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Synergistic Catalysis for the Asymmetric [3+2] Cycloaddition of Vinyl Aziridines with α,β-Unsaturated Aldehydes

Line Næsborg, Fernando Tur, Marta Meazza, Jakob Blom, Kim Søholm Halskov and Karl Anker Jørgensen*[a]

Abstract: The first asymmetric [3+2] cycloaddition of vinyl aziridines with α,β-unsaturated aldehydes, based on synergistic catalysis, is disclosed. This methodology allows for the formation of attractive pyrrolidine structures in good yields (up to 84%), moderate diastereoselectivities and high enantioselectivities (up to >99% *ee*). Additionally, a tricyclic pyrrolidine core structure found in biologically active molecules is synthesized in a one-pot fashion using the presented reaction concept. Finally, a mechanistic proposal is outlined.

Nitrogen heterocycles are important structural motifs due to their frequent presence in natural products and pharmaceuticals.[1] Therefore, the development of efficient and selective synthetic strategies for the construction of nitrogen containing heterocycles is a long-standing goal in organic synthesis.[2] Among the various investigated approaches, aziridines have proven to be useful building blocks for the formation of nitrogen heterocycles.[3] Specifically, vinyl aziridines can be activated by transition metal catalysis to perform asymmetric allylic additions[4] and [3+2] cycloadditions (Figure 1, a).[5-8] Earlier examples employed highly activated electrophiles (*e.g.* isocyanates and related heterocumulenes) and double-activated alkenes;[5] however, more recent examples, requiring only mono-activated alkenes, alkynes and allenes have been disclosed.[6] In this context, Maruoka *et al*. recently disclosed a catalytic diastereoselective [3+2] cycloaddition between vinyl aziridines and electron-rich alkenes promoted by a thiyl radical-based organocatalyst.[7] Noteworthy, the majority of these reactions of vinyl aziridines with alkenes are diastereoselective versions.[6,7] Only two enantioselective reactions using vinyl aziridines have been disclosed;[8] however, these are restricted to *N*-tosyl vinyl aziridines having an alkyl substituent (except one case with very low diastereoselectivity) at the alkene reacting with vinyl ketones[8a] or methylene indolinones.[8b] Furthermore, the application of chiral transition metal catalysts with highly sophisticated ligands was necessary in order to achieve the desired reactivity and selectivity. This highlights that the asymmetric, catalytic [3+2] cycloaddition employing simple vinyl aziridines remains underdeveloped and is a challenging reaction. Furthermore, to the best of our knowledge, no examples of enantioselective reactions involving α,β-unsaturated aldehydes have been disclosed. Some of the challenges associated with this transformation are the diastereo- and enantiocontrol, as well as the use of substrates bearing different substitution patterns or protecting groups on the nitrogen. Therefore, novel methodologies selectively providing variations on the pyrrolidine ring are worth targeting for diversity-oriented synthesis.[9]

Recently, the field of synergistic catalysis has emerged as a new and powerful reaction concept, where the simultaneous catalytic activation of both substrates allows for unprecedented reactivity.[10] These synergistic catalytic systems offer the opportunity to induce enantioselectivity by using easily available and robust organocatalysts, circumventing *e.g.* the need for chiral ligands on the transition metal and also allows for reactions which have not been possible applying only transition-metal catalysis.

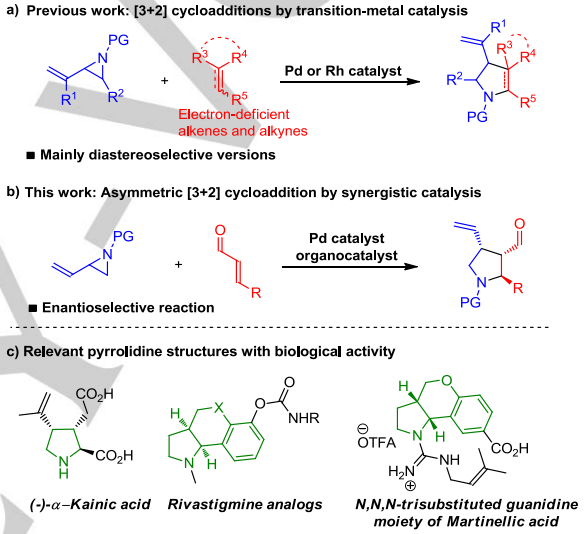


Figure 1. a) Previous work: [3+2] cycloadditions of vinyl aziridines with electron-deficient alkenes or alkynes. b) This work: [3+2]-cycloaddition of vinyl aziridines with α,β-unsaturated aldehydes based on synergistic catalysis. c) Relevant pyrrolidine structures with biological activity.

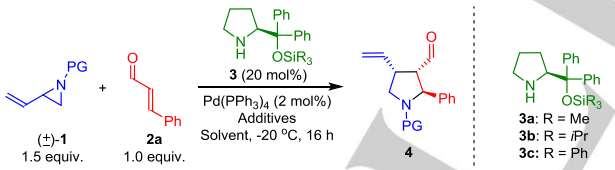
Inspired by previous works, in which synergistic catalysis was achieved by the combination of aminocatalysis and transition metal catalysis,[11] we envisioned that such an approach could mediate the reaction between simple vinyl aziridines and α,β-unsaturated aldehydes (Figure 1, b), as this reaction has not been possible by previous methods. The present reaction would afford highly attractive pyrrolidine scaffolds bearing 3 continuous stereocenters. The pyrrolidine structure represents an important substructure of nitrogen heterocycles, which is found in natural products, biologically active compounds as well as useful building blocks for organic synthesis (Figure 1, c).[12] The importance of pyrrolidines can be exemplified by α-Kainic acid[13] and the tricyclic pyrrolidine core structures illustrated in Figure 1, c. These tricyclic alkaloids display biological activity *e.g.* the inhibitory effects on acetylcholinesterase (Rivastigmine analogs),[14] and bradykinin B_1 and B_2 (Martinellic acid).[15] These compounds have been subjected to biological testing, as well as synthetic efforts towards concise total syntheses.[13-15]

In the following, we will disclose the first [3+2] cycloaddition of α,β-unsaturated aldehydes with vinyl aziridines by synergistic catalysis. The initial attempt for this reaction was performed with vinyl aziridine **1a** (PG = Bn), cinnamaldehyde **2a**, diphenylprolinolsilyl ether **3a** and $Pd(PPh_3)_4$ as the transition metal catalyst;

[a] L. Næsborg, Dr. F. Tur, Dr. M. Meazza, J. Blom, Dr. K. S. Halskov, Prof. Dr. K. A. Jørgensen
Department of Chemistry, Aarhus University, Langelandsgade 140, 8000 Aarhus C (Denmark)
E-mail: kaj@chem.au.dk

however, no significant reactivity was observed (Table 1, entry 1). Inspired by previous reports describing the importance of halide salts as additives,[6a,8a] we investigated the reaction in the presence of tetrabutylammonium chloride (TBAC) and benzoic acid (Table 1, entries 2,3). Without addition of benzoic acid, no conversion was observed. The combination of TBAC and benzoic acid provided 84% conversion into the desired product **4a** in excellent enantioselectivity. Various salt additives were investigated; however, none provided high conversions compared to TBAC (Table 1, entries 4-6). In attempts to achieve full conversion other solvents were tested (Table 1, entries 7,8) and Et_2O provided full conversion to **4a**, with good d.r. (90:10) and high enantioselectivity (96% *ee*). We also attempted to improve the diastereoselectivity by increasing the steric shielding of catalyst **3**. The diastereoselectivity increased to >95:5 d.r. employing catalysts **3b** or **3c**; however the conversion decreased considerably (Table 1, entries 9,10). In order to improve the conversion, a series of reactions were performed at higher temperature; however, these reactions gave a decrease in diastereoselectivity and therefore we focused only on the application of catalyst **3a** (see Supporting Information). We have also tested other *N*-protecting groups on the vinyl aziridine. Applying *N*-(*o*-nitrobenzyl) vinyl aziridine **1b** gave a slower reaction leading to 40% yield, 90:10 d.r. and moderate enantioselectivity (67% *ee*) (Table 1, entry 11). Subsequently, *N*-tosyl vinyl aziridine **1c** was also tested under the optimized conditions, but unexpectedly no reactivity was observed (Table 1, entry 12). The latter observations indicate that electron-deficient protecting groups on the vinyl aziridine **1** result in lower reactivity, potentially due to the lower nucleophilicity of the nitrogen. Thus, the present development complements the application of *N*-tosyl vinyl aziridines used previously,[8] as the novel system allows the application of a different class of *N*-protecting group on the vinyl aziridine.

Table 1: Optimization of the reaction conditions for the synergistic catalytic asymmetric [3+2] cycloaddition of vinyl aziridines **1** with cinnamaldehyde **2a**.[a]



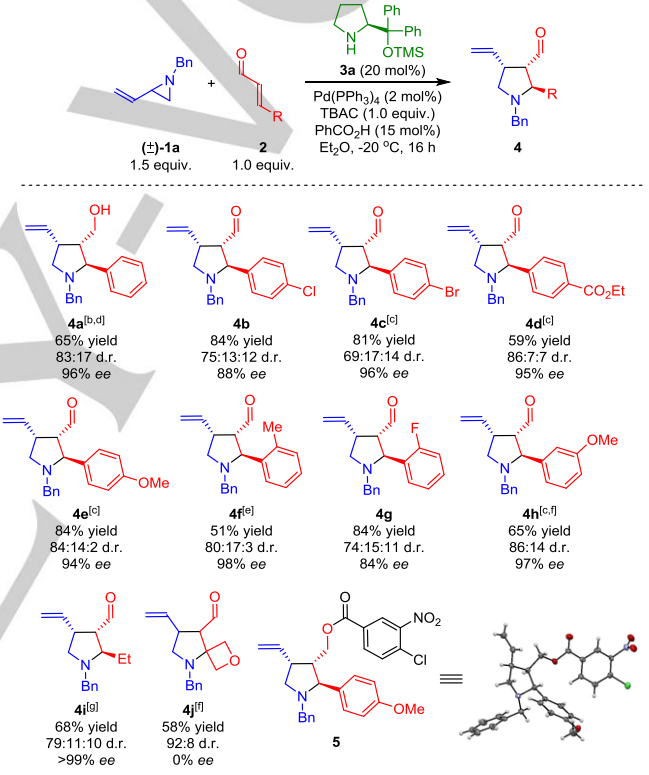
1a: PG = Bn; **1b**: PG = (*o*-NO_2)Bn; **1c**: PG = Ts

Entry	Solvent	Add.[b]	(±)-**1**	Conv. (%)[c]	d.r.[d]	*ee* (%)[e]
1	THF	-	**1a**	<5	-	-
2	THF	TBAC	**1a**	<5	-	-
3[f]	THF	TBAC, BA	**1a**	84	87:13	96
4[f]	THF	TBAB, BA	**1a**	<5	-	-
5[f]	THF	KCl, BA	**1a**	27	-	-
6[f]	THF	KBr, BA	**1a**	27	-	-
7	MeCN	TBAC, BA	**1a**	71	81:16:3	96
8	Et_2O	TBAC, BA	**1a**	100 (65)[g]	90:10	96
9[h]	Et_2O	TBAC, BA	**1a**	23	>95:5	-
10[i]	Et_2O	TBAC, BA	**1a**	56	>95:5	-
11	THF/Et_2O[j]	TBAC, BA	**1b**	87	90:10	67
12	Et_2O	TBAC, BA	**1c**	<5	-	-
13[k]	Et_2O	TBAC, BA	**1a**	<5	-	-
14[l]	Et_2O	TBAC, BA	**1a**	<10	-	-

[a] Reactions were performed on a 0.1 mmol scale. See Supporting Information for details. [b] 1.0 equiv. of halide source additive and 0.15 equiv. of BA were added. [c] Conversion of limiting reagent determined by ^{1}H NMR analysis of the crude reaction mixture of **4**. [d] d.r. determined by ^{1}H NMR analysis of the crude reaction mixture of **4**. [e] Determined by chiral stationary phase UPC^2. [f] Reaction performed with 4 mol% Ph_3P as ligand (premixed with $Pd(dba)_2$). [g] An *in-situ* reduction was performed prior to isolation. Isolated yield of **4a** is shown in parenthesis. [h] Catalyst **3b** was used, reaction time: 24 h. [i] Catalyst **3c** was used, reaction time: 24 h. [j] THF/Et_2O 1:1 as solvent mixture, reaction time: 48 h. [k] No palladium catalyst was added. [l] No diphenylprolinol-silyl ether catalyst **3** was added. TBAC = Tetrabutylammonium chloride, TBAB = Tetrabutylammonium bromide, BA = Benzoic acid.

With the best conditions in hand, we set out to explore the scope of the reaction. The vinyl aziridine **1a** was tested in the reaction with a wide range of different α,β-unsaturated aldehydes **2** (Scheme 1).

Scheme 1: Scope of the asymmetric [3+2] cycloaddition of vinyl aziridine **1a** with α,β-unsaturated aldehydes **2**.[a]



[a] Reactions were performed on a 0.1 mmol scale. Absolute configuration was determined by X-ray crystallography analysis of **5** and the remaining structures were assigned by analogy (see Supporting Information for details). d.r. was determined by ^{1}H NMR analysis of the isolated products. *ee* was determined by chiral stationary phase UPC^2. [b] An *in-situ* reduction was performed prior to isolation. [c] THF/Et_2O 1:4 as solvent mixture. [d] THF/Et_2O 1:1 as solvent mixture. [e] Reaction time: 24 h. [f] Reaction time: 48 h. [g] 1.0 equiv. of **1a** and 1.5 equiv. of **2g** were used.

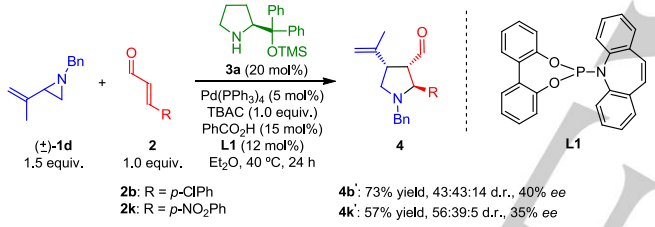
We focused first on α,β-unsaturated aldehydes having aromatic moieties with substitution in the *para*-position. These substrates performed well in the reaction giving good yields, good to moderate diastereoselectivities and high to excellent enantioselectivities (88-96% *ee*) for products **4b**-**e**. The diastereoselectivities obtained were satisfactory, as the diastereocontrol was an anticipated challenge for this type of transformation since general methods providing high selectivities are rare.[6a,8a] *Ortho*-substituted aromatic moieties also reacted under the optimized reaction conditions obtaining products **4f,g** in 98% *ee* and 84% *ee* respectively. A *meta*-substituted aromatic moiety

also reacted smoothly, providing the desired product **4h** in good yield, modest to good diastereoselectivities and excellent enantioselectivity.

We also decided to test aliphatic α,β-unsaturated aldehydes. For 2-pentenal, the reaction proceeded smoothly giving **4i** in moderate yield, good diastereoselectivity and excellent enantioselectivity (>99% *ee*). We have also tried to apply crotonaldehyde and 2-heptenal as α,β-unsaturated aldehydes. For crotonaldehyde a 1:1 d.r. was found, while 2-heptenal provided a 6:1 d.r. However, it was observed that the aldehydes and products decomposed under the reaction conditions and only low conversions were achieved. Finally, we included an α,β-unsaturated aldehyde containing an oxetane as a privileged moiety in *e.g.* medicinal chemistry.[16] Unexpectedly, we observed that the product **4j** was formed as a racemate (*vide infra*).

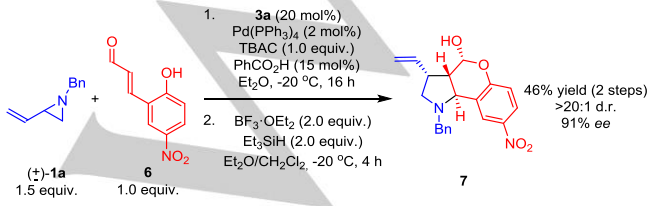
In the only previous example of a chiral transition metal catalyzed reaction of vinyl aziridines with vinyl ketones,[8a] an alkyl substituent on the alkene was necessary to obtain good diastereoselectivity. Therefore, we tested vinyl aziridine **1d** bearing a methyl substituent on the allylic moiety. However, this substrate required modified reaction conditions and the use of an achiral phosphoramidite ligand **L1** to obtain the necessary reactivity at the expense of decreasing stereoselectivity for products **4b'**,**k'**. (Scheme 2).

Scheme 2: Reaction of vinyl aziridine **1d** with α,β-unsaturated aldehydes **2**.



Subsequently, we turned our attention towards further applications of the developed catalytic system. As the tricyclic structures displayed above (Figure 1, c) are of interest, we set out to exploit the novel methodology in order to obtain a similar core-structure. It was envisioned that an α,β-unsaturated aldehyde bearing an aromatic moiety with an *ortho*-OH functionality **6** could react in the presented [3+2] cycloaddition with vinyl aziridine **1a** followed by a ring-closing reaction to afford the desired tricyclic scaffold. Unexpectedly, the hemiacetal was not reduced under the reaction conditions; however, the product **7** could be obtained in a decent yield and in excellent diastereo- and enantioselectivity (Scheme 3).

Scheme 3: Asymmetric [3+2] cycloaddition of vinyl aziridine **1a** with α,β-unsaturated aldehyde **6**, followed by a ring-closing reaction affording tricyclic pyrrolidine **7**.



Moreover, we tested the methodology with vinyl thirane and vinyl epoxide. The vinyl thirane gave no conversion to the desired product under the optimal reaction conditions. The vinyl epoxide reacted without aminocatalyst to give the 1,2-addition adduct in 89% yield and moderate diastereomeric ratio (see Supporting Information).

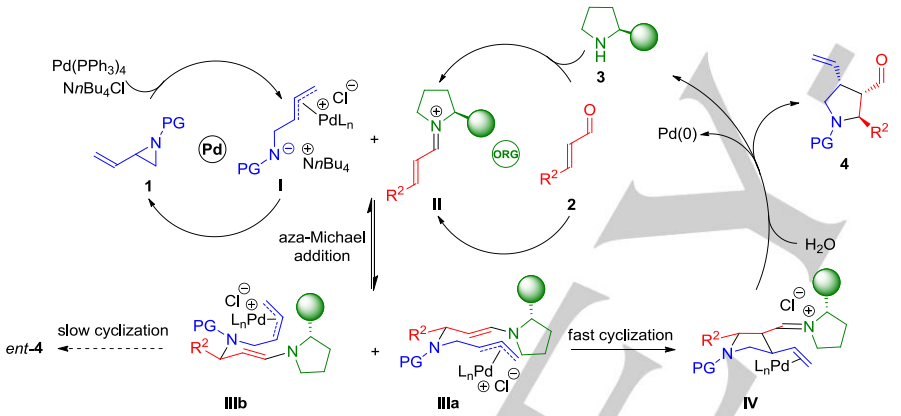
At this point, we focused on the mechanism of the novel synergistic reaction. We started out with a series of control experiments, employing only aminocatalyst **3a** in the model reaction of vinyl aziridine **1a** and cinnamaldehyde **2a**. Under the optimized reaction conditions we observed almost no conversion (<5%) to the intended product **4a**. Conducting the reaction only in the presence of $Pd(PPh_3)_4$ as catalyst led to the formation of **4a** in very low conversion (<10%). Therefore, a synergistic amino- and Pd(0) catalytic system is operating to facilitate the asymmetric [3+2] cycloaddition.

Previously reported examples with donor-acceptor cyclopropanes, epoxides or aziridines activated by transition-metal catalysis,[17] are described to operate through a dynamic kinetic asymmetric transformation (DYKAT).[4,18] Accordingly, the synergistic catalytic system was further investigated for the reaction of vinyl aziridine **1a** with 3-methoxycinnamaldehyde **2h**. To rule out the possibility of achieving high enantioselectivities from a dynamic kinetic resolution[19] we found that the racemic product **4h** did not undergo noticeable kinetic resolution under the optimized reaction conditions, using the chiral aminocatalyst **3**. Moreover, prolonged reaction times (up to 72 h) allowed us to recover the chiral product **4h** in a reproducible yield (65%) and unaltered enantiomeric purity (96% *ee*), thus leaving the enantioselective [3+2] cycloaddition as the only plausible reaction pathway. Reaction of **1a** with **2h** was also monitored to check the enantioselectivity of product **4h** at different time intervals. There was no deleterious effect on the enantioselectivity of **4h** as the conversion increased, suggesting that the cyclization step is not reversible. Further attempts to investigate whether the aza-Michael addition step of the zwitterionic π-allyl-Pd(II) intermediate onto the α,β-unsaturated aldehyde was reversible and enantioselective failed. Simplified synthetic equivalents of **1a** (*e.g. N*-benzylbut-3-en-1-amine) did not react with **2a** under the organocatalytic conditions with catalyst **3a**. Noteworthy is the intriguing result obtained for oxetane-derived α,β-unsaturated aldehyde **2j** which provided product **4j** as a racemate. This might be due to the lack of prochirality on the β-carbon atom of the α,β-unsaturated aldehyde employed in the reaction which could point towards a DYKAT type IV process.[20] However, when testing acrolein, 3-methyl-2-butenal or 3-methyl-cinnamaldehyde in the reaction, none of these α,β-unsaturated aldehydes reacted under the optimized reaction conditions.

Based on our experimental results and the previous works on Pd-based activation of vinyl aziridines[4] and iminium-ion catalyzed activation of α,β-unsaturated aldehydes,[21] we tentatively propose the mechanism outlined in Figure 2. First, the Pd(0) catalyst facilitates the ring-opening of the vinyl aziridine **1** by oxidative addition to form a zwitterionic π-allyl-Pd(II) intermediate **I**. A crucial role is assigned to the N*n*Bu_4Cl additive, as it

increases the nucleophilicity of intermediate **I** by preventing ion-pairing of the anionic nitrogen atom with the Pd(II).[6a] In a simultaneous separate cycle, an iminium-ion intermediate **II** is formed from the condensation of an α,β-unsaturated aldehyde **2** with the aminocatalyst **3**. Then, reversible aza-Michael addition of the *in-situ* generated intermediate **I** to intermediate **II** results in a rapid epimerization of diastereomeric intermediates **IIIa**, **IIIb** under the reaction conditions. Next, diastereomer **IIIa** preferentially undergoes a fast irreversible intramolecular cyclization which takes place on the *Si*-face of the chiral enamine. Subsequently, hydrolysis of iminium-ion intermediate **IV**, and concomitant decomplexation of the Pd(0) allow regeneration of both catalysts, thus completing the synergistic catalytic cycle. Overall, the asymmetric reaction can be considered as an asymmetric formal [3+2] cycloaddition, which is likely to proceed in a stepwise manner through a DYKAT type IV, generating the chiral pyrrolidine **4**.

Figure 2. Mechanistic proposal for the formal asymmetric [3+2] cycloaddition of vinyl aziridine **1** and α,β-unsaturated aldehyde **2**.



In conclusion, we have developed the first asymmetric [3+2] cycloaddition between vinyl aziridines and α,β-unsaturated aldehydes, based on synergistic palladium and aminocatalysis. It has been demonstrated that simple *N*-benzyl protected vinyl aziridines are compatible with α,β-unsaturated aldehydes expanding the substrate scope of current methodologies. The present strategy provides access to highly attractive pyrrolidine structures in good yields (up to 84%), moderate diastereoselectivities and high enantioselectivities (up to >99% *ee*). In addition, the utility of the products was demonstrated by a transformation resulting in a tricyclic core structure found in biologically active molecules. The novel synergistic reaction presented, complements the palladium catalyzed reactions in which enones and *N*-tosyl protected vinyl aziridines, bearing a methyl substituent on the allylic moiety, gave the best results. Furthermore, mechanistic investigations were performed and a mechanistic proposal was outlined.

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Keywords: Synergistic Catalysis • Vinyl Aziridines • Organocatalysis • Transition Metal Catalysis

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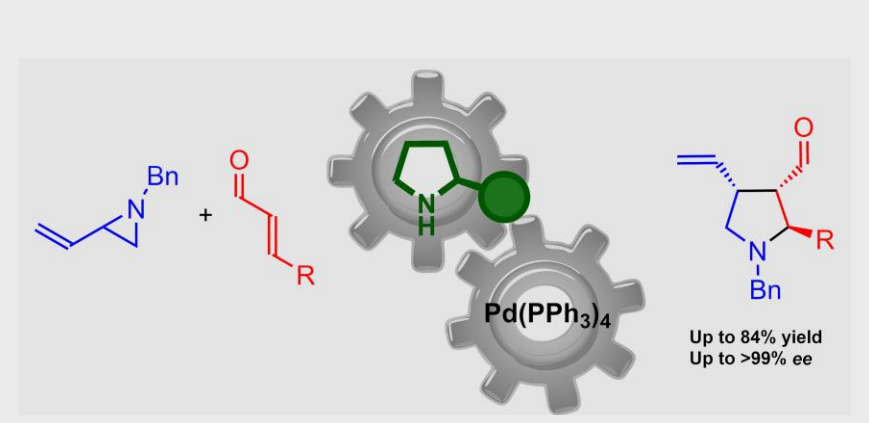

*Line Næsborg, Fernando Tur, Marta Meazza, Jakob Blom, Kim Søholm Halskov and Karl Anker Jørgensen**

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