Synthesis of Nafoxidine via Copper-Catalyzed Carboarylation

**Significance:** Nafoxidine is a nonsteroidal anti-estrogenic agent. The synthesis depicted features a copper-catalyzed alkyne carboarylation initiated through activation of diphenyliodonium triflate (B). The resultant catalytically generated aromatic electrophile equivalent reacts with the electron-rich alkyne A to form a stabilized trisubstituted vinyl cation type intermediate C that then undergoes a regioselective intramolecular Friedel–Crafts reaction to afford the dihydronaphthalene E preferentially.

**Comment:** The scope of the carboarylation was explored via 31 examples, 28 of which were successful. The electronic requirements for the substituent on the alkyne were more rigid: It is essential to have a group capable of stabilizing the vinyl cation. Unsymmetrical analogues of the iodonium triflate B bearing a substituted arene and a mesityl group transferred the arene selectively. One example of an intermolecular carboarylation is described.

**SYNFACTS Contributors:** Philip Kocienski

**SYNFACTS** is a product of Thieme and is protected by copyright.

*CATALOGUE OF THE MONTH*

**Category**
Synthesis of Natural Products and Potential Drugs

**Key words**
nafoxidine  
copper-catalyzed carboarylation  
diaryliodonium triflates  
alkynes  
vinyl cations