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SHORT COMMUNICATION

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Mild Chemical and Biological Synthesis of Donor–Acceptor Flanked Reporter Stilbenes: Demonstration of a Physiological Wittig Olefination Reaction

David McLeod[a] and James McNulty*[a]

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Unprecedented chemoselectivity is reported for the Wittig olefination reaction leading to the formation of reporter stilbenes under physiological conditions.

Introduction

The development of a privileged set of reaction manifolds classified as "click" reactions[1] has advanced rapidly over the last decade in view of an expanding array of applications in diverse fields including chemical biology,[2] materials sciences, and hybrid bioconjugate areas.[3] The quintessential click reaction evolved from the copper-catalyzed small-molecule/small-molecule Huisgen azide/alkyne cycloaddition (CuAAC) yielding functionalized 1,2,3-triazoles.[1c] Although the CuAAC reaction is very successful in chemical and materials applications, requirements that the reaction occur under physiological conditions and not require toxic solvents, reagents, or metal catalysts (etc.) are of concern in biological applications. Reagents that display orthogonal reactivity to the myriad of functionality present in living cells further restricts the set of amenable reaction parameters.[4] The CuAAC reaction is most often employed in materials and bioconjugation applications, and issues of copper metal and azide toxicity[4b,4c] have encouraged the development of copper-free Huisgen cycloadditions using strained alkynes.[5] A few alternate reaction manifolds have been developed including Staudinger ligation,[4c] amine or hydrazine carbonyl additions,[4c,4e] Michael addition,[4d] and Diels–Alder cycloaddition reactions.[4f] The development of innovative alternatives to metal and azide-free click manifolds applicable for the synthesis of functionalized materials and bioconjugates is an active area of investigation.[4a]

On initial consideration, the Wittig olefination reaction does not appear to be a suitable candidate as a potential physiological reaction manifold. The classical reaction[6] requires the use of dry organic solvents such as diethyl ether or tetrahydrofuran and strong non-aqueous bases such as butyllithium or lithium diisopropylamide. In addition, protecting groups are usually required on any exposed acidic hydrogen atoms (alcohol, phenol, amino, etc.). Nonetheless, significant advantages may be envisioned were satifactory conditions for such a process realized (Scheme 1). The coupling of functionalized aldehyde **1** with functionalized phosphonium salt **2** would produce donor–acceptor flanked "reporter" stilbene **3**, which could be detected by using standard analytical methods (NMR, UV, and/or fluorescence spectroscopy, mass spectrometry). In addition to facilitating the conjugation of two functionalized units, such a process would open a novel approach to labeling or fluorescent tagging. The reporter unit is not appended as an existing tag but constructed as a designed element intrinsic to the conjugation process. Stilbene units form the core of a range of valuable materials including pharmaceuticals,[7] light-emitting diodes,[8] and dye-sensitized photovoltaic solar cells.[9] Stilbene cores have been conjugated as structural and reporter units on varied materials[10] including dendrimers,[11] as well as to biological constructs such as nucleic acids[12] and proteins (including lysozomes[13] and antibody binding[14]) and even to viral particles.[15] Development of a mild olefination "click" process could thus prove of strategic value to the conjugation and detection of a wide range of materials, bioconjugates, and other applications. We have investigated aqueous Wittig olefination reactions over the last few years under increasingly milder chemical conditions showing that stabilized and semistabilized ylides can be efficiently generated and trapped to give a range of useful alkenes, including stilbenes.[16] More recently, we demonstrated the first organocatalytic aqueous Wittig olefination reactions using weakly and non-basic amines including L-proline, tosylamide, and diphenylamine.[16d] We proposed a catalytic cycle for this process proceeding through an iminium ion intermediate[16d] as a carbonyl surrogate.[17] To extend to even milder conditions, we decided to investigate the critical issue of whether a Wittig olefination process is compatible and achievable under physiological conditions.

[a] Department of Chemistry and Chemical Biology, McMaster University
1280 Main Street West, Hamilton, Ontario, L8S 4M1, Canada
E-mail: jmcnult@mcmaster.ca
Homepage: http://www.chemistry.mcmaster.ca/mcnulty/index.html

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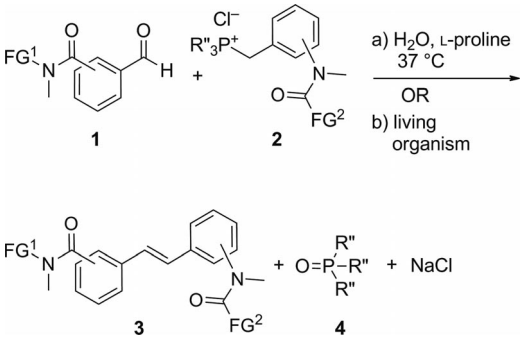
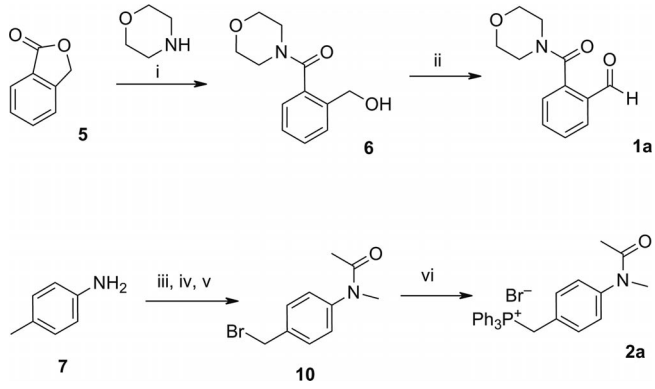
In this article we report the chemical synthesis of donor–acceptor flanked reporter stilbenes under extremely mild chemical conditions by employing L-proline organocatalysis (water, 37 °C, pH = 8.0). Most significantly, we also report the unprecedented synthesis of reporter stilbenes under completely natural physiological conditions in living plants conducted hydroponically and in soil through separate feeding of the Wittig reaction partners.



Scheme 1. Organocatalytic and bioorthogonal Wittig process. Synthesis of donor–acceptor flanked reporter stilbene **3** under mild chemical conditions and under physiological conditions.

Results and Discussion

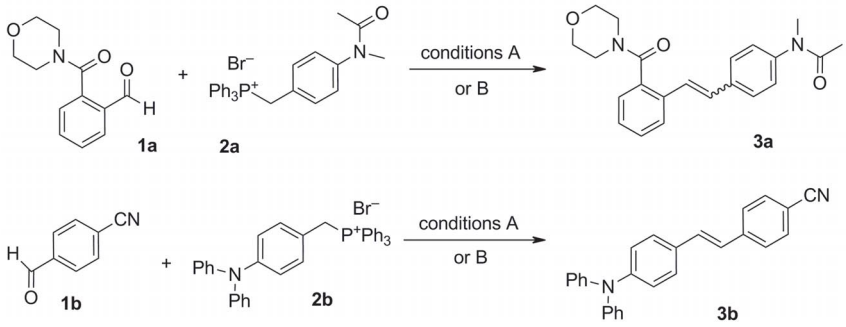
We designed and prepared amide-containing dual-functionalized test substrates **1a** and **2a** as reaction partners (Scheme 2). Wittig olefination was expected to yield donor–acceptor flanked reporter stilbene **3a**. Amides were chosen to connect the functional groups on both the aldehyde and phosphonium salt reaction partners, suggesting immediate locations for alternative variations on this process on what is effectively a reporter amino acid derivative. The phosphonium salt reactivity is intrinsically orthogonal, and we elected to make this the "donor" substituent and settled on 4-*N*-methylacetanilide **2a**.[18] Aldehydes are known partners in bioorthogonal reactions[4a,4b] and have also been used in the "aldehyde tag" process for site-specific protein encoding and covalent labeling.[2b] To limit possible oxidoreductase reactions and to increase the electrophilicity of the aldehyde, we opted to functionalize the aldehyde with an *ortho*-electron-withdrawing group and thus settled on morpholin-amide derivative **1a**. Nucleophilic opening of phthalide **5** with morpholine in the presence of a stoichiometric amount of $AlCl_3$ gave **6**, which was subjected to Swern oxidation to provide a short entry to aldehyde **1a**. Acylation of 4-methylaniline proceeded smoothly and subsequent *N*-methylation using LiHMDS and iodomethane followed by benzylic bromination yielded desired substituted benzyl bromide **10**. Quaternization with triphenylphosphane yielded phosphonium salt **2a**. An alternative synthetic route to salt **2a** was also developed (see the Supporting Information) from 4-aminobenzyl alcohol.



Scheme 2. Synthesis of aldehyde **1a** and phosphonium salt **2a**. Reagents and conditions: (i) morpholine, $AlCl_3$, 1,2-DCE, r.t., 88%; (ii) $(COCl)_2$, DMSO, Et_3N, DCM, –78 °C, 84%; (iii) Ac_2O, Et_3N, DCM, r.t. gave **8** (99%); (iv) LiHMDS, MeI, THF, r.t. gave **9** (95%); (v) NBS, BPO, PhH, reflux, 3 h, (80%); (vi) PPh_3, PhMe, reflux, 6 h, (96%).

The Wittig olefination reaction of **1a** and **2a** was first investigated under a range of chemical conditions (Scheme 3, A). The reaction was observed to proceed slowly in water at 37 °C in the presence of sodium hydrogen carbonate and a catalytic quantity of L-proline as the sole organic catalyst. This reaction was complete in 24 h, and donor–acceptor stilbene **3a** was isolated in 84% yield as a 1:1 (*E*)/(*Z*) mixture. The olefination reaction could also be completed more rapidly in water by using the relatively stronger base potassium carbonate at 70 °C. Under these conditions, the reaction was complete within 3 h, yielding stilbene **3a** in 76% isolated yield as a 65:35 (*E*)/(*Z*) mixture, selectivity in accord with the literature data.[16d] Full spectroscopic characterization of the (*E*) and (*Z*) isomers was accomplished, and the NMR spectroscopic data of the olefinic protons of each isomer are clearly resolved. The mass spectrum (EI-TOF) gave the molecular ion at *m*/*z* = 364 (87%) and readily identifiable fragments at *m*/*z* = 277 (100%) and *m*/*z* = 236/237 (48/86%). The compounds could be readily detected at low concentrations by using LC and LC–MS and also by UV and fluorescence spectroscopy. The LC–MS (Phenomenex Luna C18, H_2O, 0.1% formic acid/CH_3CN gradient elution, see Supporting Information for full details) showed clear resolution of two distinct near-baseline resolved peaks for the (*E*) and (*Z*) stereoisomers (t_R = 13.5 and 14.1 min), each displaying a similar fragmentation pattern. LC–MS–MS analysis of **3a** demonstrated clearly that the fragmentation at *m*/*z* = 277.9 led to secondary fragmentation at *m*/*z* = 235.8, thus providing a definitive fingerprint for the identification of the stilbenes. In a similar fashion (Scheme 3), 4-cyanobenzaldehyde (**1b**) was treated with phosphonium salt **2b** to yield stilbene **3b**, which was likewise characterized. Fluorescence measurements on **3a** by using excitations at both 219 and 301 nm produced broad emission just outside the visible region at 395 nm.

The aqueous organocatalytic Wittig olefination reaction requires the presence of a catalytic quantity of a primary or secondary amine. Endogenous amines and nitrogen het-



Scheme 3. Wittig olefination of aldehyde **1a** and phosphonium salt **2a** under mild chemical conditions. Conditions A: 37 °C, L-pro 24 h, $NaHCO_3$, 84% **3a**, 80% **3b**. In a bioorthogonal process, conditions B: *Calystegia sepium*, 25 °C; or *P. sativum* 25 °C.

erocycles are ubiquitous in living organisms, occurring as both primary and secondary metabolites (for examples, see Figure 1).[19] We now focused on testing the feasibility of conducting a Wittig olefination reaction under purely physiological conditions in living tissue. We initially chose the plant *Calystegia sepium* (Convolvulaceae) as a vehicle for several reasons. The plant is a well-known member of the Convolvulaceaea (bindweed or morning glory) family known to produce a small assemblage of nortropane secondary amine alkaloid natural products known as the calystegines (Figure 1).[19a] Seeds of the plant are commonly available, are easily and rapidly germinated in water, and can be cultivated in soil or hydroponically under laboratory-controlled conditions. Root and tissue cultures of the plant can also be prepared.[19b,19c] We investigated the germination of seedlings of *C. sepium* grown under hydroponic conditions, to minimize interference from soil-borne microorganisms, in a custom-built growth chamber. Soaking in water allowed seedling germination to occur usually within 2–3 d. Plants were grown to a height of 3–4 cm under three conditions: in soil, in pure water, and in a dilute aqueous NPK blend [total nitrogen 10%, available phosphoric acid (P_2O_5) 52%, soluble potash (K_2O) 10%, micronutrients 1%]. Upon germination, the plant materials were irradiated with a sunlamp for 6 h/d at a constant temperature of 25 ± 2 °C. Seedlings were then injected separately with aqueous solutions of aldehyde **1a** and phosphonium salt **2a** (Scheme 3, B). Each solution was 2 mM in water; 100 μL of each was added twice a day. The growth of the plants was visually unaffected by treatment with compounds **1a** and **2a**, and relative to non-labeled controls, no evidence of herbicidal activity was observed. Non-labeled control and labeled plants were harvested after 8 d, and the organic solubles were extracted into methanol. LC–MS analysis of the control plant extracts (non-labeled) and control media, consisting of compounds **1a** and **2a** in pure water and compounds **1a** and **2a** in the NPK solution, showed conclusively that no olefination reaction occurs. Individual plants treated with **1a** and **2a** grown in soil (above-ground leaves/stems) and under hydroponic conditions were carefully removed and washed thoroughly with water. The methanol extract of each was analyzed by using the LC–MS–MS method described. The analysis demonstrated conclusive formation of the reporter stilbenes in labeled plants grown in soil and those grown hydroponically. Two peaks were observed with identical retention times in comparison to the synthetic controls. Detection of the fragment at *m/z* = 278 and the secondary fragmentation of each isomer was identical to the stilbene standards. Similarly, separate feeding of **1b** and **2b** to hydroponically grown *C. sepium* (see the Supporting Information) resulted in formation of analytically detectable quantities of stilbene **3b**.

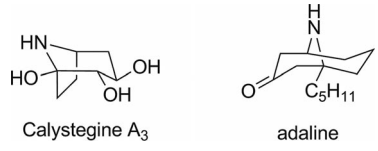


Figure 1. Examples of naturally occurring secondary amines in plants and animals. Calystegine A_3 a common ornithine-derived nortropane secondary amine metabolite from *Calystegia sepium*.[19a] Adaline, a fatty-acid-derived amine from the ladybird *Adalia 2-punctata*.[19d]

Microscopic analysis of root, stem, and leaf sections of *C. sepium* after feeding with compounds **1a** and **2a** were taken at 20× magnification with a Leica DMI 6000B deconvolution microscope (excitation 377 nm, emission 447 nm). In addition to general background fluorescence, these images showed an accumulation of stilbene **3a** on the plant cell surface and/or intercellular media of the stem (Figure 2).

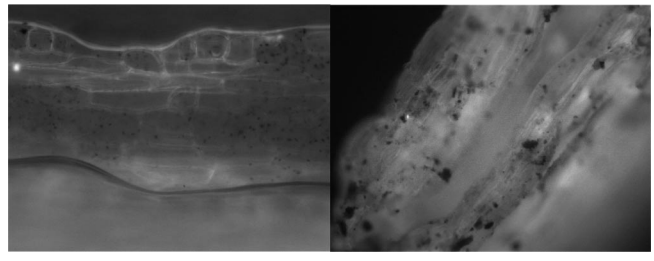


Figure 2. Deconvolution micrographs of labeled (left) and unlabeled (right) stems of *C. sepium* showing localization of the reporter stilbene on the cell wall and/or intercellular media.

Lastly, because *C. sepium* accumulates toxic secondary amines (see Figure 1) in addition to endogenous amino acids, it was of interest to investigate a possible physiological

olefination in a more benign plant. The reaction of **1a** and **2a** was investigated in the pea plant *Pisum sativum*, an innocuous vehicle known for primary amino acid production and nitrogen-free secondary products.[20] Seeds of *P. sativum* are readily available, and the plant is rapidly germinated in soil or under hydroponic conditions. Separate injection of compounds **1a** and **2a** into rapidly growing seedlings of *P. sativum* and harvesting of the plant tissue after 8 d followed by LC–MS analysis (see above) allowed unequivocal identification of stilbene **3a** in stem and leaf tissue.

The synthesis of precursors **1a** and **2a** (Scheme 2) is rapid and its modular nature should enable application to analogous reaction partners to connect functional units of interest and to customize the properties of the chromophore. The initial process connects an amine (here morpholine) to a carboxylic acid (here acetate) through amide bonds by an in situ and in vivo constructed reporter stilbene linkage. The technology to construct such a molecularly defined chromophore/fluorophore directly, while conjugating two differentially functionalized entities, provides a new approach that is envisaged to be widely useful in installing such a "reporter" in these systems, including in living tissues. Stilbene **3a** was chosen as a proof-of-principle for the physiological olefination process and not designed as a tissue-specific target. It is not yet known if the olefination reaction occurs within the plant cell or if it is promoted by endogenous amines in the extracellular media. Nonetheless, it has now been demonstrated that Wittig-type olefination reactions are compatible under mild physiological conditions. The mild conditions, simplicity, and efficiency of the chemical process (Scheme 3, conditions A) validate the click-stilbene paradigm, whereas the applicability to physiological conditions (Scheme 3, conditions B) opens olefination chemistry to new and exciting applications.

Conclusions

In summary, we report the synthesis of useful dual-functionalized donor–acceptor reporter stilbenes under extremely mild chemical organocatalytic olefination conditions and, secondly, under physiological conditions within plant tissues. The reporter molecules can be isolated in large quantities by using the chemical technique and can be readily identified at low concentrations by fluorescence or LC–MS–MS. The unprecedented chemoselectivity demonstrated here opens a new paradigm in olefination chemistry, extending the applicability to bioorthogonal applications. The success of the chemical and bioorthogonal processes will suggest many applications for conjugation/detection in materials, biochemicals, and hybrid areas. Olefination chemistry continues to illuminate with new relevance a quarter century beyond Wittig's passing.[21] Further refinements and applications towards the synthesis of functionalized materials and intracellularly targeted conjugates is now under active investigation in our laboratory.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, ^{1}H NMR and ^{13}C NMR spectra, LC–MS (MS) spectra, UV/Vis spectra, and fluorescence spectra.

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[18] No reaction occurred on attempted aqueous Wittig olefination (using either mild base or organocatalysis) under these conditions with salts such as **9a** and aldoses such as D-glucose, indicating orthogonal reactivity to these common aldehydes.

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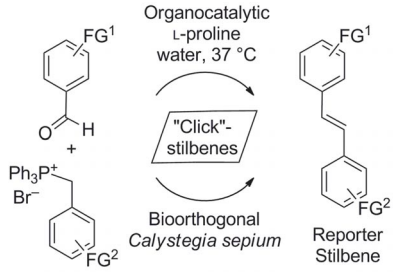
Chemoselective Olefination

Unprecedented chemoselectivity is reported for the Wittig olefination reaction leading to the formation of reporter stilbenes under physiological conditions.



Keywords: Organocatalysis / Water chemistry / Wittig reactions / Bioorthogonal chemistry

