Asymmetric Catalysis

DOI: 10.1002/anie.200601889

Enantioselective Palladium-Catalyzed Decarboxylative Allylic Alkylations**

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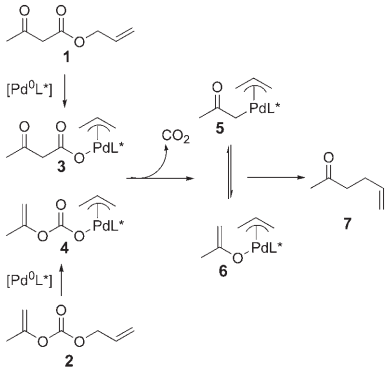
Keywords:
allylic alkylation · asymmetric catalysis · enols · ketones · palladium

Palladium-catalyzed asymmetric allylic alkylation (AAA) has become one of the most efficient ways to construct carbon–carbon bonds with stereocenters.[1] Although a high level of enantioselectivity can be achieved with soft nucleophiles, until recently ketone enolates, which are non-stabilized enolates, have been deemed as poor substrates and have afforded products with low enantioselectivities. It is thought that they attack palladium instead of the π-allyl during the reaction. Recently, studies on palladium-catalyzed decarboxylative AAA reactions (Tsuji protocol) have greatly expanded the scope of the nucleophile, in particular, with ketone enolates.

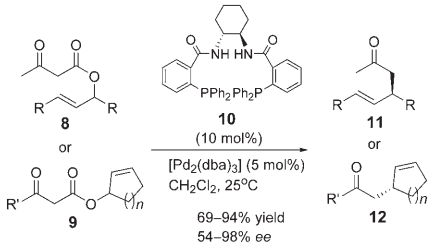
There are two main substrate types for the palladium-catalyzed decarboxylative AAA reaction (Scheme 1). In the presence of palladium(0), allyl β-keto carboxylate **1** can undergo facile oxidative addition to give a metal β-keto carboxylate **3**, which can subsequently undergo decarboxylation (also known as the Carroll rearrangement). Alternatively, vinyl carbonate **2** undergoes oxidative addition to produce palladium vinyl carbonate **4**, which can undergo decarboxylation to give the palladium enolate. Allylic alkylation product **7** is obtained upon reductive elimination or nucleophilic attack on the π-allyl by the enolate.



Scheme 1. The two main substrate types, **1** and **2**, for palladium-catalyzed decarboxylative AAA reactions. L* = chiral ligand.

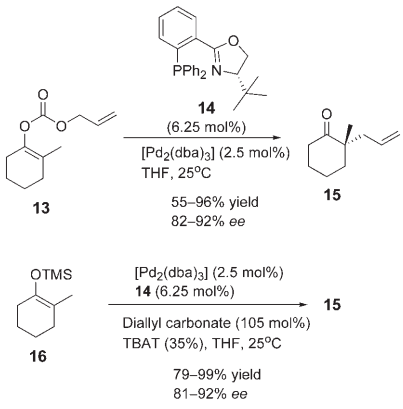
Tsuji and co-workers reported the palladium-catalyzed decarboxylative allylation reaction as early as 1980, when they observed it during their attempts at intramolecular allylic alkylation.[2] Since then, many substrates including β-nitro, cyano, and trifluoromethyl keto acetates have proved suitable therein.[2c–e] However, the asymmetric version of this class of reaction has been less explored until quite recently.

Tunge and Burger recently reported asymmetric palladium-catalyzed decarboxylative allylic alkylations utilizing Trost's ligand **10**.[3] Under optimized conditions, several α-unsubstituted β-keto esters **8** and **9** smoothly underwent the decarboxylative AAA reaction to afford the products in 69–94% yield and with 54–98% *ee* (Scheme 2). A study on cyclic substrates revealed that a larger ring size could lead to higher enantioselectivities.



Scheme 2. Decarboxylation of α-unsubstituted β-keto esters. dba = dibenzylideneacetone.

Stoltz and Behenna observed that decarboxylation of allyl enol carbonate **13** led to formation of a ketone with a quaternary stereocenter at the α-position (Scheme 3).[4] Screening of several ligands revealed that use of the *tert*-butyl-phox ligand **14** resulted in the highest enantioselectivities. A variety of cyclohexanone-derived allyl carbonates could undergo decarboxylation to provide products in high yields (55–96%) and with good enantioselectivities (82–92% *ee*). The reaction between trimethylsilyl enol ethers **16** and diallyl



Scheme 3. Decarboxylation of allyl enol carbonates using ligand **14**. TMS = trimethylsilyl; TBAT = $Bu_4NPh_3SiF_2$.

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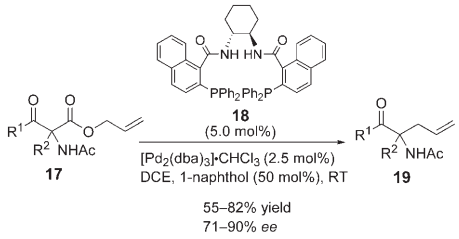
[**] We gratefully acknowledge the Chinese Academy of Sciences for generous financial support.

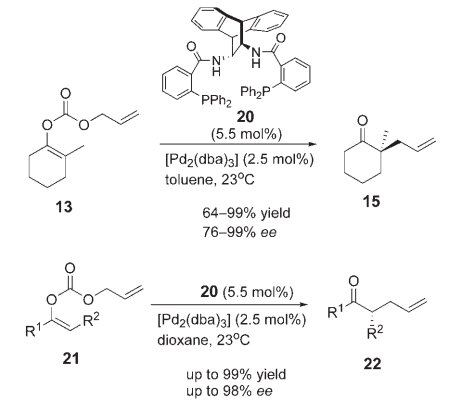
carbonates also proceeded smoothly in the presence of the palladium catalyst and a substoichiometric amount of $Bu_4NPh_3SiF_2$ (TBAT) to give an array of quaternary cycloalkanones **15**.

Murakami and co-workers recently reported that palladium-catalyzed asymmetric decarboxylation of allyl α-acetamido-β-keto carboxylates **17** using Trost's ligand **18** gave optically active γ,δ-unsaturated α-aminoketones **19** with up to 90% *ee* (Scheme 4).[5] They observed that addition of phenol derivatives brought about an enhancement of the enantioselectivity.



Scheme 4. Decarboxylation of allyl α-acetamido-β-keto carboxylates. DCE = 1,1-dichloroethene.

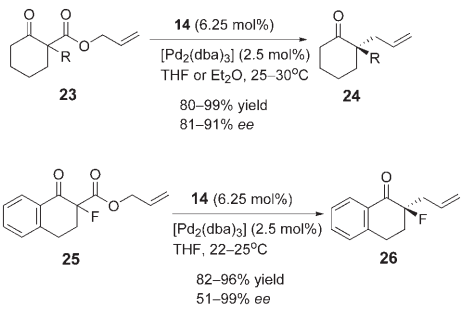
In their search of a process wherein enolate alkylation could be performed under neutral conditions and using a low concentration of enolate, Trost and Xu reported the palladium-catalyzed decarboxylation of allyl enol carbonates (Scheme 5).[6] Using chiral ligand **20**, the reaction was carried out with a wide variety of cyclic ketone-derived substrates **13** under optimized conditions. In general, the monoalkylated ketone products were obtained in good yields (64–99%) with high enantioselectivities (76–99% *ee*). The enol carbonate of 1-tetralone, a substrate often used to prepare ketones with a tertiary carbon center, was somewhat problematic because of potential racemization and the possibility of dialkylation. After screening the reaction conditions, Trost and Xu found that high yields and enantioselectivity could be attained by using dioxane as the solvent instead of toluene, as preferred previously. Following the success with the synthesis of cyclic ketones with tertiary carbon centers, Trost and Xu further expanded the substrate scope to acyclic carbonates **21**.[7] High yields and enantioselectivities were obtained for a wide range of acyclic ketones **22**.



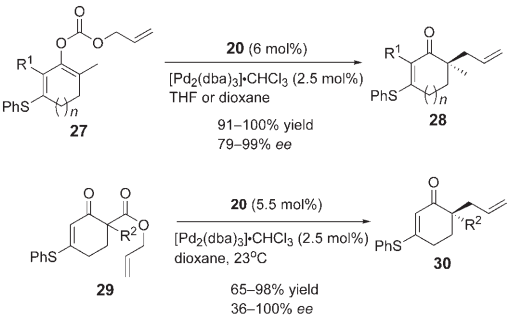
Scheme 5. Decarboxylation of allyl enol carbonates using ligand **20**.

Stoltz and co-workers recently reported a catalytic enantioconvergent synthesis of quaternary stereocenters from racemic β-keto carboxylates **23**.[8] By using ligand **14**, a variety of α-substituted 2-carboxyallyl cyclic ketones **23** were found to undergo decarboxylation and afford ketones **24** with quaternary stereocenters in good yields (80–99%) and with high enantioselectivities (81–91% *ee*; Scheme 6). Meanwhile, Nakamura et al. applied a very similar catalytic system to the decarboxylation of α-fluoro-2-carboxyallyl ketone **25**.[9] In general, high enantioselectivities were obtained for cyclic ketones (>85% *ee*), whereas only moderate enantioselectivities were reported for acyclic ketones (51–55% *ee*). Note that α-fluoro-2-carboxyallyl cyclohexanone was also used as a substrate in the report by Stoltz and co-workers,[8] who obtained the product in 80% yield and with 91% *ee*.

Trost et al. recently developed an efficient synthesis of vinylogous thioesters **28** and **30** by decarboxylation of enol carbonates and β-keto carboxylates (Scheme 7).[10] The products thus obtained are precursors for γ,γ-disubstituted cycloalkenones.



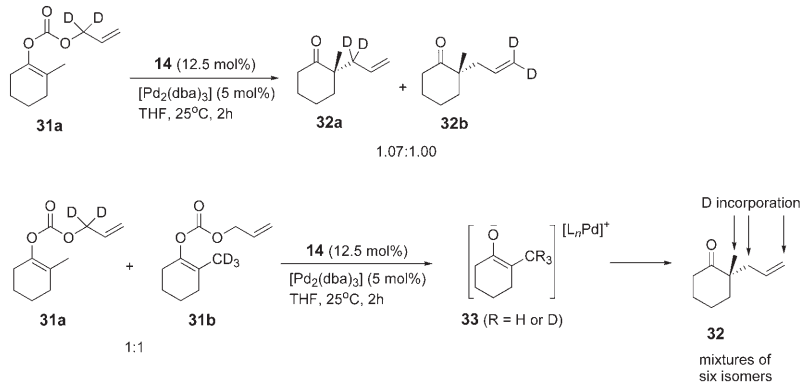
Scheme 6. Decarboxylation of allyl β-keto carboxylates.



Scheme 7. Decarboxylation of vinylogous thioesters.

The promising synthetic applications of this palladium-catalyzed decarboxylative AAA reaction have triggered extensive mechanistic investigations. As β-keto carboxylates with quaternary stereocenters, such as **23**, **25**, and **29**, smoothly undergo decarboxylative allylation, it suggests that the decarboxylation likely precedes C–C bond formation and that ketone enolates are possibly true intermediates. An interesting mechanistic study was carried out using deuterium-labeled substrates (Scheme 8),[8] concluding the existence of ketone enolates in solution. The reaction of dideuterated carbonate **31a** was performed under decarboxylative allylation conditions, and the deuterium label was almost equally distributed between the termini of the allyl fragment in the products. In a crossover experiment, an equimolar amount of carbonates **31a** and **31b** was subjected to the same reaction conditions. NMR spectroscopic analysis of the product showed deuterium scrambling between the allyl termini as expected. Furthermore, from mass spectrometric analysis of the product mixture it appeared that all six possible products were formed in the reaction, including those derived from crossover reactions. Interpretation of these results suggests that an achiral ketone enolate **33** must exist in solution for some period under the above reaction conditions.

In summary, by tethering the allyl moiety and nucleophile togeth-



Scheme 8. Mechanistic study using deuterium-labeled enol carbonates **31a**, **b**.

er, the palladium-catalyzed decarboxylative AAA reaction provides a facile means to alkylate relatively hard nucleophiles such as ketone enolates. With appropriate chiral ligands, the reaction can be delivered in high yields and with excellent selectivity. The utilization of neutral conditions and the possibility to prepare products that are not accessible by traditional Tsuji–Trost allylic alkylation warrant its wide applications in organic synthesis.[11]

Published online: July 21, 2006

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[11] After submission of this manuscript, Stoltz and McFadden reported the total synthesis of (+)-dichroanone utilizing a Pd-catalyzed decarboxylative AAA reaction as a key step to install a chiral quaternary carbon center. For details, see: R. M. McFadden, B. M. Stoltz, *J. Am. Chem. Soc.* **2006**, *128*, 7738–7739.

