Palladium-Catalysed Cyclisation of Enantiopure Allenic Lactams Prepared from a Pyroglutamic Acid Derived Organozinc Reagent

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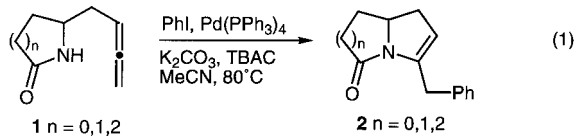
Abstract: A route for the synthesis of enantiopure allene-substituted lactams has been developed. The key-step involves the copper(I) mediated S_N2' substitution of propargylic tosylates by a (*S*)-pyroglutamic acid derived organozinc reagent. Pd-catalysed reaction of these allenes with iodobenzene afforded enantiopure bicyclic enamides. Furthermore the unexpected formation of an interesting diene is reported.

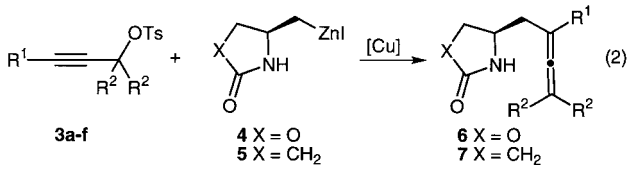
Palladium-catalysed reaction of heteroatom nucleophiles with allenes provides access to a manifold of interesting compounds.[1-3] In most examples the nucleophile attacks one of the sp^2-carbon atoms of the allene.[4] Recently, we showed that in the palladium-catalysed reaction between iodobenzene and allenic lactams **1** an unprecedented process occurs in which the allenic tether is attacked by nitrogen at the central sp-carbon atom, leading to cyclic enamides **2** (eq 1).[5,6]



(1)

Equation 1

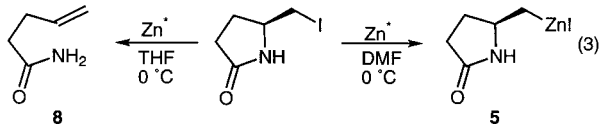
Herein we report the extension of this methodology to enantiopure substituted derivatives of **1** and **2**, which greatly increases the synthetic potential of this interesting reaction. Our previous allene synthesis, based on the Crabbé reaction,[7] does not allow the introduction of substituents at the newly formed allenic double bonds. However, by using a copper(I)-mediated S_N2' displacement of propargylic tosylates **3** with zinc reagents **4** and **5**, allenes are accessible with a high degree of substitution and functionality (eq 2).[8–11] Moreover, the iodides needed for the synthesis of zinc reagents **4** and **5** are easily synthesised from L-serine[12,13] and (*S*)-pyroglutamic acid,[14] respectively.



(2)

Equation 2

Our work extends the findings of Knochel and coworkers who showed that the copper(I)-mediated reaction of zinc reagent **4** with propargyl mesylate in the presence of CuCN·2LiCl in THF leads to enantiopure allenic oxazolidinone **6a** (Table 1) in 29% yield (based on the 5-(iodomethyl)oxazolidin-2-one).[11] By changing to propargyl tosylate (**3a**) and using a stoichiometric amount of the electrophile (instead of 0.35 equiv), we raised the yield to 39%. Similarly, zinc reagent **4** reacted with **3b** to give the methyl-substituted allene **6b** in a 49% yield (Table 1).



(3)

Equation 3

Our initial attempts to apply the same conditions to the new zinc reagent **5** met with failure (eq 3). The main product appeared to be unsaturated amide **8**, formed as a result of β-elimination. However, if the solvent used in the formation of the zinc reagent **5** was changed from THF to DMF, which is known to stabilise organozinc reagents,[14] β-elimination was less than 10%. This side reaction was suppressed completely by rinsing the activated zinc with DMF and lowering the reaction temperature to 0 °C (see experimental procedure).[15]

Having established conditions to generate a sufficiently stable zinc reagent, reactions of **5** with several propargylic tosylates were investigated (Table 1). A catalytic quantity of $CuBr{\cdot}SMe_2$ was preferred over a stoichiometric amount of CuCN·2LiCl, because of experimental convenience. Although the yields were moderate, this method allowed the introduction of oxygen containing substituents and aromatic groups (entries 6-8).

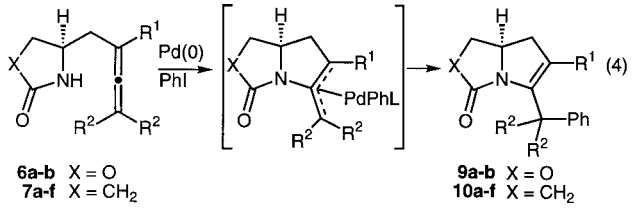
Table 1. Synthesis and cyclisation of **6a-b** and **7a-f**

entry	X	tosylate	R^1, R^2	allene[a]	cyclisation product[a]
1	O	**3a**	H, H	**6a** (39)[b]	**9a** (60)
2	O	**3b**	Me, H	**6b** (49)[b]	**9b** (73)
3	CH_2	**3a**	H, H	**7a** (58)	**10a** (65)
4	CH_2	**3b**	Me, H	**7b** (59)	**10b** (70)
5	CH_2	**3c**[c]	H, Me	**7c** (54)	**10c** (16)[d]
6	CH_2	**3d**	Ph, H	**7d** (56)	**10d** (74)
7	CH_2	**3e**	CH_2OTBS, H	**7e** (51)	**10e** (83)
8	CH_2	**3f**	CH_2OAr[e], H	**7f** (54)	**10f** (7)[f]

[a]Isolated yield in parentheses; [b]Knochel's procedure was used; see ref. 11; [c]The propargylic mesylate was used instead of the tosylate; [d]For byproducts, see eq 5; [e]Ar = p-*tert*-butylphenyl; [f]For byproduct, see eq 6

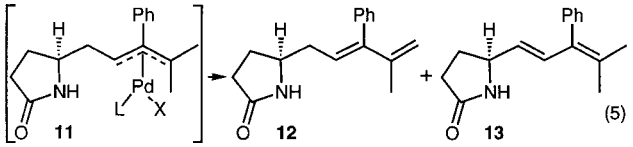
Subjection of the allenic oxazolidinones **6** and allenic lactams **7** to the previously developed cyclisation conditions[15] gave rise to the cyclic enamides **9** and **10**, presumably *via* a π-allylpalladium complex (eq 4).[16] From the Table it is clear that alkyl and phenyl substituents on the lactam side of the allene (R^1 = Me, Ph entries 2, 4 and 6) led to comparable yields in the cyclisation reaction.

However, subjection of trisubstituted allene **7c** to the cyclisation conditions, led to a low yield (16%) of the usual cyclic product **10c** (entry 5). This might be explained by steric interactions of the two methyl groups with the nucleophile, slowing down the attack of



Equation 4

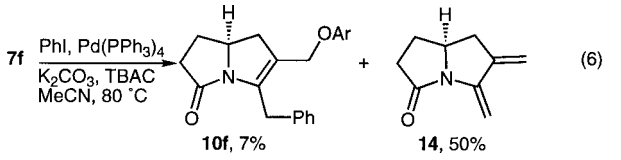
nitrogen. In this case transfer of the phenyl group to the central allenic carbon competes with nucleophilic attack, leading to the non-cyclised π-allylpalladium complex **11** (eq 5).[4] Interestingly, **11** did not cyclise, but underwent palladium hydride elimination to give the dienes **12** and **13** in 65% combined yield in a ratio of 2:5.



Equation 5

A TBS-protected alcohol adjacent to the allene did not interfere with the normal reaction pathway as indicated by the cyclisation of **7e** to **10e** in an excellent yield of 83% (entry 7). This is in sharp contrast with the cyclisation of **7f**, containing a phenolic group (entry 8). Only 7% of the anticipated **10f** was isolated, along with 50% of the interesting enantiopure diene **14** (eq 6).[17]

The mechanism for formation of **14** probably involves the formation of the usual π-allylpalladium complex (cf. eq 4). Reductive elimination leads to **10f**. However, if the palladium complex undergoes a deoxypalladation reaction, it will lead to **14**. The difference with **7e** might be ascribed to the better leaving group ability of the phenoxide anion compared to $TBSO^-$. At present we are investigating the synthetic utility of enantiopure dienes of type **14**. Moreover, the subtle mechanistic details of the palladium-catalysed cyclisation reaction will be probed by utilising intrinsically chiral allenes.



Equation 6

In conclusion, we have shown that organozinc reagent **5** is a useful reagent for the preparation of enantiopure lactams. These lactams as well as their oxazolidinone analogues undergo the expected cyclisation-coupling reaction to give bicyclic enamides in good yields, provided they are not too sterically hindered. If a relatively good leaving group is present allylic to the allene a cyclisation-elimination process may occur to give a bicyclic diene.

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References and Notes

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15. *Typical experimental procedures were as follows:*
*Formation of organozinc reagent **5**:* Under an atmosphere of nitrogen, 1,2-dibromoethane (85 µL, 1.0 mmol) was added to a suspension of zinc powder (654 mg, 10.0 mmol) in dry DMF (2 ml), after which it was stirred at 60 °C for 10 min. The reaction mixture was cooled, followed by the addition of TMSCl (100 µL, 0.80 mmol) and sonication at room temperature for 30 min. The zinc was allowed to settle and the supernatant was removed by syringe. DMF (2 mL) was added and the suspension was cooled to 0 °C, followed by the addition of (*S*)-5-(iodomethyl)pyrrolidin-2-one (1.13 g, 5.0 mmol) in DMF (2 mL) and the mixture was stirred at 0 °C for 4-6 h until no starting material remained (TLC).

At this point the excess of zinc was allowed to settle.

Reaction of organozinc reagent **5** with propargylic tosylates:

Propargylic tosylate **3b** (1.23 g, 5.5 mmol) was dissolved in DMF (10 mL), and CuBr·SMe_2 (51 mg, 0.25 mmol) was added. The mixture was cooled to -20 °C using an ice-salt bath, and the previously formed DMF solution of **5** was slowly added by cannula, rinsing the residual excess of zinc with DMF (1 mL). The reaction mixture was allowed to warm to room temperature overnight. The mixture was quenched with a saturated ammonium chloride solution (25 mL) and extracted with ethyl acetate (4 × 50 ml). The combined extracts were washed with brine (2 × 20 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, MeOH/CH_2Cl_2 5:95) afforded **10b** as a pale yellow oil: yield 443 mg (59%); $[\alpha]_D$ = +73.3 (*c* = 2.7 in $CHCl_3$); IR (neat) 3227, 1960, 1692, 1423, 1284 cm^{-1}; ^1H NMR δ 6.77 (br. s, 1H), 4.57-4.64 (m, 2H), 3.75 (quint., *J* = 6.6 Hz, 1H), 2.15-2.31 (m, 3H), 2.02-2.07 (m, 2H), 1.64-1.72 (m, 1H), 1.62 (t, *J* = 3.1 Hz, 3H); ^{13}C NMR δ 206.1, 178.0, 95.2, 75.1, 52.6, 40.5, 29.9, 26.9, 19.0; MS (EI, 70 eV) *m/z* (relative intensity) 151 (M^+, 7), 84 (100),41 (44), 29 (65), 15 (76); HRMS calcd for $C_9H_{13}NO$ (M^+) 151.0997, *m/z* found 151.0999

Palladium catalysed cyclisations of the allenes:

Under an argon atmosphere, a mixture of **7b** (76 mg, 0.50 mmol), K_2CO_3 (276 mg, 2.0 mmol), PhI (408 mg, 2.0 mmol), Bu_4NCl (208 mg, 0.75 mmol) and $Pd(PPh_3)_4$ (57 mg, 0.05 mmol) in MeCN (10 mL) was refluxed for 2-3 h (TLC showed complete conversion). The mixture was cooled, diluted with water (10 mL) and extracted with ether (3 × 15 mL). The combined ether extracts were washed with water (20 mL) and brine (20 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, EtOAc/hexanes 1:2) afforded **10b** as a colorless solid: yield 80 mg (70%); mp = 86-89 °C (CH_2Cl_2/pentane); $[\alpha]_D$ = -15.2 (*c* = 1.2 in $CHCl_3$); IR (neat) ν_{max} 1698, 1403, 1371, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.31 (m, 4H), 7.15-7.19 (m, 1H), 4.21-4.30 (m, 2H), 3.65 (AB, *J* = 14.8 Hz, 1H), 2.60-2.69 (m, 1H), 2.34-2.47 (m, 3H), 2.21-2.27 (m, 1H), 1.76-1.86 (m, 1H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 139.1, 134.0, 128.5, 128.2, 126.0, 120.5, 62.1, 40.4, 36.9, 30.2, 28.7, 12.8; MS (EI, 70 eV) *m/z* (relative intensity) 357 (M^+, 36), 300 (30), 226 (100), 91 (12). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 78.95; H, 7.44; N 5.92.

16. In principle, the π-allylpalladium complex can lead to two different regioisomers. However, in the cases reported in Table 1 only one isomer was isolated. For examples giving both possible products see ref. 5.

17. *Spectral data of diene **14**:* $[\alpha]_D$ = +63.8 (*c* = 1.0 in $CHCl_3$); IR (neat) ν_{max} 2974, 2930, 1698, 1397, 1313 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.44 (dd, *J* = 3.4, 1.3 Hz, 1H), 5.43 (s, 1H), 5.02 (dd, *J* = 3.0, 1.2 Hz, 1H), 4.95 (s, 1H), 4.07-4.15 (m, 1H), 2.69-2.76 (m, 2H), 2.50 (ddd, *J* = 16.8, 8.8, 0.9 Hz, 1H), 2.27-2.33 (m, 2H), 1.72-1.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 145.3, 139.6, 107.5, 89.8, 60.7, 38.1, 36.0, 28.4; MS (EI, 70 eV) *m/z* (relative intensity) 149 (M^+, 25), 94 (37), 31 (100), 29 (45), 17 (39). HRMS calcd for $C_9H_{11}NO$ (M^+) 149.0841, *m/z* found 149.0842.