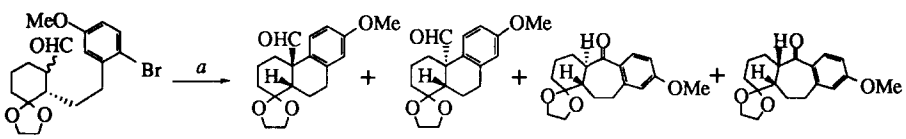


7a: *trans*
7b: *cis*

8a **8b** **9a** **9b**

Entry	Substrate	Solvent	Temp.	Time (h)				
5	**7a**	toluene	reflux	3	49	4	22	—
6	**7a**	THF	100°C [b]	3	52	9	—	—
7	**7b**	toluene	reflux	3	52	22	trace	6
8	**7b**	THF	100°C [b]	3	48	7	—	—

(Entry 9, 10)

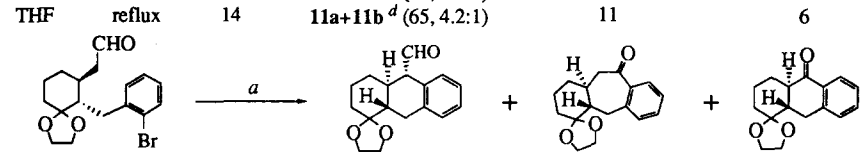


10: *trans* / *cis* = 2.2

11a **11b** **12a** **12b**

Entry	Solvent	Temp.	Time (h)			
9	toluene	reflux	3.5	**11a+11b** [d] (14, 7.5:1)	34	10
10	THF	reflux	14	**11a+11b** [d] (65, 4.2:1)	11	6

(Entry 11, 12)

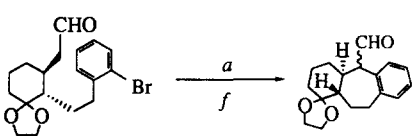


13

14 [e] **15** **6a**

Entry	Solvent	Temp.	Time (h)			
11	toluene	reflux	1.5	32	23	—
12	THF	reflux	14	—	23	30

(Entry 13)



16

17 [e] 40%

a : All reactions were carried out with $PdCl_2(Ph_3P)_2$ (10 mol%) and Cs_2CO_3 (3 eq).
b : The reaction was heated in a sealed tube.
c : Inseparable mixture; separated and characterized after reduction with $NaBH_4$.
d : The ratios were determined by GC.
e : Isolated and characterized after reduction with $NaBH_4$.
f : The reaction was executed in refluxing toluene for 4 h.

Scheme 2

[2] Under the standard Heck reaction conditions using tertiary amine as the base, no reaction other than epimerization of the formyl group occurred. For example, attempted cyclization of **4a** with $Pd(OAc)_2$ (10 mol%), P(*o*-tol)$_3$ (25 mol%) and *i*-Pr_2NEt (1.5 eq) in toluene under reflux for 17 h resulted in formation of the epimer **4b** (14%) along with recovery of **4a** (41%).

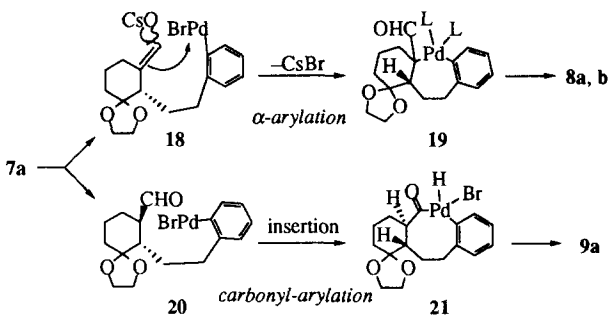
[3] Use of stronger bases such as NaH, $(TMS)_2NK$ or *tert*-BuONa resulted in considerably lower yields. For example, on treatment of **10** with $PdCl_2(Ph_3P)_2$ (10 mol%), $(TMS)_2NK$ (5 eq) in THF under reflux for 15 h, a mixture of **11a+11b** (20:1) (41%) was obtained, where the stereoselection of *cis* **11a** to *trans* **11b** was much higher than that with Cs_2CO_3.

15, depending on the reaction solvent. Thus, when the cyclization reaction was carried out in THF, the *α-arylation* tended to increase. On the other hand, the *carbonyl-arylation* increased in toluene (entry 2 *vs* 1, 6 *vs* 5, 8 *vs* 7 and 10 *vs* 9).

(2) There was no significant difference between the products from a *trans* or *cis* substrate in THF (entry 2 *vs* 4 and 6 *vs* 8), whereas the products in toluene reflected the configuration of the starting material to some extent (entry 1 *vs* 3 and 5 *vs* 7).

(3) A six-membered ring was formed in preference to five- and seven-membered rings. Thus, even in THF solvent, six-membered *carbonyl-arylation* products **6a,b** were the major products from the substrates **4a,b** (entry 2 and 4). Furthermore, six-membered *α-arylation* products **8a,b** were formed preferentially from **7a,b** in toluene (entry 5 and 7). On the other hand, in the case of the substrate **10** having a methoxy group on the benzene ring, the used solvent exerted a greater influence upon the products; seven-membered *carbonyl-arylation* products **12a,b** were obtained as major products in toluene (entry 9).

These results are attributable to fast enolization of the formyl group with Cs_2CO_3 in a more polar solvent, THF, giving intermediates **18** and **19** for the *α-arylation* products from **7a**, for example (entry 6)(Scheme 3). On the other hand, the enolization is so slow in the less polar solvent, toluene, that the *carbonyl-arylation* products were formed through intermediates **20** and **21** (entry 5). There is a precedent reporting insertion of a σ-arylpalladium(II) complex to the formyl C-H bond [10].



Scheme 3

The mechanism for the formation of a deformylated byproduct **6a** (entry 12) is unclear at this moment. The *α-arylation* products **14** and **17** (entry 11 and 13) were isolated as their reduction products with $NaBH_4$ due to their difficulty for purification, since the α-arylated secondary aldehydes partially exist as the enol form. A mixture of **11a+11b** partially crystallized on standing and repeated recrystallization from CH_2Cl_2–hexane afforded **11a** (mp. 130–131°C), whose structure was unequivocally confirmed by single crystal X-ray analysis (Figure 1).[4, 5]

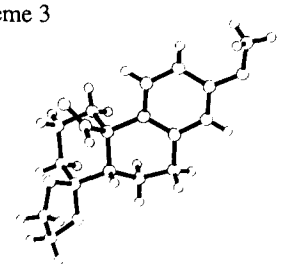


Figure 1. ORTEP diagram of **11a**

Next, we turned our attention to the intramolecular α-arylation of a nitro terminating group. As the α-position of nitroalkane is acidic enough to generate a salt with Cs_2CO_3 even in a non-polar solvent, the resulting cesium salt is expected to cyclize to an intramolecular arylpalladium species. Several nitro substrates (**22a,b**; **24a,b**; **27a,b**; **31** and **33**) were synthesized,[1] and the cyclization was carried out as above. The following results were obtained from entries 1–8 (Scheme 4).[5]

(1) Cyclization of the simple substrates **22a,b** afforded bicyclic α-tetralone (**23a**) and **23b** only in moderate yields (entry 1 and 2). In contrast, stereochemically more restricted substrates **24a,b**; **27a,b** and **33** gave tricyclic products in high combined yields, around 90% (entry 3–6 and 8).

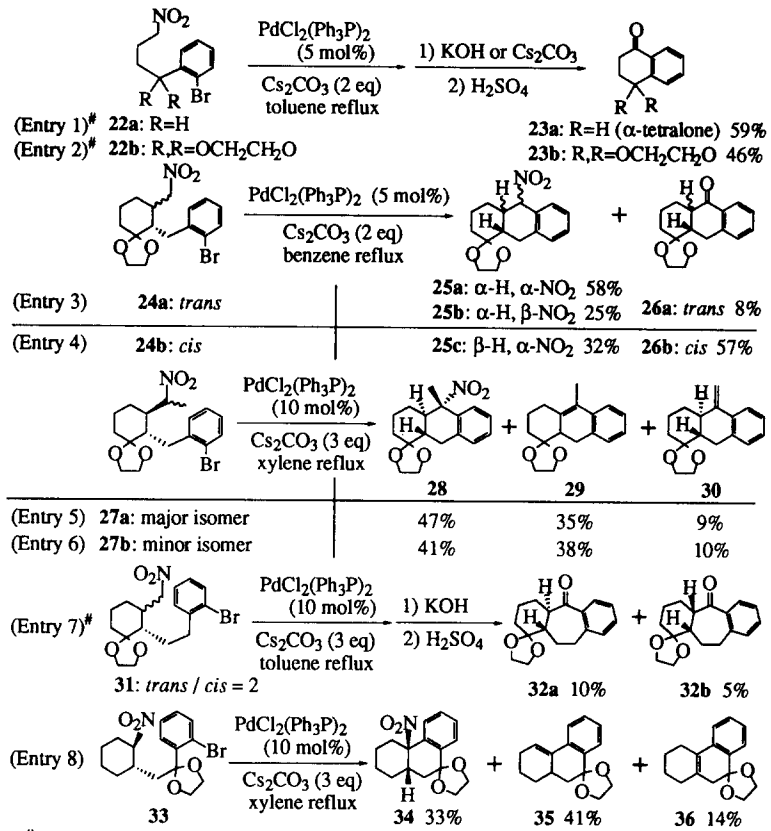
(2) Primary nitro derivatives cyclized readily at the temperature of benzene reflux (entry 3 and 4), whereas

[4] Crystal data for **11a**: $C_{18}H_{22}O_4$, MW=302.37, monoclinic, space group $P2_1/c$, a =17.395 (3) Å, b =7.419 (2) Å, c =11.989 (2) Å, β =98.80 (1)°, V=1529.0 (5) Å^3, molecules / cell = 4, d_{calcd} =1.313 gcm^{-3}.

[5] All new compounds gave satisfactory analytical (microanalysis and/or high resolution mass spectrometry) and spectral data.

secondary ones required an elevated temperature (entry 5, 6 and 8).

(3) The secondary nitro group of the products was partially transformed into the ketone group (entry 1, 2, 3, 4 and 7) to form **23a,b**; **26a,b** and **32a,b**, and the tertiary nitro group was partially eliminated to a styrene type of olefin (entry 5, 6 and 8) to form **29**, **30**, **35** and **36**.



The products were isolated as ketones with 1) KOH or Cs_2CO_3, 2) H_2SO_4, since initially formed nitro derivatives were gradually converted to the ketone derivatives during purification on silica gel.

Scheme 4

In summary, the formyl and nitro groups were found to function as efficient terminators in the intramolecular $PdCl_2(Ph_3P)_2$–Cs_2CO_3 catalyzed arylation reaction to form various carbocyclic compounds. The *α-arylation* of the formyl group presents a useful tool for preparation of the compounds bearing an angular formyl group such as **5**; **8a,b** and **11a,b**. The *carbonyl-arylation* of the formyl group and the α-arylation of the nitro group would be evaluated as weak basic intramolecular acylation methods which take the place of the strongly acidic Friedel-Crafts acylation.

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