EurJOC
European Journal of Organic Chemistry

A Journal of ChemPubSoc Europe

Accepted Article

Title: 3-Aryl Propenals and Propenones by Heck Reaction of Aryl Bromides and Acrolein or Enones – Application to Consecutive Three-component and Pseudo Four-component Pyrazole Syntheses

Authors: Marvin Stephan, Jesco Panther, Fabio Wilbert, Pauline Ozog, and Thomas J. J. Müller

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202000066

Link to VoR: http://dx.doi.org/10.1002/ejoc.202000066

Supported by ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.202000066

WILEY-VCH

3-Aryl Propenals and Propenones by Heck Reaction of Aryl Bromides and Acrolein or Enones – Application to Consecutive Three-component and Pseudo Four-component Pyrazole Syntheses

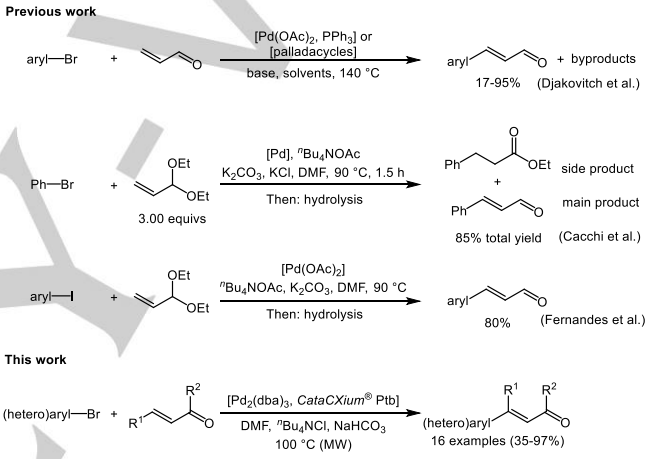
Marvin Stephan,[a] Jesco Panther,[a] Fabio Wilbert,[a] Pauline Ozog,[a] and Thomas J. J. Müller[a]*

Abstract: 3-(Hetero)aryl propenals and propenones are efficiently prepared by Heck reaction of (hetero)aryl bromides and acrolein or vinyl ketones using Beller's *CataCXium*® Ptb ligand under Jeffery's and Fu's conditions. The formation of these three-carbon building blocks is embedded into consecutive three- and pseudo four-component syntheses of 3-(hetero)aryl and 3,5-diarylpyrazoles with a broad substitution pattern in moderate to excellent yield.

Introduction

α,β-Unsaturated ketones and aldehydes constitute a highly important class of functional groups in organic chemistry.[1] Their structural motif is often found in natural products,[2] in fragrances,[3] as well as in pharmaceuticals.[4] In particular, cinnamic aldehyde derivatives find widespread application in food,[3a] cosmetic[5] and perfume, agrochemical[6] and pharmaceutical industry. As Michael systems α,β-unsaturated ketones and aldehydes are valuable three carbon building blocks in syntheses of five-, six- and seven-membered nitrogen heterocycles, such as pyrazoles,[7] quinolines,[8] or pyridines.[9] In addition they have recently received considerable attention as substrates in organocatalysis.[10]

Although often synthesized by aldol condensation of aryl aldehydes with acetaldehyde cinnamic aldehydes are obtained only in modest yields, after long reaction times and with a limited substrate scope.[11] While the Wittig and Horner-Wadsworth-Emmons reactions offer a synthetically efficient alternative, the preceding preparation of phosphorus ylids or dialkyl phosphonates renders syntheses of α,β-unsaturated carbonyl less efficacious. An efficient and selective method for the preparation of α,β-unsaturated compounds could be achieved by direct synthesis from a C3 building block. Acrolein, one of the most used C3 building blocks, is a component that has become increasingly important in recent years and can be derived from renewable raw materials.[12] For this, the Heck reaction, as a standard instrument in the chemist's toolbox, with acrolein would fit perfectly. Unfortunately, Heck reactions with acrolein as starting material with palladacycles or $Pd(OAc)_2/PPh_3$ as catalysts either turned out to be quite inactive for electron rich arylbromides or bromobenzene often leading to unselective side reactions and polymerization due to the inherently high electrophilicity and reactivity of acrolein.[13] To avoid these disadvantages, in the literature either the dialkyl acetal derivative is used to deactivate the Michael system and ensure synthetic handling,[14] or the more reactive, but atom-inefficient, aryl iodides are used instead (Scheme 1).[15]



Scheme 1. Heck synthesis of cinnamic aldehydes with acrolein and derivatives as substrates.

Cinnamic aldehydes are important C3 building blocks in heterocycle syntheses. Particularly interesting are pyrazoles, which as aromatic 1,2-diazoles cover a broad spectrum of biological[16] and pharmacological[17] activity, such analgesics,[18] antiglaucoma agents, antihypercholestrolemics, anti-*Alzheimer's* agents, as well as anticancer,[19] antihyperglycemic, anti-inflammatory,[20] antimalarial, antimicrobial,[21] antiparkinsonian, antipsychotic, antiviral, and neuroprotective activity (Figure 1). Due to broad applicability of pyrazoles, the demand for modular syntheses for pyrazoles has never ceased.

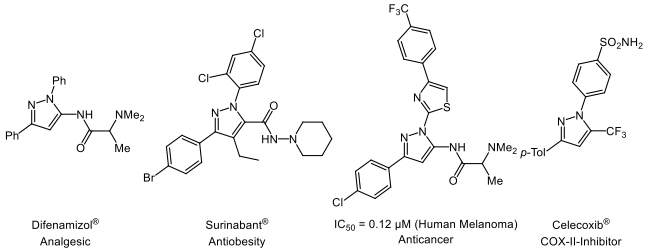


Figure 1. Selected pharmaceutically relevant pyrazole based drugs.

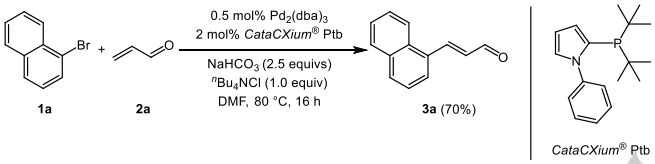
Based upon our previous studies,[22] we herein report, to the best of our knowledge, the first use of palladium *CataCXium*® Ptb complexes in Heck reactions providing selective formation of 3-

[a] M. Sc. M. Stephan, Dr. J. Panther, M. Sc. F. Wilbert, M. Sc. P. Ozog, Prof. Dr. T. J. J. Müller
Institut für Organische Chemie und Makromolekulare Chemie
Heinrich-Heine-Universität Düsseldorf, Universitätsstraße 1, D-40225 Düsseldorf, Germany
E-Mail: ThomasJJ.Mueller@uni-duesseldorf
http://www.orgchem.hhu.de
Supporting information for this article is given via a link at the end of the document.

(hetero)aryl propenals in high yields and with a broad substitution pattern in an efficient protocol under mild reaction conditions. In addition, the Heck synthesis of 3-(hetero)aryl propenals provides an excellent entry to consecutive three-component syntheses of pyrazoles.

Results and Discussion

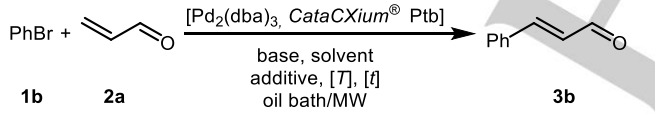
In the course of our program to provide catalytic entries to three-carbon building blocks for consecutive multicomponent syntheses of heterocycles[23] and functional chromophores,[24] we identified a combination of Jeffery's and Fu's conditions as most favorable for performing catalytic coupling of allyl alcohols for furnishing 3-(hetero)aryl propanals.[22] Jeffery *et al* carried out the reaction in the presence of a phase transfer catalyst, and under Fu's conditions the ligands are changed to sterically demanding phosphane ligands. In an initial study 1-naphthyl bromide (**1a**) and acrolein (**2a**) were reacted in DMF at 80 °C for 16 h in the presence of catalytic amounts of Pd_2dba_3, *CataCXium*® Ptb, $NaHCO_3$ as a base, $^nBu_4NCl$ as a phase transfer catalyst to give enal **3a** in 70% yield (Scheme 2).



Scheme 2. Initial conditions adapted from the coupling of allyl alcohols with 1-naphthyl bromide (**1a**).

Encouraged by this result, we set out to optimize the synthesis of cinnamic aldehyde (**3b**) with bromobenzene (**1b**) and acrolein (**2a**) as substrates (Table 1).

Table 1. Optimization of the *Heck*-reaction of bromobenzene (**1b**) and acrolein (**2a**) to give cinnamaldehyde (**3b**).



Entry	Acrolein (**2a**)	Base	*T*	*t*	Yield of cinnamic aldehyde (**3b**)[a]
	[equivs]	[equivs]	[°C]	[h]	[%]
1	1.5	$NaHCO_3$ (2.5)	100	1	67
2	1.5	$NaHCO_3$ (2.5)	70	1	traces
3	1.5	Cy_2NMe (1.1)	100	1	11
4	1.5	$NaHCO_3$ (2.5)	100	2	73
5[b]	1.5	$NaHCO_3$ (2.5)	100	1	58
6[b]	1.5	$NaHCO_3$ (2.5)	100	2	53
7	1.5	$NaHCO_3$ (2.5)	100	4.5	80
8	1.5	$NaHCO_3$ (2.5)	100	3	71
9[c]	1.5	$NaHCO_3$ (2.5)	100	3	24
10	1.1	$NaHCO_3$ (2.5)	100	3	50
11	3.0	$NaHCO_3$ (2.5)	100	3	60
12	1.5	$NaHCO_3$ (2.5)	100 (MW)	3	87
13[d]	1.5	$NaHCO_3$ (2.5)	100 (MW)	3	37
14	1.5	$NaHCO_3$ (1.1)	100 (MW)	3	83
15	1.5	$NaHCO_3$ (1.1)	100 (MW)	4	92 (89)[d]
16	1.5	$NaHCO_3$ (1.1)	110 (MW)	3	73
17	1.1	$NaHCO_3$ (1.1)	100 (MW)	4	70
18[f]	1.5	$NaHCO_3$ (1.1)	100 (MW)	4	20

[a] All yields determined by gas chromatography (detector: FID; internal standard: *n*-dodecane). [b] DMF (1 mL) was applied as a solvent. [c] NMP was applied as a solvent. [d] $^nBu_4NCl$ was omitted. [e] Yield after chromatography on silica gel. [f] *CataCXium*® PtB was omitted.

Lower reaction temperatures caused a decreased yield (Table 1, entry 2), as well as increasing the temperature above 110 °C (Table 1, entry 16). As a base $NaHCO_3$ proved to be far superior to Cy_2NMe (Table 1, entry 3), which only gave trace amounts of cinnamic aldehyde **3b**. Likewise, DMF turned out to be the solvent of choice while NMP, also an aprotic polar solvent, only furnished a decreased yield (Table 1, entry 9). Prolongation of the reaction time to 4 h turned out to be favorable, often leading to full conversion (Table 1, entries 4-8 and 15). Interestingly, at higher concentration double arylation of acrolein was observed as a byproduct. Reduction and increase of the equivalents of acrolein led to somehow lower yields (Table 1, entries 10 and 11). Dielectric heating turned out to give higher yields in comparison to conductive heating at the same reaction temperature (Table 1, entries 8 and 12). To some extent this might also occur because of the smaller gas volume in a microwave vial compared to a regular Schlenk tube. Tetrabutylammonium chloride turned out to be crucial for the success of reaction (Table 1, entry 13). Also, the amount of base cannot be reduced without causing a decrease in yield (Table 1, entry 14). In summary, the Heck reaction is most successfully conducted in a microwave oven at 100 °C for 4 h with $NaHCO_3$ as a base and under Jeffery's conditions (Table 1, entry 15).

With the optimal reaction conditions in hand the substrate scope was screened with respect to the (hetero)aryl halide **1** (Table 2). The structures of the 3-(hetero)aryl substituted α,β-unsaturated compounds **3** were unambiguously assigned by ^1H and ^{13}C NMR spectroscopy and mass spectrometry, as well as the molecular composition was corroborated by combustion analyses or high-resolution mass spectrometry.

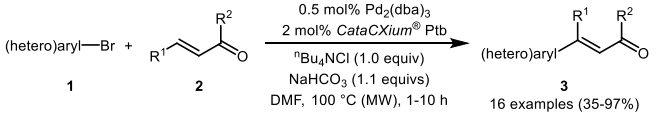
All 3-(hetero)aryl substituted α,β-unsaturated compounds **3** were obtained as *trans*-isomers. The double bond configuration was assigned by the occurrence of a single set of signals in ^1H NMR spectra with typical vicinal coupling constants of 16-17 Hz for the double bond protons.

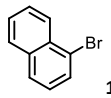
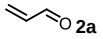
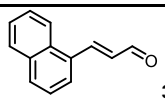
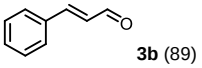
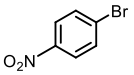
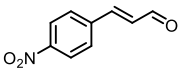
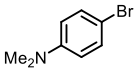
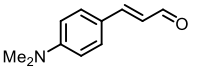
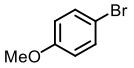
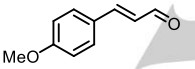
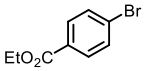
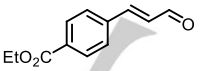
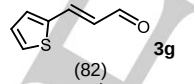
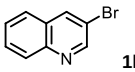
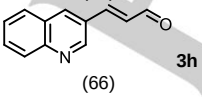
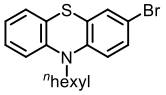
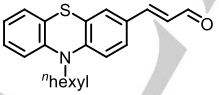
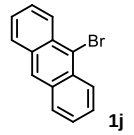
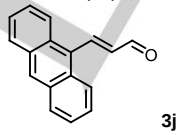
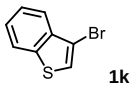
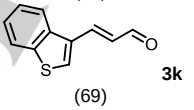
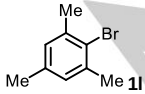
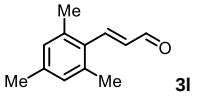
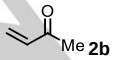
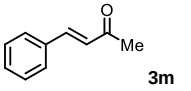
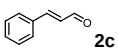
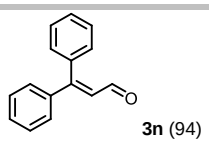
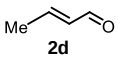
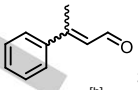
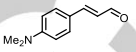
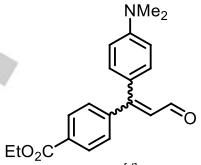
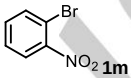
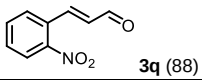
To our delight, a broad variety of substrates **1** and **2** was successfully transformed and the pure products **3** were isolated after flash chromatography on silica gel in moderate to excellent yields. The efficiency of the process was demonstrated by aryl bromides with electronically different nature (Table 2, entries 1-6). Expectedly, electron-deficient aryl bromides undergo faster coupling than electron-rich derivatives. A sterically demanding bromide such as substrate **1l** reluctantly couples and gives a lower yield (Table 2, entry 12) than sterically unbiased substrates. In addition, electron-poor and electron-rich heterocycles were coupled uneventfully and successful ligation of acrolein was demonstrated with thiophene, quinoline, phenothiazine and benzothiophene (Table 2, entries 7-9, 11). Next, the influence of the acrolein substrates was tested. Various other α,β-unsaturated aldehydes or ketones were employed and coupled in high yields (Table 2, entries 13-15, 17). The sequentially palladium-catalyzed[25] twofold coupling of acrolein with two equivalents of bromobenzene (**1b**) gave the 3,3-diphenyl acrolein (**1n**) in 95% yield (Table 2, entry 16) and also *ortho*-nitro bromobenzene (**1m**) can be transformed efficiently (Table 2, entry 18).

With this fast and efficient access to α,β-unsaturated carbonyl derivatives Michael addition-cyclocondensation steps can be readily concatenated in a one-pot fashion to obtain 1*H*-pyrazoles in an elegant and modular fashion. For optimization of the condensation step the reaction between (*E*)-4-phenylbut-3-en-2-

one (**3m**) and *p*-tolylsulfonyl hydrazide was selected as a model reaction and a reaction temperature of 80 °C for 1.5 h was identified as optimal conditions.

Table 2. Heck coupling of (hetero)aryl bromides **1** and α,β-unsaturated carbonyl compounds **2** to give 3-(Hetero)aryl substituted α,β-unsaturated ketones and aldehydes **3**

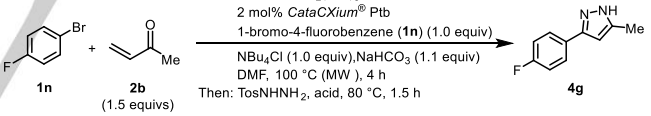


Entry	(Hetero)aryl bromide **1**	α,β-Unsaturated carbonyl compound **2**	*t* [h]	Yield of enone/enal **3** ([%])[a]
1	 **1a**	 **2a**	4	 **3a** (80)
2	 **1b**	**2a**	4	 **3b** (89)
3	 **1c**	**2a**	2	 **3c** (97)
4	 **1d**	**2a**	4	 **3d** (70)
5	 **1e**	**2a**	3	 **3e** (74)
6	 **1f**	**2a**	3	 **3f** (92)
7	 **1g**	**2a**	2	 **3g** (82)
8	 **1h**	**2a**	2	 **3h** (66)
9	 **1i**	**2a**	4	 **3i** (83)
10	 **1j**	**2a**	4	 **3j** (78)
11	 **1k**	**2a**	2	 **3k** (69)
12	 **1l**	**2a**	6	 **3l** (35)
13	**1b**	 **2b**	4	 **3m** (96)
14	**1b**	 **2c**	3	 **3n** (94)
15	**1b**	 **2d**	4	 **3o** (78)[b]
16[c]	**1b**	**2a**	8	**3n** (95)
17	**1f**	 **2e**	10	 **3p** (42)[d]
18	 **1m**	**2a**	1	 **3q** (88)

[a] All yields determined after isolation by flash chromatography. [b] ***E*/*Z*-3p** = 2.2:1. [c] A twofold excess of bromobenzene (**1b**) was employed. [d] ***E*/*Z*-3q** = 1.1:1.

For further optimization of the Heck-cyclocondensation sequence, the conditions for the cyclization were scrutinized by following the formation of the fluoro derivative **4g** from *p*-fluoro bromobenzene (**1n**), methyl vinylketone (**2b**), and tosylhydrazine (Table 3) by ^{19}F NMR spectroscopy applying an increased relaxation time of 10 s to get reliable integration. Indeed, for the cyclization step literature conditions have proven to be most successful.[26] Concentrated sulfuric acid (Table 3, entry 6) led most selectively to full conversion and the highest yield of 89% of pyrazole **4g** for the one-pot procedure was obtained after flash chromatography.

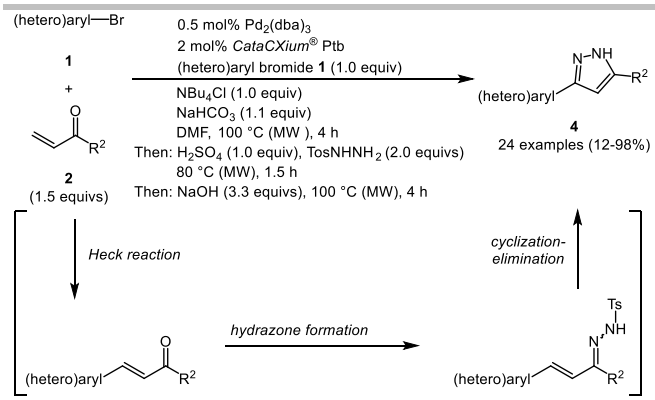
Table 3. Optimization of the cyclocondensation step of the Heck-cyclocondensation synthesis of pyrazole **4g**.



Entry	Acid (equivs)	Yield of pyrazole **4g** [%][a]
1	-	20
2	HCl (37%) (0.1)	41
3	HCl (37%) (1.0)	77
4	AcOH (1.0)	53
5	H_3PO_4 (85%) (1.0)	62
6	H_2SO_4 (95%) (1.0)	92 (89)[b]
7	*p*-toluene sulfonic acid · H_2O (1.0)	75
8	$T_3P^®$ (0.3)	30

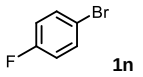
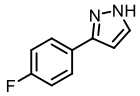
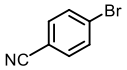
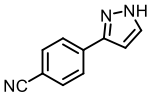
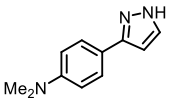
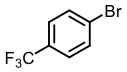
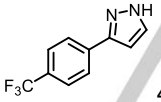
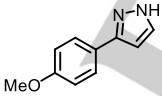
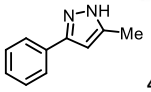
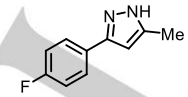
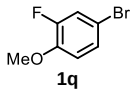
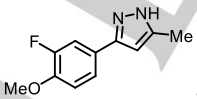
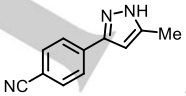
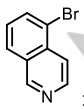
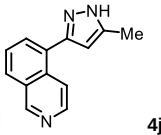
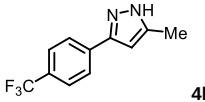
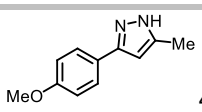
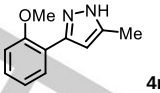
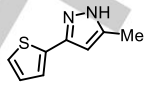
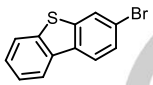
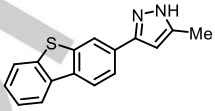
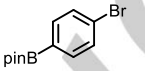
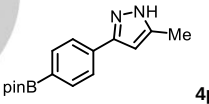
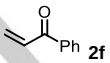
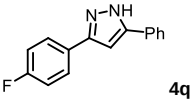
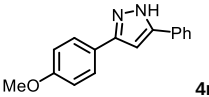
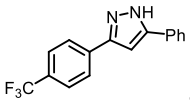
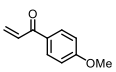
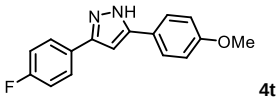
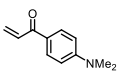
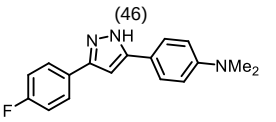
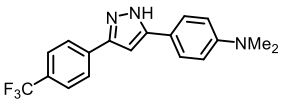
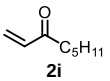
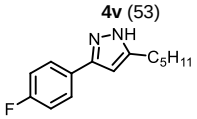
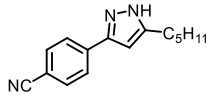
[a] All yields determined by ^{19}F NMR spectroscopy. [b] Yield (in parenthesis) determined after chromatography.

Based on the optimized conditions the scope of this one-pot sequence was scouted with different (hetero)aryl bromides **1** and a series of α,β-unsaturated carbonyl compounds **2** to furnish 3(,5)-substituted pyrazoles **4** (Scheme 3, Table 4). The pyrazole derivatives **4** were unequivocally characterized by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry, as well as the molecular composition was corroborated by combustion analyses or high-resolution mass spectrometry. Interestingly, in the ^{1}H and ^{13}C NMR spectra of pyrazoles **4** only a single set of signals could be observed, which can either be rationalized by rapid *NH*-tautomerism in solution or a single dominant tautomer. In accordance with the literature[27] the predominance of 3-aryl-1*H*-pyrazoles versus 5-aryl-1*H*-pyrazoles was assumed.



Scheme 3. Consecutive three-component Heck-cyclocondensation synthesis of 3(,5)-substituted pyrazoles **4**.

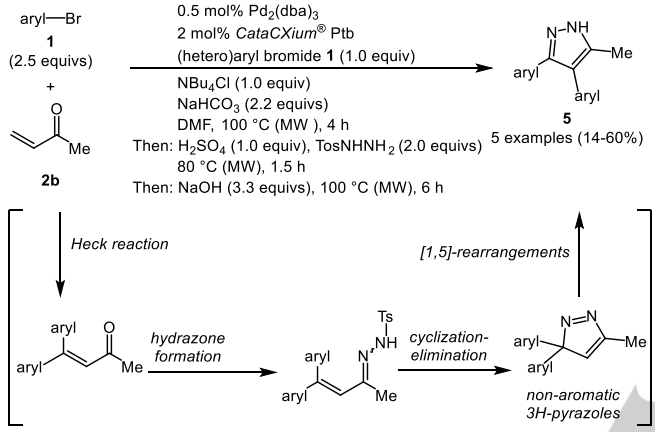
Table 4. Consecutive three-component synthesis of 3(,5)-substituted pyrazoles **4**

Entry	(Hetero)aryl bromide **1**	α,β-Unsaturated carbonyl compound **2**	Yield of 3-(hetero)aryl-1*H*-pyrazole **4** ([%])
1	 **1n**	**2a**	 **4a** (76)
2	 **1o**	**2a**	 **4b** (41)
3	**1d**	**2a**	 **4c** (45)
4	 **1p**	**2a**	 **4d** (74)
5	**1e**	**2a**	 **4e** (56)
6	**1b**	**2b**	 **4f** (88)
7	**1n**	**2b**	 **4g** (89)
8	 **1q**	**2b**	 **4h** (98)
9	**1o**	**2b**	 **4i** (82)
10	 **1r**	**2b**	 **4j** (58)
11	**1p**	**2b**	 **4k** (96)
12	**1e**	**2b**	 **4l** (67)
13	 **1s**	**2b**	 **4m** (12)
14	**1g**	**2b**	 **4n** (38)
15	 **1t**	**2b**	 **4o**
16[c]	 **1u**	**2b**	 (56) **4p** (54)
17	**1n**	 **2f**	 **4q** (57)
18	**1e**	**2f**	 **4r** (34)
19	**1p**	**2f**	 **4s** (69)
20	**1n**	 **2g**	 **4t**
21	**1n**	 **2h**	 (46) **4u** (38)
22	**1p**	**2h**	 **4v** (53)
23	**1n**	 **2i**	 **4w** (53)
24	**1o**	**2i**	 **4x** (74)

A broad variety of functionalized (hetero)aryl bromides **1** with different substitution patterns are tolerated. Bromides with electron-withdrawing groups are smoothly transformed into the corresponding pyrazoles (Table 4, entries 1, 2, 4, 7, 8, 9, 11, 17, 19, 24), while electron-rich substrates give lower yields in comparison (Table 4, entries 3, 5, 10, 12, 14, 15). Even cyano derivatives (Table 4, entries 2, 9, 24) and boronic esters (Table 4, entry 16) are uneventfully carried through the one-pot sequence. The influence of steric hindrance was probed and found to give low yields (Table 4, entry 13). Nitrogen containing heterocycles are employed with moderate yield (Table 4, entry 10). Acrolein (**2a**) derived pyrazoles give lower yields than methyl vinyl ketone (**2b**) derived congeners. This finding can be readily rationalized by the higher effective concentration of

methyl vinyl ketone (**2c**) due to its higher boiling point. α,β-Unsaturated carbonyl compounds with higher substitution patterns than methyl show significant polymerization behavior, nonetheless it is still possible to transform them in the corresponding pyrazoles **4** (Table 4, entries 17-24).

The ready access to 3,3-diaryl substituted enals **3n** and **3p** (Table 2, entries 14, 16, and 17) inspired us to probe their conversion into pyrazoles by a *pseudo*-four-component one-pot reaction. Interestingly, instead of forming non-aromatic 3*H*-pyrazoles (Scheme 4) the sequence furnishes 3,4-aryl-1*H*-pyrazoles **5** (Scheme 4, Table 5). As reported in the literature[28] 3,3-aryl 3*H*-pyrazoles undergo a series of 1,5-rearrangements upon treatment with acid and at elevated temperatures in favor of forming the heteroaromatic 3,4-aryl-1*H*-pyrazoles **5**.



Scheme 4. Consecutive pseudo four-component Heck-cyclocondensation synthesis of 3,4-diaryl-1*H*-pyrazoles **5**.

Table 5. Pseudo four-component synthesis of 3,4-diaryl-1*H*-pyrazoles **5**

Entry	(Hetero)aryl bromide **1**	Yield of 3,4-diaryl-1*H*-pyrazoles **5** ([%])
1	**1n**	**5a** (60)
2	**1b**	**5b** (50)
3	**1v**	**5c** (60)
4	**1e**	**5d** (47)
5	**1o**	**5e** (14)

After an optimization of the cyclization, the model product **5a** (Table 5, entry 1) is obtained in 60% yield. Likewise, several 3,4-aryl disubstituted pyrazoles **5** are obtained in 14 to 60% yield. All 3,4-aryl-1*H*-pyrazoles **5** were structurally distinctively assigned by ^{1}H, ^{13}C and NOESY NMR spectroscopy and mass spectrometry, and the molecular composition was confirmed by combustion analysis or high-resolution mass spectrometry.

Electron-rich to electro-neutral aryl halides are well transformed in contrast to electron-deficient derivatives. This finding is in agreement with the literature,[28c] where 3,3-aryl 3*H*-pyrazoles with electron-rich arenes undergo faster carbocation rearrangements than electron-deficient aryl or alkyl derivatives.

Conclusion

In summary 3-(hetero)aryl propenals and propenones are efficiently synthesized by Heck reaction of (hetero)aryl bromides and acrolein or vinyl ketones under a combination of Jeffery's and Fu's conditions with Beller's *CataCXium*® Ptb ligand. With this straightforward access to 3-substituted α,β-unsaturated carbonyl derivatives as three-carbon building blocks 3-(hetero)aryl and 3,5-diarylpyrazoles with a broad substitution pattern were synthesized by consecutive three- and pseudo four-component syntheses in modest to excellent yield. This concise and modular approach is perfectly suited to prepare substance libraries of decorated pyrazoles. Further studies addressing one-pot syntheses of more complex functional chromophores based upon the Heck entry to substituted enals are currently underway.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.2020xxxxx. Experimental details on syntheses of enones **2**, optimization studies, experimental details on the preparation and full characterization of enones/enals **3**, pyrazoles **4**, and **5**, ^{1}H and ^{13}C NMR spectra of compounds **3**, **4**, and **5**.

Experimental Section

Heck coupling of bromobenzene (1b) and methyl vinyl ketone (2b) to give (*E*)-4-Phenylbut-3-en-2-one (3m). A typical procedure. In a thick-walled 10 mL microwave tube with a magnetic stir bar were placed $Pd_2(dba)_3$ (5 mg, 0.5 mol%) CataCXium® Ptb (6 mg, 2 mol%), $^{n}Bu_4NCl$ (278 mg, 1.00 mmol), bromobenzene (**1b**) (157 mg, 1.00 mmol), methyl vinyl ketone (**2b**) (105 mg, 1.50 mmol), $NaHCO_3$ (92 mg, 1.10 mmol), and DMF (3 mL). The resulting suspension was reacted in a microwave reactor at 100 °C for 4 h. After cooling to room temp, ethyl acetate (10 mL) was added and the organic layer was extracted with brine (3 × 10 mL). The aqueous extract was then extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried (anhydrous magnesium sulfate) and the solvents were removed under reduced pressure. The residue was adsorbed on Celite® and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate) to give compound **3m** (140 mg, 96%) as a pale yellow solid, Mp 151 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (m, 3 H), 7.36-7.43 (m, 3 H), 6.71 (d, $J_{H\text{-}H}$ = 16.3 Hz, 1 H), 2.38 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 98.5 (C_{quat}), 143.5 (CH), 134.5 (C_{quat}), 130.6 (CH), 129.1 (CH), 128.4 (CH), 127.3 (CH), 27.6 (CH_3); EI-MS (70 eV, *m/z* (%)): 146 (M^+, 80), 131 (M^+ - CH_3, 100), 103 (M^+ - C_2H_3O, 20), 77 (C_6H_5, 28), 51 (19); IR: $\tilde{\nu}$ = 3082, 3059, 3026, 2997, 2988, 2972, 2911, 2901, 1670, 1667, 1624, 1609, 1576, 1495, 1451, 1422, 1358, 1327, 1294, 1281, 1254, 1204, 1175, 1101, 1074, 1020, 974, 907, 841, 820, 746, 689, 631 cm^{-1}; Anal calcd for $C_{10}H_{10}O$ (146.2): C 82.16, H 6.89; Found: C 82.07, H 6.84.

10.1002/ejoc.202000066

Consecutive three-component synthesis of 3,5-disubstituted pyrazole 4h. A typical procedure. In a thick-walled 10 mL microwave tube with a magnetic stir bar were placed $Pd_2(dba)_3$ (5 mg, 0.5 mol%), CataCXium® Ptb (6 mg, 2 mol%), $^nBu_4NCl$ (278 mg, 1.00 mmol), aryl bromide **1q** (205 mg, 1.00 mmol), methyl vinyl ketone (**2b**) (105 mg, 1.50 mmol), $NaHCO_3$ (92 mg, 1.1 mmol), and DMF (3 mL). The reaction mixture was overlaid with a nitrogen atmosphere and reacted in a microwave reactor at 100 °C for 4 h. Then, tosylhydrazide (372 mg, 2.00 mmol) and 95% H_2SO_4 (103 mg, 1.00 mmol) were added and reacted in the microwave reactor at 80 °C for 1.5 h. Then, NaOH (132 mg, 3.30 mmol) was added to the reaction mixture and heated in the microwave reactor at 100 °C for 4 h. After cooling to room temp, ethyl acetate (10 mL) was added and extracted with brine (3 × 10 mL). The aqueous layer was then extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried (anhydrous magnesium sulfate) and the solvents were removed under reduced pressure. The residue was adsorbed on Celite® and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate) to give compound **4h** (202 mg, 98%) as a beige solid, Mp 111-112 °C, R_f (*n*-hexane/ethyl acetate 1:1) = 0.27. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.48 – 7.38 (m, 2H), 6.93 (t, $J_{H\text{-}H}$ = 8.5 Hz, 1H), 6.24 (s, 1H), 3.89 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.8 (C_{quat}), 152.5 (d, $J_{C\text{-}F}$ = 245.1 Hz, C_{quat}), 147.4 (d, $J_{C\text{-}F}$ = 10.8 Hz, C_{quat}), 142.8 (C_{quat}), 126.2 (d, $J_{C\text{-}F}$ = 7.1 Hz, C_{quat}), 121.6 (d, $J_{C\text{-}F}$ = 3.5 Hz, CH), 113.7 (d, $J_{C\text{-}F}$ = 19.5 Hz, CH), 113.6 (d, $J_{C\text{-}F}$ = 2.2 Hz, CH), 101.9 (CH), 56.4 (CH_3), 11.6 (CH_3); ^{19}F NMR (565 MHz, $CDCl_3$): δ -135.7; EI-MS (70 eV, *m/z* (%)): 207 (13), 206 ([M]$^+$, 100), 192 ([M - CH_2]$^+$, 12), 191 ([M - CH_3]$^+$, 99), 163 (([M - CH_3N_2]$^+$, 41), 133 ([M - $C_2H_5N_2O$]$^+$, 13); IR: $\tilde{\nu}$ = 3186, 3134, 3100, 2984, 2941, 2843, 1628, 1591, 1578, 1533, 1474, 1460, 1445, 1285, 1269, 1256, 1130, 1061, 1026, 986, 876, 810, 772, 758, 716 cm^{-1}; Anal calcd for $C_{11}H_{11}FN_2O$ (206.2): C 64.07, H 5.38, N 13.58; Found: C 64.03, H 5.43, N 13.69.

Consecutive pseudo four-component synthesis of 3,4-diaryl-1H-pyrazole 5c. A typical procedure. In a thick-walled 10 mL microwave tube with a magnetic stir bar were placed $Pd_2(dba)_3$ (5 mg, 0.5 mol%), CataCXium® Ptb (6 mg, 2 mol%), $^nBu_4NCl$ (278 mg, 1.00 mmol), aryl bromide **1v** (505 mg, 2.50 mmol), methyl vinyl ketone (**2b**) (70 mg, 1.0 mmol), $NaHCO_3$ (185 mg, 2.2 mmol), and DMF (3 mL). The reaction mixture was overlaid with a nitrogen atmosphere and reacted in a microwave reactor at 100 °C for 8 h. Then, tosylhydrazide (372 mg, 2.00 mmol) and 95% H_2SO_4 (103 mg, 1.00 mmol) were added and reacted in the microwave reactor at 80 °C for 1.5 h. Then, NaOH (132 mg, 3.30 mmol) was added to the reaction mixture and heated in the microwave reactor at 100 °C for 6 h. After cooling to room temp, ethyl acetate (10 mL) was added and extracted with brine (3 × 10 mL). The aqueous layer was then extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried (anhydrous magnesium sulfate) and the solvents were removed under reduced pressure. The residue was adsorbed on Celite® and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate) to give compound **5c** (162 mg, 60%) as a colorless solid, Mp 171-172 °C, R_f (*n*-hexane/ethyl acetate 3:1) = 0.13. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (d, $J_{H\text{-}H}$ = 8.4 Hz, 1H), 7.29 (d, $J_{H\text{-}H}$ = 8.6 Hz, 1H), 7.23 (d, $J_{H\text{-}H}$ = 8.6 Hz, 1H), 7.11 (d, $J_{H\text{-}H}$ = 8.4 Hz, 1H), 2.23 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.1 (C_{quat}), 133.9 (C_{quat}), 132.8 (C_{quat}), 131.7 (C_{quat}), 131.2 (CH), 130.6 (C_{quat}), 129.1 (CH), 128.8 (CH), 128.7 (CH), 116.9 (C_{quat}), 10.8 (CH_3); EI-MS (70 eV, *m/z* (%)): 306 (11), 305 (15), 304 ([^{37}Cl-M]$^+$, 64), 302 ([^{35}Cl-M]$^+$, 100), 301 ([^{35}Cl-M - H]$^+$, 39), 268 (14), 267 (28), 263 (33), 115 (15); IR: $\tilde{\nu}$ = 3274, 3041, 3026, 2922, 2852, 2827, 2804, 278, 1502, 1483, 1437, 1419, 1396, 1278, 1261, 1172, 1113, 1092, 1013, 993, 972, 829, 790, 762, 741, 692 cm^{-1}; Anal calcd for $C_{16}H_{12}Cl_2N_2$ (303.2): C 63.39, H 3.99, N 9.24; Found: C 63.12, H 3.78, N 8.94.

Acknowledgments

The authors gratefully thank the Fonds der Chemischen Industrie.

Keywords: Acrolein • Catalysis • Heck reaction • Heterocycles • Multicomponent reactions • Palladium

References:

[1] a) A. F. D. Arntz, M. Höpp, S. Jacob, J. Sauer, T. Ohara, T. Sato, N. Shimizu, H. Schwind, *Ullmann's Encyclopedia of Industrial Chemistry*, *2 ed.*, Wiley-VCH, **2007**, *Vol. 1*, 329 – 346. b) H. Siegel, M. Eggersdorfer, *Ullmann's Encyclopedia of Industrial Chemistry*, *2 ed.*, Wiley-VCH, **2000**, *Vol. 20*, 187 – 207. c) S. Patai, Z. Rappoport, The Chemistry of Enones; John Wiley & Sons: New York, **1989**.

[2] a) J. T. Njardarson, *Tetrahedron* **2011**, *67*, 7631 – 7666; b) P. G. Baraldi, D. Preti, S. Materazzi, P. Geppetti, *J. Med. Chem.* **2010**, *53*, 5085 – 5107.

[3] a) C. Chapuis, D. Jacoby, *Appl. Catal. A.* **2001**, *221*, 93 – 117; b) J. Cocchiara, C. S. Letizia, J. Lalko, A. Lapczynski, A. M. Api, *Food Chem. Toxicol.* **2005**, *43*, 867 – 923.

[4] a) S. Amslinger, *ChemMedChem* **2010**, *5*, 351 – 356; b) L. Arshad, I. Jantan, S. N. Bukhari, M. A. Haque, *Front. Pharmacol.* **2017**, *8*, 22; c) X. Li, J. Sheng, G. Huang, R. Ma, F. Yin, D. Song, C. Zhao, S. Ma, *Eur. J. Med. Chem.* **2015**, *97*, 32 – 41; d) P. D'Arcy, X. Wang, S. Linder, *Pharmacol. Ther.* **2015**, *147*, 32 – 54; e) Xi, M. Yun, D. Lee, M. N. Park, E. O. Kim, E. J. Sohn, B. M. Kwon, *Cell. Physiol. Biochem.* **2015**, *35*, 1821 – 1830; f) L. G. León, R. M. Carballo, M. C. Vega-Hernández, P. O. Miranda, V. S. Martín, J. I. Padrón, J. M. Padrón, *ChemMedChem* **2008**, *3*, 1740 – 1747.

[5] P. Kraft, J. A. Bajgrowicz, C. Denis, G. Fráter, *Angew. Chem.* **2000**, *112*, 3106-3138; *Angew. Chem. Int. Ed.* **2000**, *39*, 2980 – 3010.

[6] S. N. A. Bukhari, I. Jantan, O. Unsal Tan, M. Sher, M. Naeem-ul-Hassan, H.-L. Qin, *J. Agr. Food Chem.* **2014**, *62*, 5538 – 5547.

[7] a) S. Fustero, M. Sánchez-Roselló, P. Barrio, A. Simón-Fuentes, *Chem. Rev.* **2011**, *111*, 6984 – 7034; b) A. C. Götzinger, F. A. Theßeling, C. Hoppe, T. J. J. Müller, *J. Org. Chem.* **2016**, *81*, 10328 – 10338; c) A. C. Götzinger, T. J. J. Müller in *Science of Synthesis, Houben-Weyl*, E. M. Carreira, Hrsg., Georg Thieme Verlag, Stuttgart, New York, *Science of Synthesis Knowledge Updates* **2017**, *3*, 1 – 228.

[8] R. Sharma, P. Kour, A. Kumar, *J. Chem. Sci.* **2018**, *130*, 73.

[9] a) Z.-Y. Mao, X.-Y. Liao, H.-S. Wang, C.-G. Wang, K.-B. Huang, Y.-M. Pan, *RSC Advances* **2017**, *7*, 13123 – 13129; b) V. P. Litvinov, *Russ. Chem. Rev.* **2003**, *72*, 69 – 85.

[10] a) H. Pellissier, *Tetrahedron* **2012**, *68*, 2197 – 2232; b) K. Jiang, Y.-C. Chen, *Tetrahedron Lett.* **2014**, *55*, 2049 – 2055.

[11] a) Y. Hayashi, D. Sakamoto, D. Okamura, *Org. Lett.* **2016**, *18*, 4 – 7; b) I. Malina, V. Kampars, B. Turovska, S. Belyakov, *Dyes Pigm.* **2017**, *139*, 820 – 830; c) L.-J. Huang, J.-P. Wang, Y.-C. Lai, S.-C. Kuo, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2742 – 2747; d) T. M. Khopade, P. K. Warghude, T. B. Mete, R. G. Bhat, *Tetrahedron Lett.* **2019**, *60*, 197 – 200.

[12] a) A. Talebian-Kiakalaieh, N. A. S. Amin, H. Hezaveh, *Renew. Sustain. Energy Rev.* **2014**, *40*, 28 – 59; b) A. Galadima, O. Muraza, *J Taiwan Inst. Chem. Eng.* **2016**, *67*, 29 – 44.

[13] A. Nejjar, C. Pinel, L. Djakovitch, *Adv. Synth. Catal.* **2003**, *345*, 612 – 619.

[14] a) W. Al-Maksoud, M. Jahjah, E. Monflier, A. Ponchel, B. Léger, C. Pinel, L. Djakovitch, *Top. Catal.* **2014**, *57*, 1550 – 1557; b) D. Mazzarella, G. E. M. Crisenza, P. Melchiorre, *J. Am. Chem. Soc.* **2018**, *140*, 8439 – 8443; c) G. Battistuzzi, S. Cacchi, G. Fabrizi, *Org. Lett.* **2003**, *5*, 777 – 780.

[15] a) C. Proença, H. M. T. Albuquerque, D. Ribeiro, M. Freitas, C. M. M. Santos, A. M. S. Silva, E. Fernandes, *Eur. J. Med. Chem.* **2016**, *115*, 381 – 392; b) R. Thomas, J. Lee, V. Chevalier, S. Sadler, K. Selesniemi, S. Hatfield, M. Sitkovsky, M. J. Ondrechen, G. B. Jones, *Bioorg. Med. Chem.* **2013**, *21*, 7453 – 7464; c) A. K. Gupta, C. H. Song, C. H. Oh, *Tetrahedron Lett.* **2004**, *45*, 4113 – 4116.

[16] a) H. Dai, G. Li, J. Chen, Y. Shi, S. Ge, C. Fan, H. He, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3818 – 3821; b) W. Zhao, Z.-H. Shen, J.-H. Xing, T.-M. Xu, W.-L. Peng, X.-H. Liu, *Lett. Drug Des. Discov.* **2017**, *14*, 323 – 329; c) J. V. Faria, P. F. Vegi, A. G. C. Miguita, M. S. dos Santos, N.

Boechat, A. M. R. Bernardino, *Bioorg. Med. Chem.* **2017**, *25*, 5891 – 5903.

[17] M. F. Khan, M. M. Alam, G. Verma, W. Akhtar, M. Akhter, M. Shaquiquzzaman, *Eur. J. Med. Chem.* **2016**, *120*, 170 – 201.

[18] R. Nassini, C. Fusi, S. Materazzi, E. Coppi, T. Tuccinardi, I. M. Marone, F. De Logu, D. Preti, R. Tonello, A. Chiarugi, R. Patacchini, P. Geppetti, S. Benemei, *Br. J. Pharmacol.* **2015**, *172*, 3397 – 3411.

[19] M.-Y. Zhao, Y. Yin, X.-W. Yu, C. B. Sangani, S.-F. Wang, A.-M. Lu, L.-F. Yang, P.-C. Lv, M.-G. Jiang, H.-L. Zhu, *Bioorg. Med. Chem.* **2015**, *23*, 46 – 54.

[20] B. M. Chougala, S. Samundeeswari, M. Holiyachi, L. A. Shastri, S. Dodamani, S. Jalalpure, S. R. Dixit, S. D. Joshi, V. A. Sunagar, *Eur. J. Med. Chem.* **2017**, *125*, 101 – 116.

[21] a) M. F. El Shehry, M. M. Ghorab, S. Y. Abbas, E. A. Fayed, S. A. Shedid, Y. A. Ammar, *Eur. J. Med. Chem.* **2018**, *143*, 1463 – 1473; b) S. M. Anush, B. Vishalakshi, B. Kalluraya, N. Manju, *Int. J. Biol. Macromol.* **2018**, *119*, 446 – 452; c) Z. Xu, C. Gao, Q.-C. Ren, X.-F. Song, L.-S. Feng, Z.-S. Lv, *Eur. J. Med. Chem.* **2017**, *139*, 429 – 440.

[22] a) J. Panther, T. J. J. Müller, *Synthesis* **2016**, *48*, 974 – 986; b) T. Jeffery, *J. Chem. Soc.*, *Chem. Commun.* **1984**, 19, 1287-1289; c) A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed*. **2002**, 41, 4176-4211; *Angew. Chem.* **2002**, 114, 4350- 4386.

[23] a) T. J. J. Müller, *Top. Heterocycl. Chem.* **2010**, *25*, 25 – 94; b) T. J. J. Müller, in *Applied Homogeneous Catalysis with Organometallic Compounds*, M. Beller, ed., Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2018**, 1463 – 1483; c) K. Deilhof, T. J. J. Müller, in *Multicomponent Reactions in Organic Synthesis*, J. Zhu, Q. Wang, M.-X. Wang, eds., Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2015**, 333 – 378; d) C. F. Gers-Panther, T. J. J. Müller in *Advances in Heterocyclic Chemistry: Heterocyclic Chemistry in the 21st Century: A Tribute to Alan Katritzky*, E. F. V. Scriven, C. A. Ramsden, eds., **2016**, *120*, 67 – 98.

[24] a) L. Levi, T. J. J. Müller, *Eur. J. Org. Chem.* **2016**, 2907 – 2918; b) T. J. J. Müller, *Drug Discov. Today Technol.* **2018**, *29*, 19 – 26.

[25] For reviews on sequential Pd-catalysis in one-pot syntheses, see e.g. a) T. Lessing, T. J. J. Müller**,** *Appl. Sci.* **2015**, *5*, 1803 – 1836; b) T. J. J. Müller, in *Molecular Catalysts: Structure and Functional Design*, L. H. Gade, P. Hofmann, eds., Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2014**, 255 – 279; c) T. J. J. Müller, *Top. Organomet. Chem.* **2006**, *19*, 149 – 205.

[26] J. Wen, Y. Fu, R.-Y. Zhang, J. Zhang, S.-Y. Chen, X.-Q. Yu, *Tetrahedron* **2011**, *67*, 9618 – 9621.

[27] a) T. Harada, J. M. Rudziński, S. Shinkai, *J. Chem. Soc., Perkin Trans. 2* **1992**, 2109 – 2115; b) M. Begtrup, G. Boyer, P. Cabildo, C. Cativiela, R. M. Claramunt, J. Elguero, J. I. García, C. Toiron, P. Vedsø, *Magn. Reson. Chem.* **1993**, *31*, 107 – 168.

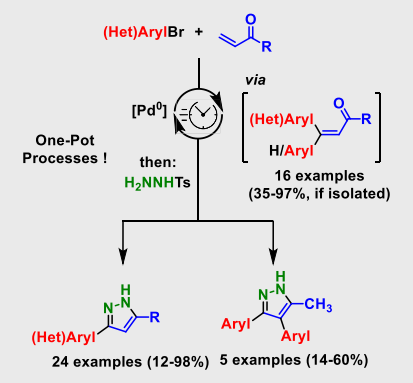
[28] a) J. van Alphen, *Recl. Trav. Chim. Pays-Bas* **1937**, *56*, 343 – 350; b) J. van Alphen, *Recl. Trav. Chim. Pays-Bas* **1943**, *62*, 485 – 490; c) *R. Hüttel, K. Franke, H. Martin, J. Riedl, Chem. Ber.* **1960**, 93, 1433 – 1446; d) G. Snatzke, H. Langen, *Chem. Ber.* **1969**, *102*, 1865 – 1868.

Entry for the Table of Contents

Layout 1:

FULL PAPER

The Heck reaction of (hetero)aryl bromides and acrolein or vinyl ketones using *CataCXium*® Ptb as a ligand, $NaHCO_3$ as a base, and $^nBu_4NCl$ gives an efficient access to 3-(hetero)aryl propenals/propenones, which are directly employed in consecutive multicomponent syntheses of pyrazoles in a one-pot fashion.



Multicomponent Reactions

*Marvin Stephan, Jesco Panther, Fabio Wilbert, Pauline Ozog, and Thomas J. J. Müller**

Page No. – Page No.

3-Aryl Propenals and Propenones by Heck Reaction of Aryl Bromides and Acrolein or Enones – Application to Consecutive Three-component and Pseudo Four-component Pyrazole Syntheses