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Pd-catalyzed intermolecular consecutive double Heck reaction “on water” under air: facile synthesis of substituted indenenes†

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An efficient and environmentally benign method for the preparation of substituted indene derivatives has been developed by using water as the sole solvent. This reaction proceeded under air, tolerated a wide range of functional-groups and was easily scaled up. Bioactive natural products like indriline were synthesized *via* the developed protocol. Preliminary results demonstrate that the enantioselective variant can also be achieved.

Solvent selection is perhaps the major consideration in green chemical design, and usually accounts for the vast majority of mass and energy wasted in syntheses and processes.¹ Thus, water has gained wide attention within the last several decades for many potential advantages in organic chemistry such as abundance, low cost, simple operation and environmental benefits.² Despite the great achievements in green and sustainable chemistry, less attention has been paid to the potential of water to promote organic reactions, especially in transition-metal catalysis. Indeed, “on-water” catalysis³ which showed significant rate acceleration in water compared to those performed in organic solvents, has recently sparked research interest and an impressive variety of modifications have been reported.⁴ However, the relevant studies on multi-step transition-metal catalyzed reactions remain largely unexplored.

Pd-catalyzed Heck-type reactions currently stand as highly reliable methods for the construction of carbo- and heterocyclic complex molecules.⁵ In view of numerous benefits of using water as the reaction medium, extensive efforts has been

devoted to the development of Pd-catalyzed aqueous Heck reactions.⁶ These strategies were mainly focusing on the coupling of aryl (pseudo)halides or boronic acids with conjugated alkenes, involving a direct intermolecular one-step Heck-type transformation, and organic solvents were generally employed as the co-solvents to improve the poor solubility of substrates (Scheme 1a). With regard to multi-step reactions, although the sequential intermolecular Heck-type reactions have been well-studied in normal organic solvents,⁷ the aqueous version is a continuing challenge. A possible reason is the increased difficulty in reconciling the added reaction steps with the aqueous reaction condition.

Indenes are important structural skeletons which are integral parts of a wide variety of biologically active natural products^{8a} and medicines,^{8b} as well as functional materials^{8c} and chiral ligands.^{8d} Although a great number of synthetic methods have been explored to afford indene derivatives,⁹ the development of green methods for the synthesis of indene derivatives with simple operation is still highly desirable. Herein, we report a Pd-catalyzed aqueous domino process involving the “on-

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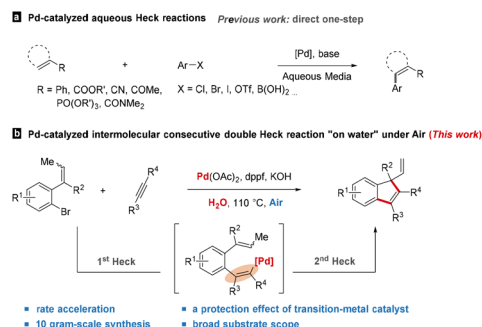
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Scheme 1 Pd-catalyzed consecutive double Heck reaction “on water”.

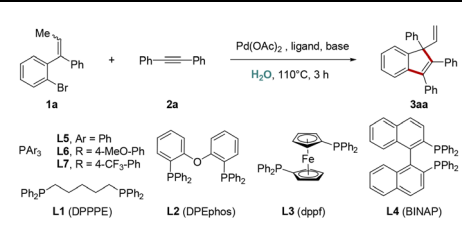


water” mechanism under air to construct functionalized indenenes featuring all-carbon quaternary stereocenters *via* an intermolecular consecutive double Heck reaction of alkenes and alkynes (Scheme 1b).

This domino process was initially investigated by using tri-substituted alkene **1a** and diphenylacetylene **2a** as model substrates in the presence of Pd(OAc)₂, ligand and base. With DPPPE as a ligand, KOH as a base and dioxane as a solvent, the desired product **3aa** was obtained in 47% yield (entry 1). However, there was no improvement in the yield of **3aa** by the screening of several kinds of bases (entries 2–5) and reaction media (entries 6–8). Based on the effect of water in Heck reactions that the aqueous media might exert an influence on the rate of cyclization,⁶ we then turn our attention to examine solvents, using water as a co-solvent. To our delight, the yields were sharply increased to 74–77% (entries 9 and 10) and further attempt by using pure H₂O as a solvent gave an increased reaction yield of 87% (entry 11). Next, the outcome was further improved by introducing several well-known mono- or bis-phosphorus ligands (entries 12–17), and dppf was identified as the optimal choice (entry 13). The reaction would be totally suppressed in the absence of a ligand (entry 18). Gratifyingly, the control experiments indicated that the reaction could also perform efficiently without inert gas protection (entry 19), and the same excellent reaction yield was maintained under air atmosphere. Interestingly, good reaction yield was also observed under O₂ atmosphere (entry 20), which hints a protection effect of H₂O to the active Pd intermediate from oxidation.¹⁰ Finally, efforts to lower the reaction temperature or decrease the catalyst/ligand loading were unsuccessful, and markedly lower yields of **3aa** were obtained (entries 21 and 22) (Table 1).

With the optimal catalytic system established, we examined the generality of this protocol (Scheme 2). Various tri-substituted alkenes were found to be compatible with the present procedure to afford the corresponding indenyl products in good to excellent yields. Substrates with electron withdrawing and donating mono/di substituents on phenyl ring **A** exhibited excellent reactivity, producing substituted indenenes in the yield of 77–92% (**3aa–ha**). Furthermore, we undertook X-ray crystal structure analysis of **3ha** to determine the existence of quaternary center. Alkenes bearing substituents on the phenyl ring **B** were suitable as well, and expected products were generated in comfortable yields (**3ia–na**). Moreover, the transformations were also effective when employing naphthyl (**3oa**), thienyl (**3pa**) or alkyl (**3qa** and **3ra**) group instead of the phenyl ring **B**.

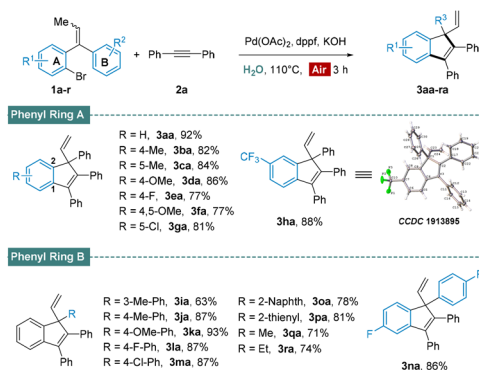
Subsequently, we turned our attention to the scope of the alkyne coupling partner. As summarized in Scheme 3, most diphenylacetylenes were well-tolerated and delivered desired indenenes in good yields (**3ac–ag**). As a comparison, When surfactants (sodium dodecyl sulfate, SDS) and TPGS-750 M were used to the reaction under standard conditions (**3ac**), the yields of **3ac** were sharply reduced to 55% and 62%. A possible reason is the oxidation of metal catalyst. However, while increasing the steric hindrance of the phenyl group, it disfavoured the process and led to trace yield (**3ab**). Additionally, the reactions

Table 1 Optimization of conditions^a


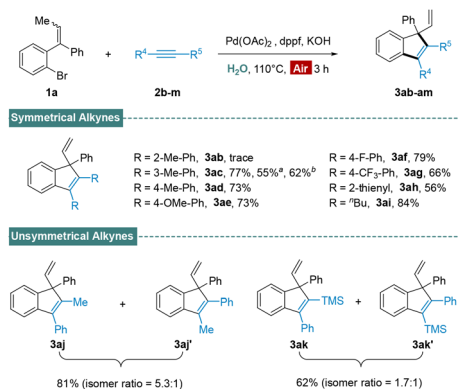
Entry	Ligand	Base	Solvent	Atmosphere	Yield (%)
1	L1	KOH	Dioxane	Ar	47
2	L1	KOAc	Dioxane	Ar	23
3	L1	K ₂ CO ₃	Dioxane	Ar	37
4	L1	NaHCO ₃	Dioxane	Ar	43
5	L1	TEA	Dioxane	Ar	14
6	L1	KOH	DMF	Ar	27
7	L1	KOH	DMSO	Ar	14
8	L1	KOH	CH ₃ CN	Ar	n.r.
9	L1	KOH	Dioxane/H ₂ O = 4 : 1	Ar	74
10	L1	KOH	Dioxane/H ₂ O = 2 : 1	Ar	77
11	L1	KOH	H ₂ O	Ar	87
12	L2	KOH	H ₂ O	Ar	75
13	L3	KOH	H ₂ O	Ar	99
14	L4	KOH	H ₂ O	Ar	73
15	L5	KOH	H ₂ O	Ar	83
16	L6	KOH	H ₂ O	Ar	59
17	L7	KOH	H ₂ O	Ar	88
18	—	KOH	H ₂ O	Ar	n.r.
19	L3	KOH	H ₂ O	Air	99
20	L3	KOH	H ₂ O	O ₂	65
21 ^b	L3	KOH	H ₂ O	Air	41
22 ^c	L3	KOH	H ₂ O	Air	54
23 ^d	—	KOH	H ₂ O	Air	67

^a Reaction conditions: **1a** (0.20 mmol, 1.0 equiv.), **2a** (1.2 equiv.), Pd(OAc)₂ (0.05 equiv.), L1–L4 (0.1 equiv.), L5–L7 (0.2 equiv.), base (0.40 mmol, 2.0 equiv.), solvent (1 mL). Yields determined by NMR analysis using CH₂Br₂ as an internal standard. ^b 90 °C. ^c Pd(OAc)₂ (0.025 equiv.), L3 (0.05 equiv.). ^d PdCl₂(dppf) (0.05 equiv.).

employed heteroaryl alkyne (**3ah**) or dialkyl alkyne (**3ai**) also proceeded smoothly and afforded indenenes in acceptable yield. Encouraged by the success of the scope with symmetrical



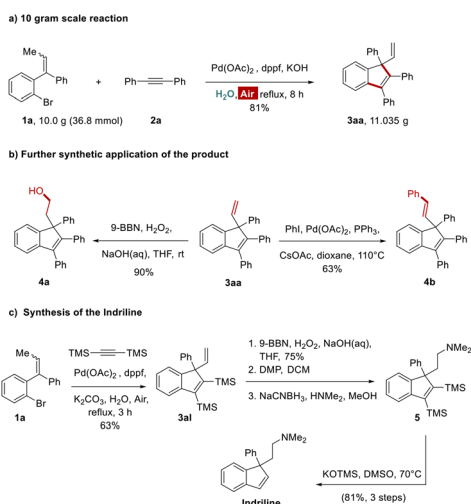
Scheme 2 Substrate scope of alkenes. Reaction conditions: **1a–s** (0.30 mmol, 1.0 equiv.), **2a** (1.2 equiv.), Pd(OAc)₂ (0.05 equiv.), dppf (0.1 equiv.), KOH (0.60 mmol, 2.0 equiv.), H₂O (1.5 mL).



Scheme 3 Substrate scope of alkyne. Reaction conditions: **1a** (0.30 mmol, 1.0 equiv.), **2b–m** (1.2 equiv.), Pd(OAc)₂ (0.05 equiv.), dpfp (0.1 equiv.), KOH (0.60 mmol, 2.0 equiv.), H₂O (1.5 mL), ^aC₁₂H₂₅SO₄Na (1.0 equiv.) ^b 2 wt% solution of TPGS-750 M/H₂O (1.5 mL).

alkynes, we then submitted two unsymmetrical substrates (**2j**, **2k**) to this aqueous process. Reaction of **1a** with 1-phenyl-1-propyne delivered the expected product in good yield with 5.3 : 1 regioselectivity (**3aj** + **3aj'**). Nevertheless, the outcome was significantly reduced when trimethyl(phenyl-ethynyl)silane was examined (**3ak** + **3ak'**). The observed effect is likely due to the steric effects of palladium species involved in the alkyne insertion step.

The practicability of this protocol was also demonstrated by the synthesis on the 10 gram level and versatile transformations of terminal alkenes. The presented methodology could be scaled up easily and afford compound **3aa** in 81% yield, similar to that run on small scale (Scheme 4a). The terminal alkene moiety of **3aa** could be elaborated through hydroboration-oxidation, which would be further transformed into other indenenes possessing all-carbon quaternary centers contained different functional groups. Furthermore, the length of conjugated chain could be extended *via* a Heck coupling (Scheme 4b). The scope of the present methodology was also successfully



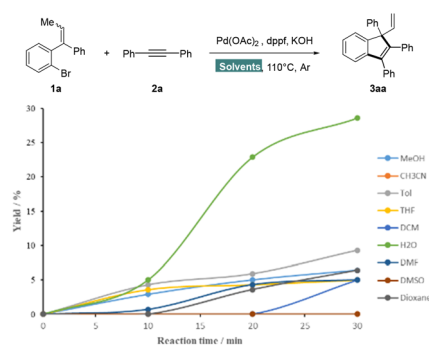
Scheme 4 Studies on the synthetic utility.

extended to the efficient synthesis of biologically important indene derivatives like indriline.¹¹ First, bis(trimethylsilyl)acetylene was subjected to our developed Pd-catalyzed protocol with alkene **1a**, which furnished indene **3al**. This intermediate was then converted to the imine **5** through a three-step sequence: (i) borohydride oxidation using 9-BBN, (ii) Dess–Martin oxidation, (iii) reductive amination by treatment with NaBH₃CN and HNMe₂. Finally, treatment of imine **5** with KOTMS at 70 °C for 4 hours afforded indriline in good yield (Scheme 4c).

We have begun to develop an enantioselective variant of this process. We anticipated that this might be challenging, due to issues such as the effect of *E/Z* isomers of the starting material **1** on the enantioselectivity of the reaction and the difficulty in controlling facial selectivity of the second Heck process in aqueous media under air. Yet we were pleased to measure a promising enantiomeric excess of 12% in the presence of (*S*)-BINAP at 60 °C (see the ESI† for details), which provides an example of using water-insoluble ligand in transition-metal catalyzed asymmetric aqueous transformations.

In order to understand “on water” reactivity, an array of kinetic experiments were performed under the same catalytic system (Scheme 5). Different organic solvents were introduced to assess the rate enhancement as compared to water. As a remarkable improvement of reaction rate was observed in water, this process could be defined to follow an “on-water” mechanism. In this regard, the properties of Pd catalysts at the macroscopic phase boundary between water and oil¹² seem to play a role in reaction acceleration. In addition, the redistribution of surface species driven by surface-tension energetics,¹³ high concentration of starting materials and good solubility of bases may also be relevant.

Thereafter, we conducted several control experiments (see the ESI† for details) to gain the support of our hypothesis. Treatment of **1a** with **2a** under Ar in dioxane furnished the desired product in 47% yield (entry 1), while the outcome was sharply reduced to 4% under air (entry 2). Moreover, the transformation does not proceed in dioxane under O₂ (entry 3). In contrast, indene **3aa** was also successfully obtained under air without a decrease in the yield by using water as a solvent (entry 4 and 5). Surprisingly, replacement of air with O₂ still



Scheme 5 “On-water” effect reaction. condition: **1a** (0.20 mmol, 1.0 equiv.), **2a** (1.2 equiv.), Pd(OAc)₂ (0.05 equiv.), dpfp (0.1 equiv.), KOH (0.40 mmol, 2.0 equiv.), solvent (1 mL). Yields determined by NMR analysis using CH₂Br₂ as an internal standard.

maintained the reactivity (entry 6). Next, the stability of PdCl₂(dppf) was tested under O₂, which exhibited good efficiency to afford the desired product **3aa** in 67% yield (Scheme 1, entry 23). After stirring at 110 °C under O₂ for 3 hours, there was a small decline of catalyst, only about 8% in the presence of water (see the ESI† for details). On the contrary, the use of dioxane led to deactivation. The above experiments demonstrate convincingly that aqueous medium has shown to protect catalysts. This effect likely arises from the low solubility of catalysts and dissolved oxygen in water, which significantly prevents the unexpected behavior of O₂ at the air–water interface.

In conclusion, we have developed a Pd-catalyzed consecutive double Heck coupling of substituted alkenes with internal alkynes in water under open air involving the “on-water” mechanism and a catalyst protection effect, which affords substituted indene derivatives bearing all-carbon quaternary centers with broad substrate scope and functional group tolerance. In addition, the synthetic utility of the aqueous process was demonstrated by a 10 gram scale reaction, several transformations and the synthesis of indriline. Preliminary studies have also shown that an enantioselective variant can be achieved.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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