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Supported Catalysis

Asymmetric Allylation of Ketones and Subsequent Tandem Reactions Catalyzed by a Novel Polymer-Supported Titanium–BINOLate Complex**

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Abstract: By using a novel, simple, and convenient synthetic route, enantiopure 6-ethynyl-BINOL (BINOL = 1,1-binaphthol) was synthesized and anchored to an azidomethylpolystyrene resin through a copper-catalyzed alkyne–azide cycloaddition (CuAAC) reaction. The polystyrene (PS)-supported BINOL ligand was converted into its diisopropoxytitanium derivative in situ and used as a heterogeneous catalyst in the asymmetric allylation of ketones. The catalyst showed good activity and excellent enantioselectivity, typically matching the results obtained in the corresponding homogeneous reaction. The allylation reaction mixture could be submitted to epoxidation by simple treatment with *tert*-butyl hydroperoxide (TBHP), and the tandem asymmetric allylation epoxidation process led to a highly enantioenriched epoxy alcohol with two adjacent quaternary centers as a single diastereomer. A tandem asymmetric allylation/Pauson–Khand reaction was also performed, involving simple treatment of the allylation reaction mixture with $Co_2(CO)_8$/*N*-methyl morpholine *N*-oxide. This cascade process resulted in the formation of two diastereomeric tricyclic enones in high yields and enantioselectivities.

Introduction

Heterogenization of small molecule catalysts is an effective strategy to combine the attributes of homogeneous and heterogeneous catalysis.[1] Such an approach enables catalyst development and optimization under homogeneous conditions, yet ultimately affords catalysts with the stability and recyclability of heterogeneous systems. Despite the seeming simplicity of this approach to catalyst development, it is not without challenges.[2] The choice of linker and solid supports are crucial to successful catalyst immobilization without loss of selectivity or reactivity. Supporting homogeneous catalyst is particularly challenging in the case of asymmetric catalysts, for which subtle affects exerted by the support can undermine enantioselectivities observed in solution phase.[3]

Recently, one of our teams successfully employed the copper-catalyzed alkyne–azide cycloaddition (CuAAC) reaction[4] to covalently immobilize ligands[5] and organocatalysts onto polystyrene resins (PS).[6] Given the generality and utility of click reactions, we decided to immobilize one of the privileged proligands of asymmetric catalysis, BINOL,[7] to synthesize early transition-metal and lanthanide-based asymmetric Lewis acid catalysts. Herein, we report the covalent immobilization of BINOL to polystyrene by employing a 1,2,3-triazole linker to heterogenize a titanium-BINOLate catalyst and its application in the enantioselective allylation of ketones, the tandem asymmetric allylation/epoxidation of enones, and the tandem asymmetric allylation/Pauson–Khand reaction with ynones. We also demonstrate recyclability of the supported BINOL derivatives with minimal erosion of enantioselectivity over three reaction cycles.

Results and Discussion

Synthesis of PS-supported BINOL

The first step toward covalent catalyst immobilization is the design of a suitable linker to tether the homogeneous ligand to the support. We envisioned a novel alkyne-functionalized BINOL derivative and subsequent anchoring of the chiral ligand onto azide terminated polystyrene using CuAAC. Although several linkers have been successfully applied to cova-

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[**] BINOL = 1,1-binaphthol

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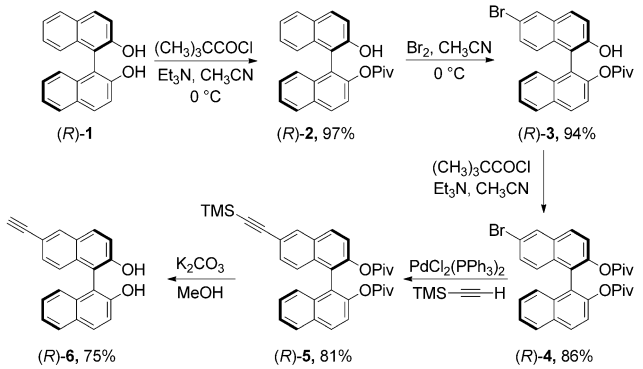
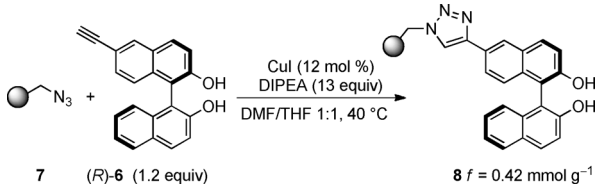
lently immobilize BINOL through the 6-position, we chose to use the CuAAC reaction[4] due to its generality, high-yields, and because of the existence of diagnostic spectroscopic handles (alkyne and azide IR stretching bands) for reaction monitoring. To synthesize the alkyne-functionalized BINOL ligand, we modified the synthetic route described by Uozumi and co-workers.[8] To selectively functionalize the 6-position and avoid 6,6′-difunctionalization of the naphthyl groups,[9] a selective monoesterification of the hydroxyl groups was performed with bulky pivaloyl chloride to provide (*R*)-**2** in 97% yield (Scheme 1). Next,



Scheme 1. Preparation of (*R*)-6-ethynyl-BINOL.

chemoselective bromination at the 6-position of the monopivalate (*R*)-**2** afforded (*R*)-**3** in 94% yield.[10] We planned to use monoprotected (*R*)-**3** in a palladium- catalyzed Sonogashira coupling reaction[11] to introduce the trimethylsilylethynyl substituent. However, bromide (*R*)-**3** resulted in the formation of a complex mixture when subjected to Sonogashira coupling conditions.[12] Alternatively, treatment of intermediate (*R*)-**3** with pivaloyl chloride yielded diester (*R*)-**4** in 86% yield, and subsequent Sonogashira coupling with trimethylsilylacetylene furnished intermediate (*R*)-**5** in 81% yield. The latter Intermediate was hydrolyzed and desilylated by treatment with K_2CO_3 in methanol to afford the desired unsymmetrical BINOL derivative (*R*)-**6** in 75% yield.

Tethering of the alkynyl-functionalized BINOL to the polymer support was accomplished by using the CuAAC reaction as shown in Scheme 2. Azidomethylpolystyrene resin (**7**) with a functionalization of 0.48 mmol g^{-1} was synthesized from commercially available Merrifield resin (1% DVB, f= 0.5 mmol g^{-1}). The IR spectrum of the azide-functionalized resin exhibited a characteristic azide band at 2096 cm^{-1} (see



Scheme 2. Anchoring of the functionalized BINOL to the polymer support by CuAAC.

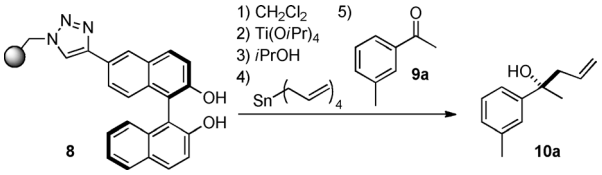
the Supporting Information, Figure S1). The CuAAC reaction was performed in DMF/THF (1:1) at 40 °C, by using a slight excess of (*R*)-**6** (1.2 equiv) and in the presence of 12 mol% CuI and DIPEA (13 equiv).

The progress of the reaction was monitored by IR spectroscopic analysis of the resin by following the disappearance of the azide stretch at 2096 cm^{-1}. Upon consumption of the azide, the polymer was sequentially washed with water, MeOH, THF and CH_2Cl_2, and dried as outlined in the Experimental Section. From the elemental analysis of the resin, the functionalization of the polystyrene-supported BINOL was determined to be 0.42 mmol g^{-1}.

Use of PS-supported BINOL 8 in the catalytic asymmetric allylation of ketones

We next turned our attention to applications of the supported BINOL ligand. Based on our prior experience with titanium-based catalysts,[13] we chose the titanium-catalyzed asymmetric allylation of ketones to evaluate the performance of the tethered ligand/support network. To the best of our knowledge, there have been no reports of the titanium catalyzed asymmetric ketone allylation under heterogeneous conditions, despite the utility of enantioenriched tertiary homoallylic alcohols in synthesis,[14] and the generality of the reported homogeneous method.[15]

The decreased reactivity of ketones relative to aldehydes requires the use of stronger allylating agents such as tetraallylstannane, in the homogeneous reactions.[13c–e, 15] The reaction of 3-methylacetophenone (**9a**) with tetraallyltin mediated by the polymer-supported (BINOLate)Ti catalyst system was selected to optimize reaction conditions (Scheme 3).



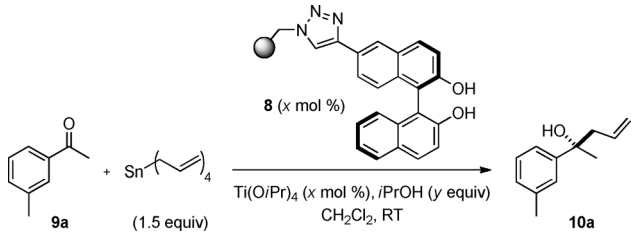
Scheme 3. Allylation of **9a** mediated by the PS-supported (BINOLate)Ti species derived from **8**.

We first examined the impact of different orders of addition of the substrate and reagents to the supported BINOL ligand. When PS-supported BINOL **8** was treated sequentially with dichloromethane, titanium tetraisopropoxide, isopropyl alcohol, and tetraallyltin, followed by the addition of ketone **9a**, the allylated product **10a** was obtained with 95% *ee*, which is comparable to the result of the homogeneous reaction.[13c] On the other hand, when a period of catalyst aging (24 h) was introduced before the ketone substrate was added, a slight decrease in enantioselectivity was observed (90%). To determine whether the order of addition of titanium tetraisopropoxide and tetraallyltin to the reaction mixture could affect the enantioselectivity of the reaction, two additional experiments were performed. In one of them, a mixture of **8**, dichloromethane,

and isopropyl alcohol was treated with titanium tetraisopropoxide for 20 min, followed by the addition of tetraallyltin. After 10 min, ketone **9a** was added leading to the formation of **10a** with 94% *ee*. In the second experiment, all parameters were kept equal, but the order of addition of titanium tetraisopropoxide and tetraallyltin was reversed. In this case, 93% enantioselectivity was observed, indicating that the order of addition of these two reagents does not impact the product *ee*. Following this result, a reaction protocol involving the simple sequential addition of reagents in the order shown in Scheme 3 (see Experimental Section) was adopted for the rest of this study.

It has been previously established that under homogeneous conditions, the presence of 2-propanol is critical for the achievement of high levels of enantioselectivity in the allylation of ketones catalyzed by the (BINOLate)Ti system.[13c–e] As illustrated in Table 1, the presence of 2-propanol had a dramatic

Table 1. Optimization of reaction conditions for the asymmetric allylation of 3-methylacetophenone (**9a**) mediated by the PS-supported (BINOLate)-Ti species derived from **8**.[a]



Entry	2-Propanol [*y* equiv]	**8** [*x* mol%]	*ee* of **10a** [%][b]
1	0	30	76
2	5	30	90
3	10	30	92
4	20	30	95
5	50	30	93
6	100	30	85
7	20	20	92
8	20	10	86
9	20	5	74

[a] The reactions were run at a 0.1 mmol scale and monitored by TLC. [b] The *ee* was determined by HPLC analysis (see the Supporting Information for conditions).

impact on the performance of the heterogenized system. Thus, the *ee* values of the products gradually increase from 76% without added 2-propanol (entry 1) to 95% (entry 4) with 20 equiv 2-propanol, whereas addition of more than 20 equiv 2-propanol led to diminished selectivity (entries 5 and 6). The effect of catalyst loading on the product yield and *ee* was also investigated. As shown in entries 7–9, the product *ee* decreased from 95 to 74% as the catalyst loading was diminished from 30 (entry 4) to 5 mol% (entry 9). According to this, the optimized reaction conditions involved the use of 30 mol% PS-supported BINOL **8**, 30 mol% $Ti(OiPr)_4$, 1.5 equiv tetraallyltin, and 20 equiv 2-propanol at room temperature (entry 4).

We then planned to explore the recycling and reuse of PS-immobilized BINOL (**8**). In its simplest version, recycling would only involve the addition of the two reactants (ketone and tetraallyltin), solvent, and additive 2-propanol to a (BINOLate)Ti species arising from a previous reaction cycle. However, when catalyst recovered by filtration was reused in this way, a decrease in enantioselectivity was observed. It was subsequently established by ICP-MS analysis that up to 96% of its initial titanium content is leached from the resin in a single reaction cycle.[16] Based on these results, it was evident that intercycle remetallation with titanium tetraisopropoxide was also required for effective reuse. Very gratifyingly, when treatment with $Ti(OiPr)_4$ (30 mol%) was incorporated between cycles, both yield and enantioselectivity were essentially preserved. By using this approach, the allylation product was obtained in good yield and *ee* after three consecutive reaction cycles (Table 2).[17]

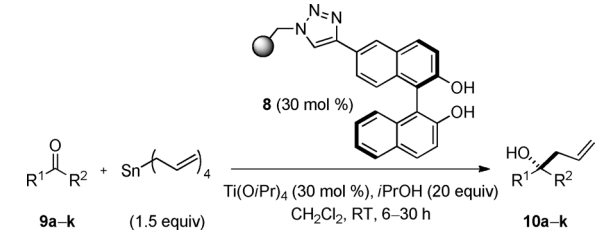
Table 2. Recycling of the PS-supported (BINOLate)Ti species derived from **8** in the asymmetric allylation of 3-methylacetophenone (**9a**).[a]

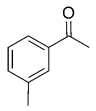
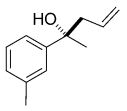
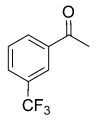
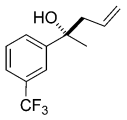
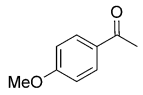
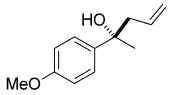
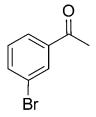
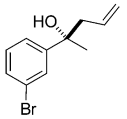
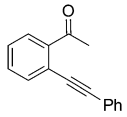
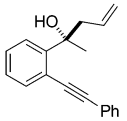
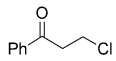
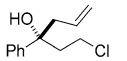
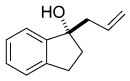
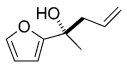
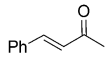
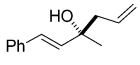
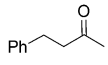
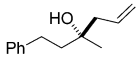
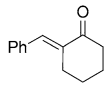
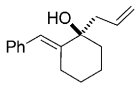
Cycle	Yield [%][b]	*ee* [%][c]
1	96	95
2	93	91
3	90	82

[a] The reactions were run at a 0.3 mmol scale, using the optimized reaction conditions (Table 1, entry 4). Upon completion of the reaction, the polymer-supported BINOL-titanium catalyst **8** was separated by simple filtration and washed with dichloromethane in a glovebox before the next reaction cycle. [b] Isolated yield. [c] The *ee* was determined by HPLC analysis (see the Supporting Information).

With the optimal conditions for the heterogeneous asymmetric allylation reaction in place, we turned our attention to the ketone substrate scope. We have summarized in Table 3 the yields and enantioselectivities observed with the catalytic system derived from the PS-supported BINOL (**8**) in the allylation of a representative family of ketones. When available, the enantioselectivity recorded with the homogeneous catalyst[13c–d] has been included for comparison purposes. With substituted acetophenones, the most common substrates for this reaction, very high enantioselectivities were observed. Enantioselectivities comparable to those recorded with the corresponding homogeneous catalytic system,[13c] were achieved in the cases of *meta*- (entries 1, 2, and 4) and *ortho*-substituted (entry 5) substrates, whereas the *ee* achieved with a *para*-substituted substrate was lower than with the homogeneous catalyst. With linear ketones (entries 6 and 10), enantioselectivies essentially replicated those previously recorded with the homogeneous catalyst, whereas the behavior of α,β-unsaturated ketones depended on the structural characteristics of the substrate. Thus, whereas the allylation of benzylideneacetone **9i** (entry 9) took place with lower enantioselectivity than with the homogeneous catalyst, the introduction of a substituent α to the carbonyl group and rigidification of the system in **9k** (entry 11) substantially improved the enantioselectivity. In any case, both α,β-unsaturated substrates underwent exclusively 1,2-allylation at the carbonyl site. As deduced from the com-

Table 3. Substrate scope in the asymmetric allylation of ketones mediated by the PS-supported (BINOLate)Ti species derived from **8**.[a]



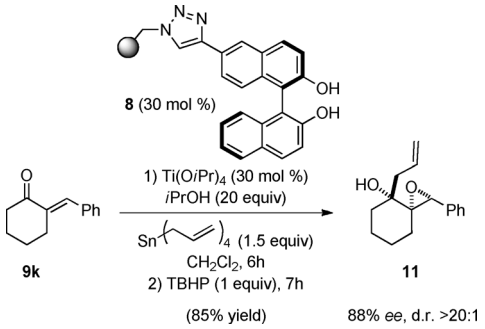
Entry	Substrate	9	Product	10	Yield [%][b]	*ee* [%][c]
1		**9a**		**10a**	96	95 (96)[d]
2		**9b**		**10b**	91	94 (92)[d]
3		**9c**		**10c**	80	70 (89)[d]
4		**9d**		**10d**	95	93
5		**9e**		**10e**	94	92[e]
6		**9f**		**10f**	67	73 (76)[d]
7		**9g**		**10g**	81	70 (87)[f,g]
8		**9h**		**10h**	70	86 (84)[d]
9		**9i**		**10i**	85	77 (90)[d]
10		**9j**		**10j**	98	76 (80)[d]
11		**9k**		**10k**	91	88 (96)[f]

[a] The reactions were run at a 0.2 mmol scale and monitored by TLC. [b] Isolated yield. [c] The *ee* was determined by GC or HPLC analysis (see the Supporting Information). [d] Value in parentheses refers to the homogeneous catalytic system reported in [13c]. [e] Stereochemistry was assigned by analogy with other allylation products in the table. [f] Value in parentheses refers to the homogeneous catalytic system reported in [13d]. [g] Reaction performed at 0 °C.

parison of entries 7 and 11, cyclohexanones were superior to cyclopentanones as substrates for asymmetric allylation mediated by the immobilized (BINOLate)Ti species derived from **8**. In the case of the heteroaromatic substrate 2-acetylfuran (**9h**), the desired homoallylic alcohol **10h** was obtained with 86% *ee* (entry 8), slightly beating the homogeneous catalyst. According to these results, some of the most common structural types of ketones are appropriate substrates for the asymmetric allylation mediated by the PS-supported (BINOLate)Ti species derived from **8**. The reactions take place at room temperature affording the target homoallylic alcohols in high yield. Remarkably, this is one of the very few examples of catalytic creation of quaternary centers involving the use of a heterogenized catalytic species.[18]

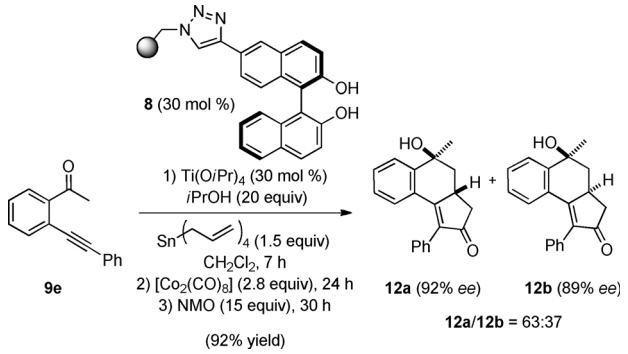
Use of PS-supported BINOL 8 in tandem processes initiated by the catalytic asymmetric allylation of ketones

Tandem reactions represent an important avenue to improve synthetic efficiency by rapidly increasing molecular complexity while minimizing the number of isolation and purification steps.[19] We have previously demonstrated that a tandem asymmetric allylation/diastereoselective epoxidation can be performed with enones to provide epoxy alcohols with excellent enantio- and diastereoselectivities over three contiguous stereocenters.[13d] It was of interest to determine whether a similar tandem reaction could be performed by using the heterogenized titanium catalyst. After subjecting (*E*)-2-benzylidenecyclohexanone (**9j**) to the asymmetric allylation with the heterogenized catalyst (Scheme 4), anhydrous *tert*-butyl hydroperoxide (TBHP; 1 equiv.) was added to the allylation reaction mixture at room temperature. As shown in Scheme 4, the supported titanium catalyst subsequently catalyzed a directed epoxidation reaction of the dienol intermediate **10k**. It is well-known that titanium catalysts exhibit excellent chemoselectivities, promoting epoxidation of allylic alcohols over homoallylic alcohols.[20] In the present instance, standard workup provided the epoxy alcohol product **11** as a single diastereomer and with the same enantioselectivity as in the simple asymmetric allylation of **9k** (Table 3, entry 11). Remarkably, **11** contains two adjacent quaternary centers, the formation of which is sequentially mediated by the same immobilized catalytic system.



Scheme 4. Tandem asymmetric allylation/epoxidation reaction of **9k**.

Another reaction that efficiently builds complexity and introduces functionality typically found in natural products is the Pauson–Khand reaction (PKR).[21,22] We envisioned that



Scheme 5. Tandem asymmetric allylation/intramolecular Pauson–Khand reaction of **9e**.

a tandem asymmetric allylation of alkyne substituted **9e** (Table 3, entry 5) could be followed by an intramolecular PKR to afford tricyclic ketones with high enantioselectivity (Scheme 5). To test substrate suitability, the isolated homoallylic alcohol product **10e** was first subjected to intramolecular PKR by treatment with $[Co_2(CO)_8]$ and using *N*-methyl morpholine *N*-oxide (NMO) as the promoter.[23] The desired product **12** was obtained in 95% yield as a 57:43 mixture of *syn* and *anti* diastereomers, according to NMR spectroscopic analysis (see the Supporting Information). We next performed the allylation/PKR in a tandem fashion (Scheme 5). In this experiment, the asymmetric allylation was conducted by using the optimized conditions (Table 3, entry 5) with the PS-supported catalyst and, when the allylation was complete (TLC), dicobalt octacarbonyl (2.8 equiv) was added to the reaction vessel and the reaction mixture stirred for 24 h to ensure complete complexation of the alkyne. NMO (15 equiv) was then added, and the reaction mixture was stirred at room temperature until disappearance (TLC) of the intermediate dicobalt hexacarbonyl complex (30 h). A 63:37 mixture of the diastereomeric products **12a** and **12b** could be isolated in 92% yield after work-up and purification. As expected from the result in the simple allylation of **9e** (Table 3, entry 5), the tricyclic compounds **12a** and **12b** were obtained in high enantiomeric purity. It is noteworthy that the present tandem allylation/intramolecular PKR process results in the formation of complex, highly enantioenriched tricyclic systems in a one-pot manner from simple achiral substrates.

Conclusion

A new polystyrene-supported BINOL ligand has been prepared, and the derived (BINOLate)Ti complex has been successfully used in the challenging catalytic asymmetric allylation of ketones. The heterogenized catalyst exhibits good activity and, for some of the most common ketone types, excellent enantioselectivities that replicate those reported with the homogeneous catalyst. The reusability of the immobilized BINOL ligand has been demonstrated, and the heterogenized catalytic species has been successfully used in the tandem asymmetric allylation/epoxidation and tandem asymmetric allylation/intramolecular Pauson–Khand reaction. In particular, the tandem allylation/epoxidation process delivers, in a highly diastereo- and enantioselective manner, a product with two adjacent quaternary centers and shows the unique potential of the (BINOLate)-Ti species derived from **8** for the catalytic asymmetric creation of these elusive structural units.

Experimental Section

General procedure for the asymmetric allylation of ketones

Polymer-supported BINOL **8** ($f = 0.42$ mmol g^{-1}, 143 mg, 0.06 mmol, 30 mol%) was weighed into a cylindrical reaction vessel in a glovebox (N_2 atmosphere). Dichloromethane (0.57 mL) and titanium(IV) isopropoxide (1:1 ratio with **8**, 18 μL, 0.06 mmol, 30 mol%) were added and the mixture was stirred for 10 min at RT. During this time, the polymer became red. 2-Propanol (0.3 mL, 4 mmol, 20 equiv) and tetraallyltin (72 μL, 0.3 mmol, 1.5 equiv) were then added, followed by the ketone (0.2 mmol, 1 equiv). The flask was capped tightly and stirred at RT until the reaction mixture became pale-yellow. When the reaction was complete as determined by TLC analysis (6–30 h), dichloromethane (5 mL) was added to the reaction mixture and the reaction was quenched with saturated aqueous NH_4Cl and extracted with dichloromethane (2×5 mL). The combined organic layer was dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. Hexanes (15 mL) was added and the solution was filtered through Celite, and concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel.

Procedure for the recycling

The reusability of the catalyst in the allylation reaction was checked at 0.3 mmol scale. Polymer-supported BINOL **8** ($f = 0.42$ mmol g^{-1}, 30 mol%, 214 mg, 0.09 mmol) was weighed into a cylindrical reaction vessel in a glovebox (N_2 atmosphere). Dichloromethane (0.81 mL) and titanium(IV) isopropoxide (1:1 ratio with **8**, 30 mol%, 0.09 mmol, 27 μL) were added and the mixture was stirred for 10 min at RT. During this time, the polymer became red. 2-Propanol (20 equiv, 6 mmol, 0.46 mL) and tetraallyltin (1.5 equiv, 0.45 mmol, 0.1 mL) were added, followed by 1-(*m*-tolyl)-ethanone **9a** (1 equiv, 0.3 mmol, 41 μL). The reaction was monitored by TLC and, upon completion (8 h), the polymer-supported BINOL-titanium-based catalyst was separated by simple filtration and washed with dichloromethane (50 mL) in the glovebox. The filtrate was taken out of the glovebox and quenched with saturated aqueous NH_4Cl for product isolation (see General procedure, above). The polymer was again taken in a cylindrical reaction vessel and dichloromethane (0.81 mL) was added. Then, the catalyst was recharged with 30 mol% titanium isopropoxide (0.09 mmol, 27 μL) and another portion of reactants was added for the next reaction cycle.

Tandem asymmetric allylation/epoxidation reaction of 9k

Performed as described in the general procedure. Upon completion of the allylation (6 h), anhydrous TBHP (5.5 M in decane, 1 equiv.) was added to the reaction mixture at RT, and the reaction was stirred for an additional 7 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) followed by addition of dichloromethane (5 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2×5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. Hexanes (15 mL) was

added and the solution was filtered through Celite, and concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel.

Tandem asymmetric allylation/intramolecular Pauson–Khand reaction of 9e

Performed as described in the general procedure. Upon completion of the allylation (7 h), $Co_2(CO)_8$ (2.8 equiv.) was added to the reaction mixture at RT and stirring was continued for an additional 24 h. After this period, NMO (15 equiv.) was added and stirring was continued for another 30 h. The reaction was quenched with saturated aqueous NH_4Cl followed by addition of EtOAc (5 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2×5 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated under vacuum and the remaining oil was purified by column chromatography on silica gel.

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