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Towards Continuous Flow, Highly Enantioselective Allylic Amination: Ligand Design, Optimization and Supporting

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This paper is dedicated to Professor Luis Castedo on the occasion of his 70th birthday.

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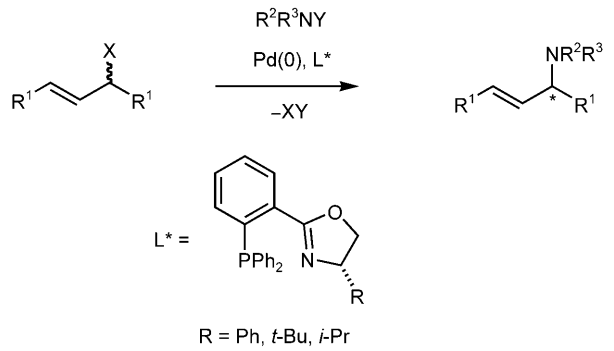
Abstract: A family of enantiopure diphenylphosphinooxazolines (PHOX) containing in their structures a sterically tunable alkoxymethyl group (-CH_2OR) has been optimized for the palladium-catalyzed asymmetric allylic amination. The optimal catalyst ($R = CH_3$), depicting very high catalytic activity and broad scope applicability, has been further modified to include an ω-alkynyloxy substituent of variable length for polymer supporting *via click chemistry*, and has been anchored onto slightly cross-linked azidomethyl poly(styrene). The length of a polymethylene chain connecting the PHOX unit with the 1,2,3-triazole linker has been optimized, and the first polymer-supported PHOX ligands for the highly enantioselective allylic amination have been prepared in this manner. Conditions for catalyst recovery and reuse in microwave-promoted amination reactions have been established, and the system has been finally adapted to continuous flow operation.

Keywords: amination; catalyst recycling; flow process; immobilization; palladium; P,N ligands

Introduction

The palladium-catalyzed asymmetric allylic substitution reaction is a versatile and widely employed methodology for the enantioselective construction of carbon-carbon and carbon-heteroatom bonds.[1] The development of new chiral ligands for asymmetric allylations, mainly phosphorus-, nitrogen- or sulfur-containing bidentate species, has attracted a considerable degree of attention over the last years.[1d] In particular, the efficiency of chiral phosphinooxazoline- and other related P,N-palladium complexes in the asymmetric allylic amination reaction has been well established.[1,2]

Phosphinooxazolines (PHOX) belong to a non-C_2 symmetrical class of bidentate ligands which present the advantage of producing electronic discrimination between the two terminal allylic carbons in the η^3-allylpalladium intermediates due to the combination of the characteristics of a "soft" phosphorus donor group with π-acceptor properties and a "hard" nitrogen σ-donor group.[2] In a pioneering study, Pfaltz and Helmchen described moderate to high enantioselection in the allylic amination of symmetrical π-allyl substrates with various nitrogen nucleophiles in the presence of 2-(diphenylphosphinophenyl)ozaxoline ligands (Scheme 1).[3] These initial results, and those obtained with analogous PHOX ligands[4] suggest that the asymmetric allylic amination is quite sensitive to modifications in the electronic characteristics of the structural aryl group or in the environment of the stereogenic center adjacent to the nitrogen in the oxazoline moiety (C-4). The modification of the spacer between the two coordinating heteroatoms in the ligand framework has provided a diversity of PHOX[5] and oxazoline-based P,N ligands[6] with useful characteristics in this palladium mediated process. However, substrate specificity and low reaction rates are still important limitations to overcome, commonly for unhindered disubstituted substrates and especially in case of the monosubstituted ones, which have proved to require more active catalysts.[1] Although several ex-



Scheme 1. Enantioselective allylic amination of 1,3-disubstituted allyl substrates in the presence of a Pfaltz–Helmchen chiral PHOX ligand.

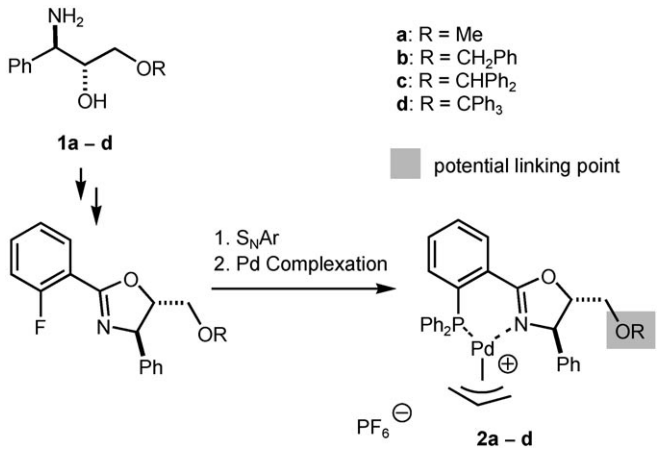


Figure 1. Polymer-supportable, modular phosphinooxazoline complexes **2a–d**.

amples of solid-supported chiral phosphine ligands, and bidentate N,N-, P,N- and P,S-palladium complexes as catalysts for asymmetric allylic substitution reactions can be found in the literature,[1d,7] the use in catalysis of immobilized chiral phosphinooxazoline ligands remains completely unexplored.[8]

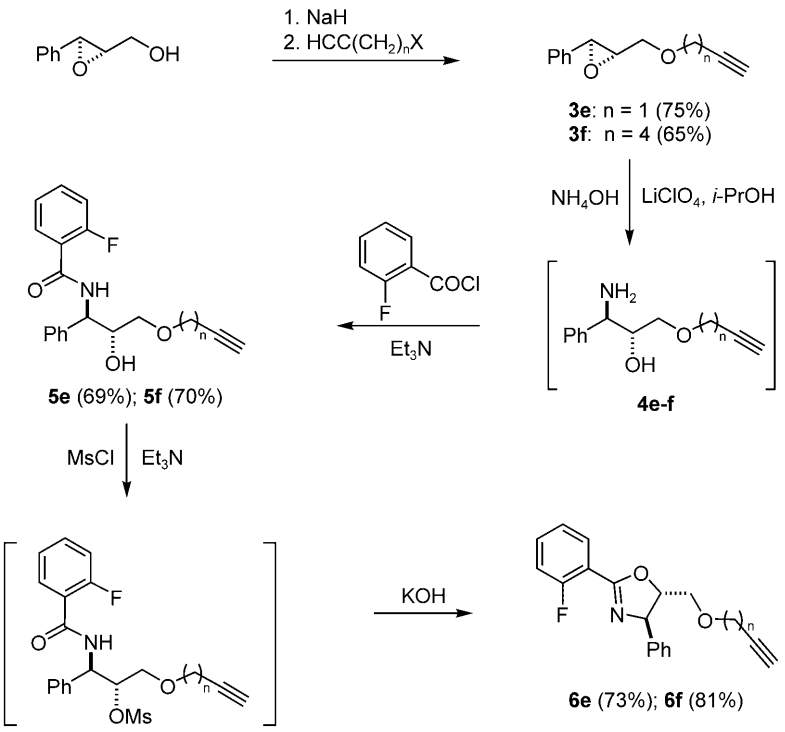
The preparation and use of solid-supported catalytic systems able to induce enantioselective transformations is an area of increasing relevance in chemistry due to the improved sustainability characteristics of this type of process. Thus, the suppression of complex work-up operations for catalyst separation and the removal of metal-containing by-products from reaction mixtures lead to cleaner alternatives for the production of metal-free, enantioenriched compounds. As an additional bonus, the recovery and reuse of the catalytic system becomes possible.[9]

The ultimate goal in this type of catalysis is performing chemical transformations in a continuous mode in a flow reactor under single-pass conditions, where reaction and catalyst separation are carried out simultaneously.[10] In spite of these potential advantages, the application of flow-through processes in catalytic enantioselective reactions has received little attention, probably due to the apparently inherent low activity associated to supported systems and to the need of *engineering* effort for the optimization of the different parameters controlling conversion and enantioselectivity in this kind of process.

In recent years, we have been involved in the design and synthesis of functional amino alcohol ligands that could be immobilized onto inorganic or polymeric supports without perturbation of the molecular regions where the catalytic activity resides.[11] As a fruit of this effort, we have recently succeeded in developing the first polymer-supported ligand for the fast, continuous-flow, highly enantioselective alkylation of aldehydes.[11g] Taking into account the limitations associated to ligand anchoring through nucleophilic substitution, we have thoroughly investigated a new strategy for supporting catalysts onto Merrifield-type resins through copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition (*click chemistry*)[12–14] and have shown that the resulting resins behave as highly active, enantioselective and diastereoselective, yet reusable, catalysts.[11f,13]

On the other hand, we have recently described a new family of PHOX ligands derived from modular, enantiopure β-amino alcohols (Figure 1). The presence of an additional alkoxymethyl substituent at C-5 in the oxazoline ring of **2a–d** leads to improved catalytic characteristics with respect to analogous PHOX ligands also bearing a phenyl substituent in C-4, but lacking the alkoxymethyl substituent at C-5. Thus, palladium complexes **2a–d** have proved to be highly efficient chiral mediators for the asymmetric allylic alkylation.[15] Besides its primary effect on catalytic activity and on enantioselectivity, the alkoxymethyl susbstituents at C-5 offer the additional possibility of allowing the heterogenization of the PHOX ligands onto insoluble supports. The remarkably good performance and robustness of complexes **2a–d** make them attractive for evaluation as catalysts in the more challenging asymmetric allylic amination.[1] Moreover, the results of a benchmark-guided structure optimization suggest that their immobilization onto polymers should lead to minimal deterioration of catalytic properties, thus opening the way to continuous flow operation.

Herein we report the development of modular, polymer-supported chiral phosphinooxazoline ligands and their use in the palladium-catalyzed enantioselective amination of allyl acetates under batch and continuous flow conditions.



Scheme 2. Preparation of 2-fluorophenyloxazolines **6e–f**.

Results and Discussion

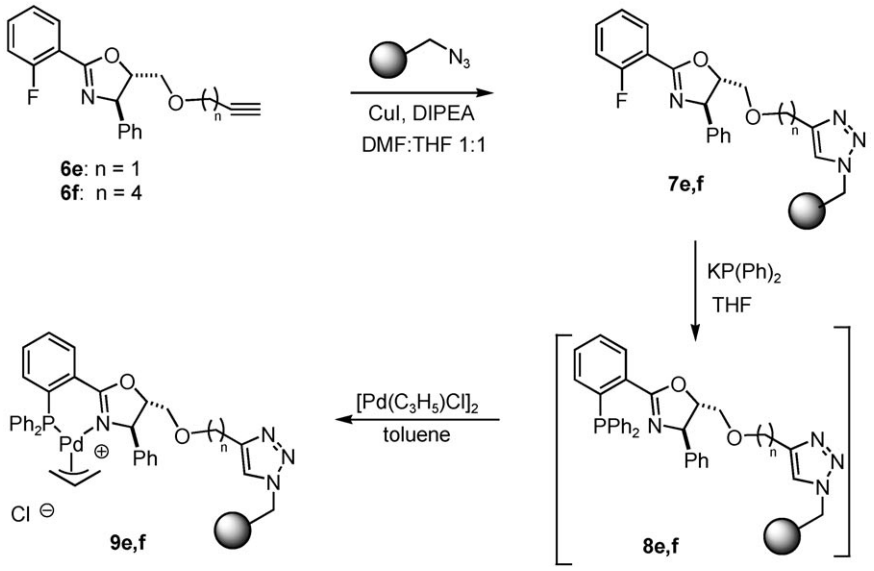
Ligand Synthesis

The starting point of this research was the modular phosphinooxazoline π-allylpalladium complexes **2a–d**, readily available from Sharpless epoxy ethers through well established synthetic transformations (Figure 1).[15] The preparation of oxazolines **6**, specifically designed for polymer-supporting, was planned through a similar, five-step sequence (Scheme 2). The presence of alkynyloxy side chains in **6** is instrumental for the supporting of PHOX ligands onto slightly cross-linked polystyrene resins through a click chemistry strategy. Within this strategy, the variable length spacers were designed to allow testing the effect of the distance between the bulky polymeric backbone and the catalytic site on the performance of the catalytic process.

The alkynyl fragments were installed on enantiopure phenylglycidol (>99% *ee*) by alkylation with the corresponding halides in the first step of the sequence.[16] The so-prepared epoxy ethers **3e–f** were next submitted to aminolysis in 25% aqueous ammonia with thermal activation.[17] The epoxide ring-opening took place stereospecifically and with complete regioselectivity leading to amino alcohols **4e,f** which were not isolated. The crude amino alcohols were directly *N*-acylated under standard conditions with 2-fluorobenzoyl chloride in the presence of triethylamine to afford hydroxybenzamides **5e,f** (69–70% overall yield from **3e,f**). Finally, the hydroxybenzamides were converted into the oxazolines **6e,f** by a two-step sequence[18] involving mesylation and base-induced cyclization (5% KOH/MeOH) through an S_N2 mechanism. Due to the limited stability of the mesylates, the cyclization was carried out within a few hours after their preparation. The activation-cyclization sequence took place in 73–81% overall yield for the two steps. The *trans* stereochemistry at C-4/C-5 in the oxazoline ring was confirmed by the values of the coupling constant ($J = 7.2$–7.3 Hz) between C-4 ad C-5 protons, similar to those reported for analogous, *trans*-4,5-disubstituted oxazolines.[15] (See Supporting Information for NOE experiments on **6f**).

Polymer-Supported Phosphinooxazolines

Our strategy for the preparation of click-PHOX resins is outlined in Scheme 3. The complementary azido group for the dipolar cycloaddition was incorporated onto commercial Merrifield resin (1% DVB, $f_0 = 0.81$ mmol Cl g^{-1} resin) by reaction with sodium azide.[19] According to elemental analysis data,[11a] the calculated degree of functionalization of the resulting azido resin was $f = 0.8$ mmol g^{-1}. Oxazolines **6e,f** were grafted onto that resin by a Cu-catalyzed Huisgen cycloaddition to afford 2-fluorophenyl oxazoline-functionalized resins **7e,f**. As a general rule, stirring the re-



Scheme 3. Synthesis of click-supported PHOX and of their π-allyl Pd-complexes.

action mixture (shaker) in 1:1 DMF/THF at 45 °C for 16 h led to complete conversion. The progress of the cycloaddition reaction could be easily followed by IR spectroscopy, through the disappearance of the azide band (*ca.* 2094 cm^{-1}). Elemental analysis of the final resins in conjunction with high-resolution magic angle spinning (HRMAS) ^{13}C NMR spectroscopy allowed us to establish that the oxazoline anchors to the resin in quantitative yield. Treatment of resins **7e,f** with potassium diphenylphosphide in THF at 0 °C provided the desired click-PHOX resins **8e,f**. The ^{19}F NMR spectra (gel phase) of the resulting resins provided evidence for total conversion in the nucleophilic displacement of the fluoride group. Finally, formation of the π-allyl complexes **9** was easily performed by addition of π-allylpalladium chloride dimer $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ to the resins previously swollen in toluene. The final resins **9e,f** had functionalization degrees $f=$ 0.49–0.53 mmol g^{-1}, in agreement with those expected for quantitative complexation. This was also indicated by ^{31}P NMR (See Supporting Information for ^{31}P NMR spectra of **8e,f** and **9e,f**).

For comparison purposes, compounds **11e,f** (Figure 2) were prepared following a similar procedure. The Cu(I)-catalyzed reaction between **6e,f** and *in situ* generated benzyl azide (from benzyl bromide and sodium azide), took place uneventfully in 1:1 *t*-BuOH/water under microwave irradiation to afford compounds **10e,f** in 81–82% yield. The nucleophilic displacement of fluoride from **10** with potassium diphenylphosphide proceeded smoothly in THF at −20 °C, the corresponding PHOX ligands being isolated in essentially pure form in 85–90% yield after filtration through a short pad of deoxygenated SiO_2. The crude PHOX ligands were directly converted to

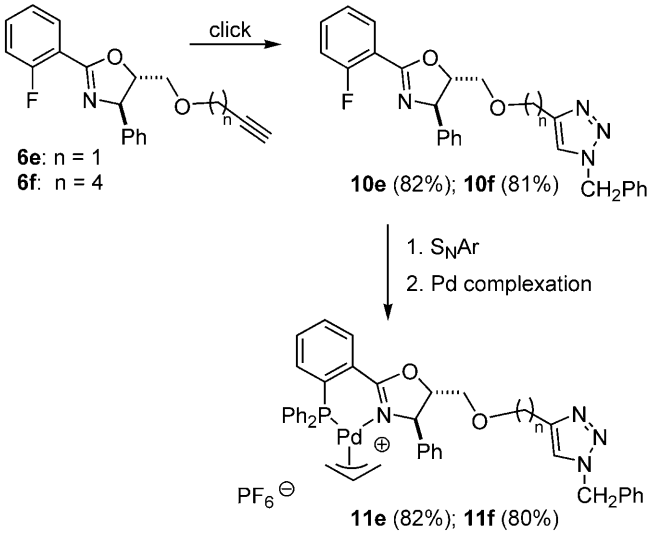
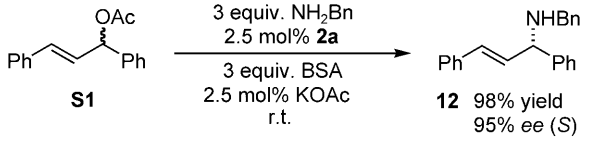


Figure 2. Preparation of reference, monomeric PHOX-Pd complexes **11e–f**.

the corresponding π-allylpalladium complexes **11e,f** by reaction with π-allylpalladium chloride dimer $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ in ethanol in the presence of NH_4PF_6.[18] Complexes **11e,f** were isolated in 80–82% yield by precipitation from the reaction mixture at 4 °C.

Allylic Aminations with Pd-PHOX Complexes 2

The modular π-allylpalladium complexes **2a–d** were first evaluated in the amination reaction of *rac*-(*E*)-3-acetoxy-1,3-diphenyl-prop-1-ene (**S1**) with benzylamine (both widely used as a model substrates).[3–6]



Scheme 4. Asymmetric allylic amination of **S1** with benzylamine catalyzed by **2a**.

Since **2a** (R = Me) had proven to be the optimal catalyst for the allylic alkylation of **S1** with dimethyl malonate,[15] experiments aimed at optimizing reaction conditions were performed with this catalyst. To our delight, 98% yield and 95% *ee* were achieved in 2 h in the presence of 2.5 mol% of **2a** at room temperature under solvent-free conditions, by using an excess of benzylamine, *N,O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate as additives (Scheme 4). It is interesting to note that this result is among the best ones reported in the literature for this particular reaction using PHOX-like ligands.[3–4] In addition, the reaction was remarkably fast and nearly total conversion was achieved after 2 h at room temperature. On the basis of previously reported data, the absolute configuration of **12** formed in the reaction was determined to be *S*.[3]

Encouraged by these results we next examined the activity of complexes **2b–d** under our optimized experimental conditions (Table 1). While complexes **2b–d** (entries 2–4) provided full conversion after 2 h, the corresponding enantioselectivities were significantly lower than those with **2a**, ranging from 83 to 88% *ee*. Thus, the presence of a non-bulky alkoxymethyl substituent at C-5 in the oxazoline ring is the key to high enantioselectivity in the asymmetric allylic amination reaction (entry 1).

To extend the scope of the asymmetric allylic amination, the reaction of **S1** was evaluated using a wide range of nitrogen nucleophilic compounds (Table 2). Excellent results were obtained in terms of yield and enantioselectivity except in the case of phthalimide potassium salt, which required higher temperatures and longer reaction times (65% yield, entry 6). In any case, this result is comparable with those observed for this nucleophile with other PHOX-based ligands.[4a] Under the optimized reaction conditions, *p*-methoxybenzylamine, propargylamine and diallylamine reacted in 2–4 h to give the expected products with excellent enantiomeric excess and in essentially quantitative yield (entries 1–3). Interestingly, neither propargylamine nor diallylamine have been previously studied as nitrogen nucleophiles in asymmetric allylic amination processes, despite the potential application of the resulting products **14** and **15** in Pauson–Khand, enyne cyclization, or metathesis-type reactions. With bulkier nucleophiles such as benzhydrylamine, benzoylhydrazine and phthalimide, longer reaction times were required for complete conversion. Although the reaction with benzoylhydrazine required a large excess of BSA, the corresponding product **17** was isolated in quantitative yield and 94% *ee* (entry 5). In any case, enantioselectivities, which range from 94 to 99% *ee*, are among the highest recorded with this type of nucleophiles.[1]

The configurations of (*S*)-**17**[3] and (*S*)-**18**[4b,20] were established by comparison of the signs of their optical rotations or the elution order in HPLC with those reported in the literature. The absolute configurations of **13–16** were assigned as *S* by analogy.[1]

Table 1. Asymmetric allylic amination of **S1** with benzylamine catalyzed by Pd/PHOX complexes **2a–d**.[a]

Entry	Catalyst	Product	Yield [%][b]	*ee* [%][c]
1	**2a**	**12**	98	95
2	**2b**	**12**	99	84
3	**2c**	**12**	99	83
4	**2d**	**12**	99	88

[a] All reactions were run at room temperature for 2 h with 2.5 mol% catalyst, 3 equiv. of benzylamine, 3 equiv. of BSA and 2.5 mol% KOAc.
[b] Yield of isolated product after purification by flash chromatography.
[c] Enantiomeric excesses were measured by chiral HPLC.

Table 2. Asymmetric allylic amination of **S1** with different N-nucleophiles catalyzed by Pd/PHOX complex **2a**.[a]

Entry	Nucleophile	Product	Time [h]	Yield [%][b]	*ee* [%][c]
1	*p*-Methoxybenzylamine	**13**	4	94	94
2	Propargylamine	**14**	2	99	97
3	Diallylamine	**15**	4	99	99
4	Benzhydrylamine	**16**	24	94	96
5	Benzoylhydrazine[d]	**17**	24	99	94
6	Phthalimide[e]	**18**	48	65	92

[a] All reactions were run at room temperature with 2.5 mol% catalyst, 3 equiv. of amine nucleophile, 3 equiv. of BSA and 2.5 mol% KOAc.
[b] Yield of isolated product after purification by flash chromatography.
[c] Enantiomeric excesses were measured by chiral HPLC.
[d] 6 equiv. of BSA were needed.
[e] Phthalimide potassium salt was used. The reaction was carried out at 50 °C.

Allylic Aminations with Polymer-Supported Pd-PHOX Complexes 9

The results obtained with complexes **2a–d** clearly indicated that a non-bulky substituent at C-5 in the oxa-

Table 3. Asymmetric allylic amination of **S1** with different N-nucleophiles catalyzed by Pd/PHOX complexes **11e**,[a] **9e**[a] and **9f**.[b]

Entry	Catalyst	Nucleophile	Product	Time [h]	Yield [%][c]	*ee* [%][d]
1	**11e**	Benzylamine	**12**	24	95	91
2	**11e**	*p*-Methoxybenzylamine[e]	**13**	24	98	91
3	**11e**	Propargylamine	**14**	30	97	93
4	**11e**	Diallylamine	**15**	48	99	99
5	**11e**	Benzhydrylamine[e]	**16**	42	99	89
6	**9e**	Benzylamine[f]	**12**	48	99	86
7	**9e**	Benzylamine[g]	**12**	2.5	99	81
8	**9e**	*p*-Methoxybenzylamine[e]	**13**	240	85[h]	85
9	**9e**	Propargylamine[f,i]	**14**	72	91	84
10	**9e**	Diallylamine[e]	**15**	72	99	88
11	**9e**	Benzhydrylamine[e]	**16**	240	89[j]	82
12	**9f**	Benzylamine	**12**	2	99	91
13	**9f**	*p*-Methoxybenzylamine[k]	**13**	2	99	85
14	**9f**	Propargylamine	**14**	4	95	93
15	**9f**	Diallylamine	**15**	12	98	87
16	**9f**	Benzhydrylamine[k]	**16**	4	99	83

[a] Unless otherwise specified, the reactions were run at room temperature with 2.5 mol% catalyst, 3 equiv. of amine nucleophile, 3 equiv. of BSA and 2.5 mol% KOAc.
[b] All reactions were run at 40 °C (setting temperature) under microwave irradiation with 7 mol% catalyst, 3 equiv. of amine nucleophile and 3 equiv. of BSA.
[c] Yield of isolated product after purification by flash chromatography.
[d] Enantiomeric excesses were measured by chiral HPLC.
[e] 9 mol% of catalyst was used.
[f] No KOAc was used
[g] Reaction was run at 40 °C (setting temperature) under microwave irradiation.
[h] 13% of **S1** was recovered with 21% *ee* determined by HPLC.
[i] 4 mol% of catalyst was used.
[j] 10% of **S1** was recovered with 27% *ee* determined by HPLC.
[k] 9 mol% of catalyst and 2.5 mol% KOAc were used.

zoline ring was optimal for high enantioselectivity in the amination reaction. This observation guided the design of the clickable precursors of the **e** and **f** families, where one or four methylene groups are intercalated between the oxygen atom in the C-5 substituent and the carbon-carbon triple bond on the same moiety.

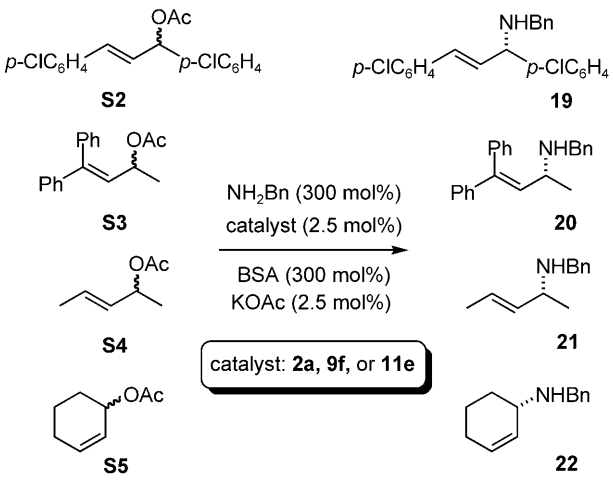
For reference purposes, we first examined the behaviour of the monomeric model for click-supported PHOX/Pd complexes **11e** (containing the short methylene spacer) in the allylic amination of **S1**. To this end, **S1** was reacted with several N-nucleophiles at room temperature in the presence of **11e**, BSA and potassium acetate. As can be seen in Table 3 (entries 1–5) the reaction was slower in all cases than with **2a**, 24–48 h being needed to achieve complete conversion. Nevertheless, the results obtained with this model catalyst are noteworthy since they are comparable with those obtained with **2a** (see Table 2). Accordingly, we anticipated that the enantioselectivity of the amination reaction would remain essentially unaffected by the immobilization of the phosphinooxazoline-palladium complexes through a 1,2,3-triazole linker as a part of the alkoxy substituent at C-5 in the oxazoline ring.

Reactions with the resin-supported Pd complex **9e** were run under the same reaction conditions as with **11e**, but with smooth stirring in an orbital shaker to avoid mechanical deterioration of the polymer beads. When the reactions were performed in this manner, the amination products could be obtained in high to excellent yields, but after long reaction times (entries 6 and 8–11 in Table 3). Except for the highly reactive benzylamine (entry 6), more than 2.5 mol% of **9e** was required in order to complete the reaction in 48 h. Taking into account that no work-up is required under these conditions, and that the catalyst can be separated by simple filtration, we decided to investigate the possibility of performing the reaction without the presence of the potassium acetate additive. This would avoid the presence of insoluble solids in the reaction media and would facilitate catalyst recovery. Interestingly, with highly reactive substrates such as benzylamine (entry 6) and propargylamine (entry 9) the reactions take place to completion in reasonable periods of time under these conditions. Microwave ir-

radiation[15] was also studied as an alternative activation method. Thus, benzylamine reacted with **S1** at 40 °C (temperature setting) providing the amination product in quantitative yield in only 2.5 h, with only slightly lower enantioselectivity than in the reaction at room temperature (compare entries 6 and 7). In summary, **9e** showed the viability of performing asymmetric allylic aminations with a click-supported phosphinooxazoline palladium complex, but its overall catalytic activity and enantioselectivity still required further refinement.

Since the reaction environment with the polymer-supported catalyst is quite different from that of the homogeneous reaction, both the catalytic activity and the enantioselectivity could be affected by the close vicinity of the bulky polystyrene backbone. To mitigate this problem, catalyst **9f** containing a longer tetramethylene spacer between the PHOX moiety and the 1,2,3-triazole linker was synthesized. Gratifyingly enough, resin **9f** exhibited an optimal catalytic performance under microwave irradiation, with improved enantioselectivity over **9e** (entries 12–16 in Table 3). Furthermore, microwave-assisted allylic amination turned out to be more effective for all the nucleophiles tested and, in general, complete conversions were achieved at 40 °C in only 2–4 h. As an additional bonus, it was in general possible to perform the aminations catalyzed by **9f** without the presence of the potassium acetate additive; only with the less reactive amines, like *p*-methoxybenzylamine and benzhydrylamine, was the presence of this additive required to ensure complete conversion in short reaction times. This characteristic is relevant in connection with our ultimate goal of developing a flow system for continuous catalytic enantioselective amination.

In a further attempt to improve the characteristics of the supported catalysts **9e,f**, we studied the effect of the counterion on their performance. Displacement of chloride anion by the poorly coordinating hexafluorophosphate anion in resins **9e,f** was easily performed in the presence of NH_4PF_6 (See Supporting Information). In particular, these anion-exchanged complexes were tested in the amination of **S1** with benzylamine in the reaction conditions optimized for **9e,f**. Somewhat dissappointingly, while the yield remained quantitative, the enantioselectivity was rather low in comparison with that recorded with **9e,f** (69–71% *ee*, see with entries 6 and 12 in Table 3 for the results with **9e,f**). As the *exo-endo* ratio of the two isomeric allylpalladium species formed in the catalytic cycle determines the stereochemical outcome of the reaction, a fast equilibrium between the two isomers is essential for elevated enantioselectivities. The equilibrium rate is affected by the anion either by ion pairing or by coordination to palladium. Anions that stick to the Pd(II) complexes (ion pairing) modify the steric hindrance around the metal, as in the case of PF_6^- anion.[21]



Scheme 5. Asymmetric allylic amination of allyl acetates **S2–S5** with benzylamine.

In summary, high activities and good to excellent enantioselectivities (in general, higher than 85% *ee*) can be achieved in the amination of **S1** with different N-nucleophiles under microwave irradiation using polymer-supported PHOX/Pd complex **9f** as the catalyst. Notably, these results are similar to those recorded with the monomeric analogue **11e** (89–99% *ee*) and, therefore, comparable with those obtained with **2a** (94–99% *ee*).

Amination of a Family of Allylic Substrates with Benzylamine

Regarding the allylic acetate counterpart, a representative set of substrates was reacted with benzylamine in the presence of the catalysts **2a** and **9f** (Scheme 5). For comparison purposes, the model complex **11e** was also tested in the reactions. The results of this study are collected in Table 4. Products **19–22** are known compounds, and their absolute configuration was confirmed by comparison of the signs of their optical rotation with those reported in the literature.

While the remarkable catalytic activity depicted by the new family of PHOX ligands is rather independent on the nature of the allylic substrate, the enantioselectivity of the process is strongly substrate-dependent, as is generally observed in this reaction. In particular, the amination of **S2** and **S3** with **2a** (entries 1 and 4) leads to *ee* values among the highest recorded with PHOX ligands in the considered reaction.[4b] Following the same trend previously observed for **S1**, resin **9f** provided slightly lower enantiomeric excesses than **2a** (entries 2 and 5). In any case, the results are

Table 4. Asymmetric allylic amination of allyl acetates **S2–S5** with benzylamine catalyzed by Pd/PHOX complex **2a**,[a] **9f**[b] and **11e**.[a]

Entry	Catalyst	Substrate	Product	Time [h]	Yield [%][c]	*ee* [%][d]
1	**2a**	**S2**	**19**	1[e]	99	94
2	**9f**	**S2**	**19**	6[f]	96	82
3	**11e**	**S2**	**19**	72	98	86
4	**2a**	**S3**	**20**	15[g]	99	89
5	**9f**	**S3**	**20**	4	70[h]	82
6	**11e**	**S3**	**20**	7[i]	85	83
7	**2a**	**S4**	**21**	4	99	63
8	**9f**	**S4**	**21**	4	99	62
9	**11e**	**S4**	**21**	72	82	43
10	**2a**	**S5**	**22**	4	99	37
11	**9f**	**S5**	**22**	3	99	29
12	**11e**	**S5**	**22**	72	96	39

[a] All reactions were run at room temperature with 2.5 mol% catalyst, 3 equiv. of benzylamine, 3 equiv. of BSA and 2.5 mol% KOAc.
[b] Reactions were run at 40 °C (setting temperature) under microwave irradiation with 5 mol% catalyst, 3 equiv. of benzylamine, 3 equiv. of BSA and 2.5 mol% KOAc.
[c] Yield of isolated product after purification by flash chromatography.
[d] Enantiomeric excesses were measured by chiral HPLC.
[e] 6 equiv. of benzylamine and 6 equiv. of BSA were used
[f] KOAc was not added.
[g] Reaction was run at 50 °C. 5 Equiv, of benzylamine were required.
[h] 28% of **S3** was recovered. Kinetic resolution was not observed.
[i] Reaction was heated at 45 °C (setting temperature) in a microwave reactor. 13% of **S3** was recovered. Kinetic resolution was not observed.

comparable with those obtained in solution with the monomeric analogue **11e** as the catalyst (entries 3 and 6). The bulkiness of the *ipso* substituent on the acetate substrate has a remarkable influence on enantioselectivity. Thus, replacement of a rather bulky aryl substituent (like in **S1** or **S2**) by a less bulky methyl group at the reaction site (as in **S3** or **S4**) is accompanied by a decrease in enantioselectivity, which is notable in case of **S4** (entries 7 and 8). Nevertheless, either **2a** or **9f** afforded product **21** in higher enantiomeric excess than related PHOX ligands reported in the literature.[4b] Notably, no decrease in enantioselectivity is observed for this substrate between **2a** and **9f**, while **11e** is much less effective (entry 9). This provides a clear indication on the importance of the spacer when phosphinooxazolines are supported onto polymers *via* click chemistry. Finally, the cyclic substrate **S5** was also explored. Although enantioselectivities are only moderate in this case (entries 10–12), these are the first results on the amination of cyclic substrates reported with PHOX ligands.

Recovery and Reuse of Polymer-Supported Catalysts 9

As a further step towards our ultimate goal of developing a continuous amination process, the possibility of recycling and reusing the polymer-supported PHOX catalysts **9e,f** in the allylic amination of **S1** with benzylamine was studied. All the reactions were carried out under the conditions previously optimized for each catalyst, without the addition of potassium acetate. After each run, the reaction mixture was separated by decantation, and the resin was simply rinsed with deoxygenated dichloromethane and dried under Ar before the next use. In the case of **9e**, the reactions were performed at room temperature with orbital shaking. Although, as already discussed, reactions mediated by this catalyst take a long time for completion, it is worth mentioning that both catalytic activity and enantioselectivity remain essentially unaffected after three consecutive runs (entries 1–5 in Table 5).

On the other hand, a significant decrease in catalytic activity was observed in the recycling of **9f** under microwave irradiation with a temperature setting of 40 °C (entries 9–13). In this case, reaction times had to be increased up to four times to achieve the conversion of the preceding cycle (compare entries 9, 11, and 13). Less satisfactory results were achieved when the reactions were performed at 55 °C (entries 6–8). Under these conditions, the decrease in the activity of the catalyst was more evident after the first cycle (compare entries 7 and 10). Since the resin turned black as the recycling progressed, we interpreted that thermally-induced precipitation of Pd(0) was taking place, and that this fact was responsible for the activity decrease. In an attempt to minimize this deactivation mechanism, a new set of recycling experiments (entries 14–17) was performed at low temperature (27 °C) with the following experimental modifications. First, the resin was pre-swollen with dichloromethane in order to improve the flow of the reactants into the polymer beads. Second, to avoid temperature peaks that could be deleterious for the stability of the palladium complex, the reactions were performed in power control mode (the reaction time was fixed at 35 min and the microwave power at 1 W). Interestingly, this importantly mitigated the loss of catalytic activity, while enantioselectivity reached 87% and remained essentially constant over four cycles. Conversion and enantioselectivity were determined after each cycle.

Taken together, these results clearly show that while microwave activation is the key to high catalytic activity when the polymer-supported PHOX catalyst **9f** is used, temperature control during these experiments is of paramount importance to avoid catalyst deactivation.

Table 5. Asymmetric allylic amination of **S1** with benzylamine catalyzed by polymer-supported Pd/PHOX complexes **9e**[a] and **9f**.[b,c]

Entry	Cycle	Catalyst	Temp. [°C]	Time [h]	Yield [%][d] (Conv. [%])[e]	*ee* [%][f]
1	1	**9e**	25	48	99	86
2	2		25	48	(90)	nd
3				57	99	86
4	3		25	48	(89)	nd
5				58	99	84
6	1	**9f**[b]	55[g]	2	99	88
7	2		55[g]	2	(20)	nd
8				8	86	82
9	1	**9f**[b]	40	2	99	91
10	2		40	2	(47)	nd
11				8	97	87
12	3		40	7	(10)	nd
13				35	95	86
14	1	**9f**[c]	27[h]	0.58	(99)	87
15	2		27[h]	0.58	(91)	87
16	3		27[h]	0.58	(82)	86
17	4		27[h]	0.58	(76)	86

[a] All reactions were run with 2.5 mol% catalyst, 3 equiv. of benzylamine and 3 equiv. of BSA.
[b] Reactions were run under microwave irradiation with 7 mol% catalyst, 3 equiv. of benzylamine and 3 equiv. of BSA.
[c] Reactions were run under microwave irradiation with 10 mol% catalyst, 4 equiv. of benzylamine, 4 equiv. of BSA and 7 equiv. of CH_2Cl_2.
[d] Yield of isolated product after purification by flash chromatography.
[e] Conversion determined by ^1H NMR of an aliquot.
[f] Enantiomeric excesses were measured by chiral HPLC.
[g] 4 mol% of catalyst was used.
[h] Reactions were performed in power control mode (1 W). Temperature of the reaction mixture was measured with a teflon-coated Pt-100 probe.

Continuous Flow System for the Single-Pass Allylic Amination of S1

With the optimal conditions for recycling the polymer-supported Pd catalyst in hand, efforts were then directed towards the implementation of **9f** in a continuous flow system. Thus, with the experience gained in the design of a system for the enantioselective ethylation of aromatic aldehydes through a single-pass, continuous flow process,[11g] we planned a similar set-up suited to the new purposes.

The simplicity of the system used for the study of the allyllic amination of **S1** with benzylamine can be appreciated in Figure 3. The continuous flow system consists of a vertical, 1/4 inch internal diameter teflon tube containing the supported catalyst, fitted with two adapters which allows to connect it with 1/16 inch internal diameter tubes to pump in the reagents and to collect the products (Figure 4). The microwave-assisted flow experiment was performed in an open-vessel manner at 1 W irradiation power. During operation, the reagents were pumped in through the bottom end of the tube using a piston pump.

Chemical reactions in continuous, flowing systems are best described by the plug flow reactor model.[22] In this model, the tubular reactor is considered as a series of infinitely thin coherent plugs, each of them characterized by a uniform composition which varies along the axial direction of the reactor as the reaction proceeds. For this model to be applicable, the fluid traveling through the reactor must be perfectly mixed in the radial direction but not in the axial one. In the flow system under consideration, where the tubular reactor is completely filled with the swollen functional resin, isothermal piston flow operates.[23] Under these conditions, conversion achieved in a given reactor (of given geometry and containing a given amount of catalyst) is only determined by the feed composition, reaction temperature, and mean residence time of the reactants in the reactor.

In the continuous flow allylic amination experiments, the resin was first swollen by pumping anhydrous dichloromethane at a 0.12 mL min^{-1} flow rate during 30 min. Then, microwave irradiation (1 W) was started and a solution of BSA, **S1** and benzylamine in the right proportions in dichloromethane, placed in a flask under argon, was pumped through the system for 180 min at the same flow rate (0.12 mL min^{-1}). Under these conditions, temperature of the reaction mixture (measured at the inlet and outlet of the tubular reactor with a Pt-100 probe) kept constant within 1 °C (22 ± 1 °C). The system was operated in single-

Figure 3. Continuous flow system used in the allylic amination of **S1** with benzylamine.

Figure 4. Detail of the teflon tube containing the polymer-supported catalyst in the microwave cavity.

pass manner, so that the output flow was directly collected. Samples of the output solution were taken every 15 min for analysis purposes. At the end of the experiment, dichloromethane was pumped for a further 30 min in order to wash the resin and the mechanical parts of the reactor. The conversion and *ee* of each aliquot are plotted in Table 6 and Figure 5. As shown, while the conversion slowly decays from 85% in the first 30 min (entry 2) to 54% after 3 h (entry 12), the *ee* increases in a slight but regular manner from 81% to 86% *ee*. Gratifyingly enough, conversion remains near 55% after 3 h of continuous flow allylic amination of **S1** (entry 12) and the level of enantioselectivity achieved (86% *ee*) is comparable with those obtained in batch processes.

Table 6. Continuous flow asymmetric allylic amination of **S1** with benzylamine catalyzed by polymer-supported Pd/PHOX complex **9f** under single-pass conditions.[a]

Entry	Time [min]	Conv.[%][b]	*ee* [%][c]
1	15	–[d]	–
2	30	85	81
3	45	86	83
4	60	80	82
5	75	75	83
6	90	70	83
7	105	66	83
8	120	63	85
9	135	60	84
10	150	55	84
11	165	55	84
12	180	54	86

[a] Reaction was run under microwave irradiation (1 W). A loading of 240 mg of resin **9f** (12 mol%) was used. The employed dichloromethane solution of reagents was prepared by mixing **S1** (9.6 mmol) in CH_2Cl_2 (4.3 mL) with benzylamine (48.1 mmol) and BSA (38.5 mmol).
[b] Conversions were determined by ^{1}H NMR.
[c] Enantiomeric excesses were measured by chiral HPLC.
[d] Only CH_2Cl_2 was collected.

The flow rate used in this experiment involves a residence time of the reagents within the catalyst bed of only 8.5 min.[24] The output flow corresponding to the whole operation period (3 h) was concentrated in

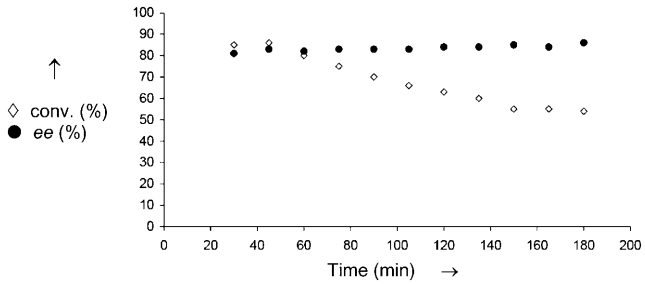


Figure 5. Results of the continuous flow allylic amination of **S1** with benzylamine.

vacuum, diluted with diethyl ether and washed with water. After evaporation, flash chromatography of the reaction crude furnished the desired product **12** in 68% yield and 83% *ee*. Using a flow rate of $0.12\,mL\,min^{-1}$ the system has a production of $9.18\,mmol\,h^{-1}$ per gram of resin **9f**, allowing the preparation of 1.98 g of pure (+)-(*S*,*E*)-*N*-benzyl-(1,3-diphenyl-2-propenyl)amine (**12**) with high enantioselectivity in a 3 h run.

The role exerted by microwave irradiation on the acceleration of these reactions is rather intriguing since, as discussed above, the very low microwave power used is not enough to provoke any significant increase in the macroscopic temperature of the flowing reaction mixture. This is in agreement with the low loss tangent values (tan δ) of dichloromethane and polystyrene,[25a] which should make very inefficient the conversion of electromagnetic energy into heat in the employed reaction system. Although the highly selective microwave heating of the Pd(I) complexes grafted onto the polymer chains could be the primary origin of the observed rate enhancement,[25b] the dissipation of the energy harvested by the metal complexes through the polymer chains where they are imbedded could also play a role in this behaviour. Thus, an increased mobility of the rather flexible polymer matrix would greatly facilitate the contact between the polymer-supported catalyst and the liquid phase containing the reactants by opening all the possible channels in the polymer structure. In this way, mass transfer limitations to reaction rate could be efficiently overcome.

Conclusions

In summary, we have described a family of highly modular PHOX ligands (**2**) for the Pd-catalyzed asymmetric allylic amination, and have used this result as a guide for the design of an analogue that could be supported onto polystyrene *via* click chemistry. The corresponding polymer-supported catalysts (**9e,f**), efficiently induce allylic amination, especially when the reactions are promoted by microvawes. The careful optimization of reaction conditions for catalyst recovery and recycling has ultimately served to fix the technological aspects allowing the conversion of the initial, batch amination process into the first, single-pass, continuous flow process of this class. During this optimization, an important acceleration of the heterogeneously-catalyzed reaction by microwave irradiation that does not involving macroscopic heating of the reaction mixture has been observed. Work aimed at improving the thermal stability of the polymer-supported palladium complex for an extended life of the catalytic system and at applying highly selective microwave activation to other processes where polymer-supported reactants or catalysts are involved is being actively pursued in our laboratories and will be reported in due course.

Experimental Section

General aspects of the experimental section can be found in the Supporting Information.

Typical Procedure for the *O*-Alkylation of (2*S*,3*S*)-3-Phenylglycidol; Synthesis of Alkynyloxy Epoxides 3e,f

A solution of enantiomerically pure (2*S*,3*S*)-3-phenylglycidol (10 mmol) in anhydrous DMF (10 mL) was added under argon to a suspension of sodium hydride (60% in mineral oil, 11.7 mmol) in anhydrous DMF (15 mL) previously cooled at −20 °C. The mixture was stirred for 20 min and then the corresponding propargyl halide (13 mmol) was added dropwise. The reaction mixture was stirred at −20 °C for 3 h, then allowed to reach room temperature and further stirred for 24 h. The reaction was quenched with MeOH (10 mL) and brine (20 mL) and extracted with CH_2Cl_2 (3× 20 mL). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. The purification of the products **3e,f** was carried by flash chromatography (hexanes/EtOAc from 100:0 to 80:20).

3e: Following the general method from (2*S*,3*S*)-3-phenylglycidol (1.4 g, 9.3 mmol), sodium hydride (0.45 g, 11.2 mmol) and propargyl bromide (80% in toluene, 1.3 mL, 12 mmol), compound **3e** was obtained as a pale yellow oil; yield: 1.32 g (75%); $[\alpha]_D^{23}$: −49.0 (*c* 1.1 in $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 7.36–7.25$ (m, 5H), 4.29–4.20 (m, 2H), 3.90 (dd, $J = 11.5$, 3.0 Hz, 1H), 3.81 (d, $J = 2.3$ Hz, 1H), 3.68 (dd, $J = 11.5$, 5.0 Hz, 1H), 3.24–3.21 (m, 1H), 2.47–2.46 (m, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 136.7$ (C), 128.5 (2CH), 128.3 (CH), 125.7 (2CH), 79.2 (C), 75.0 (CH), 69.4 (CH_2), 60.7 (CH_2), 58.6 (CH), 55.9 (CH); IR (film): $\nu = 3285$, 2854, 1461, 1100, 879, 699 cm^{-1}; HR-MS (ESI+): $m/z = 211.0721$, calcd. for $C_{12}H_{12}NaO_2$ $[M+Na]^+$: 211.0735.

3f: Following the general method from (2*S*,3*S*)-3-phenylglycidol (1.5 g, 10 mmol), sodium hydride (0.47 g, 11.7 mmol) and 6-chloro-1-hexyne (1.6 mL, 13 mmol), compound **3f** was obtained as a pale yellow oil; yield: 1.5 g (65%); $[\alpha]_D^{23}$:−148.6 (*c* 1.3 in $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta =$ 7.35–7.25 (m, 5H), 3.81–3.76 (m, 2H), 3.59–3.50 (m, 3H),

3.2–3.17 (m, 1H), 2.22 (td, $J=7.1$, 2.7 Hz, 2H), 1.95 (t, $J=$ 2.7 Hz, 1H), 1.76–1.67 (m, 2H), 1.65–1.58 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta=136.9$ (C), 128.5 (2CH), 128.2 (CH), 125.7 (2CH), 84.2 (C), 71.1 (CH_2), 70.6 (CH_2), 68.5 (CH), 61.2 (CH), 55.9 (CH), 28.7 (CH_2), 25.1 (CH_2), 18.2 (CH_2); IR (film): $\nu=3293$, 2921, 1459, 1259, 1112, 880, 750 cm^{-1}; HR.MS (ESI+): $m/z=253.1198$, calcd. for $C_{15}H_{18}NaO_2$ $[M+Na]^+$: 253.1204.

Preparation of Amino Alcohols 4e,f

The corresponding epoxy ether (1.0 mmol), 30% aqueous NH_3 (50 mmol), $LiClO_4$ (1 mmol) and isopropyl alcohol (5 mL), were heated in a sealed pressure tube at 100 °C for 6–7 h. The mixture was left to reach room temperature and the solvent was removed under reduced pressure. The crude reaction product was dissolved in CH_2Cl_2 (5 mL) and washed with water (3×5 mL). The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The resulting amino alcohols **4e,f** were used in the next step without further purification.

4e: Obtained as a pale yellow oil after flash chromatography (hexanes/AcOEt from 100:0 to 50:50); yield: 99%; $[\alpha]_D^{23}$: −33.3 (*c* 0.9 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=7.36$–7.20 (m, 5H), 4.12–4.10 (m, 3H), 3.95 (ddd, $J=5.1$, 5.1, 5.1 Hz, 1H), 3.48–3.46 (m, 2H), 2.44 (bs, 2H), 2.41–2.40 (m, 1H); ^{13}C NMR ($CDCl_3$): $\delta=141.7$ (C), 128.4 (2CH), 127.5 (CH), 127.2 (2CH), 79.4 (C), 74.8 (CH), 73.5 (CH), 71.1 (CH_2), 58.6 (CH_2), 57.8 (CH); IR (film): $\nu=3337$, 3277, 2852, 1601, 1494, 1453, 1071, 763, 701 cm^{-1}; HR-MS (ESI+): $m/z=$ 206.1178, calcd. for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1181.

4f: Obtained as a pale yellow oil after flash chromatography (hexanes/AcOEt from 100:0 to 50:50); yield: 90%; $[\alpha]_D^{23}$: −68.8 (*c* 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=7.36$–7.20 (m, 5H), 4.13 (d, $J=5.0$ Hz, 1H), 3.95 (ddd, $J=5.0$, 5.0, 5.0 Hz, 1H), 3.40–3.28 (m, 4H), 2.19 (td, $J=7.1$, 2.6 Hz, 2H), 1.94 (t, $J=2.7$ Hz, 1H), 1.69–1.62 (m, 2H), 1.69–1.52 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta=141.0$ (C), 128.5 (CH), 127.6 (CH), 127.2 (3CH), 84.2 (C), 73.0 (CH), 71.7 (CH_2), 70.9 (CH_2), 68.6 (CH), 57.8 (CH), 28.5 (CH_2), 25.1 (CH_2), 18.2 (CH_2); IR (film): $\nu=3287$, 2865, 1668, 1454, 1114, 704, 632 cm^{-1}; HR-MS (ESI+): $m/z=248.1658$, calcd. for $C_{15}H_{22}NO_2$ $[M+H]^+$: 248.1651.

Preparation of Hydroxy Amides 5e,f

Et_3N (1.95 mmol) was added under argon to a solution of the corresponding amino alcohol **4e,f** (1.0 mmol) in anhydrous THF (1.5 mL) and the mixture was cooled at 0 °C. A solution of 2-fluorobenzoyl chloride (0.95 mmol) in anhydrous THF (1.3 mL) was slowly added to the previous solution. The mixture was left to reach room temperature and stirred for an additional 2 h period. The solvents were removed under reduced pressure. The crude reaction product was diluted with CH_2Cl_2 (5 mL) and washed with brine (3× 5 mL). The organic phase was dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc from 100:0 to 60:40).

5e: Yield: 1.32 g (69%); white foam; $[\alpha]_D^{23}$: +46.1 ($c=0.8$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=8.11$ (bs, 1H), 8.06 (ddd, $J=7.8$, 1.9 Hz, 1H), 7.49–7.10 (m, 8H), 5.48–5.44 (m, 1H), 4.19–4.14 (m, 3H), 3.59 (dd, $J=9.6$, 3.6 Hz, 1H), 3.41 (dd, $J=9.8$, 5.1 Hz, 1H), 2.67 (d, $J=6.35$ Hz, 1H), 2.43–2.41 (m, 1H); ^{13}C NMR ($CDCl_3$): $\delta=162.9$ (d, $J_{C,F}=3.5$ Hz, C=O), 160.9 (d, $J_{C,F}=248.0$ Hz, CF), 138.3 (C), 133.2 (d, $J_{C,F}=$ 9.3 Hz, CH), 132.2 (d, $J_{C,F}=2.1$ Hz, CH), 128.6 (2CH), 127.7 (CH), 127.3 (2CH), 124.7 (d, $J_{C,F}=3.2$ Hz, CH), 120.9 (d, $J_{C,F}=11.0$ Hz, CH), 115.9 (d, $J_{C,F}=24.8$ Hz, CH), 78.8 (C), 75.1 (CH), 72.0 (CH), 70.8 (CH_2), 58.6 (CH_2), 56.8 (CH); IR (film): $\nu=3316$, 3266, 3032, 2941, 1636, 1613, 1527, 1481, 1452, 1099, 752, 702 cm^{-1}; HRMS (ESI+): $m/z=350.1153$, calcd. for $C_{19}H_{18}FNNaO_3$ $[M+Na]^+$: 350.1168, found.

5f: Yield: 1.32 g (70%); white foam; $[\alpha]_D^{23}$: +32.8 (*c* 1.1 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=8.35$–8.30 (m, 1H), 7.95 (dt, $J=7.9$, 1.9 Hz, 1H), 7.39–7.02 (m, 8H), 5.49–5.48 (m, 1H), 4.09–4.03 (m, 1H), 3.38–3.22 (m, 4H) 2.17 (td, $J=7.1$, 2.7 Hz, 2H), 1.95 (t, $J=2.7$ Hz, 1H) 1.69–1.64 (m, 2H), 1.58–1.52 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta=163.0$ (d, $J_{C,F}=$ 3.0 Hz, C=O), 160.4 (d, $J_{C,F}=248.2$ Hz, CF), 138.8 (C), 133.2 (d, $J_{C,F}=9.3$ Hz, CH), 131.8 (d, $J_{C,F}=2.0$ Hz, CH), 128.4 (2CH), 127.4 (CH), 127.2 (2CH), 124.6 (d, $J_{C,F}=3.3$ Hz, CH), 121.2 (d, $J_{C,F}=12.0$ Hz, CH), 115.9 (d, $J_{C,F}=24.3$ Hz, CH), 84.1 (C), 71.7 (CH), 71.6 (CH_2), 71.0 (CH_2), 68.7 (CH), 57.1 (CH), 28.4 (CH_2), 25 (CH_2), 18.2 (CH_2); IR (film): $\nu=3316$, 3266, 3032, 2941, 1636, 1613, 1527, 1481, 1452, 1099, 752, 702 cm^{-1}; HR-MS (ESI+): $m/z=392.1638$, calcd. for $C_{22}H_{24}FNNaO_3$ $[M+Na]^+$: 392.1650.

Preparation of (2-Fluoro)phenyloxazolines 6e,f

Methanesulfonyl chloride (1.1 mmol) was slowly added to a solution of the corresponding compound **5e,f** (1.0 mmol) and Et_3N (2.2 mmol) in CH_2Cl_2 (8.2 mL) under an argon atmosphere at 0 °C. The mixture was left to reach room temperature and stirred for an additional 2 h period. This mixture was added to a saturated aqueous solution of NH_4Cl (9 mL), the two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×6 mL). The organic phases were washed with brine (5 mL) and dried (Na_2SO_4). The drying agent was filtered off and the solvent was removed under reduced pressure. The residue was added to a 5% solution of KOH in MeOH (9 mL, 2.0 mmol), and the mixture was stirred for 15 h at room temperature. The reaction was quenched with water (5 mL) and the mixture extracted with CH_2Cl_2 (3×5 mL). The organic phases were dried (Na_2SO_4) and solvent removed under reduced pressure. The final product was purified by flash chromatography (hexane/EtOAc from 100:0 to 90:10).

6e: Yield: 0.85 g (73%); colourless oil; $[\alpha]_D^{23}$: +52.0 (*c* 1.2 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=7.98$ (ddd, $J=7.5$, 1.8, 1.8 Hz, 1H), 7.5–7.14 (m, 8H), 5.18 (d, $J=7.3$ Hz, 1H), 4.64 (ddd, $J=7.3$, 4.7, 4.7 Hz, 1H), 4.32–4.23 (m, 2H), 3.89–3.83 (m, 2H), 2.47–2.45 (m, 1H); ^{13}C NMR ($CDCl_3$): $\delta=161.1$ (d, $J_{C,F}=258.5$ Hz, CF), 160.8 (d, $J_{C,F}=5.4$ Hz, C=N), 141.7 (C), 133.0 (d, $J_{C,F}=8.4$ Hz, CH), 131.3 (d, $J_{C,F}=1.4$ Hz, CH), 128.7 (2CH), 127.6 (CH), 126.6 (2CH), 123.9 (d, $J_{C,F}=$ 3.8 Hz, CH), 116.6 (d, $J_{C,F}=21.0$ Hz, CH), 115.8 (d, $J_{C,F}=$ 10.2 Hz, C), 85.4 (CH), 79.1 (C), 75.1 (CH), 72.4 (CH), 70.3 (CH_2), 58.7 (CH_2); ^{19}F NMR ($CDCl_3$): $\delta=-108.8$ (s, F); IR (film): $\nu=290$, 2857, 1648, 1495, 1457, 1053, 766, 701 cm^{-1}; HR-MS (ESI+): $m/z=332.1049$, calcd. for $C_{19}H_{16}FNNaO_2$ $[M+Na]^+$: 332.1063.

6f: Yield: 0.7 g (81%); colourless oil; $[\alpha]_D^{23}$: +47.2 (*c* 1.1 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=8.00$ (ddd, $J=7.5$, 1.8,

1.8 Hz, 1H), 7.50–7.15 (m, 8H), 5.19 (d, $J=7.2$ Hz, 1H), 4.64 (ddd, $J=7.4$, 5.0, 5.0 Hz, 1H), 3.79–3.74 (m, 2H), 3.64–3.54 (m, 2H), 2.27 (td $J=7.1$, 2.7 Hz, 2H), 1.95 (t, $J=2.7$ Hz, 1H), 1.78–1.71 (m, 2H), 1.68–1.59 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta=161.5$ (d, $J_{C,F}=260.0$ Hz, CF), 160.9 (d, $J_{C,F}=5.4$ Hz, C=N), 141.9 (C), 133.0 (d, $J_{C,F}=8.9$ Hz, CH), 131.3 (d, $J_{C,F}=1.5$ Hz, CH), 128.7 (2CH), 127.6 (CH), 126.7 (2CH), 123.9 (d, $J_{C,F}=4.0$ Hz, CH), 116.7 (d, $J_{C,F}=22.0$ Hz, CH), 116.0 (d, $J_{C,F}=11$ Hz, C), 85.7 (CH), 84.2 (C), 72.5 (CH), 71.6 (CH), 71.2 (CH_2), 68.5 (CH_2), 28.6 (CH_2), 25.1 (CH_2), 18.1 (CH_2); ^{19}F NMR ($CDCl_3$): $\delta=-108.9$ (s, F); IR (film): $\nu=3300$, 2863, 1648, 1613, 1495, 1457, 1111, 760 cm^{-1}; HR-MS (ESI+): $m/z=352.1720$, calcd. for $C_{22}H_{23}FNO_2$ $[M+H]^+$: 352.1713.

Preparation of the Click Resins 7e,f

The N_3-functionalized resin[19] (1.54 g, $f=0.98$ mmol g^{-1}) was reacted with the corresponding alkynyloxymethyl oxazoline **6e,f** (1.62 mmol), CuI (2 mg, 0.01 mmol) and DIPEA (0.17 mL, 0.99 mmol) in a 1:1 mixture of DMF and THF (10 mL) at 45 °C. The progression of the reaction was monitored by IR spectroscopy. After disappearance of the azide signal (40 h) the resin was collected by filtration and sequentially washed with water (250 mL), DMF (250 mL), THF (250 mL), THF-MeOH 1:1 (250 mL), MeOH (250 mL) and THF (250 mL). The solid was dried under vacuum overnight at 40 °C.

Resin 7e: ^{1}H NMR (HRMAS, $CDCl_3$): $\delta=7.99$–7.91 (m, 1H), 7.45–6.27 (m, polymer), 5.40–5.10 (m, polymer), 5.12 (m, 1H), 4.73–4.66 (m, 2H), 4.65–4.60 (m, 1H), 3.85–3.81 (m, 2H), 2.12–0.85 (m, polymer); ^{13}C NMR (HRMAS, $CDCl_3$): $\delta=161.1$ (d, $J_{C,F}=258.5$ Hz, CF), 160.0 (C=N), 146.3–144.6 (m, polymer), 141.8 (C), 135.3 (CH), 133.2 (d, $J_{C,F}=8.4$ Hz, CH), 131.4 (CH), 128.8 (CH), 128.0 (CH), 127.7 (CH), 126.7 (CH), 125.7 (CH), 124.0 (d, $J_{C,F}=3.7$ Hz, CH), 116.6 (d, $J_{C,F}=22.0$ Hz, CH), 115.8 (C), 112.3–109.5 (m, polymer), 85.7 (CH), 72.3 (CH), 71.2 (CH_2), 68.0 (CH_2), 40.7–40.1 (m, polymer), 29.7 (CH_2), 25.6 (CH_2); ^{19}F NMR ($CDCl_3$): $\delta=-109.6$ (s, F); IR (ATR): $\nu=3058$, 3024, 2919, 1647, 1600, 1492, 1451, 1308, 1221, 1180, 1066, 1027, 753, 696, 556 cm^{-1}. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N 3.61; found: N 3.91; $f=0.71$ mmol g^{-1}.

Resin 7f: ^{1}H NMR (HRMAS, $CDCl_3$): $\delta=7.99$–7.91 (m, 1H), 7.42–6.20 (m, polymer), 5.38–4.96 (m, polymer), 5.15 (m, 1H), 4.62–4.34 (m, 1H), 3.72–3.66 (m, 2H), 3.60–3.47 (m, 2H), 2.74–2.55 (m, 2H), 2.12–0.85 (m, polymer); ^{13}C NMR (HRMAS, $CDCl_3$): $\delta=161.5$ (d, $J_{C,F}=263.9$ Hz, CF), 160.0 (C=N), 146.3–144.6 (m, polymer), 142.0 (C), 133.2 (CH), 131.4 (CH), 128.8 (CH), 128.0 (CH), 127.7 (CH), 126.8 (CH), 125.7 (CH), 124.0 (CH), 116.7 (d, $J_{C,F}=23.0$ Hz, CH), 116.1 (C), 112.3–109.5 (m, polymer), 85.9 (CH), 72.5 (CH), 71.8 (CH_2), 71.6 (CH_2), 68.0 (CH_2), 40.7–40.1 (m, polymer), 29.3 (CH_2), 26.1 (CH_2), 25.7 (CH_2), 25.5 (CH_2); ^{19}F NMR ($CDCl_3$): $\delta=-109.6$ (s, F); IR (ATR): $\nu=3058$, 3024, 2919, 1647, 1600, 1492, 1451, 1308, 1255, 1180, 1066, 1027, 753, 696, 556 cm^{-1}. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N 3.52; found: N 3.82; $f=0.68$ mmol g^{-1}.

Preparation of the Polymer-Supported Phosphinooxazolines 8e,f

A solution of $KPPh_2$ (1.37 mmol, 2.74 mL of 0.5 M solution in THF) was added dropwise under argon at 0 °C to an oven-dried Schlenk flask which contained the corresponding resin **7e,f** (0.98 mmol) previously swollen with anhydrous and degassed THF (10 mL). The reaction mixture was shaken at 0 °C for 2 h, then allowed to reach room temperature and further shaken for 12 h at this temperature. The solution was removed under argon *via* cannula and the resin was washed with anhydrous and degassed CH_2Cl_2 (7× 10 mL) and dried under vacuum for 10 h. Resins **8e,f** were characterized by gel-phase ^{31}P NMR and were immediately transformed into the corresponding palladium complexes **9e,f** to minimize oxidative deterioration.

Resin **8e**: ^{31}P NMR ($CDCl_3$): $\delta=-3.2$ (s, PPh_2).

Resin **8f**: ^{31}P NMR ($CDCl_3$): $\delta=-3.0$ (s, PPh_2).

Preparation of the Polymer-Supported Phosphinooxazoline π-Allylpalladium Complexes 9e,f

A solution of $[Pd(C_3H_5)Cl]_2$ (0.018 mmol, 67 mg) in anhydrous and deoxygenated toluene (1 mL) was added to an oven-dried Schlenk flask which contained the corresponding resin **8e,f** (0.5 g) previously swollen with anhydrous and degassed toluene (5 mL). The reaction mixture was shaken for 1 h. The resin was filtered, rinsed with toluene (10 mL) and CH_2Cl_2 (200 mL) and dried in vacuo for 12 h. Spherical beads with a 0.102 mm diameter (120 mesh) were obtained in this way.

Resin 9e: ^{1}H NMR (HRMAS, $CDCl_3$): $\delta=8.32$–8.20 (m, 1H), 7.65–6.25 (m, polymer), 5.78–5.41 (m, polymer), 5.30 (m, 1H), 4.96–4.34 (m, 2H), 4.61 (m, 1H), 4.07–3.69 (m, 4H), 3.34–3.08 (m, 2H), 2.99–2.76 (m, 2H), 2.33 (d, $J=16.5$ Hz, 2H), 2.14 (d, $J=23.6$ Hz, 2H), 1.99–0.90 (m, polymer); ^{13}C NMR (HRMAS, $CDCl_3$): $\delta=146.3$–144.3 (m, polymer), 139.6 (CH), 135.4–130.9 (m, CH), 130.7–124.8 (m, CH), 114.0–108.5 (m, polymer), 87.2 (CH), 75.2 (CH), 69.5 (CH_2), 64.5 (CH_2), 55.3–53.4 (m, CH_2), 47.1–41.5 (m, polymer), 41.3–38.5 (m, polymer), 29.7 (CH_2), 25.6 (CH_2); ^{31}P NMR ($CDCl_3$): $\delta=25.5$ (s, PPh_2, *exo*), 24.8 (s, PPh_2, *endo*); IR (ATR): $\nu=3057$, 3024, 2919, 1625, 1600, 1542, 1492, 1451, 1435, 1350, 1116, 1098, 728, 696, 538 cm^{-1}. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N 2.95; found: N 2.93; $f=0.53$ mmol g^{-1}.

Resin 9f: ^{1}H NMR (HRMAS, $CDCl_3$): $\delta=8.33$–8.24 (m, 1H), 7.71–6.18 (m, polymer), 5.65–5.08 (m, polymer), 5.48 (m, 1H), 4.89–4.46 (m, 2H), 4.61 (m, 1H), 3.93–3.64 (m, 4H), 3.62–3.46 (m, 2H), 3.32–3.05 (m, 2H), 3.03–2.80 (m, 2H), 2.79–2.54 (m, 2H), 2.34 (d, $J=18.0$ Hz, 2H), 2.14 (d, $J=24.3$ Hz, 2H), 2.03–1.21 (m, polymer); ^{13}C NMR (HRMAS, $CDCl_3$): $\delta=146.3$–144.3 (m, polymer), 139.5 (CH), 134.9–130.8 (m, CH), 129.9–124.6 (m, CH), 114.1–105.6 (m, polymer), 87.2 (CH), 75.6 (CH), 71.5 (CH_2), 70.4 (CH_2), 54.1 (CH_2), 46.4–41.8 (m, polymer), 41.6–39.4 (m, polymer), 29.6 (CH_2), 26.0 (CH_2), 25.5 (CH_2); ^{31}P NMR ($CDCl_3$): $\delta=25.5$ (s, PPh_2); IR (ATR): $\nu=3024$, 2919, 1624, 1600, 1491, 1451, 1435, 1307, 1180, 1118, 749, 695, 540 cm^{-1}. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N 2.88; found: N 2.99; $f=0.68$ mmol g^{-1}.

Preparation of Model Fluorooxazolines 10e,f

Benzyl bromide (0.13 mL, 1.07 mmol) was added to a mixture of the corresponding alkynyloxymethyloxazoline **6e,f** (1 mmol), sodium azide (0.148 g, 2.13 mmol), $CuSO_4 \cdot 5H_2O$ (5 mg, 0.002 mmol) and sodium L-ascorbate (43 mg, 0.21 mmol) in *tert*-butyl alcohol:water 1:1 (3 mL). The mixture was submitted to microwave irradiation (150 W, 100 °C, 2 min ramp and 40 min hold time). The reaction mixture was extracted with ethyl acetate (3×25 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc from 80:20 to 20:80). See Supporting Information for the physical and spectroscopic data of compounds **10e,f**.

Preparation of Model Phosphinooxazoline π-Allylpalladium Complexes 11e,f

A solution of $KPPh_2$ (0.77 mmol, 1.55 mL of 0.5 M solution in THF) was added dropwise under Ar at −78 °C to an oven-dried Schlenk flask which contained the corresponding fluorooxazoline **10e,f** (0.55 mmol) in THF (2 mL). The temperature was allowed to reach −20 °C. The reaction mixture was stirred for an additional 2 h period at this temperature, then allowed to reach room temperature, further stirred for 12 h at this temperature, quenched with $Na_2SO_4 \cdot 10H_2O$ in order to hydrolyze the excess of diphosphine, and filtered through a short SiO_2 pad eluting with CH_2Cl_2. Solvents were removed under vacuum, and the residue was purified by flash chromatography over SiO_2 under argon using deoxygenated solvents. The resulting phosphinooxazolines (see Supporting Information for ^{1}H- and ^{31}P NMR spectra) were immediately transformed into the corresponding palladium complexes **11**.

A solution of the corresponding phosphinooxazoline (0.38 mmol) in deoxygenated EtOH (4 mL) was *via* cannula to a Schlenk flask which contained a solution of $[Pd(C_3H_5)Cl]_2$ (0.20 mmol, 0.073 g) in EtOH (5 mL). The mixture was stirred 1 h under argon at room temperature; NH_4PF_6 (0.41 mmol, 0.068 g) was then added, and the resulting solution was further stirred for 14 h. Then, the mixture was cooled to −20 °C and allowed to stand at this temperature for several hours to induce crystallization of the π-allylpalladium complex. The crystallized phosphinooxazoline π-allylpalladium complex was filtered off, washed with cold EtOH (3 mL) and dried under vacuum. See Supporting Information for the physical and spectroscopic data of compound **11f**.

Model compound 11e: Yield: 82%; orange solid; $[\alpha]_D^{27}$: −27.9 (*c* 1.1 in $CHCl_3$); ^{1}H NMR (CD_3CN): δ = 8.28–8.22 (m, 2H), 7.83–6.97 (m, 42H), 6.85 (d, *J* = 7.4 Hz, 4H), 5.56 (m, 4H), 5.30 (d, *J* = 7.4 Hz, 2H), 4.74–4.61 (m, 6H), 3.95 (d, *J* = 12.0 Hz, 2H), 3.78 (d, *J* = 12.0 Hz, 2H); ^{13}C NMR (CD_3CN): δ = 165.2 (CN), 139.5 (C), 134.7 (CH), 133.9 (CH), 133.8 (CH), 133.5 (CH), 133.3 (CH), 132.7 (CH), 132.3 (CH), 132.1 (CH), 131.9 (CH), 129.8 (CH), 129.7 (CH), 129.5 (CH), 129.3 (CH), 129.2 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 128.1 (CH), 127.1 (CH), 87.0 (CH), 76.3 (CH), 69.3 (CH_2), 64.1 (CH_2), 56.0 (CH_2); ^{31}P NMR ($CDCl_3$): δ = 24.9 (s, PPh_2, *exo*), 24.4 (s, PPh_2, *endo*), −141.05 (h, *J* = 712.5 Hz, PF_6); IR (film): ν = 3060, 2920, 1622, 1480, 1456,1436, 1451, 1307, 1118, 831, 746, 694, 556, 538 cm^{-1}; HR-MS (ESI+): *m/z* = 755.1763, calcd. for $C_{41}H_{38}N_4O_2PPd$ $[M-PF_6]^+$: 755.1767.

General Procedure for the Palladium-Catalyzed Allylic Amination of S1 with Different N-Nucleophiles in the Presence of 2a–d

To an oven-dried Schlenk flask containing the corresponding phosphinooxazoline palladium complex **2a–d** (0.025 mmol) under argon were successively added (*E*)-3-acetoxy-1,3-diphenyl-1-propene (**S1**) (0.25 g, 1 mmol), the N-nucleophile (3 mmol), BSA (0.74 mL, 3 mmol) and KOAc (2.5 mg, 0.025 mmol). The mixture was stirred at room temperature for 2–24 h (unless otherwise stated, see Table 1) and then diluted with diethyl ether and washed with water. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc from 100:0 to 80:20).

(+)-(*S*,*E*)-*N*-Benzyl-(1,3-diphenyl-2-propenyl)amine (12)[3]: From **S1** (0.25 g, 1.0 mmol), **2a** (18.7 mg, 0.025 mmol), benzylamine (0.33 mL, 3.0 mmol), BSA (0.74 mL, 3.0 mmol) and KOAc (2.5 mg, 0.025 mmol). Yield: 0.29 g (98%); colourless oil; $[\alpha]_D^{23}$: +16.4 (*c* 0.85 in $CHCl_3$), 95% *ee*. The enantiomeric excess was determined by HPLC on an OD-H column (0.6 mL min^{-1} *n*-hexane/isopropyl alcohol 99:1, 254 nm): (*R*)-**12** Rt = 19.5 min, (*S*)-**12** Rt = 20.8 min.

(+)-(*S*,*E*)-*N*-(*p*-Methoxybenzyl)-(1,3-diphenyl-2-propenyl)-amine (13): From **S1** (0.25 g, 1.0 mmol), **2a** (18.7 mg, 0.025 mmol), *p*-methoxybenzylamine (0.396 mL, 3.0 mmol), BSA (0.74 mL, 3.0 mmol) and KOAc (2.5 mg, 0.025 mmol). Yield: 0.31 g (94%) yellow oil; $[\alpha]_D^{23}$: +28.2 (*c* 0.82 in $CHCl_3$), 94% *ee*. The enantiomeric excess was determined by HPLC on a AD-H column (0.7 mL min^{-1} *n*-hexane/isopropyl alcohol 94:6, 254 nm): (*S*)-**13** Rt = 18.0 min, (*R*)-**13** Rt = 20.9 min; ^{1}H NMR ($CDCl_3$): δ = 7.29–7.17 (m, 12H), 6.88–6.84 (m, 2H), 6.56 (d, *J* = 15.8 Hz, 1H), 6.30 (dd, *J* = 15.8, 7.5 Hz, 1H), 4.37 (d, *J* = 7.5 Hz, 1H), 3.79 (s, 3H), 3.75–3.68 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 158.7 (C), 143.0 (C), 137.0 (C), 132.7 (CH), 132.5 (C), 130.3 (CH), 129.4 (2CH), 128.6 (2CH), 128.5 (2CH), 127.5 (CH), 127.4 (2CH), 127.3 (2CH), 126.4 (CH), 113.8 (2CH), 64.5 (CH), 55.3 (CH_3), 50.8 (CH_2); IR (film): ν = 3024, 2832, 1610, 1510, 1492, 1245, 1174, 966, 914, 745 cm^{-1}; HR-MS (ESI+): *m/z* = 352.1666, calcd. for $C_{23}H_{23}NONa$ $[M+Na]^+$: 352.1677.

(+)-(*S*,*E*)-*N*-Propargyl-(1,3-diphenyl-2-propenyl)amine (14): From **S1** (0.25 g, 1.0 mmol), **2a** (18.7 mg, 0.025 mmol), propargylamine (0.19 mL, 3.0 mmol), BSA (0.74 mL, 3.0 mmol) and KOAc (2.5 mg, 0.025 mmol). Yield: 0.247 g (99%); yellow oil; $[\alpha]_D^{23}$: +26.6 (*c* 1.15 in $CHCl_3$), 97% *ee*. The enantiomeric excess was determined by HPLC on a AD-H column (0.5 mL min^{-1} *n*-hexane/isopropyl alcohol 90:10, 254 nm): (*R*)-**14** Rt = 17.0 min, (*S*)-**14** Rt = 18.4 min; ^{1}H NMR ($CDCl_3$): δ = 7.43–7.12 (m, 10H), 6.63 (d, *J* = 15.9 Hz, 1H), 6.26 (dd, *J* = 15.9, 7.7 Hz, 1H), 4.60 (d, *J* = 7.7 Hz, 1H), 3.43 (dd, *J* = 17.3, 2.6 Hz, 1H), 3.34 (dd, *J* = 17.3, 2.6 Hz, 1H), 2.24–2.25 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 142.0 (C), 136.8 (C), 131.6 (CH), 130.8 (CH), 128.6 (2CH), 128.5 (2CH), 127.5 (2CH), 127.4 (2CH), 126.4 (2CH), 82.1 (C), 71.5 (CH), 63.6 (CH), 35.7 (CH_2); IR (film): ν = 3290, 3025, 2832, 1491, 1449, 1330, 1110, 968, 913, 749 cm^{-1}; HR-MS (ESI+): *m/z* = 270.1259, calcd. for $C_{18}H_{17}NNa$ $[M+Na]^+$: 270.1268.

(+)-(*S*,*E*)-*N*,*N*-Diallyl-(1,3-diphenyl-2-propenyl)amine (15): From **S1** (0.25 g, 1.0 mmol), **2a** (18.7 mg, 0.025 mmol), diallylamine (0.37 mL, 3.0 mmol), BSA (0.74 mL, 3.0 mmol) and KOAc (2.5 mg, 0.025 mmol). Yield: 0.287 g (99%); yellow oil; $[\alpha]_D^{23}$: +27.3 (*c* 2.2 in $CHCl_3$), 99% *ee*. The enantiomeric excess was determined by HPLC on a AD-H column (0.4 mL min^{-1} *n*-hexane from 0 to 5 min, 0.2 mL min^{-1} *n*-hexane from 5 to 40 min, 254 nm): (*R*)-**15** Rt = 19.0 min, (*S*)-**15** Rt = 20.0 min; ^{1}H NMR ($CDCl_3$): δ = 7.39–7.20 (m, 10H), 6.54 (d, *J* = 15.7 Hz, 1H), 6.33 (dd, *J* = 15.7, 9.1 Hz, 1H), 5.92–5.82 (m, 2H), 5.19–5.12 (m, 4H), 4.43 (d, *J* = 9.1 Hz, 1H), 3.23–3.10 (m, 4H); ^{13}C NMR ($CDCl_3$): δ = 142.2 (C), 137.0 (C), 136.0 (CH), 132.4 (CH), 129.8 (CH), 128.6 (CH), 128.5 (2CH), 128.3 (2CH), 127.9 (CH), 127.5 (CH), 127.0 (CH), 126.7 (CH), 126.4 (2CH), 117.1 ($2CH_2$), 67.1 (CH), 52.6 ($2CH_2$); IR (film): ν = 3059, 3025, 2920, 2813, 1739, 1641, 1599, 1492, 1448, 1417, 1229, 1028, 968, 917, 743 cm^{-1}; HR-MS (ESI+): *m/z* = 290.1917, calcd. for $C_{21}H_{24}N$ $[M+H]^+$: 290.1909.

(+)-(*S*,*E*)-*N*-Benzhydryl-(1,3-diphenyl-2-propenyl)amine (16): From **S1** (0.25 g, 1.0 mmol), **2a** (18.7 mg, 0.025 mmol), benzhydrylamine (0.53 mL, 3.0 mmol), BSA (0.74 mL, 3.0 mmol) and KOAc (2.5 mg, 0.025 mmol). Yield: 0.287 g (94%); colourless oil; $[\alpha]_D^{23}$: +30.6 (*c* 1.2 in $CHCl_3$), 96% *ee*. The enantiomeric excess was determined by HPLC on a AD-H column (0.6 mL min^{-1} *n*-hexane/isopropyl alcohol 98:2, 254 nm): (*S*)-**16** Rt = 8.0, (*R*)-**16** Rt = 9.2 min; ^{1}H NMR ($CDCl_3$): δ = 7.75–7.05 (m, 20H), 6.49(d, *J* = 15.8 Hz, 1H), 6.29 (dd, *J* = 15.8, 7.5 Hz, 1H), 4.87 (s, 1H), 4.28 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 144.0 (C), 143.9 (C), 143.0 (C), 137.0 (C), 132.4 (CH), 130.6 (CH), 128.4 (2CH), 128.6 (2CH), 128.5 (2CH), 128.3 (2CH), 127.6 (2CH), 127.4 (2CH), 127.3 (2CH), 127.0 (2CH), 126.9 (2CH), 126.4 (2CH), 63.5 (CH), 61.9 (CH); IR (film): ν = 3025, 2925, 2850, 1949, 1810, 1598, 1492, 1180, 966, 914, 745 cm^{-1}; HR-MS (ESI+): *m/z* = 376.2056, calcd. for $C_{28}H_{25}N$ $[M+H]^+$: 376.2065.

(+)-(*S*,*E*)-*N*-(1,3-Diphenyl-2-propenyl)-*N*′-benzoylhydrazine (17)[3]: From **S1** (0.25 g, 1.0 mmol), **2a** (18.7 mg, 0.025 mmol), benzoylhydrazine (0.42 g, 3.0 mmol), BSA (1.48 mL, 6.0 mmol) and KOAc (2.5 mg, 0.025 mmol). Yield: 0.325 g (99%); $[\alpha]_D^{28}$: +36.4 (*c* 0.73 in $CHCl_3$), 94% *ee*. The enantiomeric excess was determined by HPLC on an OJ column (0.5 mL min^{-1} *n*-hexane/isopropyl alcohol 85:15, 254 nm): (*S*)-**17** Rt = 27.7 min, (*R*)-**17** Rt = 31.4 min; (AD-H column, 0.5 mL min^{-1} *n*-hexane/isopropyl alcohol 85:15, 254 nm): (*R*)-**17** Rt = 32.1, (*S*)-**17** Rt = 36.9 min.

(+)-(*S*,*E*)-*N*-(1,3-Diphenyl-2-propenyl)phthalimide (18)[4b,20]: From **S1** (0.25 g, 1.0 mmol), **2a** (18.7 mg, 0.025 mmol), potassium phthalimide (0.573 g, 3.0 mmol), BSA (0.74 mL, 3.0 mmol) and KOAc (2.5 mg, 0.025 mmol). Yield: 0.22 g (65%); $[\alpha]_D^{29}$: +21.5 (*c* 0.87 in $CHCl_3$), 92% *ee*. The enantiomeric excess was determined by HPLC on an OD-H column (0.5 mL min^{-1} *n*-hexane/isopropyl alcohol 98:2, 254 nm): (*S*)-**18** Rt = 25.6 min, (*R*)-1**8** Rt = 31.6 min.

General Procedure for the Palladium-Catalyzed Allylic Amination of Substrates S2–S5 in the Presence of 2a

The procedure was analogous to the one described above for **S1** but using **2a** as the catalyst, the corresponding allylic acetate **S2–S5** as starting material and benzylamine as *N*-nucleophile at room temperature (unless stated otherwise, see Table 2).

(+)-(*S*,*E*)-*N*-Benzyl-[1,3-bis(2-chlorophenyl)-2-propenyl]-amine (19)[4b]: $[\alpha]_D^{23}$: +3.8 (*c* 0.93 in $CHCl_3$), 94% *ee*. The enantiomeric excess was determined by HPLC on an OD-H column (0.5 mL min^{-1} *n*-hexane/isopropyl alcohol 99:1, 254 nm): (*R*)-**19** Rt = 13.1 min, (*S*)-**19** Rt = 15.6 min.

(+)-(*R*)-*N*-Benzyl-[1-methyl-3,3-diphenyl-2-propenyl]amine (20)[4b,26]: $[\alpha]_D^{28}$: +89.0 (*c* 1.28 in $CHCl_3$), 89% *ee*. The enantiomeric excess was determined by HPLC on an OJ-H column (0.6 mL min^{-1} *n*-hexane/isopropyl alcohol 90:10, 254 nm): (*S*)-**20** Rt = 12.0 min, (*R*)-**20** Rt = 18.2 min.

(+)-(*R*,*E*)-*N*-Benzyl-(1-methyl-2-butenyl)amine (21)[3,26]: $[\alpha]_D^{28}$: +16.0 (*c* 1.76 in $CHCl_3$), 63% *ee*. The enantiomeric excess was determined by HPLC on an OD-H column (0.5 mL min^{-1} *n*-hexane, 230 nm): (*R*)-**21** Rt = 30.7 min, (*S*)-**21** Rt = 36.4 min.

(*R*)-*N*-Benzyl-(cyclohex-2-enyl)amine (22)[27,28]: The enantiomeric excess was determined by HPLC on an OB-H column (0.5 mL min^{-1} *n*-hexane/isopropyl alcohol 95:5, 230 nm): (*R*)-**22** Rt = 10.7 min, (*S*)-**22** Rt = 12.0 min.

General Procedure for the Palladium-Catalyzed Allylic Amination of Substrates S1–S5 in the Presence of 11e

To an oven-dried, 5-mL conical flask equipped with a septum, containing **11e** (22.5 mg, 0.025 mmol) under argon were successively added the corresponding allylic acetate **S1–S5** (1 mmol), the corresponding N-nucleophile (3 mmol), BSA (0.74 mL, 3 mmol) and KOAc (2.5 mg, 0.025 mmol). The mixture was stirred at room temperature for 24 −72 h (unless stated otherwise, see Table 3 and Table 4) and then concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc from 100:0 to 80:20).

General Procedure for the Palladium-Catalyzed Allylic Amination of S1 in the Presence of 9e

S1 (0.05 g, 0.2 mmol), the corresponding N-nucleophile (0.6 mmol) and BSA (0.148 mL, 0.6 mmol) were syringed into an oven-dried, 5-mL conical flask equipped with a septum, containing **9e** (9.5 mg, 0.005 mmol) and KOAc (2.5 mg, 0.025 mmol) under argon. The reaction mixture was smoothly shaken (orbital shaker) at room temperature for the time indicated in Table 3. Then the resin was filtered off and rinsed with anhydrous CH_2Cl_2 (3 × 3 mL). The combined filtrates were concentrated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc from 100:0 to 80:20).

General Procedure for the Palladium-Catalyzed Allylic Amination of S1 in the Presence of 9f

Reactions were performed as described for the allylic amination of **S1** in the presence of **9e**, but in a vial for microwave reactor and without the presence of the KOAc additive, using **9f** (26 mg, 0.014 mmol) as the catalyst and heating the reaction mixture in a microwave reactor at 40 °C (setting temperature) for 2–12 h (unless stated otherwise,

see Table 3). Isolation of compounds **12–16** was performed as stated before (*vide supra*).

General Procedure for the Palladium-Catalyzed Allylic Amination of Substrates S2–S5 in the Presence of 9f

The procedure was analogous to the one described for allylic amination of **S1** under microwave-assisted conditions but using 5 mol% of **9f** (18.6 mg, 0.01 mmol) and KOAc (2.5 mg, 0.025 mmol) as co-additive (unless stated otherwise, see Table 4). Isolation of compounds **19–22** was performed as stated before (*vide supra*).

Recycling Experiments

As a representative example: **S1** (0.062 g, 0.25 mmol), benzylamine (0.107 mL, 0.98 mmol) and BSA (0.24 mL, 0.98 mmol) were added *via* syringe to an oven-dried vial for microwave reactor containing **9f** (51 mg, 0.025 mmol), previously swollen with anhydrous and degassed CH_2Cl_2 (0.11 mL, 1.72 mmol), under argon. The reaction mixture was heated in a microwave reactor in power control mode (1 W) for 35 min. The temperature of the reaction mixture, measured with an internal, teflon-coated Pt-100 probe, was 26–27 °C. Then, the solution was removed under argon *via* cannula and the resin was rinsed with CH_2Cl_2 (3×1 mL) and dried under argon for 10 min. The resin was swollen again with CH_2Cl_2 (0.11 mL, 1.72 mmol), the reactants were added and the mixture was reacted as indicated before. The same resin was used for each cycle and no further Pd source was added. Isolation of compound **12** was performed as stated before (*vide supra*).

Continuous Flow System Description and Details of the Reaction Procedure

The continuous flow system (see Figure 4) was set up around a vertically mounted 1/4 inch teflon tube, which was loaded with resin **9f** (240 mg). Teflon connectors allowed us to connect it through 1/16 inch teflon tubes to an Ismatec piston pump (reagents input) and to a collector vessel. A schematic drawing of all the pieces and connections appears in the Supporting Information. A solution of **S1** (9.63 mmol, 2.43 g), BSA (38.52 mmol, 9.56 mL), and benzylamine (48.15 mmol, 5.27 mL) in dry CH_2Cl_2 (67.42 mmol, 4.32 mL) was prepared in a flask under argon. Dry CH_2Cl_2 was kept in an independent bottle with a connector cap with valves for an easy and inert connection to the tubing. The resin was swollen by pumping CH_2Cl_2 at a 0.12 mL min^{-1} flow during 30 min. Care was taken that all the resin beads packed in the tube were inside the microwave cavity (see Figure 5). Then, the microwave apparatus was connected (1 W, open-vessel) and the solution of the reagents was pumped through the system at a 0.12 mL min^{-1} flow for 3 h. The efluent reaction mixture was collected through the upper end of the reactor, taking aliquots every 15 min to measure ^{1}H NMR spectra and to determine the *ee* of the amination product by HPLC. Temperature of the efluent (22–23 °C) was monitored with a Pt-100 probe, and turned out to be identical (±1 °C) to that of the reagents mixture. When all the reacting solution had been pumped, CH_2Cl_2 was passed for an additional 30 min period in order to wash the resin and the mechanical parts of the reactor. The collected output flow was concentrated, diluted with Et_2O (5 mL), washed with water (3×20 mL), dried ($MgSO_4$) and concentrated under vacuum. Flash chromatography of the reaction crude (hexanes/EtOAc from 100: 0 to 90:10) afforded **12** in 68% yield and 83% *ee*.

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References

[1] For reviews, see: a) B. M. Trost, D. L. van Vranken, *Chem. Rev.* **1996**, *96*, 395; b) A. Pfaltz, M. Lautens, in: *Comprehensive Asymmetric Catalysis*, Vol. 2, (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, Chap. 24; c) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921; d) Z. Lu, S. Ma, *Angew. Chem.* **2008**, *120*, 264; *Angew. Chem. Int. Ed.* **2008**, *47*, 258, and references cited therein; e) P. Butti, R. Rochat, A. D. Sadow, A. Togni, *Angew. Chem.* **2008**, *120*, 4956; *Angew. Chem. Int. Ed.* **2008**, *47*, 4878.

[2] a) C. G. Frost, J. Howart, J. M. J. Williams, *Tetrahedron: Asymmetry* **1992**, *3*, 1089; b) J. M. J. Williams, *Synlett* **1996**, 705; c) B. Bartels, G. Helmchen, *Chem. Commun.* **1999**, 741; d) G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336; e) H. A. McManus, P. J. Guiry, *Chem. Rev.* **2004**, *104*, 4151; f) A. Pfaltz, W. J. Drury III, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5723.

[3] P. von Matt, O. Loiseleur, G. Koch, A. Pfaltz, C. Lefeber, T. Feucht, G. Helmchen, *Tetrahedron: Asymmetry* **1994**, *5*, 573.

[4] a) R. Jumnah, A. C. Williams, J. M. J. Williams, *Synlett* **1995**, 821; b) A. Sudo, K. Saigo, *J. Org. Chem.* **1997**, *62*, 5508; c) R. N. Constantine, N. Kim, R. C. Bunt, *Org. Lett.* **2003**, *5*, 2279; d) P. B. Armstrong, L. M. Bennett, R. N. Constantine, J. L. Fields, J. P. Jasinski, R. J. Staples, R. C. Bunt, *Tetrahedron Lett.* **2005**, *46*, 1441.

[5] a) K. Selvakumar, M. Valentini, M. Woerle, P. S. Pregosin, A. Albinati, *Organometallics* **1999**, *18*, 1207; b) Y. M. Malone, P. J. Guiry, *J. Organomet. Chem.* **2000**, *603*, 110; c) W.-P. Deng, S.-L. You, X.-L. Hou, L.-X. Dai, Y.-H. Yu, W. Xia, J. Sun, *J. Am. Chem. Soc.* **2001**, *123*, 6508; d) S.-L. You, X.-L. Hou, L.-X. Dai, Y.-H. Yu, W. Xia, *J. Org. Chem.* **2002**, *67*, 4684; e) G. P. Xu, S. R. Gilbertson, *Tetrahedron Lett.* **2002**, *43*, 2811; f) C. Bolm, L. Xiao, M. Kesselgruber, *Org. Biomol. Chem.* **2003**, *1*, 145.

[6] a) K. Yonehara, T. Hashizume, K. Mori, K. Ohe; S. Uemura, *J. Org. Chem.* **1999**, *64*, 9374; b) O. Pàmies, M. Diéguez, C. Claver, *J. Am. Chem. Soc.* **2005**, *127*, 3646; c) Y. Mata, M. Diéguez, O. Pàmies, C. Claver, *Adv. Synth. Catal.* **2005**, *347*, 1943; d) M. Diéguez, O. Pàmies, *Chem. Eur. J.* **2008**, *14*, 3653.

[7] a) For a review of polymeric palladium catalysts, see: Y. Uozumi, *Top. Curr. Chem.* **2004**, *242*, 77. For some recent examples, see: monodentate P ligands: b) Y. Kobayashi, D. Tanaka, H. Danjo, Y. Uozumi, *Adv. Synth. Catal.* **2006**, *348*, 1561; bidentate N,N ligands: c) M. Bandini, M. Benaglia, T. Quinto, S. Tommasi, A. Umani-Ronchi, *Adv. Synth. Catal.* **2006**, *348*, 1521; bidentate P,N ligands: d) Y. Uozumi, H. Tanaka, K. Shibatomi, *Org. Lett.* **2004**, *6*, 281; e) H. Nakano, K. Takahashi, R. Fujita, *Tetrahedron: Asymmetry* **2005**, *16*, 2133; f) Y. Uozumi, *Pure. Appl. Chem.* **2007**, *79*, 1481; bidentate P,S ligands: g) H. Nakano, K. Takahashi, Y. Suzuki, R. Fujita, *Tetrahedron: Asymmetry* **2005**, *16*, 609; h) B. Martín-Matute, S. I. Pereira, E. Peña-Cabrera, J. Adrio, J. C. Carretero, *Adv. Synth. Catal.* **2007**, *349*, 1714.

[8] For the preparation of a polystyrene-supported phosphinooxazoline, see: R.-J. Chen, J.-M. Fan, *J. Chin. Chem. Soc.* **2005**, *52*, 819.

[9] Reviews on immobilized catalysts include the following: a) *Chiral Catalyst Immobilization and Recycling*, (Eds.: D. E. de Vos, I. F. Vankelecom, P. A. Jacobs), Wiley-VCH, Weinheim, **2000**; b) *Immobilized Catalysts: Solid Phases, Immobilization and Applications*, in: *Topics in Current Chemistry*, (Ed.: A. Kirschning), Springer, Berlin, **2004**, *242*, 1; c) *Polymeric Materials in Organic Synthesis and Catalysis*, (Ed.: D. R., Buchmeiser), Wiley-VCH, Weinheim, **2006**; d) M. Heitbaum, F. Glorius, I. Escher, *Angew. Chem.* **2006**, *118*, 4850; *Angew. Chem. Int. Ed.* **2006**, *45*, 4732; e) *Handbook of Asymmetric Heterogeneous Catalysis*, (Eds.: K. Ding, Y. Uozumi), Wiley-VCH, Weinheim, **2008**.

[10] For some general references on flow-through processes, see: a) G. Jas, A. Kirschning, *Chem. Eur. J.* **2003**, *9*, 5708; b) P. Hodge, *Ind. Eng. Chem. Res.* **2005**, *44*, 8542; c) F. Cozzi, *Adv. Synth. Catal.* **2006**, *348*, 1367; d) A. Kirschning, W. Solodenko, K. Mennecke, *Chem. Eur. J.* **2006**, *12*, 5972; e) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300; f) A. Corma, H. García, *Top. Catal.* **2008**, *48*, 8.

[11] a) A. Vidal-Ferran, N. Bampos, A. Moyano, M. A. Pericàs, A. Riera, J. K. M. Sanders, *J. Org. Chem.* **1998**, *63*, 6309; b) M. A. Pericàs, D. Castellnou, I. Rodríguez, A. Riera, L. Solà, *Adv. Synth. Catal.* **2003**, *345*, 1305; c) J. M. Fraile, J. A. Mayoral, J. Serrano, M. A. Pericàs, L. Solà, D. Castellnou, *Org. Lett.* **2003**, *5*, 4333; d) D. Castellnou, M. Fontes, C. Jimeno, D. Font, L. Solà, X. Verdaguer, M. A. Pericàs, *Tetrahedron* **2005**, *61*, 12111; e) D. Castellnou, L. Solà, C. Jimeno, J. M. Fraile, J. A. Mayoral, A. Riera, M. A. Pericàs, *J. Org. Chem.* **2005**, *70*, 433; f) A. Bastero, D. Font, M. A. Pericàs, *J. Org. Chem.* **2007**, *72*, 2460; g) M. A. Pericàs, C. I. Herrerías, L. Solà, *Adv. Synth. Catal.* **2008**, *350*, 927; h) F. Michalek, A. Lagunas, C. Jimeno, M. A. Pericàs, *J. Mater. Chem.* **2008**, *18*, 4692.

[12] a) C. W. Tornøe, M. Meldal, in: *Proceedings of the Second International and Seventeenth American Peptide Society Symposium*, (Eds.: M. Lebl, R. A. Houghten), American Peptide Society and Kluwer Academia Press, San Diego, **2001**, p 263; b) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057; c) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2708; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596. For a review on the concept of click chemistry, see: d) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 2056; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.

[13] a) D. Font, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2006**, *8*, 4653; b) D. Font, A. Bastero, S. Sayalero, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2007**, *9*, 1943; c) E. Alza, X. C. Cambeiro, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2007**, *9*, 3717; d) D. Font, S. Sayalero, A. Bastero, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2008**, *10*, 337.

[14] For additional examples of ligand supporting using click chemistry, see: a) A. Gheorghe, A. Matsuno, O. Reiser, *Adv. Synth. Catal.* **2006**, *348*, 1016; b) R. J. Detz, S. A. Heras, R. de Gelder, P. W. N. M. van Leeuwen, H. Hiemstra, J. N. H. Reek, J. H. van Maarseveen, *Org. Lett.* **2006**, *8*, 3227; c) A. Gissibl, M. G. Finn, O. Reiser, *Org. Lett.* **2005**, *7*, 2325; d) K. M. Kacprzak, N. M. Maier, W. Linder, *Tetrahedron Lett.* **2006**, *47*, 8721; e) M. Tilliet, S. Lundgren, C. Moberg, V. Levacher, *Adv. Synth. Catal.* **2007**, *349*, 2079; f) A. Gissibl, C. Padie, M. Hager, F. Jaroschik, R. Rasappan, E. Cuevas-Yanez, C.-O. Turrin, A.-M. Caminade, J.-P. Majoral, O. Reiser, *Org. Lett.* **2007**, *9*, 2895; g) A. Schaetz, R. N. Grass, W. J. Stark, O. Reiser, *Chem. Eur. J.* **2008**, *14*, 8262.

[15] D. Popa, C. Puigjaner, M. Gómez, J. Benet-Buchholz, A. Vidal-Ferran, M. A. Pericàs, *Adv. Synth. Catal.* **2007**, *349*, 2265.

[16] A. Vidal-Ferran, A. Moyano, M. A. Pericàs, A. Riera, *J. Org. Chem.* **1997**, *62*, 4970.

[17] M. Pastó, B. Rodríguez, A. Riera, M. A. Pericàs, *Tetrahedron Lett.* **2003**, *44*, 8369.

[18] M. A. Pericàs, C. Puigjaner, A. Riera, A. Vidal-Ferran, M. Gómez, F. Jiménez, G. Muller, M. Rocamora, *Chem. Eur. J.* **2002**, *8*, 4164.

[19] a) K. Harju, M. Vahermo, I. Mutikainen, J. Yli-Kauhaluoma, *J. Comb. Chem.* **2003**, *5*, 826; b) S. Löber, P. Gmeiner, *Tetrahedron* **2004**, *60*, 8699.

[20] T. Ohta, H. Sasayama, O. Nakajima, N. Kurahashi, T. Fujii, I. Furukawa, *Tetrahedron: Asymmetry* **2003**, *14*, 537.

[21] a) U. Burckhardt, M. Baumann, A. Togni, *Tetrahedron: Asymmetry* **1997**, *8*, 155; b) L. Hintermann, F. Lang, P. Maire, A. Togni, *Eur. J. Inorg. Chem.* **2006**, 1397.

[22] a) L. D. Schmidt, *The Engineering of Chemical Reactions*, Oxford University Press, New York, **1998**; b) O. Levenspiel, *Chemical Reaction Engineering*, Wiley, New York, **1998**.

[23] Visual inspection of the system when a dichloromethane solution of highly fluorescent *coumarin 6* [3-(2-benzothiazolyl)-7-(diethylamino)coumarin; CAS number 38215–36–0] is circulated through the tubular reaction in the dark under ultraviolet irradiation ($\lambda =$ 365 nm) shows a flat and uniform liquid front.

[24] Residence time of the reaction mixture in the resin-filled reactor was estimated by circulating a dichloromethane solution of *coumarin 6* through the column loaded with previously swollen resin **9f** in the dark under ultraviolet irradiation ($\lambda = 365$ nm), and measuring the times when fluorescence is first observed in the section of the reactor occupied by the resin and when fluorescence first appears after this section of the reactor.

[25] a) C. O. Kappe, A. Stadler, *Microwaves in Organic and Medicinal Chemistry*, Wiley-VCH, Weinheim, **2005**; b) T. Razzaq, J. M. Kremsner, C. O. Kappe, *J. Org. Chem.* **2008**, *73*, 6321.

[26] P. A. Auburn, P. B. Mackenzie, B. Bosnich, *J. Am. Chem. Soc.* **1985**, *107*, 2033.

[27] D. A. Evans, K. R. Campos, J. S. Tedrow, F. E. Michael, M. R. Gagné, *J. Am. Chem. Soc.* **2000**, *122*, 7905.

[28] D. Zhao, K. Ding, *Org. Lett.* **2003**, *5*, 1349.

