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Sequential and Cascade Palladium Catalysed Cyclisation-Anion Capture-Olefin Metathesis.

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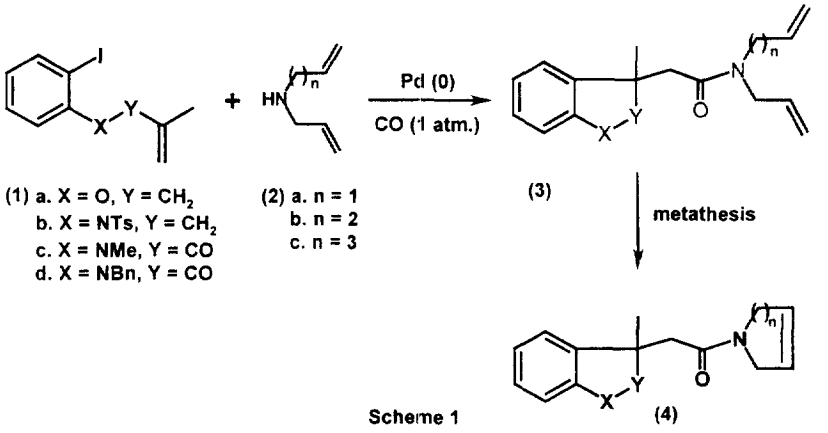
Abstract. The sequential or cascade combination of palladium catalysed cascade cyclisation-anion capture involving two- and three-component processes with olefin metathesis, provides access to fused and spirocyclic ring systems in good yield and a bridged ring forming sequence is reported.

Combination of versatile palladium catalysed processes such as our cascade cyclisation-anion capture methodology[1] with atom efficient core reactions such as 1,3-dipolar[2] or Diels-Alder[3] cycloaddition reactions provides a wealth of opportunities to efficiently enhance molecular complexity. In combinations of this type there are two available broad strategies in that the palladium chemistry can precede or follow the core reaction. Recently we reported sequential and cascade olefin metathesis - intramolecular Heck reactions[4] which provide access to fused-, bridged- and spiro-cyclic ring systems in good yield. In this communication we focus on processes where the palladium catalysed cascade precedes olefin metathesis.[5,6] Our initial approach is summarised in Scheme 1 and data on a series of successful sequential reactions are shown in Table 1.



(1) a. X = O, Y = CH_2
b. X = NTs, Y = CH_2
c. X = NMe, Y = CO
d. X = NBn, Y = CO

(2) a. n = 1
b. n = 2
c. n = 3

(3)

(4)

Scheme 1

The palladium catalysed cyclisation-carbonylation-anion capture sequence (Table 1) (catalyst system : footnote a) was carried out in toluene at 95°C and utilised CO (1atm) in conjunction with Tl_2CO_3 (2mol. eq.) to promote low pressure carbonylation.[7] Four types of aryl iodide precursor (1a-d) were evaluated in combination with three secondary amines (2a-c). The termolecular queuing processes occurred smoothly to yield the expected unsaturated amides (3a-i) in 52-76% yield.

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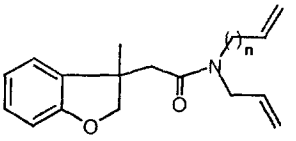
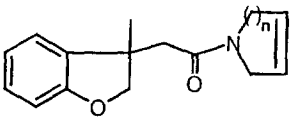
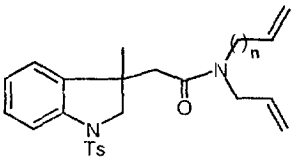
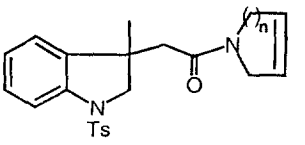
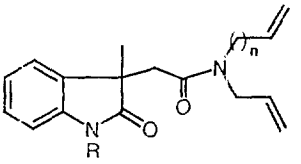
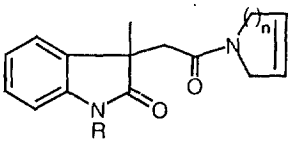
Table 1 Sequential Cyclisation - Carbonylation - Anion Capture - Metathesis Reaction

Substrates	Pd Catalysed Product(%)[a]	Metathesis Product(%)[b]
1a + 2a - c		
	(3) a. n = 1, 60% b. n = 2, 52% c. n = 3, 59%	(4) a. n = 1, 76% b. n = 2, 89% c. n = 3, 91%
1b + 2a - c		
	(3) d. n = 1, 82% e. n = 2, 61% f. n = 3, 76%	(4) d. n = 1, 86% e. n = 2, 80% f. n = 3, 80%
1c + 2a 1d + 2b, c		
	(3) g. n = 1, R = Me, 69% h. n = 2, R = Bn, 63% i. n = 3, R = Bn, 57%	(4) g. n = 1, R = Me, 88% h. n = 2, R = Bn, 91% i. n = 3, R = Bn, 83%

a. Isolated yields. Catalyst system comprised 10 mol% $Pd(OAc)_2$, 20 mol% Ph_3P and 2 mol eq Tl_2CO_3. Reactions were carried out in toluene at 95 °C with 2a - c (2 mol eq) and CO (1 atm).

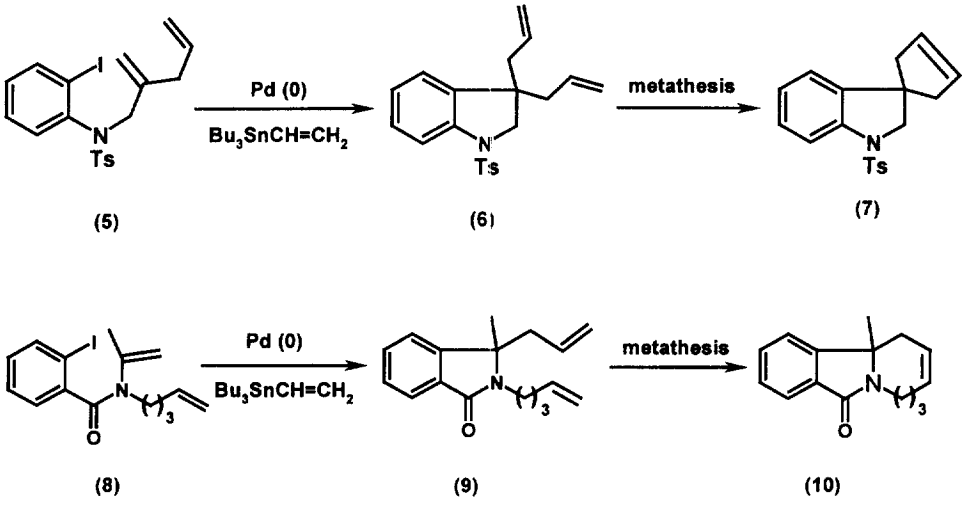
b. Isolated yields. Metathesis employed 1 - 5 mol% $(Cy_3P)_2Ru(=CHPh)Cl_2$ in DCM at 25 °C for 1 - 3h (5,6 - membered rings) or up to 16h (7 - membered rings).

The metathesis reactions proceeded to completion within a few hours at room temperature in DCM with 1-3 mol% $(Cy_3P)_2Ru(=CHPh)Cl_2$ for 5- and 6- membered ring formation. Seven membered ring formation required up to 16h with 5 mol% catalyst. The metathesis products (4a-i) were obtained in 76-91% yield. The two step termolecular queuing process results in the formation of four bonds, two rings and one tetrasubstituted carbon centre.

The potential for cascade reaction design is informed by the following observations (a) CO inhibits the metathesis catalyst (b) amine inhibits the metathesis catalyst.[8] This led to the development of the following one-pot protocol. The initial cyclisation-carbonylation-anion capture sequence was carried out in toluene on (1b) and (2a) for 16h as summarised in Table 1 and used 2 mol. eq. of (2a). The CO ballon was then removed and argon bubbled through the mixture for 5 mins. Concentrated hydrochloric acid (ca. 20 mol. eq.) was then

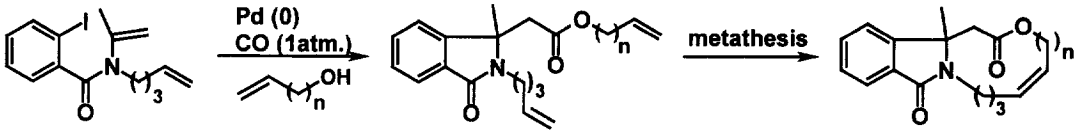
added followed by 5 mol% metathesis catalyst. The reaction was allowed to proceed at 25°C for 1h. Work up afforded (4d) in 63% yield (sequential yield 71%). The one-pot protocol can be carried out without addition of acid but requires more catalyst and is slower.

Our cyclisation-anion capture methodology is compatible with a wide range of anion capture agents.[1,9] Organotin(IV) species are a valuable source of such agents due to their ease of preparation, stability and wide structural variety.[10] It was of interest therefore to explore their combination with a subsequent metathesis process.



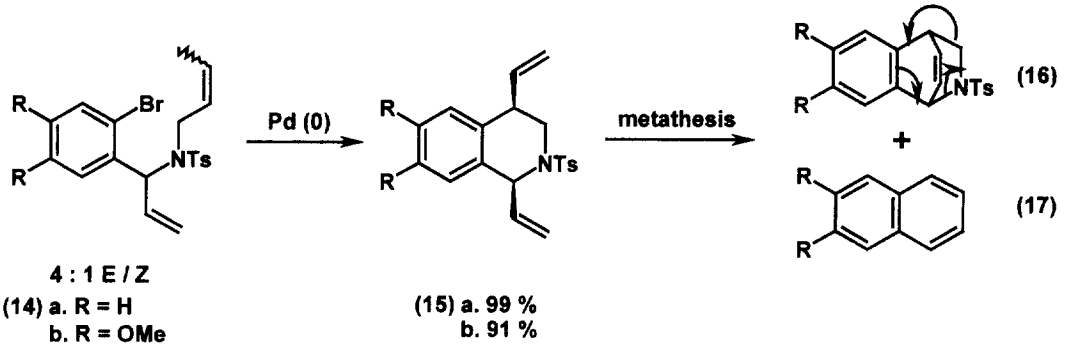
Tributylvinyltin(IV) was selected as the anion capture agent and the sequential processes (5) → (6) (77%) → (7) (85%) and (8) → (9) (67%) → (10) (43%) carried out using toluene (110°C) and *in situ* generated Pd(0) [5 - 10 mol % Pd $(OAc)_2$, 10 - 20 mol % tri(2-furyl)phosphine] for the palladium catalysed segment and $(Cy_3P)_2Ru(=CHPh)Cl_2$ (DCM, 25°C) for the metathesis segment. The conversion **5** → **7** was then developed as a 1-pot procedure in toluene employing 5 mol % $Pd(OAc)_2$/10 mol % tri(2-furyl) phosphine (110°C, 15h) followed by addition of the ruthenium catalyst (11 mol %, 25°C, 6h) to afford **7** (77%).

Another series has been developed involving cyclisation-carbonylation-alcohol capture [toluene, 95°C, 10 mol % $PdCl_2(PPh_3)_2$ CO (1 atm), K_2CO_3] **11** → **12** (61- 64%). Subsequent metathesis **12** → **13** afforded 12 - 14 membered macrocycles **13** (71 - 78%) as cis/trans mixtures.



Attempted bridged ring formation via sequential Heck-metathesis on **14** gave interesting results. Cyclisation [10 mol % $Pd(OAc)_2$, 20 mol % PPh_3, K_2CO_3, Et_4NCl, MeCN, 80°C] afforded **15** stereoselectively. Metathesis of **15a** gave mixtures of **16a** and **17a** whilst **15b** gave only **17b**. In both cases

metathesis was incomplete, with the mass balance being made up by unchanged **15b**, due to poisoning of the catalyst by the N-tosyl imine by-product. For example 10 mol % Grubb's catalyst afforded (CH_2Cl_2, 40°C, 14h) a 44:25:31 mixture of **15a**, **16a** and **17a.**



4 : 1 E / Z

(14) a. R = H
b. R = OMe

(15) a. 99 %
b. 91 %

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