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Dienyl esters synthesis: Palladium-catalyzed C–H olefination of electron-deficient alkenes with allenoates

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ABSTRACT

The palladium(II)-catalyzed direct oxidative C–H olefination of readily available *N*-tosylacrylamides and allenoates for the synthesis of dienyl esters is described. The amide and ester moieties both act as the directing groups for the regio- and the stereo-controlled C–H functionalization/cyclization, which was proved by DFT calculations. Molecular oxygen was used as the terminal oxidant in the approach, rendering the reaction more sustainable.

1. Introduction

The dienyl ester scaffold often appears in a number of natural products, pharmaceutical compounds; furthermore, dienyl esters represent a versatile and highly reactive substrate class in organic synthesis due to their unique structural and electronic features (Fig. 1).[1] Traditionally, dienyl esters were constructed through Wittig reaction,[2] Cross-Metathesis[3] and other methods.[4] However, the utility of these approaches are limited when applied to complex structures or active groups due to their instability, volatility, and poor stereoselectivity. These drastic conditions typically used and limited substitution patterns call for more straightforward and effective alternatives for the synthesis of dienyl esters.

The N-tosylacrylamide has recently been found to be capable of participating several transition-metal-catalyzed directed alkenes C–H bond functionalization reactions. In 2014, Loh and co-workers achieved the olefinic C–H alkynylation of acrylamides using a hypervalent alkynyl iodine reagent (Scheme 1-a).[5] Soon after that, the same group presented the rhodium(III)-catalyzed C–H allylation of *N*-tosylacrylamide with allyl acetates (Scheme 1-b).[6] Later, the Ma group realized a rhodium(III)-catalyzed tunable oxidative cyclization of *N*-tosyl-acrylamides and diazo compounds toward the selective synthesis of α-pyrones and furans (Scheme 1-c).[7] Recently, allenes have been used in tandem cyclizations, allylations, dienylations, and allenylations through aromatic C–H bond activation by exploiting rhodium, rhenium, palladium, cobalt or ruthenium catalysis.[8] However, the reports of using allenes in the field of the transition-metal-catalyzed C–H activation are still limited compared with alkynes and alkenes.[9] Especially, achieving chemo-, regio-, and diastereo-selectivity in C–H functionalizations with allenes is particularly difficult. Herein, we wish to report an unexpected palladium-catalyzed synthesis of dienyl esters based on an alkenyl C–H activation and cyclization reaction with allenoates, where double coordination plays an important role in achieving high stereo-selectivity (Scheme 1-d).

2. Results and discussion

We initiated our research by examining the reaction of *N*-tosylacrylamide **1a** with branched 1,1,3-trisubstituted allenoates **2a** with the starting reaction conditions based upon our previous work on the Pd-catalyzed annulation of N-tosyl benzamides with allenes to give quinolones.[8f] To our delight, we found that the reaction proceeded smoothly in the presence of $Pd(OAc)_2$ (10.0 mol%),

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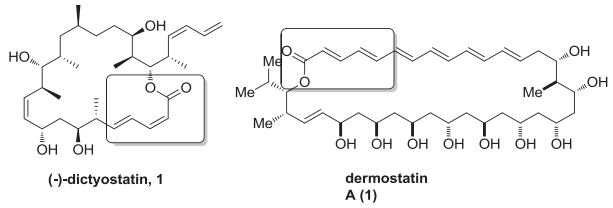
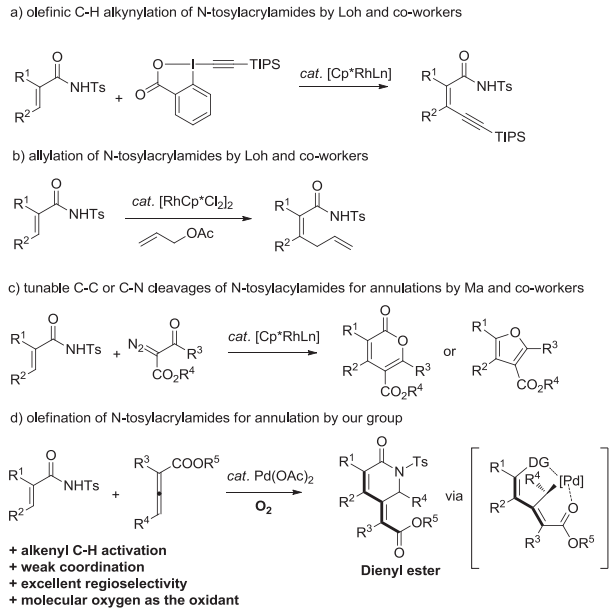


Fig. 1. Naturally occurring dienyl esters.



Scheme 1. Acylsulfonamide-assisted C–H functionalization.

$Cu(OAc)_2$ (2.0 equiv.), CsOAc (2.0 equiv.) and PivOH (0.2 equiv.) in dioxane at 100 °C, giving tetra-substituted dienyl ester **3aa** in 49% yield as a single stereoisomer (Table 1, entry 1). The structure of the product **3aa** was further confirmed by X-ray diffraction analysis (see supplementary data).[10] In order to increase the yield, other additives such as AdCOOH and MesCOOH were tried, but no better results were obtained (entries 2 and 3). Next, other oxidants were screened, but poor yields were achieved (entries 4 and 5). Palladium sources such as $Pd_2(dba)_3$ and $Pd(OCOCF_3)_2$ significantly lowered the yield of **3aa** (entries 6 and 7). Other solvents did not produce a better result. When the base was changed to KOAc or NaOAc, the yield of **3aa** dramatically decreased. Surprisingly, when the loadings of oxidant and base were both decreased to 1.2 equivalents, the yield was increased to 65%. When a lower catalyst loading (5 mol% of $Pd(OAc)_2$) was used for this transformation, the yield of desired product was decreased to 50%. Gratifyingly, when 1 atm O_2 was used as oxidant and 20% $Cu(OAc)_2$ as co-oxidant, a comparable result was achieved. Last, omission of Pd^{II} or oxidant completely shut down the reactivity (entries 15 and 16).

To evaluate the versatility of the palladium(II)-catalyzed process, the optimized reaction conditions (Table 1, entry 14) were applied to variously substituted acrylamides and allenoates, and the desired products were obtained in moderate to good yields (Scheme 2). First, the substituents on the phenyl moiety of acrylamides were investigated. Accordingly, good yields of the desired dienyl esters products were produced with electron-rich substituents (**3aa**, **3ca**), whereas strong electron-deficient aromatic compounds proved to be more challenging (**3fa**). Due to the steric hindrance, the acrylamide with the 2-methyl substitutent reacted much more slowly, providing **3ha** in comparatively lower yield. Cyclic acrylamide such as cyclopentenyl and cyclohexenyl can undergo the C–H functionalization process with excellent site-selectivity (**3ia-3ka**). Interestingly, 2-phenyl and 2-benzyl acrylamides also participated in the transformation, where 2-phenyl substituent showed poor reactivity (**3la** and **3ma**). To our disappointment, cinnamamides did not furnish the reaction.

The reaction also showed broad substrate scope in terms of the allenoates (Scheme 3). Monosubstituted and tetra-substituted allenoates did not produce any products, and both decomposed in the reaction system, whereas 1,1-disubstituted, 1,3-disubstituted, and trisubstituted allenoates can show good reactivity. 3-Ethyl allenoate gave a slightly lower yield compared to 3-methyl allenoate substrate in most of the products. When ethyl 2-methylbuta-2,3-dienoate was submitted to the standard conditions, a substituted pyridin-2(1*H*)-one was obtained in moderate yield *via* intramolecular rearrangement (**3ad**). The ester groups were also studied, and methyl, ethyl, isopropyl, tertbutyl and benzyl groups represented the comparable results. *N*-(phenylsulfonyl)benzamide was also tolerated *via* sp^2 C–H activation, however, lower yields were obtained (**4a** and **4b**).

To gain insight into the mechanism of this transformation, deuteration experiments were performed. The isotopic exchange studies of *N*-tosylmethacrylamide **1a** with 10 equiv. D_2O revealed that the olefinic C–H bond can be easily exchanged by deuterium (Scheme 4-1This is similar to those of the investigations by Loh[5,6] and Zhang,[4a] implicating that the Ts-imide may act as a directing group through coordination with Pd(II) to form the intermediate of *ortho* C-Pd(II). In addition, a primary KIE value of 5.3 was observed. This result indicated that C–H bond cleavage was involved in the rate-determining step (Scheme 4-2).[8f,11]

In addition, a possible mechanism was proposed in Scheme 5 for better understanding of this transformation. The cycle may originate from the generation of five-membered palladacycle **I** through C–H activation under the assistance of CsOAc.[12] Subsequently, the allenoate is coordinated to palladium center to form complex **II**, followed by 1,2-insertion of allenoate into the Pd-C bond to form the intermediates **III** or **III′**, which slowly isomerize to the η^3-propargylpalladium **IV** species. Nevertheless, a reductive elimination occurring preferentially through intermediate **III** affords the product **3aa**, and meanwhile, the palladium catalyst is regenerated by the oxidation of copper (II) and molecular oxygen.

To further understand the regio- and the stereo-selectivity of the reaction, a computational study was performed. Two structures are fully optimized by B3LYP method with the Gaussian 09 program,[13] and vibrational frequency analyses were calculated to confirm that they are stable minima on the potential energy surface. For C, O, N, H and S, the 6-31+G(d, p) basis set was used; for Pd and Cs, the Lanl2DZ basis set with effective core potential (ECP) was used. The calculation results show that intermediate **III** has lower energy (−2172.48 hartree, −5703834 kJ/mol) than **III′** (−2172.43 hartree, −5703726 kJ/mol), so intermediate **III** is more stable than **III′**, which further prove the coordination of the ester moieties. All the energies are corrected for zero point vibrational energies (ZPE) and the optimized structures of **III** and **III′** are shown in Scheme 5.[14]

3. Conclusions

In conclusion, we have developed an efficient Pd(II)-catalyzed alkenyl C–H activation/cyclization with allenoates. This method provides a novel and straightforward synthesis of dienyl esters with diverse substitution patterns and good stereo-selectivity. A double coordination model was proposed and confirmed by DFT calculations. In addition, molecular oxygen was used as the terminal oxidant in the approach, rendering the reaction more mild and sustainable.