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Dual catalysis; Lewis acid; Allylic substitution; Palladium; Tsuji-Trost

ABSTRACT: Double allylic substitution is an attractive approach to build molecular complexity from simple starting materials by creating two new bonds in one-pot. However, this type of reaction has been doomed by chemoselectivity and regioselectivity issues. In this manuscript, we describe a new approach to introduce *a-la-carte* two new C–C, C–N, C–O or C–S bonds in a chemo- and regioselective fashion. The reaction relies on sequential dual catalysis with Lewis acid and palladium. The scope is remarkably broad, and the reaction can be diastereoselective using secondary alcohols as the first nucleophile.

Allylic substitution is arguably one of the most powerful tools for the creation of new C–C and C–heteroatom bonds in organic synthesis.[1] The best example is the venerable Tsuji-Trost reaction, which is commonly employed as a region- and stereoselective method for the creation of C–C, C–O, C–N and C–S bonds.[2] Despite the recognized utility and existing knowledge of this reaction, double allylic substitution sequences are surprisingly scarce, considering the high level of molecular complexity that could be attained through such one-pot approach.[3-5] Indeed, the successive allylic alkylation of 3,4-difunctionalized butene derivatives presents many challenges (Scheme 1A). First, the regioselective introduction of two nucleophiles implies discriminating between electrophilic positions 1 and 3 for the first substitution and positions 2 and 4 for the second one. In particular, only reaction at C^1 in the first step will induce migration of the olefin moiety and allow a productive process, while regioisomer **B** will not allow a second allylic substitution. In addition, the fact that compound **A** resulting from a first allylic substitution is also a substrate for a second allylic substitution raises chemoselectivity issues. If one wants to introduce two different nucleophiles, a competitive reaction leading to **C** could occur in a one-pot process. Finally, in order to be a useful tool for organic chemists, the reaction needs to depend on simple precursors and be carried out in a one-pot process.[6]

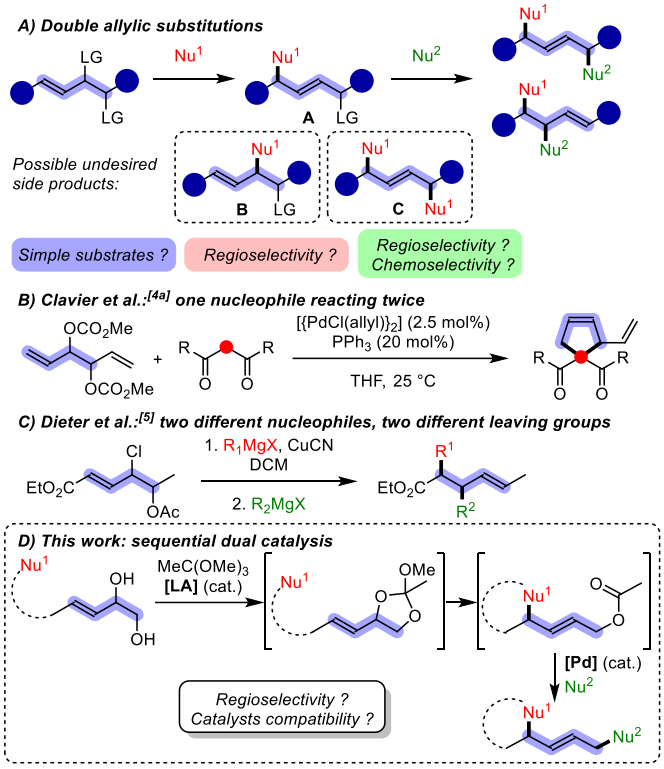
Most previous examples of double allylic substitution elude the question of chemoselectivity by employing a dual nucleophile.[4] For example, in 2012 Clavier and coworkers reported the one-pot double allylation of 1,3-diketones using an allylic dicarbonate,[4a] an elegant example from readily available substrates (Scheme 1B). On the other hand, in order to introduce two different nucleophiles in each of the substitution, one has to tune the substrate in order to have two different leaving groups which can be substituted sequentially, as reported by Dieter *et al.* in 2008 (Scheme 1C).[5] Although this latter example is chemoselective, the substrates are not readily available, require additional steps for the introduction of two different leaving groups[7] and suffer from a lack of diversity. Herein, we propose to solve the question of regio- and chemoselective double allylic substitutions from readily available alkenyl *vic*-diols using a sequential dual catalysis approach, in which each catalytic system will allow the introduction of a different nucleophile at will.[8]

Taking inspiration from the work of Borhan's group on diol activation,[9] we imagined that alkenyl *vic*-diols could be activated by trimethyl orthoacetate to form a cyclic orthoester intermediate (Scheme 1D). The addition of a Lewis acid would exacerbate the nucleophilicity of the orthoester intermediate, facilitating the first allylic substitution. During this process, ring-opening of the transient cyclic orthoester would result in the formation of an allylic acetate, which could sequentially undergo a classical Tsuji-Trost reaction in the presence of a palladium catalyst. This dual catalysis approach would solve the problems of chemoselectivity inherent to double allylic substitutions. Nevertheless, this raises the question of catalyst compatibility between the Lewis acid and Pd catalysts.[10]

The regioselectivity of each substitution will also be a key challenge for this double transformation.

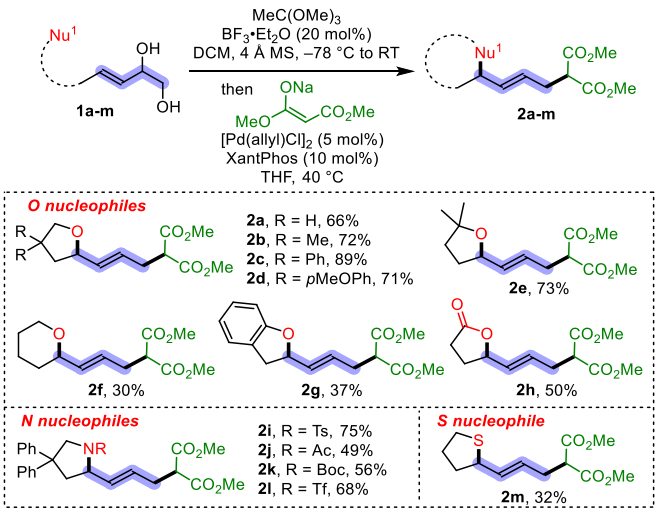
Herein, we present a novel method for the double allylic substitution of alkenyl-*vic*-diols, employing dual catalysis (Lewis acid/transition metal). This approach enables the introduction of two distinct nucleophiles, providing direct access to complex molecular scaffolds.

Scheme 1. Challenges and solutions for the double allylic substitution.



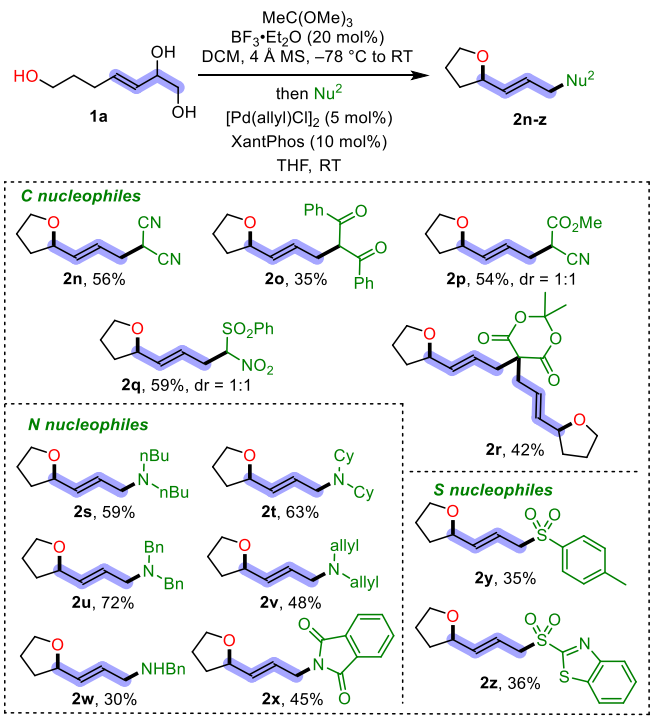
At the outset of the work, we screened conditions for the first allylic substitution. Although many Lewis acids promoted the reaction, BF_3•Et_2O proved superior to every other catalyst (see the supplementary information for detailed optimization). Moreover, the two sequential substitution reactions could be achieved in one-pot by simply adding $[Pd(allyl)Cl]_2$, XantPhos, and a THF solution of sodium dimethylmalonate as the second nucleophile. The reaction proceeded well for the formation of variously substituted tetrahydrofuran products (Scheme 2). In particular, the reaction benefited from a Thorpe-Ingold effect (**2a**-**2d**). Even sterically demanding tertiary alcohols performed well as nucleophiles. The reaction could be applied to the synthesis of tetrahydropyran **2f**, although with lower yield. Finally, other *O*-nucleophiles such as phenol and carboxylic acid also proceeded (**2g**, **2h**). Remarkably, the lactone functionality in **2h** was not affected during the subsequent Tsuji-Trost reaction. The first substitution was not limited to the formation of new C–O bonds. Indeed, various protected amines could be employed, leading to the formation of pyrrolidine derivatives **2i**-**2l** having Ts, Ac, Boc and Tf protecting groups on the amino functionality. Finally, a C–S bond could also be forged using a thiol as the nucleophile, leading to tetrahydrothiophene **2m**.

Scheme 2. Scope of nucleophiles for the first allylic substitution. Reactions were carried out using 1 (0.2 mmol), trimethyl orthoacetate (0.3 mmol), BF_3•Et_2O (0.04 mmol) in DCM, then $[Pd(allyl)Cl]_2$ (0.01 mmol), XantPhos (0.02 mmol) and a solution of sodium malonate (0.4 mmol in 1 mL THF) were added in the same pot.



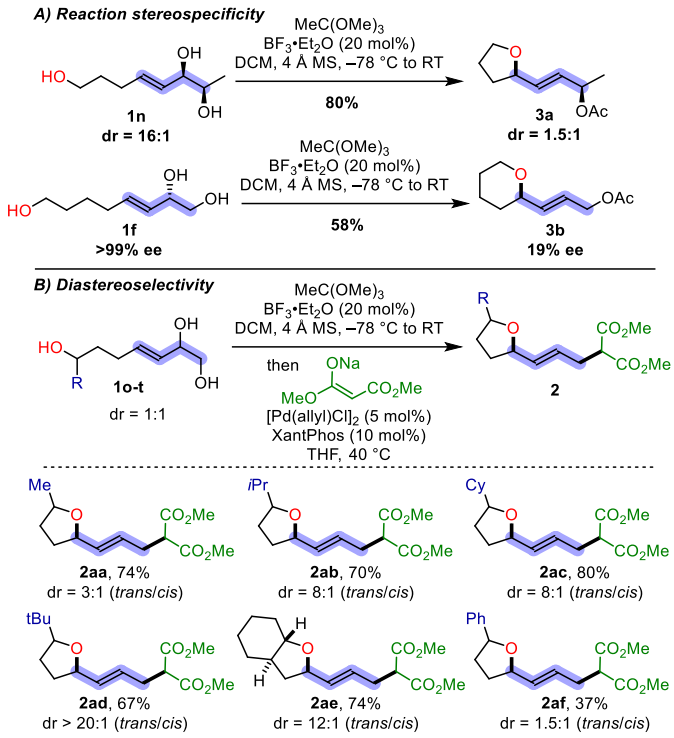
We also explored the scope of nucleophiles for the second substitution (Scheme 3). From triol **1a**, various C–C bonds could be formed in the second substitution reaction under Tsuji-Trost conditions. In particular, malonitrile (**2n**), diketone (**2o**), *β*-cyanoester (**2p**) and *β*-nitrosulfone (**2q**) led to the desired products having a new C–C bond. As expected, no diastereoselectivity was observed in the case of **2p** and **2q**. Interestingly, using Meldrum acid as the nucleophile, a double Tsuji-Trost reaction occurred, with Meldrum acid reacting twice (**2r**). New C–N bonds could be formed using amine nucleophiles. In particular, secondary amines led to the formation of products **2s**-**2v** in good yields. Primary amines such as benzylamine could also react, albeit providing lower yield (**2w**). Phthalimide was also a suitable *N*-nucleophile, leading to a protected primary amine **2x**. The use of sulfinates as nucleophile afforded sulfones **2y**-**2z**, through formation of a C–S bond. In particular, sulfone **2z** has the required benzothiazole substituent for the modified Julia olefination.[11]

Scheme 3. Scope of nucleophiles for the second allylic substitution. Reactions were carried out using 1a (0.4 mmol), trimethyl orthoacetate (0.6 mmol), BF_3•Et_2O (0.08 mmol) in DCM, then $[Pd(allyl)Cl]_2$ (0.02 mmol), XantPhos (0.04 mmol) and a solution of nucleophile (0.8 mmol in 1 mL THF) were added in the same pot.



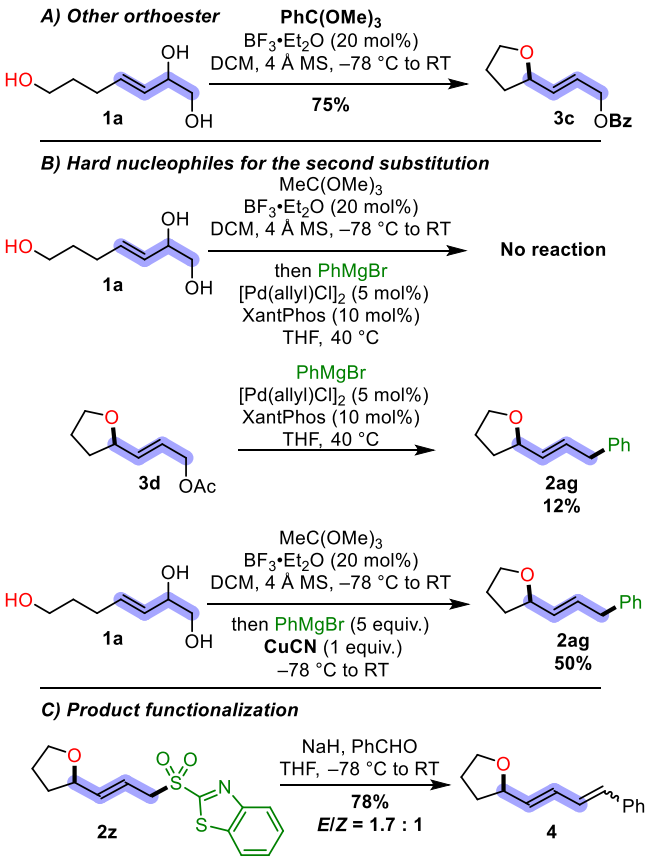
After exploring the scope of this reaction, we started to study the reaction stereoselectivity in the first allylic substitution. Starting from diastereoenriched substrate **1n** (dr = 16:1), the Lewis acid-catalyzed reaction proceeded with poor diastereoconservation (Scheme 4A). Remarkably, only one regioisomer was observed in this reaction. Similarly, from enantioenriched **1f**, the product **3b** was obtained with poor enantioconservation. Nevertheless, we could exploit the absence of stereospecificity by performing diastereoselective reactions starting from secondary alcohols (Scheme 4B). The diastereoselectivity ranged from moderate for methyl-substituted secondary alcohols (**2aa**, dr = 3:1) to good in the case of cyclohexyl or isopropyl substituents (**2ab**, **2ac**, **2ae**) to excellent in the case of more sterically demanding *tert*-butyl substituents (**2ad**, dr > 20:1). Secondary benzyl alcohol led to the desired THF product in lower yield and poor diastereoselectivity.

Scheme 4. Stereoselectivity studies.



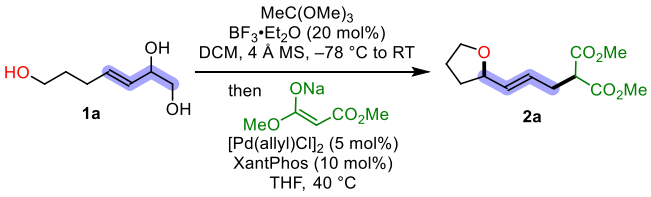
We wondered whether the first step could proceed using a different orthoester as activator. We were pleased to observe that upon treatment of **1a** with trimethyl orthobenzoate and catalytic amount of BF_3•Et_2O the cyclisation occurred, affording allylic benzoate **3c** (Scheme 5A). We were also interested by the use of hard nucleophiles in order to expand the scope of the second substitution (Scheme 5B).[12] Unfortunately, the one-pot double allylic substitution did not proceed using phenyl magnesium bromide as the second nucleophile. Starting from intermediate **3d** resulting from the first allylic substitution, the reaction mainly led to decomposition and only 12% of the desired product **2ag** was observed. On the other hand, using one equivalent of copper cyanide instead of the palladium catalyst allowed conversion of triol **1a** into **2ag** efficiently. This result is particularly surprising given the precedents suggesting that presence of copper promotes an S_N2' type reaction.[13] A deeper study on this reaction mechanism is currently ongoing. We also decided to showcase the utility of our method by achieving the synthesis of dienyl-THF structure **4**. For that, the product **2z** was subjected to modified Julia olefination conditions. Dienyl-THF structures are particularly relevant as they can be found in various fungal metabolites, and are also involved in the biosynthesis of diverse natural products.[14]

Scheme 5. Miscellaneous observations.



To further understand the role and compatibility of each catalyst, we performed control experiments. Introduction of the Pd catalyst XantPhos ligand and sodium malonate nucleophile from the beginning of the reaction led to recovery of starting **1a**. On the other hand, introduction of Pd catalyst and XantPhos ligand from the beginning of the reaction, followed by sodium malonate nucleophile after the first substitution afforded the desired product with similar efficiency compared to the general conditions. Finally, without BF_3•Et_2O the reaction did not proceed.

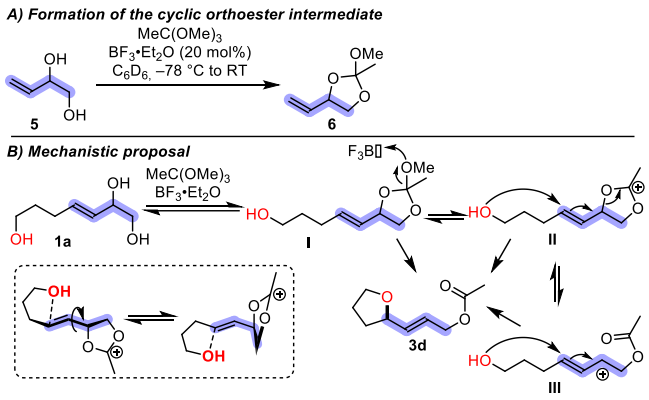
Table 1. Control experiments.



Deviation from standard conditions	Result
None	66% (isolated)
Pd/XantPhos and sodium malonate introduced from the beginning	No reaction
Pd/XantPhos introduced from the beginning, sodium malonate introduced after one night	75% (NMR yield)
Pd/XantPhos introduced from the beginning, no BF_3•Et_2O, sodium malonate introduced after one night	No reaction

In order to support our mechanistic hypothesis of preactivation of the allylic diol as a mixed cyclic orthoester, we treated alkenyl *vic*-diol **5** with trimethyl orthoacetate (Scheme 6A). We could observe in NMR the formation of mixed cyclic orthoester **5**. Therefore, we propose the mechanism described in Scheme 5B. The diol moiety **1a** reacts with trimethyl orthoacetate to form the intermediate mixed cyclic orthoester **I**. This mixed orthoester can be activated by the Lewis acid to generate an intermediate carbocation **II** or **III**, triggering the cyclization and concomitant ring-opening of the cyclic orthoester, affording the THF ring as well as the allylic acetate moiety. Alternatively, a direct substitution upon activation of **I** by the Lewis acid could also take place. The lack of stereospecificity in this reaction could be explained by the two possible faces of approach in the case of an antiperiplanar substitution of the nucleophile relative to the leaving group.

Scheme 6. Mechanistic proposal.



To conclude, in this manuscript we describe a new method involving sequential dual catalysis for the one-pot double allylic substitution of alkenyl *vic*-diols. Remarkably, this method allows to introduce two different nucleophiles at will in a regio- and chemoselective manner. The scope of nucleophiles is remarkably broad, and two new C–C, C–N, C–O or C–S bonds can be formed in this one-pot process. Although the first allylic substitution is not stereospecific, the reaction can proceed with good diastereoselectivity in the case of secondary alcohol nucleophiles. This new reactivity paves the way to the quick formation of diverse complex molecular scaffolds. Further studies regarding the reaction mechanism and stereoselectivity will be performed in the future.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and methods, synthesis of substrates and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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All authors have given approval to the final version of the manuscript.

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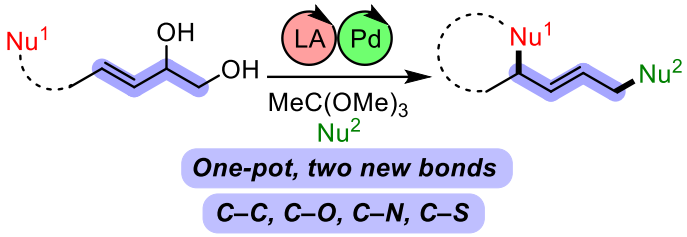

One-pot, two new bonds

C–C, C–O, C–N, C–S