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Enantioselective addition of organozinc reagents to ketones catalyzed by grafted isoborneolsulfonamide polymers and titanium isopropoxide

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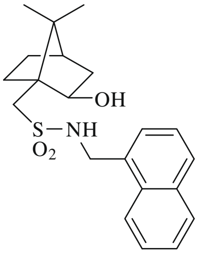
ABSTRACT

The catalytic enantioselective addition of different organozinc reagents, such as diethylzinc, or in situ generated phenylzinc derivatives to simple aryl methyl ketones was accomplished using titanium tetraisopropoxide and a polymeric ligand grafted with *trans*-1-phenylsulfonylamino-2-isoborneolsulfonylamidocyclohexane, to give the corresponding tertiary alcohols with enantioselectivities of up to >99% ee. Whereas the highest enantioselectivities were obtained in the ethylation process, the highest chemical yields were obtained in the phenylation process. The ligand could be re-used at least three times without any significant loss of activity.

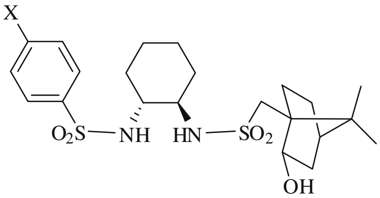
1. Introduction

Nowadays, the catalytic enantioselective generation of compounds with stereogenic tertiary carbon atoms can be easily achieved in most cases.[1] However, the related approach to compounds bearing quaternary stereocenters is still an enormous challenge for synthetic organic chemistry. Thus, every new enantioselective procedure for the construction of a fully substituted carbon center is of great value,[2] with the simplest approach for the preparation of chiral tertiary alcohols being the enantioselective 1,2-addition of organometallic reagents[3] to ketones.[4]

Recently, we introduced the isoborneolsulfonamide[5] **1** as the first chiral ligand[6] that has the ability to promote the catalytic enantioselective addition of dialkylzinc reagents to simple ketones[7] in the presence of titanium tetraisopropoxide,[8] other bisisoborneolsulfonamides having improved the initial results.[9] Among all tested ligands, *trans*-1-arylsulfonylamino-2-isobornylcyclohexane derivatives **2** gave the best results,[10] not only for alkylation but also for arylation process.[11]



1



2a: X = Me
2b: X = MeO

Although isoborneolsulfonamide ligands can be isolated from the reaction crude by flash chromatography, its complete recovery remains difficult. In general, to facilitate the separation of the homogeneous ligands or catalysts from the reaction mixture, they are usually immobilized on solid supports.[12] There are two main methods to immobilize a chiral ligand on a support: (a) the grafting of the desired ligand onto a preformed support containing reactive groups, and (b) the copolymerization of the suitable functionalized ligand with polymerizable monomers and cross-linkers. While the latter offers many possibilities for generating and controlling a specific environment around the ligand within the polymer matrix (needing more synthetic efforts), the former is often preferred since many suitable polymeric supports are commercially available.

The usual pathway of grafting a chiral molecule on a previously formed polymer is via the formation of a carbon–oxygen bond as ether or ester functionality. The functionalization of polymers via free-radical addition of mercaptans[13] has been less studied, even this protocol having the advantage of its high tolerance to different functionalities. This strategy has been only used in the grafting of chiral salen subunits to silica and single-wall carbon nanotubes,[14] as well as of a chiral styryl–proline derivative to a mercaptomethyl functionalized polystyrene.[15]

Herein, we report for the first time the preparation and use as heterogeneous chiral ligands of a mercaptomethyl functionalized polystyrene polymer grafting *trans*-1-phenylsulfanylamino-2-isobornylamino-cyclohexane moieties.

2. Results and discussion

Styryl derivative **3** was prepared in 41% overall yield starting from commercially available sodium 4-vinylbenzenesulfonate. Its reaction with thionyl chloride[16] gave the expected sulfonyl

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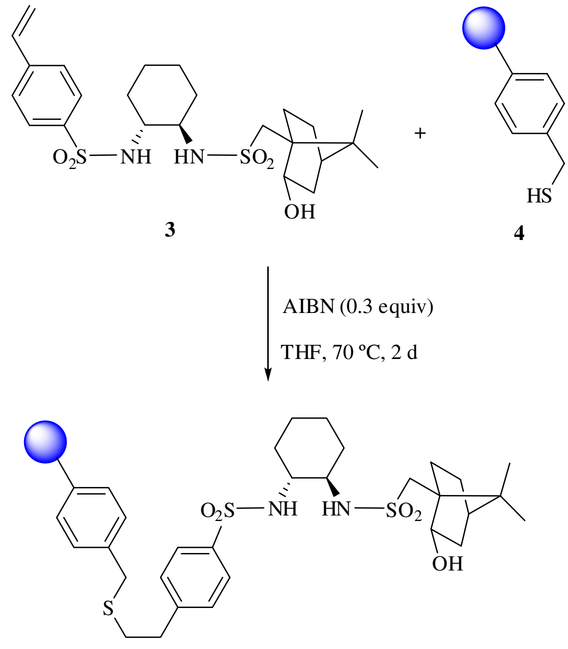
chloride derivative, which was trapped by reaction with (1*R*,2*R*)-*trans*-1,2-diaminocyclohexane under classical biphasic conditions. The final standard coupling reaction of the above prepared amine with (1*S*)-(+)-10-camphorsulfonyl chloride[17] yielded the corresponding ketone, which was diastereoselectively reduced to compound **3**, and easily isolated in pure form (>99%) by column chromatography.[18] The grafting of commercially available mercaptomethyl functionalized polystyrene polymer **4** (100–200 mesh, cross-linked with 1% divinylbenzene and functionalized in 2 mmol/g) was accomplished by a standard radical addition protocol[19] rendering the expected polymer **5**, after being washed with several portions of methanol and ethyl ether, with incorporations of the chiral subunit between 16% and 28%, according to the microanalysis data (Scheme 1).

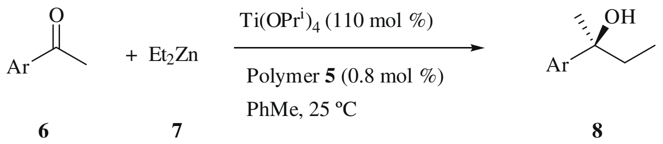


Scheme 1. Synthesis of grafted polymer **5**.

The polymeric ligand **5** was first tested in the enantioselective addition of commercially available diethylzinc **7** to acetophenone in the presence of Ti(OPr^i)$_4$. The reaction gave the expected tertiary alcohol **8a** at room temperature. Although the reaction rate was slow, the enantioselectivity was excellent, the minor (*R*)-enantiomer could not be detected by chiral column GC-analysis (Table 1, entry 1). An increase in the amount of polymeric ligand did not improve the moderate chemical yield previously obtained (compare entries 1 and 2 in Table 1). Next, we studied the influence of the electronic character of *para*-substituted groups, finding that both, electron-donating or electron-withdrawing groups, seemed to have a small negative impact on the results (entries 3 and 4 in Table 1). After these results, we changed the initial aryl methyl ketone to another α,β-unsaturated ketone with the results being excellent with regards to enantioselectivity concerns as well as chemical yield. The recyclability of polymer **5** was studied using this ketone (Table 1, entries 5–7). After performing and quenching the reaction with methanol, the polymeric ligand was successively washed with water and ether, then dried under high vacuum and re-used in a new reaction. The obtained results were concordant in all cases, rendering only one enantiomer with yields higher than 85%.

After the partial success found for the enantioselective ethylation of simple ketones, we turned our attention to the zinc reagent reactivity. The idea was to improve the reactivity of the zinc reagent in order to increase the chemical yield. Recently, the preparation of ethyl phenyl zinc reagent by transmetallation of diethylzinc with triphenylboron has been described;[20] this intermediate showed a higher reactivity and enantioselectivity in comparison to the related diethyl or diphenylzinc reagents.[21] The corresponding ethyl phenyl zinc intermediate was obtained starting from commercially available triphenyl boron **9** and diethylzinc **7** by heating in toluene at 70 °C. This intermediate was reacted in situ with *para*-bromoacetophenone in the presence of substoichiometric amounts of polymeric ligand **5** and a small excess of titanium tetraisopropoxide, giving the expected diaryl ethanol derivative **10a** with good chemical yield, but unfortunately with moderate enantioselectivity (Table 2, entry 1). This behavior has previously been described in the case of using aldehydes as electrophiles and using a homogeneous ligand.[22] The reaction gave similar enantioselectivities for other methyl aryl ketones, practically independent of the electronic character of aryl substituents (Table 2, entries 2–4).

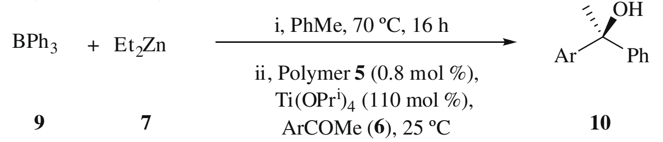
Table 1
Ethylation of methyl ketones



Entry	Time (d)	No.	Ar	Yield[a] (%)	ee[b] (%)
1	6	**8a**	Ph	36	>99 (*S*)
2	5[c]	**8a**	Ph	40	>99 (*S*)
3	17	**8b**	4-MeC$_4$H$_5$	29	96 (−)
4	17	**8c**	4-FC$_4$H$_5$	42	94 (−)
5	5	**8d**	$PhC\equiv C$	94	>99 (+)
6	5[d]	**8d**	$PhC\equiv C$	85	>99 (+)
7	5[e]	**8d**	$PhC\equiv C$	90	>99 (+)

[a] Isolated yields after bulb-to-bulb distillation.
[b] Determined by GLC using a β-CD column. In parentheses, the absolute configuration or the obtained sign of the specific rotation.
[c] Reaction performed using 2 mol % of polymer.
[d] Reaction performed after one use of the polymer.
[e] Reaction performed after two uses of the polymer.

Table 2
Phenylation of methyl ketones



Entry	Time (d)	No.	Ar	Yield[a] (%)	ee[b] (%)
1	5	**10a**	4-BrC$_6$H$_4$	92	60 (+)
2	6	**10b**	4-ClC$_6$H$_4$	98	61 (+)
3	6	**10c**	4-MeC$_6$H$_4$	38	66 (−)
4	6	**10d**	3-MeC$_6$H$_4$	90	28 (−)

[a] Isolated yields after column chromatography.
[b] Determined by HPLC using Chiracel columns. In parentheses, sign of the optical rotation.

3. Conclusion

In conclusion, we have described an easy and simple grafting of a sulfanyl-containing polymer bearing chiral *trans*-1-phenylsulfonylamino-2-isoborneolsulfonylaminocyclohexane moiety. This ligand has been shown to be a good promoter for the heterogeneous catalytic enantioselective alkylation and arylation of simple ketones, as well as its recovery and re-use.

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References

1. (a) *Stereoselective Synthesis (Houben-Weyl)*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vols. 1–10, (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vols. 1–3,.
2. (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037–2066; (b) Corey, E. J.; Guzmán-Pérez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388–401; (c) Ramón, D. J.; Yus, M. *Curr. Org. Chem.* **2004**, *8*, 149–183; (d) Ramón, D. J.; Yus, M. In *Quaternary Stereocenters-Challenges and Solutions for Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, 2005; pp 207–241; (e) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873–888; (f) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969–5994.
3. (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69; (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856; (c) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824; (d) Yus, M.; Ramón, D. J. *Recent Res. Devel. Org. Chem.* **2002**, *6*, 297–378; (e) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853–2873; (f) Yamada, K.-i.; Tomioka, K. *Chem. Rev.* **2008**, *108*, 2874–2886.
4. (a) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2004**, *116*, 286–289; (b) Hatano, M.; Ishihara, K. *Synthesis* **2008**, 1647–1675.
5. Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2479–2496.
6. (a) Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1239–1242; (b) Ramón, D. J.; Yus, M. *Tetrahedron* **1998**, *54*, 5651–5666.
7. (a) Yus, M.; Ramón, D. J. *Pure Appl. Chem.* **2005**, *77*, 2111–2119; (b) Ramón, D. J.; Yus, M. *Synlett* **2007**, 2309–2320; (c) Yus, M.; Ramón, D. J. *Latv. J. Chem.* **2007**, 345–353.
8. For reviews on enantioselective reactions promoted by titanium derivatives, see: (a) Ramón, D. J.; Yus, M. *Recent Res. Devel. Org. Chem.* **1998**, *2*, 489–523; (b) Ramón, D. J.; Yus, M. *Chem. Rev.* **2006**, *106*, 2126–2208.
9. For recent results from our group, see: (a) Yus, M.; Ramón, D. J.; Prieto, O. *Tetrahedron: Asymmetry* **2002**, *13*, 2291–2293; (b) Yus, M.; Ramón, D. J.; Prieto, O. *Tetrahedron: Asymmetry* **2003**, *14*, 1103–1114; (c) Prieto, O.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1955–1957; (d) Yus, M.; Ramón, D. J.; Prieto, O. *Eur. J. Org. Chem.* **2003**, 2745–2748.
10. (a) Forrat, V. J.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2005**, *16*, 3341–3344; (b) Forrat, V.; Prieto, O.; Ramón, D. J.; Yus, M. *Chem. Eur. J.* **2006**, *12*, 4431–4445 (corrigendum: *Chem. Eur. J.* **2006**, *12*, 6727); (c) Forrat, V. J.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 400–405.
11. For a review on enantioselective arylation processes, see: Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454–470.
12. For reviews, see: (a) Gladysz, J. A. *Chem. Rev.* **2002**, *102*, 3215–3216 (thematic issue on recoverable catalysts and reagents); (b) Corma, A.; García, H. *Chem. Rev.* **2003**, *103*, 4307–4365; (c) Dai, L.-X. *Angew. Chem., Int. Ed.* **2004**, *43*, 5726–5729; (d) Itsuno, S.; Haraguchi, N.; Arakawa, Y. *Recent Res. Devel. Org. Chem.* **2005**, *9*, 27–47; (e) Ding, K.; Wang, Z.; Shi, L. *Pure Appl. Chem.* **2007**, *79*, 1531–1540.
13. Justynska, J.; Hordyjewicz, Z.; Schlaad, H. *Polymer* **2005**, *46*, 12057–12064 and literature quoted therein.
14. Baleizão, C.; Gigante, B.; García, H.; Corma, A. *Tetrahedron* **2004**, *60*, 10461–10468.
15. (a) Giacalone, F.; Gruttadauria, M.; Marculescu, A. M.; Noto, R. *Tetrahedron Lett.* **2007**, *48*, 255–259; (b) Gruttadauria, M.; Giacalone, F.; Marculescu, A. M.; Lo Meo, P.; Riela, S.; Noto, R. *Eur. J. Org. Chem.* **2007**, 4688–4698.
16. Yus, M.; Ramón, D. J.; Prieto, O. *Tetrahedron: Asymmetry* **2002**, *13*, 1573–1579.
17. Prieto, O.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2000**, *11*, 1629–1644.
18. Forrat, V. J.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2054–2058.
19. Forrat, V. J.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19*, 537–541.
20. For examples on the enantioselective phenylation of aldehydes after boron/zinc transmetallation, see: (a) Rudolph, J.; Schmidt, F.; Bolm, C. *Adv. Synth. Catal.* **2004**, *346*, 867–872; (b) Rudolph, J.; Hermanns, N.; Bolm, C. *J. Org. Chem.* **2004**, *69*, 3997–4000; (c) Bolm, C.; Zani, L.; Rudolph, J.; Schiffers, I. *Synthesis* **2004**, 2173–2180; (d) Bolm, C.; Schmidt, F.; Zani, L. *Tetrahedron: Asymmetry* **2005**, *16*, 1367–1376; (e) Özçubukçu, S.; Schmidt, F.; Bolm, C. *Org. Lett.* **2005**, *7*, 1407–1409; (f) Rudolph, J.; Lormann, M.; Bolm, C.; Dahmen, S. *Adv. Synth. Catal.* **2005**, *347*, 1361–1368; (g) Dahmen, S.; Lormann, M. *Org. Lett.* **2005**, *7*, 4597–4600; (h) Schiffers, I.; Rantanen, T.; Schmidt, F.; Bergmans, W.; Zani, L.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 2320–2331; (i) Sedelmeier, J.; Bolm, C. *J. Org. Chem.* **2007**, *72*, 8859–8862.
21. (a) Rudolph, J.; Rasmussen, T.; Bolm, C.; Norrby, P.-O. *Angew. Chem., Int. Ed.* **2003**, *42*, 3002–3005; (b) Fontes, M.; Verdaguer, X.; Solà, L.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 2532–2543; (c) Rudolph, J.; Bolm, C.; Norrby, P.-O. *J. Am. Chem. Soc.* **2005**, *127*, 1548–1552.
22. Martínez, R.; Zoli, L.; Cozzi, P. G.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19*, 2600–2607.