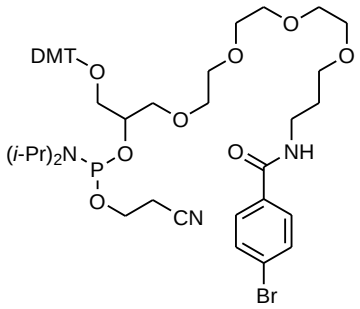
Cross-Coupler CEP
Product No. BA 0322
Product Information

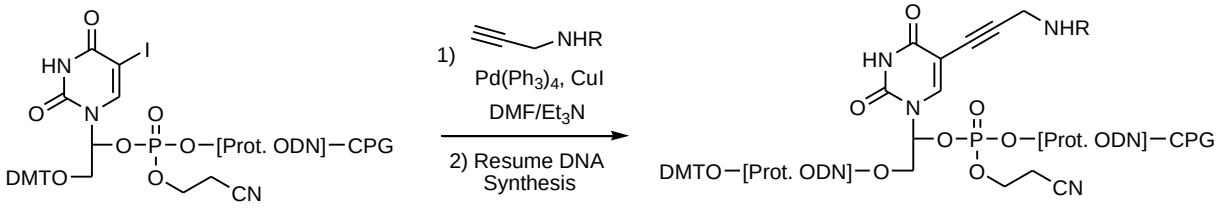


$C_{49}H_{65}BrN_3O_{10}P$
Mol. Wt.: 966.93

May be used for the installation of a p-bromocarboxamide into an oligonucleotide internally or at the 5'-terminus. Potentially useful for the site-specific modification of an oligonucleotide via transition metal-mediated cross-coupling.

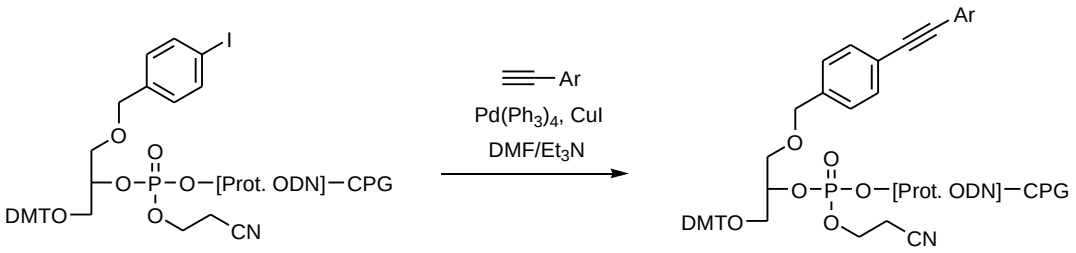
Introduction: While solid-phase synthesis using phosphoramidites is a direct way to incorporate modifications into oligonucleotides, in some cases post-synthetic modification may be advantageous. A popular example is the acylation of amine-modified oligonucleotides with an acylating agent of interest. Other chemistries for post-synthetic derivatization of oligonucleotides are of interest. A few reports of the use of transition metal cross-coupling reactions, primarily using palladium catalysis, have been reported.[1-4]

In 1999, Kahn and Grinstaff[1,4] reported a novel procedure for site-specific modification of oligonucleotides (Scheme 1). In this application, a Sonogashira coupling was used to functionalize oligonucleotides with propargylamines, biotin, or a ruthenium complex, stopping the DNA synthesis midway to perform the coupling by passing reagents through the column. Reinstallation of the column and continuation of the synthesis afforded the desired full-length material with an internal modification. Apparently, performing the Sonogashira coupling at an internal position after the entire oligonucleotide is formed is not as efficient for steric reasons.



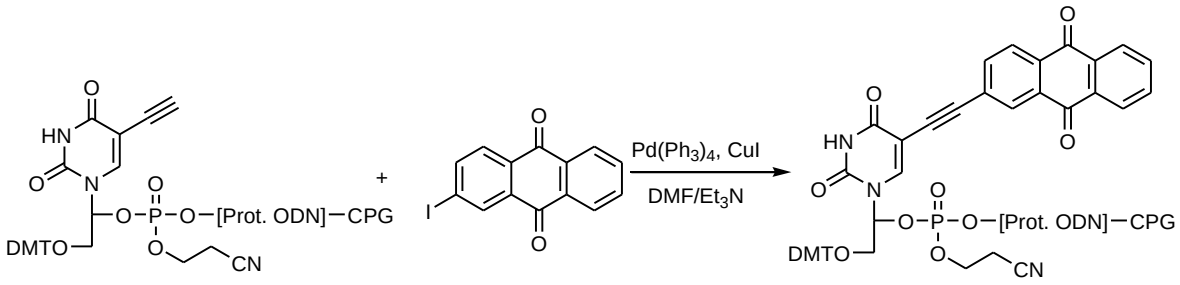
Scheme 1: Internal functionalization via on-column modification using a Sonogashira coupling.[1]

Pedersen, *et al.*[2] described the post-synthetic on-column elaboration of oligonucleotides bearing a 5'-aryl iodide via Sonogashira couplings with aryl-substituted terminal alkynes (Scheme 2).



Scheme 2: 5'-Functionalization via on-column modification using a Sonogashira coupling.[2]

Successful post-synthetic modifications have also been reported by Barton *et al.,*[3] this time with the alkyne present on the oligonucleotide (Scheme 3). In this report an internal modification *via* a Sonogashira coupling was performed by removing the beads from the column and stirring them with a solution of the coupling reagents prior to removal from the solid support. The coupling was reportedly very efficient.



Scheme 3: Internal functionalization via on-column modification *via* Sonogashira coupling.[3]

Cross-Coupler CEP (BA 0322) allows the incorporation of a nucleotide containing an aryl bromide for post-synthetic modification *via* transition metal-mediated cross-coupling, e.g., using a Sonogashira coupling. A longer tether is employed than in the prior studies cited above in order to remove the sterically-demanding palladium chemistry further from the oligonucleotide.

Using Cross-Coupler CEP: For oligonucleotide synthesis, the phosphoramidite should be diluted with dry acetonitrile and coupled using standard protocols as recommended by the synthesizer manufacturer, where coupling yields of >95% are observed with 15 minute coupling times. After on-column transition metal cross-coupling, standard cleavage and deprotection conditions should be used.

Literature:

1. Kahn, S. I.; Grinstaff, M.W. *J. Am. Chem. Soc*. **1999**, *121*, 4704-4705.

2. Filichev, V. V.; Pedersen, E. B. *J. Am. Chem. Soc*. **2005**, *127*, 14849-14858.

3. Gorodetsky, A. A.; Green, O.; Yavin, E.; Barton, J. K. *Bioconjugate Chem*. **2007**, *18*, 1434-1441.

4. For a similar study involving the installation of a ferrocene by Sonogashira coupling of a ferrocene-containing propargylamine with an 8-bromoadenosine nucleotide, see: Beilstein, A. E.; Grinstaff, M. W. *J. Organomet. Chem*. **2001**, *637-639*, 398-406.