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Heterogenization of ferrocene palladacycle catalysts on ROMP-derived monolithic supports and application to a Michael addition†

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The anchoring of well-defined molecular catalysts on a surface is an attractive strategy to develop sustainable catalytic processes. This article describes the first syntheses of monolith-supported ferrocene palladacycle catalysts. Monolithic supports were prepared *via* ring-opening metathesis polymerization (ROMP) using the "1st generation Grubbs catalyst". Fluorinated carboxylates were surface-grafted utilizing living Ru-termini. The immobilization of the palladacycles onto the monolithic support was accomplished by ligand substitution on the fluorinated carboxylates of the graft polymer. An investigation of these supported catalysts on the efficiency and reusability under different reaction conditions in a direct Michael addition generating a quaternary C-atom is reported. Whereas stereoselectivity was found to be significantly lower than in a comparable homogeneous system, Pd-leaching was not detected in all analyzed samples indicating a permanently immobilized catalyst system.

Introduction

Asymmetric synthesis using chiral catalysts is, in principle, the most efficient way to synthesize optically active compounds and is therefore of great importance for both industrial applications and academic research.[1] However, the application of these often expensive chiral catalysts in commercial syntheses is severely limited owing to difficulties in separation and recycling. Therefore, a catalytic system that allows for the straightforward separation of expensive chiral catalysts from the reaction mixture with minimum product contamination by metal leaching and which can be recycled efficiently is highly desirable. Since most of these difficulties are primarily due to the homogeneous nature of the catalysts, the heterogenization by the immobilization of homogeneous catalysts on an inorganic or organic support is considered to be the most promising way to overcome these difficulties.[2] In this context, monolithic supports prepared by ROMP have received considerable attention in recent years.[3] The monolithic supports of this class having suitable porous properties and functional groups can be prepared easily and have been widely used in heterogeneous catalysis as well as in separation science.[4] The low back pressure, easily accessible surface-bound catalytic sites as well as the fast mass transfer of the support allow for the running of such devices in a continuous flow-through set-up with high TONs and low catalyst leaching.[2b] Quite recently, a variety of heterogenization techniques for the immobilization of expensive catalysts and enzymes on a ROMP-derived monolithic support has been reported by Buchmeiser *et al.*[4b,5]

The use of mono- and bimetallic planar chiral palladacycle catalysts in the asymmetric direct conjugate addition of α-cyanoacetates to cyclic enones, forming adjacent quaternary and tertiary stereocenters, has recently been reported by Peters *et al.*[6] Here we report the immobilization of these catalysts: the bimetallic ferrocene bisimidazoline bispalladacycle **FBIP**[7–10] and the monometallic ferrocene imidazoline palladacycle **FIP**[11] on a ROMP-derived monolithic support. The goal of this immobilization technique has been to facilitate the efficient recovery and reuse of the noble-metal catalysts along with high stereoselectivities, comparable to those for the homogeneous catalyst systems.

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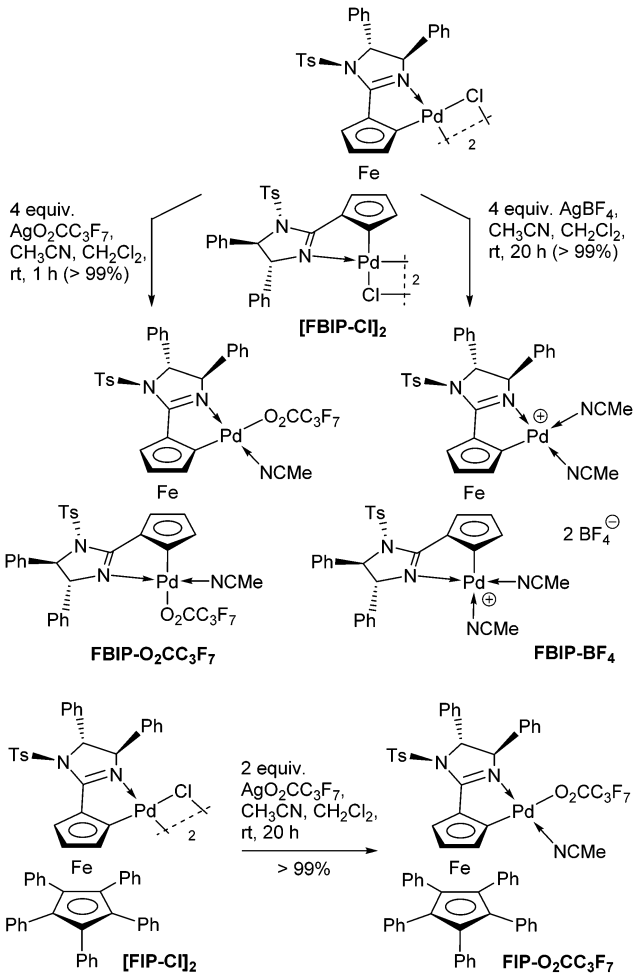
Results and discussion

Transformation of the dimeric precatalysts into monomeric complexes suitable for catalyst grafting

The chiral bimetallic precatalyst **[FBIP-Cl]$_2$** and the monometallic precatalyst **[FIP-Cl]$_2$** exist as dimeric, chloride-bridged species (Scheme 1), which are relatively inert towards ligand exchange.

However, catalytically active monomeric complexes **FBIP-O$_2$CC$_3$F$_7$** and **FIP-O$_2$CC$_3$F$_7$** can be obtained by activation with silver heptafluorobutyrate in dichloromethane containing acetonitrile (Scheme 1).[6a] These activated palladacycles offer high catalytic activity along with a high level of stereocontrol in 1,4-additions of α-cyanoacetates to cyclic enones. In the case of the bis-Pd catalyst a highly organized transition state, in which both metal centers cooperate, has been proposed to be responsible for the good stereocontrol.[6,12] We envisaged that catalyst immobilization might be achieved through a ligand exchange of these complexes with the carboxylate groups of the grafted polymer.

In addition, we have investigated the use of the biscationic complex **FBIP-BF$_4$** containing BF_4^- as counterion. **FBIP-BF$_4$** was obtained by the analogous reaction of the precatalyst **[FBIP-Cl]$_2$** with silver tetrafluoroborate–acetonitrile in dichloromethane.



Scheme 1 Activation of the precatalysts **[FBIP-Cl]$_2$** and **[FIP-Cl]$_2$** by silver salts to form the monomeric homogeneous catalysts.

Synthesis of monolithic supports

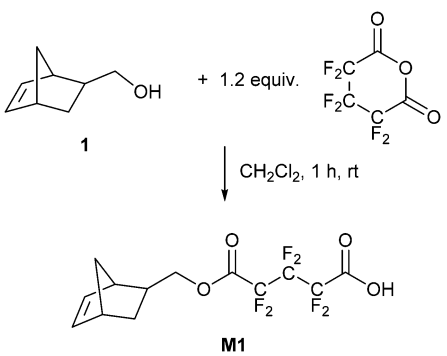
The ROMP-derived monolithic support was prepared from NBE and $(NBE–CH_2O)_3SiCH_3$ in a suitable mixture of porogens by using the "1st generation Grubbs catalyst", $RuCl_2(PCy_3)_2(=CHPh)$, according to a previously published protocol.[3a,5d,13] After rod formation, the 'living' ruthenium termini located at the surface were used for the grafting of the functional monomers. Earlier, Buchmeiser *et al.* reported a successful immobilization of a Ru-based metathesis initiator *via* the halogen exchange by a fluorinated carboxylate ligand.[5d] This approach was more straightforward and convenient as there are no intermediate steps involved. In addition, the unreacted catalyst can be fully recovered.

Synthesis of supported catalyst C1a *via* surface grafted monomer M1

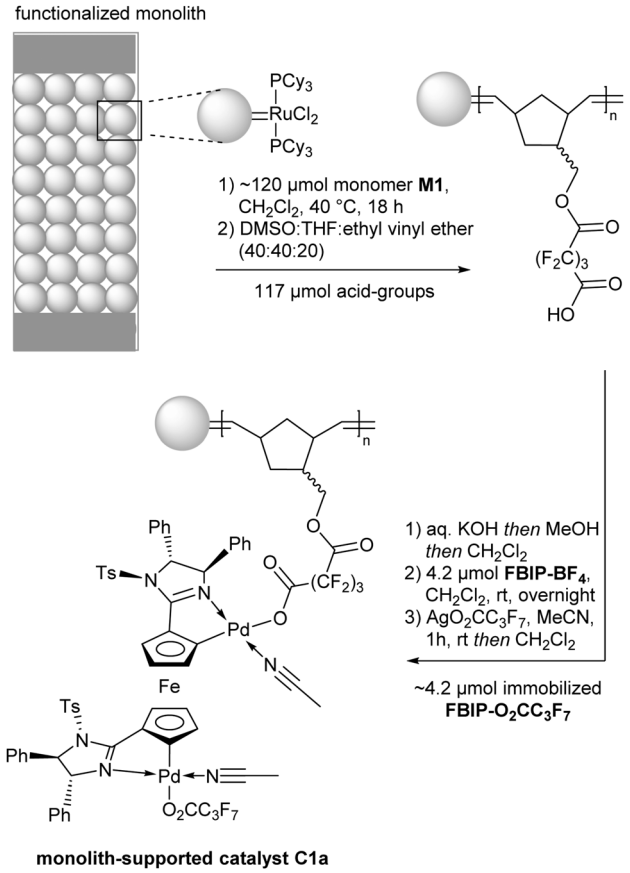
We began the immobilization following a previously published procedure,[5d] where mono(norborn-5-ene-2-ylmethyl) hexafluoroglutarate (**M1**) was used as the functional monomer. Monomer **M1** can be readily obtained by a simple ring-opening of hexafluoroglutaric anhydride with 5-norbornene-2-methanol (**1**) in dichloromethane (Scheme 2).[5d]

After the reaction, the solution containing **M1** was used as such without further purification and grafted on to the monolithic surface *via* the living Ru-termini (Scheme 3). The initiator was removed by extensive flushing with a mixture of DMSO : THF : EVE (ethylvinylether) (40 : 40 : 20), which results in a ruthenium free monolithic matrix as evidenced by inductively coupled plasma optical emission spectroscopy (ICP-OES) measurements.[3a,c] The amount of chemically accessible carboxylate groups of the graft polymer were quantified at this stage by acid–base titration using phenolphthalein as indicator. For this purpose, a known volume of standard KOH solution was injected into the monolith. The amount of carboxylate groups were determined by comparing the concentration of this solution with the one of a standard KOH solution. This way, a carboxylic acid content of 370 μmol g^{-1}, was found.

The potassium carboxylate groups of the graft polymer were directly utilized for the immobilization of the activated complex **FBIP-BF$_4$**. The remaining BF_4^- counterion in the grafted complex



Scheme 2 Synthesis of functional monomer **M1**.



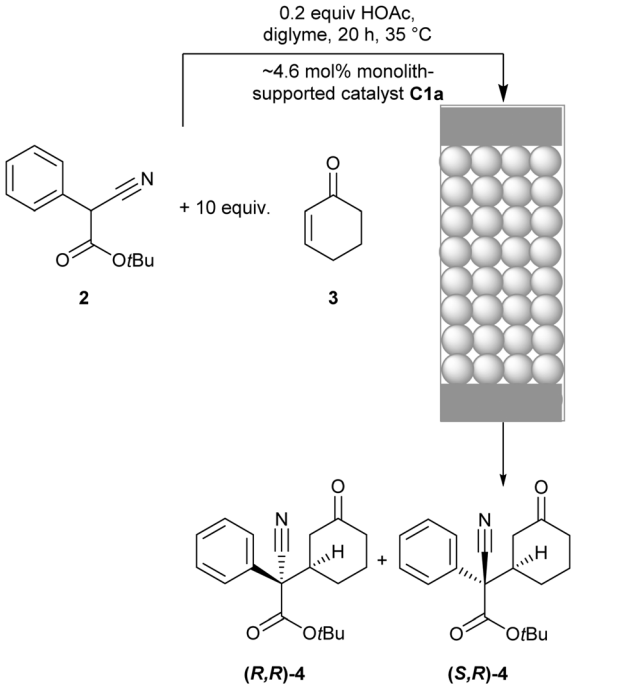
Scheme 3 Synthesis of monolith-supported catalyst **C1a** *via* immobilization of **FBIP-BF$_4$** by carboxylate groups.

was subsequently substituted by an excess of silver heptafluorobutyrate. Following this procedure, **FBIP** was bound to the support with a concentration of 20 mg g^{-1}. Since the complex is intensively dark-red, any leaching of the complex would be easily determined in the eluent. To our pleasure, no leaching of the catalyst was observed, indicative for a successful immobilization of the catalyst (Scheme 3).

Catalytic performance of the supported catalyst C1a

To study the activity of the **FBIP** derived monolith-supported catalyst **C1a**, the 1,4-addition of *tert*-butyl-2-cyano-2-phenylacetate (**2**) to 2-cyclohexen-1-one (**3**) was carried out in diglyme at 35 °C. All catalytic experiments using supported catalysts described in this article have been done under sealed conditions. In the optimized homogeneous version of this reaction using **FBIP-O$_2$CC$_3$F$_7$** as catalyst the (*R*,*R*)-diastereomer **4** is formed in excess with high enantioselectivity, whereas the enantioselectivity for the epimer is only moderate (Table 1, entry 1). The results of the same transformation using the monolith-supported catalyst **C1a** are also summarized in Table 1. Despite the successful immobilization, variations in the results of four identical experiments in terms of conversion and selectivity (Table 1, entries 2 to 5) indicate that a gradual decomposition of the catalytic species or the linker between monolith and catalyst might occur.

Table 1 Results of the Michael addition reaction using the supported catalyst **C1a**[a]



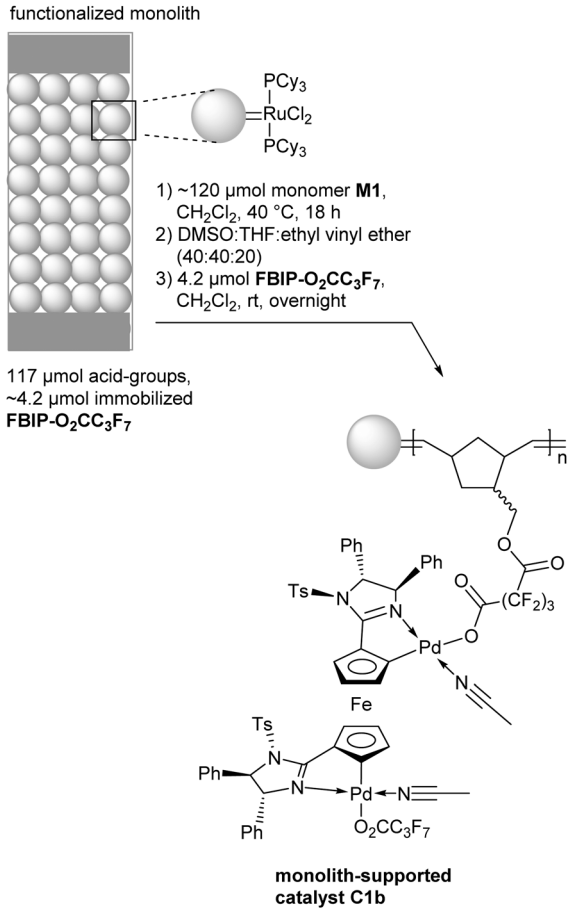
Entry	Yield[b] [%]	ee$_{(R,R)}$[c] [%]	ee$_{(S,R)/(R,S)}$[c,d] [%]	dr[c,e]
1[f]	99	94	65	89 : 11
2	41	68	−4	41 : 59
3	29	50	5	41 : 59
4	54	22	5	52 : 48
5	36	28	4	57 : 43

[a] Conditions: diglyme, 92 µmol of **2**, 10 equiv. of **3**, 0.2 equiv. of HOAc, 0.2 mL of diglyme. All results (if not indicated otherwise) were produced with identical monolithic support. [b] Determined by ^{1}H NMR spectroscopy using an internal standard. [c] Determined by HPLC. [d] A minus sign indicates that the (*R*,*S*)-enantiomer is formed in excess. [e] (*R*,*R* + *S*,*S*):(*S*,*R* + *R*,*S*). [f] Under optimized conditions using the homogeneous **FBIP-O$_2$C$_4$F$_7$** catalyst,[6a] 92 µmol of **2**, 2 equiv. of **3**, 1 mol% of **FBIP-O$_2$C$_4$F$_7$**, 0.2 equiv. of HOAc, 0.17 mL of diglyme.

Alternative route to the supported catalyst C1b by direct immobilization and application of C1b

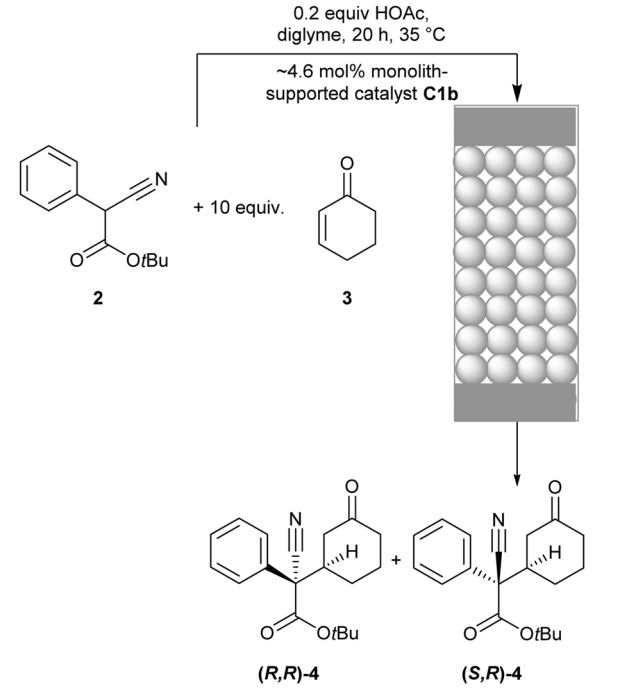
In order to overcome the inconsistencies in the catalytic activities of the supported catalyst, the immobilization was carried out *via* an approach, by which the supported catalyst was obtained directly carrying the desired heptafluorobutyrate counterion. This alternative synthesis of the supported catalyst used the direct substitution of one heptafluorobutyrate ligand of **FBIP-O$_2$C$_4$F$_7$** by free carboxylic acid groups of the graft polymer thus releasing heptafluorobutyric acid as side product (Scheme 4).

The driving force of this method is the almost 30-fold excess of free acid groups on the monolith relative to the injected catalyst. The difference of the pK_a values of heptafluorobutyrate (pK_a ≈ 0.63)[14] and of the carboxylate group of the graft polymer (pK_a ≈ 0.6)[14] is very small and should only slightly influence the equilibrium. Following this procedure, **FBIP-O$_2$C$_4$F$_7$** was bound to the support with a concentration of 20 mg g^{-1}.



Scheme 4 Alternative route to the monolith-supported catalyst **C1b** *via* direct immobilization of **FBIP-O$_2$CC$_3$F$_7$**.

Table 2 Results of the Michael addition reactions using the supported catalyst **C1b**[a]



Entry	Yield[b] [%]	ee$_{(R,R)}$ [c] [%]	ee$_{(S,R)/(R,S)}$ [c,d] [%]	dr[c,e]
1[f]	99	94	65	89 : 11
2	56	56	0	50 : 50
3	51	60	3	48 : 52
4[g]	27	27	−14	48 : 52
5	27	52	4	42 : 58
6[h]	40	87	−5	52 : 48
7[h]	35	38	7	52 : 48

[a] Conditions: diglyme, 92 µmol of **2**, 10 equiv. of **3**, 0.2 equiv. of HOAc, 0.2 mL of diglyme. All results (if not indicated otherwise) were produced with identical monolithic support. [b] Determined by ^{1}H NMR spectroscopy using an internal standard. [c] Determined by HPLC. [d] A minus sign indicates that the other enantiomer is formed in excess. [e] (*R*,*R* + *S*,*S*):(*S*,*R* + *R*,*S*). [f] Under optimized conditions using the homogeneous **FBIP-O$_2$C$_4$F$_7$** catalyst,[6a] 92 µmol of **2**, 2 equiv. of **3**, 1 mol% of **FBIP-O$_2$C$_4$F$_7$**, 0.2 equiv. of HOAc, 0.17 mL of diglyme. [g] 5 equiv. of **3**. [h] 180 µmol of **2**, 10 equiv. of **3**, 0.2 equiv. of HOAc, 0.2 mL of solvent.

No catalyst leaching was observed indicative of a quantitative immobilization of the catalyst. In contrast to the first synthesis of the supported catalyst, no base was necessary for catalyst immobilization. Thus no base-catalyzed product formation has to be expected as competing reaction pathway, which might have been an issue in the previous approach.

The results of the enantioselective Michael additions using this supported catalyst **C1b** are summarized in Table 2. Under the studied conditions moderate to good enantiomeric excess was obtained for the (*R*,*R*)-diastereomer, while the (*S*,*R*)/(*R*,*S*)-isomer was formed in almost racemic form. However, the ee's, diastereomeric ratios, as well as the yields of the conjugate addition product **4** were changing from run to run and no obvious trend was found.

Nevertheless, there is some improvement of the enantioselectivity for the (*R*,*R*)-isomer compared to the previous approach and an ee of up to 87% could be attained in one run (Table 2, entry 6). However, there are several important criteria that an immobilized chiral catalyst should fulfil in order to be useful for a chemical process. In general, it is of interest to evaluate a supported catalyst in terms of activity, stereoselectivity, stability, homogeneous distribution on the solid support and reusability. In order to fulfil the above outlined features, the catalyst should ideally be immobilized in a way that the geometry of the homogeneous catalyst is maintained in the heterogeneous mode. In fact this is a critical issue due to the interactions of the catalyst with the support, which often leads to a negative change in enantioselectivity.[2d] At this stage, both the stability and accessibility of the linker ligand should be taken into account. Hydrolyzable groups such as ester moieties at the functionalized monomer should ideally be avoided to guarantee stability of the linker under the conditions of catalysis. Furthermore, a homogeneous distribution of the catalyst over the support is an important issue. Analysis of the support after usage showed in the above-described case an inhomogeneous distribution of the catalyst with a decreasing catalyst concentration from the top to the bottom of the column (Fig. 1). The reaction rate on the top and bottom of the column can be expected to differ significantly and the consequence might be an incomplete conversion.

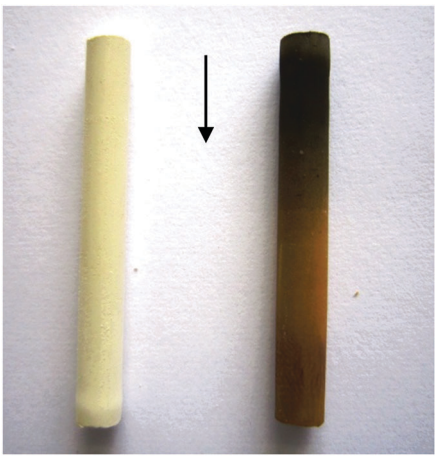


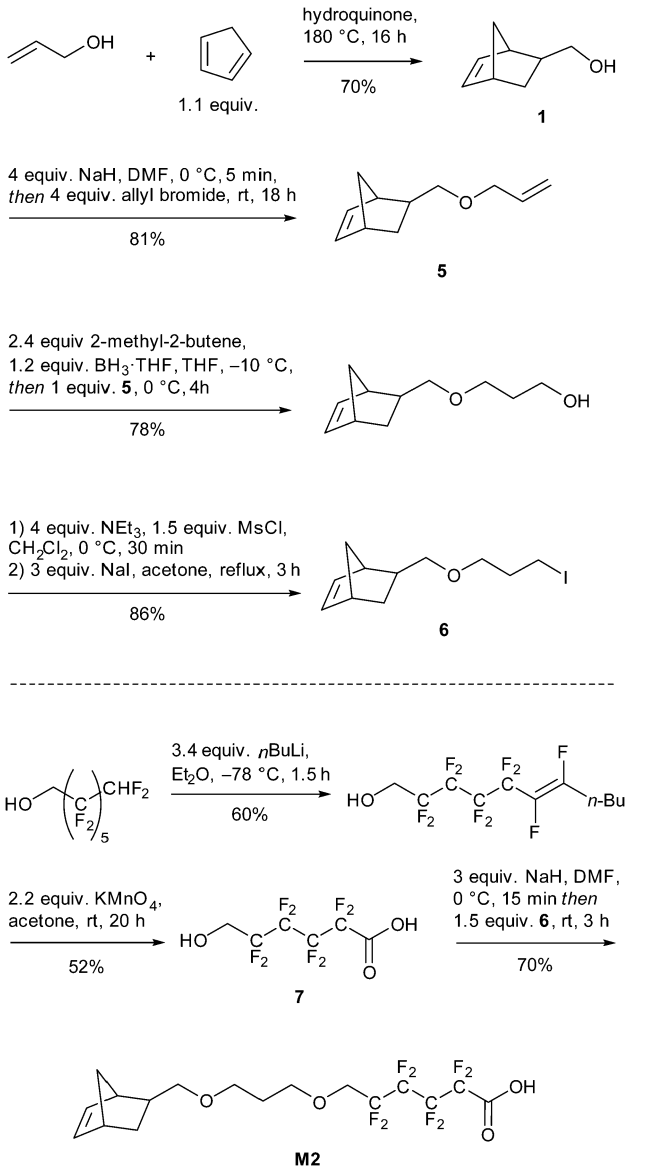
Fig. 1 Left: monolithic support without immobilized catalyst. Right: monolithic support with immobilized **FBIP-O$_2$CC$_3$F$_7$** (monolith supported catalyst **C1b**). Flow direction from top to bottom, indicated by the arrow.

Synthesis of the supported catalyst C2 *via* surface-grafted monomer M2

To overcome the above issues, the fluorinated monomer (**M2**) having a sufficient chain length with no readily hydrolyzable groups was synthesized in six steps from **1** (Scheme 5). The synthesis of the functionalized monomer **M2** was accomplished by the coupling of fragment **6** with the sodium alcoholate of **7** in dry DMF. Compounds **6**[15] and **7**[16] were in turn synthesized starting from 5-norbornene-2-methanol (**1**) and 1*H*,1*H*,7*H*-dodecafluoro-1-heptanol, respectively, following a previously published protocol. The new designed monomer **M2** was expected to have a sufficient chain length to connect the complex and the support, so that the complex can move far away from the solid surface and into the liquid phase. This should maintain the geometry of the supported catalysts to a better extent similar to the homogeneous system, while the CF_2-groups of the linker contribute to the electronic structure of the palladium-center similar as the heptafluorobutyrate counterion, which has significant influence on the stereoselectivity outcome of the homogeneous reaction.[6] In addition, the absence of any hydrolyzable groups in monomer **M2** should improve the stability of the linker ligand thereby reducing the leaching of both the metal and ligand. Therefore monomer **M2** should also improve the reusability of the supported-catalysts.

As described above, monomer **M2** was surface-grafted onto the ROMP-derived monolith and then treated with the activated complex **FBIP-O$_2$C$_4$F$_7$** to achieve the supported catalyst **C2** (Scheme 6). The amount of grafted monomer **M2** and thereby the amount of free acid groups of the monolith was reduced to 50 μmol to provide a more uniform distribution of the catalyst all over the monolith.

Immobilization was again achieved through the direct substitution of the heptafluorobutyrate counterion of the activated complex **FBIP-O$_2$CC$_3$F$_7$** by the free acid groups of the functionalized monolith. This way, 83% (3.67 μmol) of the **FBIP-O$_2$C$_4$F$_7$** complex used were bound to the support. The remaining 17% were recovered as precatalyst **[FBIP-Cl]$_2$**, indicating a successful immobilization. The amount of immobilized catalyst after the

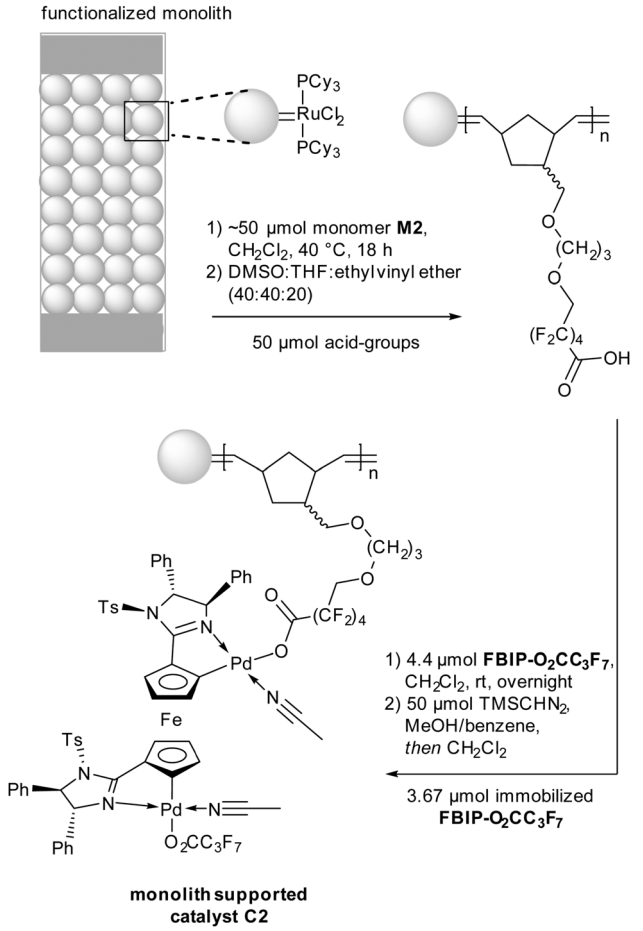


Scheme 5 Synthesis of the functional monomer **M2**.

performed catalysis reactions was calculated from the Pd-amount of the monolith, determined by ICP-OES (see the ESI†). The excess of acid groups on the monolith was transformed into the corresponding methyl esters by $TMSCHN_2$, because the pK_a value of the Brønsted-acid co-catalyst (usually HOAc) has previously been shown to have a strong influence on the selectivity of the reaction and a negative influence has been observed for strong acids such as trifluoroacetic acid.[6a] With the new monomer **M2** and a reduced amount of free carboxylic acid groups on the monolith a consistent distribution of the catalyst **FBIP-O$_2$CC$_3$F$_7$** has been achieved (Fig. 2, supported catalyst **C2** shown after use in catalysis).

Catalytic performance of the supported catalyst C2

The catalytic activity of the supported catalyst **C2** was again investigated by the asymmetric Michael addition of *tert*-butyl-2-cyano-2-phenylacetate (**2**) to 2-cyclohexen-1-one (**3**) to form the



Scheme 6 Synthesis of the **FBIP**-containing monolith-supported catalyst **C2**.

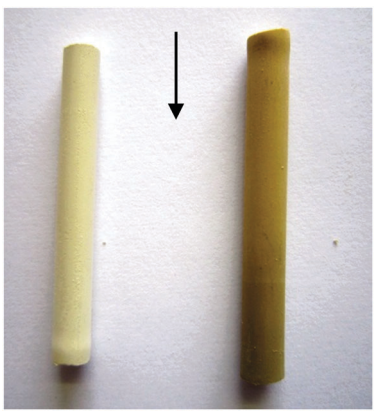
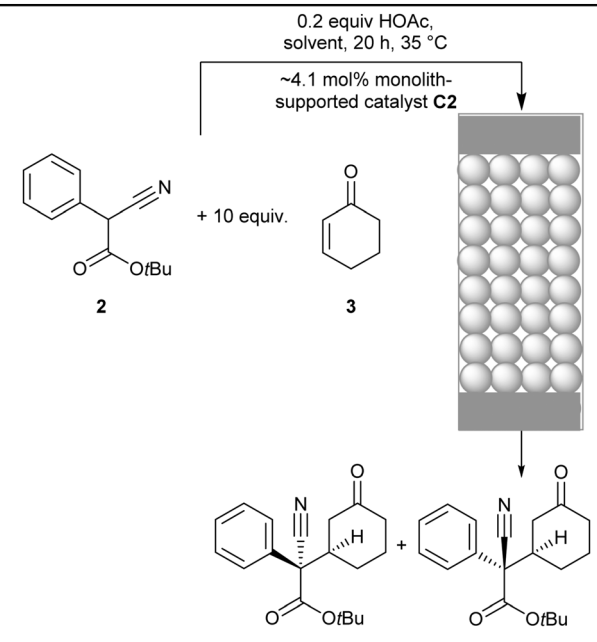


Fig. 2 Left: monolithic support without immobilized catalyst. Right: monolithic support with immobilized **FBIP-$O_2C_3F_7$** (monolith supported catalyst **C2**). Flow direction from top to bottom, indicated by the arrow.

densely functionalized product **4**.[17,18] The results of a solvent screening using 3.67 µmol of the immobilized catalyst **C2** (Table 3, entries 2 to 5) and the results with diglyme as preferred solvent are summarized in Tables 3 and 4, respectively.[19]

The reaction in CH_2Cl_2 proceeded with poor yield while the enantioselectivity was good for the major (*R*,*R*)-isomer

Table 3 Results of the Michael addition reactions carried out by using the supported catalyst **C2** and different solvents[a]



Entry	Solvent	Yield[b] [%]	$ee_{(R,R)}$[c] [%]	$ee_{(S,R)/(R,S)}$[c,d] [%]	dr[c,e]
1[f]	Diglyme	99	94	65	89 : 11
2	CH_2Cl_2	2	69	−22	73 : 27
3	Diglyme	29	66	27	63 : 37
4	Et_2O	15	72	4	59 : 41
5	EtOAc	98	12	0	59 : 41

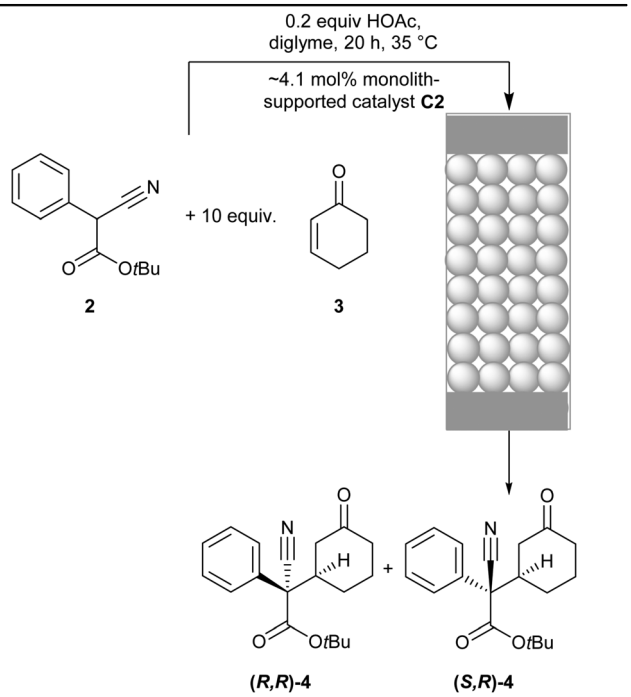
[a] Conditions: 92 µmol of **2**, 10 equiv. of **3**, 0.2 equiv. of HOAc, 0.2 mL of solvent. All results (if not indicated otherwise) were produced with identical monolithic support. [b] Determined by ^{1}H NMR spectroscopy using an internal standard. [c] Determined by HPLC. [d] A minus sign indicates that the (*R*,*S*)-enantiomer has been formed in excess. [e] (*R*,*R* + *S*,*S*):(*S*,*R* + *R*,*S*). [f] Under optimized conditions using the homogeneous **FBIP-$O_2C_4F_7$** catalyst,[6a] 92 µmol of **2**, 2 equiv. of **3**, 1 mol% of **FBIP-$O_2C_4F_7$**, 0.2 equiv. of HOAc, 0.17 mL of diglyme.

(Table 3, entry 2). More promising were the results of reactions carried out in diglyme and diethylether (Table 3, entries 3 and 4),[20] where 66% and 72% ee were obtained for the major diastereomer, while the minor diastereomer was formed in almost racemic form. High yields were obtained with ethyl acetate as solvent (Table 3, entry 5), but the product was formed in almost racemic form. Diglyme was chosen as solvent for further experiments to examine the stability and reusability of the catalyst system (Table 4).

The results showed varying yields between 9 and 80% of the Michael addition product **4**, while the ee of the (*R*,*R*)-diastereomer maintained in a moderate range and was still not constant. The enantioselectivity of the (*S*,*R*)/(*R*,*S*)-diastereomer was rather low. Interestingly, starting from the second run this isomer was formed as the major product, whereas in the first run the (*R*,*R*)-diastereomer was preferred.

All analysed reaction samples did not show any palladium-leaching and only negligible Fe-amounts were determined by ICP-OES (see the ESI†). Loss of Pd in the catalyst and cleavage

Table 4 Results of the Michael addition reactions carried out by using diglyme and the supported catalyst **C2**[a]



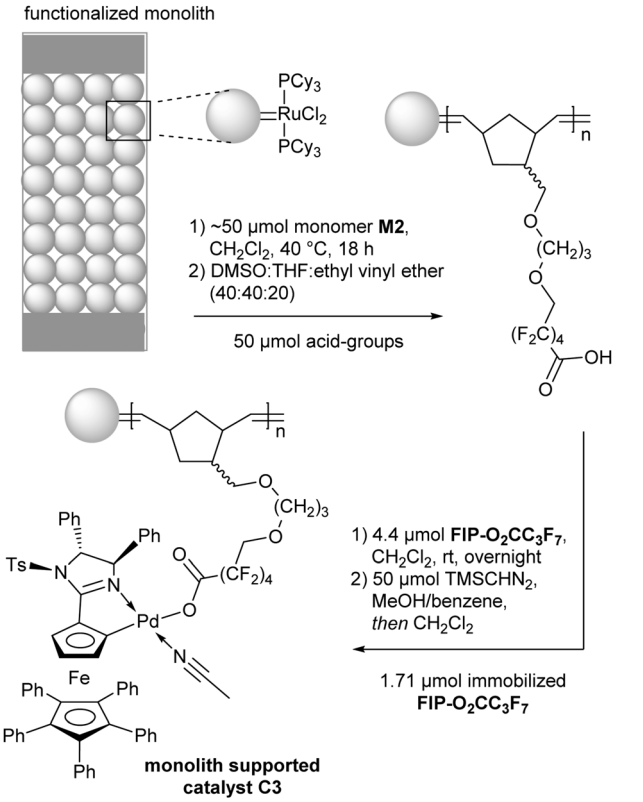
Run	Yield[b] [%]	$ee_{(R,R)}$[c] [%]	$ee_{(S,R)/(R,S)}$[c,d] [%]	dr[c,e]
1	29	66	27	63 : 37
2	9	50	16	48 : 52
3	23	43	13	44 : 56
4	26	54	9	37 : 63
5	68	34	11	30 : 70
6	14	24	8	42 : 58
7	44	46	4	32 : 68
8	80	39	10	28 : 72
9	53	40	7	30 : 70
10	47	17	2	31 : 69
11	38	41	2	28 : 72

[a] Conditions: 92 μmol of **2**, 10 equiv. of **3**, 0.2 equiv. of HOAc, 0.2 mL of diglyme. All results were produced with identical monolithic support. [b] Determined by ^{1}H NMR spectroscopy using an internal standard. [c] Determined by HPLC. [d] A minus sign indicates that the (*R*,*S*)-enantiomer has been formed in excess. [e] (*R*,*R* + *S*,*S*):(*S*,*R* + *R*,*S*).

of the linker unit between catalyst and monolith under the reaction conditions can thus be excluded. On the other side, the permanently changing stereoselectivity might be partly explained by a changing environment of the Pd-centers, *e.g.* caused by product ligation.

Synthesis of the supported catalyst C3 *via* surface-grafted M2

A highly enantioselective preferred formation of the (*S*,*R*)/(*R*,*S*)-diastereomer of **4** has been previously described with the monometallic catalyst **FIP-$O_2CC_3F_7$** in a homogeneous reaction system.[6a] Since the results presented above show similar preferences for the (*S*,*R*)/(*R*,*S*)-diastereomer after the first run in diglyme, the immobilization of the monometallic palladacycle **FIP-$O_2CC_3F_7$** on the **M2**-based graft-polymer was investigated and applied to the conjugate addition of *tert*-butyl-2-cyano-2-phenylacetate (**2**) to 2-cyclohexen-1-one (**3**). The heterogenization



Scheme 7 Synthesis of the **FIP**-containing monolith-supported catalyst **C3**.

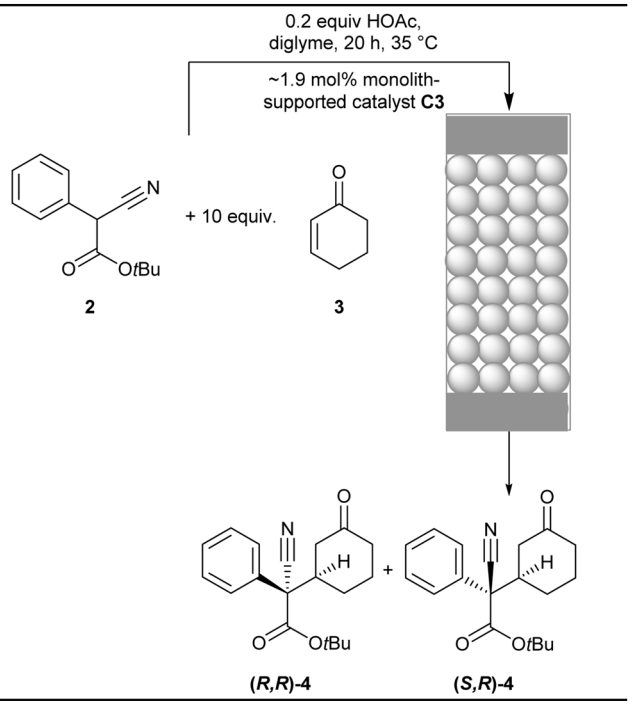
of **FIP-$O_2CC_3F_7$** was accomplished in analogy to **FBIP-$O_2CC_3F_7$** *via* direct immobilization using the free acid groups of the monolithic support, followed by esterification of the residual carboxylic acid groups with $TMSCHN_2$ (Scheme 7). Following this procedure, 39% (1.71 μmol) of the injected catalyst (4.4 μmol) were immobilized, while the rest was recovered as precatalyst **[FIP-Cl]$_2$**. Again, the amount of immobilized catalyst was calculated after the catalytic runs from the Pd-amount of the monolith, determined by ICP-OES (see the ESI†).

Catalytic performance of the supported catalyst C3

Diglyme was used as solvent for catalysis, to allow for a direct comparison with the catalytic performance of the monolith-supported catalyst **C2** (*vide supra*). In the first two runs almost quantitative yields of **4** were obtained (Table 5, entries 2 and 3). However, in the subsequent reactions the yield dropped to <10% (Table 5, entries 4 to 8). The (*R*,*R*)-diastereomer was formed with low to moderate enantioselectivity, while the (*S*,*R*)/(*R*,*S*)-diastereomer was formed in almost racemic form. As expected the latter (*S*,*R*)/(*R*,*S*)-diastereomer is formed in excess.

Albeit the immobilization of the monometallic catalyst **FIP** proceeds with lower yield (39% immobilization compared to 88% immobilization with the bimetallic catalyst **FBIP** under otherwise identical conditions) no palladium leaching occurred during the catalytic runs. The analyzed catalysis reaction samples contained no Pd and only negligible amounts of Fe were determined by ICP-OES (see the ESI†). The loss of enantioselectivity compared to the homogeneous reaction can be tentatively

Table 5 Results of the Michael addition reactions carried out by using the supported catalyst **C3**[a]



Entry	Yield[b] [%]	$ee_{(R,R)}$[c] [%]	$ee_{(S,R)/(R,S)}$[c,d] [%]	dr[c,e]
1[f]	90	33	89	29 : 71
2	99	59	1	35 : 65
3	97	45	−1	31 : 69
4	6	20	−7	32 : 68
5[g]	9	17	−2	39 : 61
6	8	23	4	31 : 69
7	6	25	4	30 : 70
8	6	12	10	33 : 67

[a] Conditions: 92 μmol of **2**, 10 equiv. of **3**, 0.2 equiv. of HOAc, 0.2 mL of diglyme. All results (if not indicated otherwise) were produced with identical monolithic support. [b] Determined by ^{1}H NMR spectroscopy using an internal standard. [c] Determined by HPLC. [d] A minus sign indicates that the (*R*,*S*)-enantiomer has been formed in excess. [e] (*R*,*R* + *S*,*S*):(*S*,*R* + *R*,*S*). [f] Under optimized conditions using the homogeneous **FIP-O$_2$C$_4$F$_7$** catalyst,[6a] 92 μmol of **2**, 2 equiv. of **3**, 1 mol% of **FIP-O$_2$CC$_3$F$_7$**, 0.2 equiv. of HOAc, 0.17 mL of diglyme. [g] Reaction time of 3 d.

ascribed to the different catalyst environment, affected by the monolithic support, and the lower amount of immobilized catalyst. Nevertheless, the diastereoselectivity was comparable to the homogeneous reaction.

Conclusions

Two methodologies are described for the heterogenization of planar chiral palladacycle catalysts on ROMP-derived monolithic supports using either potassium carboxylate groups or free acid groups (to avoid traces of basic impurities) on the monolith. Furthermore, the application of the new, hydrolysis-stable monomer **M2** in the graft-polymers was examined in terms of stability and influence on the activity of the bound catalyst. Immobilization of the mono- and bimetallic catalysts **FIP-O$_2$CC$_3$F$_7$** and **FBIP-O$_2$CC$_3$F$_7$** was accomplished *via* substitution of the heptafluorobutyrate counterion by carboxylate-groups of the functionalized monolith. Activity, selectivity and reusability of the monolith-supported catalysts were studied for the Michael addition of *tert*-butyl-2-cyano-2-phenylacetate (**2**) to 2-cyclohexen-1-one (**3**) to form the addition product **4** with adjacent quaternary and tertiary stereocenters. Moderate to good enantiomeric excesses were attained for the (*R*,*R*)-isomer, while the (*S*,*R*)/(*R*,*S*)-diastereomer was usually formed in almost racemic form. Often this latter diastereomer was formed in excess, comparable to the monometallic catalyst **FIP-O$_2$CC$_3$F$_7$** in the homogeneous reaction. The loss of the immobilized catalysts was investigated by ICP-OES measurements: no Pd-leaching and negligible Fe-amounts were detected in all analyzed reaction samples, indicating a permanently immobilized catalyst system. However, the steadily changing stereoselectivity data from run to run suggest that the nature/composition of the catalyst is also changing from run to run. Compared to the recently developed homogeneous version of this reaction, both the diastereoselectivity as well as the enantioselectivity are considerably lower. This indicates that interactions between the catalytically active centers and either the monolithic support or the linkers used have a negative impact. Nevertheless, this study has established the proof of principle for a successful immobilization of ferrocene derived planar chiral palladacycles. The new immobilization procedure and the novel graft-polymer system might be interesting for other catalytic reactions.

Experimental

General remarks

All reactions were performed under a nitrogen atmosphere in a glovebox or in oven dried (150 °C) glassware and were magnetically stirred. A positive pressure of nitrogen (*ca.* 0.2 bar) was used as protective atmosphere for Schlenk technique. For all reactions liquids and solutions were added *via* syringe and septa. Working with the PEEK columns all solvents, reagents and reaction mixtures were injected by luer lock syringe technique using a syringe pump. Solvents were removed by rotary evaporation at 40 °C bath temperature and 600–10 mbar pressure or by a constant stream of nitrogen. Non-volatile compounds were dried *in vacuo* at 0.1 mbar.

Diethyl ether, tetrahydrofuran (THF), toluene, *n*-pentane, acetonitrile and dichloromethane were distilled and further purified by an MBraun solvent purification system. Diglyme (anhydrous, >99.5%) was stored over 4 Å molecular sieves in crown capped bottles under nitrogen atmosphere. 2-Cyclohexen-1-one (**3**, >98%) was distilled in vacuum prior to use and stored at −30 °C under inert atmosphere. The precatalysts **[FBIP-Cl]$_2$** (ref. 7*a* and *c*) and **[FIP-Cl]$_2$**,[11a] *tert*-butyl-2-cyano-2-phenylacetate[21] **2** and the activated catalysts **FBIP-O$_2$CC$_3$F$_7$** and **FIP-O$_2$CC$_3$F$_7$** (ref. 6*a*) were prepared according to literature procedures. Preparation of the monolithic support inside a PEEK column (100 × 7 mm i.d.) and grafting of functionalized monomer **M1** to the monolithic support was performed according to literature procedures.[5b,d] All other chemicals were purchased

and used without any further purification. For work-up procedures and column chromatography distilled technical grade solvents (CH_2Cl_2, diethyl ether, petrol ether and ethyl acetate) were used.

Reactions were either monitored by HPLC (Hewlett Packard Series 1050, reverse phase, acetonitrile–water as eluent) or by thin layer chromatography (TLC) with silica-plates (silica gel 60 F_{254}). Visualization was achieved by fluorescence quenching under UV light (λ = 254 nm) and/or by staining with basic $KMnO_4$-solution (1.5 g $KMnO_4$, 10 g K_2CO_3, 5 mL 1 M NaOH in 200 mL water). Preparative column chromatography for compound purification was performed on silica (0.040–0.063 mm), using a positive pressure of nitrogen (*ca.* 0.2 bar). Yields refer to pure isolated products and are calculated in mol% of the used starting material. Conversions refer to unconsumed cyanoacetate **2** and were either determined by ^{1}H-NMR using an internal standard or by RP-HPLC with a corresponding calibration curve. The dr- and ee-values of the Michael addition products **4** were determined by chiral stationary phase HPLC (ELITE LaChrom with Hitachi-modules and a Chiracel OD-H column, iPrOH : heptane (99 : 1) as eluent at a flow of 0.9 mL min^{-1}, room temperature, 210 nm). The assignment of the configuration of product **4** is based on comparison of the HPLC retention times with literature data.[6a]

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance 250, Bruker Avance 500 or Bruker Avance III 400 spectrometer at 25 °C operating at 250, 500 or 400 MHz for ^{1}H and 63, 125 or 100 MHz for ^{13}C. ^{19}F NMR spectra were recorded at 235 MHz. $CDCl_3$ was distilled from CaH_2 and stored over molecular sieves (4 Å). Other deuterated solvents were used without further purification and are mentioned after the corresponding frequency. Chemical shifts in ppm refer to tetramethylsilane (δ = 0) as internal standard. Coupling constants J are given in Hz and the following abbreviations are used for multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), b (broad signal). GC-MS data were recorded on an Agilent Technologies device consisting of a 7693 autosampler, a 7890A GC and a 5975C quadrupole mass detector. Dodecane was used as internal standard. An SPB-5 fused silica column (34.13 m × 0.25 mm × 0.25 μm film thickness) was used. The injection temperature was set to 150 °C. The column temperature ramped from 45 °C to 250 °C within eight minutes, and was then held for further five minutes. The column flow was 1.05 mL min^{-1}. IR spectra were recorded with a Bruker Vector 22 with an Mk II Golden Gate ATR-unit from Speace. Signals are listed by wave numbers (cm^{-1}). Metal contents of the columns and of catalysis samples were determined by ICP-OES measurements on an Ametek Spektro Arcos instrument. High resolution mass spectra were recorded on a Bruker MicroTOFQ instrument using ESI for ionization.

Activation of the precatalyst [FBIP-Cl]$_2$ with silver tetrafluoroborate–acetonitrile: bis(diacetonitrile)[μ-(1*S*$_p$,1′*S*$_p$)-2,2′-bis[(4*R*,5*R*)-4,5-dihydro-1-[(4-methyl-phenyl)sulfonyl]-4,5-diphenyl-1*H*-imidazol-2-yl-κ*N*3]-1,1′-ferrocendiyl-κ*C*1:κ*C*1′]di-palladium(II) di-tetrafluoroborate (FBIP-BF$_4$). Silver tetrafluoroborate (7.04 mg, 36 μmol, 4 equiv.) was dissolved in acetonitrile (~2 mL) and the solution was stirred for a few minutes. The solvent was then removed by a constant stream of nitrogen. A solution of the precatalyst **[FBIP-Cl]$_2$** (22.0 mg, 9 μmol, 1 equiv.) in CH_2Cl_2 (1 mL per 5 mg silver salt) was added and the suspension was stirred overnight at room temperature. Afterwards the suspension was filtrated over celite and the solvent was removed *in vacuo* at room temperature to give pure **FBIP-BF$_4$** as a red solid (26.7 mg, 18 μmol, quantitative). $C_{62}H_{56}B_2F_8FeN_8O_4Pd_2S_2$, MW: 1483.59 g mol^{-1}. Mp.: decomposition > 200 °C. $[\alpha]_D^{20}$: +22.4 (c = 0.10, CH_2Cl_2) ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.46–7.44 (m, 8H, arom. H), 7.33 (b, 4H, arom. H), 7.27–7.25 (m, 4H, arom. H), 7.21–7.18 (m, 4H, arom. H), 7.08 (t, J = 7.5, 4H, arom. H), 6.58 (t, J = 7.4, 4H, arom. H), 5.59 (b, 2H), 4.93 (b, 4H), 4.54 (b, 2H), 2.47 (s, 6H, CH_3), 2.12 (s, free CH_3CN), 1.71 (b, 6H, Pd ← CH_3CN), 1.51 (b, 6H, Pd ← CH_3CN). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 144.7, 138.2, 131.1, 128.8, 127.9, 127.4, 127.1, 126.9, 125.7, 124.3, 123.6, 121.3, 73.6, 71.9, 51.6, 20.0. ^{19}F NMR (235 MHz, $CDCl_3$, 25 °C): δ = −151.6, −151.7. IR (in $CDCl_3$): 3142, 3064, 3033, 2937, 2324, 2296, 1595, 1553, 1465, 1453, 1365, 1305, 1260, 1171, 1100, 1051, 970. MS (ESI) m/z: 122.03 ([M − 4CH$_3$CN − BF$_4$]$^+$, 11%), 573.01 ([M − 4CH$_3$CN − 2BF$_4$]$^{2+}$, 100%). HRMS (ESI) m/z: calcd for [M − 4CH$_3$CN − 2BF$_4$]$^{2+}$: 573.0119; found: 573.0106; calcd for [M − 4CH$_3$CN − BF$_4$]$^+$: 1233.0280; found: 1233.0282.

Immobilization of planar chiral palladacycle catalysts on ROMP-derived monolithic supports

Immobilization of FBIP-BF$_4$ *via* potassium carboxylate groups on the graft-polymer with M1: monolith-supported catalyst C1a. An aqueous solution of KOH (10 mL, 5.2 mM) was introduced to the monolith grafted with **M1** (~120 μmol) at a flow rate of 0.1 mL min^{-1} and flushed with water until reaching a neutral eluent. The column was then flushed with methanol followed by CH_2Cl_2, each for 30 min at a flow rate of 0.2 mL min^{-1}. A solution of **FBIP-BF$_4$** (4.2 μmol) in dry CH_2Cl_2 (1 mL) was injected to the monolith by using luer syringe technique at a flow rate of 0.05 mL min^{-1}. The column was then sealed and kept at room temperature overnight. Then silver heptafluorobutyrate (32.1 mg, 100 μmol) in anhydrous CH_3CN (1.5 mL) was introduced into the monolith, which was again sealed and kept at room temperature for 1 h for anion exchange. Finally, the monolith was first flushed with acetonitrile (3 mL, colourless eluent) followed by dichloromethane (30 min). Monolith-supported catalyst **C1a** was used directly for catalysis.

Direct immobilization of FBIP-O$_2$CC$_3$F$_7$ *via* carboxylic acid groups on graft-polymer with M1: monolith-supported catalyst C1b. The catalyst **FBIP-O$_2$CC$_3$F$_7$** was prepared from the precatalyst **[FBIP-Cl]$_2$** (5.0 mg, 2.1 μmol, 1 equiv.) and $AgO_2CC_3F_7$ (2.6 mg, 8.4 μmol, 4 equiv.) with acetonitrile in CH_2Cl_2 according to the literature procedure.[6a] A solution of **FBIP-O$_2$CC$_3$F$_7$** (4.2 μmol) in dry CH_2Cl_2 (1 mL) was introduced to the monolith (grafted with monomer **M1**, ~120 μmol) at a flow rate of 0.1 mL min^{-1}. The column was then sealed and kept at room temperature. After 24 h, the column was flushed with dry CH_2Cl_2 at a flow rate of 0.1 mL min^{-1} for 30 min (colourless eluent). The prepared monolith-supported catalyst **C1b** was used directly for catalysis.

Direct immobilization of FBIP-O$_2$CC$_3$F$_7$ *via* carboxylic acid groups on graft-polymer with M2: monolith-supported catalyst C2. The catalyst **FBIP-O$_2$CC$_3$F$_7$** was prepared from the precatalyst **[FBIP-Cl]$_2$** (5.0 mg, 2.1 μmol, 1 equiv.) and $AgO_2CC_3F_7$

(2.6 mg, 8.4 μmol, 4 equiv.) with acetonitrile in CH_2Cl_2 according to the literature procedure.[6a] A solution of **FBIP-O$_2$CC$_3$F$_7$** (4.4 μmol) in dry CH_2Cl_2 (1 mL) was introduced to the monolith (grafted with monomer **M2**, ~50 μmol) at a flow rate of 0.1 mL min^{-1}. The column was then sealed and kept at room temperature. After 24 h, the column was flushed with dry CH_2Cl_2 at a flow rate of 0.1 mL min^{-1} for 30 min so that the eluent was colourless (elution of excess catalyst as **[FBIP-Cl]$_2$**). In order to transform residual carboxylic acid groups of the monolith support into the corresponding methyl ester the column was first washed with a MeOH–benzene mixture (4.5 mL, 2/7), then trimethylsilyldiazomethane ($TMSCHN_2$, 50 μmol, 1 equiv. corresponding to the determined carboxylic acid groups amount, 2 M in hexane) was injected and the column was further washed with a MeOH–benzene mixture (4.5 mL, 2/7), followed by CH_2Cl_2 at a flow rate of 0.1 mL min^{-1} for 30 min. The prepared monolith-supported catalyst **C2** was used directly for catalysis. The amount of immobilized catalyst on the functionalized column **C2** (3.67 μmol **FBIP-O$_2$CC$_3$F$_7$**) after the performed catalysis reactions was calculated by the palladium amount in the monolith, determined by ICP-OES (see ESI†).

Direct immobilization of FIP-O$_2$CC$_3$F$_7$ *via* carboxylic acid groups on graft-polymer with M2: monolith-supported catalyst C3. The catalyst **FIP-O$_2$CC$_3$F$_7$** was prepared from the precatalyst **[FIP-Cl]$_2$** (4.5 mg, 2.1 μmol, 1 equiv.) and $AgO_2CC_3F_7$ (2.6 mg, 8.4 μmol, 4 equiv.) with acetonitrile in CH_2Cl_2 according to the literature procedure.[6a] A solution of **FIP-O$_2$CC$_3$F$_7$** (4.4 μmol) in dry CH_2Cl_2 (1 mL) was introduced to the monolith (grafted with monomer **M2**, ~50 μmol) at a flow rate of 0.1 mL min^{-1}. The column was then sealed and kept at room temperature. After 24 h, the column was flushed with dry CH_2Cl_2 at a flow rate of 0.1 mL min^{-1} for 30 min so that the eluent was colourless. In order to transform residual carboxylic acid groups of the monolith support into the corresponding methyl ester the column was first washed with a MeOH–benzene mixture (4.5 mL, 2/7), then $TMSCHN_2$ (50 μmol, 1.0 equiv. corresponding to the determined carboxylic acid groups amount, 2 M in hexane) was injected and the column was further washed with a MeOH–benzene mixture (4.5 mL, 2/7), followed by CH_2Cl_2 at a flow rate of 0.1 mL min^{-1} for 30 min. The prepared monolith-supported catalyst **C3** was used directly for catalysis. The amount of immobilized catalyst on the functionalized column **C3** (1.71 μmol **FIP-O$_2$CC$_3$F$_7$**) after the performed catalysis reactions was calculated by the palladium amount in the monolith, determined by ICP-OES (see ESI†).

Asymmetric Michael additions with immobilized palladacycle catalysts on monolithic supports (general procedure)

tert-Butyl-2-cyano-2-phenylacetate **2** (20 mg, 92 μmol, 1 equiv.) was dissolved in anhydrous diglyme–solvent (100 μL) and HOAc dissolved in diglyme–solvent (21.1 μL, 18 μmol, 0.2 equiv., c = 0.87 mol L^{-1}) and 2-cyclohexen-1-one **3** (89 μL, 0.92 mmol, 10 equiv.) were added successively. The mixture was injected into the prepared corresponding column (**C1** to **C3**) followed by additional diglyme–solvent (100 μL) using the luer lock syringe technique. The column was sealed and heated for 20 h at 35 °C. Afterwards the column was washed with diglyme–solvent (4 mL) to elute the reaction mixture. The solvent of the eluent was removed *in vacuo* to give a mixture of Michael addition product **4** and residual *tert*-butyl-2-cyano-2-phenylacetate **2**. The samples were used for analytics without further purification.

The dr- and ee-values of the Michael addition products **4** were determined by chiral stationary phase HPLC (Chiracel OD-H column, iPrOH : heptane (99 : 1), 0.9 mL min^{-1} flow, room temperature, 210 nm, $t_{(R,R)}$ = 13.3 min, $t_{(S,S)}$ = 41.3 min, $t_{(S,R)}$ = 17.8 min, $t_{(R,S)}$ = 12.1 min) according to the literature.[6a] The yield of Michael addition product **4** was determined according to the literature[6a] by RP-HPLC (RP-18 column, gradient of acetonitrile–water as eluent, detection at 210 nm, $t_{\text{cyanoacetate 2}}$ = 2.0 min, $t_{\text{Michael addition product 4}}$ = 2.3 min) using a corresponding calibration curve.

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