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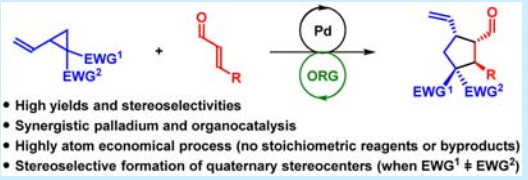
Asymmetric [3 + 2] Cycloaddition of Vinylcyclopropanes and α,β-Unsaturated Aldehydes by Synergistic Palladium and Organocatalysis

Kim Søholm Halskov, Line Næsborg, Fernando Tur, and Karl Anker Jørgensen*

Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

Supporting Information

ABSTRACT: The stereoselective [3 + 2] cycloaddition between vinylcyclopropanes and α,β-unsaturated aldehydes promoted by combined palladium and organocatalysis is disclosed. The unique synergistic catalytic system allows for the stereoselective formation of highly substituted cyclopentanes with up to four stereocenters in high yields and selectivities. Vinylcyclopropanes with two different geminal substituents facilitate the formation of cyclopentanes containing a quaternary stereocenter. Furthermore, the developed reaction performs well on gram scale, and a number of transformations are demonstrated.



One of the most important challenges in contemporary organic synthesis is to develop and integrate sustainable processes that allow for the synthesis of useful compounds in an environmentally friendly and streamlined fashion that minimizes energy consumption and conserves natural resources. As illustrated by the introduction of terms and concepts such as atom economy,[1] step economy,[2] redox economy,[3] and pot economy,[4] more emphasis is put on performing syntheses in a highly efficient manner in order to strive for a more "ideal" synthesis. In essence, this means that synthetic steps should be high yielding and highly selective, generate no byproducts, and be promoted by a minimal amount of reagent.[5] Given the increasing focus on these principles in chemistry, it is not surprising that catalysis holds a prominent position in modern synthetic chemistry, due to its many attractive features, and the role of catalytic methods only seems to continue to grow.[6]

The recent development and application of combined catalytic systems has made it possible to attain unprecedented levels of efficiency in synthesis.[7] Reactions, which had previously been achieved by stoichiometric prefunctionalization of one substrate in combination with catalytic activation of the other, may now be achieved by catalytic activation of both substrates. Therefore, more "ideal" syntheses may be achieved. A particularly successful area of combined catalysis has been the allylation of carbonyl compounds. Typically, an organocatalyst activates the carbonyl compounds, whereas a transition-metal catalyst activates the allylic reaction partner (Figure 1, a). Reported examples include combinations of aminocatalysts and palladium-based catalysts[8] as well as various other combinations.[9]

Vinylcyclopropanes may be catalytically activated by palladium[10] or other transition metals[11] in a parallel fashion to the classic π-allyl systems applied in allylations, and the intermediate 1,3-dipole can react with various dipolarophiles in [3 + 2] cycloadditions to form 5-membered rings. An appealing feature of such systems is that they display an excellent atom economy, since no byproducts are formed from the reaction. On the other hand, asymmetric versions of this type of reaction has proven to be challenging.[10d−l] This is linked to the low stability of the reactive 1,3-dipole intermediate in the presence of chiral ligands e.g. phosphines (Figure 1, b).[10d,e,12] The problems associated with the low stability of the vinylcyclopropane can be compensated by the application of specific substrates, although such a strategy consequently entails limitation in the substrate scope. Another relevant challenge with regards to stereoselective versions is the ability to achieve high diastereoselectivity, when

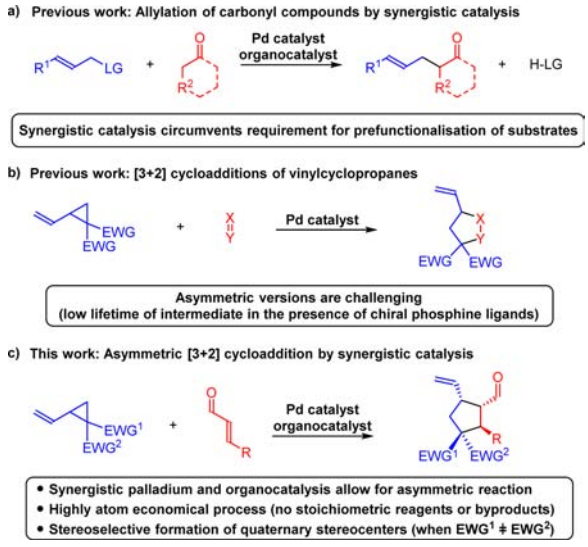


Figure 1. (a) Previous work on allylation of carbonyl compounds by synergistic catalysis; (b) [3 + 2] cycloadditions of vinylcyclopropanes; (c) asymmetric [3 + 2] cycloadditions of vinylcyclopropanes and α,β-unsaturated aldehydes by synergistic catalysis.

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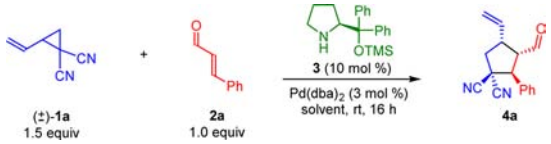
prochiral dipolarophiles are applied as reaction partners, as the ligands must exert remote stereocontrol.[10d,e]

Inspired by the successful application of combined catalytic systems in stereoselective allylations,[8,9] we envisioned a novel reaction development in which the activated vinylcyclopropane could react with a dipolarophile activated by an organocatalyst. Notably, the application of a chiral organocatalyst may help overcome some of the challenges associated with achieving stereoinduction in such reactions by the application of chiral ligands. In the following, we will disclose an asymmetric [3 + 2] cycloaddition of vinylcyclopropanes and α,β-unsaturated aldehydes achieved by combined palladium and organocatalysis (Figure 1, c). The developed reaction displays excellent atom economy as both reaction partners are catalytically activated and no byproducts are formed. The methodology allows for the formation of densely substituted cyclopentanes with up to four continuous stereocenters in high yields and excellent stereoselectivities. It will be shown that, by application of vinylcyclopropanes carrying two different geminal electron-withdrawing substituents, quaternary stereocenters can be formed in high stereocontrol. The possibility of applying such substrates is attributed to the unique features of the novel synergistic catalytic system since, to the best of our knowledge, this represents the first example in which stereoselective formation of quaternary stereocenters has been achieved by the application of vinylcyclopropanes.

Initial experiments were performed with vinylcyclopropane **1a** with two geminal nitrile substituents, cinnamaldehyde **2a** and diphenylprolinol silyl ether catalyst **3**,[13] and $Pd(dba)_2$, and selected optimization results are shown in Table 1. In line with the previous observations,[10d] the presence of a phosphine ligand led to rapid decomposition of **2a** with no formation of the desired product (entry 1). It was found, however, that the reaction was feasible in the absence of a phosphine (entry 2). A screening of solvents in the absence (entries 2–5) and presence (entries 6–9) of an acid additive revealed that full conversion could be attained with MeCN as the solvent with 10 mol % of $PhCO_2H$, and the product **4a** was isolated in good yield, high diastereoselectivity with two different minor diastereomers being formed, and excellent enantioselectivity (entry 9). By reversing the stoichiometry of the reagents, a boost in yield was achieved, which highlights the stability of the activated vinylcyclopropane intermediate under the applied reactions conditions (entry 10). Conducting the reaction in the absence of catalyst **3** led to no formation of the desired product (entry 11). It should be noted that the corresponding vinylcyclopropane with two ester substituents did not show any conversion under the applied reaction conditions, probably due to additional steric hindrance as opposed to nitrile substituents.

With the optimal reaction conditions in hand we moved on to explore the scope of the reaction (Scheme 1).

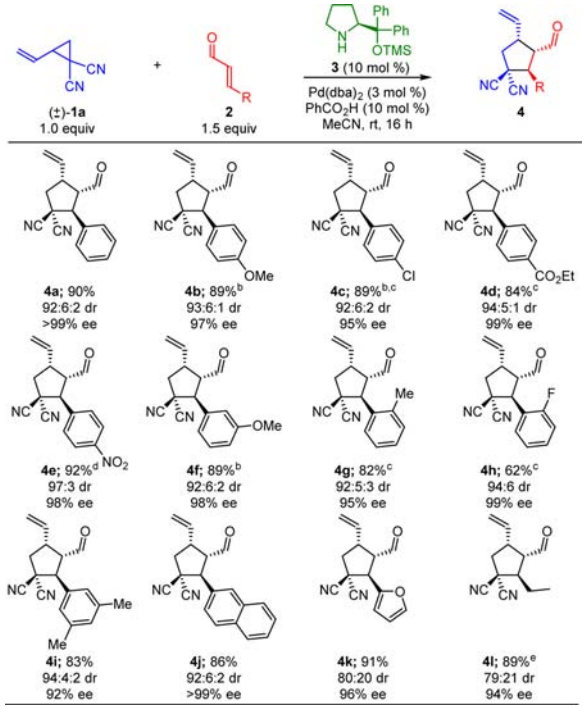
Table 1. Optimization of the Asymmetric [3 + 2] Cycloaddition of Vinylcyclopropane 1a and α,β-Unsaturated Aldehyde 2a[a]



entry	solvent	conversion[b] (%)	dr[c]	ee[d] (%)
1[e]	CH_2Cl_2	<5		
2	CH_2Cl_2	58	87:7:6	
3	THF	11		
4	toluene	5		
5	MeCN	10		
6[f]	CH_2Cl_2	40	92:4:4	
7[f]	THF	<5		
8[f]	toluene	5		
9[f]	MeCN	>95(76)	92:6:2	>99
10[f,g]	MeCN	>95 (90)	92:6:2	>99
11[f,g,h]	MeCN	<5		

[a]Reactions were performed on a 0.1–0.2 mmol scale. See the Supporting Information for details. [b]Conversion of limiting reagent as determined by ^{1}H NMR analysis of the crude reaction mixture of **4a**. Isolated yield of **4a** is shown in parentheses. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture of **4a**. [d]Determined by chiral stationary phase UPC^2. [e]Reaction performed with 10 mol % of triphenylphoshine as ligand (premixed with $Pd(dba)_2$). Full consumption of **1a** was observed. [f]10 mol % $PhCO_2H$ was employed as an additive. [g]1.0 equiv **1a** and 1.5 equiv **2a** were employed. [h]Reaction performed in the absence of catalyst **3**.

Scheme 1. Scope of Asymmetric [3 + 2] Cycloaddition of Vinylcyclopropane 1a and α,β-Unsaturated Aldehydes 2[a]



[a]Reactions were performed on a 0.2 mmol scale. See the Supporting Information for details and assignment of absolute configuration. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. In all cases, ratios in the same range were found in the isolated products. The enantiomeric excess was determined by chiral stationary phase UPC^2. [b]Reaction performed with 1.5 equiv of **1a** and 1.0 equiv of **2**. [c]96 h reaction time. [d]48 h reaction time. [e]Reaction performed with 3.0 equiv of **2**.

When the reaction was performed with cinnamaldehyde, product **4a** was obtained in high yield, high diastereoselectivity, and excellent enantioselectivity. Products were formed with similar results when α,β-unsaturated aldehydes with electron-donating (**4b**) and electron-withdrawing substituents (**4c–e**) in the *para* position of the aromatic moiety were applied. A *meta*-

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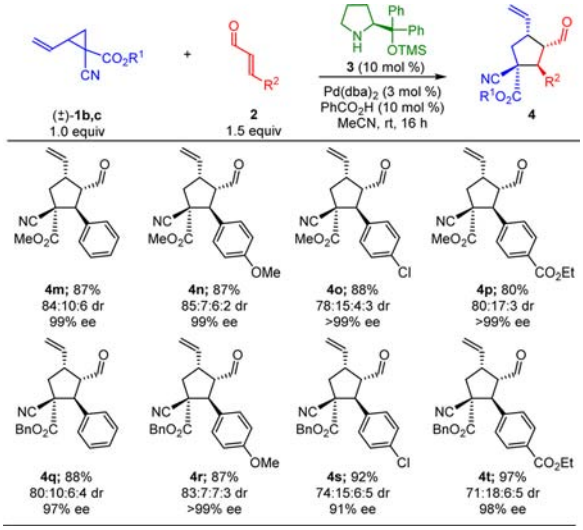
substituted substrate performed equally well in the reaction (**4f**); however, prolonged reaction times were necessary for *ortho*-substituted substrates, although the products were still isolated in decent yields (**4g,h**). The application of disubstituted aromatic α,β-unsaturated aldehydes also provided their respective products in high yields and diastereoselectivity and excellent enantioselectivities (**4i,j**). α,β-Unsaturated aldehydes with β-heteroaryl and β-alkyl substituents also performed well in the reaction, although a slightly lower diastereoselectivity was observed for these entries (**4k,l**).

Having ascertained the scope of the reaction of vinylcyclopropane **1a** with a variety of α,β-unsaturated aldehydes, we turned our attention to the possible application of other vinylcyclopropanes in the reaction. In particular, vinylcyclopropane substrates with two different geminal substituents were enticing since the reaction of such substrates could allow for selective construction of a quaternary stereocenter, which is a long-standing challenge in organic synthesis.[14] Gratifyingly, when vinylcyclopropane **1b**, carrying a nitrile and a methyl ester substituent, was applied in combination with cinnamaldehyde **2a** under the same reactions conditions, the intended product **4m** was formed in high yield, good diastereoselectivity, and excellent enantioselectivity (Scheme 2). The same vinylcyclopropane was

Scheme 2. Scope of Asymmetric [3 + 2] Cycloaddition of Vinylcyclopropane 1 and α,β-Unsaturated Aldehydes 2[a]

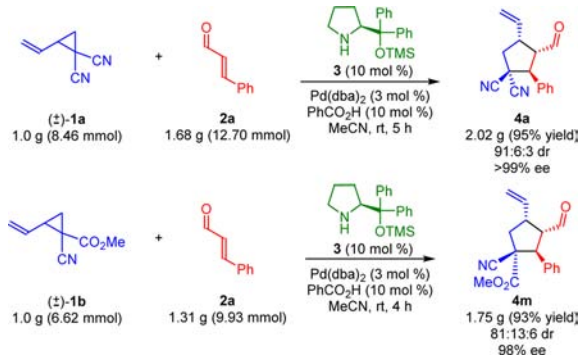


[a]Reactions were performed on 0.2 mmol scale. See the Supporting Information for details. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. In all cases, ratios in the same range were found in the isolated products. Enantiomeric excess was determined by chiral stationary phase UPC^2.

tested with some representative α,β-unsaturated aldehydes, which all gave their respective products with excellent enantioselectivity (**4n−p**). A vinylcyclopropane with a benzyl ester (**1c**) was also reacted with a variety of α,β-unsaturated aldehydes, which provided similar results (**4q−t**).

Subsequently, the performance of the reaction on gram scale was tested (Scheme 3). It was demonstrated that cyclopentane products **4a,m** could be synthesized in similar yields and selectivities as when the reaction was performed on smaller scale. Taking into account the easy access of all reactants and reagents (vinylcyclopropanes can be synthesized in one step; all other reagents are commercially available) in combination with the

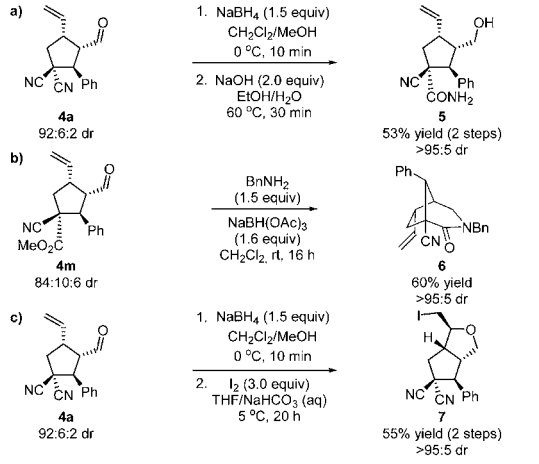
Scheme 3. Asymmetric [3 + 2] Cycloaddition of Vinylcyclopropane 1a,b and α,β-Unsaturated Aldehyde 2a on Gram Scale



scalability, the high yields, high selectivities, the simple reaction setup (no precautions to exclude air or moisture are necessary), and the presence of multiple functional groups in the product, we believe that the developed methodology may serve as an appealing starting point in target-oriented synthesis.

At this point, we set out to explore the synthetic potential of the cyclopentane products (Scheme 4).

Scheme 4. Synthetic Transformations of Cyclopentanes 4[a]



[a]Reactions were performed on 0.1−0.2 mmol scale. See the Supporting Information for details. The reported diastereomeric ratios are those found in the isolated products.

First, we questioned whether a quaternary stereocenter could be formed from **4a** by selective hydrolysis of one of the two diastereotopic nitrile substituents. An initial reduction allowed for isolation of the major diastereomer of the corresponding alcohol. The subsequent hydrolysis furnished amide **5** (Scheme 4, a). Given the prevalence of heterocycles in biologically active compounds, we also decided to investigate the possibility of obtaining such structures. A reductive amination facilitated a spontaneous cyclization to form the bicyclic lactam **6** in good yield (Scheme 4, b). Furthermore, a reduction of the aldehyde moiety followed by a iodoetherification allowed for the formation of **7** (Scheme 4, c).

Based on the previous work on palladium-based activation of vinylcyclopropanes[10] and iminium-ion catalyzed activation of α,β-unsaturated aldehydes,[15] we propose the mechanism outlined in Figure 2. The palladium(0) catalyst facilitates ring

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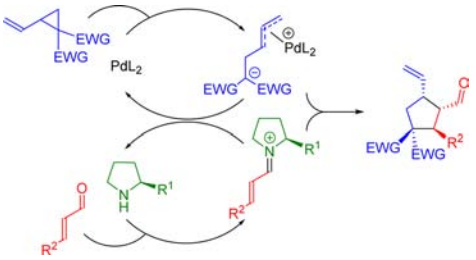

Figure 2. Mechanistic proposal for asymmetric [3 + 2] cycloaddition of vinylcyclopropane and α,β-unsaturated aldehydes.

opening of the vinylcyclopropane by oxidative addition to form a zwitterionic π-allylpalladium intermediate. In a separate cycle, an iminium ion intermediate is formed from condensation between an aminocatalyst and an α,β-unsaturated aldehyde. The two intermediates combine in a formal [3 + 2] cycloaddition, which is likely to proceed in a stepwise manner, generating the cyclopentane product.

In summary, we have developed an asymmetric [3 + 2] cycloaddition of vinylcyclopropanes and α,β-unsaturated aldehydes. The reaction is promoted by synergistic palladium and organocatalysis and allows for asymmetric formation of highly substituted cyclopentanes with up to four stereocenters in high yields and stereoselectivities. Notably, products containing a quaternary stereocenter could be formed. In addition, the reaction was shown to perform well on gram scale, and the synthetic potential of the obtained products was evaluated. Furthermore, a mechanistic proposal for the reaction was outlined.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00852.

Details of all experimental procedures and spectroscopic data of new compounds (PDF)

X-ray crystallographic data for **5** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kaj@chem.au.dk.

Notes

The authors declare no competing financial interest.

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