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A cascade Heck–Aldol–Heck reaction by a combination of transition-metal catalysis and aminocatalysis†

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An unprecedented cascade Heck–Aldol–Heck reaction was developed to form two C–C single bonds and one C=C double bond in one process by a combination of palladium(0) catalysis and aminocatalysis. Various aryl iodides could perform the cascade reaction with readily available propenol and formaldehyde to afford novel (*E*)-trisubstituted alkenes in 66–81% yields.

Cascade reactions that involve two or more bond-forming reactions in one process have great potential to be used widely in the synthesis of natural products and pharmaceuticals, in the chemical industry, *etc.*[1] They reduce reagents, solvents, energy supplies, waste, *etc*, decreasing the environmental impact as well as production costs. In recent decades, a lot of effort has been invested into the development of catalytic cascade reactions, which are mainly performed by transition-metal catalysis[1a–d] or organocatalysis.[1a,e–g] With the increasing importance of transition-metal catalysis and the rapid advancement of organocatalysis, another catalytic mode, a combination of transition-metal catalysis and organocatalysis for a cascade reaction has emerged. By the new catalytic mode, a number of excellent cascade reactions were recently disclosed.[2] Aminocatalysis is a crucial type of organocatalysis, and there are some reports on cascade reactions by the combinations of transition-metal catalysis and aminocatalysis.[2] However, more examples of the cascade reactions by the combinations of transition-metal catalysis and aminocatalysts involve alkyne derivatives as substrates, in which transition-metal catalysts, such as silver, gold and copper catalysts are used to activate triple bonds of alkyne moieties rather than construct C–C bonds.[2] It is well known that C–C bond formation by transition-metal catalyzed coupling reactions is one of the most important strategies in contemporary organic synthesis. Among them, Heck-type reactions are very important and classic transition-metal catalyzed coupling reactions.[3] However, to the best of our knowledge, there is no report on a cascade reaction combining a transition-metal catalyzed Heck-type reaction and an aminocatalytic reaction. Further considering that the aldol condensation reaction is a widely-used method for the formations of C–C bonds in organic synthesis,[4] and as a continuation of our research on the synthetic methodology by dual transition-metal catalysis and organocatalysis,[5] we began to carry out an investigation on a cascade reaction combining a transition-metal catalyzed Heck-type reaction and an aminocatalytic aldol condensation.

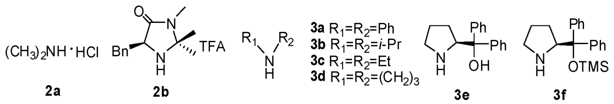

Fig. 1 Various aminocatalysts.

In our initial study, phenyl iodide **1a** (1.0 equiv.) and propenol (1.1 equiv.) were employed for Heck arylation of propenol, and formaldehyde (5.0 equiv.) was employed for aldol reaction under the catalysis of $Pd(OAc)_2$ and Et_2NH. To our delight, in the presence of *n*-Bu_4NCl and $NaHCO_3$ in acetonitrile, we obtained the desired Heck coupling/aldol condensation product, disubstituted alkene **4a** in a 45% yield with a small amount of trisubstituted alkene **5a** as a Heck coupling/aldol condensation/Heck coupling product. It is obvious that both **4a** and **5a** resulted from β-phenylated propanal as a product of the Heck reaction, and no compound resulting from α-phenylated propanal was gained. Encouraged by these results, excess phenyl iodide **1a** (2.0 equiv.) was employed to perform the cascade reaction under the above reaction conditions, and fortunately, an improved yield of **5a** was achieved without observation of **4a** (for details, see ESI†). As expected as well, when the amount of propenol was increased to 2.5 equiv., only **4a** was obtained in a 58% yield without obtaining **5a** (for details, see ESI†). Then, we further screened the reaction conditions for **5a**. First, various palladium catalysts, such as $Pd(OAc)_2$, $PdCl_2$, $Pd[(PhCHCH)_2CO]_2$, $Pd(Ph_3P)_4$, and $Pd(Ph_3P)_2Cl_2$ were examined, and $Pd(OAc)_2$ was found to be the best transition-metal catalyst among them (for details, see ESI†). Second, aminocatalysts **2–3** (Fig. 1) were probed, and pyrrolidine was proved to be the optimal aminocatalyst to give trisubstituted alkene **5a** in a 62% yield without **4a** (entry 6, Table 1; and ESI†). Among the various solvents examined, strong polar solvents such as acetonitrile, NMP and DMF seem more beneficial to the reaction than

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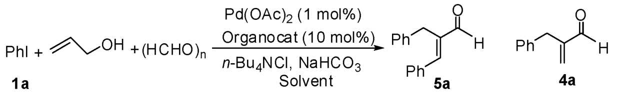
Table 1 Optimization of the cascade reaction conditions for trisubstituted alkene **5a**[a]



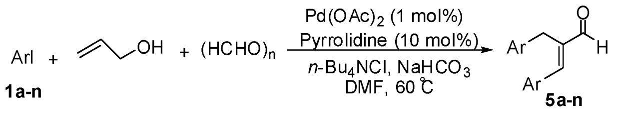
Entry	Organocatalyst	Time (h)	Solvent	T (°C)	Yield (%)[b]
1	**2a**	12	MeCN	60	52
2	**2b**	24	MeCN	60	26
3	**3a**	12	MeCN	60	56
4	**3b**	24	MeCN	60	41
5	**3c**	12	MeCN	60	54
6	**3d**	10	MeCN	60	62
7	**3e**	10	MeCN	60	50
8	**3f**	12	MeCN	60	46
9	**3d**	8	NMP	60	60
10	**3d**	24	THF	60	41
11	**3d**	24	$CHCl_3$	60	45
12	**3d**	16	1,4-Dioxane	60	51
13	**3d**	8	DMF	60	70
14	**3d**	12	DMF	40	42
15	**3d**	12	DMF	80	50
16	**3d**	12	DMF	110	45
17	—	36	DMF	60	18

[a] The reaction of **1a** (0.90 mmol), propenol (0.45 mmol) and paraformaldehyde (2.25 mmol) in a solvent (0.5 mL) was probed by the catalysis of $Pd(OAc)_2$ (0.0045 mmol) and an organocatalyst (0.045 mmol) in the presence of n-Bu_4NCl (0.90 mmol) and $NaHCO_3$ (0.95 mmol) under nitrogen. [b] Isolated yields of **5a**.

weak polar solvents, such as THF, 1,4-dioxane and chloroform. The experiment also indicated that DMF was the best solvent for the reaction with a 70% yield of **5a** (entry 13, Table 1). Screening the reaction temperatures showed that 60 °C was a suitable reaction temperature (entries 13–16, Table 1). When other bases, such as Et_3N, Bu_3N, K_2CO_3, or Na_2CO_3, were employed, the yields of **5a** were decreased significantly. Using a quaternary ammonium salt as an additive was important for the reaction, without it a poor yield (10–53%) of **5a** was obtained (for details, see ESI†). The screening experiment also showed that n-Bu_4NCl was best for the cascade reaction. It is noteworthy that without pyrrolidine, very low yield (18%) of **5a** was obtained in a long reaction time (entry 17, Table 1).

After screening of various transition metal catalysts, aminocatalysts, solvents, bases, additives, reaction temperatures and amounts of reactants, it can be concluded that the optimized reaction conditions are as follows: the cascade reaction of 2.0 equiv. aryl iodide **1**, 1.0 equiv. propenol and 5.0 equiv. paraformaldehyde in DMF is performed under the catalysis of 1 mol% $Pd(OAc)_2$ and 10 mol% pyrrolidine in the presence of n-Bu_4NCl and $NaHCO_3$ at 60 °C. Under the optimal reaction conditions, a variety of aryl iodides **1a–n** were examined in the cascade Heck–Aldol–Heck reaction. The experimental results showed that various substituted phenyl iodide **1a–l** could undergo the cascade reaction smoothly to furnish the desired trisubstituted alkenes **5a–l** in satisfactory yields (67–81%) with *E*-configuration (entries 1–12, Table 2). When *p*-nitrophenyl iodide was employed, only disubstituted alkene, 2-(4-nitrobenzyl)acrylaldehyde was obtained in 56% yield. 4-Methoxyphenyl iodide led to 4-methoxybiphenyl as a coupling product and no desired trisubstituted alkene was observed under the optimal conditions. The phenyl iodides bearing an electron-withdrawing group on the benzene ring **1b–i** resulted in better yield than those bearing an electron-donating group **1j–l**. The aryl iodides bearing other aromatic rings than benzene, 1-naphthalenyl iodide **1m** and 9-phenanthrenyl iodide **1n** could also undergo the cascade reaction readily to give the corresponding trisubstituted alkene **5m** and **5n** in 66% and 68% yield, respectively (entries 13–14, Table 2). The *E*-form of **5k** was confirmed by NOE experiments, which demonstrated

Table 2 The cascade Heck–Aldol–Heck reaction with aryl iodides[a]



Entry	Ar	Time (h)	Product **5**	Yield (%)[b]
1	C_6H_5	8	**5a**	70
2	4-FC_6H_4	6	**5b**	81
3	4-ClC_6H_4	8	**5c**	75
4	4-BrC_6H_4	8	**5d**	77
5	4-$CH_3COC_6H_4$	6	**5e**	73
6	4-$CH_3OCOC_6H_4$	10	**5f**	78
7	3-FC_6H_4	6	**5g**	78
8	3-ClC_6H_4	8	**5h**	74
9	3-BrC_6H_4	8	**5i**	76
10	4-$CH_3C_6H_4$	12	**5j**	69
11	3-$CH_3C_6H_4$	12	**5k**	68
12	2-$CH_3C_6H_4$	12	**5l**	67
13	Naphthalen-1-yl	10	**5m**	66
14	Phenanthren-9-yl	10	**5n**	68

[a] The reaction of **1** (0.90 mmol), propenol (0.45 mmol) and paraformaldehyde (2.25 mmol) in DMF (0.5 mL) was performed by the catalysis of $Pd(OAc)_2$ (0.0045 mmol) and pyrrolidine (0.045 mmol) in the presence of n-Bu_4NCl (0.90 mmol) and $NaHCO_3$ (0.95 mmol) at 60 °C under nitrogen. [b] Isolated yield.

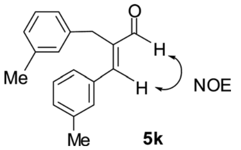
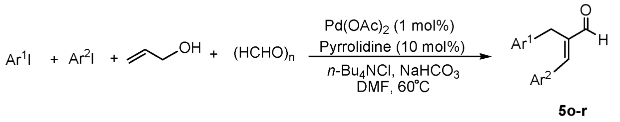


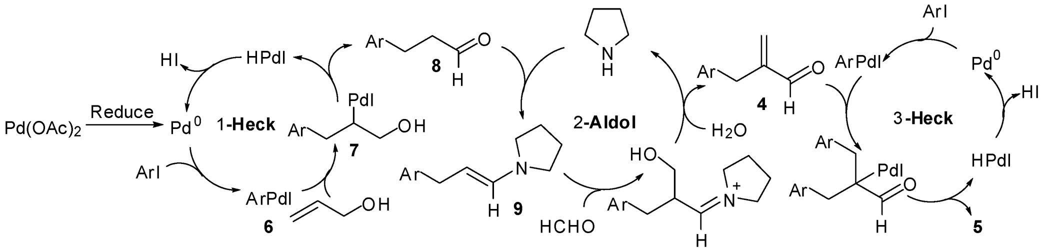
Fig. 2 NOE spectrum of trisubstituted alkene **5k**

Table 3 The cascade Heck–Aldol–Heck reaction with two different aryl iodides[a]



Entry	Ar^1	Ar^2	Time (h)	Product **5**	Yield (%)[b]
1	4-FC_6H_4	C_6H_5	12	**5o**	62
2	4-FC_6H_4	4-$CH_3C_6H_4$	12	**5p**	56
3	3-FC_6H_4	C_6H_5	12	**5q**	60
4	3-FC_6H_4	4-$CH_3C_6H_4$	12	**5r**	54

[a] The reaction of Ar^1I (0.45 mmol), Ar^2I(0.45 mmol), propenol (0.45 mmol) and paraformaldehyde (2.25 mmol) in DMF (0.5 mL) was performed by the catalysis of $Pd(OAc)_2$ (0.0045 mmol) and pyrrolidine (0.045 mmol) in the presence of n-Bu_4NCl (0.90 mmol) and $NaHCO_3$ (0.95 mmol) at 60 °C under nitrogen. [b] Isolated yields.



Scheme 1 Possible mechanism of the Heck–Aldol–Heck cascade reaction.

that the olefinic proton (7.46 ppm) had strong correlation with the aldehyde proton (9.70 ppm) (Fig. 2, also see ESI†). This suggests that the two proton are close in space and are at the same side of the C=C bond. The cascade reaction participated by various aryl iodides **1a–n** also has excellent regio- and stereoselectivities, because no product from α-arylated propanal and no *Z*-isomer of **5** was obtained. All of the assembled compounds **5**, except (*E*)-2-benzyl-3-phenylacrylaldehyde **5a**, are new trisubstituted alkenes **5b–n**.

Encouraged by these results, we tried to employ two different aryl iodides for the synthesis of mixed trisubstituted alkenes through the cascade Heck–Aldol–Heck reaction. Our experimental results showed that when the two aryl iodides which have quite different electron densities on the benzene ring, that is one more reactive and the other less, were employed, the cascade reaction could proceed smoothly to furnish the mixed trisubstituted alkenes **5o–r** in moderate yields (54–62%) (entries 1–4, Table 3).

A plausible mechanism of the cascade reaction is depicted in Scheme 1. At first, $Pd(OAc)_2$ is reduced to palladium(0) by alkene, amine, *etc*[3a] in the reaction system to start the first catalytic cycle. Insertion of a C=C double bond of allyl alcohol to organopalladium intermediate **6** leads to β-arylated intermediate **7** preferentially rather than its α-arylated counterpart due to steric hindrance.[6a] β-Arylated propanal **8** as the product of the first cycle for Heck reaction enters into the second catalytic cycle for the aldol condensation catalyzed by pyrrolidine to afford disubstituted alkene **4**.[7] If aryl iodide **1** is insufficient at this time, the cascade reaction stops at the second cycle (see the 2nd paragraph). If aryl iodide **1** is in excess, **4** smoothly enters into the third catalytic cycle for the second Heck reaction to give the desired trisubstituted alkene **5**.

In conclusion, we combined three C–C bond forming reactions into one cascade process to develop an unprecedented Heck–Aldol–Heck reaction. Various aryl iodides **1a–n** could perform the cascade reaction with readily available propenol and formaldehyde by the combination of palladium and pyrrolidine catalysts, assembling the novel (*E*)-trisubstituted alkenes **5a–n** in 66–81% yields with excellent chemo-, regio- and stereoselectivities. Investigations on the cascade reactions combined by classic transition-metal catalyzed coupling reactions and organocatalyzed C–C bond forming reactions are currently under way.

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7 Because the amount of formaldehyde (2.05 mmol) is in excess over pyrrolidine (0.045 mmol) and the amount of its iminium under basic conditions could not be estimated based on a lack of related literature, formaldehyde is thought to be a suitablee substrate to subject to a nucleophilic attack by enamine **9**.