

Silica-Supported Catalyst for Enantioselective Arylation of Aldehydes under Batch and Continuous-Flow Conditions

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ABSTRACT: A silica-supported 3-aryl H_8 -BINOL-derived titanium catalyst exhibited high performance in the enantioselective arylation of aromatic aldehydes using Grignard and organolithium reagents not only under batch conditions but also under continuous-flow conditions. Even with a simple pipet reactor packed with the heterogeneous catalyst, the enantioselective production of chiral diarylmethanols could be achieved through a continuous introduction of aldehydes and mixed titanium reagents generated from the organometallic precursors. The pipet reactor could be used repeatedly in different reactions without appreciable deterioration of the activity.

I mmobilization of chiral molecular catalysts on solid supports has been an active area of research to enhance practicality.¹ The resulting heterogeneous catalysts would not only simplify separation and the recycling process when used in a batch system but also enable continuous production of enantiopure products when used in a flow system.² In spite of these potential advantages, immobilization often results in lower activities and enantioselectivities as compared to those observed for their homogeneous counterparts due to limited access to the active catalysts and their restricted degrees of freedom.^{1d}

For the enantioselective carbonyl addition reactions, a number of chiral ligands have been grafted on polymers and silicas since the pioneering work by Fréchet³ and Soai.^{4,5} Recently, Pericas and co-workers reported highly efficient, chiral amino alcohol based, polymer-supported catalysts⁶ that can be successfully employed under continuous flow conditions.⁷ Despite these advances, and with very few exceptions,7b the reported immobilized catalysts have been developed and evaluated for the reaction of diorganozincs, particularly Et₂Zn. Recently, we have developed a heterogeneous titanium catalyst derived from silica-supported 3-aryl (SSA-) H₈-BINOL ligand (Scheme 1) that exhibits high activity and enantioselectivity in the reactions using not only Et₂Zn but also Et₃B and aryl Grignard reagents as mixed titanium reagents with Ti(O'Pr)4.8 It has been demonstrated that the catalyst is robust enough to be reused up to 14 times in batch conditions without appreciable deterioration of the activity.

In the present study, the potential of the SSA- H_8 -BINOLderived catalyst was further exploited in the enantioselective Scheme 1. Enantioselective Carbonyl Addition by a Silica-Supported Heterogeneous Catalyst



carbonyl arylation reactions using aryl Grignard reagents, including functionalized derivatives, and PhLi under the batch and flow conditions. Herein, we report the results of the study together with the characterization of the immobilized ligands by solid-state NMR spectroscopy.

SSA-H₈-BINOL (*R*)-3 was prepared by grafting hydrosilane precursor (*R*)-1 on the surface of amorphous silica (480 m²/g) under B(C₆F₅)₃ (6 mol %) catalysis⁹ and then capping the free silanol groups of the resulting silica (*R*)-2 with EtMe₂SiH under similar conditions (Scheme 2).⁸ Thus, prepared grafted silica (*R*)-3 was estimated to contain 0.072–0.114 mmol/g of the (*R*)-H₈–BINOL unit with a cap/ligand ratio (*n*) of 6.9–15 (depending on the runs) by elemental analyses.

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Table 1. Enantioselective Arvlation of Aldehvdes Using a Pipet Reactor Packed with SSA-H₈-BINOL (R)-3^a

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Scheme 2. Preparation of SSA-H₂-BINOL (R)-3



Figure 1. ²⁹Si CP-MAS NMR spectrum of amorphous silica (a) and ¹³C NMR spectrum of (R)-1 (e) and ²⁹Si and ¹³C CP-MAS NMR spectra of silica grafted with EtMe₂SiH (1.46 mmol/g) (b and f), (R)-2 (0.075 mmol/g) (c and g), and (R)-3 (0.073 mmol/g, n = 15) (d and h).

SSA-H₈-BINOL (R)-3 was characterized further by ²⁹Si and ¹³C CP-MAS NMR measurements (Figure 1). Before capping, the grafted silica (*R*)-2 exhibited the ²⁹Si resonance at 13.8 ppm (c), which is a typical chemical shift for trialkylsilyloxy groups $(M; R_3 SiOSi)$ on the silica surface and ¹³C signals in aromatic (110–160 ppm) and aliphatic (15–45 ppm) region (g) in accord with the spectrum of precursor (R)-1 (e), thus indicating that the chiral ligand was immobilized on the surface with Si-O bonding. After capping, strong ¹³C resonances derived from EtMe₂Si group appeared from -8 to 12 ppm (h and f) in addition to the aromatic and aliphatic signals. The ratio of the aliphatic ¹³C signals (15-45 ppm) to those of the EtMe₂Si group was consistent with the cap/ligand ratio (n) of 15 determined by elemental analyses. The ²⁹Si resonance of EtMe₂SiOSi overlapped with that of (R)-2 at 13.8 ppm (d and c). In comparison with unmodified silica (a), the intensity of signals derived from Si species Q2 $(Si(OH)_2(OSi)_2)$ was decreased and that of Q4 $(Si(OSi)_4)$ was significantly increased in (R)-3 (d). The observation showed that a large portion of the silanol groups on the silica surface was silvlated in SSA-H₈–BINOL (R)-3 and that the cross-polarization effectively occurs from ¹H nuclei of the capping groups to ²⁹Si of Q4 near the surface.

High turnover frequency, enantioselectivity, and robustness observed in the previous recycle experiments⁸ prompted us to use SSA-H₈-BINOL (R)-3 under flow conditions in the arylation of aldehydes with a mixed reagent of Grignard reagents

$R^{1} \xrightarrow{O}_{H} A M, B mL/h$ $MgBr \xrightarrow{(R)-3}_{(1.3 g, 90 \mu m)} \xrightarrow{R^{1}} \xrightarrow{OH}_{6} R^{2}$ $R^{2} \xrightarrow{OH}_{7} \xrightarrow{(I, 3 g, 90 \mu m)}_{CH_{2}Cl_{2}, 0 \circ C} \xrightarrow{R^{1}}_{6} \xrightarrow{OH}_{6} R^{2}$								
\bigcirc	63	`CI	Ľ) [6h		ont 6a		
	va			00		conversion	ee	
entry	\mathbb{R}^1	R ²	A^{b}	B^{c}	product	(%)	(%)	
$A1^d$	Н	Cl	0.2	1.25	6a	77	89	
A2	Η	Cl	0.2	2.5	6a	71	92	
A3	Н	Cl	0.2	5.0	6a	57	92	
A4 ^{e,f}	Н	Cl	0.2	2.5	6a	72^g	87	
-2 h	Н	Cl				78	92	
-4 h	Н	Cl				70	87	
-6 h	Н	Cl				80	89	
B1"	m-MeO	Н	0.4	1.25	6b	78	83	
B2	m-MeO	Н	0.4	2.5	6b	77	88	
B3	m-MeO	Н	0.4	5.0	6b	55	89	
B4 ^c	m-MeO	Н	0.4	2.5	6b	58 ⁸	84	
-2 h						59	85	
-4 h						61	84	
-8 h	C1			1.05		59	83	
	p-Cl	H	0.2	1.25	ent-6a	79	85	
C2	p-Cl	н	0.2	2.5	ent-6a	74	91	
U3 C⊿d,h,i	p-Cl	н	0.2	5.0	ent-6a	68 658	87	
04	p-CI	н	0.1	5.0		03°	88	
-2 n 4 h						83 72	94	
-4 n 4 h						/3	83 97	
-0 n						/3	0/	

^aUnless otherwise noted, flow reactions were carried out consecutively with the same pipet reactor. ^bMolar concentration of aldehydes. Unless otherwise noted, the concentration of mixed titanium reagents is 0.5 times that of aldehydes. ^cFlow rate (mL/h) of aldehydes. Unless otherwise noted, the flow rate of mixed titanium reagents is four times that of aldehydes. ^dA new pipet reactor was used. ^eA pipet reactor used in previous entries was employed after washing and reactivation. For details, see the text and the Supporting Information. ^fFlow time is 8 h. ^gIsolated yield. ^hFlow time is 9.1 h. ⁱConcentration and flow rate of the mixed titanium reagent are 0.13 M and 7.5 mL/min, respectively. Flow time is 7 h.

5 and $Ti(O^{i}Pr)_{4}$ (Table 1).¹⁰ A disposable pipet (6 × 100 mm), fitted with a rubber septum, was packed with 1.25 g (90 μ mol) of (R)-3 (0.072 mmol/g). A solution of a mixed reagent of p- ClC_6H_4MgBr and $Ti(O'Pr)_4$ (1:2.5 molar ratio) in CH_2Cl_2 (0.1 M with respect to the *p*-chlorophenyl group) was first introduced to the pipet reactor cooled at 0 °C with a syringe pump to prepare a yellow, immobilized chiral titanium catalyst. The flow rate of the mixed titanium reagent was adjusted as 5 mL/h, and then a solution of benzaldehyde (4a) in CH₂Cl₂ (0.2 M) was introduced additionally at 1.25 mL/h so that the molar ratio of the reagent to the aldehyde is 2. The reaction mixture eluted from the reactor for 0.5 h was quenched with aqueous 1 N HCl to give p-chlorophenyl adduct (S)-6a in 89% ee with 77% conversion (entry A1). The enantioselectivity was increased to 92% ee by the

increase of a flow rate of the substrate (2.5 and 5.0 mL/h) and the reagent (10 and 20 mL/h) albeit with concurrent lowering of the conversion (entries A2 and A3). A preparative-scale experiment was carried out under conditions similar to those of entry A2. Continuous introduction of the aldehyde and reagent solution for 8 h provided 0.65 g (72% yield) of (S)-6a in 87% ee (entry A4). During this experiment, aliquots of the eluate were withdrawn at 2, 4, and 6 h to monitor conversion and enantioselectivity. As shown in entries A4-2 h, -4 h, and -6 h, the conversion and selectivity remained almost constant throughout the reaction. It should be noted that these four experiments (entries A1-4) were performed in this order with the same pipet reactor, which was washed successively with 0.5 N HCl in 50% aqueous ethanol, ethanol, and CH₂Cl₂ and then activated with the flow of the mixed titanium reagent before the preparative experiment (entry A4).

Another series of experiments were carried out with manisaldehyde (4b) and PhMgBr at higher concentrations using a new pipet reactor (entries B1-4). From an increase of a flow rate of the aldehyde solution (0.4 M) and mixed titanium reagent solution (0.2 M), the enantioselectivity of the corresponding adduct (R)-6b was increased from 84% ee to 89% ee with decreasing conversion (entries B1-B3). A preparative experiment conducted under the conditions of entry B2 for 9.1 h afforded 1.95 g (59% yield) of (R)-6b in 84% ee (entry B4). Again, the activity of the catalyst was maintained throughout the reaction judging from the result of aliquot monitoring (entries B4-2h, -4h, and -8h). Under the flow conditions, the reaction of *p*-chlorobenzaldehyde (4c) (0.1 M) and a mixed titanium reagent (0.13 M) derived from PhMgBr provided 0.49 g (65% yield) of ent-6a (R enantiomer of 6a) in high enantioselectivity (88% ee) (entry C4). The conversion and selectivity for this reaction followed similar trends as those observed in entries A and B (entries C1–C3).¹¹

Optically active functionalized diarylmethanols are in demand as synthetic precursors to many biologically active compounds.¹² We recently reported an efficient method for the enantioselective preparation of these alcohols that is based on the arylation of aromatic aldehydes with functionalized Grignard reagents under homogeneous chiral titanium catalysis.^{10b,13} It was shown the thermally unstable functionalized reagents could be employed in the enantioselective addition as a mixed titanium reagents with $Ti(O^iPr)_4$. We examined the potential of the present heterogeneous catalysis in the functionalized arylation first under the batch conditions.

3-Iodobenzonitrile (7a) (2 equiv) was treated with c- C_5H_9MgBr in Et_2O at -40 °C, and the resulting Grignard reagent 5 bearing a cyano group was mixed with $Ti(O^{i}Pr)_{4}$ (3.3) equiv) (Table 2). The mixed titanium reagent was added to a well-stirred mixture of 1-naphthaldehyde (4d), $Ti(O^{i}Pr)_{4}$ (1.7 equiv), and (R)-3 (10 mol %) in CH₂Cl₂ at 0 °C for 3 h. After an additional 2 h of stirring, centrifugation of the reaction mixture and hydrolysis of the supernatant afforded the *m*-cyanophenyl adduct (R)-6c in 97% yield and 94% ee (entry A1). The residual silica-supported catalyst was used in the next run. Following this method, we managed to run up to six cycles for three different aldehydes 4d, 4a, and 4e with the same immobilized catalyst keeping high selectivity (83-96% ee) and yield (64-99%) (entries A2-A6). Under similar conditions, another series of recycle experiments were carried out using 1-bromo-3iodobenzene (7b) as a source of the mixed titanium reagent (entries B1-4). The four consecutive reactions of aldehydes 4d



Table 2. Enantioselective Arvlation of Aldehvdes Using

^{*a*}Unless otherwise noted, reactions were carried out with aldehyde 4 (0.5 mmol), iodoarene 7 (2 equiv), $c-C_5H_{11}MgCl$ (2.2 equiv), Ti(O'Pr)₄ (4.7 equiv), and (*R*)-3 (10 mol %) in Et₂O and CH₂Cl₂ at 0 °C for 5 h. ^{*b*}The reaction was carried out under flow conditions using a pipet reactor. For details, see the text and Supporting Information.

and 4a exhibited high enantioselectivity (81-91% ee) albeit with moderate yields (51-71%).

The functionalized arylation could be also carried out under flow conditions using a pipet reactor packed with 1.34 g of (R)-3 (0.094 mmol/g). Simultaneous introduction of a functionalized titanium reagent (0.1 M, 10 mL/h) generated from 7a and aldehyde 4d (0.2 M, 3.1 mL/h mL/h) for 4 h afforded 0.25 g (40% yield) of (R)-6c in high enantioselectivity (92% ee) (entry C).

The chiral immobilized catalyst is also applicable to the enantioselective addition of PhTi(O'Pr)₃ generated in situ from PhLi (Table 3).¹⁴ Treatment of PhLi with ClTi(OⁱPr)₃ in CH_2Cl_2 and addition of the resulting $PhTi(O^iPr)_3$ (2 equiv) to a CH_2Cl_2 solution of 1-naphthaldehyde (4d) and $Ti(O^iPr)_4$ (0.2) equiv) in the presence of (R)-3 (5 mol %) at 0 °C for 3 h provided the phenyl adduct (R)-**6h** of 76% ee in 92% yield (entry A1). In the following recycle experiments (entries A2-10), the enantioselectivity of (*R*)-**6h** was improved by the increase of the stirring rate, as shown in the second and the third cycle. With vigorous stirring, high selectivities (86-92% ee) as well as the quantitative yields were preserved up to the tenth cycle. According to our previous study on a relevant homogeneous catalyst system,¹⁴ PhTi(OⁱPr)₃ is reactive enough to undergo non-enantioselective addition to aldehydes. To realize high enantioselectivity, the high activity of the catalyst system is indispensable in overwhelming the background reaction. The rapid stirring might promote material transfer on the surface of

Table 3. Enantioselective Phenylation of 1-Naphthaldehyde(4d) with in Situ Generated Phenyltitanium Reagent^a

PhLi CITi(O ⁱ Pr) ₃	$\frac{4d}{(R)-3} (5 \bmod \%)$ $\frac{\text{Ti}(\text{O}^{j}\text{Pr})_{3}}{\frac{\text{Ti}(\text{O}^{j}\text{Pr})_{4}}{\text{CH}_{2}\text{Cl}_{2}, 0 \degree \text{C}}}$	OH Eh
entry	conversion (%)	ee (%)
A1	>99	76
A2	84	82
A3	100	88
A4	100	93
A5	100	92
A6	100	91
A7	100	87
A8	100	90
A9	97	91
A10	93	86
B ^b	44 ^c	95

"Unless otherwise noted, reactions were carried out with aldehyde 4d (0.5 mmol), PhTi(O'Pr)₃ (2 equiv), Ti(O'Pr)₄ (0.4 equiv), and (R)-3 (5 mol %) in CH₂Cl₂ at 0 °C. ^bThe reaction was carried out under flow conditions using a pipet reactor. For details, see the text and Supporting Information. ^cIsolated yield.

the catalyst, promoting the activity of heterogeneous catalyst. It should be noted that the present silica supported catalyst is of enough mechanical strength to be used up to the tenth cycle under vigorous stirring.

A pipet reactor packed with (R)-3 exhibited high performance for this reaction as well. A 4 h flow reaction employing in situ generated $PhTi(O^{i}Pr)_{3}$ (0.1 M, 10 mL/h) and 4d (0.2 M, 3.1 mL/h) provided 0.22 g (44% yield) of (R)-9h in excellent enantioselectivity (95% ee) (entry B).

In summary, it has been demonstrated that well-characterized silica-supported SSA-H₈–BINOL-derived catalyst exhibits high performance in enantioselective carbonyl arylation using Grignard and organolithium reagents under the batch and flow conditions.¹⁵ Even with a simple pipet reactor packed with the heterogeneous catalyst, the enantioselective production of chiral diarylmethanols has been realized through a continuous introduction of aromatic aldehydes and mixed titanium reagents generated from the organometallic precursors. The synthetic potential of the silica-supported catalyst was further indicated by the fact that the pipet reactor could be used repeatedly in different reactions without appreciable deterioration of the activity.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00945.

Experimental procedures and characterization of products (PDF)

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Notes

The authors declare no competing financial interest.

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