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The first samarium(II)-mediated aryl radical cyclisation onto an aromatic ring

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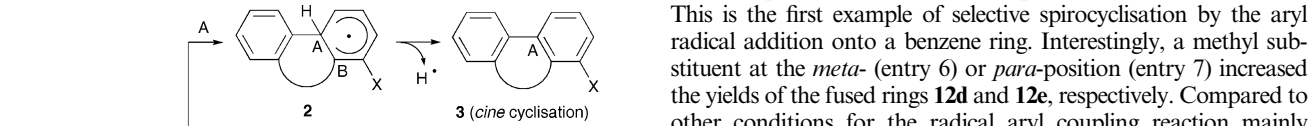
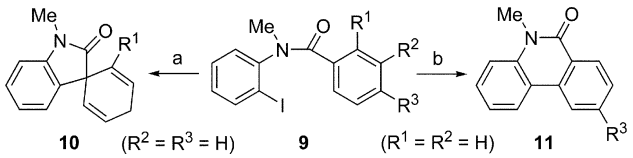
Intramolecular arylation of aryl radicals was mediated by SmI_2/HMPA in the presence of *i*-PrOH to give spirocycles and/or reduced *cine*-cyclised products, while the reaction in the absence of *i*-PrOH gave the rearomatised fused rings.

Aryl radical addition onto an aromatic ring has become an important tool in organic synthesis. The traditional method is heavy metal-mediated oxidative radical arylation of arenes through the cation radical intermediates, which is a useful procedure for the biaryl coupling of electron-rich arenes.[1] Recently, intramolecular reductive radical arylation using Bu_3SnH or other hydrogen sources has been extensively studied. As shown in Scheme 1, the intramolecular addition of aryl radical **1** can take place at three different carbons (A, B, and C). (1) The reaction at the carbon A forms the cyclohexadienyl radical intermediate **2**, which was converted into the fused ring **3** by hydrogen abstraction.[2,3] (2) Attack at the carbon B generates the unstable spirocyclohexadienyl radical intermediate **4**, which easily undergoes aryl migration to give **5**.[4] Otherwise, the intermediate **4** was trapped to give the spirocyclic compounds such as **6**.[5] (3) Attack of the aryl radical at the carbon C followed by elimination of the X radical gives the cyclised product **8**.[6] In some cases, the intramolecular radical arylation suffers from low regioselectivity of the radical addition.[7]

Recently, synthesis of spirocycles has attracted a great deal of attention due to their unique molecular structure and diverse biological activities.[8] In our ongoing study on samarium(II)-mediated[9] cyclisation reaction onto an aromatic ring,[10,11] we planned to synthesize the spirocycles by radical aryl coupling. Generally, the aryl radical cyclisation onto an aromatic ring to form spirocycles such as **6** is extremely difficult, producing a considerable amount of the *cine*-cyclisation product **3**,[5] except for the reaction of indole derivatives.[12] This is presumably due to both the instability of spirocyclohexadienyl radical intermediate **4** and the reversible nature of the radical addition. In some cases, the unstable intermediate **4** rearranges to a fused-ring radical such as **2** or **7**.[2,4c] Based on our previous results, we expected that samarium(II) iodide would effectively trap the intermediate **4** by single electron transfer, which could realize the spirocyclisation. In this communication, we report a selective synthesis of spirocycles **10** and fused rings **11** mediated by samarium(II) iodide, by simply changing the substrate structure and reaction conditions (Scheme 2). This is the first example of samarium(II)-mediated arylation of aryl radicals.



Scheme 1 Intramolecular addition of aryl radical **1** onto an aromatic ring.



Scheme 2 Reaction conditions: (a) SmI_2, HMPA, *i*-PrOH, THF, −35 °C; (b) SmI_2, HMPA, THF, 0 °C.

We prepared various aryl radical precursors and investigated the samarium(II)-mediated intramolecular biaryl coupling reaction. First, we examined the reaction of 2-iodophenyl benzoate or *N*-(2-iodophenyl)benzamide with SmI_2/HMPA and obtained a complex mixture of unidentified products. However, we found that treatment of *N*-methylbenzamide derivative **9a** with SmI_2 and HMPA in the presence of *i*-PrOH (2 equiv.) gave spirocycle **10a** in 34% yield (Table 1, entry 1). Although increased loading of *i*-PrOH (20 equiv., entry 2) or lowering of the reaction temperature to −35 °C (entry 3) was not effective for improvement of the yield of spirocycle **10a**, a considerable amount of the reduced fused ring **12a** was obtained in both cases (28% and 30% yield, respectively). In contrast, the radical coupling reaction of the corresponding *ortho*-substituted analogues **9b** (entry 4) and **9c** (entry 5) afforded high yields of spirocycles **10b** and **10c**, respectively, in good selectivities. This is the first example of selective spirocyclisation by the aryl radical addition onto a benzene ring. Interestingly, a methyl substituent at the *meta*- (entry 6) or *para*-position (entry 7) increased the yields of the fused rings **12d** and **12e**, respectively. Compared to other conditions for the radical aryl coupling reaction mainly yielding biaryl products,[2–7] formation of the spirocycles **10** and fused rings **12** with a loss of aromaticity is a unique reactivity of the SmI_2/HMPA/*i*-PrOH system. When the reaction of **9a–e** was conducted in the absence of *i*-PrOH, the biaryl coupling products **11a–e** were selectively obtained in low to moderate yields (entries 8–12). For a reason that is unclear, the *para*-substituted benzamide derivative **9e** showed the best result affording the biaryl product **11e** in 60% yield, without producing other cyclised products (entry 12). This type of intramolecular radical biaryl coupling is also promoted by Bu_3SnH or other reagents;[2] however, it is extremely interesting that the cyclisation mode can be completely controlled by changing the reaction conditions and the substituent pattern (compare entries 4 and 5 *vs.* 12).

A plausible mechanism for the samarium(II)-mediated radical aryl coupling reaction is shown in Scheme 3. Single electron transfer (SET) to the iodide **9** by SmI_2 generates the aryl radical **13**, which would cyclise into the spirohexadienyl radical intermediate

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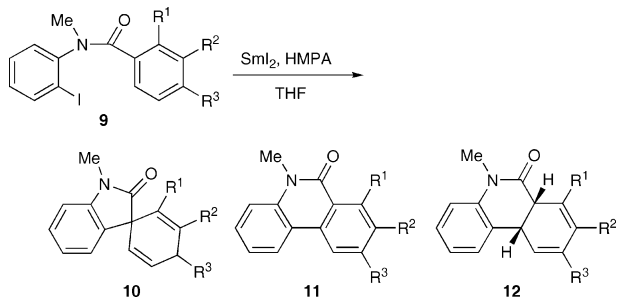
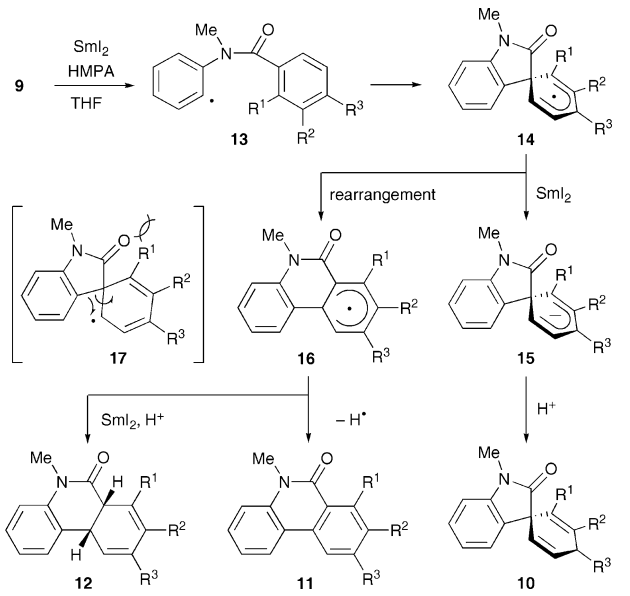
Table 1 Samarium(II)-mediated aryl coupling reaction[a]



Entry	Substrate	R^1	R^2	R^3	*i*-PrOH (equiv.)	*T*/°C	Product yield (%) 10	11	12
1	**9a**	H	H	H	2	0	34	0	trace
2	**9a**	H	H	H	20	0	39	0	28
3	**9a**	H	H	H	2	−35	36	0	30
4	**9b**	Me	H	H	2	−35	89	0	6
5	**9c**	OMe	H	H	2	−35	89	0	9
6	**9d**	H	Me	H	2	−35	29	0	65
7	**9e**	H	H	Me	2	−35	31	0	53[b]
8	**9a**	H	H	H	0	0	0	26	0
9	**9b**	Me	H	H	0	0	0	26	0
10	**9c**	OMe	H	H	0	0	0	15	0
11	**9d**	H	Me	H	0	0	0	29[c]	0
12	**9e**	H	H	Me	0	0	0	60	0

[a] All the reactions were carried out in THF using SmI_2 (5 equiv.) and HMPA (18 equiv.). [b] Obtained as a mixture of regioisomers (1:1). [c] Obtained as a mixture of regioisomers (2:1).



Scheme 3 A plausible mechanistic pathway.

14. Further SET by SmI_2 and the protonation of the resulting cyclohexadienyl anion **15** by *i*-PrOH affords the spirocyclic 1,4-cyclohexadiene **10**. In contrast, rearrangement of the unstable intermediate **14** to the fused ring **16** followed by SET and the subsequent protonation would give the reduced fused ring **12**, while, in the absence of *i*-PrOH, the hydrogen abstraction from **16** yields aromatized product **11**. The presence of *i*-PrOH would promote the SET to **16**, by trapping the anionic intermediate.[11b] When the *ortho*-substituted benzamide derivatives **9b** and **9c** (R^1=Me or OMe) were used, the spirocycles **10b** and **10c** were selectively obtained (entries 4 and 5, Table 1). This is presumably due to the unfavourable steric interaction in the rearrangement of **14** to **16** as shown in the structure **17**, which provides more time to **14** for the SET and the subsequent protonation without rearrangement to **16**.

In conclusion, we have demonstrated a reductive cyclisation of aryl radicals onto an aromatic ring mediated by SmI_2/HMPA in the presence of *i*-PrOH. This is the first example of the highly selective synthesis of spirocycles by the aryl radical addition onto a benzene ring.

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