Heck Reactions of Crotonaldehyde

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Abstract: A direct method for the synthesis of β,β-disubstituted-α,β-unsaturated aldehydes via Heck reaction of aryl halides with crotonaldehyde and related substrates has been developed. The reaction provides rapid access to products usually prepared via multistep sequences. The power of the method in combination with an organocatalytic transfer hydrogenation is illustrated with a short asymmetric synthesis of (*S*)-Florhydral®.

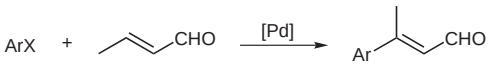
Key words: Heck reaction, unsaturated aldehydes, palladium, arylations, cross-coupling, crotonaldehyde

During our studies on organocatalytic transfer hydrogenations of enals[1] we needed a practical synthetic approach to β-methyl- or alkyl-substituted cinnamaldehydes. Reported methods involve multistep sequences such as Wittig olefination of an acetophenone derivative to the α,β-unsaturated ester followed by reduction to the allylic alcohol and re-oxidation to the aldehyde.[2] Other methods, such as the palladium-catalyzed reaction of 1,2-dien-4-ols with aryl or alkenyl halides,[3] the Vilsmeyer–Haack formylation of olefins,[4] the oxidative rearrangement of tertiary allylic alcohols via PCC,[5] or the Meyer–Schuster rearrangement of acetylenic alcohols,[6] lack generality, require tedious substrate syntheses, or require drastic reaction conditions.

A simple and elegant approach would be the direct substitution of the vinylic hydrogen in β-position of crotonaldehyde or a related aldehyde. One interesting but little investigated approach is the direct, oxidative coupling of crotonaldehyde with benzene under palladium catalysis as described by Tsuji.[7] The Heck reaction of aryl halides with crotonaldehyde appeared to be a potentially more general alternative (Scheme 1).

However, while acrolein has been used by several groups already,[8] only a single example of a low yielding (20%) Heck coupling of crotonaldehyde with bromobenzene has been reported.[9] In addition, subjecting 1-iodo-4-methylbenzene and crotonaldehyde to Heck reaction conditions resembling those previously employed in the reaction of cinnamaldehyde with iodobenzene[10] gave the desired product in only 35% yield.

We have now developed efficient and practical conditions for Heck couplings with crotonaldehyde. By (a) using two equivalents of crotonaldehyde, (b) running the reactions at 90 °C, (c) using *N*-methyl pyrrolidinone (NMP) as the solvent, (d) with 2 mol% of $Pd(OAc)_2$ as the catalyst, and (e) with tetrabutylammonium chloride as the phase-transfer catalyst, greatly enhanced reaction rates and yields of the desired cinnamaldehyde derivatives were obtained.



Scheme 1 Proposed route to α,β-unsaturated aldehydes via Heck reaction of crotonaldehyde

With our optimal conditions in hand,[11] we set out to probe the scope and limitations of the reaction of both aryl and vinyl bromides and iodides with crotonaldehyde (Table 1). We first investigated the influence of steric hindrance (entries 1–6). Both *para* and *meta* substitution are well tolerated and the corresponding products **1** are obtained in good yields. Slightly reduced yields are obtained when a substituent in *ortho* position is introduced (entry 4). Almost no conversion is observed when both *ortho* positions are occupied (entry 5).

Varying the electronic nature of the aromatic ring led to the surprising finding that electron-rich substituents allow the product formation in very good yields (entries 8 and 9), while a mildly electron-deficient substituent gave only moderate yields (entry 10). The desired reaction is barely observed at all with a strongly electron-deficient arene (entry 11). In this case the competing homocoupling reaction of the aryl halide becomes the predominant reaction pathway. The same homocoupling is also observed with 2-iodothiophene (entry 12), which did not yield the product of the desired Heck reaction in synthetically useful quantities. Vinyl halides can also be employed as substrates (entries 13 and 14), yielding α,β,γ,δ-unsaturated aldehydes in moderate to good yields.[12]

As commonly observed, the reactivity of bromides is generally lower compared to the corresponding iodides, and slightly lower yields were accordingly obtained from bromides. In general, mixtures of *E*- and *Z*-isomers were obtained, although Heck reactions are normally *trans*-selective. The *E*/*Z*-ratio of the products seems to be thermodynamically controlled. When we subjected pure (*E*)-3-(*p*-tolyl)-2-butenal to isomerization conditions, the equilibrium ratio corresponds to that obtained in the Heck reaction of entry 2. We suspect the isomerization to occur during the reaction, possibly via a nucleophilic pathway. Separation of the isomers was possible during chromatographic purification.

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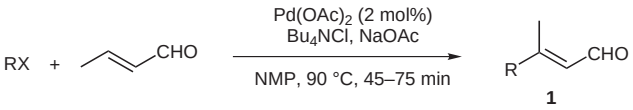
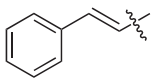
Table 1 Heck Reaction of Crotonaldehyde with Different Aryl and Vinyl Halides



Entry	R	Yield (%) X = Br	Yield (%) X = I	*E*/*Z*[a]
1	Ph	50	68	2.8:1
2	4-MeC_6H_4	70	77	2.8:1
3	3-MeC_6H_4	70	70	3.0:1
4	2-MeC_6H_4	46	55	1:2.9
5	2,2′-Me$_2C_6H_3$	–	trace	n.d.[b]
6	3-*i*-PrC_6H_4	65	–	2.5:1
7	naphth-2-yl	71	43	1:2.1
8	4-Me$_2$NC_6H_4	76	87	4:1[c]
9	4-MeOC_6H_4	73	92	3.3:1
10	4-FC_6H_4	40	44	3.0:1
11	4-O$_2$NC_6H_4	<10	< 10	n.d.[b]
12	thiophen-2-yl	trace	n.d.[b]	n.d.[b]
13		74	60	1.7:1
14		44	–	6.7:1

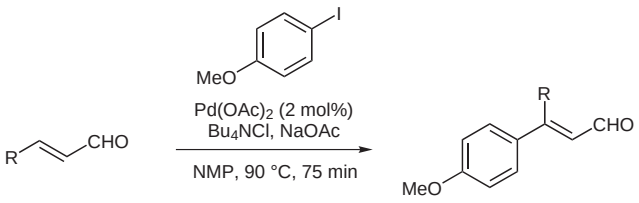
[a] Determined by GC analysis of the crude reaction mixture.
[b] Not determined.
[c] Determined by ^{1}H NMR after column chromatography.

Our reaction conditions can be readily extended to other α,β-unsaturated aldehydes as probed with the reaction of 4-iodoanisole (Table 2). The reaction works well with different enals but with increasing steric bulk and chain length the yields are decreasing. For example, an isopropyl group at the enal is not tolerated (entry 5).

To illustrate the utility of our Heck approach for the synthesis of chiral β-branched aldehydes, we have developed a short synthesis of (*S*)-Florhydral®, the more intense smelling enantiomer of a chiral fragrance marketed by Givaudan.[13] A route for the preparation of enantiomerically pure Florhydral® has been described.[14] It requires seven steps with an overall yield of less than 3% starting from commercially available diene **2** and relies on a yeast-mediated reduction of α,β-unsaturated aldehyde **3** (used as a 5:1 *E*/*Z*-mixture) to the corresponding saturated alcohol as the key step (Scheme 2, route a).

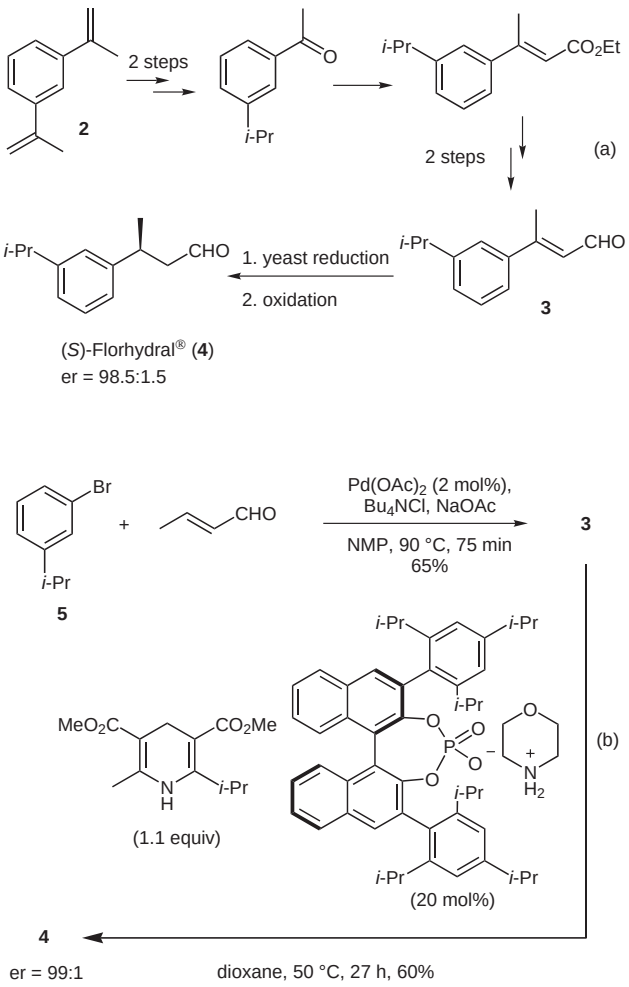
Our approach requires only two steps (Scheme 2, route b). The synthesis of aldehyde **3** was achieved employing the standard conditions developed for the Heck reaction of

Table 2 Heck Reaction of Various α,β-Unsaturated Aldehydes with 4-Iodoanisole



Entry	R	Yield (%)	*E*/*Z* ratio[a]
1	Me	92	3.3:1
2	Et	61	1.4:1
3	*n*-Pr	80	1.6:1
4	*n*-Hex	65	1.4:1
5	*i*-Pr	<5	n.d.[b]
6	Ph	52	1.7:1

[a] Determined by GC analysis of the crude reaction mixture.
[b] Not determined.



Scheme 2 Previous synthesis (a) and our approach (b) to (*S*)-Florhydral®

crotonaldehyde, starting from commercially available 1-bromo-3-isopropylbenzene **5**, in 65% yield (Table 1, entry 6). The resulting *E*/*Z*-mixture (2.5:1) was directly employed in the asymmetric counteranion-directed (ACDC) organocatalytic transfer hydrogenation under the standard conditions developed in our lab.[15] As this reaction is stereoconvergent, both olefin geometric isomers were transformed into the same enantiomer in 60% yield and with an excellent er of 99:1. With no optimization studies undertaken on either reaction we obtained a 39% yield of the essentially enantiopure target compound over two steps.

In conclusion, we have developed a protocol that allows for the rapid access of α,β-unsaturated, β-disubstituted aldehydes via the Heck reaction of crotonaldehyde and related aldehydes. Our method relies on a simple and relatively inexpensive reaction system, employing palladium(II)acetate as the catalyst and sodium acetate as the stoichiometric base. The reactions are generally finished in approximately one hour, rendering them highly practical. Furthermore, we were able to utilize our protocol in shortening a formerly lengthy synthesis of the odorant Florhydral®.

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(11) **Representative Experimental Procedure for the Heck Reaction of Crotonaldehyde (Table 1, Entry 2)**
4-Bromotoluene (256.4 mg, 1.5 mmol), TBACl (438 mg, 1.57 mmol), and NaOAc (148 mg, 1.80 mmol) were suspended in NMP (8 mL). Palladium acetate (6.8 mg, 0.03 mmol) in NMP (4 mL) was added, followed by crotonaldehyde (250 μL, 3 mmol). Oxygen was removed by two cycles of freeze-pump-thaw. The mixture was then heated at an oil-bath temperature of 90 °C for 75 min. After being cooled, the reaction mixture was poured into a half-concentrated aqueous solution of $NaHCO_3$ (80 mL) and extracted three times with CH_2Cl_2 (120 mL in total). The combined organic fractions were washed with brine once, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting solution in NMP was directly loaded onto a column packed with silica gel and eluted with Et_2O–pentane (15:85, v/v) to yield the product in fractions of pure *E*- and *Z*-isomers (70% combined yield).

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