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A palladium-catalysed enolate alkylation cascade for the formation of adjacent quaternary and tertiary stereocentres

Jan Streuff[1], David E. White[1], Scott C. Virgil[2] and Brian M. Stoltz[1]*

The catalytic enantioselective synthesis of densely functionalized organic molecules that contain all-carbon quaternary stereocentres is a challenge to modern chemical methodology. The catalytically controlled, asymmetric α-alkylation of ketones represents another difficult task and is of major interest to our and other research groups. We report here a palladium-catalysed enantioselective process that addresses both problems simultaneously and allows the installation of vicinal all-carbon quaternary and tertiary stereocentres at the α-carbon of a ketone in a single step. This multiple bond-forming process is carried out on readily available β-ketoester starting materials and proceeds by conjugate addition of a palladium enolate, generated *in situ*, to activated Michael acceptors. As a result, the CO_2 moiety of the substrate is displaced by a C–C fragment in an asymmetric cut-and-paste reaction with high yield, diastereomeric ratio and enantiomeric excess.

The enantioselective generation of carbon stereocentres with four other carbon substituents (also called quaternary or all-carbon quaternary stereocentres) is a task synthetic chemists are confronted with regularly[1]. Several methods have been developed to address this problem, but catalytic approaches remain challenging[2,3]. Furthermore, when additional carbon stereocentres adjacent to the quaternary carbon are required, the available choices to install both in one reaction are extremely limited. Although the combination of quaternary and secondary stereocentres can be introduced by aldol, cycloaddition, Michael or even cross-coupling reactions, only a few catalytic methods exist that forge adjacent quaternary and tertiary carbon stereocentres. This motif was introduced successfully into organic molecules by α-functionalization of carbonyl groups, as demonstrated in recent reports[4–9]. However, these approaches mostly rely on organic catalysts based on quinine or proline[4–7] and only two enantioselective transition-metal catalysed examples have been published so far[8,9]. Interestingly, in both cases strongly coordinating substrates, such as 1,3-diketones, β-ketoesters or α-cyanoesters, were required to achieve good selectivity. Other examples, for instance the elegant work of Overman and co-workes, demonstrated the feasibility of palladium catalysis to construct adjacent quaternary, tertiary or even vicinal quaternary stereocentres in a single double-Heck reaction[10,11]. These diastereoselective reactions employ an achiral catalyst and rely on substrate-directed stereocontrol. Palladium-catalysed tandem reactions of this type have applications in intramolecular, diastereoselective coupling reactions[12]. Intermolecular examples, especially those that involve π-allyl palladium species, are less common, but some examples with high diastereoselectivities have been reported recently[13–15]. Therefore, an approach to the formation of vicinal quaternary and tertiary stereocentres that proceeds via a palladium-catalysed multiple bond-forming process is appealing.

The enantioselective α-functionalization of ketones has been achieved by means of palladium catalysis, and over the past decade significant progress has been made in α-allylation[16], vinylation[17] and arylation[18] reactions. A transition-metal catalysed α-alkylation of ketones was reported by Jacobsen and co-workers who used chromium–salen complexes as catalysts to yield quaternary stereocentres[19,20]. The requirement for tin enolates, which have to be synthesized in advance and are presumably toxic, as starting materials is a strong limitation in this case.

Over the past few years, our group has been interested in novel methodologies for the generation of all-carbon quaternary stereocentres, which led to the development of an enantioselective, palladium-catalysed allylic α-alkylation of ketones. This process allows the construction of such stereocentres from silyl enol ethers, enol carbonates[21] or readily available racemic β-ketoesters **1** (path I, Fig. 1)[22]. We also demonstrated that the intermediate of this reaction, presumably a palladium enolate (**A**)[23], can be intercepted by a strong electrophile-like H^+ to generate enantioenriched α-protonated products (path II, Fig. 1)[24,25].

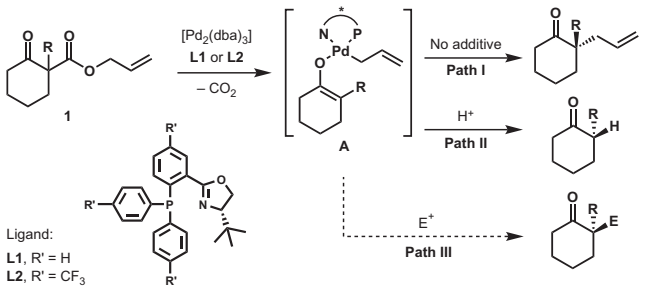
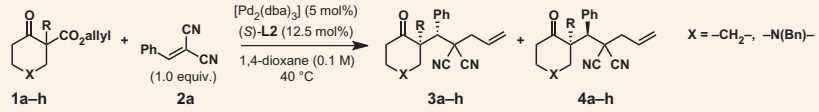


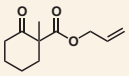
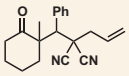
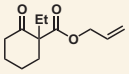
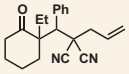
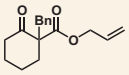
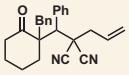
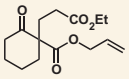
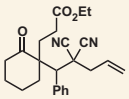
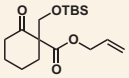
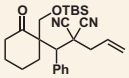
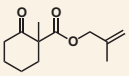
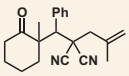
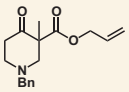
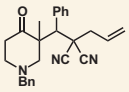
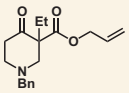
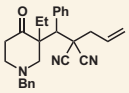
Figure 1 | Concept for the enantioselective functionalization of palladium enolates. Three pathways for the palladium-catalysed generation of α-functionalized ketones are shown. A palladium catalyst generated from $[Pd_2(dba)_3]$ and ligand L undergoes oxidative addition to β-ketoester **1** with the loss of CO_2 to form an enolate intermediate **A**. This palladium enolate can either react to yield enantioenriched α-alkylated products (path I) or, in the presence of a proton source, to give α-protonated products (path II). The envisioned path III would form miscellaneous enantioenriched, α-substituted ketones depending on other electrophilic additives (E^+) that intercept enolate **A**.

[1]The Arnold and Mabel Beckman Laboratories of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, 1200 E. California Blvd, Pasadena, California 91125, USA, [2]Caltech Center for Catalysis and Chemical Synthesis, California Institute of Technology, 1200 E. California Blvd, Pasadena, California 91125, USA. *e-mail: stoltz@caltech.edu

Table 1 | Enantioselective decarboxylative enolate alkylation cascade.



1a–h 2a 3a–h 4a–h

Entry	Substrate	Product	Time (hours)	Yield (%)*	d.r. 3:4†	e.e. 3 (%)	e.e. 4 (%)
1	 1a	 3a, 4a	24	99	1:6.1	77	87
2	 1b	 3b, 4b	48	91	1:3.5	95	99
3‡			72	88	1:3.4	88	97
4	 1c	 3c, 4c	40	49	1:1.9	85	88
5§			65	65	1:1.9	93	94
6	 1d	 3d, 4d	24	56	1:3.3	82	89
7‖	 1e	 3e, 4e	24	56	1:1.3	69	70
8¶	 1f	 3f, 4f	72	57	1:2.4	75	81
9	 1g	 3g, 4g	20	97	1: >20	-	89
10	 1h	 3h, 4h	48	99	1: >20	71	97

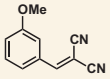
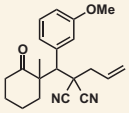
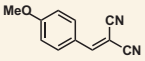
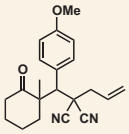
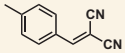
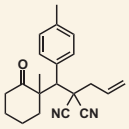
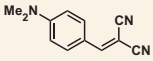
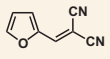
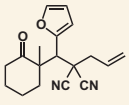
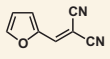
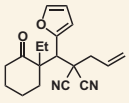
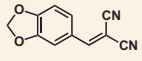
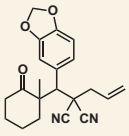
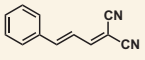
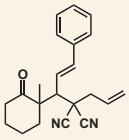
General reaction conditions: **1** (0.3 – 0.5 mmol), **2** (1.0 equiv.), [$Pd_2(dba)_3$] (5 mol%), **L2** (12.5 mol%), 1,4-dioxane (0.1 M), 40 °C. *Combined isolated yield. †Determined by ^{1}H NMR spectroscopy. ‡Reaction carried out on a 1 mmol scale with 2.5 mol% [$Pd_2(dba)_3$] and 6.25 mol% **L2**. §Reaction carried out at 23 °C. ‖Pd(pmdba)$_2$ (10 mol%) was used as a precatalyst (pmdba = bis(4-methoxybenzylidene)acetone). ¶Reaction carried out at 60 °C.

To expand this enolate-trapping approach towards the broader goal of establishing vicinal stereocentres and to provide a general approach for the α-functionalization of ketones, we examined the use of other prochiral electrophiles (path III, Fig. 1). An electrophilic additive had to be identified that met the following crucial requirements:

- There should be no interference with the oxidative addition of the palladium(0) catalyst into the allyl ester functionality.
- The reaction of the palladium enolate with the electrophilic additive must be preferred to intramolecular allylic α-allylation.
- A scavenger for the allyl fragment must be provided.

In our first experiments carbon electrophiles, such as acyclic or cyclic enones, were probed for their capability to intercept the intermediate enolate, but in these cases only the regular allylic alkylation product was observed. As a consequence, we were drawn to earlier reports by Yamamoto and co-workers of intercepted enolate alkylation by highly electrophilic conjugate acceptors, such as benzylidenemalononitrile **2a** (Table 1)[26,27]. Herein, we describe the development of an enantioselective, palladium-catalysed decarboxylative alkylation of ketones that forges all-carbon quaternary stereocentres with an adjacent tertiary stereocentre in good yield and stereoselectivity. This reaction represents a rare example of an asymmetric palladium-catalysed tandem process.

Table 2 | Asymmetric enolate alkylation of substrates 1a or 1b with different electrophiles.

Entry	Electrophile	Product	Time (hours)	Yield (%)*	d.r. 3:4†	e.e. 3 (%)	e.e. 4 (%)
1	 2b	 3i, 4i	68	78	1:8.2	71	86
2	 2c	 3j, 4j	36	87	1:7.8	73	88
3	 2d	 3k, 4k	16	76	1:6.2	75	87
4	 2e	 3l, 4l	18	22	1:8.9	78	99
5‡			18	54	1: >20	n.d.	99
6	 2f	 3m, 4m	36	87	1:3.5	65	81
7	 2f	 3n, 4n	36	92	1:2.3	89	96
8	 2g	 3o, 4o	24	99	1:14.0	58	95
9§	 2h	 3p, 4p	24	83	1:9.4	64	82

For general reaction conditions, see Table 1. *Combined isolated yield. †Determined by ^{1}H NMR spectroscopy. ‡$Pd(dmdba)_2$ (10 mol%) was used as a catalyst precursor and the reaction carried out on 0.1 mmol scale (n.d. = not determined). §Only the 1,4-addition product was observed as determined by gradient heteronuclear multiple-bond correlation NMR spectroscopy.

Results

In our initial experiments, we found that the exposure of the β-ketoester (±)-**1a** (Table 1)[28] to catalytic amounts of tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$] and (*S*)-*t*-butylphosphinooxazoline (**L1**)[29] in the presence of electrophile **2a** followed the desired reaction pathway, and efficiently produced diastereomers **3a** and **4a** (82% conversion), albeit with moderate diastereomeric ratio (d.r.) and enantiomeric excess (e.e.) (1:3.1 d.r., 42% and 63% e.e.; see Supplementary Information for details). After careful optimization, the combination of an electronically modified phosphinooxazoline ligand (**L2**, 12.5 mol%)[30] and [$Pd_2(dba)_3$] (5 mol%) in 1,4-dioxane at 40 °C produced diastereomers in high enantioselectivity. With only one equivalent of electrophile **2a**, the diastereomeric products **3a** and **4a** were isolated in 99% yield, 1:6.1 d.r., and 77% e.e. and 87% e.e., respectively (Table 1, entry 1).

We then applied these conditions to a series of substrates with different substitutions at the α-carbon, the allyl functionality or the backbone of the cyclic ketone. The enantiomeric excess

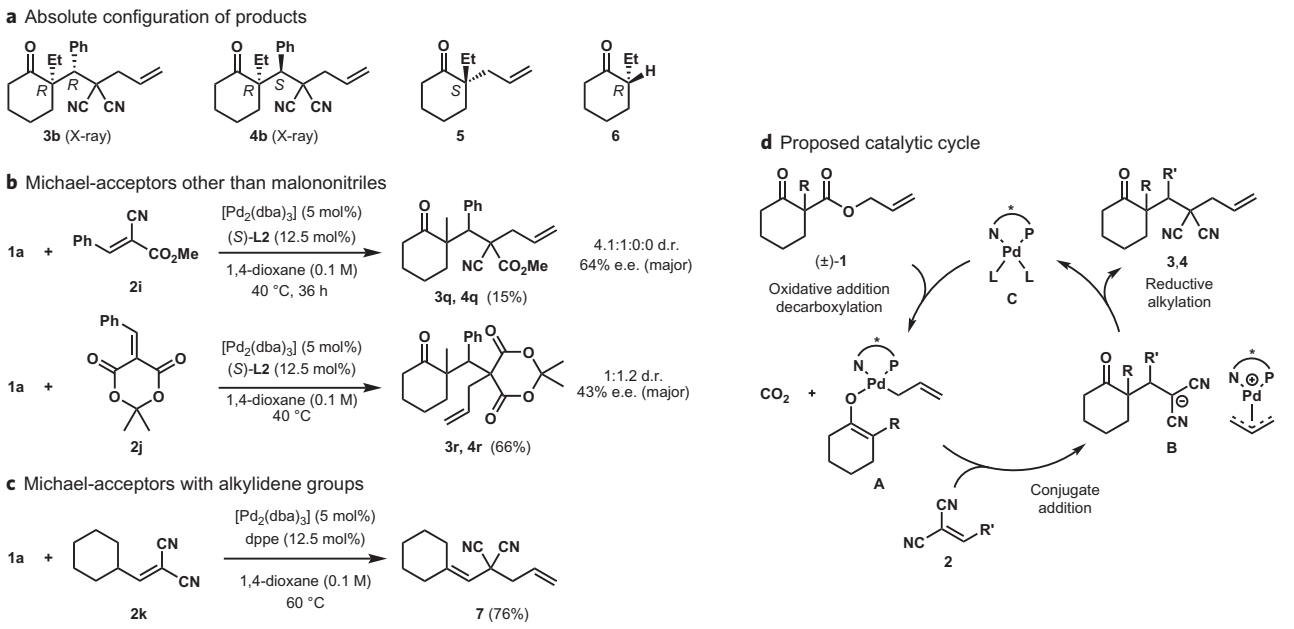


Figure 2 | Absolute stereochemistry and limitations of the palladium-catalysed enolate alkylation. a, The absolute configuration at the α-carbon of the major diastereomer **4b** matched the product from the previously reported palladium-catalysed decarboxylative protonation (**6**) and is opposite to the configuration of the regular decarboxylative allylic alkylation (**5**). **b**, For Michael acceptors (other than malononitriles), electrophiles **2i** and **2j** also led to the required products, but with diminished yields and stereoselectivities. Products **3q** and **4q**, however, have three continuous quaternary and tertiary stereocentres. **c**, An alkyl-substituted electrophile (alkylidene Michael acceptor) did not yield any desired product. Instead, olefin isomerization and allylic alkylation of **2k** were observed. **d**, A catalytic cycle is proposed, which starts with an oxidative addition to the substrate that involves decarboxylation to give intermediate **A**, followed by conjugate addition (intermediate **B**) and reductive alkylation to give intermediate **C**.

improved significantly when the α-substituent was changed to an ethyl group, and the desired product was isolated with 99% e.e. (Table 1, entry 2). Other α-substituents, such as benzyl groups, esters or protected alcohols, were also tolerated (Table 1, entries 4–7), but in some cases allylic alkylation of the enolate was observed as a side reaction, which led to decreased yields (Table 1, entries 4, 6 and 7). This side reaction was suppressed by lowering the reaction temperature to 23 °C (Table 1, entry 5). Moreover, the reaction also tolerated substitution on the allyl fragment (Table 1, entry 8). In addition to cyclohexanones, 1,4-piperidinone-derived substrates furnished the corresponding products in high yield and good enantioselectivity, with remarkably high diastereomeric ratio (Table 1, entries 9 and 10).

Next, the scope of the electrophile was explored. The reaction performed well with arylidenemalononitriles derived from *m*- and *p*-anisaldehyde, which allowed the introduction of substituted aryl groups at the stereocentre β to the ketone (Table 2, entries 1 and 2). Methyl or dimethylamino substituents were also introduced at the 4-position (Table 2, entries 3 and 4). Although the diastereo- and enantioselectivity were impressive in the latter case, the yield was again low because of significant allylic enolate alkylation. Here, a change of the palladium precursor to $Pd(dmdba)_2$ (dmdba = bis(3,5-dimethoxybenzylidene)acetone) slightly increased the reaction outcome towards the conjugate addition product (Table 2, entry 5). Importantly, the versatile 2-furanyl substituent was installed with both high yield and high enantioselectivity (Table 2, entries 6 and 7). Finally, a benzodioxole and a styrene group were introduced successfully at the tertiary centre in good yield and selectivity (Table 2, entries 8 and 9), with exclusive regioselectivity in the latter case.

As an initial probe to study the mechanism, the absolute stereochemistry of diastereomeric products **3b** and **4b** was determined as (*R*,*R*) and (*R*,*S*) by single-crystal X-ray analysis (Fig. 2a, see Supplementary Information for details). Interestingly, the absolute configuration at the α-quaternary centre is inverted compared with the products from our standard, asymmetric allylic alkylation (compare **3b** and **4b** with **5**), but matches the cyclohexanone products obtained from our protonation procedure (for example, **6**) (Fig. 2).

Strong electron-withdrawing groups on the Michael acceptor are necessary to achieve the desired conjugate addition. It was possible to use reagents other than malononitriles, such as α-cyanoacetate and Meldrum's acid derivatives, but the yields and stereoselectivities were reduced significantly (Fig. 2b). Although products **3q** and **4q** were isolated in only 15% yield, in this case a series of two quaternary and one tertiary neighbouring stereocentres was formed by a single palladium-catalysed transformation, albeit with 64% e.e. Notably, the conversion increased significantly with the achiral, but more electron-rich, bis(diphenylphosphino)ethane (dppe) ligand (96%) and the same two predominant diastereomers were observed as with ligand **L2**. However, initial attempts to use alkyl-substituted acceptors were not successful and, instead, transfer of the allyl group to the alkylidenemalononitrile proceeded to yield adduct **7** (Fig. 2c).

Discussion

In general, the diastereoselectivity is good for most products and some examples show remarkable results with only trace amounts of a second diastereomer formed. The amount of direct allylic alkylation, as observed in some cases, was lowered either by a temperature change or by using a different palladium precursor, which suggests a possible dependence on the coordination behaviour of the acceptor and the catalyst. Indeed, preliminary experimental results suggest a resting state different to that of the η^1-allylpalladium carboxylate observed for the enantioselective allylic alkylation of ketones and may involve coordination of the electrophile[31]. Further studies are currently underway and any comment on the specific details of the process is speculative at this stage. Although

it is not possible to provide a detailed picture at this time, a plausible simplified catalytic cycle is outlined in Fig. 2d. First, palladium(0) catalyst **C** reacts with substrate **1**, with the loss of CO_2, to form the η^1-allylpalladium enolate **A**. Next, conjugate addition to **2** occurs and results in stabilized intermediate **B**, which consists of a π-allyl palladium cation and a deprotonated malononitrile. Reductive alkylation then yields the diastereomeric products **3** and **4** and regenerates catalyst **C**.

In conclusion, a highly enantio- and diastereoselective, palladium-catalysed α-alkylation process has been developed that proceeds via the trapping of an intermediary palladium-enolate species by conjugate addition to a prochiral activated Michael acceptor. From simple racemic β-ketoester starting materials, the reaction allows the asymmetric construction of densely functionalized molecules that possess an all-carbon quaternary centre next to a tertiary centre. Currently, expansion of this methodology to include other substrates and applications in multistep synthesis is in progress. Finally, mechanistic studies are also underway and will be reported in due course.

Methods

A flame-dried 50 ml Schlenk tube was charged with $[Pd_2(dba)_3]$ (13.7 mg, 0.015 mmol, 5 mol%) and **L2** (22.2 mg, 0.0375 mmol, 12.5 mol%) under argon, and 3 ml of freshly distilled 1,4-dioxane added. After stirring for 30 minutes at 23 °C, **1** (0.3 mmol, 1.0 equiv.) and **2** (0.3 mmol, 1.0 equiv.) were added simultaneously. The resulting yellow–green solution was stirred at the reported temperature for the reported amount of time (see Tables 1 and 2). The consumption of starting material was monitored by thin layer chromatography ($KMnO_4$ stain) or by NMR analysis of a small sample. The solvent was removed under reduced pressure and the diastereomeric ratio determined by crude ^{1}H NMR spectroscopy. Isolation and separation of products **3** and **4** were achieved by flash chromatography in hexane–ethyl acetate mixtures in the given combined yields (Tables 1 and 2). The enantiomeric excess was determined by either high-performance liquid chromatography or supercritical fluid chromatography of the purified product (see Supplementary Information).

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Author contributions

J.S. planned and carried out the experimental work and wrote the manuscript. D.E.W. and S.C.V. took part in the initial reaction development and screening experiments. B.M.S. initiated and directed the project. All authors commented on the manuscript.

Additional information

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