

# A Base-Free Catalytic Wittig Reaction for the Synthesis of (-)-Centrolobine

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Central to the synthesis of (-)-Centrolobine is the construction of an alkene (16) from a phosphonium salt (15) and an aldehyde (9). A Wittig reaction using *n*-BuLi and THF is used in the total synthesis by Latif and coworkers. Several health and safety concerns exist with this reaction, however, which makes it a suitable candidate for a green chemistry alternative. *n*-BuLi is a pyrophoric reagent which constitutes a severe safety risk, while THF is a highly flammable solvent. Utilizing a base-free catalytic replacement reaction would use safer solvents and pose less risk of harm.

## Stereoselective Construction of 2,6-cis-Disubstituted Tetrahydropyrans via Intramolecular Amide Enolate Alkylation: Total Synthesis of (-)-Centrolobine

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**Table 5.** Substrate scope for aromatic aldehydes under base-free catalytic Wittig conditions.<sup>[a]</sup>

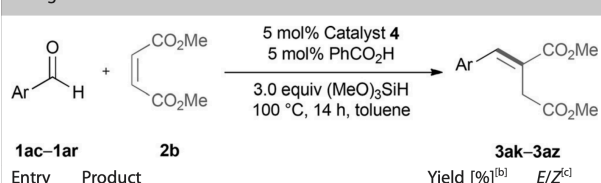


Fig 2: Base-free catalytic Wittig reaction conducted by Schirmer and coworkers.

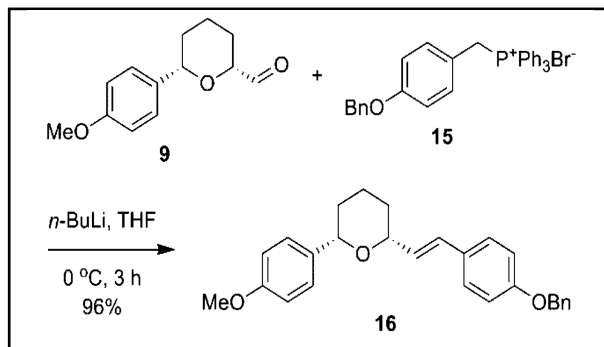


Fig 1: Wittig reaction from Latif and coworkers' total synthesis using *n*-BuLi and THF.

A novel technique developed by Schirmer and coworkers is a promising candidate for a replacement reaction, and uses a catalytic system instead of a base to facilitate a Wittig reaction. In this reaction, 3-methyl-1-phenyl-2-phospholen-1-oxide is used as the precatalyst, benzoic acid ( $\text{PhCO}_2\text{H}$ ) functions as a Brønsted acid additive, Trimethoxysilane ( $\text{MeO}_3\text{SiH}$ ) is used to reduce the catalyst and toluene is used as the solvent. The aldehyde, substrate,  $\text{PhCO}_2\text{H}$ , and  $\text{MeO}_3\text{SiH}$  are added successively to a reaction containing a solution of 3-methyl-1-phenyl-2-phospholen-1-oxide (catalyst 4) in toluene. The reaction vial is degassed with argon and the reagents are allowed to stir for 14 hours at 100 °C.

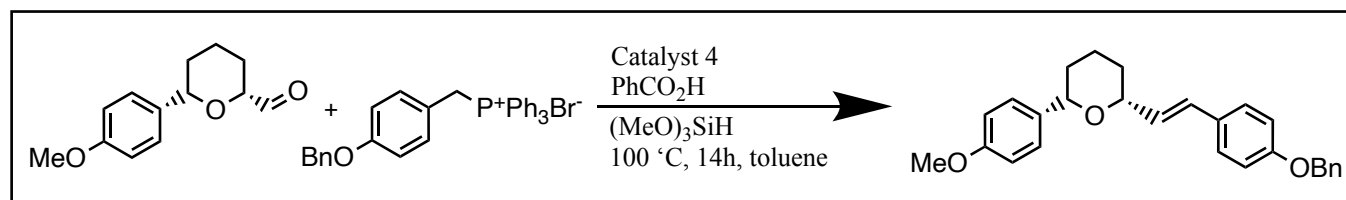


Fig 3: Proposed replacement reaction using Schirmer and coworkers' base-free catalytic Wittig reaction technique.

This replacement reaction is suitable due to its selectivity for aldehydes. A yield of 93% was recorded for substrate 7 by Schirmer and coworkers, which shares an anisole group in common with the substrate used for the synthesis of (-)-Centrolobine and confirms the selectivity for the aldehyde over the methoxy group.

## Novel Base-Free Catalytic Wittig Reaction for the Synthesis of Highly Functionalized Alkenes

M.-L. Schirmer, S. Adomeit, A. Spannenberg, T. Werner, Chem. Eur. J. 2016, 22, 2458 DOI: 10.1002/chem.201503744

Entry	Product	Yield [%] <sup>[b]</sup>	E/Z <sup>[c]</sup>
7		93	89:11

Fig 4: Anisole containing substrate and yield as reported by Schirmer and coworkers.

Although the reaction conducted by Schirmer featured a nucleophilic attack on the  $\alpha$ -carbon of a carboxylic ester, the use of this catalytic system is expected to still conduct a nucleophilic attack on the alpha carbon adjacent to the phosphorus in our substrate of interest.

This replacement reaction accomplishes several of the principles of green chemistry. Improved atom economy through the use of a catalyst, using safer solvents, a less hazardous chemical synthesis, catalysis, and inherently safer chemistry are the principles of green chemistry improved via this alteration.