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$Pd^{II/IV}$ catalyzed oxidative cyclization of 1,6-enynes derived by Ugi-4-component reaction

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ABSTRACT

A variety of 1,6-enynes were synthesized by an Ugi-reaction and further elaborated by a $Pd^{II/IV}$ catalyzed oxidative cyclization to produce N-substituted 3-aza-bicyclo[3.1.0]hexan-2-ones. Different substitution patterns were tested to examine the scope and limitations of the amide tethered substrates.

Palladium catalyzed transformations are among the most powerful and versatile methods in organic synthesis to construct C–C and C-heteroatom bonds and often offer a unique access to structures which are otherwise difficult to obtain.[1] While most of these reactions proceed through Pd^0/Pd^{II} catalytic cycles an increasing number of reactions involving Pd^{IV} complexes as key intermediates have been reported during the last years.[2]

Compared to the Pd^0/Pd^{II} catalysis Pd^{II}/Pd^{IV} has several advantages: (i) It requires the use of only weak bases and a strict exclusion of air and moisture is not necessary making them operationally simpler; (ii) the newly formed bonds (e.g., sp^2 and sp^3 C–OAc, C–OCH_2CF_3, C–I, C–F) are often highly complementary to those achievable by classical $Pd^{0/II}$ catalysis and so is (iii) the tolerance for functional groups (e.g., Ar-Br and Ar-I are completely stable under oxidative catalytic reaction conditions).[1]

The $Pd^{II/IV}$ catalyzed oxidative cyclization of 1,6-enynes developed by the Sanford[3] and Tse[4] groups offers a facile entry to the bicyclo[3.1.0]hexane skeleton. This structural motif is found in several natural products with potent antibiotic activity[5] and various drugs,[6] for example, anticonvulsant *pregabalin* or protein kinase C-β inhibitor JTT-010. Furthermore it has been utilized as a key intermediate in the synthesis of the cyclopropane containing natural product ambruticin S by Martin and co-workers[7] and for the stereoselective synthesis of highly functionalized organic molecules via nucleophilic ring opening of the bicyclic core structure.[8]

As part of our ongoing research project to find new postmodifications for structures obtained by multicomponent reactions (MCRs) we were interested if we could use this cyclization with enynes generated by an Ugi-reaction (Fig. 1). While several $Pd^{0/II}$-mediated postmodifications have been published,[9] to the best of our knowledge there are no examples involving $Pd^{II/IV}$-chemistry.

MCRs in general and especially the isocyanide based reactions offer a robust, versatile, and fast access to molecules with several points of diversity.[10] The excellent atom economy and the inherent high convergence in combination with cheap starting materials make these reactions the optimal choice for our hit identification and optimization program.

As initial test system, phenylpropiolic acid was chosen because of its high stability and good reactivity in Ugi-reactions. Allylamine served as small and flexible unsubstituted alkene (the rates of olefin insertion of substituted alkenes are known to be slow compared to the undesired side reactions[6]). With bulky *tert*-butylisocyanide that will minimize potential side reactions with the secondary amide formed,[9e] and with benzaldehyde as the carbonyl compound, the expected Ugi-product **1a** was obtained in 64% yield. Subsequent heating at 80 °C with 1.1 equiv of iodosobenzenediacetate, 5 mol % $Pd(OAc)_2$ and 6 mol % 2,2′-bipyridyl in dry acetic acid under a N_2 atmosphere[4] lead to a cyclic product **1b**. Although HPLC-analysis showed no formation of any specific byproducts the conversion did not proceed cleanly probably due to the Pd-mediated intermolecular reactions between the unsaturated functionalities and/or further reactions of the double acceptor-substituted cyclopropane ring moiety.[11] ^{1}H NMR-analysis showed a mixture of two

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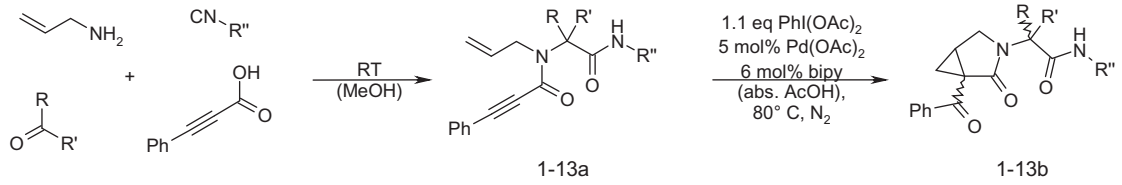

Figure 1. General reaction scheme.

Table 1
Synthesized Ugi- and cyclization products

Entry	R, R′	R″	Ugi-product	Isolated yield (%)	Cyclization product	Isolated yield (%)	dr
1	Ph, H	^{t}Bu	**1a**	64	**1b**	51	3:2
2	H, H	^{t}Bu	**2a**	96	**2b**	47	—
3	H, H	^{t}Bu			**2b**[a]	45	—
4	H, H	^{t}Bu			**2b**[b]	—	—
5	H, H	^{t}Bu			**2b**[c]	52	—
6	Me, Me	^{t}Bu	**3a**	70	**3b**	49	—
7	^{i}Pr, H	^{t}Bu	**4a**	99	**4b**	17[d]	5:4
8	*p*-Cl–C_6H_4, H	^{t}Bu	**5a**	92	**5b**	9	1.1:1
9	*p*-MeO–C_6H_4, H	^{t}Bu	**6a**	93	**6b**	—	—
10	H, H	Et	**7a**	80	**7b**	38	—
11	H, H	Ph	**8a**	33	**8b**	20	—
12	H, H	Bn	**9a**	89	**9b**	43	—
13	H, H	CH_2COOMe	**10a**	88	**10b**	29	—
14	H, H	C_2H_4OMe	**11a**	91	**11b**	0	—
15	H, H	C_2H_4OMe			**11b**[c]	40	—
16	^{i}Pr, H	Et	**12a**	85	**12b**[e]	—	—
17	Ph, H	Bn	**13a**	84	**13b**	32	1.1:1

[a] Microwave.
[b] Without bipy.
[c] No aqueous workup.
[d] Purity 85%.
[e] 105 °C.

diastereomers in a ratio of 3:2 (Table 1, entry 1).[12] In order to simplify the spectra achiral compounds **2a** and **3a** were synthesized in good to excellent yields. Subsequent cyclization was slower for both of them compared to **1a** and accordingly the cyclopropanes **2b** and **3b** were isolated in lower yield (entries 2 and 6). Compound **3b** demonstrates that a bulky substitution at the lactam nitrogen is tolerated.

Reaction monitoring for **2b** showed increased side product formation and therefore the reaction was repeated using microwave heating. It was expected that a shorter reaction time would produce less side products and polymer. Indeed complete conversion was achieved after 9 h at 80 °C with a substantial decrease in byproducts, but disappointingly the isolated yield was lower than with the conventional heating. Closer investigation revealed that the product degrades during the purification on silica. Switching to neutral aluminum oxide could obviate this problem. When iodosobenzenediacetate was substituted with hydrogen peroxide as a milder oxidant[2] the reaction proceeded with more side products and a worse conversion.

Entry 4 shows an experiment without using 2,2′-bipyridyl as an additional ligand which leads only to the degradation of the starting material and demonstrates the necessity of this additive to avoid side reactions[13,14] such as β-hydride elimination or protonolysis of the carbon–palladium bond (which is in agreement with the results published by Lyons and Sanford[6]).

After this proof of concept the influence of both the aldehyde and the isocyanide moieties on the cyclization was examined. Though they may seem remote to the alkene and alkyne they have been found to influence the cyclization by altering the electronic properties of the lactam nitrogen.[15,16] Additionally, the secondary amide stemming from the isocyanide can act as ligand for the palladium and it may alter the catalytic properties of the intermediate palladium complexes. Finally, the tolerance for functional groups can be easily tested by placing them at the distant (isocyanide derived) end. The results are summarized in Table 1.

First the steric influence of the aldehyde derived residue was tested with iso-butyraldehyde as the carbonyl component. While the MCR went smoothly subsequent cyclization led to a complex mixture with only minor amounts of the product (entry 7). Replacement of the bulky *tert*-butyl isocyanide with ethylisocyanide and therefore reduction in the steric strain in the Ugi-product did not improve the reaction. An increase of the reaction temperature to 105 °C caused complete degradation of the starting material (entry 16).

Substituted benzaldehydes were examined next. Again, the Ugi-reaction afforded the enynes **5a** and **6a** in very good yields but in contrast to the unsubstituted benzaldehyde the cyclization went poorly, yielding only small amounts of the desired cyclopropanes **5b** (9%) and traces of **6b** which degraded during the aqueous workup (entries 8 and 9).

Finally we tested the influence of the exocyclic amide substituent using an array of different isocyanides (small and bulky aliphatic, phenylic, benzylic, functionalized aliphatic). Most MCR-products were easily obtained with good to excellent yields and the following cyclization produced the corresponding bicycles. Among the tested isocyanides benzyl isocyanide performed best (entry 12) whereas phenyl isocyanide gave the lowest yield in this series indicating that the cyclization is susceptible to subtle changes in the substrate structure. Cyclization of **10a** and **11a** so far showed the cleanest conversion (judged by HPLC). This may be attributed to the oxygen atom(s) acting as an intramolecular ligand for the catalyst, stabilizing the intermediates. Both reactions suffered from severe degradation during aqueous workup (entries

13 and 14). Indeed, **11b** could only be obtained after skipping the extraction step (entry 15). Transferring this procedure to substrate **2a** improved the yield slightly (entry 5). Compound **7a** performed similar but showed an increased tendency for degradation upon prolonged heating.

In summary it was shown that the Ugi-reactions is well suited to synthesize enynes in excellent yields. The resulting 1,6-enynes were further elaborated by a $Pd^{II/IV}$ catalyzed oxidative cyclization to produce varied N-substituted 3-aza-bicyclo[3.1.0]hexan-2-ones with three points of diversity. Different substitution patterns were tested to examine the scope and limitations of the amide tethered substrates. The reactions perform best with benzylic amide substituents or with substituents bearing a functional group that can act as an intramolecular ligand for the catalyst.

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12. Typical reactions procedure for the synthesis of **1a**: 1 mmol of allylamine and benzaldehyde were dissolved in 1 ml of methanol and stirred for 2 h. After cooling the reaction mixture to 0 °C 1 mmol of phenylpropiolic acid and 1 mmol of *tert*-butylisocyanide were added and the mixture was stirred for another 16 h. After evaporation of the solvent the crude product was washed with small quantities of cold acetone to yield the product as a white solid (64%). ^{1}H NMR (400 MHz, $CDCl_3$): major diastereomer only: 7.53–7.51 (m, 2H), 7.43–7.33 (m, 8H), 5.92 (s, 1H), 5.66 (s(br), 1H), 5.58–5.49 (m, 1H), 4.98–4.88 (m, 2H), 4.39 (dd, 1H, ^3J = 5.7 Hz, ^2J = 16.7 Hz), 4.20 (dd, 1H, ^3J = 6.0 Hz, ^2J = 16.7 Hz), 1.36 (s, 9H). Typical reactions procedure for the synthesis of **3a**: 1 mmol of allylamine and acetone were dissolved in 1 ml of methanol and stirred for 2 h at 0 °C. Then 1 mmol of phenylpropiolic acid and 1 mmol of *tert*-butylisocyanide were added and the mixture was stirred overnight. After evaporation of the solvent the crude product was purified by column chromatography over silica gel (ethyl acetate–hexane = 1:2, R_f = 0.36, 70%). ^{1}H NMR (400 MHz, $CDCl_3$), main rotamer only: 7.62–7.58 (m, 2H), 7.55–7.45 (m, 3H), 6.46 (s(br), 1H), 6.04–5.94 (m, 1H), 5.39 (d, 1H, ^3J = 16.4 Hz), 5.23 (d, 1H, ^3J = 10.5 Hz), 4.39 (d, 1H, ^3J = 5.5 Hz), 1.37 (s, 3H), 1.23 (s, 9H). Typical reactions procedure for the synthesis of **9a**: In a pressure tube 1 mmol of each allylamine, para-formaldehyde, benzylisocyanide and phenylpropiolic acid were dissolved in 1 ml of 2,2,2-trifluoroethanol and stirred at 50 °C for 36 h. After evaporation of the solvent the product was purified by column chromatography (ethyl acetate–hexane = 1:2, R_f = 0.19) yielding 295 mg (89%) of a white solid. ^{1}H NMR (400 MHz, $CDCl_3$), main rotamer only: 7.54 (d, 2H), 7.47–7.22 (m, 8H), 6.60 (s(br), 1H), 5.93–5.72 (m, 1H), 5.32–5.21 (m, 2H), 4.45 (d, 2H, ^3J = 6.0 Hz), 4.37 (d, 2H, ^3J = 6.0 Hz), 4.09 (s, 2H).
General reaction procedure for the synthesis of **1b**, **3b**, **9b**: In a dry pressure tube with a stirring bar filled with an inert gas (argon or nitrogen) to 150 mg of enyne, 5 mol % $Pd(OAc)_2$, 6 mol % 2,2′-bipyridyl and 1.1 equiv of iodosobenzenediacetate were added and dissolved in 4 ml of dry acetic acid. The reaction mixture was heated at 80 °C (oil bath temperature) until TLC or HPLC showed complete conversion of the starting material. Then 30 ml of water were added to form a milky suspension which was extracted with 2 × 25 ml ethyl acetate, the combined organic phase were washed with 2 × 50 ml water and 1 × 50 ml brine, dried over Na_2SO_4, filtrated and the solvent evaporated. The crude product was further purified by column chromatography. **1b**: ethyl acetate–hexane = 1:5→4:1, off-white solid, 51%. ^{1}H NMR (400 MHz, $CDCl_3$), 2 diastereomers A/B = 3:2: 7.97–7.93 (m, 2H, A), 7.82–7.77 (m, 2H, B), 7.56–7.51 (m, 2 × 1H, AB), 7.46–7.28 (m, 2 × 7H, AB), 5.70 (s, 1H, B), 5.68 (s(br), 1H, A), 5.56 (s, 1H, A), 5.47 (s(br), 1H, B), 4.27 (dd, 1H, *J* = 5.8 Hz, *J* = 10.8 Hz, A), 3.90 (d, 1H, *J* = 10.5 Hz, B), 3.23 (dd, 1H, *J* = 5.9 Hz, *J* = 10.5 Hz, B), 3.04 (d, 1H, *J* = 10.9 Hz, A), 2.36–2.28 (m, 2 × 1H, AB), 2.05 (dd, 1H, *J* = 4.2 Hz, *J* = 8.2 Hz, A), 1.99 (dd, 1H, *J* = 4.9 Hz, *J* = 7.8 Hz, B), 1.50–1.45 (m, 1H, B), 1.35 (s, 9H, A), 1.31 (s, 9H, B), 0.93 (t, 1H, *J* = 4.8 Hz, A). **3b**: ethyl acetate–hexane = 1:1→9:1, off-white solid, 49%. ^{1}H NMR (400 MHz, $CDCl_3$): 7.87 (m, 2H), 7.54 (m, 1H), 7.44 (m, 1H), 5.97 (s(br), 1H), 3.95 (dd, 1H, *J* = 5.6 Hz, *J* = 10.3 Hz), 3.63 (d, 1H, *J* = 10.3 Hz), 2.37 (dt, 1H, *J* = 7.9 Hz, *J* = 5.6 Hz), 2.07 (dd, 1H, *J* = 7.9 Hz, *J* = 4.6 Hz), 1.54 (s, 3H), 1.50 (s, 3H), 1.30 (s, 9H), 1.12 (t, 1H, *J* = 4.6 Hz). **9b**: (ethyl acetate–hexane = 1:2, R_f = 0.30) and yielded 51 mg (43%)of a white-brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): 7.87 (d, 2H, ^3J = 7.4 Hz), 7.52 (t, 1H, ^3J = 7.4 Hz), 7.38 (t, 2H, ^3J = 7.9 Hz), 7.33–7.22 (m, 5H), 6.46 (s(br), 1H), 4.46–4.35 (m, 2H), 3.97 (dd, 1H, *J* = 5.8 Hz, *J* = 10.3 Hz), 3.96 (d, 1H, ^2J = 15.7 Hz), 3.80 (d, 1H, ^2J = 15.7 Hz), 3.65 (d, 1H, *J* = 10.3 Hz), 2.47 (dt, 1H, *J* = 7.8 Hz, *J* = 5.8 Hz), 2.05 (dd, 1H, *J* = 4.9 Hz, *J* = 7.8 Hz), 1.22 (t, 1H, *J* = 4.9 Hz).
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