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$Zn(OTf)_2$-Catalyzed Synthesis of 2-Alkynylazetidines and their Ring Expansion to Functionalized 1,4,5,6-Tetrahydropyridines

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Abstract. A zinc(II) triflate catalyzed reaction of β-chloro aldimines with terminal alkynes leading to a rapid and efficient formation of 2-alkynylazetidines in good to excellent yield has been described. The catalytic hydrogenation of the 2-alkynylazetidines resulted in acyclic secondary amines by reductive cleavage of the 2-alkynylazetidine. Further, these non-activated 2-alkynylazetidines were ring expanded in a reaction with dimethyl acetylenedicarboxylate in the presence of zinc(II) triflate to give 4-alkynyltetrahydropyridines. Catalytic reduction of these 4-alkynyltetrahydropyridines led to an efficient conversion to 4-alkyltetrahydropyridine carboxylates.

Keywords: Alkyne; 2-Alkynylazetidine; β-Chloro imine; Cycloaddition; Ring expansion; Schiff base; Tetrahydropyridine; Zinc

Introduction

Azetidines represent an important class of strained cyclic compounds from both biological[1] and synthetic point of view.[2] The azetidine moiety is a valuable constituent of many naturally occurring products e.g. azetidine-2-carboxylic acid, penarisidine A and B,[3,4] polyoxin and mugineic acid and others.[5-7] Recently, substituted azetidines have attracted considerable attention because of the diverse biological activities associated to this type of compounds. For instance, 3-alkoxy- and 3-aryloxyazetidines have been described as G-protein coupled receptor agonists,[8] inhibitors of stearoyl-coenzyme A Δ-9 desaturase,[9] and as antibacterial agents.[10] Azetidines also act as building blocks for some drugs such as Azelnidipine, a calcium channel blocker which is used as antihypertensive agent[11a] and in lincosamides, which are antibacterial protein synthesis inhibitors[11b].

The chemistry of azetidines has not been explored as intensively as that of their lower homologue, aziridines, which already have demonstrated their broad applicability as versatile building blocks through a variety of ring-opening and ring-transformation reactions.[12a] Although some syntheses of highly functionalized azetidines have been described with the purpose of converting them by ring expansion methods to biologically active heterocyclic moieties, these examples are still exceptions compared to aziridines.[12b,c] Simple methods for the synthesis of 1,2,3-trisubstituted azetidines are rare. The synthesis of 2-alkynylazetidines remains a new and challenging task as these compounds bear the potential to be ring expanded to other azaheterocyclic compounds. So far, 2-alkynylazetidines have been reported in literature as intermediates or as side products.[13] For instance Ohno and Tanaka *et al.*[14] isolated 2-alkynylazetidines as side products from the Pd(0) catalyzed cyclization of aminoalkyl substituted bromoallenes. The synthesis of 1-tosyl-2-alkynylazetidine in 38% yield by the intramolecular Mitsunobu reaction of a 1,3-aminoalcohol can be mentioned as a single example.[15]

The most general approach to 2-alkynylazetidines is the controlled reduction of the corresponding azetidin-2-ones with chloroalane.[13b,16] Alkynyl substituted azetidinones may be prepared via Mitsunobu cyclization of *N*-(3-hydroxypropanoyl) amides (Scheme 1, route a)[16], ketene-alkynylimine cycloaddition (Scheme 1, route b)[16,17] or ester enolate-alkynyl imine cycloaddition (Scheme 1, route c)[16]. Finally, Yanpeng *et al.* described the Cu(I) iodide catalyzed synthesis of highly functionalized 4-alkynyl-2-imino azetidines starting from terminal alkynes, sulfonyl azides and imidoyl chlorides while by using triethylamine as base for this reaction.[18] No reduction of these compounds to the corresponding azetidines has been reported.

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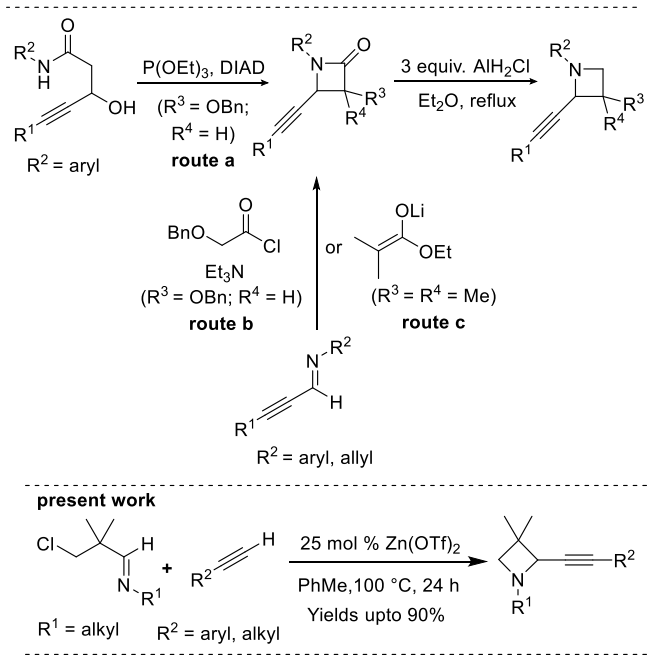
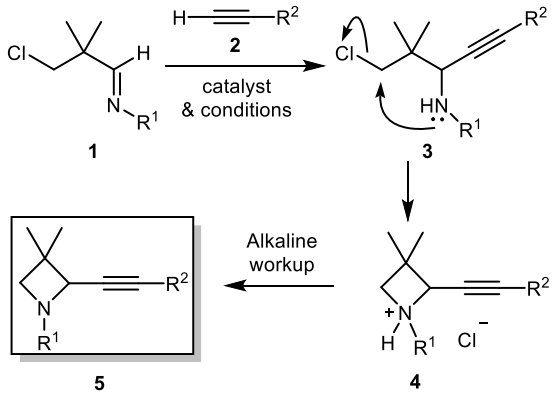


Scheme 1. Previous and current approaches to synthesize 2-alkynyl azetidines.

From the literature overview, it can be concluded that there is still room for new syntheses of 2-alkynylazetidines, especially because the reactivity of these bifunctional compounds has not been investigated in detail.

Herein, we describe the efficient synthesis of 2-alkynyl azetidines **5** starting from β-chloro aldimines **1** and terminal alkynes **2** in good to excellent yields using $Zn(OTf)_2$ as catalyst. The method includes initial alkynylation of β-chloro aldimines **1** to give propargyl amines **3**, followed by ring closure to deliver 1,2,3-trisubstituted azetidine **5** in one step through the formation of azetidinium salt **4** (Scheme 2).



Scheme 2. Proposed synthesis of 2-alkynylazetidines.

Results and Discussion

For the initial optimization, *N*-(3-chloro-2,2-dimethylpropylidene)pentan-1-amine (**1g**) and phenylacetylene (**2a**) were used as model substrates. β-Chloro aldimine **1g** was synthesized by condensation of 3-chloro-2,2-dimethylpropanal and *n*-pentylamine in the presence of $MgSO_4$ as dehydrating agent.

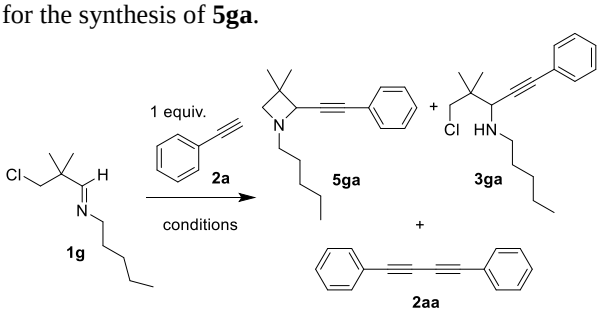
In a first attempt, one equivalent of phenylacetylene (**2a**) was reacted with one equivalent of β-chloro aldimine **1g** using 25 mol % AgOTf at 50 °C in dichloromethane. The analysis of the reaction mixture showed highly unsatisfactory results with only 3% conversion to azetidine **5ga** and 3% of imine-alkyne coupling to give **3ga** (ring open product) namely 5-chloro-4,4-dimethyl-*N*-pentyl-1-phenylpent-1-yn-3-amine (Table 1, entry 1). The use of Cu-salts under similar conditions mainly gave homocoupling of phenylacetylene with no trace of azetidine **5ga** (Table 1, entries 2-4), while ferric chloride did not provoke any reaction and $InCl_3$ gave only 9% yield of azetidine (Table 1, entries 5-6). With 25 mol % of $Cu(OTf)_2$ in toluene at elevated temperature (80 °C) under argon, the imine-alkyne coupling and ring closure could be improved with less formation of the homo-coupled product **2aa** (Table 1, entry 7).

Since combination of two catalysts sometimes enhances the overall catalytic activity, a combination of 25 mol % $In(OTf)_3$ and 10 mol % CuBr was employed. Both reactions in dichloromethane and toluene gave unsatisfactory results (Table 1, entries 8-9).

In view of previous observations by our group where $In(OTf)_3$ was found to be the best catalyst for the alkynylation of chlorinated aldimines,[19] its application provided promising yields regarding the alkynylation of **1g** (formation of **3ga**) despite the fact that in most cases, a mixture of azetidine **5ga** and non-cyclized product **3ga** was obtained

A major improvement in the yield of **5ga** was observed when reaction was performed with 50 mol % $ZnCl_2$ in toluene at 100 °C. More importantly, besides 80% yield of the desired azetidine **5ga**, no ring opened product **3ga** was observed (Table 1, entry 19).

Table 1. Preliminary screening of the reaction conditions for the synthesis of **5ga**.



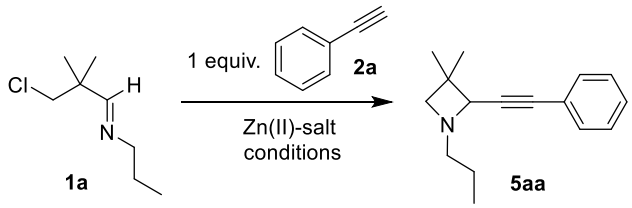
Entry[a]	Catalyst/ mol%	T/t (°C/h)	Solvent	Yield (%)[b] **5ga/3ga/2aa**
1	AgOTf/25	50/18	CH_2Cl_2	3/3/0
2	CuBr/25	50/18	CH_2Cl_2	0/4/12
3	$Cu(OTf)_2$/25	50/18	CH_2Cl_2	0/7/25

4	$CuBr_2$/25	50/18	CH_2Cl_2	0/2/10
5	$FeCl_3$/25	50/18	CH_2Cl_2	NR[c]
6	$InCl_3$/25	50/18	CH_2Cl_2	9/3/0
7	$Cu(OTf)_2$/25	80/18	PhMe	21/12/8[d]
8	$In(OTf)_3$/ CuBr (25/10)	50/18	CH_2Cl_2	0/25/5
9	$In(OTf)_3$/ CuBr (25/10)	100/18	PhMe	0/30/13
10	$In(OTf)_3$/25	50/18	CH_2Cl_2	0/25/0
11	$In(OTf)_3$/50	50/24	CH_2Cl_2	0/39/0
12	$In(OTf)_3$/25	100/18	DMSO	complex
13	$In(OTf)_3$/25	100/24	PhMe	10/33/0
14	$In(OTf)_3$/50	70/24	DCE	SM[e]
15	$In(OTf)_3$/50	70/24	THF	SM[e]
16	$In(OTf)_3$/50	120/24	PhMe	25/50/0
17	$In(OTf)_3$/100	55/24	CH_2Cl_2	SM[e]
18	$In(OTf)_3$/50	55/24	CH_2Cl_2	29/0/0
19	**$ZnCl_2$/50**	**100/18**	**PhMe**	**80/0/0**

[a)] Reactions were performed at 0.5 mmol scale of **2a** and **1g** in 2 mL of solvent. [b)] Yields were calculated from the ^{1}H NMR from the reaction mixture after basic work up using 1,3,5-trimethoxybenzene as internal standard. [c)] No Reaction. [d)] Reaction was performed under argon. [e)] Starting Material.

In order to simplify the NMR spectral analysis further optimization was performed using *N*-(3-chloro-2,2-dimethylpropylidene)propan-1-amine (**1a**). By applying the conditions from entry 19 (Table 1) to compound **1a**, 89 % of the corresponding azetidine was obtained (Table 2, entry 1). By using lower amounts of $ZnCl_2$, or at lower temperature or for shorter times, lower yields of **5aa** were obtained (Table 2, entries 2-5). Under microwave conditions at 100 °C for 30 min, only 35% yield of 2-alkynyl azetidine **5aa** was obtained (Table 1, entry 6).
In the next step, the effect of other Zn(II) salts, like $ZnBr_2$, ZnI_2, $Zn(OAc)_2$ and $Zn(OTf)_2$ was investigated (Table 2, entries 8-10). The use of 50 mol % of the stronger Lewis acid $Zn(OTf)_2$ gave an optimum yield of 97% of the desired azetidine **5aa** (Table 2, entry 9). As there is a great difference from a sustainability point of view, the catalyst loading was reduced to 25 mol % of $Zn(OTf)_2$ giving a little lower but still acceptable yield of 87% compared to entry 9 (Table 2, entry 11). The same reaction using dry toluene gave a 93% yield of the respective azetidine **5aa** (Table 2, entry 13). As both the aldimine and $Zn(OTf)_2$ are moisture sensitive compounds the following experiments were performed in dry toluene.

Table 2. Optimization of imine-alkyne coupling with different zinc(II) salts.



Entry[a]	Catalyst/ mol%	T/t (°C/h)	Solvent	Yield **5aa** (%)[b]
1	$ZnCl_2$/50	100/24	PhMe	89
2	$ZnCl_2$/50	100/6	PhMe	29
3	$ZnCl_2$/25	100/6	PhMe	6
4	$ZnCl_2$/25	100/18	PhMe	40
5	$ZnCl_2$/25	50/18	DCM	16
6	$ZnCl_2$/50	100/0.5	PhMe	35[c]
7	$ZnBr_2$/50	100/24	PhMe	55
8	ZnI_2	100/24	PhMe	13
9	$Zn(OTf)_2$/50	100/24	PhMe	97
10	$Zn(OAc)_2$/50	100/24	PhMe	NR[d]
11	$Zn(OTf)_2$/25	100/24	PhMe	87
12	$Zn(OTf)_2$/50	100/12	PhMe	72
13	$Zn(OTf)_2$/25	100/24	PhMe[e]	93
14	$Zn(OTf)_2$/20	100/24	PhMe[e]	90
15	$Zn(OTf)_2$/15	100/24	PhMe[e]	76
16	$Zn(OTf)_2$/10	100/24	PhMe[e]	49

[a)] Reactions were performed at 0.5 mmol scale of **1a** and **2a** in 2 mL of solvent. [b)] ^{1}H NMR yields after washing with 0.5 N NaOH. [c)] MW: microwave conditions: 200 W, 100 psi. [d)] No reaction. [e)] Toluene was dried over molecular sieves.

Finally, using the optimized conditions for the alkyne coupling and azetidine formation, a one pot reaction starting from β-chloropropanal, *n*-propylamine and phenylacetylene (**2a**) was investigated. This approach was abandoned as it did not provide the expected azetidine **5aa** and only starting materials were recovered. Based on the results of the catalyst screening (Table 1) and optimization experiments with $Zn(OTf)_2$ (Table 2), the best reaction condition was established to be the reaction of one equivalent of alkyne (**2**) and aldimine (**1**) in the presence of 25 mol% of $Zn(OTf)_2$ as catalyst in dry toluene at 100 °C for 24 h, in a sealed vial (Table 2, entry 13).
With these optimized conditions in hand, the scope of $Zn(OTf)_2$-catalyzed alkynylation of β-chloro aldimines, containing various nitrogen substituents was explored. The β-chloro aldimines **1** were prepared in good yield by the condensation of 3-chloro-2,2-dimethylpropanal with different primary amines in dichloromethane in the presence of anhydrous $MgSO_4$ (see SI). For instance, under optimized conditions, β-chloro aldimines with *N*-*i*-propyl (**1b**), *N*-allyl (**1c**), *N*-cyclopentyl (**1d**) and *N*-cyclohexyl (**1e**) groups reacted with phenylacetylene (**2a**) to deliver the expected 2-alkynylazetidines in good to excellent yields (Table 3, **5aa-ea**). Various

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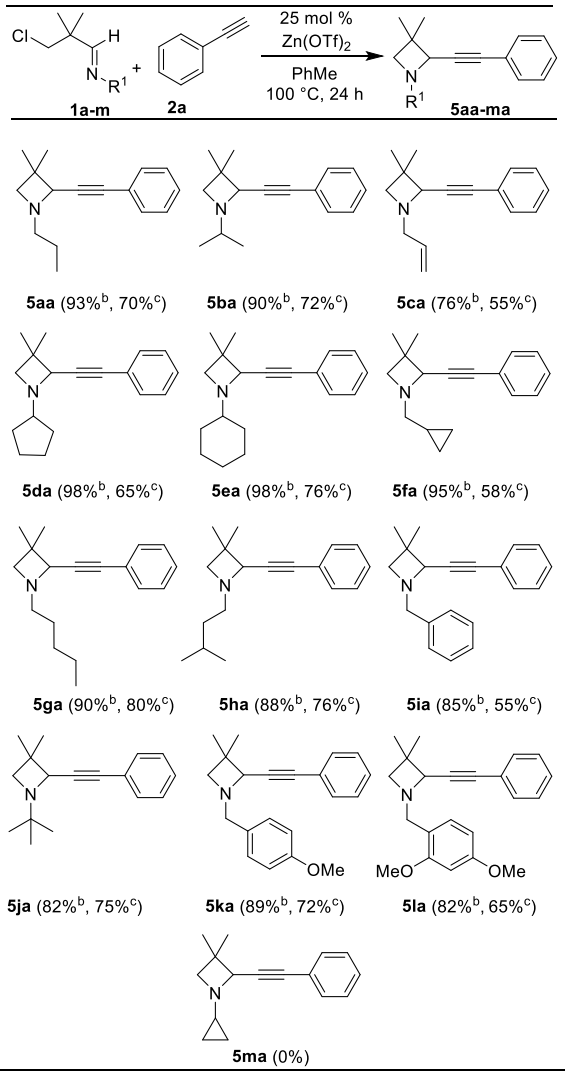
other *N*-substituents such as, methylcyclopropyl (**1f**), *n*-pentyl (**1g**), *i*-amyl (**1h**), *t*-Bu (**1i**), benzyl (**1j**), 4-methoxybenzyl (**1k**) and 2,4-dimethoxybenzyl (**1l**) gave corresponding azetidines in moderate to good yields (Table 3, **5fa-la**). In case of *N*-cyclopropylaldimines (**1m**), instead of the expected azetidine **5ma**, an unidentified product was obtained.

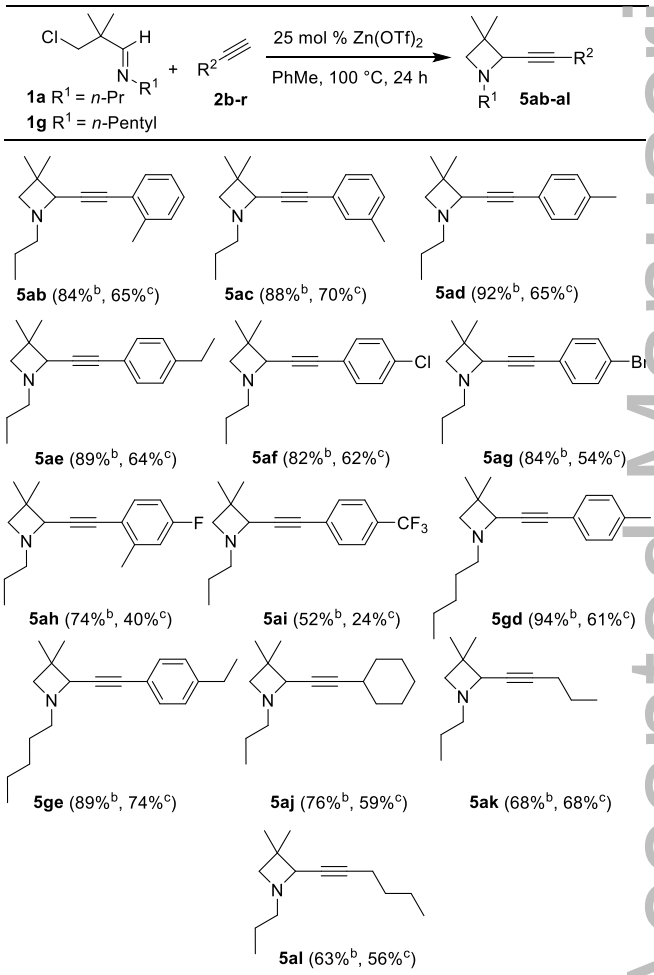
Table 3. Scope of the azetidine synthesis: variation of amine component.[a]



[a] All reactions were performed using 0.5 mmol of **1a-m** and **2a** in 2 mL of toluene in a sealed vial under air for 24 h. [b] ^{1}H NMR yield after basic workup. [c] Isolated yields after chromatography using a short column of silica gel.

Further, this reaction was extended to aryl and alkyl acetylenes (Table 4). The reaction of *N*-propylaldimine **1a** with various aromatic alkynes furnished good to excellent yields of azetidines. A variety of mild electron-donating substituents such as *o*-, *m*-, *p*-methyl and *p*-ethyl (**2a-e**) groups were well tolerated under the optimized reaction conditions and the corresponding 2-alkynylazetidines were obtained in good yields (92-84%) (Table 4, **5ab-ae**). Inductively electron-withdrawing groups such as 4-chloro, 4-bromo and 2-methyl-4-fluoro groups (**2f-h**) were also well tolerated and afforded the corresponding products in moderate to good yield (Table 4, **5af-ah**). Strong electron withdrawing groups like in 4-(trifluoromethyl)phenylacetylene (**2i**) gave the lowest yield of 52% (Table 4, **5ai**).
Besides arylacetylenes, a number of acyclic and cyclic aliphatic acetylenes **2j-l** was also evaluated. With cyclohexylacetylene (**2j**), a good yield (77%) was obtained (Table 4**, 5aj**). With *n*-pentyne (**2k**) and *n*-hexyne (**2l**) moderate yields (68% & 63%) of respective azetidines were obtained after simple aqueous basic workup (Table 4, **5ak-al**).

Table 4. Scope of the azetidine synthesis: variation of the alkyne component.[a]



[a] All reactions were performed using 0.5 mmol **1a or 1g** with 1 equiv. **2b-l** in toluene (2 mL) in a sealed vial under air for 24 h. [b] ^{1}H NMR yield after basic workup. [c] Isolated yield after chromatography using a short column of silica gel.

Surprisingly, a different reaction product **6a** was isolated in 68 % yield in the reaction of 4-methoxyphenylacetylene (**2m**) and β-chloro aldimine **1a** in the presence of $Zn(OTf)_2$ (Scheme 3).

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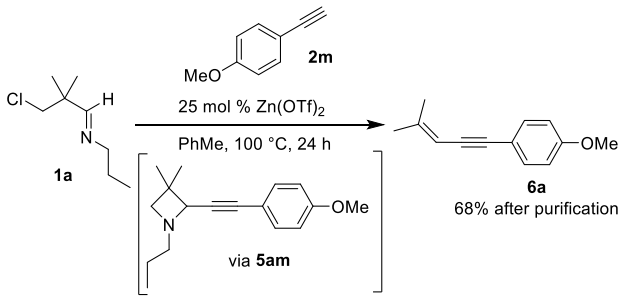


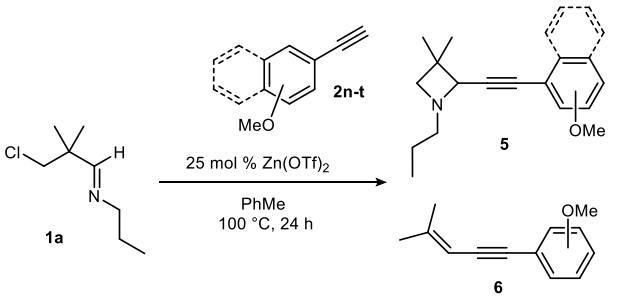
Scheme 3. Reaction of 4-methoxyphenylacetylene with *N*-propyl-β-chloro aldimine.

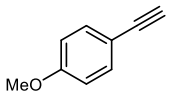
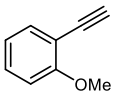
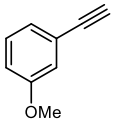
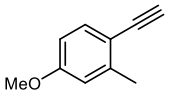
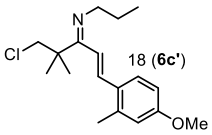
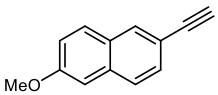
In order to confirm that the *n*-propyl group is not playing any role in this transformation, a reaction involving 4-methoxyphenylacetylene (**2m**) and *N-iso*propyl β-chloro aldimine (**1b**) was performed. Again, in this case 1-methoxy-4-(4-methylpent-3-en-1-yn-1-yl)benzene **6a**, was obtained after flash column chromatography.

In order to gain some understanding of this reaction it was extended to a series of differently substituted methoxyarylacetylenes, e.g. 2-methoxy (**2n**), 3-methoxy (**2o**), 2-methyl-4-methoxy (**2p**) phenylacetylenes and 5-methoxynaphthylacetylene (**2q**). Interestingly, the reaction of **1a** with 2-methoxyphenylacetylene (**2n**) or 6-methoxynaphthylacetylene (**2q**) furnished both the corresponding 2-alkynylazetidines **5an** and **5aq** and the 1,3-enyne product **6b** and **6d** respectively (Table 5**,** entry 2 and 5).

The reaction with an electron withdrawing 3-methoxy substituent on phenylacetylene (**2o**) gave only the corresponding 2-alkynylazetidine **5ao** with a low yield (26%) (Table 5, entry 3) and no 1,3-enyne product was observed. For further understanding the reaction was performed between **1a** and 2-methyl-4-methoxyphenylacetylene (**2p**). Besides the formation of the azetidine fragmentation product, 4-methoxy-2-methyl-1-(4-methylpent-3-en-1-yn-1-yl)benzene (**6c**) in 40% yield, another side product **6c'** was obtained in 18% yield (Table 5, entry 4).

Table 5. Effect of methoxy substituted aryl acetylenes on 2-alkynylazetidine synthesis.



Entry[a]		Alkyne	Yield **5/6'** (%)	Yield **6** (%)[b]
1	**2m**		0	68 (**6a**)
2	**2n**		40 (**5an**)	30 (**6b**)
3	**2o**		26 (**5ao**)	0 (**6b**)
4	**2p**	 	18 (**6c'**)	40 (**6c**)
5	**2q**		50 (**5aq**)	20 (**6d**)

[a)] Reactions were performed at 0.5 mmol scale of **1a** and **2** in 2 mL of toluene. [b)] Yields after column chromatography on silica gel. [c)] Besides **6c** also an imine **6c'** was isolated in 18% yield.

To confirm whether the enyne **6** is formed directly from **3a** and **4** or via the alkynylazetidine **5**, 2-((2-methoxyphenyl)ethynyl)-3,3-dimethyl-1-propylazetidine (**5an**) was dissolved in toluene and heated in the absence and in the presence of 25 mol % of $Zn(OTf)_2$ (Scheme 4). The reaction mixture containing $Zn(OTf)_2$ afforded both starting azetidine **5an** and 1-3-enyne type product **6b** in 2:3 ratio (shown by ^{1}H NMR spectrum) (Scheme 4, route b), while the mixture without $Zn(OTf)_2$ showed not even trace of 1,3-enyne product **6b**, only starting material with few extra peaks were observed (Scheme 4, route a). Based on this result it may be concluded that $Zn(OTf)_2$ is involved in the cleavage of azetidine ring.

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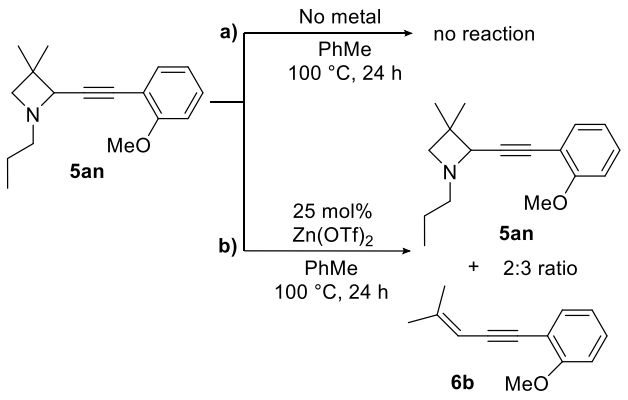
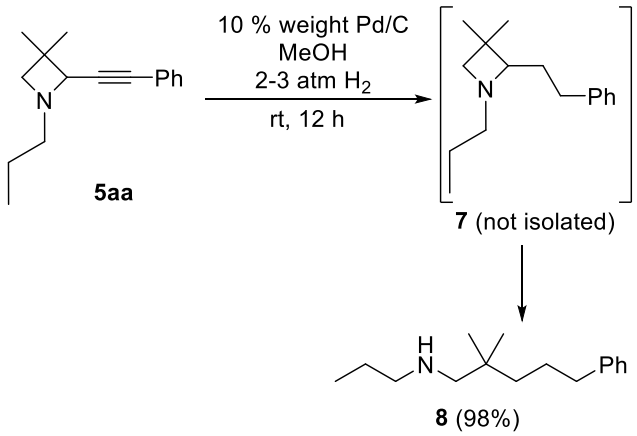


Scheme 4. Formation of 1,3-enyne product **6b** through Zn-catalyzed azetidine ring cleavage.

A plausible mechanism was proposed for the azetidine ring cleavage and for the formation of 1,3-en-yne product (see SI).

As a synthetic application of the developed azetidines, the catalytic hydrogenation of *N*-propyl-3,3-dimethyl-2-phenylethynylazetidine (**5aa**) was attempted. After stirring **5aa** for 12 h at room temperature in the presence of Pd/C in MeOH and under 2-3 bar H_2 pressure, the ring opened product **8** was obtained in 98 % yield. Similar reductive cleavage of azetidines have been observed in literature with 2-arylazetidines.[13b]



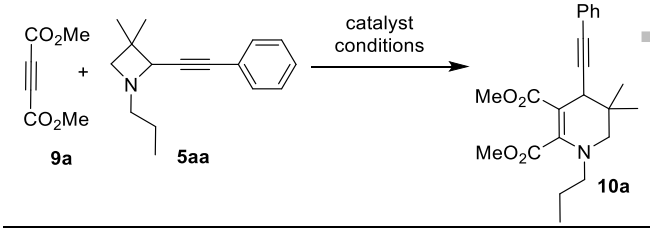
Scheme 5. Reductive cleavage of 2-alkynylazetidine **5aa**.

Azetidine ring expansion reactions are far less studied than aziridines and the ones which have been reported start from *N*-protected or activated azetidines.[15-18] The ring expansion of unactivated or *N*-alkyl azetidines is rarely reported. Bearing in mind our recent work on the synthesis of 1,6-dihydropyridines via a $Zn(OTf)_2$-catalyzed three-component cascade reaction of *in situ* formed propargylamines and dimethylacetylene dicarboxylate (DMAD)[20] we aimed to explore the ring expansion study of the synthesized 2-alkynylazetidines using DMAD (**9a**) as a strong electrophile. Since most of the reactions of DMAD with nucleophiles occur very well in coordinating and polar solvents the screening was started in DMF and DMSO, using $ZnCl_2$ as catalyst. The first reaction was performed using equimolar amounts of azetidine **5aa** and DMAD **9a** in the presence of 20 mol % $ZnCl_2$ in DMF at 100 °C for 24 h. To our delight a 44% yield of [4+2]-cycloaddition type product **10a** namely dimethyl 5,5-dimethyl-4-(phenylethynyl)-1-propyl-1,4,5,6-tetrahydropyridine-2,3-dicarboxylate was obtained. In DMSO the yield was reduced to 38% (Table 6, entry 1-2), while in a non-polar solvent like toluene, a similar yield (41%) was obtained (Table 6, entry 3).

When the reaction was performed at 90 °C for 24 h using 20 mol % of $ZnCl_2$ in the presence of 2-methyltetrahydrofuran, a very promising 85% yield was obtained, while on changing the solvent to THF and MTBE, yields were reduced to 54% and 36%, respectively (Table 6, entries 4-6). In dichloromethane no product was obtained at all (Table 6, entry 7).

Having 2-methyltetrahydrofuran as the preferred solvent, other Zn-salts were evaluated. Between $ZnBr_2$, ZnI_2 and $Zn(OTf)_2$, the latter was found to be the best catalyst giving a 96% yield (Table 6, entries 8-10). Then, the catalyst loading was lowered and even at 2 mol %, a very high yield of 95% could be obtained (Table 6, entry 12). The reduction of both, reaction temperature and time, gave lower yields or incomplete conversions (Table 6, entries 15-16).

Table 6. Optimization of the ring expansion of 2 alkynylazetidines with dimethyl-2-butynedioate.



Entry	Catalyst/ mol%	T/t (°C/h)	Solvent	Yield **10a** (%)[a,b]
1	$ZnCl_2$/20	100/24	DMF	44
2	$ZnCl_2$/20	100/24	DMSO	38
3	$ZnCl_2$/20	100/24	PhMe	41
4	**$ZnCl_2$/20**	**90/24**	**2-MeTHF**	**85**
5	$ZnCl_2$/20	66/16	THF	54
6	$ZnCl_2$/20	60/24	MTBE	36
7	$ZnCl_2$/20	50/16	CH_2Cl_2	NR[c]
8	$ZnBr_2$/10	50/16	2-MeTHF	45
9	ZnI_2/10	90/24	2-MeTHF	39
10	$Zn(OTf)_2$/10	90/24	2-MeTHF	96
11	$Zn(OTf)_2$/5	90/24	2-MeTHF	96
12	$Zn(OTf)_2$/2	90/24	2-MeTHF	95
13	$Zn(OTf)_2$/2	50/24	2-MeTHF	67+SM[d]
14	**$Zn(OTf)_2$/2**	**90/15**	**2-MeTHF**	**94**
15	$Zn(OTf)_2$/2	90/8	2-MeTHF	67
16	No catalyst	90/24	2-MeTHF	NR
17[e]	$Zn(OTf)_2$/2	90/15	2-MeTHF	SM[d]

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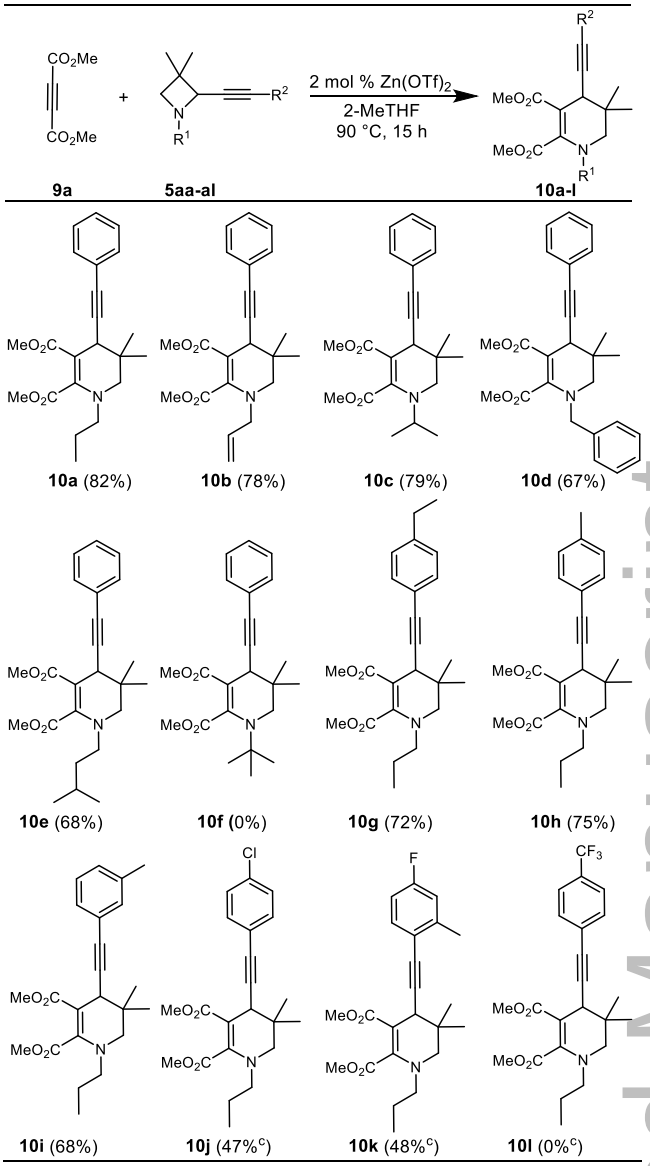
18[f]	$Zn(OTf)_2$/25	100/24	PhMe	60

[a] All reactions were performed at 0.5 mmol scale of azetidine **5aa** with 1 equiv. of DMAD in 2 mL of solvent in a sealed vial. [b] Yield of crude reaction mixture determined by ^{1}H NMR. [c] No Reaction. [d] Starting Material. [e] One pot reaction of β-chloro aldimine **1a**, phenylacetylene **2a** and DMAD. [f] β-chloro aldimine **1a** is first reacted with phenylacetylene **2a** in the presence of $Zn(OTf)_2$ in toluene for 24 h at 100 °C, then DMAD was added and reacted for another 24 h.

The one pot reaction starting from β-chloro aldimine **1a**, terminal alkyne **2a** and DMAD was also investigated, but only starting material was recovered (Table 6, entry 17). When the reaction was performed in a sequential way, where first β-chloro aldimine **1a** was reacted with phenylacetylene **2a,** to deliver azetidine **5aa** *in situ*, which later reacted with DMAD, the final product **10a** was isolated in 60% yield (Table 6, entry 18).

With the optimized conditions in hand, the substrate scope of different azetidines in reaction with DMAD was explored. First the effect of the *N*-substituents on the azetidine was explored and it was observed that azetidines with primary and secondary (*n*-propyl **5aa** and *iso*-propyl **5ba**) groups reacted very well along with other azetidines having primary substituents such as allyl **5ca**, *iso*-amyl **5da** and benzyl **5ja** groups (Table 7, **10a-10e)**, while the azetidine with the bulky *tert*-butyl group **5ia** gave a complex reaction mixture from which, the desired product could not be isolated. The generality of developed conditions was then extended to variously alkyne-substituted azetidines. Azetidines having alkynes with moderately electron donating groups such as 3-methyl **5ac**, 4-methyl **5ad** and 4-ethyl **5ae** groups, gave good to moderate yields (Table 7, **10g-10i**), while moderate electron withdrawing groups such 4-chloro **5af** and 2-methyl-4-fluoro **5ah** had a decreasing effect on the yield (Table 7, **10j-10k**). With strong electron withdrawing group such as 4-CF_3 **5al**, no product was obtained.

Table 7. [4+2]-Cycloaddition of 2-alkynylazetidines **5** with DMAD for the synthesis of **10a-l**.[a,b]



[a] All reactions were performed on 0.50 mmol scale of azetidines **5** with 1 equiv. of DMAD (**9a**) in 1 mL of 2-MeTHF in sealed vials. [b] Yields after column chromatography. [c] Reaction time is 20 h.

In order to show the robustness and ease of use of the developed method a gram-scale experiment was conducted. On a 1 g scale of **5aa** with DMAD, the product **10a** could be isolated in 90% yield. Next, the regiospecificity of the ring expansion was evaluated by the reaction of azetidine **5aa** with methyl propiolate (**9b**). We were delighted to see that 2-alkynylazetidine **5aa** reacted very well with one equivalent of methyl propiolate (**9b**) under the optimized conditions to give only one product **11a,** namely methyl 5,5-dimethyl-4-(phenylethynyl)-1-propyl-1,4,5,6-tetrahydropyridine-3-carboxylate (Scheme 6). This suggested that the reaction is regiospecific due to the nucleophilic attack of the azetidine on the more electrophilic alkyne carbon of **9b**.

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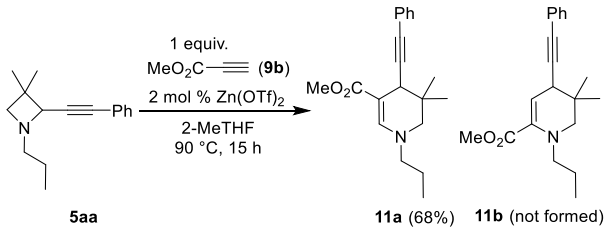
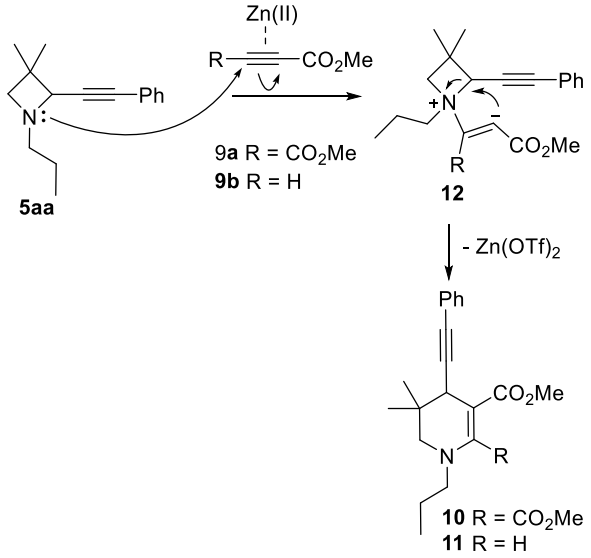


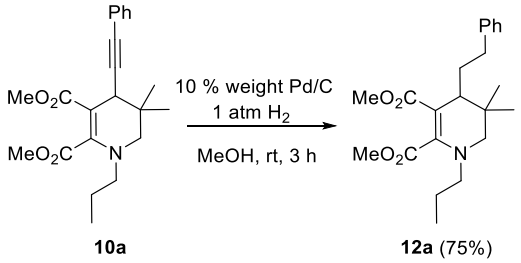
Scheme 6. Formation of 4-alkynyltetrahydropyridine-3-carboxylate **11a** from **5aa** and methyl propiolate (**9b**).

A plausible mechanism, was proposed for this transformation which could be described as 1,4-dipolar cycloaddition on an alkyne (Scheme 7). However, no experimental proof for this was obtained.



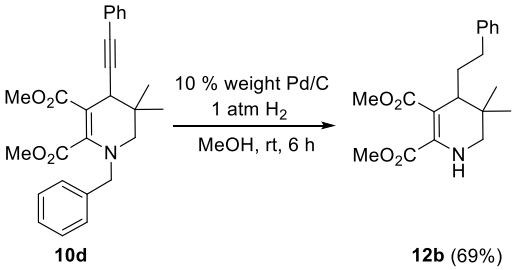
Scheme 7. Proposed mechanism for the synthesis of 4-alkynyltetrahydropyridines **10**-**11**.

The synthesized tetrahydropyridine-2,3-dicarboxylate **10a** could be hydrogenated in the presence of Pd/C in methanol. The triple bond was reduced completely within 3 h under one atmosphere of H_2, while the double bond remained intact to deliver **12a** as final product in good yield (Scheme 8).



Scheme 8. Catalytic reduction of 4-alkynyltetrahydropyridine-2,3-dicarboxylate **10a**.

The reaction of *N*-benzyl 4-alkynyltetrahydopyridine-2,3-dicarboxylate (**10d**) with hydrogen gas, led to debenzylation and reduction of the triple bond leading to *N*-deprotected enamine **12b** in 69% yield (Scheme 9).



Scheme 9. Catalytic debenzylation/reduction of *N*-benzyl-4-alkynyltetrahydropyridine-2,3-dicarboxylate **10d**.

Conclusion

In summary, a highly efficient and operationally simple Zn(II)-catalyzed synthesis of 2-alkynylazetidines **5** starting from imines and acetylenes has been developed. The reaction proceeds via a zinc(II)-catalyzed addition of an acetylide to a β-chloro aldimine, followed by a cyclization of the *in situ* formed γ-chloro propargylic amine. The generality of the reaction was illustrated with various substituents on the imino nitrogen atom and the alkynes. The use of electron rich acetylenes like methoxy substituted phenylacetylenes led to fragmentation of the initially formed 2-alkynylazetidine to give 1,3-enyne type products **6**.
The limitation of the substrates to *gem*-dimethyl substituted β-chloro aldimines can be rationalized by the fact that after addition of the acetylide to the C=N bond, the cyclization of the resulting propargylamine to the corresponding azetidines, will be accelerated by the Thorpe-Ingold effect.[21] Besides this kinetic effect, α,α-dimethyl substitution of β-chloro aldimines also avoids the formation of less reactive enamines, which do not easily react with acetylides.
The presence of a triple bond in combination with a strained azetidine makes compounds **5** interesting building blocks for further elaboration. The *N*-alkyl-2-alkynylazetidines behaved, in combination with electrophilic alkynes **9a-b** like 1,4-dipoles and led to ring expanded products, 4-alkynyltetrahydropyridine carboxylates **10**. The catalytic hydrogenation of 2-alkynylazetidines not only reduced the triple bond but also opened the ring to give amino alkanes with the desired substituents. The reactivity of 2-alkynylazetidines towards strong electrophiles such as phenylisothiocyanates is underway.

Experimental Section

General experimental procedure for the synthesis of 2-alkynylazetidines

In an oven dried 10 mL vial containing of dry toluene (2 mL) and a stirring bar, the aldimines (**1a-k**) (0.50 mmol), acetylenes (**2a-p**) (0.50 mmol, 1 equiv.) and $Zn(OTf)_2$ (0.046 g, 0.25 mmol) were added successively and the vial was sealed under air. The reaction mixture was stirred at 100 °C for 24 h. Afterwards the reaction mixture was diluted with CH_2Cl_2 (10 mL) washed and extracted with 0.5 N NaOH (10 mL). The organic phase was dried using $MgSO_4$ and the solvent was removed under reduced pressure. The crude reaction mixture was purified by chromatography over silica gel using *n*-heptane/ethyl acetate (80:20) as eluent to afford the pure products.

General experimental procedure for the synthesis of 4-alkynyltetrahydropyridine carboxylates (10-11)

The 2-alkynyl-*N*-alkylazetidine (**5aa-al**) (0.50 mmol) was added in a 10 mL oven dried pressure tube containing a magnetic bar, followed by addition of activated alkyne (**9a-b**) (0.50 mmol) and $Zn(OTf)_2$ (3.6 mg, 10.00 µmol, 2 mol %). Then, 2-methyltetrahydrofuran (1 mL) was added. The vial was sealed under air and heated at 90 °C for 15 h. Afterwards the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with 0.5 N NaOH (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried using $MgSO_4$, filtered and the solvent was removed in vacuo. The crude reaction mixture was purified by chromatography over silica gel using *n*-heptane/ethyl acetate (80:20) as eluent to afford the final products (**10a-k** and **11a**).

Acknowledgements

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FULL PAPER

$Zn(OTf)_2$-Catalyzed Synthesis of 2-Alkynylazetidines and their Ring Expansion to Functionalized 1,4,5,6-Tetrahydropyridines

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