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## RESEARCH ARTICLE

# MICROWAVE-ASSISTED BENZYLIC C-H ACTIVATION USING RUTHENIUM CATALYSTS. SYNTHESIS OF β-LACTAMS

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**ABSTRACT**

An expeditious synthesis of β-lactams from benzyl-tethered trichloroacetamides using ruthenium catalysts in toluene under microwave activation was achieved. The new $C(sp^3)$-$C(sp^3)$ bond formation takes place through a "Ru"complex promoted activation of a benzylic position in a radical process.



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## INTRODUCTION

Grubbs catalysts are usually used for olefin metathesis (Vougioukalakis *et al.* 2010; Ogba *et al.* 2018) nevertheless many other non-metathetic behaviours have been reported for these ruthenium complexes (Alcaide *et al.* 2009; Arisawa *et al.* 2007; Kotha *et al.* 2013). One of the foremost processes is the kharasch process, which generally follows a ruthenium catalysed ring closing metathesis for the preparation of highly functionalised polycyclic systems from acyclic halogenated dienes (Seigal *et al.* 2005; Schmidt *et al.* 2004; Tallarico *et al.* 1999). Few years ago, we reported the first Grubbs II catalysed intramolecular dearomative ATRC with trichloroacetamides embodying an electron-rich arene for the preparation of 2-azaspirodecadienes **A2** (Diaba *et al.* 2014). The investigation was an extension to a previous work where the same reaction leading to **A1** was achieved on unactivated benzenes using Cu(I) as a catalyst (Diaba *et al.* 2013) (Scheme 1). Herein we report an unprecedented ruthenium catalysed synthesis of -lactams from readily available *N*-benzyltrichloroacetamides through benzylic C-H activation. Even if -lactams have been prepared using a wide range of strategies (Hosseyni *et al.* 2018; Davies *et al.* 2003; Doyle *et al.* 2010) to our knowledge there's only one example reported in the literature (Saget *et al.* 2014) where a saturated $C(sp^3)$-$C(sp^3)$ bond formation is achieved through an asymmetric C-H functionalisation from chloroacetamides catalysed by Palladium(0). The reaction takes place in the presence of $Pd(dba)_2$, a bulky taddolphosphoramiditeligant, adamantly carboxylic acid and $Cs_2CO_3$ in toluene at 110 ºC.

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## RESULTS AND DISCUSSION

The reaction was accidently discovered when dibenzyltrichloroacetamide **1a** was submitted to the same reaction conditions in which spiroderivatives type **A2** were isolated (Diaba *et al.* 2014). Thus, when **1a** was heated with 10% of grubbs II catalyst (**Ru2**) in toluene (0.1 mL) at 160 ºC for 2 h, after chromatography **2a** was isolated in a 26% yield (Table 1, entry 1). Additionally, *N*,*N*-dibenzyl- and *N*-benzyldichloroacetamides were also isolated in minor yields. It is worth noting that the same reaction under diluted conditions (1 mL of toluene) did not take place when achieved using standard heating. Nevertheless, under microwave activation and at 100 ºC a full conversion was observed after only 30 min obtaining **2a** in a slightly better yield (entry 2). After these unexpected results, we started an investigation to explore the scope and limitations of this reaction. In order to improve the reaction yield, we switched to **1b** since the bulky *tert*-butyl substituent on the nitrogen atom is well known to lock the

substrate in a conformation prone to cyclization (Stork *et al.* 1989; Yu *et al.* 2010).

As it was expected, when **1b** was heated at 100 ºC under microwave activation for only 10 min, lactam **2b** was isolated with 48% yield (entry 3). Reducing the quantity of catalyst although prolonging the reaction time did not improve the yield (entry 4). When the reaction was carried out at 80 ºC, 20 min were necessary to obtain **2b** with 48% yield (entry 5). Switching to acetonitrile a full conversion was observed after only 5 min although the yield for lactam **2b** was lower (entry 6). We next sought to explore the scope of the reaction on trichloroacetamides **1c**-**1h** with different substituents on the benzene ring. Treatment of substrates **1c**-**1e** all of them with a methyl group in the ortho, meta and para position respectively with **Ru2** (10%) under microwave activation for 10 min and at 100 ºC provided the corresponding lactams **2c**-**2e** with moderate yields (entries 7-9). With anisole derivative **1f**, a similar yield of lactam **2f** was obtained (entry 10). Even if with these substrates almost of the time some starting material was recovered, prolonging the reaction time yielded poorer results.

Completely different results were attained with trichloroacetamides **1g** and **1h** with a deactivated benzene ring. Whereas with **1g** a degradation of the starting material was observed (entry 11), with **1h** lactam **2h** was isolated with a very low yield together with product **3h** which was not observed in the reaction crude but after chromatography using dichloromethane stabilized with ethanol as the eluent (entry 12). It is worth noting that when dichloromethane stabilised with amylene was used instead, we recover only degradation products. After these results with **Ru2** we decided to investigate Grubbs' 1st generation catalyst (**Ru1**) using the best reaction conditions established with **Ru2** (Table 2). With dibenzyl derivative **1a** the reaction provided lactam **2a** with a comparable yield (entry 1). Nevertheless, with trichloroacetamide **1b** only **3b** was isolated after chromatography (entry 2). As it was mentioned before, **3b** was not observed in the crude but isolated after purification. A similar result was achieved with substrates **1g** and **1h** with an unactivated benzene since only **3g** and **3h** were isolated respectively (entries 7 and 8). With tolyl derivatives **1c**-**1e**, besides lactams **2c**-**2e** isolated in modest yields, amides **3c**-**3d** were detected in some fractions after chromatography but were not isolated in pure forms (entries 3-5). It is worth noting that with trichloroacetamide **1c** a better yield of lactam **2c** was obtained (entry 3). Additionally, with anisole **1f** only **3f** was isolated after purification (entry 6).

With these results in hand, we set out to explore another more accessible ruthenium catalyst for these unusual reactions (Table 3).$RuCl_2(PPh_3)_3$ (Ru3) is the precursor of **Ru1** and has been successfully used for Kharasch–type additions (Severin *et al.* 2006; Delaude *et al.* 2004). When **1a** was treated with 10% of **Ru3** at 100 °C in toluene for 15 min using microwaves, we were delighted to see that lactam **2a** was isolated with a modest yield (Table 3, entry 1). Running the same reaction at 80 °C improved the yield considerably (41%, entry 2). Better results were also achieved from trichloacetamides **1b**-**1e** where only lactams **2b**-**2e** were isolated with 40-58% yields (entries 3-8). Additionally, with electron-poor derivatives **1g** and **1h** a different behaviour was observed. Whereas with **1g** only degradation compounds were detected in the crude, with **1h** a slight improvement in the yield of lactam **2h** was achieved isolated with **3h** (entry 11).

Using catalyst **Ru3** the reaction worked also with amides 1i-1k where the substituents on the nitrogen are a *n*-butyl, isopropyl and cyclohexyl groups respectively (entries 12-14). In all cases lactams **2i**-**2k** were isolated with acceptable yields. It is worth noting that with **1i** and **1k** we isolated also small quantities of the partially reduced lactams **4** and **5** (Van Driesshe *et al.* 2006). Finally, with trichloroacetamide **1l**, only dichloroacetamide **6l** was isolated (entry 13).

In this investigation we have described an unprecedented behaviour of ruthenium catalysts leading to -lactams **2** from trichloroacetamides **1** through benzylic CH activation. The presence of the catalyst is necessary to achieve the process since after heating **1b** alone in toluene at 80 °C under microwave activation for 10 min no reaction took place and **1b** was recovered intact. As it was expected, a radical process is involved in this transformation since running the reaction in the presence of TEMPO either from **1a** or **1b** inhibits the lactam formation. Whereas under microwave activation only degradation compounds were detected in the crude, when **1a** was heated at 160 ºC with **Ru3** (10%) in the presence of 1 equiv. of TEMPO besides **1a** a small quantity of **7a** was detected resulting from a coupling between TEMPO and the dichlorocarbamoil radical followed by hydrolysis (Baker *et al.* 1978). **7a** was identified by high-resolution mass spectroscopy (ESI-TOF) which confirmed the molecular formula $C_{25}H_{32}N_2O_3$ (calculated for $C_{25}H_{33}N_2O_3$409.2486 $[M+H]^+$; found 409.2488). This indicates that the first step of the reaction is abstraction of a chloro atom by "Ru" catalyst from **1** to generate dichlorocarbamoil radical **I** and "RuCl" complex (Matsumoto *et al.* 1976; Hayes *et al.* 1986).

The "RuCl" complex abstacts then a hydrogen atom from radical **I** to generate diradical species **II** with the concomitant release of HCl and regeneration of "Ru" catalyst (Scheme 2). Indeed analysis of some reaction crudes in which **Ru3** was successfully used in the synthesis of lactams **2** showed a strong acidic pH of the reaction medium. Next, transient diradical **II** undergoes an intramolecular cross coupling to generate -lactams **2**. On the other hand amides **3** results from cleavage of the *tert*-butyl group in acid medium (Clayden *et al.* 2006) and a 1,4-H shift in radical **I** (Quirante *et al.* 2001, Nechab *et al.* 2014) generating radical **III** followed by a chloro atom transfer from "RuCl" complex or amide **1** to provide chloroderivative **IV**. The latter undergoes substitution during purification providing ethers **3** (Hiemstra *et al.* 1985). As it was mentioned before, ethers **3** were not present in the reaction crudes but were isolated after purification by chromatography using $CH_2Cl_2$ stabilized with ethanol. Formation of chloroderivative **IV** was reinforced by analysis of the reaction mixture when achieved from **1h** and **Ru1** (Table 2, entry 8) since $^1$H NMR spectrum exhibits 2 determinant signals, a singlet at 5.89 ppm and a doublet at 6.32 ppm consistent with a $COCHCl_2$ and a benzylic CHCl respectively. This argument is supported by the experiments achieved with **1l** where only alkene **6l** was isolated. With this substrate, we believe that after formation of the dichlorocarbamoil radical, a 1,4-H shift takes place to generate a tertiary benzylic radical followed by a chloro atom transfer and elimination to furnish **6l**.

## MATERIALS AND METHODS

***General methods*:** Commercial reagents and anhydrous solvents were used as supplied. $^1$H and $^{13}$C NMR spectra were

recorded in $CDCl_3$ solution. Chemical shifts are reported as values (ppm) relative to internal $Me_4Si$, $^{13}C$ NMR spectra are referenced to the deuterated solvent signal ($CDCl_3$: 77.00 ppm). All NMR data assignments are supported by COSY and HSQC experiments. Infrared spectra were recorded on a Nicolet 320 FT-IR spectrophotometer. TLC was performed on $SiO_2$ (silica gel 60 $F_{254}$, Merck). The spots were located by UV light (254 nm) or a 1% $KMnO_4$ aqueous solution. Chromatography refers to flash chromatography and was carried out on $SiO_2$ (Silica Flash P60, Wet Dry, 200-500 mesh). Microwave irradiation experiments were performed using a single-mode Discover System from CEM Corporation using standard Pyrex vessel (capacity 10 mL).

**Synthesis of trichloroacetamides 1a-1l**: For the preparation of trichloroacetamides **1e-1g, 1l** we followed the same procedure used in the preparation of **1a-1d** and **1h**, **1k** (Diaba *et al.* 2013).

***N-tert*-Buty l-2,2,2- trichloro-*N*-(4-methylbenzyl) acetamide (1e)**. White solid (40%), mp 117-120 °C, $R_f$ = 0.48 (*n*-hexane-$CH_2Cl_2$ 1:1). IR (NaCl): 2998, 2973, 2923, 2867, 2857, 1685 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.15 (br s, 4H, ArH), 4.99 (br s, 2H, $CH_2Ar$), 2.34 (s, 3H, $CH_3$), 1.41 (s, 9H, *t*-Bu). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 160.8 (CO), 136.8, 135.5, 129.1, 126.4 (Ar), 95.4 ($CCl_3$), 61.8 (C), 50.8 ($CH_2Ar$), 28.1 ($CH_3$), 21.0 ($CH_3$). HRMS (ESI-TOF) *m/z*: Calcd for $C_{14}H_{19}Cl_3NO$ $[M+H]^+$ 322.0527; found 322.0528.

***N-tert*-Butyl-2,2,2-trichloro-*N*-(3-methoxybenzyl)acetamide (1f)**. White solid (50%), mp 80-82 °C, $R_f$ = 0.45 (*n*-hexane-$CH_2Cl_2$ 1:2). IR (NaCl): 3001, 2965, 2937, 1685, 1601 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.26 (t, *J* = 7.8 Hz, 1H, ArH), 6.76-6.89 (m, 3H, ArH), 5.01 (br s, 2H, $CH_2Ar$), 3.80 (s, 3H, $CH_3$), 1.44 (s, 9H, *t*-Bu). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 160.7 (CO), 159.7, 140.3, 129.5, 118.7, 112.3 (Ar), 95.2 ($CCl_3$), 61.9 (C), 55.2 ($CH_3$), 50.9 ($CH_2Ar$), 28.0 ($CH_3$). HRMS (ESI-TOF): Calcd for $C_{14}H_{19}Cl_3NO_2$ $[M+H]^+$ 338.0476; found 338.0464.

***N-tert*-Butyl-2,2,2-trichloro-N-(4-nitrobenzyl)acetamide (1g).** White solid (30%), mp 143-145 ºC, $R_f$ = 0.74 (n-hexane-$CH_2Cl_2$ 3:7). IR (NaCl, neat): 3081, 2981, 2934, 2676, 1688, 1600 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 8.24 (d, *J* = 6.7 Hz, 2H, ArH), 7.48 (d, *J* = 6.7 Hz, 2H, ArH), 5.15 (br s, 2H, $CH_2Ar$), 1.44 (s, 9H, *t*-Bu).$^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 160.6 (CO), 147.2, 146.4, 127.2, 123.9 (Ar), 94.9 ($CCl_3$), 62.2 (C), 50.6 ($CH_2Ar$), 28.1 ($CH_3$). HRMS (ESI-TOF) m/z: Calcd for $C_{13}H_{16}Cl_3N_2O_3$ $[M+H]^+$ 353.0221; found 353.0224.

**(*S*)-*N*-Benzyl-2,2,2-trichloro-*N*-(1-phenylethyl)acetamide(1l).** White solid (70%), mp 81-83 ºC, $R_f$ = 0.57 (*n*-hexane-$CH_2Cl_2$ 1:1). IR (NaCl, neat): 3106, 3088, 3062, 3030, 2988, 2939, 1673, 1602 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 6.96-7.43 (m, 10H, ArH), 5.93 (br s, 1H), 4.76 (br d, *J* = 15.8 Hz, 1H, $CH_2Ar$), 3.88 (br d, *J* = 15.8 Hz, 1H, $CH_2Ar$), 1.58 (s, 3H, $CH_3$). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 161.2 (CO), 139.1, 137.3, 128.7, 128.4, 127.8, 126.9, 126.6 (Ar), 93.7 ($CCl_3$), 57.3 (CHAr), 49.4 ($CH_2Ar$), 17.9 ($CH_3$). HRMS (ESI-TOF) *m/z*: Calcd for $C_{17}H_{17}Cl_3NO$ $[M+H]^+$ 356.0370; found 356.0369; Calcd for $C_{17}H_{20}Cl_3N_2O$ $[M+NH_4]^+$ 373.0636; found 373.0636.

**General procedure for the reaction of trichloroacetamides 1 with "Ru" catalysts:** In a 10 mL vessel was placed trichloroacetamide **1** (100 mg, 0.32 mmol) and ruthenium catalyst (0.032 mmol, 10%) in toluene (1 mL). The mixture was heated with stirring using microwave irradiation for 5 to 30 min at 80 °C or 100 °C. After chromatography (hexane-$CH_2Cl_2$, 9:1 to $CH_2Cl_2$) lactam **2** and/or amide **3** were isolated.

**1-Benzyl-3,3-dichloro-4-phenylazetidin-2-one (2a).** Colorless oil, $R_f$ = 0.32 (*n*-hexane-$CH_2Cl_2$ 1:1).IR (NaCl, neat): 3088, 3064, 3032, 2923, 2852, 1790 $cm^{-1}$.$^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.35-7.40 (m, 3H, ArH), 7.23-7.28 (m, 3H, ArH), 7.15-7.20 (m, 2H, ArH), 7.05-7.10 (m, 2H, ArH), 4.90 (d, *J* = 15.0 Hz, 1H, $CH_2N$), 4.77 (s, 1H, H-4), 3.88 (d, *J* = 15.0 Hz, 1H, $CH_2N$). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 161.7 (C-2), 133.5, 131.7, 129.9, 129.1, 128.8, 128.4, 128.1 (Ar), 84.8 (C-3), 73.2 (C-4), 45.0 ($CH_2N$). HRMS (ESI-TOF) *m/z*: calcd for $C_{16}H_{14}Cl_2NO$ $[M+H]^+$ 306.0447; found 306.0450.

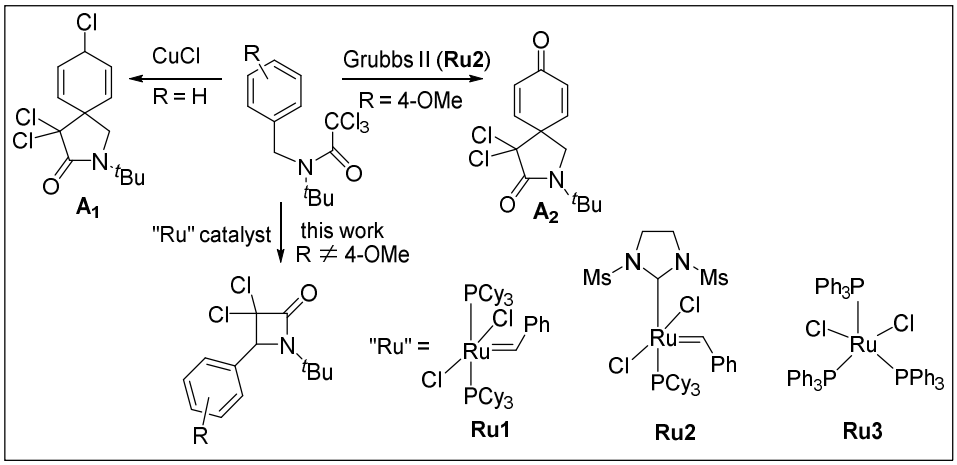
**1-(*tert*-Butyl)-3,3-dichloro-4-phenylazetidin-2-one (2b)**. White solid, mp 81-83 °C, $R_f$ = 0.40 (*n*-hexane-$CH_2Cl_2$ 1:1). IR (NaCl, neat): 3065, 3036, 2976, 2931, 2872, 2856, 1778 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.35-7.46 (m, 5H, ArH), 5.05 (s, 1H, H-4), 1.33 (s, 9H, *t*-Bu). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 161.6 (C-2), 134.6, 129.7, 128.5 (Ar), 83.4 (C-3), 73.6 (C-4), 55.7 (C), 27.9 ($CH_3$). HRMS (ESI-TOF) *m/z*: calcd for $C_{13}H_{16}Cl_2NO$ $[M+H]^+$ 272.0603; found 272.0606.

**1-(*tert*-Butyl)-3,3-dichloro-4-(*o*-tolyl)azetidin-2-one (2c)**. Amorphous pale solid, $R_f$ = 0.38 (*n*-hexane-$CH_2Cl_2$ 1:1). IR (NaCl, neat): 3074, 3029, 2980, 2937, 2876, 1769 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.22-7.37 (m, 4H, ArH), 5.31 (s, 1H, H-4), 2.44 (s, 3H, $CH_3$), 1.37 (s, 9H, *t*-Bu). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 161.9 (C-2), 136.5, 133.2, 130.6, 129.0, 126.9, 125.8 (Ar), 83.2 (C-3), 69.9 (C-4), 55.5 (C), 27.8 ($CH_3$), 19.7 ($CH_3$). HRMS (ESI-TOF) *m/z*: calcd for $C_{14}H_{18}Cl_2NO$ $[M+H]^+$ 286.0760; found 286.0761.

**1-(*tert*-Butyl)-3,3-dichloro-3-(*p*-tolyl)azetidin-2-one (2d).** Colorless liquid, $R_f$ = 0.34 (*n*-hexane-$CH_2Cl_2$ 1:1). IR (NaCl, neat): 3029, 2975, 2926, 2871, 1781 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.15-7.34 (m, 4H, ArH), 5.00 (s, 1H, H-4), 2.40 (s, 3H, $CH_3$), 1.33 (s, 9H, *t*-Bu). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 161.7 (C-2), 138.3, 134.5, 130.4, 128.4 (Ar), 83.8 (C-3), 73.6 (C-4), 55.7 (C), 27.9 ($CH_3$), 21.4 ($CH_3$). HRMS (ESI-TOF) *m/z*: calcd for $C_{14}H_{18}Cl_2NO$ $[M+H]^+$ 286.0760; found 286.0764.

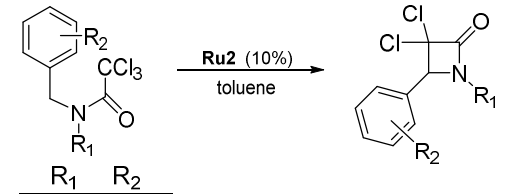
**1-(*tert*-Butyl)-3,3-dichloro-4-(*p*-tolyl)azetidin-2-one (2e).** Pale solid, mp 106-110 ºC, $R_f$ = 0.46 (*n*-hexane-$CH_2Cl_2$ 1:1). IR (NaCl, neat): 3053, 3028, 2976, 2934, 2873, 1778 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.26 (d, *J* = 8.5 Hz, 2H, ArH), 7.23 (d, *J* = 8.5 Hz, 2H, ArH), 5.01 (s, 1H, H-4), 2.39 (s, 3H, $CH_3$), 1.32 (s, 9H, *t*-Bu). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 161.7 (C-2), 139.8, 131.5, 129.2, 128.2 (Ar), 83.5 (C-3), 73.5 (C-4), 55.6 (C), 27.9 ($CH_3$), 21.3 ($CH_3$). HRMS (ESI-TOF) *m/z*: calcd for $C_{14}H_{18}Cl_2NO$ $[M+H]^+$ 286.0760; found 286.0766.

**1-(*tert*-Butyl)-3,3-dichloro-4-(3-methoxyphenyl)azetidin-2-one (2f).** Colorless oil, $R_f$ = 0.30 (*n*-hexane-$CH_2Cl_2$ 1:1). IR (NaCl, neat): 3071, 3060, 3064, 2975, 2935, 2876, 2853, 2837, 1778 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.34 (t, *J* = 7.9 Hz, 1H ArH), 6.93-6.98 (m, 2H, ArH), 6.89 (m, 1H, ArH), 5.01 (s, 1H, H-4), 3.84 (s, 3H, $CH_3O$), 1.34 (s, 9H, *t*-Bu). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 161.6 (C-2), 159.7, 136.1, 129.6, 120.5, 115.0, 113.8 (Ar), 83.4 (C-3), 73.5 (C-4), 55.7 (C), 55.3 ($CH_3O$), 27.9 ($CH_3$). HRMS (ESI-TOF) *m/z*: calcd for $C_{14}H_{18}Cl_2NO_2$ $[M+H]^+$ 302.0709; found 302.0709.




**Scheme 1. Previous and present work**

**Table 1. Ru2 promoted formation of lactams 2**

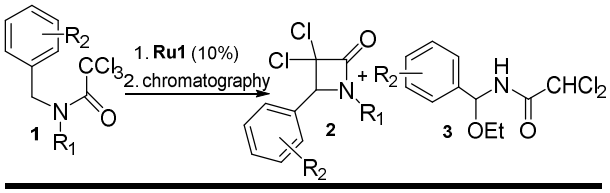



| | $R_1$ | $R_2$ | | $R_1$ | $R_2$ |
|---|---|---|---|---|---|
| **1a** | Bn | H | **1f** | *t*-Bu | 3-OMe |
| **1b** | *t*-Bu | H | **1g** | *t*-Bu | 4-$NO_2$ |
| **1c** | *t*-Bu | 2-Me | **1h** | *t*-Bu | 3,5-diF |
| **1d** | *t*-Bu | 3-Me | | | |
| **1e** | *t*-Bu | 4-Me | | | |

| Entry | compd | Method[a] | Time (min) | Compd (yield %) |
|---|---|---|---|---|
| **1** | **1a** | A | 120 | **2a** (26) |
| **2** | **1a** | B | 30 | **2a** (30) |
| **3** | **1b** | B | 10 | **2b** (48) |
| **4** | **1b** | B[b] | 20 | **2b** (38) |
| **5** | **1b** | B[c] | 20 | **2b** (48)[d] |
| **6** | **1b** | B[e] | 5 | **2b** (36) |
| **7** | **1c** | B | 10 | **2c** (30)[f] |
| **8** | **1d** | B | 10 | **2d** (38)[g] |
| **9** | **1e** | B | 10 | **2e** (28) |
| **10** | **1f** | B | 5 | **2f** (25)[h] |
| **11** | **1g** | B | 10 | **2g** (-) |
| **12** | **1h** | B | 5 | **2**h (11)[i], **3h** (24)[j] |

[a]A: 100 mg scale in 0.1 mL of toluene at 160 °C. B: 100 mg scale in 1 mL of toluene (≈ 0.3 M) at 100 °C, μW. [b]5% of **Ru2** was used, 35% of **1b** was recovered. [c] At 80 ºC. [d]7% of **1b** was recovered. [e]Acetonitrile was used as a solvent. [f] 22% of 1c was recovered. [g]20% of **1d** was recovered. [h]23% of **1f** was recovered. [I]8% of 1h was recovered. [j]For the structure of **3h** see table 2.

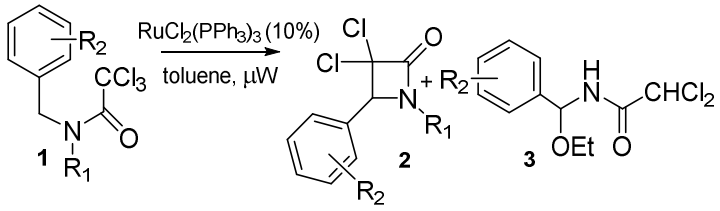
**Table 2. Reactions of trichloroacetamides1 with Ru1[a]**




| Entry | compd | Time (min) | 2 (yield %) | 3 (yield %) |
|---|---|---|---|---|
| **1** | **1a** | 20 | 2a (28) | **3a** (-) |
| **2** | **1b** | 5 | 2b (-) | **3b** (38) |
| **3** | **1c** | 10 | 2c (40) | **3c** (9) |
| **4** | **1d** | 5 | 2d(16) | **3d** (8)[b] |
| **5** | **1e** | 10 | 2e (34) | **3e** (-)[c] |
| **6** | **1f** | 5 | 2f (-)[c] | **3f** (37) |
| **7** | **1g** | 10 | 2g (-) | **3g** (17) |
| **8** | **1h** | 5 | 2h (-) | **3h** (46) |

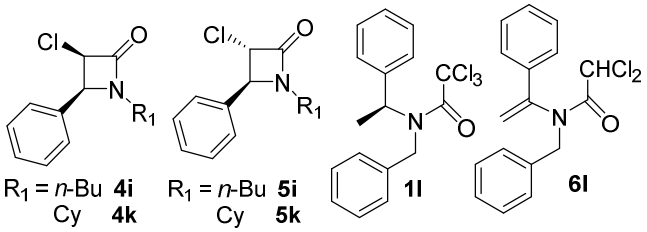
[a]All the reactions were carried out using 100 mg scale of **1** in 1 mL of toluene (≈ 0.3 M) at 100 °C, μW.[b]12% of **1d** was recovered. [c] Only traces were detected.

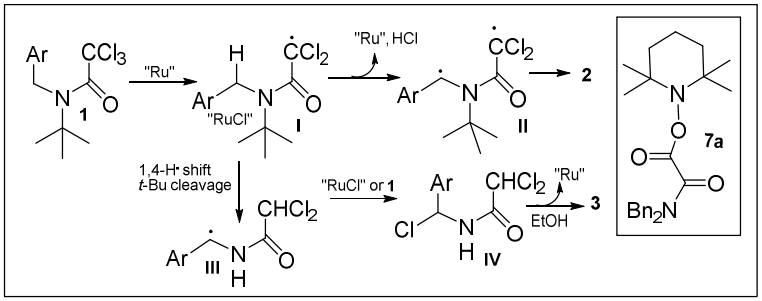
**Table 3.$RuCl_2(PPh_3)_3$promoted formation of lactams 2[a]**




| Entry | $R_1$ | $R_2$ | compd | T °C | Time (min) | Compd (yield %) |
|---|---|---|---|---|---|---|
| 1 | Bn | H | **1a** | 100 | 15 | **2a** (20) |
| 2 | Bn | H | **1a** | 80 | 20 | **2a** (41) |
| 3 | $^t$Bu | H | **1b** | 100 | 10 | **2b** (49) |
| 4 | $^t$Bu | H | **1b** | 80 | 10 | **2b** (58) |
| 5 | $^t$Bu | H | **1b** | 80 | 10 | **2b** (55)[c] |
| 6 | $^t$Bu | 2-Me | **1c** | 80 | 10 | **2c** (56)[d] |
| 7 | $^t$Bu | 3-Me | **1d** | 80 | 10 | **2d** (40), 3d (8) |
| 8 | $^t$Bu | 4-Me | **1e** | 80 | 5 | **2e** (40) |
| 9 | $^t$Bu | 3-OMe | **1f** | 80 | 10 | **2f** (18) |
| 10 | $^t$Bu | 4-$NO_2$ | **1g** | 80 | 10 | - |
| 11 | $^t$Bu | 3,5-diF | **1h** | 80 | 10 | **2h** (21), 3h (18) |
| 12 | *n*-Bu | H | **1i** | 80 | 10 | **2i** (30)[e] |
| 13 | *i*-Pr | H | **1j** | 80 | 10 | **2j** (28[f] |
| 14 | Cy | H | **1k** | 80 | 10 | **2k** (38)[g] |
| 13 | (*S*)-α-MeBn | H | **1l** | 80 | 10 | **6l** (40)[h] |

[a] All the reactions were carried out using 100 mg scale of **1** in 1 mL of toluene (≈ 0.3 M), μW.[b] 6% of **1a** was recovered. [c] With 200 mg of **1b**. [d] 12% of **1c** was recovered. [e] Were also isolated **4i** (4%), **5i** (9%), **1i** (25%). [f] Traces of **4j** and **5j** were detected. [g] Were also isolated **4k** (8%), **5k** (9%). [h] 48% of **1l** was recovered, when the reaction was run for 20 min the yield dropped to 22% even if the conversion was 100%.




**Scheme 2. Proposed mechanism for the formation of 2 and 3**

**1-(*tert*-Butyl)-3,3-dichloro-4-(3,5-difluorophenyl)azetidin-2-one (2h).** Amorphous pale solid, $R_f$ = 0.51 (*n*-hexane-$CH_2Cl_2$ 1:1). IR (NaCl, neat): 3094, 3063, 2977, 2931, 2875, 2855, 1784 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 6.84-6.96 (m, 3H, ArH), 4.99 (s, 1H, H-4), 1.35 (s, 9H, *t*-Bu). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 163.0 (dd, *J* = 249.3, 12.4 Hz, 2C, C-F), 161.3 (C-2), 138.8 (t, *J* = 8.6 Hz, ArC), 111.0 (br s, 2C, ArCH), 105.3 (t, *J* = 25.1 Hz, 1C, ArCH), 83.0 (C-3), 72.4 (C-4), 56.0 (C), 27.9 ($CH_3$). HRMS ESI-TOF) *m/z*: calcd for $C_{13}H_{14}Cl_2F_2NO$ $[M+H]^+$ 308.0415; found 308.0412.

**1-Butyl-3,3-dichloro-4-phenylazetidin-2-one (2i).** Colorless oil, $R_f$ = 0.51 ($CH_2Cl_2$).IR (NaCl, neat): 3065, 3035, 2960, 2932, 2873, 1789 $cm^{-1}$.$^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.43-7.49 (m, 3H, ArH), 7.28-7.32 (m, 2H, ArH), 7.05-7.10 (m, 2H, ArH), 5.05 (s, 1H, H-4), 3.62 (dt, *J* = 14.0, 7.8 Hz, 1H), 2.96 (dt, *J* = 14.0, 6.6 Hz, 1H), 1.51-1.60 (m, 2H, $CH_2$), 1.29-1.41 (m, 2H, $CH_2$), 0.92 (t, *J* = 7.3 Hz, 3H, $CH_3$). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 161.8 (C-2), 132.0, 129.9, 128.8, 128.1 (Ar), 84.7 (C-3), 74.0 (C-4), 40.9 ($CH_2$), 29.1 ($CH_2$), 20.0 ($CH_2$), 13.5 ($CH_3$). HRMS (ESI-TOF) *m/z*: calcd for $C_{13}H_{16}Cl_2NO$ $[M+H]^+$ 272.0603; found 272.0604.

**(3*RS*,4*SR*)-1-Butyl-3-chloro-4-phenylazetidin-2-one (4i).** Colorless oil, $R_f$ = 0.47 ($CH_2Cl_2$). IR (NaCl, neat): 3063, 3035, 2958, 2925, 2871, 1770 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.37-7.47 (m, 3H, ArH), 7.25-7.30 (m, 2H, ArH), 5.10 (d, *J* = 4.9 Hz, 1H, H-3), 4.96 (d, *J* = 4.9 Hz, H-4), 3.55 (dt, *J* = 14.0, 7.7 Hz, 1H), 2.90-2.99 (m, 2H), 1.45-1.56 (m, 2H), 1.26-1.38 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H, $CH_3$). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 164.3 (C-2), 133.2, 129.1, 128.5, 128.2, (Ar), 61.0 (C-3), 60.9 (C-3), 40.9 ($CH_2$), 29.3 ($CH_2$), 20.2 ($CH_2$), 13.5 ($CH_3$).

HRMS (ESI-TOF) *m/z*: calcd for $C_{13}H_{17}ClNO$ $[M+H]^+$ 238.0993; found 238.0997.

**(3*RS*,4*RS*)-1-Butyl-3-chloro-4-phenylazetidin-2-one (5i).** Colorless oil, $R_f$ = 0.43 ($CH_2Cl_2$). IR (NaCl, neat): 3064, 3032, 2958, 2931, 2872, 1772 $cm^{-1}$.$^1$H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.47 (m, 3H, ArH), 7.30-7.33 (m, 2H, ArH), 4.54 (d, *J* = 1.7 Hz, 1H, H-3), 4.49 (br d, *J* = 1.7 Hz, H-4), 3.52 (dt, *J* = 14.1, 7.6 Hz, 1H), 2.86 (dt, *J* = 14.1, 7.0 Hz, 1H), 1.44-1.53 (m, 2H, $CH_2$), 1.24-1.36 (m, 2H, $CH_2$), 0.89 (t, *J* = 7.3 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 163.8 (C-2), 135.2, 129.4, 129.3, 126.6 (Ar), 66.0 (C-3), 63.1 (C-4), 40.8 ($CH_2$), 29.4 ($CH_2$), 20.0 ($CH_2$), 13.5 ($CH_3$). HRMS (ESI-TOF) *m/z*: calcd for $C_{13}H_{17}ClNO$ $[M+H]^+$ 238.0993; found 238.0993.

**1-Isopropyl-3,3-dichloro-4-phenylazetidin-2-one (2j).** Colorless oil, $R_f$ = 0.30 (*n*-hexane-$CH_2Cl_2$ 1:1). IR (NaCl, neat): 2954, 2923, 2852, 1789 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.49 (m, 3H, ArH), 7.32-7.39 (m, 2H, ArH), 5.03 (s, 1H, H-4), 1.75 (hept, *J* = 6.8 Hz, 1H), 1.40 (d, *J* = 6.8 Hz, 3H, $CH_3$), 1.18 (d, *J* = 6.8 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 161.5 (C-2), 133.1, 129.9, 128.7, 128.3, (Ar), 84.0 (C-3), 73.3 (C-4), 46.5 (CH), 20.8 ($CH_3$), 20.1 ($CH_3$). HRMS (ESI-TOF) *m/z*: calcd for $C_{12}H_{14}Cl_2NO$ $[M+H]^+$ 258.0447; found 358.0447.

**3,3-Dichloro-1-cyclohexyl-4-phenylazetidin-2-one (2k).** Pale solid, mp 98-100 °C, $R_f$ = 0.50 (*n*-hexane-$CH_2Cl_2$ 1:1). IR (NaCl, neat): 3035, 2933, 2857, 1784 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.42-7.49 (m, 3H, ArH), 7.31-7.39 (m, 2H, ArH), 5.05 (s, 1H, H-4), 3.40 (tt, *J* = 11.4, 3.8 Hz, 1H), 2.08 (dm, *J* = 12.6 Hz, 1H), 1.65-1.90 (m, 4H), 1.58 (m, 1H), 1.103-1.36 (m, 4H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 161.5 (C-2), 133.2, 129.8, 128.6, 128.3 (Ar), 84.1 (C-3), 73.2 (C-4), 53.8 (CH), 30.9 ($CH_2$), 30.2 ($CH_2$), 25.0 (2 $CH_2$), 24.7 ($CH_2$). HRMS (ESI-TOF) *m/z*: calcd for $C_{15}H_{18}Cl_2NO$ $[M+H]^+$ 298.0760; found 398.0762.

**(3*RS*,4*SR*)-3-Chloro-1-cyclohexyl-4-phenylazetidin-2-one (4k).** Colorless oil, $R_f$ = 0.21 (*n*-hexane-$CH_2Cl_2$ 1:1). IR (NaCl, neat): 3031, 2932, 2855, 1761 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.45 (m, 3H, ArH), 7.30-7.35 (m, 2H, ArH), 5.03 (br d, *J* = 5.0 Hz, 1H, H-3), 4.97 (br d, *J* = 5.0 Hz, H-4), 3.43 (tt, *J* = 11.5, 3.9 Hz, 1H), 2.03 (dm, *J* = 12.5 Hz, 1H), 1.84 (m, 1H), 1.76 (m, 1H), 1.51-1.70 (m, 3H), 0.99-1.30 (m, 4H).$^{13}$C NMR ($CDCl_3$, 100 MHz): δ 164.0 (C-2), 134.4, 129.1, 128.4, 128.3 (Ar), 60.2 (C-3), 60.0 (C-4), 53.6 (CH), 31.3 ($CH_2$), 30.4 ($CH_2$), 25.1 ($CH_2$), 25.0 ($CH_2$), 24.9 ($CH_2$). HRMS (ESI-TOF) *m/z*: calcd for $C_{15}H_{19}ClNO$ $[M+H]^+$ 264.1150; found 264.1154.

**(3*RS*,4*RS*)-3-Chloro-1-cyclohexyl-4-phenylazetidin-2-one (5k).** Colorless oil, $R_f$ = 0.13 (*n*-hexane-$CH_2Cl_2$ 1:1). IR (NaCl, neat): 3031, 2931, 2855, 1768 $cm^{-1}$.$^1$H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.40 (m, 5H, ArH), 4.53 (br d, *J* = 1.7 Hz, 1H, H-3), 4.44 (br d, *J* = 1.7 Hz, H-4), 3.38 (tt, *J* = 11.4, 3.8 Hz, 1H), 2.00 (dm, *J* = 12.5 Hz, 1H), 1.71-1.82 (m, 2H), 1.50-1.70 (m, 3H), 0.97-1.30 (m, 4H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 163.6 (C-2), 136.7, 129.3, 129.1, 126.7 (Ar), 65.1 (C-3), 62.6 (C-4), 53.5 (CH), 31.2 ($CH_2$), 30.4 ($CH_2$), 25.1 ($CH_2$), 25.0 ($CH_2$), 24.9 ($CH_2$). HRMS (ESI-TOF) *m/z*: calcd for $C_{15}H_{19}ClNO$ $[M+H]^+$ 264.1150; found 264.1153.

**2,2-Dichloro-*N*-(ethoxyphenylmethyl)acetamide (3b).** Amorphous white solid, $R_f$ = 0.74 ($CH_2Cl_2$). IR (NaCl, neat): 3260, 3060, 3005, 2974, 2922, 2853, 1673 $cm^{-1}$.$^1$H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.48 (m, 5H, ArH), 6.87 (br d, *J* = 9.1 Hz, 1H, NH), 6.22 (d, *J* = 9.3 Hz, 1H), 5.97 (s, 1H, $CHCl_2$), 3.81 (dq, *J* = 9.4, 7.0 Hz, 1H), 3.68 (dq, *J* = 9.4, 7.0 Hz, 1H), 1.30 (t, *J* = 7.0 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 164.3 (CO), 138.4 (C), 128.8, 128.7, 125.8 (Ar), 80.7 (CH), 66.4 ($CHCl_2$), 64.5 ($CH_2$), 15.1 ($CH_3$). HRMS (ESI-TOF) *m/z*: calcd for $C_{11}H_{13}Cl_2NNaO_2$ $[M+Na]^+$ 284.0216; found 284.0227.

**2,2-Dichloro-*N*-[ethoxy(3-methoxyphenyl)methyl] acetamide (3f).** $R_f$ = 0.74 ($CH_2Cl_2$). IR (NaCl, neat): 3261, 3061, 3005, 2977, 2925, 2855, 2835, 1674 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.30 (t, *J* = 8.0 Hz, 1H, ArH), 6.99-7.05 (m, 2H, ArH), 6.89 (ddd, *J* = 8.2, 2.6, 0.7 Hz, 1H, ArH), 6.85 (br s, 1H, NH), 6.18 (d, *J* = 9.3 Hz, 1H), 5.97 (s, 1H, $CHCl_2$), 3.82 (s, 3H, $CH_3$), 3.80 (dq, *J* = 9.4, 7.0 Hz, 1H), 3.67 (dq, *J* = 9.4, 7.0 Hz, 1H), 1.30 (t, *J* = 7.0 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 164.2 (CO), 159.9, 140.0, 129.8, 118.0, 114.3, 111.4 (Ar), 80.6 (CH), 66.4 ($CHCl_2$), 64.5 ($CH_2$), 55.3 ($CH_3$), 15.0 ($CH_3$). HRMS (ESI-TOF) *m/z*: calcd for $C_{12}H_{14}Cl_2NO_3$ $[M-H]^-$ 290.0356; found 290.0360.

**2,2-Dichloro-*N*-[ethoxy(4-nitrophenyl)methyl]acetamide (3g).** $R_f$ = 0.48 ($CH_2Cl_2$). IR (NaCl, neat): 3234, 3062, 3012, 2978, 2916, 1685 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.25 (d, *J* = 9.0 Hz, 2H, ArH), 7.65 (dd, *J* = 9.0, 0.6 Hz, 2H, ArH), 6.83 (br d, *J* = 9.1 Hz, 1H, NH), 6.32 (d, *J* = 9.4 Hz, 1H), 6.00 (s, 1H, $CHCl_2$), 3.86 (dq, *J* = 9.4, 7.0 Hz, 1H), 3.71 (dq, *J* = 9.4, 7.0 Hz, 1H), 1.33 (t, *J* = 7.0 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 164.5 (CO), 145.3, 128.3, 127.0, 123.9 (Ar), 79.8 (CH), 66.2 ($CHCl_2$), 64.9 ($CH_2$), 15.0 ($CH_3$). HRMS (ESI-TOF) *m/z*: calcd for $C_{11}H_{11}Cl_2N_2O_4$ $[M-H]^-$ 305.0101; found 305.0115.

**2,2-Dichloro-*N*-[ethoxy(3,5-difluorophenyl)methyl] acetamide (3h)**. $R_f$ = 0.71 ($CH_2Cl_2$). IR (NaCl, neat): 3276, 3057, 3005, 2981, 2930, 2915, 2901, 2889, 1685 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz): δ 6.96-7.03 (m, 2H, ArH), 6.80 (br s, 1H, NH), 6.80 (tt, *J* = 8.8, 2.4 Hz, 1H, ArH), 6.19 (d, *J* = 9.4 Hz, 1H), 5.98 (s, 1H, $CHCl_2$), 3.82 (dq, *J* = 9.4, 7.0 Hz, 1H), 3.68 (dq, *J* = 9.4, 7.0 Hz, 1H), 1.31 (t, *J* = 7.0 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 164.4 (CO), 163.1 (dd, *J* = 248.1, 12.5 Hz, 2C, CF), 142.4 (t, *J* = 8.9 Hz, 1C, ArC), 109.1 (d, *J* = 26.4 Hz, 2C, ArCH), 104.2 (t, *J* = 25.1 Hz, 1C, ArCH), 79.6 (CH), 66.2 ($CHCl_2$), 64.8 ($CH_2$), 15.0 ($CH_3$). HRMS (ESI-TOF) *m/z*: calcd for $C_{11}H_{10}Cl_2F_2NO_2$ $[M-H]^-$ 296.0062; found 296.0052.

***N*-benzyl-2,2-dichloro-*N*-(1-phenylvinyl)acetamide (6l).** From **1l** (100 mg, 0.28 mmol) and $RuCl_2(PPh_3)_3$ (27 mg, 0.028 mmol, 10%) in toluene (1 mL). The mixture was heated with stirring at 80 °C using microwave irradiation for 10 min. After chromatography (hexane-$CH_2Cl_2$, 1:0 to 1:1) **3l** was isolated (36 mg, 40%). In this reaction 48 mg of **1l** was also recovered. $R_f$ = 0.38 (*n*-hexane-$CH_2Cl_2$ 1:1). IR (NaCl, neat): 3061, 3029, 2952, 2924, 2854, 1690, 1625, 1576 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.45 (m, 5H, ArH), 7.21-7.30 (m, 5H, ArH), 6.38 (s, 1H, $CHCl_2$), 4.98 and 5.70 (2 s, 1H each, $=CH_2$), 4.66 (br s, 2H, $CH_2Ar$). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 164.8 (CO), 144.5 (C=), 135.8, 134.0, 129.9, 129.3, 129.2, 128.5,

127.9, 126.0 (Ar), 116.0 (=$CH_2$), 64.0 ($CHCl_2$), 50.7 ($CH_2Ar$). HRMS (ESI-TOF): Calcd for $C_{17}H_{16}Cl_2NO$ $[M+H]^+$ 320.0603; found 320.0603.

## Conclusion

As a conclusion, herein we have reported a new behaviour of ruthenium catalysts towards benzyl-tethered trichloroacetamides allowing formation of -lactams through C-H benzylic activation. The best results were achieved in the presence of a catalytic amount of $RuCl_2(Pph_3)_3$ under microwave activation in a very short reaction time. Even if the lactams are isolated with moderate yields, the simplicity of the process and the challenging unprecedented reaction involved bring new insights into the chemistry of ruthenium catalysts. Future efforts will be steered toward expanding the reaction to more substrates for the synthesis of other nitrogen heterocycles and also to shed more light on the mechanism of this *C($sp^3$)-C($sp^3$)* bond formation.

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