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Efficient 1,3-oxazolidin-2-one synthesis through heterogeneous Pd(II)-catalyzed intramolecular hydroamination of propargylic carbamates

Michael Oschmann[a], Clotilde Placais[a], Anuja Nagendiran[a], Jan-E. Bäckvall[a]*, Oscar Verho[a]*

Abstract: Herein, we present an operationally simple protocol for the cycloisomerization of propargylic carbamates in which a heterogeneous catalyst consisting of Pd nanoparticles immobilized on amino-functionalized siliceous mesocellular foam (Pd(II)-AmP-MCF) is used. This Pd nanocatalyst displayed high efficiency at low catalyst loading and reaction temperatures, which allowed for the efficient and mild synthesis of a wide range of 1,3-oxazolidin-2-one derivatives and related compounds. Moreover, it proved possible to re-use the Pd nanocatalyst for several reactions, although a gradual decrease in activity was observed in the subsequent cycles.

Oxazolidinones and their derivatives have been found to possess a wide range of biological activities, which have made them a highly important compound class in therapeutics and agricultural research. These compounds are perhaps most well-known for their antimicrobial effects,[1] but there also exist examples of oxazolidinone derivatives that display immunomodulatory[2] and neuroleptic activities.[3] In the field of organic synthesis, chiral oxazolidinones are frequently encountered as a chemical motif in synthetic intermediates, most often as chemical auxiliaries to assist in different asymmetric transformations.[4] Because of the many applications of oxazolidinone derivatives, significant efforts have been dedicated towards their synthesis. Here, the most common methods to prepare oxazolidinones have relied primarily on three different synthetic strategies; (i) the reaction of amino alcohols with phosgene or chloroformate reagents as the carbonyl precursor,[5] (ii) carboxylative cyclizations utilizing CO_2[6] or (iii) catalytic cyclizations of propargyl carbamates.[7]

Although many methods are known for the efficient preparation of oxazolidinones, a majority of them suffer from various drawbacks. When designing new protocols for oxazolidinone synthesis, it would be attractive if they like many of the CO_2-based cyclisation methods would use an immobilized catalyst, and in this way simplify catalyst separation and recycling. However, for practical purposes it would be desirable to avoid a method that relies on the use of CO_2 as a reagent since this requires special reaction equipment. In this regard, the cycloisomerization of propargyl carbamates that employs a heterogeneous catalyst would constitute the ideal approach for accessing oxazolidinones. Such a procedure would only require standard experimental set-ups, while benefitting from the typical advantages that is associated with the use of heterogeneous catalysts, such as simple catalyst separation and recycling.[8]

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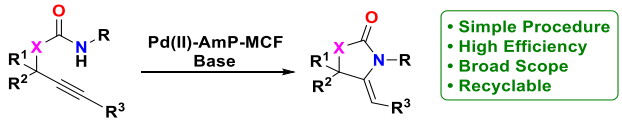
Supporting information for this article is given via a link at the end of the document.

Most available methods based on cycloisomerization chemistry requires the use of high high loadings of homogeneous catalysts[7a,b,d,f,g] or a strong base.[7c] However, recently Saavedra *et al*. reported an example of a heterogeneous Pd(II)-catalyzed protocol for the cycloisomerization of propargylic carbamates to the corresponding 1,3-oxazolidin-2-ones.[9] Although this protocol led to improvements, it still suffered from a few issues that limited its practicality. For instance, this protocol was only applied to a limited number of propargyl carbamate substrates and most of the reactions called for extended reaction times and high reaction temperatures (5 h−4 days at 50-90 °C). Furthermore, all reactions were carried out using water as the solvent. Although water is an attractive solvent from a green chemistry perspective, it is not ideal for this transformation since certain cyclic carbamates are susceptible to hydrolysis, which can lead to the formation of ring-opened products.

In 2011, we reported on the synthesis of a heterogeneous Pd(0)-catalyst, consisting of Pd nanoparticles immobilized on amino-functionalized siliceous mesocellular foam (Pd(0)-AmP-MCF). It was demonstrated that this catalyst could efficiently mediate the racemization of amines.[10] Since then, the Pd(0)-AmP-MCF has been successfully employed in a wide range of organic transformations, including oxidations,[11] reductions,[12] Suzuki cross-couplings[13] and various cooperative reaction protocols.[14] Interestingly, the Pd(II)-precursor of this Pd(0) nanocatalyst, can also be used as a catalyst for a number of useful reactions. For example, this Pd(II)-AmP-MCF catalyst has been employed for the cycloisomerization of alkynoic acids[15] and for the oxidative carbocyclization-borylation of enallenols.[16] Additionally, this Pd(II)-AmP-MCF could be utilized as a catalyst in the chemodivergent syntheses of γ-lactones and γ-lactams via different oxidative tandem processes.[17]

Following up on this work, we were interested in studying if our Pd(II)-AmP-MCF catalyst could also be used for the related cycloisomerization of propargyl carbamates to the corresponding 1,3-oxazolidin-2-ones. Here, our goal was to develop a more practical and recyclable heterogeneous system for the preparation of these valuable compounds (Scheme 1).



Scheme 1. Envisioned heterogeneous Pd(II)-catalyzed protocol for the cyclization of propargylic carbamates into 1,3-oxazolidin-2-ones.

The cycloisomerization of prop-2-yn-1-yl tosylcarbamate (**1a**) into 4-methylene-3-tosyloxazolodin-2-one (**2a**) using the Pd(II)-AmP-MCF catalyst was chosen as the model reaction for the screening of reaction conditions, where the effects of base, solvent and catalyst loading were investigated. Some selected entries are presented in Table 1 (for a more detailed presentation

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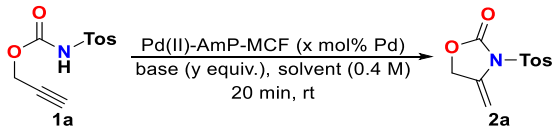
of these results, see Figure S1-3 and Table S1 in the Supporting Information, SI). The optimization began with a screening of different bases using 0.5 mol% Pd(II)-AmP-MCF in CH_3CN at room temperature (rt). Modest reaction performances were observed when using the organic bases DBU and NEt_3, which gave 39% and 46% yield of oxazolidinone **2a**, respectively (Table 1, entries 1−2). With n-Bu_4NOAc as base, the yield of the cycloisomerization reaction could be improved to 62% (Table 1, entry 3). Full conversion was obtained for these reactions within one hour (Figure S1); however, at the end of this reaction a clear color change of the Pd(II)-AmP-MCF had occurred, indicating reduction to Pd(0). Best results were achieved when using inorganic and non-coordinative bases, such as K_2CO_3, $CsCO_3$ and NaOAc, which gave 73%, 69% and 90% yield, respectively (Table 1, entries 4−6). Interestingly, the reaction also worked well when 0.25 mol% Pd(II)-AmP-MCF was used, giving 62% yield (Table 1, entry 7) and full conversion after 30 min.

Table 1. Base and solvent screening for the cycloisomerization of **1a** to **2a**.



1a 2a

Entry	Catalyst (mol%)	Base (equiv.)	Solvent	2a (%)[a]
1	0.5	DBU (0.1)	CH_3CN	39
2	0.5	NEt_3 (0.1)	CH_3CN	46
3	0.5	n-Bu_4NOAc (0.1)	CH_3CN	62
4	0.5	K_2CO_3 (0.1)	CH_3CN	73
5	0.5	Cs_2CO_3 (0.25)	CH_3CN	69
6	0.5	NaOAc (0.1)	CH_3CN	90
7	0.25	NaOAc (0.1)	CH_3CN	62
8	0.25	NaOAc (0.1)	CPME	<5
9	0.25	NaOAc (0.1)	$PhCH_3$	<5
10	0.25	NaOAc (0.1)	DCE	35
11	0.25	NaOAc (0.1)	THF	49
12	0.25	NaOAc (0.1)	EtOAc	77
13	0.25	NaOAc (0.1)	Acetone	>95
14[b]	0.125	NaOAc (0.1)	Acetone	16

[a] conversion determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard. [b] concentration 0.2 M.

The cycloisomerization of **1a** was found to proceed slowly in non-polar solvents such as cyclopentyl methyl ether (CPME) and toluene, yielding only trace amounts of **2a** after 30 min (Table 1, entries 8−9). These poor results can most likely be ascribed to the low solubility of NaOAc in these non-polar solvents. The reaction worked moderately well in DCE and THF, giving 35% and 49% yield, respectively (Table 1, entries 10−11). EtOAc, on the other hand, was found to be a good solvent for the reaction, allowing oxazolidinone **2a** to be acquired in 77% yield (Table 1, entry 12). However, when the reaction was carried out in acetone it was possible to match the performance of the reactions run in MeCN, allowing for >95% yield after 20 min (Table 1, entry 13). A further reduction of the catalyst loading to 0.125 mol% and performing the reaction under more dilute conditions (0.2 M) gave full conversion within 3 h (Table 1, entry 14). As acetone exhibits a better safety and green chemistry profile than MeCN, it was chosen as the solvent for further studies. No product formation could be observed in absence of base or Pd(II)-AmP-MCF (entry not shown in Table 1).

Comparing the performance of our Pd(II)-AmP-MCF to that of other heterogeneous Pd catalysts showed that it was superior to the other catalysts tested for this cycloisomerization reaction (see SI, Figure S4). When using either Pd(0)-AmP-MCF or commercial Pd/C as catalysts for our model reaction, a significantly lower yield of product **2a** was obtained compared to that obtained with the Pd(II)-AmP-MCF catalyst. In a previous study we had observed that additions of BQ to the Pd(II)-AmP-MCF catalyst gave a highly active catalyst with surface-confined Pd(II) species;[15] however, this approach did not lead to any improvements in the present cycloisomerization reaction with the Pd(II)-AmP-MCF.

With the optimized reaction conditions in hand, we next investigated the substrate scope of our catalytic protocol (Table 12). The work-up procedure were conceivably simple. After completion of the reactions, the catalyst was filtered off and washed with acetone, and the collected liquid fractions were concentrated under reduced pressure. In many cases, the products were obtained in high purity without the need of further purifications. Following this work-up procedure, it was for example possible to isolate product **2a** from our initial model reaction, in an excellent yield of 99% after only 20 min. To our delight, the catalytic protocol also worked efficiently for the cyclization of carbamates derived from *sec*-alcohols, such as **1b−1d**, which gave the corresponding oxazolidinones in 83−91% yield after 0.5−6 h at rt (Entries 2−4). Quaternary substrates could also be converted to the corresponding products in high yields and short reactions times (Entries 5−6). Product **2e** was found to be unstable and therefore the yield was determined by NMR against an internal standard (90% yield after 2 h at rt). On the other hand, the spirocyclic product **2f** was more stable and could be isolated in 88% yield after 30 min. For substrates with substituents in the terminal position of the alkyne moiety, elevated temperatures and extended reaction times were generally required to ensure high yields of the oxazolidinone products (Entries 7−12). Moreover, for these reactions, a high selectivity for the expected *Z* isomer of the products were typically observed. For the cycloisomerization of substrate **1g** with a terminal methyl substituent, an excellent yield of 95% and a *Z*:*E* ratio of 88:12 was obtained for product **2g** within 7 h at 40 °C (Entry 7). In the case of substrate **1h** with a terminal phenyl substituent, the cycloisomerization reaction was found to favor the formation of the *Z* conformer of product **2h** almost exclusively (>95%), although a longer reaction time of 20 h was required for a high yield (94%, Entry 8). The *p*-CN-phenyl substituted **2i** was found to be unstable, which required yield determination to be done by NMR against an internal standard. Product **2i** was obtained in 80% yield and in a *Z*:*E* ratio of 95:5 after 24h.

For substrate **2j** with a *p*-EtO_2C-phenyl substituent, an excellent yield of 88% and exclusive formation of the *Z* isomer

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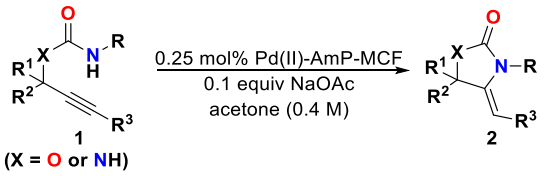
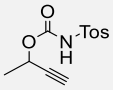
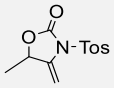
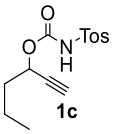
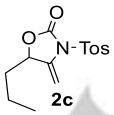
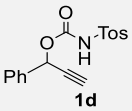
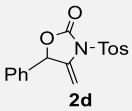
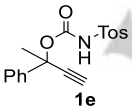
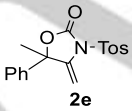
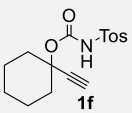
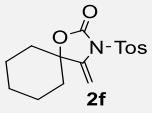
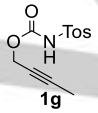
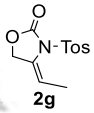
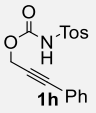
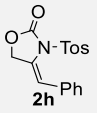
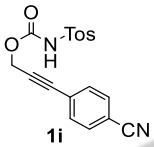
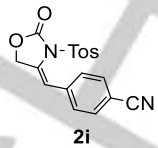
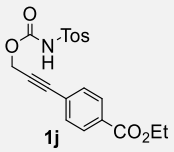
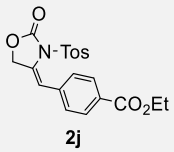
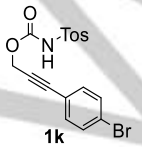
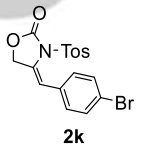
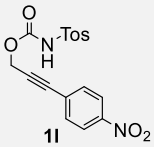
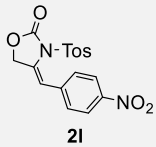
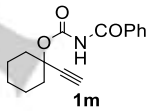
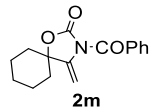
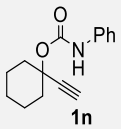
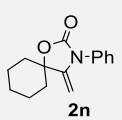
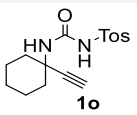
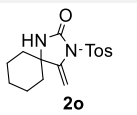
were observed after 18 h (Entry 10). In the case of *p*-Br-phenyl substituted substrate **1k**, a slower reaction was observed and 80% yield was obtained after 48 h (Entry 11). The selectivity towards the *Z* isomer of product **2k** was excellent (>95%). Similarly, excellent *Z* selectivity was also observed for the *p*-NO_2-phenyl substituted product **2l**, which was obtained in 91% yield after 24 h (Entry 12).

As demonstrated in Entry 13, the cycloisomerization protocol could also be extended to propargylic benzylcarbamates when using n-Bu_4NOAc as the base and oxazolidinone **2m** was obtained in 85% yield after 22 h at rt. Unfortunately, propargylic phenylcarbamate **1n** was found to be beyond the scope of our protocol (Entry 14), which most likely can be ascribed to the lower acidity of the N–H proton in this substrate. On the other hand, propargylic tosylureas proved to be suitable substrates(Entry 15), as exemplified by the cycloisomerization of **1o** to the cyclic urea **2o** (75% yield after 48 h at rt).

Table 2. Synthesis of oxazolidinones and related compounds.



1 (X = O or NH) → 2

entry	substrate	product	t /T (°C)	yield (%)
1	 1a	 2a	20 min / rt	99
2	 1b	 2b	30 min / rt	91
3	 1c	 2c	6 h / rt	86
4	 1d	 2d	2 h / rt	83
5	 1e	 2e	2 h / rt	90[a]
6	 1f	 2f	30 min / rt	88
7[b]	 1g	 2g	7 h / 40	88 [*E*:*Z* 12:88]
8[b]	 1h	 2h	20 h / 40	80 [<5:>95]
9[b]	 1i	 2i	24 h / 40	80[a] [5:95]
10[b]	 1j	 2j	18 h / 40	88 [<5:>95]
11[b]	 1k	 2k	48 h / 40	80 [<5:>95]
12[b]	 1l	 2l	24 h / 40	91 [<5:>95]
13[c]	 1m	 2m	22 h / rt	85[a]
14	 1n	 2n	24 h / rt	nr[a]
15	 1o	 2o	48 h / rt	75

All yields are isolated if not otherwise stated; [a] yield determined by ^{1}H-NMR with 1,3,5-trimethoxybenzene as internal standard, due to instability of product; [b] 0.5mol% catalyst; [c] 0.1 equiv. *n*-Bu_4NOAc

An important aspect of a heterogeneous catalyst is the potential to recycle it. Therefore, to assess the recyclability of our Pd(II)-AmP-MCF catalyst, it was subjected to three reactions cycles using substrate **1a** (Figure 1) and the formation of product **2a** was followed over time. From this recycling study, we could observe a gradual decrease of the catalyst's activity over each cycle. Comparing to the first reaction which reached completion after 20 min, the subsequent two cycles required longer reaction times to give comparable results (e.g. 1 h for cycle 2 and 2 h for cycle 3). To elucidate the cause of this deactivation process and to get further insights into the mechanism of our Pd(II)-AmP-MCF catalyst, aliquots were withdrawn from each cycle and studied by Inductively Coupled Plasma-Optical Emission Spectrometry (ICP-OES) to determine the extent of Pd leaching. These measurements revealed a considerable Pd leaching of 22.5 ppm (15.9% of total Pd) in the first cycle, which decreased to 4.8 ppm

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(3.5% of total Pd) in cycle 2 and 2.0 ppm in Cycle 3 (1.4% of total Pd). This result suggests that the Pd(II)-AmP-MCF can to a certain degree operate through a release-and-catch mechanism,[18] in which the Pd(II)-AmP-MCF function as a reservoir of homogeneous and catalytically-active Pd(II) species that can contribute in the reaction. However, it seemed unlikely that all of the observed catalytic activity can be ascribed to homogeneous Pd species, as the levels of leached Pd(II) did not correlate linearly with product formation. We therefore carried out a hot filtration test (see SI, Figure S5), and here we could see that the homogeneous species only contributed marginally to the observed reaction. The participation of the heterogeneous component was further supported by a second recycling study (see SI), in which the cycloisomerization of **1a** was performed over 5 cycles using 0.5 mol% Pd(II)-AmP-MCF over 30 min at rt. Here in the fifth cycle, a yield of 90% of **2a** was obtained when, interestingly, no homogeneous Pd(II) could be detected by ICP-OES. Furthermore, this second recycling study also showed that if one wish to maintain a satisfactory reaction performance over multiple cycles with the Pd(II)-AmP-MCF catalyst, despite the observed catalyst deactivation, it is possible to do so by simply increasing the catalyst loading to 0.5 mol%. With this increased catalyst loading it was possible to achieve >90% yield of **2a** over all five cycles within 30 min.

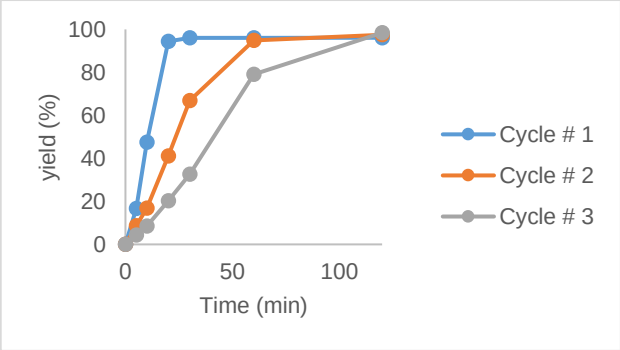

Figure 1. Recycling study of the cycloisomerization of **1a**. Reaction conditions: Prop-2-yn-1-yl tosylcarbamate (**1a**, 0.2 mmol), Pd(II)-AmP-MCF (0.25 mol% Pd), NaOAc (0.1 equiv), acetone (0.4 M) at r.t. Yields were determined by ^{1}H-NMR against an internal standard.

In summary, we have developed an efficient and operationally simple protocol for the cycloisomerization of propargylic carbamates, based on the Pd(II)-AmP-MCF catalyst. Interestingly, high reaction performances could be observed even when using very low catalyst loading and mild reaction conditions. In addition this protocol exhibited excellent functional group tolerance which made it possible to prepare a wide range of 1,3-oxazolidin-2-one derivatives in high yields. Moreover, it was found to be possible to recycle the Pd(II)-AmP-MCF catalyst, although a gradual decrease in performance was observed upon reuse when using 0.25 mol% catalyst. Interestingly, the use of 0.5 mol% catalyst led to more robust performance, which enabled recycling up to 5 times with >90% yield in all cycles after 30 min. Seen overall, this Pd(II)-AmP-MCF based protocol constitutes a highly attractive alternative for preparing various oxazolidinones derivatives on a laboratory scale.

Acknowledgements

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Keywords: heterogeneous catalysis • palladium • mesoporous silica • cycloisomerization • oxazolidinones

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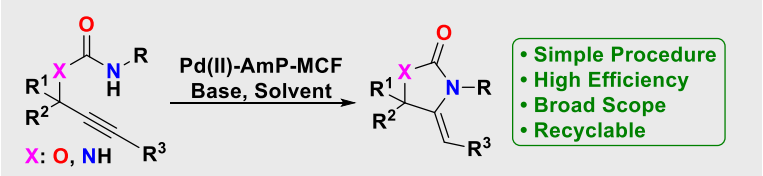

Closing the cycle: Herein, we report on a heterogeneous catalyst consisting of Pd(II)-species immobilized on amino-functionalized mesocellular foam, and its use in the cycloisomerization of propargylic carbamates and ureas. The developed catalytic protocol was found to operate efficiently at mild conditions and it was possible to recycle.

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