Pergamon

Tetrahedron Letters 42 (2001) 961–964

TETRAHEDRON LETTERS

A new cascade radical reaction for the synthesis of biaryls and triaryls from benzyl iodoaryl ethers

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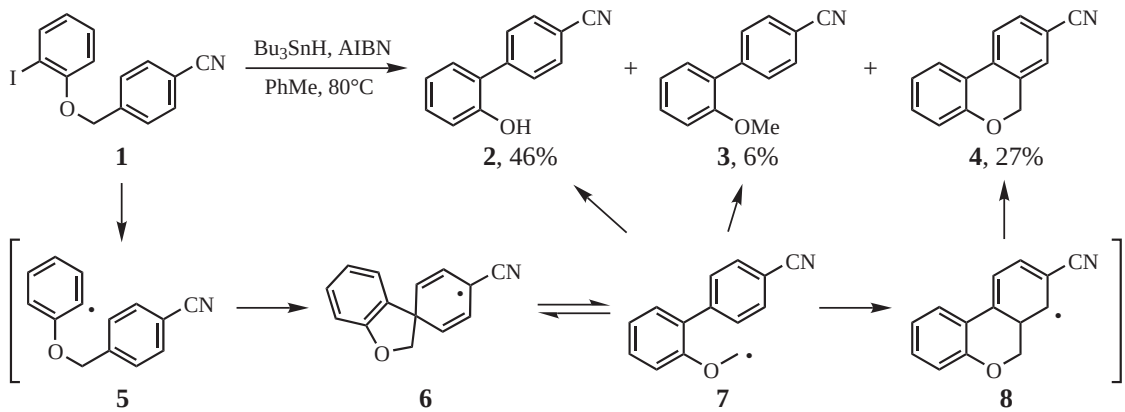
Received 20 October 2000; accepted 15 November 2000

Abstract—The paper describes a new method of synthesizing biaryls and triaryls through an intramolecular *ipso*-substitution reaction initiated by the addition of an aryl radical to a benzyl ether. A tandem variant of the reaction has also been demonstrated. A short synthesis of isoaucuparin **27**, a natural product found in the sapwood tissue of *Sorbus aucuparia*, is also described.

Intramolecular radical additions to arenes often proceed at a useful rate yet generally give rise to complex product mixtures.[1] Buoyed by our successful addition of an aryl radical to a pyridine during a synthesis of the alkaloid toddaquinoline, we decided to investigate further processes involving radical additions to arenes.[2] One such study, in which intramolecular additions of aryl radicals to benzyl ethers were examined, has uncovered some intriguing substitution reactions leading to biaryls.[3] In this Letter we present a number of key observations.

The first substrate examined was benzyl ether **1** which, on treatment with tributyltin hydride under standard radical forming conditions, unexpectedly gave phenol **2** as the major product in 46% yield (Scheme 1). Two minor components, methyl ether **3** and 8-cyanobenzo[*c*]chromene **4**,[4] were also furnished in 6% and 27% yield, respectively. We presume that the reaction proceeds via a 5-*exo*-trig cyclisation of **5**. The resulting spirocycle **6** next fragments to **7** to re-establish the aromatic ring. At this juncture many processes compete. A hydrogen atom abstraction from tributyltin hydride gives methyl ether **3**. The radical intermediate **7** may also add to the arene: a 5-*exo*-trig cyclisation leading back to spirocycle **6** while the slower 6-*endo*/*exo*-trig course to **8** ultimately gives benzo[*c*]chromene **4**.[4] The fragmentation process leading to phenol **2** is



Scheme 1.

Keywords: radicals and radical reactions; natural products; aromatic chemistry; cascade reactions.
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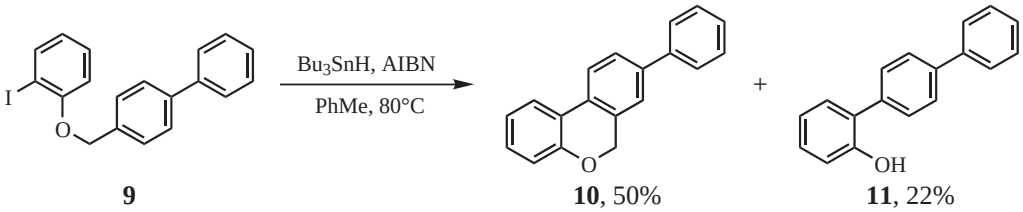
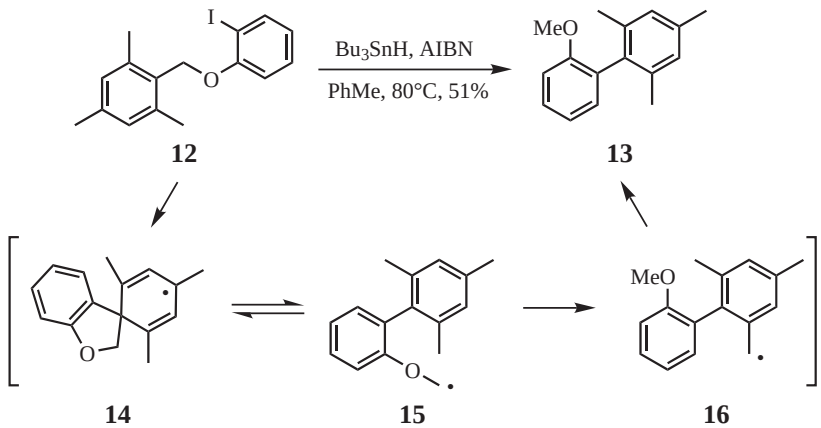
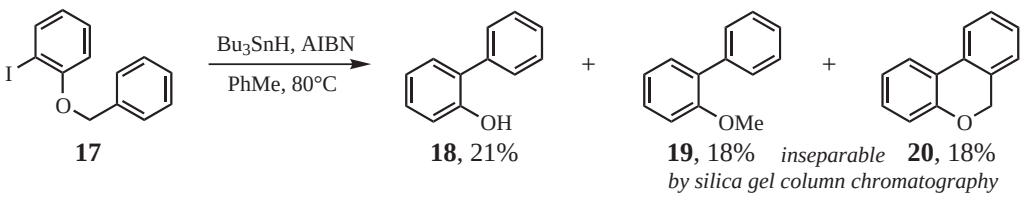


Scheme 2.



Scheme 3.



Scheme 4.

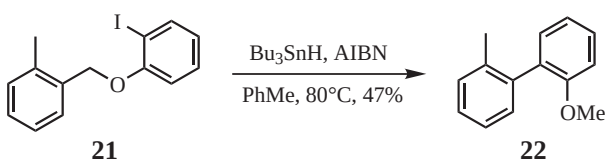
less easily rationalized and its formation is the subject of further investigation.[5] Presumably a redox reaction between **7** and a stannane, or an intermolecular quench giving rise to a carbon to heteroatom bond, is involved.

Several examples of the reaction have been realized. For electron deficient arenes the phenol generally predominates while for the biaryl benzyl ether **9** the major product formed was benzo[*c*]chromene **10** (50%). In this case phenol **11** accounted for 22% of the mass balance (Scheme 2). Blocking the 6-*endo*-trig cyclisation pathway with two *ortho*-methyl substituents also changed the course of the reaction. Thus, exposure of 2,4,6-trimethylbenzyl ether **12** to tributyltin hydride under standard radical forming conditions gave methyl ether **13** in good yield. In this case we believe that the intermediate methylene radical **15** first abstracts a hydrogen atom from a proximal methyl group to give **16** which is then quenched by tributyltin hydride (Scheme 3).

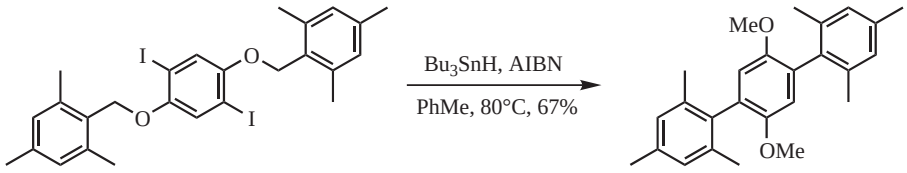
Intramolecular hydrogen atom abstraction [akin to **15→16**] is presumed to operate when one *ortho*-methyl substituent is present on the benzyl ether. Thus, while benzyl ether **17** gave rise to a complex mixture of products including phenol **18**, methyl ether **19** and benzo[*c*]chromene **20** (Scheme 4), the *o*-tolyl ether **21** provided biaryl methyl ether **22** as the major product in 47% yield (Scheme 5).

A remarkable tandem variant of this cascade sequence has also been uncovered. Thus, when applied to diiodide **23** the terphenyl **24** was given in 67% yield (Scheme 6).

Likewise, the reaction has been applied to the synthesis of isoaucuparin **27**, a natural product found in the sapwood tissue of *Sorbus aucuparia* (Scheme 7).[6] Simply exposing dimethoxybenzyl ether **25** to tributyltin hydride under standard radical forming conditions gave benzo[*c*]chromene **26** as the major product together

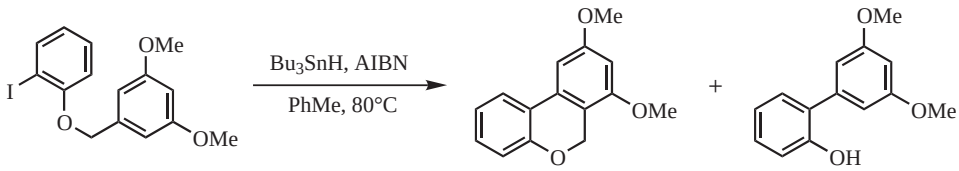


Scheme 5.



23 **24**

Scheme 6.



25 **26**, 40% **27**, 22% *isoaucuparin*

Scheme 7.

with isoaucuparin **27**.[4] That this was the only phenol observed in the product mixture is notable from a mechanistic standpoint.

In conclusion, we have uncovered a new method of synthesizing biaryls and triaryls through an intramolecular *ipso*-substitution reaction initiated by the addition of an aryl radical to a benzyl ether. A tandem variant of the reaction has also been demonstrated, as has the method's utility in target synthesis. We are presently investigating further extensions of the reaction and are seeking to apply it in some more demanding total synthesis programs.

Acknowledgements

The authors thank Pfizer Global Research and Development and the EPSRC for their financial support through an Industrial CASE award (to MITN) and a Quota studentship (to NAN).

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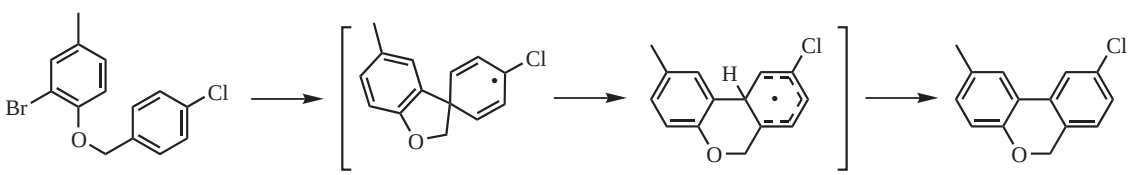
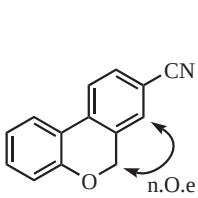
3. For related radical *ipso*-substitution reactions developed within our group, see (a) Harrowven, D. C.; Browne, R. *Tetrahedron Lett*. **1995**, *36*, 2861; (b) Harrowven, D. C.; Browne, R. *Tetrahedron Lett*. **1993**, *34*, 5653.
4. The synthesis of benzo[*c*]chromenones from benzyl bromoaryl ethers (**28**→**31**) has recently been described: Bowman, W. R.; Mann, E.; Parr, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2991. The mechanism proposed to account for this observation involved 5-*exo* cyclisation (**28**→**29**) followed by a neophyl rearrangement (**29**→**30**).
As aryl iodide **1** and **9,** respectively provide benzo[*c*]chromenones **4** and **10** rather than benzo[*c*]chromenones **32** and **33** [NOE studies showing enhance-



28 **29** **30** **31**



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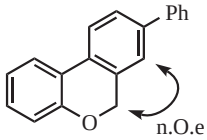

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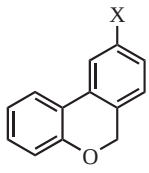
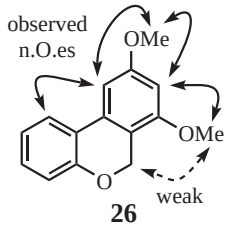


32 X = CN
33 X = Ph



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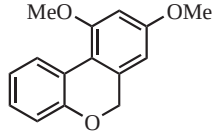

34

ment of an aromatic singlet on irradiation of the OCH_2 signal] the course outlined in Scheme 1 is implicated. The identity of **26** has likewise been confirmed by NOE (GOSEY) experiments, providing further evidence in favour of the sequential 5-*exo* cyclisation–fragmentation–6-*endo*/*exo* cyclisation mechanism (a neophyl rearrangement would give **34**).

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