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An Efficient and Versatile Approach for the Immobilization of Carbene Precursors *via* Copper-Catalyzed [3+2]-Cycloaddition and their Catalytic Application

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Abstract: Different classes of alkynyl-substituted heterazolium derivatives could be covalently immobilized on an azide-functionalized support *via* copper-catalyzed 1,3-dipolar cycloaddition, which efficiently yields a rigid and robust 1,2,3-triazole linkage. The catalytic performance of the corresponding nucleophilic carbenes (NHCs) was examined in intramolecular Stetter reactions (chroman-4-one products) and organocatalytic redox esterifications (α,β-unsaturated esters). The MeOPEG-immobilized organocatalysts are highly active, and show comparable diastereoselectivities to non-supported derivatives. Additionally, they allow simplified work-up procedures and also have proven to be recyclable.

Keywords: carbenes; catalyst immobilization; click chemistry; organocatalysis; redox esterification; Stetter reaction

Within the rapidly growing field of organocatalysis,[1] N-heterocyclic carbene (NHC)-catalyzed processes have proven to be highly versatile not only considering substrate variations, but also with regard to different types of transformations, which depend on the nature of the applied catalyst and the properties of the starting materials. The scope of these carbene catalysts[2] is impressively illustrated by synthetic applications ranging from "classic" umpolung reactions, transesterifications and cyanosilylation etc. to newer developments within the class of "extended" umpolung reactions,[3] such as hetero-Diels–Alder reactions[4] or oxy-Cope rearrangements.[5]

A general approach for the immobilization of this class of catalysts seems therefore to be highly desirable. Advantages of catalyst fixation not only lie in the context of simplified product isolation and catalyst recycling,[6] but can also be seen with regard to changes in the catalyst's solubility properties or its stabilization.[7] Therefore, immobilization has become an important tool for combinatorial library synthesis.[8]

Only very few examples are known for the successful use of immobilized organocatalytic carbenes,[9] such as a recently reported thiazolium-catalyzed intramolecular Stetter reaction in ionic liquids under microwave irradiation[10] or Barrett's ROMPgel-supported thiazolium iodide for intermolecular Stetter reactions.[11] Usually, lower yields are obtained compared to non-supported thiazolium salts and catalyst recycling generally seems to be problematic.[12]

As part of our ongoing studies, we herein report a highly versatile and efficient method for the immobilization of several classes of heterazolium carbene precursors by a Cu-mediated cycloaddition approach. Their catalytic application in two different organocatalytic umpolung reactions is documented.

In recent years, the copper-catalyzed azide-alkyne cycloaddition reaction ("CuAAC"),[13] a mild and regioselective version of a Huisgen-type 1,3-dipolar cycloaddition,[14] has proven to be one of the most efficient tools for the covalent assembly of highly functionalized molecules or their ligation to various supports.[15]

Based on its favorable thermodynamics, high modularity, orthogonality to other functional groups and tolerance towards changing reaction conditions, this selective transformation of terminal alkynes with azides yielding a 1,2,3-triazole linkage presents an almost ideal case of so-called "click reactions".[16] Additionally, it therefore fulfills many of the crucial requirements for a mild catalyst immobilization method which include high linker stability,[17] especially towards hydrolysis and temperature. Furthermore, the lack of by-products for this atom economic[18] coupling reaction turns it into an enviromentally highly attractive approach for the generation of immobilized and recyclable catalysts. However, whereas this cyclo-

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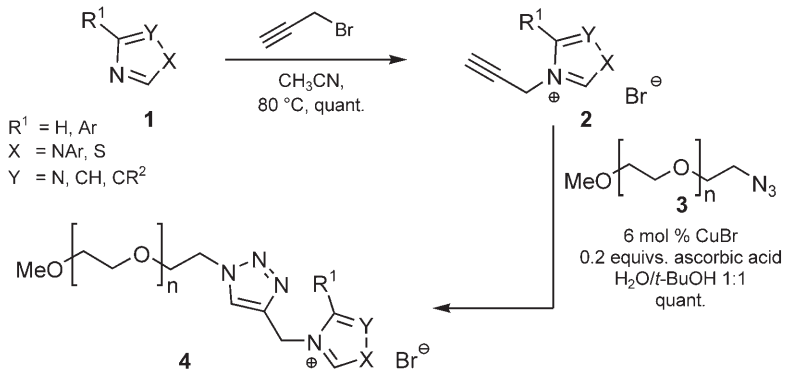

Scheme 1. Synthesis of supported heterazolium precatalysts *via* "CuAAC".

addition concept has been widely used not only in synthesis, drug discovery and biochemistry, but also in material and polymer sciences,[19] there appear to be only few examples in the context of ligand or catalyst linkages. Apart from its efficient use for the immobilization and property modulation of TEMPO derivatives,[20] the fixation of ligands to polymeric supports has been reported,[21] but proven to be somewhat problematic in terms of providing a potential further metal binding site.[22] Only recently, an insoluble, CuAAC-immobilized hydroxyproline derived organocatalyst[23] was successfully employed for asymmetric aldol reactions.[24]

Due to the advantages of MeOPEG-resins[25] for the characterization of the supported catalyst (simple determination of loading by NMR, etc.), we turned our attention to the ligation of heterazolium ions onto these soluble polymeric supports.

The catalyst preparation works straight-forward in two steps starting from the different heterazoles **1** and MeOPEG-supported azide **3**, which was conveniently synthesized as reported.[26] An anchor for the triazole-linkage was provided by base-free propargylation to yield the desired heterazolium precursors **2** in quantitative yield (Scheme 1). Several conditions for triazole formation were tested, indicating that water plays a crucial role for the successful copper(I)-catalyzed cycloaddition of these cationic substrates.[27] Only the desired 1,4-substituted triazole regioisomer was formed during the copper(I)-mediated transformation. Performing the reaction in aprotic solvents, such as CH_2Cl_2, THF or toluene, did not yield the desired immobilized catalysts. However, pure water could be used, but generally afforded lower catalyst loadings. This case presents an example for the strong solvent dependence of such usually insensitive "click" transformations. Nolan[28] similarly observed poor conversions in organic solvents and a strong acceleration in water using NHC-containing Cu(I) complexes for the 1,3-dipolar cycloaddition of azides and alkynes.[29]

In order to avoid anion scrambling, the use of Cu(I) bromide in a water/*t*-butyl alcohol mixture containing additional ascorbic acid proved to work best in our hands. The MeOPEG-supported catalysts could be isolated by precipitation in almost quantitative yields with catalyst loadings generally ranging from 80% to 100% as judged by ^{1}H NMR. Figure 1 provides an overview on the different types of heterazolium precatalysts prepared by this method. Apart from immobilized imidazolium, thiazolium and triazolium catalysts also some benzyl-substituted derivatives (**Bn-5** and **Bn-7**) have been prepared to compare their catalytic performance.

The intramolecular Stetter-type cyclization to form substituted chroman-4-one derivatives **12**, representing a large class of natural products with diverse biological activities,[30] has become a benchmark to test catalyst efficiency.[31] Our initial experiments for the application of the MeOPEG-supported heterazolium precatalysts with the salicylaldehyde-derived substrate **11** concentrated on the evaluation of reaction parameters, such as solvent, catalyst type, catalyst loading and different bases (Table 1).

From these studies with our test substrate **11** Hünig's base (DIPEA) emerged as the most suitable base giving best conversions in chloroform as solvent for thiazolium catalyst **5** or **6** at room temperature.

Gratifyingly, the supported catalyst **5** showed similar catalytic performance as compared to the benzyltriazole derivative **Bn-5** (entries 3 and 5). Furthermore, the catalyst loading could be decreased to 10 mol% without loss of activity. An attempt to apply Rovis' conditions[32] using supported triazolium salt **9** (entry 8) and **10** only gave moderate yields, which is probably due to different electronic properties of these catalysts. Imidazolium catalyst **7** did not show any catalytic activity for this transformation (entry 7).

The use of stronger bases favors by-product formation such as 1-methylbenzoxepin-4-carboxylate **13**,[33] which stems from olefin isomerization and subsequent aldol-type cyclization. While performing the reaction using DBU as base, without any heterazolium catalyst, the product formation could be shifted from the Stetter product towards benzoxepin **13**, which was ob-

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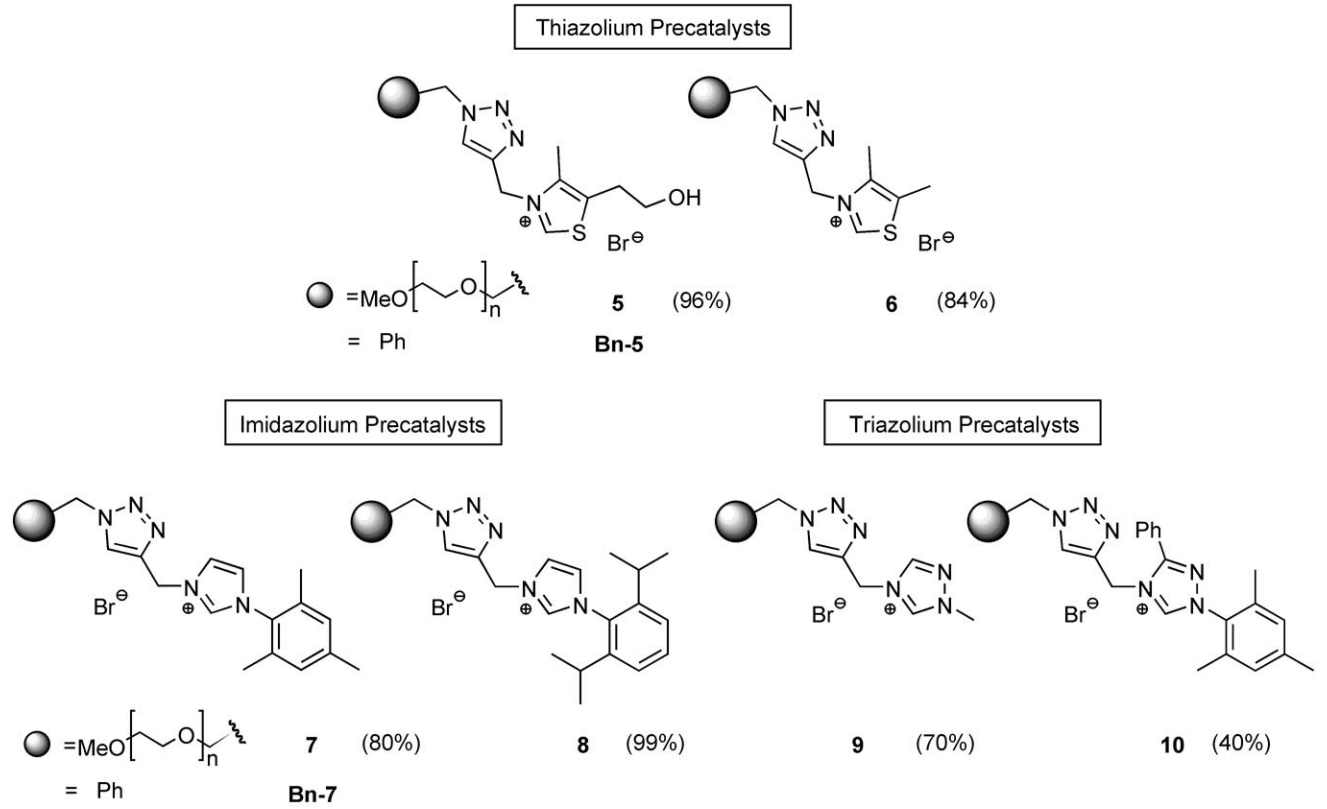
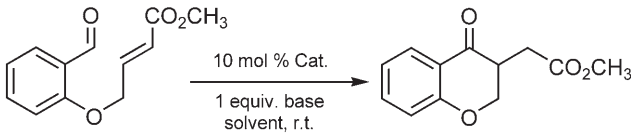


Figure 1. 1,2,3-Triazolo-linked heterazolium precatalysts (loading in %).

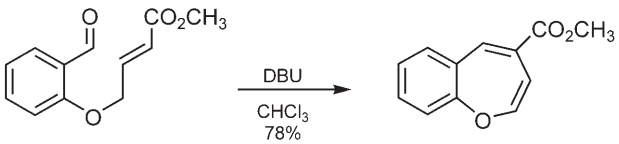
Table 1. Optimization of the conditions for the intramolecular Stetter reaction.



11 **12**

Entry[a]	Catalyst	Base	Solvent	Yield [%][b]
1	**5**	DIPEA	CH_2Cl_2	73[c]
2	**5**	DIPEA	THF	traces
3	**5**	DIPEA	$CHCl_3$	81
4	**5**	DBU	$CHCl_3$	<10 %[d]
5	**Bn-5**	DIPEA	$CHCl_3$	84
6	**6**	DIPEA	$CHCl_3$	82
7	**7**	DIPEA	$CHCl_3$	–
8	**9**	KHDMS[e]	toluene	40
9	**10**	DIPEA	$CHCl_3$	30

[a] All reactions were performed using 10 mol % of catalyst at room temperature, 16 h.
[b] Isolated yields.
[c] Reaction does not go to completion. 14 % of starting material was reisolated.
[d] Mainly by-product **13** is formed (see Scheme 2).
[e] 10 mol % KHDMS were used; reaction time 24 h.



11 **13**

Scheme 2. Benzoxepin formation.

tained as the sole product in good yields under mild conditions (Scheme 2).

Using our optimized conditions for the intramolecular Stetter reaction, further experiments focussed on exploring the scope of the transformation (Table 2). Different aromatic substrates could be converted to the corresponding products in good yields, irrespective of whether electron-donating or electron-withdrawing substituents were present. Indicatively, the mild reaction conditions may account for the successful cyclization of nitro derivative **17**, which was reported to be problematic earlier.[10] Additionally, the formation of a quaternary center was smoothly achieved in very good yields starting from methyl-substituted substrate **19** (entry 7).[34]

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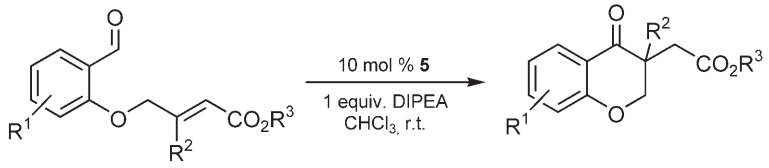
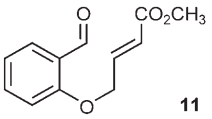
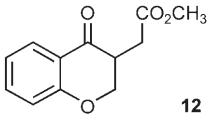
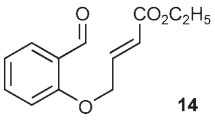
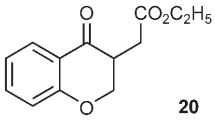
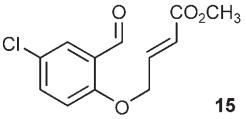
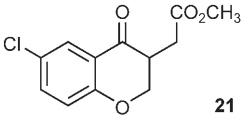
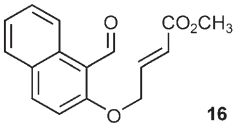
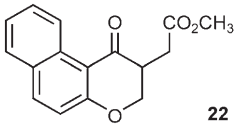
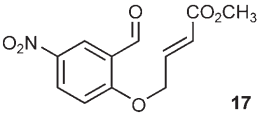
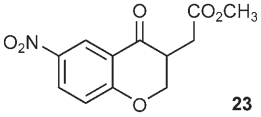
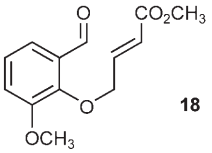
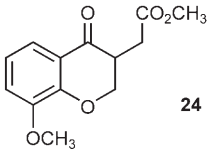
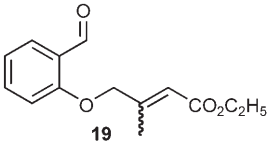
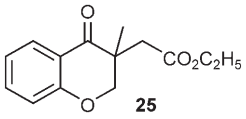
Table 2. Intramolecular Stetter reactions with immobilized thiazolium catalyst.



Entry[a]	Substrate	Product	Yield[b] [%]
1	 **11**	 **12**	84
2	 **14**	 **20**	82;[c] 81[d]
3	 **15**	 **21**	84
4	 **16**	 **22**	43
5	 **17**	 **23**	86
6	 **18**	 **24**	89
7	 **19**	 **25**	86

[a] All reactions were performed using 10 mol% catalyst in $CHCl_3$, room temperature, 16 h.
[b] Isolated yields.
[c] Yield after column chromatography.
[d] Yield after catalyst precipitation and aqueous work-up.

An important advantage of the application of MeOPEG-immobilized thiazolium catalysts is the simplified product isolation. Instead of applying standard column chromatography the desired, pure product[35] can be obtained following a minimal work-up procedure in similar yields (entry 2). Removal of the catalyst after precipitation with Et_2O or *i*-PrOH by filtration is followed by a simple aqueous wash of the remaining organic phase in order to remove base traces. If catalyst reuse is not required, the product can be easily obtained after addition of small amounts of silica and subsequent filtration, thereby providing a beneficial simplification for combinatorial applications.

In further experiments we investigated the recyclability of our catalyst. So far, only two examples of successful carbene organocatalyst recycling have been reported.[10,11] However, these approaches use higher catalyst loadings and harsher conditions (15 mol%, $T = 80\,^{\circ}C$).[36] Taking advantage of NMR analysis of the polymer-bound catalyst, we could only detect intact thiazolium species when the reaction was per-

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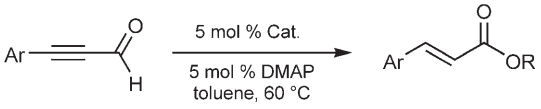
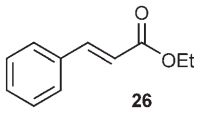
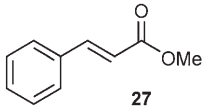
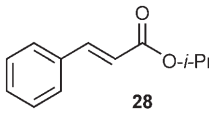
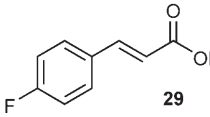
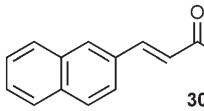
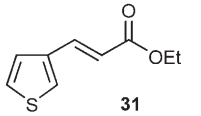
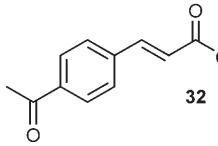
formed in the presence of a cosolvent, such as EtOH, which unfortunately lowered the yield to 49% (not optimized). However, in a second cycle only a slight decrease in catalytic activity was observed, to afford the product in 36% yield.

Following the successful application of MeOPEG-supported thiazolium catalysts in intramolecular Stetter reactions, we decided to examine the catalytic activity of the corresponding immobilized imidazolium salts **7** and **8** in our recently developed diastereoselective redox esterification[37] (Table 3). Presenting an example for the powerful concept of using these soluble MeOPEG-linked catalysts, their application under standard conditions yielded the desired α,β-unsaturated esters in good yields without the need of optimization. In fact, linkage to MeOPEG polymers turned out to be beneficial for this transformation. In comparison to the corresponding *N*-benzyltriazolo precatalyst **Bn-7**, the supported derivatives **7** and **8** generally generated higher yields.

Table 3. Carbene-catalyzed redox esterification with immobilized imidazolium precatalysts.



Entry[a]	Catalyst	Product	Yield[b]	Ratio *E/Z*[c]
1a	**Bn-7**	 **26**	63	11:1
1b	**7**		77	18:1
1c	**8**		83 77[d] 75[e]	>95:5
2	**8**	 **27**	67	8:1
3	**8**	 **28**	63	>95:5
4	**8**	 **29**	59	11:1
5	**8**	 **30**	71	14:1
6	**8**	 **31**	72	8:1
7	**8**	 **32**	28	>95:5

[a] All reactions were performed using 5 mol% catalyst in toluene, 60°C, 12 h.
[b] Isolated yields.
[c] As determined by ^{1}H NMR.
[d] 2nd cycle.
[e] 3rd cycle.

Similar to previous results the diastereoselectivity of the reaction was influenced by the steric hindrance of the catalyst. Whereas the monomesityl-substituted precatalyst **7** gave *E/Z*-ratios of 18:1 (entry 1b), the monoisopropylimidazolium precatalyst **8** essentially provided selectivities of greater than 95:5 (entry 1c). Various aromatic propargylic aldehyde substrates could be transformed to the corresponding esters, irrespective of the electronic nature of the aryl substituent (Table 3).

The attractive transformation proceeds under mild conditions with low catalyst loadings, providing further operational simplicity and practicability through the immobilized catalyst. Simple removal of the catalyst after its precipitation and subsequent aqueous washing of the organic phase allows the direct isolation of the *trans*-configurated unsaturated esters in high yields and with diastereoselectivities, generally greater than 10:1. After having developed an efficient protocol for this transformation, we wondered whether the catalyst could be recycled and reused. NMR spectroscopic analysis of the recovered catalyst promised conserved catalytic activity. Whereas the recyclability of the thiazolium catalyst used for the Stetter reaction was found to be strongly dependent on the reaction conditions, in the case of the redox esterification the immobilized imidazolium catalysts could be recycled very efficiently. Within two further subsequent cycles the recycled imidazolium catalyst remained highly productive (75% yield in 3rd cycle) with virtually no loss in diastereoselectivity (Table 3; entry 1c).

In summary, we have developed a new and efficient, atom-economic immobilization of various heterazolium salts, which could conveniently be prepared *via* Cu-catalyzed [3+2]-cycloaddition. The high catalytic activity of their corresponding carbene derivatives, which is comparable to standard non-supported catalysts, was demonstrated in both intramolecular Stetter reactions and redox esterifications, representing examples of classic and extended umpolung reactions, respectively. Furthermore, mild reaction conditions, low catalyst loadings and simple removal of the supported catalysts contribute to operational simplicity and practicability. Additionally, the successful recycling of different types of heterazolium catalysts offers a highly attractive extension to previously applied carbene-catalyzed procedures.

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Experimental Section

General Procedure for the Immobilization *via* Cu-Catalyzed [3+2]-Cycloaddition

A round-bottom flask was charged with MeOPEG-azide **3**[26] (0.20 mmol) and 6 mL of a degassed 1:1 mixture of H_2O and *t*-BuOH. To this solution was added the propargylated heterazolium salt **2** (1.2 equivs.). After the subsequent addition of ascorbic acid (0.2 equivs.) and CuBr (6 mol%) the solution was allowed to stir at ambient temperature for 24 h (typically). The mixture was extracted three times with CH_2Cl_2; the combined organic phases were washed with water, brine and dried over $MgSO_4$. Concentration under vacuum, followed by precipitation with Et_2O and subsequent filtration afforded the immobilized catalyst as a colorless solid in analytical purity. Catalyst loading was determined by ^1H NMR using the MeOPEG-OCH_3 signal as reference.

General Procedure for the Intramolecular Stetter Reaction with MeOPEG-Thiazolium Precatalysts

To an oven-dried screw-capped, N_2-filled test tube was added thiazolium precatalyst **5** (0.020 mmol, 10 mol%) and 0.6 mL dry $CHCl_3$. To this solution was added DIPEA (0.20 mmol, 1 equiv.) and the mixture was stirred at ambient temperature for 10 min. Subsequently, substrate aldehyde (0.20 mmol, 1 equiv.) was added and the resulting solution was allowed to stir at room temperature for 18 h (TLC control).

Work-up procedure A: After addition of some silica the mixture was stirred for 15 min, followed by filtration to yield the chromanone product.

Work-up procedure B (catalyst recycling): After cooling to 0 °C the reaction mixture was treated with Et_2O to precipitate the catalyst and filtered. After washing with Et_2O and drying under vacuum the separated catalyst could be reused. The resulting filtrate was washed with small amounts of H_2O, dried over $MgSO_4$ and concentrated under reduced pressure to afford pure product.

General Procedure for the Redox Esterification with MeOPEG-Imidazolium Precatalysts

To an oven-dried screw-capped, N_2-filled test tube was added imidazolium precatalyst **8** (0.020 mmol, 5 mol%), and suspended in 0.6 mL dry toluene. To this mixture was added sequentially alkynal aldehyde (0.40 mmol, 1.0 equiv.) in 0.3 mL in dry toluene, alcohol (1.2 mmol, 3 equivs.) and finally DMAP (0.020 mmol, 5 mol%). After exchange of the septum with a screw cap, the sealed tube was stirred at 60 °C for 2 to 12 h (TLC control). The mixture was then cooled to 0 °C, the catalyst was precipitated upon addition of Et_2O and filtered off (the so obtained catalyst can be reused in further reaction cycles without need of purification). The resulting solution was washed with 1.1 M $KHSO_4$ solution and brine and dried over $MgSO_4$. Concentration under reduced pressure afforded the pure unsaturated ester.

Alternatively, addition of small amounts of silica and subsequent filtration yielded the product in similar purity, although without the possibility to recycle the catalyst.

Supporting Information

General experimental conditions, preparation of catalysts and characterization of compounds.

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