

Research Highlight

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Pd-H/Lewis base cooperative catalysis confers asymmetric allylic alkylation of esters atom-economy and stereodivergence

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Abstract

The construction of Csp^3-Csp^3 with high stereoselectivity, even in a stereodivergent way, has been a long-standing theme in organic synthesis. As an atom- and step-economic transformation, transition metal hydride-mediated allylic alkylation of enolizable carbonyl compounds with readily available allenes, alkynes or 1,3-dienes as the unconventional allylating reagents has recently emerged as a promising protocol for the stereoselective construction of Csp^3-Csp^3 bonds with high efficiency. Due to their less enolizability and weak nucleophilicity, simple esters remain challenging substrates for these coupling reactions. On the other hand, the strategy of metal/organo combined catalysis has recently emerged as one of the wide-ranging disciplines and powerful tools in asymmetric synthesis. Considering the recent achievements of chiral Lewis base catalysis in catalytic asymmetric α -functionalization of esters through a "rebound" mechanism, the cooperative combination of chiral Lewis bases and metal hydride catalysis may offer great opportunities to the aforementioned chemistry. Recently, the groups of Snaddon and Zi have made remarkable progresses in this area through palladium and chiral Lewis base cooperative catalysis.

Keywords: Combined catalysis, chiral Lewis base, asymmetric catalysis, allenes, dienes

The construction of Csp^3-Csp^3 with high stereoselectivity, even in a stereodivergent way, has been a long-standing theme in organic synthesis. As an atom- and step-economic transformation, transition metal



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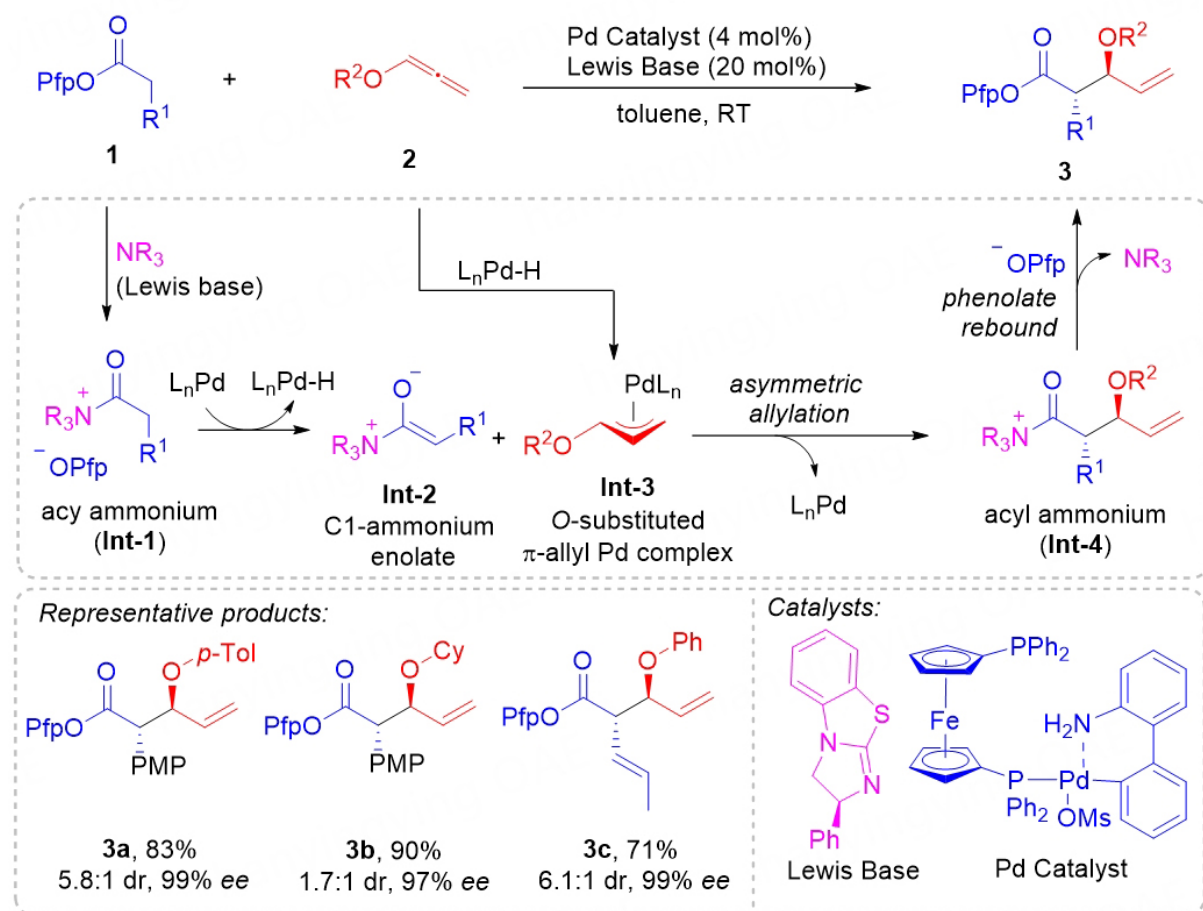
hydride-mediated allylic alkylation of enolizable carbonyl compounds with readily available allenes, alkynes or 1,3-dienes as the unconventional allylating reagents has recently emerged as a promising protocol for the stereoselective construction of Csp³-Csp³ bonds with high efficiency^[1-3]. Due to their less enolizability and weak nucleophilicity, simple esters remain challenging substrates for these coupling reactions. Additionally, the strategy of metal/organo combined catalysis has recently emerged as one of the wide-ranging disciplines and powerful tools in asymmetric synthesis^[4-7]. Considering the recent achievements of chiral Lewis base catalysis in catalytic asymmetric α -functionalization of esters through a “rebound” mechanism^[8-13], the cooperative combination of chiral Lewis bases and metal hydride catalysis may offer great opportunities to the aforementioned chemistry. Recently, the groups of Snaddon and Zi have made remarkable progress in this area through palladium and chiral Lewis base cooperative catalysis^[14-16].

In 2022, Snaddon described an enantioselective α -alkylation of esters **1** with oxyallenes **2** enabled by Pd/chiral isothioureia cooperative catalysis^[14] [Scheme 1]. In this procedure, the isothioureia catalyst is believed to first react with the pentafluorophenyl (Pfp) ester **2** to liberate PfpO⁻ anion and generate an acylammonium ion (**Int-1**), which is intercepted by the Pd catalyst to afford the C1-ammonium enolate (**Int-2**) and a palladium hydride species. Then nucleophilic intermediate (**Int-2**) synergistically combines with O-substituted π (allyl)-Pd intermediate (**Int-3**) generated through the hydropalladation of the terminal π -bond of allene **2** to give acylammonium (**Int-4**). Nucleophilic attack of the PfpO⁻ anion to (**Int-4**) releases the Lewis base catalyst and delivers product **3**. The designed catalytic system enabled a broad reaction scope with excellent enantioselectivities and high *anti*-selectivity, which is arduous to access via classical aldol reactions due to the undesired retro-aldol fragmentation. Furthermore, the products **3** could be readily converted to enantiomerically pure 1,2-amino alcohols in good overall yield through a two-step NH₃ aminolysis and Hofmann rearrangement sequence^[11].

Simultaneously, Zi, Tang and co-workers independently developed a stereodivergent coupling of alkoxyallenes **2** with pentafluorophenyl esters **1** through the combined catalysis of a chiral Lewis base and a chiral palladium catalyst^[15] [Scheme 2]. Through the combination of (*S*)-L1-Pd and (*S*)-LB-1, *anti*-**4** could be obtained with up to > 99% ee and > 20:1 dr. Instead, (*R*)-L2-Pd and (*S*)-LB-1 together rendered the reaction highly *syn*-selective with excellent enantioselectivities. In this way, all four possible stereoisomers could be obtained from a given pair of substrates through a rational selection of the corresponding catalysts. Notably, DFT studies suggested a protonative hydropalladation pathway rather than a Pd hydride migratory insertion occurred during the formation of the π -allyl Pd species.

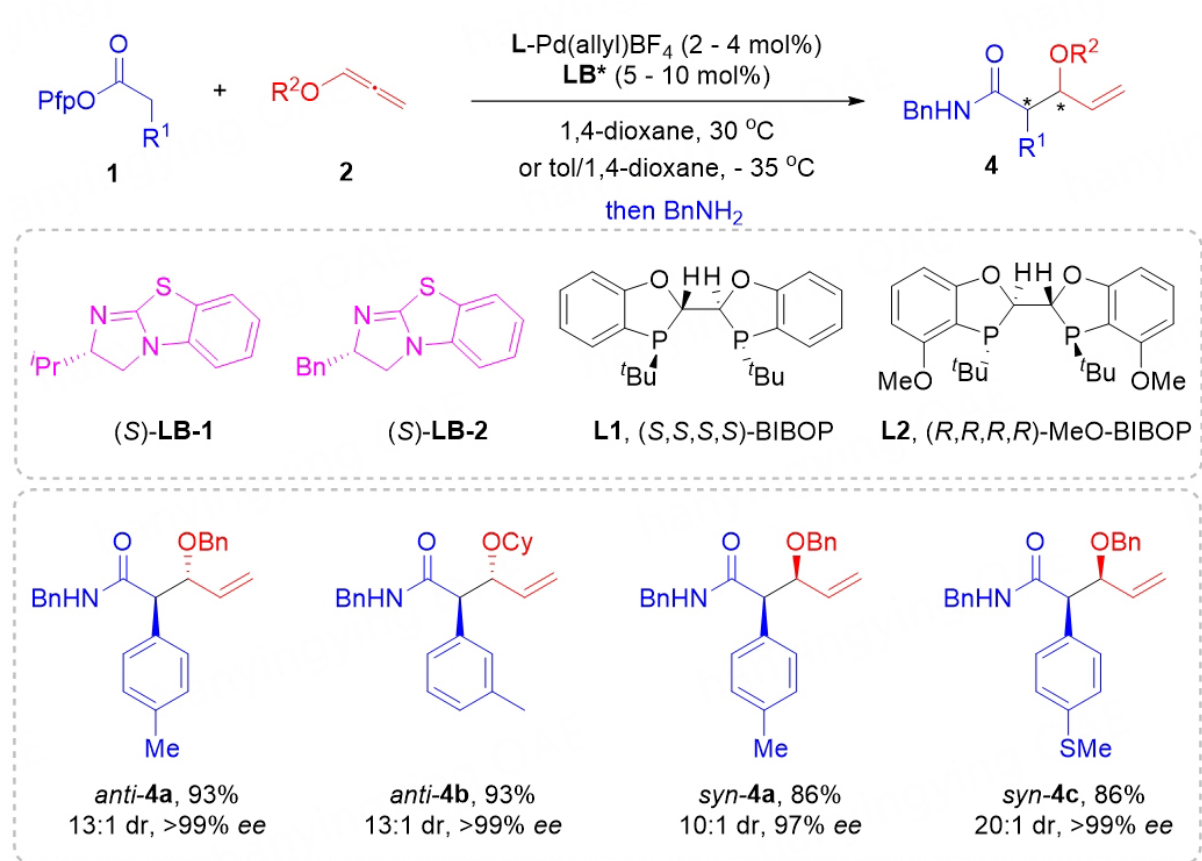
Very recently, Zi group contributed another stereodivergent protocol by describing the diastereodivergent alkylation of 1,3-dienes **5** with pentafluorophenyl esters employing Pd/chiral Lewis base cooperative catalysis, providing structurally important **6** in high yields with excellent selectivities^[16] [Scheme 3]. The absolute and relative stereochemistry of the product could be selected via a judicious choice of palladium and isothioureia combinations. Under the optimized conditions, a variety of 1,3-dienes with an aryl or heteroaryl substituent, as well as a broad scope of pentafluorophenyl acetates **1**, were successfully tolerated in this transformation. As a synthetic utility of this protocol, the coupling products were converted through the transformation of the pentafluorophenyl group to alcohols, esters, and amides with two adjacent chiral centers with high levels of diastereo- and enantio-selectivity. Moreover, based on the current protocol, a concise synthesis of the analgesic tapentadol **9** could be realized with an overall yield of 47% in eight steps.

In summary, the groups of Snaddon and Zi have established several impressive protocols describing highly stereoselective α -alkylation of esters employing simple allenes and dienes via palladium hydride/chiral Lewis base catalysis. These are the few examples that successfully combine the chemistry of metal hydride-

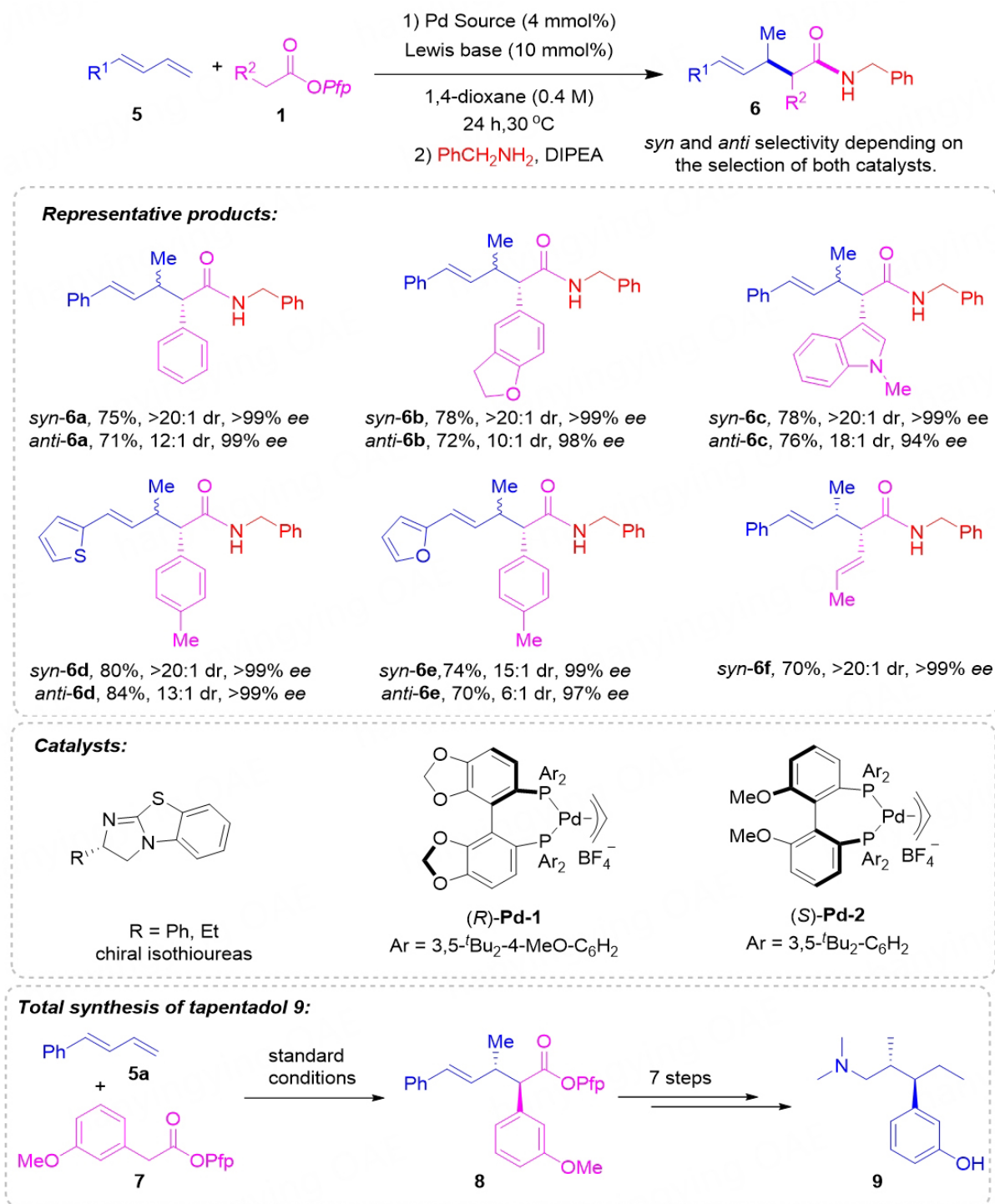


Scheme 1. Pd/Lewis base cooperative catalysis for direct alkylation of acyclic esters with alkoxyallenes.

mediated asymmetric allylations and chiral Lewis base catalysis, allowing for the access of structurally diverse products with high efficiency and excellent stereocontrol. It is anticipated that the concept of metal/Lewis base cooperative catalysis will inspire more exciting discoveries in the future.



Scheme 2. Stereodivergent coupling of alkoxyallenes with pentafluorophenyl esters employing Pd/ chiral Lewis base cooperative catalysis.



Scheme 3. Stereodivergent alkylation of esters with 1,3-dienes enabled by Pd/isothioureas cooperative catalysis.

DECLARATIONS

Authors' contributions

Wrote the draft manuscript: Sayed M

Revised and rewrote some parts of the manuscript: Han Z, Gong L

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Conflicts of interest

All authors declared that there is no conflict of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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