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Synergistic N-Heterocyclic Carbene/Palladium-Catalyzed Umpolung 1,4-Addition of Aryl Iodides to Enals

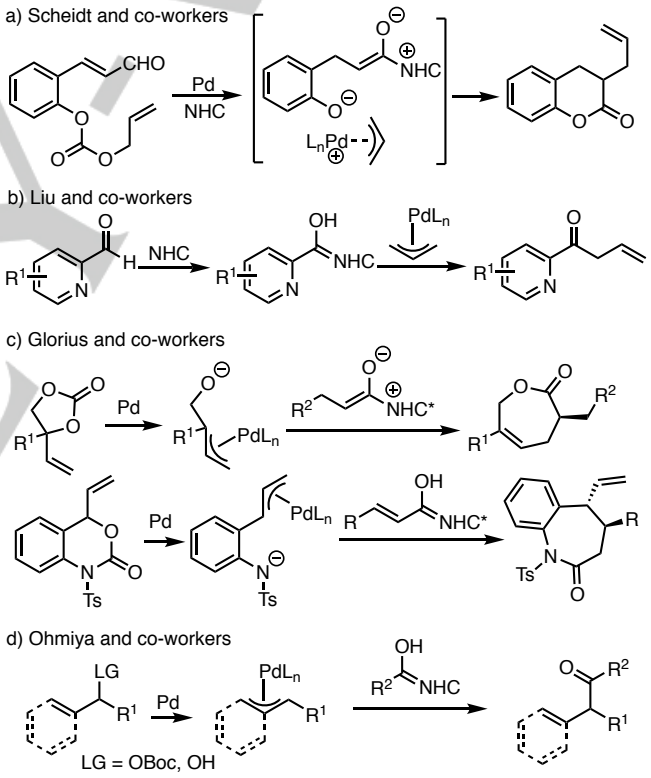
Wenjun Yang, Bo Ling, Bowen Hu, Haolin Yin, Jianyou Mao,* and Patrick J. Walsh*

Abstract: A (terpy)Pd/NHC cooperative catalyzed umpolung 1,4-addition of aryl iodides to enals to generate various bioactive β,β-diaryl propanoate derivatives is described. The system developed herein not only represents the first palladium-catalyzed arylation of NHC-bound homoenolates but also expands the scope of NHC-induced umpolung transformations. A diverse array of functional groups such as esters, nitriles, alcohols and heterocycles are tolerated under the mild conditions. This protocol also circumvents use of moisture-sensitive organometallic reagents.

Introduction

A powerful synthetic strategy is synergistic or cooperative catalysis, wherein one catalyst activates the nucleophile and a second catalyst activates the electrophile.[1] The two catalytic cycles intersect at the bond-forming event. The marriage of organocatalysts with transition metals in synergistic catalysis enables exploitation of the unique reactivity of these two catalyst classes, making possible novel bond-forming processes.[2] Recent progress employing amine[3] or phosphoric acid[4] catalysts with transition metal catalysts have met with significant success.[2], [5] *N*-Heterocyclic carbenes (NHCs) also rank among the most useful organocatalysts, promoting a host of unique transformations.[6] The partnering of NHCs with transition-metals in synergistic catalysis, however, remains less developed, presumably due to catalyst quenching via strong binding of the NHC to transition metals.[7]

We were attracted to NHCs because of their exceptional nucleophilicity and ability to invert the reactivity of aldehydes from electrophilic to nucleophilic, generating NHC-bound intermediates, including acyl anions,[8] homoenolate equivalents,[9] or enolates.[10] These species are best partnered with very reactive electrophiles, diminishing their applications. Activation of the electrophile with a transition metal catalyst, however, could dramatically increase the pool of electrophiles potentially suitable for reactions with NHC-activated intermediates. As shown by Scheidt[11] and co-workers (Scheme 1a), the NHC-activated species could react with allylic electrophiles upon interception of a palladium intermediate in the Tsuji-Trost reaction. Subsequently, an efficient allylation of (O-azaaryl)-carboxaldehydes was introduced by the Liu group using Pd/NHC dual catalysis (Scheme 1b).[12a][12b] Glorius and co-workers developed a highly enantioselective umpolung annulation of enals (Scheme 1c).[13] More recently, Ohmiya and co-workers reported NHC/Pd-catalyzed allylation/benzylation of alkyl aldehydes (Scheme 1d).[14] These impressive applications highlight the utility of Pd(π-allyl) and related intermediates in combination with NHCs in synergistic catalysis. To broaden the synthetic utility of NHC-bound nucleophilic intermediates in C–C bond-forming reactions, we set out to develop their union with less reactive electrophiles promoted by transition metal catalysts.



Scheme 1. The merger of NHC organocatalysis with palladium catalysis.

Herein, we disclose the first palladium-catalyzed 1,4-aryl addition to NHC-bound homoenolates with aryl iodides (Scheme 2). This work represents a valuable complement to traditional 1,4-addition of aryl organometallics to *α,β*-unsaturated esters with the advantage of avoiding moisture sensitive aryl zinc, lithium, magnesium, and boron reagents. These organometallic reagents are usually prepared from the aryl halides,[15] although in some cases they may be generated in situ (cross-electrophile coupling).[16] Our work also complements reductive Heck reactions, which require an external reducing agent.[17] Furthermore, the products generated herein are important

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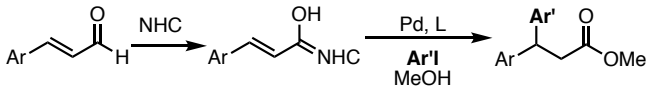
scaffolds in pharmaceutical chemistry and natural product synthesis.[18]



Scheme 2. NHC/Pd co-catalyzed 1,4-addition of aryl iodides to enals.

Our mechanism-based design was motivated by the nucleophilicity of NHC-bound homoenolates and the idea that they might undergo nucleophilic substitution with $L_nPd(Ar)I$ (Figure 1), in analogy to a transmetallation. In the organocatalytic cycle, addition of the NHC to an enal leads to formation of the NHC-bound homoenolate intermediate (**A**).[9i] In the Pd cycle, oxidative addition of the aryl iodide generates the activated electrophile (**B**).[19] The two catalytic cycles intersect when the homoenolate attacks the palladium to form a Pd–C bond in **C**, envisioned to proceed by displacement of the iodide. Reductive elimination from **C** forms the C–C bond. The NHC-bound intermediate (**D**) reacts with basic MeOH affording the *β*,*β*-diaryl propanoate (**3**), liberating the NHC catalyst. Despite the simplicity of the proposed mechanism, several challenges must be overcome: 1) NHCs are well known to exhibit strong coordination to palladium, resulting in catalyst quenching. 2) The addition of NHCs to enals can also generate enolates and acyl anions. These two species could be envisioned to react with aryl palladium intermediates, leading to byproducts. 3) The palladium-catalyzed Mizoroki-Heck reaction of aryl halides with α,β-unsaturated carbonyl compounds is known,[20] and would lead to undesired *β*,*β*-diaryl enals.

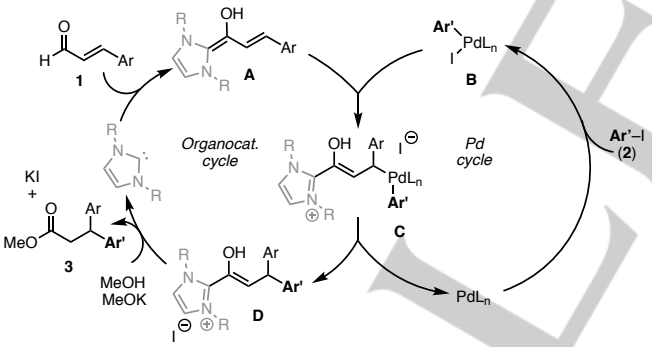
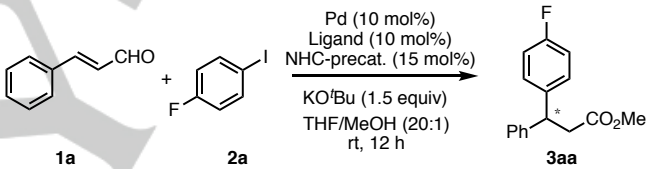


Figure 1. Strategy for the umpolung arylation.

With these formidable challenges in mind, our optimization was initiated with *trans*-cinnamaldehyde (**1a**) and iodobenzene (**2a**). Our hypothesis was that multidentate ligands on palladium would be needed to prevent coordination of the NHC. Thus, we examined 4 different NHC precursors (**N1 – N4**, 15 mol %, Table 1, bottom), using $Pd_2(dba)_3$ (5 mol %)/BINAP (10 mol %) as the metal catalyst, KO^{t}Bu (to deprotonate the NHC-precatalyst in Figure 1) in THF : MeOH (20 : 1) at room temperature for 12 h (Table 1, entries 1–4). To our delight, more sterically hindered NHC precursor **N1** furnished the 1,4-addition product methyl *β*,*β*-diphenyl propanoate (**3aa**) in 22% AY (entry 1, AY = assay yield, determined by ^{1}H NMR integration of the unpurified reaction mixture against an internal standard). Other NHCs either gave little or no product **3aa** (0–14% AY, entries 2–4). Since palladium sources affect reactivity, we tested $Pd(OAc)_2$, and $Pd(PPh_3)_4$ under the conditions of entry 1, but these complexes did not promote this transformation (entry 1 vs. 5 and 6). Thus, $Pd_2(dba)_3$ was used in further optimizations. We next screened a series of mono- and bidentate phosphines and pyridine derivatives under the conditions of entry 1 (entries 7–10). Terpyridine (**L5**) afforded the desired product in 59% AY, while bipy provided the product in 50% yield (see Supporting Information for details). Continuing with terpy, decreasing the reaction concentration from 0.1 molar to 0.05 molar improved the AY to 75% (entry 11). Control experiments indicated that in the absence of NHC or Pd and **L5**, no reaction was observed (entries 12 and 13). The combination of $Pd_2(dba)_3$ and NHC, but without a phosphine or pyridine-based ligand for Pd, the product **3aa** was obtained in 14% AY. Therefore, our optimized conditions are 1 equiv enal (**1a**), 2 equiv iodobenzene (**2a**), 1.5 equiv KO^{t}Bu, 5 mol % $Pd_2(dba)_3$, 10 mol % terpy (**L5**) and 15 mol % **N1** in THF/MeOH at room temperature for 12 h.

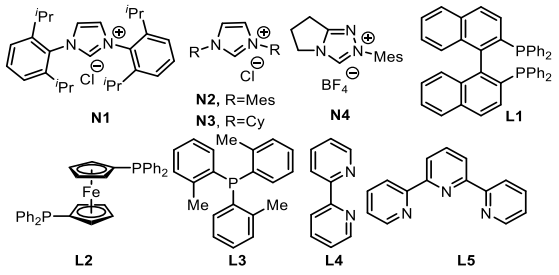
Table 1. Reaction Optimization[a]



1a **2a** **3aa**

entry	Pd source	NHC	Ligands	AY (%)[b]
1	$Pd_2(dba)_3$	**N1**	**L1**	22
2	$Pd_2(dba)_3$	**N2**	**L1**	14
3	$Pd_2(dba)_3$	**N3**	**L1**	trace
4	$Pd_2(dba)_3$	**N4**	**L1**	trace
5	$Pd(PPh_3)_4$	**N1**	**L1**	trace
6	$Pd(OAc)_2$	**N1**	**L1**	trace
7	$Pd_2(dba)_3$	**N1**	**L2**	trace
8	$Pd_2(dba)_3$	**N1**	**L3**	48
9	$Pd_2(dba)_3$	**N1**	**L4**	50
10	$Pd_2(dba)_3$	**N1**	**L5**	59
11[c]	$Pd_2(dba)_3$	**N1**	**L5**	75
12	--	**N1**	--	0
13	$Pd_2(dba)_3$	**--**	**L5**	0
14[c]	$Pd_2(dba)_3$	**N1**	--	14

[a] Reactions were conducted with **1a** (0.1 mmol), **2a** (0.2 mmol), THF (1 mL), MeOH (50 µL), 25 °C, 12 h. [b] Assay yields determined by ^{1}H NMR using CH_2Br_2 as internal standard. [c] 2 mL THF and 100 µL MeOH were used.



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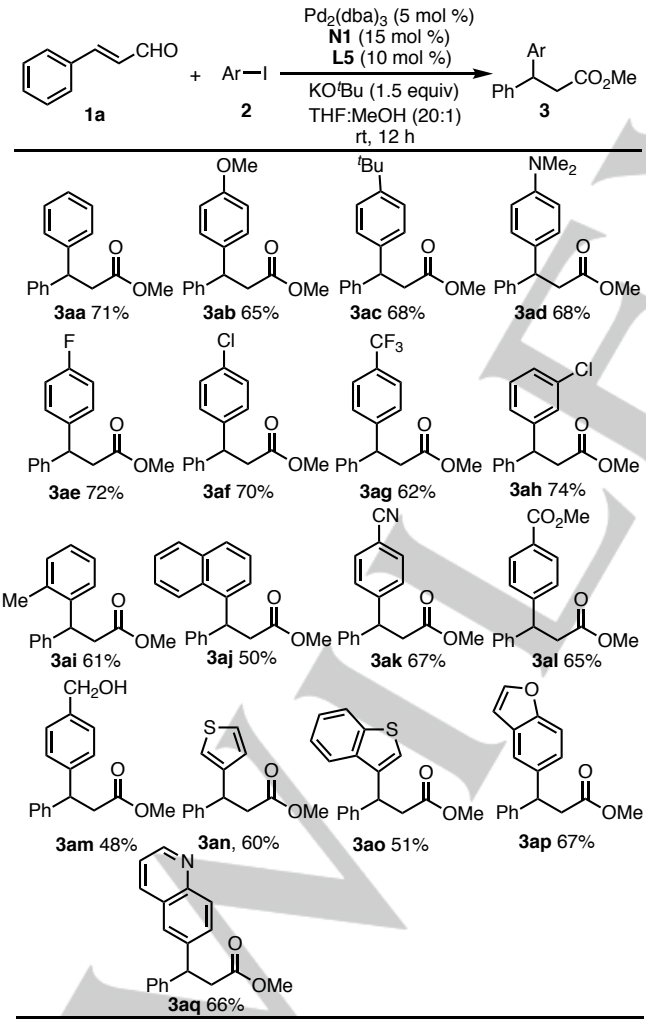
With the optimized conditions in hand, we next explored the substrate scope of aryl iodides with *trans*-cinnamaldehyde (**1a**). In general, a broad range of substitution patterns were tolerated in this umpolung transformation (Scheme 3). The parent iodobenzene underwent reaction affording the desired product in 71% isolated yield. Aryl iodides bearing electron-donating groups, such as 4-iodoanisole **2b**, 4-*tert*-butyl iodobenzene **2c**, and 4-*N*,*N*-dimethylamino iodobenzene **2d**, exhibited good reactivity, furnishing **3ab**–**3ad** in 65–68% yield. Aryl iodides containing electronegative or electron-withdrawing groups are also good partners. 4-Fluoroiodobenzene (**2e**), 4-chloroiodobenzene (**2f**) and 4-trifluoromethyl iodobenzene (**2g**) produced the corresponding products in 72, 70 and 62% yields, respectively. *Meta*-substituted 3-chloroiodobenzene (**2h**) gave **3ah** in 74% yield. Sterically hindered 2-iodotoluene and 1-iodonaphthalene reacted with **1a** and afforded the products in 61 and 50% yields, respectively. Aryl iodides bearing reactive functional groups, such as cyano, ester and alcohol, also reacted with **1a** to generate the corresponding products **3ak**–**3am** in 48–67% yield. *β*,*β*'-Diaryl propanoates containing thiophene, benzothiophene, benzofuran and quinoline groups could be prepared with our method, as exemplified by the generation of **3an**–**3aq** in 51–67% yield.

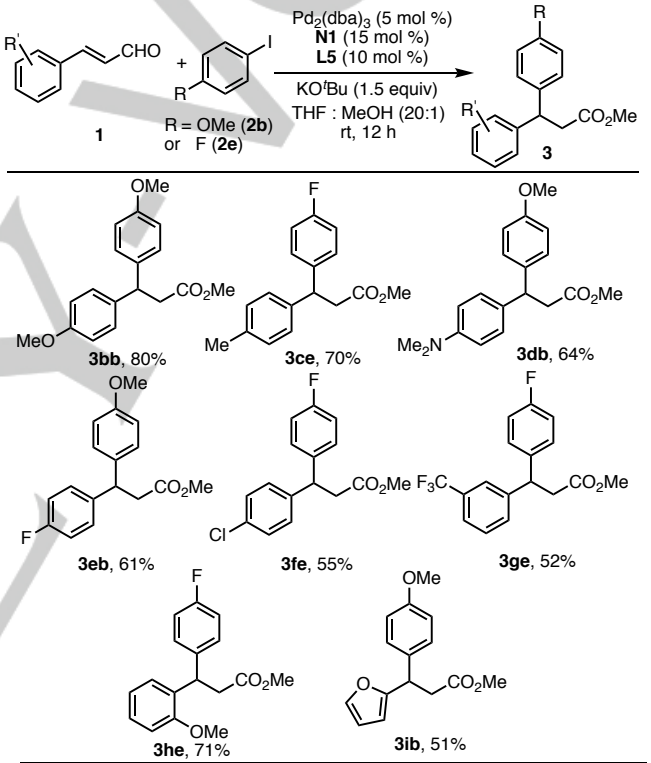
Scheme 3. Substrate scope of aryl iodides.[a], [b]



[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), $Pd_2(dba)_3$ (5 mol%), precatalyst **N1** (15 mol%), ligand **L5** (10 mol%), KO^tBu (0.15 mmol), MeOH (100 uL), and THF (2 mL) at rt for 12 h. [b] Yields of isolated and purified products.

We next turned our attention to the scope of the enals in this umpolung process. As shown in Scheme 4, enals containing electron-donating groups on the arene ring, such as 4-methoxy (**1b**), 4-methyl (**1c**), and 4-*N*,*N*-dimethylamino (**1d**) afforded the corresponding products in 80, 70, and 64% yields, respectively. Enals bearing electronegative groups, such as 4-fluoro (**1e**) and 4-chloro (**1f**), generated **3ec** and **3fe** in 61 and 55% yield, respectively. Substituents at the *meta* and *ortho* positions were both tolerated, generating the products in 52–71% yields (**3ge** and **3he**). A heteroaryl containing enal was also compatible with our approach, furnishing **3ib** in 51% yield. However, the aliphatic enal was not compatible with this reaction, and no desired product was observed when crotonaldehyde (**1j**) was treated with iodobenzene under standard condition for 24 h.

Scheme 4. Substrate scope of aryl enals.[a], [b]



[a] Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), $Pd_2(dba)_3$ (5 mol%), precatalyst **N1** (15 mol%), ligand **L5** (10 mol%), KO^tBu (0.15 mmol), MeOH (100 uL), and THF (2 mL) at rt for 12 h. [b] Yields of isolated and purified products.

As indicated in Figure 2a, the 1 mmol scale 1,4-addition of 3-iodothiophene (**2n**) proceeded smoothly to produce the corresponding product **3an** in 56% yield. To further study the application of this reaction, a pharmaceutically active compound fendiline was synthesized (Figure 2b). *trans*-Cinnamaldehyde (2 mmol) was coupled with iodobenzene under the standard reaction conditions to form the corresponding methyl *β*,*β*-diphenyl propanoate (**3aa**), which was then hydrolyzed to propanoic acid in 99% yield. Conversion of carbonic acid to acyl chloride and further amidation with benzyl amine afforded amide **5** in 98% yield. Finally, compound **6** (fendiline) was obtained in 77% yield by reduction with $LiAlH_4$.

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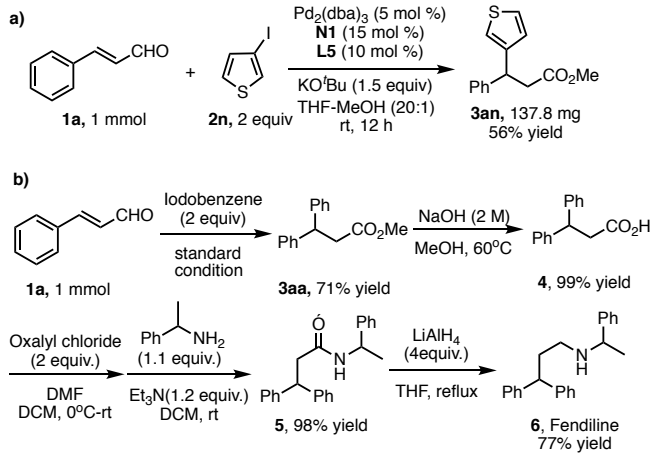

Figure 2. a. 1 mmol scale reaction. b. Synthesis of Fendiline.

To obtain insight into possible reaction pathways and discount others, additional experiments were conducted. When the reaction of *trans*-cinnamaldehyde (**1a**) and iodobenzene (**2a**) was performed without NHC precursor, but with $Pd_2(dba)_3$ and terpy, no Heck reaction product (**7**) was observed and no **3a** was detected (Figure 3a). Treating compound **7** with **N1**, KO*t*Bu and methanol in THF did not afford product **3aa** (Figure 3b). These results disfavor a possible Heck arylation pathway followed by redox esterification.[21] Next, we independently synthesized the (bipy)Pd(Ar)I complex **8** to probe the cooperative catalytic cycle (bipyridine and terpyridine showed similar activities in Table 1). The reaction of **8** with **1a** was performed in the presence of stoichiometric **N1** and KO*t*Bu in THF/MeOH, providing 1,4-addition product in 55% yield. Moreover, only trace amounts of free bipy was found in the crude reaction mixture (^{1}H NMR), which suggests that bipy was not displaced by NHC **N1**. Given that NHC's are well known to activate enals and palladium catalysts renowned for their ability to promote oxidative addition of aryl halides and perform reductive elimination to form C–C bonds, a mechanism akin to that outlined in Scheme 1 seems quite likely.

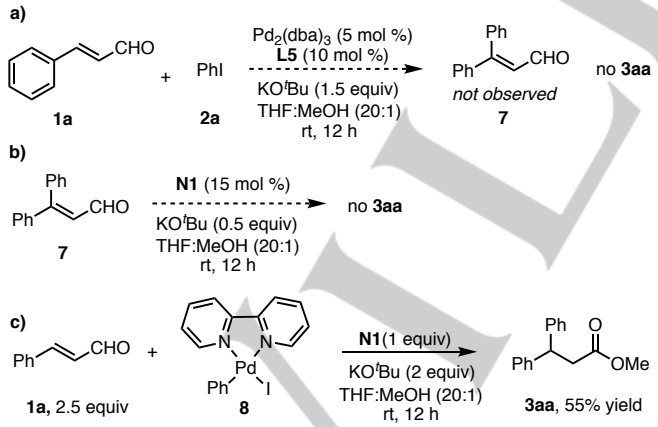

Figure 3. Mechanistic studies.

In conclusion, we have developed the first umpolung 1,4-addition of aryl iodides to enals through a Pd/NHC cooperative catalytic process. This umpolung process complements traditional 1,4-additions to α,β-unsaturated esters with organometallic reagents, as well as the reductive Heck reaction. The clear-cut advantage of this approach is it avoids the use of preformed organometallic reagents, greatly streamlining the synthesis of such conjugate addition products. Furthermore, the mild nature of this method enables the tolerance of a diverse array of functional groups. Studies toward the asymmetric version of this umpolung 1,4-addition reaction are ongoing in our laboratories.

Acknowledgements

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Keywords: Cooperative catalysis • Umpolung 1,4-Addition • *N*-Heterocyclic Carbene • Palladium catalysis

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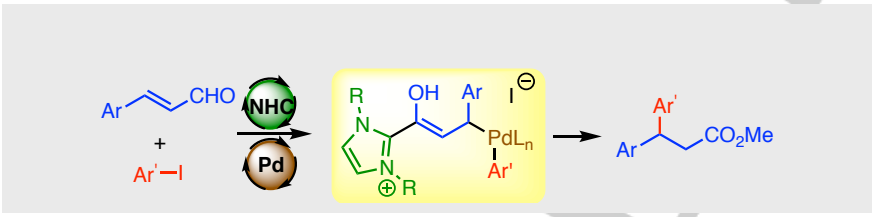

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