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Advanced Synthesis & Catalysis

Phosphine(III)-Triggered One-Pot Domino Sequences towards 5,6-Dihydropyridine-2-(1*H*)-One and Pyridine-2(1*H*)-One Scaffolds

Zsófia Makra,[a] Ramóna Madácsi,[a] Tamás A. Martinek,[b] Attila Bényei,[c] László G. Puskás,[a] Mário Gyuris,[a,*] and Iván Kanizsai[a,*]

[a] AVIDIN Ltd., Alsó kikötő sor 11/D, Szeged, H-6726, Hungary
Tel.: +3662202107
Fax: +3662202108
E-mail: m.gyuris@avidinbiotech.com; i.kanizsai@avidinbiotech.com
Homepage: https://avidinbiotech.com
[b] University of Szeged, Department of Medical Chemistry, Dóm tér 8, Szeged, H-6720, Hungary
[c] University of Debrecen, Department of Physical Chemistry, Laboratory for X-ray Diffraction, Egyetem tér 1, Debrecen, H-4032, Hungary

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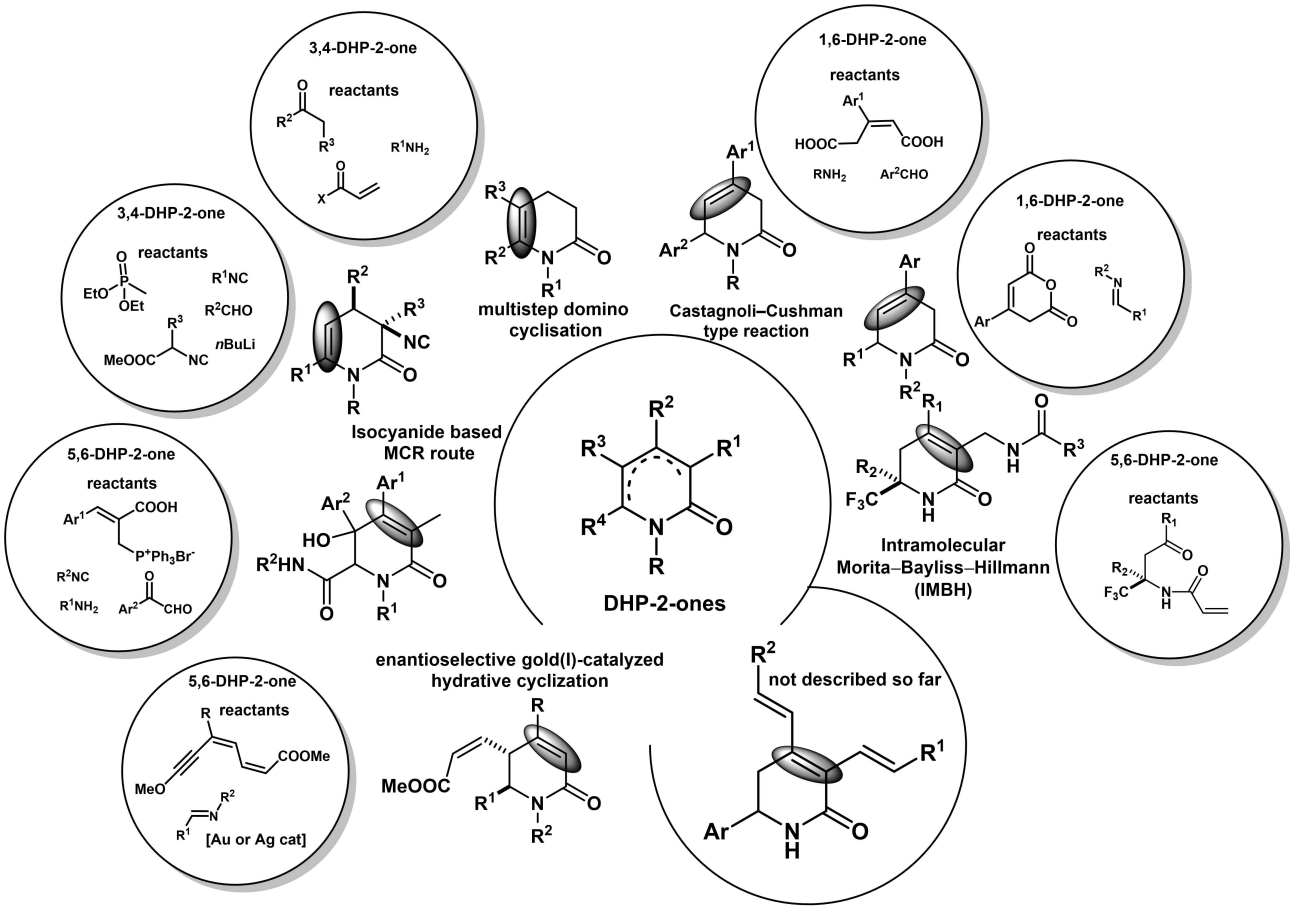
Abstract: An elegant P(nBu)$_3$-triggered synthetic approach has been developed towards multisubstituted 5,6-dihydropyridin-2(1*H*)-one and pyridin-2(1*H*)-one derivatives exploiting a domino process involving *retro*-Claisen/*intra*-MBH/Wittig/vinylogous aldol transformations as well as *retro*-Claisen/*intra*-MBH/ylide hydrolysis/oxidation sequences. This transformation demonstrates chemo- and regioselectivity as well as accessible high diversity enchancement in 17–90% isolated yield.

Keywords: Phosphine(III); One-pot domino synthesis; Mannich precursor; 5,6-Dihydropyridine-2(1*H*)-one; Pyridine-2(1*H*)-one

Introduction

Phosphine-catalysed/initiated inter- and intramolecular transformations are powerful tools for the achievement of diversity-oriented synthetic procedures towards carbocyclic and heterocyclic frameworks.[1,2] In all assemblies, phosphine ligands assist the formation of a new carbon-carbon bond. The initial step includes the nucleophilic addition of a phosphine into an activated multiple bond of the substrate, producing a reactive zwitterionic phosphonium ylide, which is a suitable intermediate to react with an electron-deficient acceptor or a nucleophile partner. Exploiting this possibility allows the synthesis of valuable precursors via the Wittig reaction affording alkenes in the treatment of phosphor ylide with aldehydes or ketones or through the Stetter transformation leading to 1,4-dicarbonyls and γ-ketoamides.[2] The synthesis of more complex cyclic structures could also be achieved via the Morita-Baylis-Hillman reaction[3] and its intramolecular version (IMBH)[4] or the Rauhut-Currier (RC)[5] reactions its vinylogous variant. These processes involve the assembly of aldehydes with activated olefins (ethyl acrylate, acrylonitrile, alkyl vinyl ketones besides aryl vinyl sulfones) in the presence of nucleophilic phosphine catalyst (or tertier amines).[6–8] By the application of intramolecular MBH synthetic strategies, numerous cyclic products such as cyclopenta[*b*]-annulated arenes, heteroarenes or cyclohexene derivatives could be synthesised including ricciocarpin A.[9–11] In addition, the synthesis of bioactive *N*-heterocyclic scaffolds such as 5,6-dihydropyridin-2(1*H*)-ones as potent MGAT2 inhibitors has also been accomplished.[12–14]

Multisubsituted DHP-2-one architectures decorated at several positions exhibit biological activities. For example, the pyridinone moiety is responsible for anti-HIV, antidiabetic as well as antifungal properties.[12,15] A number of synthetic approaches have been developed reporting elegant methods for the construction of 5,6-, 3,4- and 1,6-DHP-2-ones (Scheme 1).



Scheme 1. Facile synthetic methods for the construction of DHP-2-one frameworks.

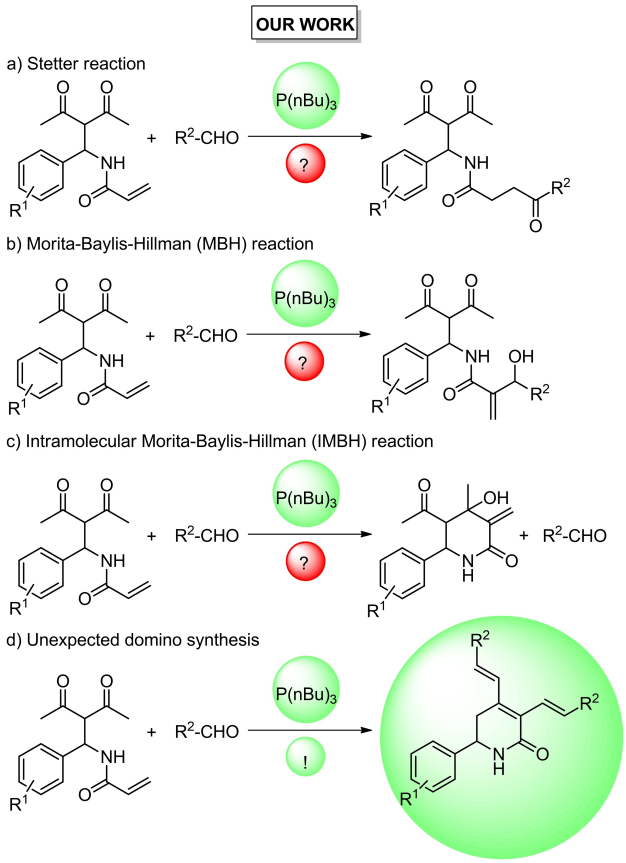
Exploiting an isocyanide-based multicomponent strategy (iMCR), diastereoselective four-component reactions were developed utilising phosphonates, nitriles, aldehydes and isocyanoacetates as building blocks to construct multifunctionalised 3,4-dihydro-2-pyridones through the formation of 1-azadiene as intermediate.[16] A similar scaffold with less diversity points has been achieved by using a multistep pathway including condensation (formation of an enamine intermediate), Michael-addition (the assembly of acrylate and enamine) and then *N*-acylation transformations (aza-annulation step).[17]

An assembly of 3-arylglutaconic anhydrides and imines through the Castagnoli-Cushman pathway followed by a decarboxylation step afforded 1,4,6-trisubstituted 1,6-dihydropyridin-2-(3*H*)-ones. Its aliphatic variant, 3-arylglutaconic acids in the Castagnoli-Cushman 3CR with amines and aromatic aldehydes resulted in the formation of 4,6-diarylated 1,6-dihydropyridine-2(3*H*)-ones, *cis*-4,6-diaryl-2-piperidones their aromatised 2-pyridone counterparts as well as their isomerised 5,6-dihydropyridin-2(1*H*)-one derivatives.[18,19]

To access target 5,6-DHP-2-one frameworks decorated at the C-3, C-4 and C-5 positions, a prominent multicomponent way has been elaborated via an isocyanide-based multicomponent reaction starting with Baylis – Hillman phosphonium salts, primary amines, isocyanides and arylglyoxals leading to the formation of 5,6-dihydropyridin-2(1*H*)-ones.[20] Alternatively, the IMBH ring-closing method of multisubstituted *N*-acrylamides in the presence of DABCO or an intermolecular diastereo- and regioselective heterodehydro-Diels-Alder reaction furnished 5,6-dihydropyridin-2-ones.[12,21]

In addition, an enantioselective gold(I)-catalysed hydrative cyclisation has also been executed starting from *N*-propargyl-ynamides in the presence of PTSA and chiral gold(I) diphosphine complexes to deliver *N*-tosyl-3,6-dihydropyridin-2(1*H*)-ones.[22]

Our envisioned survey focused on the treatment of Mannich substrate with aldehydes in the presence of trialkylphosphine catalyst outlining three possible outcomes (Scheme 2). Definitely, either the Stetter process or the Morita-Bayliss-Hillman reaction or its intramolecular variation (IMBH) may possibly take place leading to further functionalised Mannich derivatives



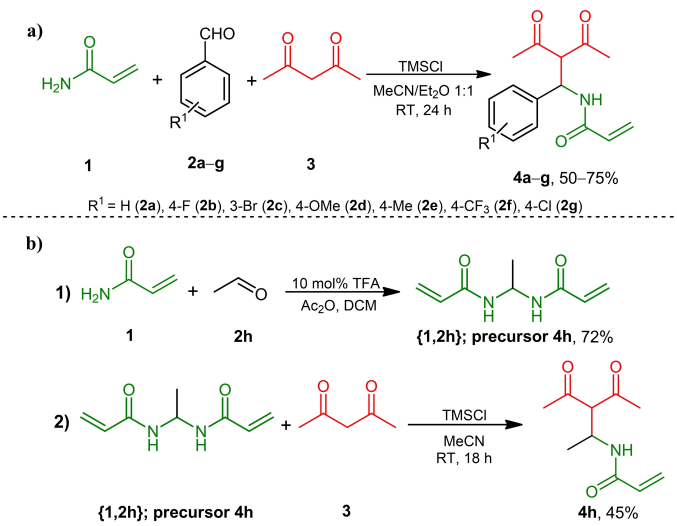
Scheme 2. Our envisioned reaction possibilities of Mannich adduct and nBu$_3$P.

(Stetter/MBH, Scheme 2a) and 2b) as well as cyclic DHP-2-one (IMBH, Scheme 2c). Surprisingly, an unexpected domino pathway also occurred furnishing 5,6-DHP-2-one frameworks with unique decoration pattern (Scheme 2d).

In this manuscript, we disclose a P(nBu)$_3$-triggered serendipity domino synthetic methodology observing the formation of a 5,6-dihydropyridin-2(1*H*)-one scaffold with exclusive substitution patterns in the C-3 and C-4 positions via sequential retro-Claisen/intramolecular-MBH/Wittig/vinylogous aldol cascade reactions and demonstrate a new phospine-initiated intramolecular annulation.

Results and Discussion

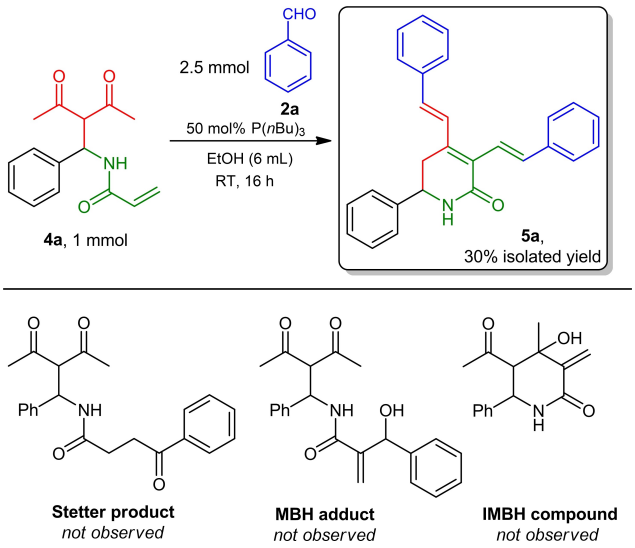
Starting materials **4 a**–**g** have been synthesised according to a slightly modified Mannich-3CR (Scheme 3a).[23] The assembly of acrylamide **1**, aromatic aldehydes **2 a**–**g** and acetylacetone **3** in the presence of trimethylsilyl chloride (TMSCl) furnished Mannich precursors **4 a**–**g** isolated in yields of 50–75% after column chromatography purification. Precursor **4 h** was prepared according to a modified litheral[24]



Scheme 3. Synthetic methods for the formation of **4 a**–**h** Mannich type products.

two step protocol which included TFA catalysed synthesis of aminal, *N*,*N*′-(ethane-1,1-diyl)-diacrylamide (**{1,24}; precursor 4 h**, Scheme 3b1) and addition of acetylacetone **3** in a precence of TMSCl to obtain methyl-containing Mannich-type product **4 h** in 45% isolated yield (Scheme 3b2).

Initially, *N*-(2-acetyl-3-oxo-1-phenylbutyl) acrylamide **4 a** was selected and reacted with benzaldehyde **2 a** in the presence of a catalytic amount of P(nBu)$_3$ in EtOH, stirring overnight at room temperature (Scheme 4). Next day precipitation occurred and TLC monitoring indicated that the transformation was completed. After simple filtration and recrystallisation from ethanol, the isolated pure product was identified



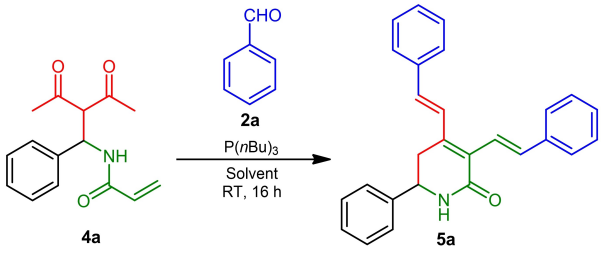
Scheme 4. The pioneer reaction.

as 6-phenyl-3,4-di((*E*)-styryl)-5,6-dihydropyridin-2(1*H*)-one (**5a**) bearing a unique architecture. Other envisioned frameworks were not found in the reaction mixture.

A rapid test with respect to solvent scope and additive loadings of P(*n*Bu)$_3$ revealed a remarkable solvent effect on conversion as well as the most advantageous additive amount (Table 1). Application of 1 or 1.2 equivalents of phosphine in ethanol led to 64% and 78% isolated yields of **5a**, respectively (Entries 1 and 2). On the other hand, a higher loading resulted in slightly lower yield (72%, Entry 3). Exploiting other alcohols such as MeOH or *n*-BuOH furnished similar yields (75 and 76%, Entries 4 and 5). Surprisingly, no conversion was found in other C3 and C4 alcohols (Entry 6–8), either in polar aprotic (THF and MeCN, Entries 10 and 11) or apolar solvents (toluene, Entry 12). Since no attempts were effective in increasing the yield, Entry 2 provides the optimal conditions using 2.5 equivalents of aldehyde and 1.2 equivalents of P(*n*Bu)$_3$ in EtOH at room temperature.

Next, other phosphines (Table S1, *See* Supporting Information) including triphenylphosphine, alkylphosphines (tri-*tert*-butylphosphine, *tert*-butyl-diisopropyl phosphine, tricyclohexylphosphine), tris(dimethylamino) phosphine as well as phosphites (tris(trimethylsilyl) phosphite, dimethyl phosphite, triethyl phosphite) were tested. Unfortunately, neither phosphines nor phosphites proved to be effective to induce product formation.

Table 1. Optimization of the reaction conditions: additive loadings and solvents.

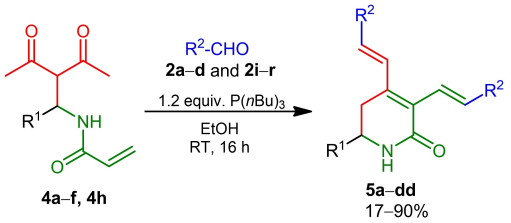


Entry	n_i [P(*n*Bu)$_3$]	Solvent	Yield [%][a]
1	1	EtOH	64
2	1.2	EtOH	78
3	1.5	EtOH	72
4	1.2	MeOH	75
5	1.2	*n*-BuOH	76
6	1.2	*sec*-BuOH	–
7	1.2	*t*-BuOH	–
8	1.2	iPrOH	–
9	1.2	DCM	–
10	1.2	THF	–
11	1.2	MeCN	–
12	1.2	toluene	–

[a] Isolated yield after simple filtration.

To gain insight into the applicability of this synthetic protocol to access a 5,6-dihydropyridin-2(1*H*)-one chemical library, various aldehydes such as aryl, alkyl, vinyl and heteroaryl derivatives were tested (Table 2). All aromatic aldehydes were suitable starting materials affording desired cycloadducts **5a–v** in yields of 17–82%. The subsequents of Mannich precursors have significant substitution effects, Mannich substrates bearing strong electron-donating and electron-withdrawing groups have reductive effects on

Table 2. Substrate scope.



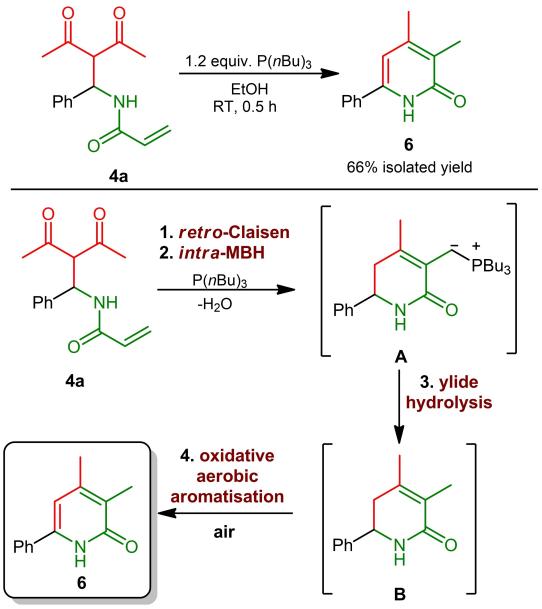
A	S	R^1	R^2	P	Yield [%][a]
2a	**4a**	C_6H_5	C_6H_5	**5a**	78
2b	**4a**	C_6H_5	4-FC_6H_4	**5b**	76
2c	**4a**	C_6H_5	3-BrC_6H_4	**5c**	70
2d	**4a**	C_6H_5	4-$OMeC_6H_4$	**5d**	72
2a	**4b**	4-FC_6H_4	C_6H_5	**5e**	82
2b	**4b**	4-FC_6H_4	4-FC_6H_4	**5f**	75
2c	**4b**	4-FC_6H_4	3-BrC_6H_4	**5g**	68
2d	**4b**	4-FC_6H_4	4-$OMeC_6H_4$	**5h**	71
2a	**4c**	3-BrC_6H_4	C_6H_5	**5i**	80
2b	**4c**	3-BrC_6H_4	4-FC_6H_4	**5j**	77
2c	**4c**	3-BrC_6H_4	3-BrC_6H_4	**5k**	74
2d	**4c**	3-BrC_6H_4	4-$OMeC_6H_4$	**5l**	75
2a	**4d**	4-$OMeC_6H_4$	C_6H_5	**5m**	40
2i	**4d**	4-$OMeC_6H_4$	3-ClC_6H_4	**5n**	20
2a	**4e**	4-MeC_6H_4	C_6H_5	**5o**	71
2b	**4e**	4-MeC_6H_4	4-FC_6H_4	**5p**	69
2c	**4e**	4-MeC_6H_4	3-BrC_6H_4	**5q**	74
2d	**4e**	4-MeC_6H_4	4-$OMeC_6H_4$	**5r**	71
2a	**4f**	4-$CF_3C_6H_4$	C_6H_5	**5s**	32
2i	**4f**	4-$CF_3C_6H_4$	3-ClC_6H_4	**5t**	17
2a	**4h**	Me	C_6H_5	**5u**	90
2i	**4h**	Me	3-ClC_6H_4	**5v**	56
2j	**4h**	Me	Cy	**5w**	57
2j	**4a**	C_6H_5	Cy	**5x**	50
2k	**4a**	C_6H_5	cBu	**5y**	40
2l	**4a**	C_6H_5	cPr	**5z**	35
2m	**4a**	C_6H_5	4-CH_2=CHC_6H_4	**5aa**	33
2n	**4a**	C_6H_5	3-furyl	**5bb**	51
2o	**4a**	C_6H_5	3-thiophenyl	**5cc**	60
2p	**4a**	C_6H_5	3-benzthiophenyl	**5dd**	54
2q	**4a**	C_6H_5	3-pyridyl	**5ee**	–
2r	**4a**	C_6H_5	3-indolyl	**5ff**	–

A-aldehyde; **S**-substrate; **P**-product. **Reaction conditions**: 1 mmol **4**, 2.5 mmol **2**, 1.2 mmol P(*n*Bu)$_3$, 6 mL EtOH, RT, 16 h

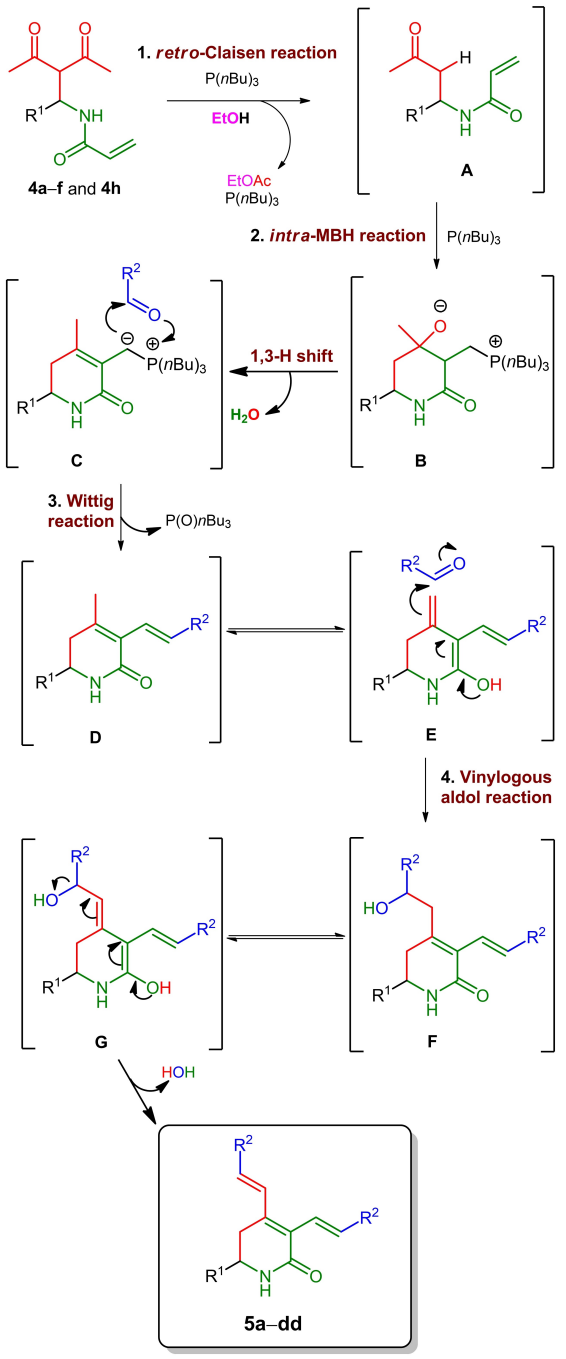
[a] Isolated yields.

isolated yields (**5 m–n** and **5 s–t**, 17–40%), lowest yield was observed in combination of R^1 = 4-$CF_3C_6H_4$ and R^2 = 3-ClC_6H_4 subunits (**5 t**, 17%). In contrast, aliphatic substituted Mannich precursor provide the highest yield (**5 u**, 90%) in combination of R^1 = Me and R^2 = phenyl unit. Full aliphatic combination (R^1 and R^2 = Me and Cy) provides moderate yield (**5 w**, 57%). Furthermore, the method was utilised to synthesize derivatives containing alkyl, vinyl as well as heteroaryl motifs at position R^2. The assembly of **4 a** with cycloalkanecarboxaldehydes as well as cinnamaldehyde underwent smoothly with the desired conversion, but diminished isolated yields were obtained (**5 x–aa**, 33–50%). The efforts to improve the outcomes for the formation of cyclopropyl derivative **5 z** (amounts of reagent and additive, different solvents and solvent mixtures as well as temperature, *See* Supporting Information, Table S2 and S3) did not lead to any notable improvement. Reactions with heterocyclic aldehydes such as 3-furancarboxaldehyde and 3-thiophenecarboxaldehyde afforded decreased but still satisfactory isolated yields (**5 bb–dd**, 51–60%). Unfortunately, no desired products were accomplished (**5 ee** and **5 ff**) by using formyl-substituted *N*-heterocycles.

Interestingly, treatment of the Mannich substrate with tri-*n*-butylphoshine in the absence of aldehyde led to the formation of 3,4-dimethyl-6-substituted pyridin-2(1*H*)-one **6** in a yield of 66% (Scheme 5). This "aldehyde-free" protocol shed light into the possible reaction pathway serving a basis for mechanistic study (Scheme 6). Presumably, the Mannich substrate in the presence of phosphine was transformed into intermediate **A** via a domino sequence including *retro*-Claisen reaction and an *intra*-MBH transformation. Following the loss of water and ylide hydrolysis,[25] dimethylated 5,6-dihydropyridinone **B** could undergo an oxidative aerobic aromatisation to give final pyridinone **6**.



Scheme 5. Representation of the "aldehyde-free" reaction and a plausable mechanistic insight.



Scheme 6. The proposed reaction mechanism.

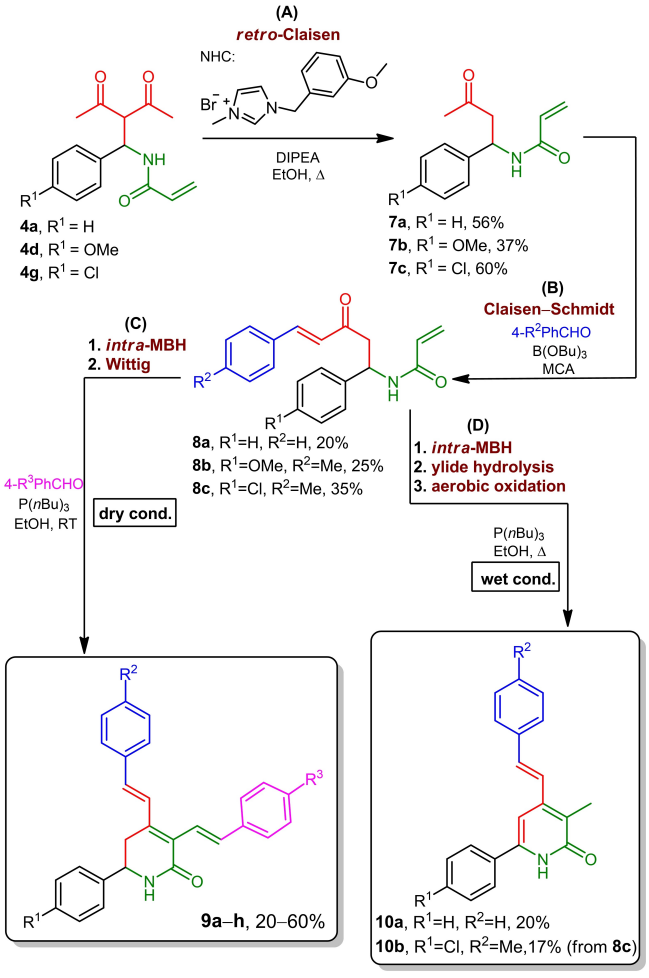
The tentative reaction mechanism for the formation of 3,4-di(*E*)-substituted 5,6-dihydropyridin-2(1*H*)-one analogues **5 a–dd** is outlined in Scheme 6. Presumably, the transformation is initiated by P(*n*Bu)$_3$-mediated

retro-Claisen process forming intermediate **A** followed by removal of EtOAc. The nucleophilic addition of P(*n*Bu)$_3$ into **A** triggers an intramolecular MBH cyclisation towards the generation of zwitterionic **B**. Next a 1,3-H shift and loss of water afford *intra*-MBH adduct **C**, which reacts with the starting aldehyde undergoing Wittig-reaction[26] and leading to intermediate **D**. Tautomerisation gives **E**, which is capable of intercepting the second aldehyde generating vinylogous aldol[27] 5,6-dihydropyridinone **F**. Finally, the latter gives the desired heterocycles **5a–dd** through intermediate **G**.

In continuation of our study, the access towards the C-3 and C-4 non-symmetric analogues **9** and **10** was accomplished (Scheme 7). An NHC-catalysed *retro*-Claisen reaction (route **A**) was carried out to produce **7a–c** with yields of 37–60%. Following the assembly of **7a–c**, addition of equimolar amounts of aromatic aldehydes in the presence of tributyl borate and morpholinium chloroacetate (MCA) catalyst (route **B**) led to Claisen-Schmidt adducts **8a–c** in yields up to 35%. Afterwards, using "dry and inert conditions" (pathway **C**), the synthesis of non-symmetric 5,6-dihydropyridinones was achieved via phoshine-mediated *intra*-MBH followed by Wittig reaction. This insertion of the second aryl constituent provides analogues **9a–h** introducing different aryl substituents at C-3, C-4 and C-6 positions. In contrast, when **8a** and **8c** were subjected to P(*n*Bu)$_3$-triggered transformation under "wet conditions" (**D**), the formation of trisubstituted pyridinone scaffolds **10a,b** took place in isolated yields of 17 and 20% through *intra*-MBH cyclisation, ylide hydrolysis then aerobic oxidation sequence.

Exploiting our new synthetic methodology, nine unique 5,6-dihydropyridinones **9b–9h** and pyridinones **10a,b** substituted in a non-symmetric manner have been prepared in yields up to 60% decorating the heterocyclic skeleton with alkyl and/or aryl units at C-3, C-4 and C-6 positions (Scheme 8).

One of the non-symmetrical aryl-substituted species **9** was prepared for X-ray crystallography analysis. The defined structure in regard to the compound **9b** has been depicted in the Figure 1.



Scheme 7. Multistep synthetic routes demonstrating the accessible diversity.

Conclusion

In summary, a convenient, unique P(*n*Bu)$_3$-triggered one-pot, multi-step domino methodology has been successfully developed furnishing trisubstituted 5,6-dihydropyridin-2(1*H*)-one and pyridin-2(1*H*)-one frameworks. The method involves highly effective multiple cascade reaction sequences consisting of *retro*-Claisen reaction, phosphine-mediated *intra*-MBH transformation as well as Wittig coupling and subsequent vinylogous aldol reaction leading to the formation of multisubstituted 5,6-dihydropyridin-2(1*H*)-ones. Furthermore, an "aldehyde-free" approach provides an easy access to the pyridin-2(1*H*)-one moieties

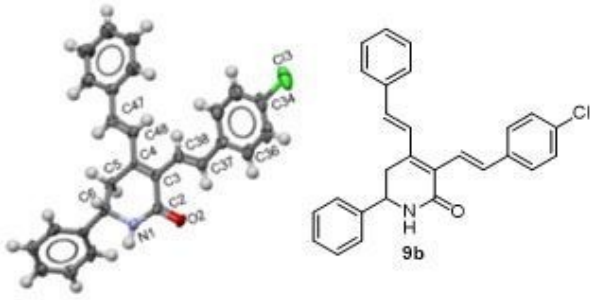
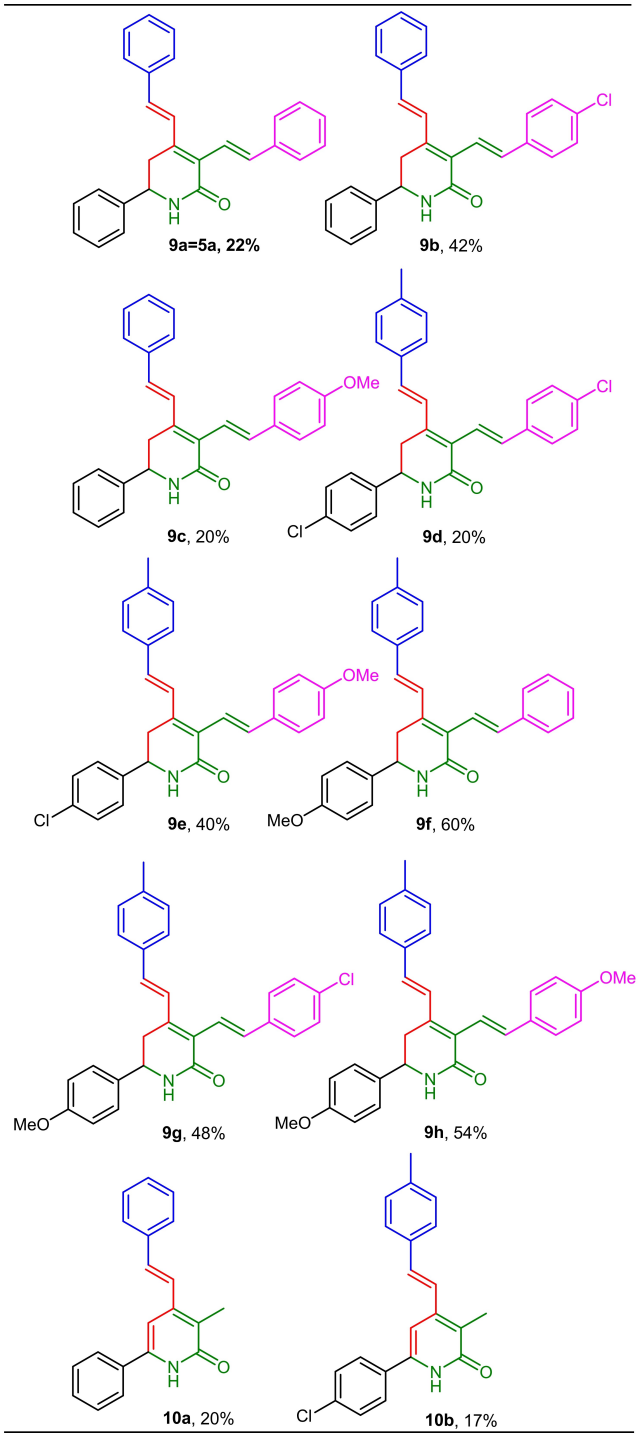


Figure 1. ORTEP style view of **9b** at 50% probability level with partial numbering scheme. Selected bond length data (Å): C2-O2: 1.252(6) C3-C4: 1.363(8) C37-C38: 1.338(8) C47-C48: 1.356(8) C34-Cl3: 1.730(7). For further details *see* Supplementary.



Scheme 8. The constructed 5,6-dihydropyridinone and pyridinone library.

owing to the accomplishment of an alternative pathway including *retro*-Claisen/*intra*-MBH/phosphine hydrolysis/auto-oxidation key steps. The full control for regioselective outcomes and chemoselectivity was also achieved in this work.

Experimental Section

General Information

NMR spectra were recorded at ambient temperature on a Bruker Avance DRX500 spectrometer equipped with standard 5-mm broadband probe or on a Bruker Avance III 600 MHz spectrometer equipped with 5-mm CP-TCI triple-resonance cryoprobe or Bruker Ascend 500 with 5-mm BBO Prodigy Probe. Chemical shifts (δ) are given in ppm, and coupling constants (J) are given in Hz. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet etc.), coupling constants and integration. Compounds were dissolved in [D_6]DMSO and [D_8]THF and chemical shifts were referenced to the solvent signal. Melting points were recorded with an Electrothermal IA9100 Digital Melting Point Apparatus or Buchi Melting Point B-545. IR spectra were recorded on an Agilent Cary 630 FTIR spectrometer. High-resolution mass spectra (HRMS) were measured on a Thermo Scientific Q Exactive hybrid quadrupole-Orbitrap mass spectrometer using HESI ion source. Samples (5 µL of 1 µg/ml solution) were injected to the MS using flow injection method (200 µL/min, acetonitrile/water = 50:50 with 0.1% TFA). HPLC (or LCMS) analyses were recorded on Agilent 1100/1200 Series instrument equipment with an Agilent G1946D MS detector (APCI, operated in positive mode) with Kinetex C18 column (100 Å, 5 µm, 250 × 4.6 mm, Phenomenex), Eluent: acetonitrile/water = 70:30 or 90:10). Visualisation was accomplished under UV (254 nm). TLC was performed on aluminum sheets coated with silica gel 60 F_{254} (Merck, 1.05554). Column chromatography was performed with Kieselgel 60 (Merck, 0.063–0.200 mm; elution mixtures: isomeric hexane mixture/ethyl acetate, chloroform/ethyl acetate or toluene/acetonitrile). Mannich substrates **4a–f** and Claisen-Schmidt adducts **8a–c** were synthesised either following a literature[23] method or a slightly modified procedure, **4h** was prepared according reference [24] or with modification. 3-(3-Methoxybenzyl)-1-methyl-1*H*-imidazol-3-ium bromide (Imidazolium NHC)[28] and morpholinium chloroacetate[29] were prepared according to the literature. All other chemicals and solvents were of commercial grade and used without further purification.

General Procedures for the Preparation of Mannich Precursors 4 a–g

To the solution of acrylamide (20 mmol), acetylacetone (19.6 mmol) and the corresponding aryl aldehyde (19,6 mmol) in solvent mixture of acetonitrile/diethyl ether (1:1, 200 mL) at room temperature, chlorotrimethylsylane (1,2 equiv.) was added. The reaction mixture was stirred further for 24 hours. Path **A**): Afterwards, the reaction mixture was filtered and the solid was suspended in 200 mL of ethyl acetate and stirring further. After 10 minutes, the suspension was filtrated on silica (40 mL) and washed with ethyl acetate (100 mL). The solvent was evaporated by vacuo, and the residue was recrystallised from diethyl ether to have **4a–g** Mannich precursors in pure forms. Path **B**): After 24 h, the TLC monitoring indicated that the reaction was fully completed. Saturated bicarbonate solution was added to the reaction mixture and the aqueous layer was separated and extracted with EtOAc (3 × 25 mL). The combined

organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed by vacuo and the residue was purified on column chromatography (Kieselgel 60, hexane/ethyl acetate 4:1) and recrystallised from diethyl ether.

Procedure for the Preparation of {1,2 h}; Precursor of 4 h

Compound has been synthesized according to literature procedure.[24] Yield: 72%/3.31 g (white powder).

Procedure for the Preparation of Mannich Type Product 4 h

To a suspension of the precursor (11 mmol, 1.1 equiv.) in MeCN (20 mL), acetylacetone (10 mmol, 1 equiv.) and chlorotrimethylsilane (11 mmol, 1.1 equiv.). were added and stirred at room temperature for 18 hours. Upon the completion of the reaction (monitored by TLC with *n*-hexane/acetone 2:1), the reaction mixture was evaporated then purified on flash chromatography eluting with *n*-hexane/acetone 100:0 to 75:25 gradient. The pure product **4 h** was obtained as white solid in yield of 45%.

General Procedure for the Preparation of 5,6-Dihydropyridin-2(1*H*)-Ones 5 a–dd

To a stirred solution of Mannich precursors **4 a–f** and **4 h** (1 mmol) in 6 mL of dry EtOH under argon atmosphere, the corresponding aldehyde (2.5 mmol) and tri-*n*-butylphosphine (1.2 mmol; 300 µL) were added. After further stirring for overnight at ambient temperature, vivid yellow crystals precipitated from the reaction mixture for aryl, heteroaryl and vinyl derivatives. The solids were collected by simple filtration and washed with EtOH (50 mL) then with 50 mL of 50:1 EtOH/THF mixture. After drying, final products **5 a–v** and **5 aa–dd** were isolated in 17–90% yield as yellow or orange (**5 aa**) powders. In the case of alkyl variants **5 w–z**, flash column chromatography purification (gradients of toluene/MeCN: 50:1, 30:1, 20:1, 10:1) then recrystallisation with diethyl ether or diethyl ether and methanol (10:1) were needed to obtain the pure products in yields of 35–57%.

Procedures for the Preparation of Product 6

In a 20-mL reaction tube equipped with a magnetic stirrer, Mannich (**4 a**; 1 mmol) precursor was dissolved in 6 mL of EtOH. After addition of 1.2 mmol of tri-*n*-butylphosphine (300 µl), the reaction mixture was stirred at room temperature for 30 min followed by dilution with 5 mL saturated Na_2CO_3 solution and further stirring for 1 hour at the initial temperature. Next the reaction mixture was poured into water (20 mL) and extracted with EtOAc (2 × 20 mL). The organic phase was dried over Na_2SO_4, the solvent was removed at reduced pressure, then the residue was subjected to the flash column chromatography (Silica gel; eluent: $CHCl_3$:EtOAc 19:1) and recrystallised from diethyl ether to give the pure final product **6**.

General Method for the Preparation of Retro-Claisen Intermediates 7 a–c

To the solution of the corresponding Mannich precursor (**4 a**, **4 d** or **4 g**; 10 mmol) in EtOH (60 mL), 3-(3-methoxybenzyl)-1-methyl-1*H*-imidazol-3-ium bromide[21] (4 mmol, 40 mol%) and DIPEA (12 mmol, 1.2 equiv.) were added and stirred for 24 h at 60 °C. Then the reaction was quenched by addition of 10 mmol formic acid, and after a 1 h further stirring EtOH was removed at reduced pressure. The residue was washed with water and extracted with EtOAc (2 × 30 mL). The organic phase was dried over Na_2SO_4, the solvent was evaporated at vacuo, then the residue was chromatographed on silica gel (gradient of eluent: hexane:EtOAc 4:1; 2:1; 1:1) and recrystallised from diethyl ether to give **7 a–c** as white crystals.

General Procedure for the Preparation of 8 a–c

The preparation of Claisen-Schmidt adducts **8 a–c** were accomplished followed by reference 23 starting from 5 mmol of *retro*-Claisen precursors **7 a–c**.

General Procedure for the Preparation of 9 a-h

To the solution of Claisen-Schmidt adduct (**8 a–c**; 0.5 mmol), the corresponding aldehyde (0.5 mmol), 3 Å molecular sieve (30 mg) in 3 mL absoluted EtOH and tri-*n*-butylphosphine (0.6 mmol, 150 µL) were added. The mixture was stirred at ambient temperature monitored by TLC. When the transformation was completed (after 16 hours), the reaction mixture was diluted by 2 mL diethyl ether then the precipitated solid was filtrated. The observed mixture of yellow solid and molecular sieve was dissolved in THF, filtred on 10 cm^3 Celite and washed with THF. The solvent was removed under reduced pressure to afford pure products (**9 a–h**) as vivid yellow powders. Single crystal data of **9 b** was deposited under depositon number 2110876. These data can be obtained free of charge at www.ccdc.cam.ac.ul/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033; email: deposit@ccdc.cam.ac.uk].

General Procedure for the Preparation of 10 a,b

Claisen-Schmidt (**8 a** or **8 b**; 1 mmol) adducts were dissolved in 6 mL of EtOH. After addition of 1.2 mmol of tri-*n*-butylphosphine (300 µl), the reaction mixture was stirred at 60 °C for 60 min, followed by dilution with 5 mL saturated Na_2CO_3 solution and then stirring was continued for another 1 hour at the initial temperature. After being cooled to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (2 × 20 mL). The organic phase was dried over Na_2SO_4, the solvent was removed under vacuo, then the residue was subjected to the flash column chromatography separation (Silica gel; eluent: $CHCl_3$: EtOAc 19:1). After recrystallisation from diethyl ether, pure final products **10 a,b** were filtered.

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References

[1] C. Gomez, J.-F. Betzer, A. Voituriez, A. Marinetti, *ChemCatChem* **2013**, *5*, 1055–1065.

[2] H. Guo, Y. C. Fan, Z. Sun, Y. Wu, O. Kwon, *Chem. Rev.* **2018**, *118*, 10049–10293.

[3] a) K. Morita, Japan Patent 6803364, 1968, *Chem. Abstr.* **1968**, *69*, 58828s; b) K. Morita, Z. Suzuki, H. Hirose, *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815–2815; c) A. B. Baylis, M. E. D. Hillman, German Patent, 2155113, 1972 Chem. Abstr., **1972**, *77*, 34174q; d) D. Basavaiah, P. D. Rao, R. S. Hyma, *Tetrahedron* **1996**, *52*, 8001–8062; e) E. Ciganek, *Org. React.* **1997**, *51*, 201–341; f) S. E. Drewes, G. H. P. Roos, *Tetrahedron* **1988**, *44*, 4653–4670; g) P. Langer, *Angew. Chem. Int. Ed.* **2000**, *39*, 3049–3052; *Angew. Chem.* **2000**, *112*, 3177–3180; For selected recent reviews on MBH reactions, *see*: h) Y. Wei, M. Shi, *Chem. Rev.* **2013**, *113*, 6659–6690; i) H. Pellissier, *Tetrahedron* **2017**, *73*, 2831–2861; j) D. Basavaiah, R. T. Naganaboina, *New J. Chem.* **2018**, *42*, 14036–14066.

[4] Representative examples of tertiary amine or phosphine catalysed IMBH and intramolecular RC reactions: a) J. W. Cran, M. E. Krafft, K. A. Seibert, T. F. N. Haxell, J. A. Wright, C. Hirosawa, K. A. Abboud, *Tetrahedron* **2011**, *67*, 9922–9943; b) K. C. Bharadwaj, *RSC Adv. Review* **2015**, *5*, 75923–75946.

[5] M. M. Rauhut, H. Currier, *US Patent*, 3,074,999, 1963 *Chem.Abstr.* **1963**, *58*, 11224a.

[6] a) M. K. Kundu, S. B. Mukherjee, N. Balu, R. Padmakumar, S. V. Bhat, *Synlett* **1994**, 444–444; b) J. S. Hill, N. S. Isaacs, *Tetrahedron Lett.* **1986**, *27*, 5007–5010; c) A. Kamimura, Y. Omata, H. Mitsudera, A. Kakehi, *J. Chem. Soc. Perkin Trans. 1* **2000**, 4499–4504.

[7] a) C. Yu, L. Hu, *J. Org. Chem.* **2002**, *67*, 219–223; b) V. K. Aggarwal, I. Emme, S. Y. Fulford, *J. Org. Chem.* **2003**, *68*, 692–700; c) C. Faltin, E. M. Fleming, S. J. Connon, *J. Org. Chem.* **2004**, *69*, 6496–6499; d) W. Guo, W. Wu, N. Fan, Z. Wu, C. Xia, *Synth. Commun.* **2005**, *35*, 1239–1251; e) F. C. Pigge, R. Dhanya, E. R. Hoefgen, *Angew. Chem. Int. Ed.* **2007**, *46*, 2887–2890; *Angew. Chem.* **2007**, *119*, 2945–2948; f) X. Tang, B. Zhang, Z. He, R. Gao, Z. He, *Adv. Synth. Catal.* **2007**, *349*, 2007–2017; g) M. Davoust, F. Cantagrel, P. Metzner, J.-F. Brière, *Org. Biomol. Chem.* **2008**, *6*, 1981–1993; h) E. S. Kim, H. S. Lee, J. N. Kim, *Tetrahedron Lett.* **2009**, *50*, 6286–6289; i) R. M. Singh, K. C. Bharadwaj, D. K. Tiwari, *Beilstein J. Org. Chem.* **2014**, *10*, 2975–2980.

[8] K. C. Bharadwaj, *ChemistrySelect* **2017**, *2*, 5384–5389.

[9] B. Satpathi, S. S. V. Ramasastry, *Synlett* **2016**, *27*, 2178–2182.

[10] K. Agapiou, M. J. Krische, *Org. Lett.* **2003**, *5*, 1737–1740.

[11] a) Y. Wang, A. Jaunet, P. Geoffroy, M. Miesch, *Org. Lett.* **2013**, *15*, 6198–6201; b) R. Boehringer, P. Geoffroy, M. Miesch, *Org. Biomol. Chem.* **2015**, *13*, 6940–6943; c) C. Peter, P. Geoffroy, M. Miesch, *Org. Biomol. Chem.* **2018**, *16*, 1381–1389.

[12] a) B. A. Johns, T. Kawasuji, J. G. Weatherhead, T. Taishi, D. P. Temelkoff, H. Yoshida, T. Akiyama, Y. Taoda, H. Murai, R. Kiyama, M. Fuji, N. Tanimoto, J. Jeffrey, S. A. Foster, T. Yoshinaga, T. Seki, M. Kobayashi, A. Sato, M. N. Johnson, E. P. Garvey, T. Fujiwara, *J. Med. Chem.* **2013**, *56*, 5901–5916; b) A. Li, Y. Ouyang, Z. Wang, Y. Cao, X. Liu, L. Ran, C. Li, L. Li, L. Zhang, K. Qiao, W. Xu, Y. Huang, Z. Zhang, C. Tian, Z. Liu, S. Jiang, Y. Shao, Y. Du, L. Ma, X. Wang, J. Liu, *J. Med. Chem.* **2013**, *56*, 3593–3608; c) A. Haga, H. Tamoto, M. Ishino, E. Kimura, T. Sugita, K. Kinoshita, K. Takahashi, M. Shiro, K. Koyama, *J. Nat. Prod.* **2013**, *76*, 750–754; d) J. Xiao, Q. Zhang, Y.-Q. Gao, J.-J. Tang, A.-L. Zhang, J.-M. Gao, *J. Agric. Food Chem.* **2014**, *62*, 3584–3590; e) D. A. Wacker, Y. Wang, M. Broekema, K. Rossi, S. O'Connor, Z. Hong, G. Wu, S. E. Malmstrom, C.-P. Hung, L. LaMarre, A. Chimalakonda, L. Zhang, L. Xin, H. Cai, C. Chu, S. Boehm, J. Zalaznick, R. Ponticiello, L. Sereda, S.-P. Han, R. Zebo, B. Zinker, C. E. Luk, R. Wong, G. Everlof, Y.-X. Li, C. K. Wu, M. Lee, S. Griffen, K. J. Miller, J. Krupinski, J. A. Robl, *J. Med. Chem.* **2014**, *57*, 7499–7508.

[13] Y. Nishiura, K. Kurahashi, N. Ohyabu, Y. Sasaki, *US Patent*, US2018/0353492A1, **2018**.

[14] J. H. Gong, Y. J. Im, K. Y. Lee, J. N. Kim, *Tetrahedron Lett.* **2002**, *43*, 1247–1251.

[15] Representative examples for synthetic strategies of pyridinone scaffolds, *see*: a) G. Cardillo, S. Fabbroni, L. Gentilucci, R. Perciaccante, F. Piccinelli, A. Tolomelli, *Tetrahedron* **2004**, *60*, 5031–5040; b) S. Rakshit, C. Grohmann, T. Besset, F. Glorius *J. Am. Chem. Soc.* **2011**, *133*, 2350–2353; c) S. Alvarez, S. Medina, G. Domínguez, J. Perez-Castells, *J. Org. Chem.* **2013**, *78*, 9995–10001; d) M. Fujii, T. Nishimura, T. Koshiba, S. Yokoshima, T. Fukuyama, *Org. Lett.* **2013**, *15*, 232–234; e) K. D. Collins, F. Glorius, *Tetrahedron* **2013**, *69*, 7817–7825; f) L. Grigorjeva, O. Daugulis, *Org. Lett.* **2014**, *16*, 4684–4687; g) Y. Yu, L. Huang, W. Wu, H. Jiang, *Org. Lett.* **2014**, *16*, 2146–2149; h) L. Ackermann, *Acc. Chem. Res.* **2014**, *47*, 281–295; i) K. Ozols, Y.-S. Jang, N. Cramer *J. Am. Chem. Soc.* **2019**, *141*, 5675–5680. For the synthesis of 5,6-dihydro-pyridinone motifs, *see*: j) A. Niida, H. Tanigaki, E. Inokuchi, Y. Sasaki, S. Oishi, H. Ohno, H. Tamamura, Z. Wang, S. C. Peiper, K. Kitaura, A. Otaka, N. Fujii, *J. Org. Chem.* **2006**, *71*, 3942–3951; k) M. Paravidino, R. Scheffelaar, R. F. Schmitz, F. J. J. de Kanter, M. B. Groen, E. Ruijter, R. V. A. Orru, *J. Org. Chem.* **2007**, *72*, 10239–10242; l) L. Yang, Qi–Yu Zheng, De-Xian Wang, Zhi-Tang Huang, M.-X. Wang, *Org. Lett.* **2008**, *10*, 2461–2464; m) D. Ji, K. Liu, J. Sun, *Org. Lett.* **2018**, *20*, 7708–7711.

[16] M. Paravidino, R. S. Bon, R. Scheffelaar, D. J. Vugts, A. Znabet, R. F. Schmitz, F. J. J. de Kanter, M. Lutz, A. L. Spek, M. B. Groen, R. V. A. Orru, *Org. Lett.* **2006**, *8*, 5369–5372.

[17] A. S. Wagman, L. Wang, J. M. Nuss, *J. Org. Chem.* **2000**, *65*, 9103–9113.
[18] O. Bakulina, D. Dar'in, N. Guranova, M. Krasavin, *J. Org. Chem.* **2020**, *85*, 6822–6829.
[19] A. Firsov, E. Chupakhin, D. Dar'in, O. Bakulina, M. Krasavin, *Org. Lett.* **2019**, *21*, 1637–1640.
[20] X.-H. Zeng, H.-M. Wang, M.-W. Ding, *Org. Lett.* **2015**, *17*, 2234–2237.
[21] J. M. Fernández-García, M. Á. Fernández-Rodríguez, E. Aguilar, *Org. Lett.* **2011**, *13*, 5172–5175.
[22] J. Febvay, Y. Sanogo, P. Retailleau, M. P. Gogoi, A. K. Sahoo, A. Marinetti, A. Voituriez, *Org. Lett.* **2019**, *21*, 9281–9285.
[23] M. Gyuris, L. Hackler Jr., L. I. Nagy, R. Alföldi, E. Redei, A. Marton, T. Vellai, N. Faragó, B. Ozsvári, A. Hetényi, G. K. Toth, P. Sipos, I. Kanizsai, L. G. Puskás, *Arch. Pharm. Chem.* Life Sci. **2017**, *350*, e1700005.
[24] T. Yurino, Y. Aota, D. Asakawa, T. Kano, K. Maruoka, *Tetrahedron* **2016**, *72*, 3687–3700.
[25] a) A. Schnell, J. G. Dawber, J. C. Tebby, *J. Chem. Soc.-Perkin Trans.* **1976**, *2*, 633–636; b) J.-B. Zhu, P. Wang, S. Liao, Y. Tang, *Org. Lett.* **2013**, *15*, 3054–3057.
[26] For Wittig olefination between phosphines, aldehydes, and allylic carbonates, *see*: R. Zhou, C. Wang, H. Song, Z. He, *Org. Lett.* **2010**, *12*, 976–979.
[27] a) G. Casiraghi, F. Zanardi, *Chem. Rev.* **2000**, *100*, 1929–1972; b) S. E. Denmark, J. R. Heemstra, Jr., G. L. Beutner, *Angew. Chem. Int. Ed.* **2005**, *44*, 4682–4698; *Angew. Chem.* **2005**, *117*, 4760–4777; c) S. V. Pansare, E. K. Paul, *Chem. Eur. J.* **2011**, *17*, 8770–8779.
[28] M. Rodrigues, L. Russo, E. Aguiló, L. Rodríguez, I. Ott, L. Pérez-García, *RSC Adv.* **2016**, *6*, 2202–2209.
[29] M. Gyuris, L. Puskás, I. Kanizsai, B. Ózsvári, L. Hackler, L. I. Nagy, *WO Patent*, WO2013/041895A1, **2013**.

