Pd-catalyzed cascade Heck–Saegusa: direct synthesis of enals from aryl iodides and allyl alcohol†

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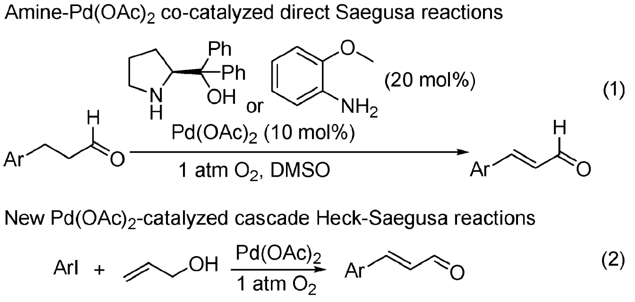
A new efficient Pd-catalyzed cascade Heck–Saegusa protocol for the synthesis of synthetically useful α,β-unsaturated aldehydes in high yields from readily available aryl iodides and allyl alcohol has been developed.

α,β-Unsaturated aldehydes (enals) as versatile synthetic building blocks, are widely used in the cosmetic,[1] pharmaceutical[2] and agrochemical[3] industries. Moreover, notably, they have embraced recent dramatic growing interest as a result of their broad applications in organocatalysis.[4] In the past, a variety of synthetic strategies toward their synthesis have been developed. These are the palladium-catalyzed arylation of acrolein diethyl acetal,[5] the oxidation of allylic alcohols,[6] Peterson olefinations,[7] or formylation,[8] cross-metathesis reactions of acrolein,[9] cross-aldol condensations,[10] Wittig olefinations,[11] and oxidation–eliminations of α-selenoaldehydes.[12] However, these methods are flawed due to low synthetic efficiency such as extensive polymerization, harsh reaction conditions, multiple step synthesis, use of not readily available substances, or the generation of a large amounts of chemical waste and hazards. A practical synthesis of enals would employ commercially available and inexpensive reagents, use a catalytic approach under mild reaction conditions, and be atom economical. Furthermore, the transformation should be amenable to a one-pot procedure to enable rapid generation of an array of enals. Driven by the ever-growing demand for enals and environmentally benign technologies in fine chemical synthesis, new, direct, and more efficient approaches are urgently needed. Herein we disclose a direct, yet broadly applicable, one-pot catalytic approach to give α,β-unsaturated aldehydes in high yields from simple aryl iodides and allyl alcohol.

Recently, we have developed a novel amine–Pd(OAc)$_2$ co-catalyzed direct Saegusa oxidation reaction of unmodified β-aryl aldehydes to α,β-unsaturated aldehydes (Scheme 1, eqn (1)).[13] In our continuing efforts aimed at developing more efficient synthetic tools toward the highly valuable building blocks, we questioned whether it might be possible to merge the widely used Heck reaction with the direct Saegusa oxidation process to create a new one-pot approach to these substances (Scheme 1, eqn (2)). We envisioned that a Pd-catalyzed Heck reaction[14,15] of aryl iodides and allyl alcohol would produce β-aryl aldehydes, which would serve as starting materials for the subsequent Saegusa reaction to directly produce enals. Despite the significant challenges regarding reagent/reaction condition compatibility and their potential interference, it may be feasible to develop such a cascade process since the same Pd(OAc)$_2$ is used as a promoter in both reactions.

To prove the working hypothesis, we performed a reaction of iodobenzene **1a** with allyl alcohol **2** by combining a typical Heck reaction protocol with the direct Saegusa reaction procedures we have developed at 60 °C (Table 1, entries 1 and 2). Under the conditions, the desired enal product **4a** was observed in 18% and 39% yield with (*S*)-diphenylprolinol and *o*-anisidine as co-catalysts, respectively. In addition, a considerable amount of 3-phenylpropionaldehyde **3a** was also produced in respective 27% and 9% yields. Gratifyingly, the yields (46% and 39%, entries 3 and 4) were improved significantly for the desired **4a** whereas those of by-product **3a** were reduced to 1% and 2% when DMF was employed as the solvent. Further optimization led to the use of a 1 : 1 mixture of DMSO and DMF and the yield dramatically increased to 67% and 61% (entries 5 and 10). Probing the reaction temperature using (*S*)-diphenylprolinol as catalyst revealed that 60 °C was optimal (entries 5–9). Unexpectedly, even higher yield (79%) was obtained in the absence of the amine catalyst (entry 11). Moreover, it was found that the NaHCO$_3$ base and the phase transfer reagent ($Bu_4N^+Cl^-$) were both essential for the reaction and without either substance, no product **4a** was observed (entries 12 and 13). Reducing the concentration of O$_2$ led to lower yield (29%) of the desired **4a** (entry 14). Finally, the use of other Pd



Scheme 1 Design of Pd(OAc)$_2$ catalyzed cascade Heck–Saegusa reactions.

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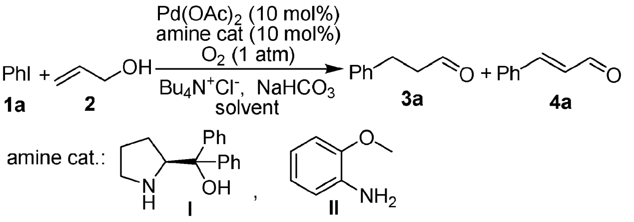
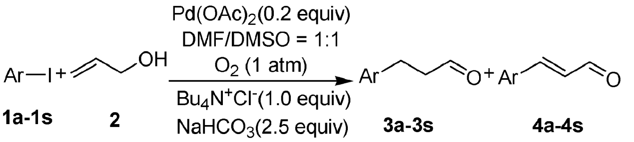
Table 1 Exploration of the catalytic Heck–Saegusa cascade reaction[a]



Entry	Solvent	Catalyst	T/°C	t/h	Yield **3a** : **4a** (%)[b]
1[c]	DMSO	**I**	60	4	27 : 18
2[c]	DMSO	**II**	60	4	9 : 39
3[c]	DMF	**I**	60	4	1 : 46
4[c]	DMF	**II**	60	4	2 : 39
5	DMSO : DMF (1 : 1)	**I**	60	10	2 : 67
6	DMSO : DMF (1 : 1)	**I**	45	10	25 : 42
7	DMSO : DMF (1 : 1)	**I**	90	10	1 : 52
8	DMSO : DMF (1 : 1)	**I**	110	10	2 : 59
9[d]	DMSO : DMF (1 : 1)	**I**	110	10	1 : 41
10	DMSO : DMF (1 : 1)	**II**	60	10	6 : 61
11	**DMSO : DMF (1 : 1)**	—	**60**	**15**	**1 : 79**
12[e]	DMSO : DMF (1 : 1)	—	60	15	0 : 0
13[f]	DMSO : DMF (1 : 1)	—	60	15	0 : 0
14[g]	DMSO : DMF (1 : 1)	—	60	15	17 : 29

[a] Unless stated otherwise, the reaction was carried out with **1a** (0.49 mmol) and **2** (0.74 mmol) under standard conditions: [Pd(OAc)$_2$ (0.2 equiv.), aminocatalysis (0.2 equiv.), O$_2$ (1 atm), NaHCO$_3$ (2.5 equiv.) and Bu$_4$N$^+$Cl$^-$ (1.0 equiv.)]. [b] Isolated yield. [c] 0.1 equiv. Pd(OAc)$_2$ used. [d] 0.4 equiv. Pd(OAc)$_2$ used. [e] NaHCO$_3$ was removed. [f] In the absence of Bu$_4$N$^+$Cl$^-$. [g] Air (1 atm) used.

Table 2 Synthesis of enols from aryl iodides and allyl alcohol in one pot[a]



Entry	Aryl iodides	t/h	Yield (%)[b]
1	**1a**, PhI	15	**3a** : **4a** 1 : 79
2	**1b**, 2-Me-C_6H_4I	24	**3b** : **4b** 0 : 81
3	**1c**, 2-Cl-C_6H_4I	9	**3c** : **4c** 0 : 81
4	**1d**, 2-MeO_2C-C_6H_4I	7	**3d** : **4d** 0 : 80
5	**1e**, 4-CN-C_6H_4I	4	**3e** : **4e** 3 : 68
6	**1f**, 4-NO_2-C_6H_4I	5	**3f** : **4f** 5 : 60
7	**1g**, 4-Et-C_6H_4I	30	**3g** : **4g** 0 : 72
8	**1h**, 4-Me-C_6H_4I	6	**3h** : **4h** 0 : 81
9	**1i**, 4-Cl-C_6H_4I	20	**3j** : **4j** 0 : 62
10	**1j**, 4-MeCO-C_6H_4I	3	**3j** : **4j** 0 : 67
11	**1k**, 4-MeO_2C-C_6H_4I	8	**3k** : **4k** 0 : 80
12	**1l**, 4-Ph-C_6H_4I	19	**3l** : **4l** 0 : 80
13	**1m**, 3-Me-C_6H_4I	6	**3m** : **4m** 0 : 78
14	**1n**, 3-F-C_6H_4I	12	**3n** : **4n** 0 : 59
15	**1o**, 2,4-di-Cl-C_6H_3I	12.5	**3o** : **4o** 0 : 77
16	**1p**, 2-Me-4-NO_2-C_6H_3I	5	**3p** : **4p** 0 : 58
17	**1q**, 2-F-4-Me-C_6H_3I	5.5	**3q** : **4q** 0 : 67
18	**1r**, 3-I-pyridine	20	**3r** : **4r** 0 : 57
19	**1s**, 1-I-naphthalene	16	**3s** : **4s** 0 : 82

[a] Unless specified, all reactions were carried out with **1** (0.49 mmol) with **2** (0.74 mmol), Pd(OAc)$_2$ (0.2 equiv.), O$_2$ (1 atm), NaHCO$_3$ (2.5 equiv.) and Bu$_4$N$^+$Cl$^-$ (1.0 equiv.) at 60 °C in DMSO : DMF = 1 : 1. [b] Isolated yields.

sources, such as palladium chloride, bis(acetonitrile)dichloropalladium(II), tris(dibenzylideneacetone)dipalladium and, tetrakis(triphenylphosphine) palladium(0), resulted in 6%, 18%, 45% and 0% yields, respectively, indicative of the sensitive nature of the Pd catalyst for the cascade process.

Having established the optimal reaction conditions, we next explored the scope and generality of the methodology. The powerful cascade served as a general approach to enals with significant structural variation of aryl iodides (Table 2). The desired enal products **4** were generated dominantly in good yields. A variety of substituents on the aryl ring including halogens, alkyl groups, CN, CO$_2$Me, NO$_2$, carbonyls, *etc.* were tolerated well. This indicated that the electronic effects were limited. It appeared that the aryl iodides bearing electron-neutral (entry 1) and -rich substituents (entries 2, 7, 8 and 13) gave higher yields. The same observation was seen for the moderately electron-withdrawing groups (entries 4 and 11). Nevertheless, relatively lower yields were obtained with strongly electron-withdrawing substituents such as cyano, nitro, acetyl, fluoro (entries 5, 6, 10 and 14). We also investigated the steric effect of the aryl iodides on the cascade processes. All *para*-, *meta*-, and *ortho*-substituted substrates were smoothly transformed into the desired products, indicating that the steric effect had little impact on the reaction (Table 2, entries 2–4 and 16–17). Finally, heterocyclic (entry 18) and conjugated aromatic substrates (entries 12 and 19) could efficiently participate in the cascade transformations as well.

A plausible reaction mechanism of the Pd(II) catalyzed cascade Heck–Saegusa process for the formation of cinnamaldehydes is proposed (Fig. 1). Alternatively, the oxidation may happen first to give cinnamaldehydes **4**, followed by the Heck reaction. A typical Heck pathway is involved and results in the formation of enol **8** or allylic alcohol **9** from β-elimination reaction.[14] Enol **8** as substrate engages in the subsequent Saegusa process with a similar mechanism to that of a classic Saegusa process,[13,16] which was validated by a control reaction (bottom section, Scheme 2). It is noteworthy that the proposed cycle also explains why no amine catalyst is needed since the resulting enol **8** or allylic alcohol **9** are able to directly participate in the Saegusa reaction under the developed reaction conditions. Our preliminary control studies prove the hypothesis (Scheme 2). Under the standard conditions [Pd(OAc)$_2$, Bu$_4$N$^+$Cl$^-$, NaHCO$_3$, O$_2$ (1 atm), DMSO : DMF = 1 : 1 (1 mL), 60 °C], allylic alcohol **9a** was smoothly transformed to cinnamaldehyde **4a** in a good yield (87%) (eqn (3)). Moreover, 3-phenylpropionaldehyde **10a** underwent tautomerization to form enol **8a** under the basic conditions (eqn (4)). The *in situ* formed enol **8a** was oxidized *via* a classic Saegusa process to afford cinnamaldehydes **4** in 71% yield.

In conclusion, we have developed a new and practical Pd-catalyzed cascade Heck–Saegusa reaction for one-pot synthesis of useful cinnamaldehydes using readily available aryl iodides and allyl alcohol under mild reaction conditions. The cascade reactions are compatible with a variety of functional groups on the aryl ring and even with heterocycles in good yields. The detailed mechanistic aspects and application of the cascade reaction in the preparation

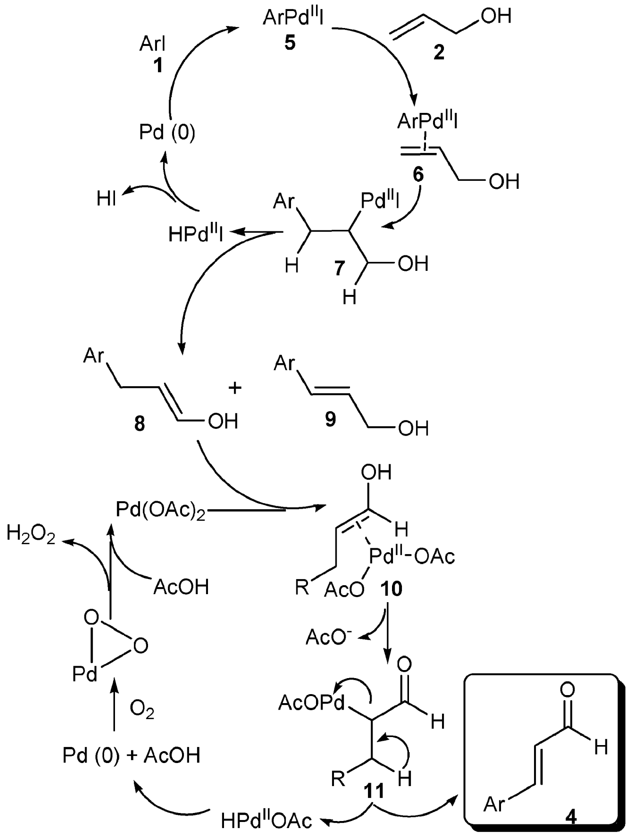
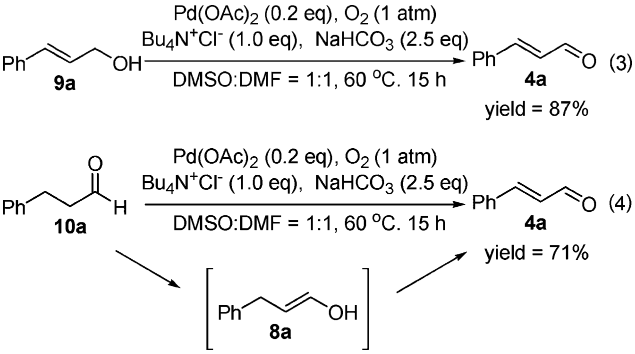


Fig. 1 Proposed mechanism for Pd-catalyzed cascade Heck–Saegusa reactions.



Scheme 2 Conversion of respective **9a** and **10a** to cinnamaldehyde **4a**.

of bioactive molecules are currently being pursued in our laboratory.

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Notes and references

1 (*a*) M. Friedman, N. Kozukue and L. A. Harden, *J. Agric. Food Chem.*, 2000, **48**, 5702; (*b*) J. Cocchiara, C. S. Letizia, J. Lalko, A. Lapczynski and A. M. Api, *Food Chem. Toxicol.*, 2005, **43**, 867.
2 For recent selected examples, see: (*a*) G. Brackman, T. Defoirdt, C. Miyamoto, P. Bossier, S. Van Calenbergh, H. Nelis and T. Coenye, *BMC Microbiol.*, 2008, **8**, 149; (*b*) L. K. Chao, K. F. Hua, H. Y. Hsu, S. S. Cheng, I. F. Lin, C. J. Chen, S. T. Chen and S. T. Chang, *Food Chem. Toxicol.*, 2008, **46**, 220; (*c*) C. W. Lee, S. H. Lee, J. W. Lee, J. O. Ban, S. Y. Lee, H. S. Yoo, J. K. Jung, D. C. Moon, K. W. Oh and J. T. Hong, *J. Pharmacol. Sci.*, 2007, **104**, 19; (*d*) K. Sato, S. Krist and G. Buchbauer, *Biol. Pharm. Bull.*, 2006, **29**, 2292.
3 For selected examples, see: (*a*) E. J. Lee, J. R. Kim, D. R. Choi and Y. J. Ahn, *J. Econ. Entomol.*, 2008, **101**, 1960; (*b*) A. Rodríguez, C. Nerín and R. Batlle, *J. Agric. Food Chem.*, 2008, **56**, 6364; (*c*) S. T. Chang and S. S. Cheng, *J. Agric. Food Chem.*, 2002, **50**, 1389; (*d*) I. K. Park, H. S. Lee, S. G. Lee, J. D. Park and Y. J. Ahn, *J. Agric. Food Chem.*, 2000, **48**, 2528.
4 (*a*) D. Almasi, D. A. Alonso and C. Najera, *Tetrahedron: Asymmetry*, 2007, **18**, 299; (*b*) S. B. Tsogoeva, *Eur. J. Org. Chem.*, 2007, 1701; (*c*) J. L. Vicario, D. Badía and L. Carrillo, *Synthesis*, 2007, 2065; (*d*) D. Enders, C. Grondal and M. R. M. Huttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570; (*e*) X.-H. Yu and W. Wang, *Org. Biomol. Chem.*, 2008, **6**, 2037.
5 G. Battistuzzi, S. Cacchi and G. Fabrizi, *Org. Lett.*, 2003, **5**, 777.
6 G. Tojo and M. Fernándes, in *Oxidation of Alcohols to Aldehydes and Ketones: A Guide to Current Common Practice*, ed. G. Tojo, Springer, Berlin, 2006, p. 1.
7 D. J. Ager, *Synthesis*, 1984, 384.
8 (*a*) B. Breit, *Acc. Chem. Res.*, 2003, **36**, 264; (*b*) H. Neumann, A. Sergeev and M. Beller, *Angew. Chem., Int. Ed.*, 2008, **47**, 4887.
9 M. T. Crimmins and B. W. King, *J. Am. Chem. Soc.*, 1998, **120**, 9084.
10 P. R. Mackie and C. E. Foster, in *Comprehensive Organic Group Transformations II*, ed. A. R. Katritzky, R. J. K. Taylor and S. Jone, Elsevier, Dordrecht, 2004, vol. 3, p. 59.
11 B. E. Maryanoff and A. B. Reitz, *Chem. Rev.*, 1989, **89**, 863.
12 R. C. Larock, *Comprehensive Organic Transformations*, John Wiley & Sons, New York, 1999.
13 (*a*) J. Zhu, J. Liu, R.-Q. Ma, H.-X. Xie, J. Li, H.-L. Jiang and W. Wang, *Adv. Synth. Catal.*, 2009, **351**, 1229; (*b*) J. Liu, J. Zhu, H.-L. Jiang, W. Wang and J. Li, *Chem.–Asian J.*, 2009, **4**, 1712.
14 (*a*) J. B. Melpolder and R. F. Heck, *J. Org. Chem.*, 1976, **41**, 265; (*b*) A. J. Chalk and S. A. Magennis, *J. Org. Chem.*, 1976, **41**, 273; (*c*) A. J. Chalk and S. A. Magennis, *J. Org. Chem.*, 1976, **41**, 1206; (*d*) G. Dyker and P. Grundt, *Tetrahedron Lett.*, 1996, **37**, 619; (*e*) J. T. Li, A. W. Mau and C. R. Strauss, *Chem. Commun.*, 1997, 1275.
15 K. E. Torraca, S. Kuwabe and S. L. Buchwald, *J. Am. Chem. Soc.*, 2000, **122**, 12907.
16 S. Porth, J. W. Bats, D. Trauner, G. Giester and J. Mulzer, *Angew. Chem., Int. Ed.*, 1999, **38**, 2015.