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Palladium-Catalyzed Intramolecular α-Arylation of Aliphatic Ketones

Hideaki Muratake* and Mitsutaka Natsume*

Research Foundation Itsuu Laboratory
2-28-10 Tamagawa, Setagaya-ku, Tokyo 158, Japan

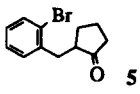
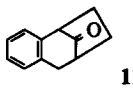
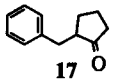
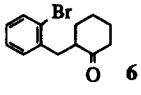
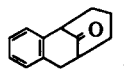
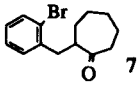
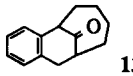
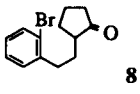
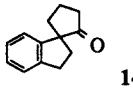
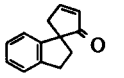
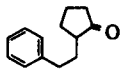
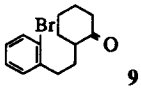
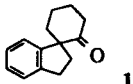
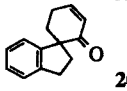
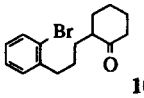
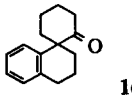
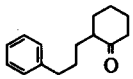
Abstract: Cyclization reaction of **5** — **10** using 10 mol% of $PdCl_2(Ph_3P)_2$ in the presence of 3 eq. of Cs_2CO_3 in hot THF or toluene afforded bridged or spiro compounds **11** — **16** in good to modest yields.

In the preceding paper, we reported a new procedure for preparation of heteroaromatic phenol derivatives using a palladium-catalyzed intramolecular cyclization reaction of **1** to form **2**.[1] This reaction comprizes a coupling reaction between an aryltriflate and a methyl ketone functionality, and *per se* constitutes an intramolecular version of the α-arylation reaction of alphatic ketones, which has been widely studied.[2,3] In view of the high yield conversion of **1** to **2**, we started extensive studies to explore applicability of our reaction conditions to a general reaction, **3** to **4**. In the literatures, these types of intramoleculer reactions were reported by Sakan,[2a] Semmelhack,[2b, 2c] and most recently by Snider and co-workers.[2p]

1 **2** **3** **4**

For the cyclization reaction of **5** – **10** (Table), suitable conditions were found to be heating of a substrate in toluene or THF in the presence of 10 mol% of $PdCl_2(Ph_3P)_2$ and 3 eq. of Cs_2CO_3 under an Ar atmosphere. Addition of Ph_3P was unneccesary. 2-Bromobenzyl-substituted cycloalkanones **5**, **6**, and **7** afforded bridged compounds **11**, **12**, and **13**, whereas cycloalkanones **8** – **10** having 2-bromophenethyl and 3-(2-bromophenyl)-propyl substituents afforded spiro derivatives **14** – **16**. Among these reaction products, **12**,[4] **13**, **14**, and **15** were obtained in good yields (entries 2, 3, 4, and 5). When the reaction gave the products **11**[5] and **16** in only modest yields, considerable amounts of debromo compounds **17** and **21** were produced as by-products (entries 1 and 6). Occasionaly enones **18** and **20** were obtained in trace amounts as by-products. Probably these were formed by palladium-catalyzed dehydrogenation of the ketone derivatives. In entries 1 and 4, inseparable reaction mixtures of **11** and **17**, and **14** and **19** were once converted into mixtures of ethylene acetals, followed by separation and acid hydrolysis to give pure **11** and **14**. Generally speaking, our reaction conditions using a palladium catalyst and Cs_2CO_3 worked well for the cyclization of **3** to **4**.

Table Cylization Reaction with 10 mol% $PdCl_2(Ph_3P)_2$ and 3 eq. of Cs_2CO_3 under Ar Atmosphere

Entry	Substrate	Solvent	Temp.	Time	Product	Yield	By-product	Yield
1	 5	THF[a]	100°C	16 h	 11	26%	 17	19%
2	 6	THF[a]	100°C	13 h	 12[b]	83%		
3	 7	THF[a]	100°C	14 h	 13[b]	61%		
4	 8	THF[a]	100°C	14 h	 14	71%	 18 2%	 19 2%
5	 9	toluene	reflux	12 h	 15	57%	 20	4%
6	 10	THF[a]	100°C	14 h	 16	35%	 21	29%

a : In a sealed tube. *b* : Contained trace amounts (less than 2%) of inseparable contaminants.

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