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Assessing the Suitability of 1,2,3-Triazole Linkers for Covalent Immobilization of Chiral Ligands: Application to Enantioselective Phenylation of Aldehydes

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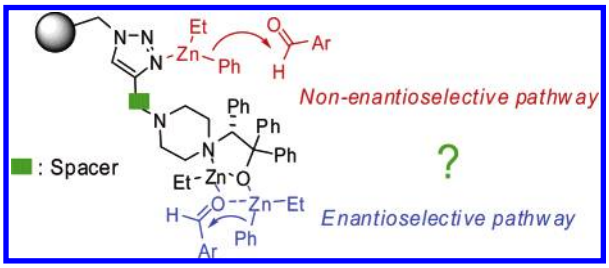

Alkynyl-functionalized amino alcohols have been covalently supported on azidomethylpolystyrene resins with different levels of functionalization through Cu(I)-catalyzed 1,3-dipolar cycloadditions ("click chemistry"). The resulting 1,2,3-triazole-substituted resins, characterized by different levels of ligand loading and, depending on the nature of the alkynyl-functionalized amino alcohol, the presence of a one-carbon, four-carbon, or eight-carbon linear spacer, have been tested as catalysts in the enantioselective phenyl transfer from zinc to aldehydes. High catalytic activities and enantioselectivities (up to 82% ee) have been recorded. The influence of structural characteristics of the resin on enantioselectivity are discussed, and the limitations in enantiocontrol inherent to the use of a 1,2,3-triazole linker have been rationalized with the help of DFT calculations on model systems.

Introduction

Catalysts are often the most expensive ingredients in mixtures leading to chemical reactions and frequently difficult to separate from the reaction product. Therefore, use of catalysts supported onto different platforms is of great interest since it can allow simpler product separation while offering the possibility of catalyst recycling as an additional bonus.[1] Additional attractiveness of the immobilized catalysts lies in the possibility of performing catalytic reactions in continuous mode, and this is of interest for industrial applications.[2] Different types of polymeric, inorganic, or hybrid materials are widely used as insoluble supports. Depending on the nature of both the support and the catalyst to be anchored, the immobilization strategy is based on covalent or noncovalent grafting (e.g., electrostatic interaction, hydrogen bond, adsorption, or entrapment).[3] Covalent grafting implies, in general, a more stable interaction and therefore a broader applicability of the immobilized catalysts. However, it usually requires greater synthetic effort since the catalyst has to be chemically modified with a group that enables anchoring to the polymer.

We previously reported the immobilization of chiral ligands to resins following different synthetic routes.[4,5] As a guide to

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(1) Reviews on immobilized catalysts include the following: (a) Immobilized Catalysts: Solid Phases, Immobilization and Applications. In *Topics in Current Chemistry*; Kirschning, A., Ed.; Springer GmbH: Berlin, 2004; Vol. 242, pp 1−336. (b) In *Polymeric Materials in Organic Synthesis and Catalysis*; Buchmeiser, D. R., Ed.; VCH Publishers: Weinheim, 2003.

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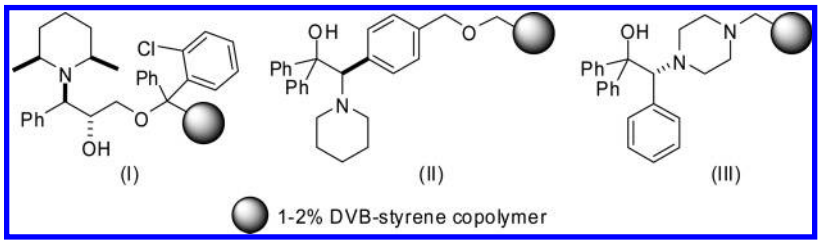

FIGURE 1. Some modular amino alcohol ligands anchored to polymers through remote functions for minimal perturbation of catalytic sites.

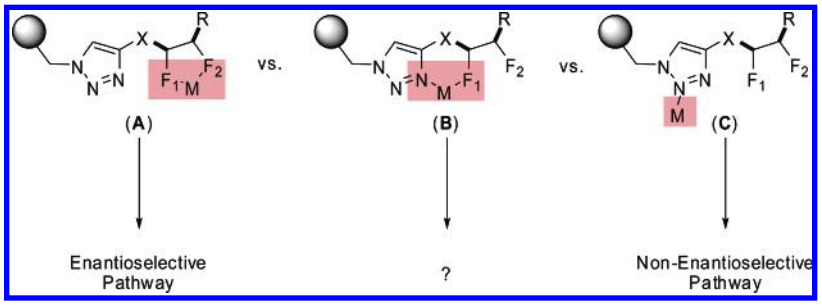

FIGURE 2. Possible pathways in metal catalysis with click-supported ligands.

this work, we designed the monomeric ligands in such a way that anchoring to the polymer would involve positions remote from the catalytic center and the transition states involved in the catalytic cycle would remain essentially unaffected. Use of polymers functionalized with amino alcohol residues and designed according to these principles (I−III) as catalysts for enantioselective carbonyl additions[4b,5] has led to very good results in terms of catalytic activity and enantioselectivity (Figure 1). However, anchoring these ligands onto polymers critically depends on the success of nucleophilic substitution reactions, and this poses some limitation with respect to the ligand structure and prevents use of the anchoring step as a source of diversity for the preparation of libraries of supported ligands.

"Click" chemistry categorizes highly efficient, specific, and functional-group-tolerant chemical transformations to make molecular connections.[6] The most popular click reaction is the copper(I)-catalyzed regioselective Huisgen dipolar cycloaddition reaction between alkynes and azides to yield 1,2,3-triazoles.[7,8] This reaction has seen enormous application in the last years in different fields from drug discovery[9] to material science,[10] but has been barely used as a tool to support reagents[11] or catalysts on polymers.[12,13]

Taking into account the limitations associated to ligand anchoring through nucleophilic substitution, click chemistry appeared to be a most convenient synthetic alternative. It is to be noted, however, that the 1,2,3-triazole moiety, conceived as a mere linker between the chiral ligand and the polymer, could also interact with the catalytic metal and trigger non-enantioselective reaction pathways (Figure 2).

Whereas formation of chelates like **B** have been shown in a recently reported type of achiral phosphines for palladium-catalyzed processes,[14] the coexistence of enantioselective and non-enantioselective pathways is strongly suggested in click-polymer-supported chiral aza(bisoxazolines) for Cu(II)-catalyzed processes since much higher enantioselectivities are recorded when the 1,2,3-triazole moiety is avoided as a linker.[12] In fact, the only reported example where a click-supported ligand depicts very high enantioselectivity is in organocatalysis, where the 1,2,3-triazole should act as a mere spectator.[13]

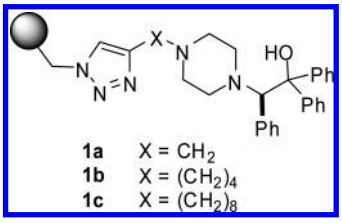

FIGURE 3. Target polymer-supported amino alcohols (**1a**−**c**) assembled through click chemistry and containing variable-length spacers (X).

In order to critically assess the usefulness of click chemistry as a tool for supporting on polymers chiral ligands for asymmetric catalysis purposes, we decided to prepare a family of polymer-supported amino alcohols (**1**), assembled through 1,2,3-triazole linkers onto slightly cross-linked polystyrene resins and containing variable length spacers (X) (Figure 3). We hoped that long-chain spacers could contribute to isolate the amino

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(7) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, pp 1−176.
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(11) Gheorge, A.; Matsuno, A.; Reiser, O. *Adv. Synth. Catal.* **2006**, *348*, 1016−1020.
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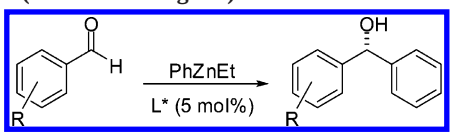
(13) Font, D.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2006**, *8*, 4653−4655.
(14) Detz, R. J.; Arévalo Heras, S.; de Gelder, R.; van Leeuwen, P. W. N. M.; Hiemstra, H.; Reek, J. N. H.; van Maarseveen, J. H. *Org. Lett.* **2006**, *8*, 3227−3230.

SCHEME 1. Catalytic Asymmetric Phenyl Transfer to Aldehydes (L*: Chiral Ligand)



alcohol moiety from the triazole one, thus favoring **A**- over **B**-type chelates and facilitating enantioselective pathways.

The amino alcohol moiety present in these polymers is known to efficiently control the enantioselective arylation of aldehydes when linked to a Merrifield resin through nucleophilic substitution,[5d] and we decided to use the click resins **1a**−**c** as insoluble catalysts in the asymmetric phenyl transfer to aldehydes (Scheme 1).

This reaction represents the most convenient way to obtain enantiopure diarylmethanols,[15] which are important intermediates for the synthesis of biologically active compounds.[16] For example, (*R*)-neobenodine, (*R*)-orphenadrine, and (*S*)-carbinoxamine are compounds of this class that have been used for a long time as muscle relaxants or antihistaminics (Figure 4).[17]

Complete catalyst separation from products is one of the most strict requisites for the catalytic synthesis of pharmaceutically relevant products, and use of covalently immobilized catalysts appears to be a convenient strategy toward this goal. In the case of enantioselective arylation of aldehydes, although many different homogeneous catalytic systems able to promote the reaction have been developed,[18] the search for polymer-based catalytic systems has been accompanied by much less success. Indeed, the first examples of recyclable catalytic systems for this reaction showed that enantioselectivity was only achieved for soluble polymeric supports.[19] Attempts to use a catalyst bound to a cross-linked polymer failed and led to racemic products,[19b] probably due to an unfavorable balance with the noncatalyzed background reaction. Only quite recently the first examples have been reported where high enantioselectivity is achieved by promoting the reaction with highly active ligands[5a,b] anchored to insoluble resins.[5c]

Herein we report the use of click chemistry as a most suitable strategy for the preparation of polymer-supported amino alcohols **1a**−**c**. We also describe the use of these insoluble materials as catalysts in the asymmetric phenylation of aldehydes and the results of a systematic investigation of the influence on enantioselectivity of the degrees of functionalization and cross-linking of the polymer chain and the length of the spacer (X) between the triazole and the amino alcohol moieties on the same parameter. In addition, DFT calculations on the possible interference of the triazole moiety in the reaction are presented.

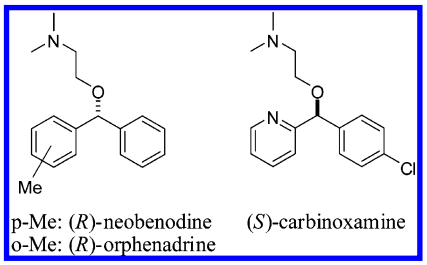
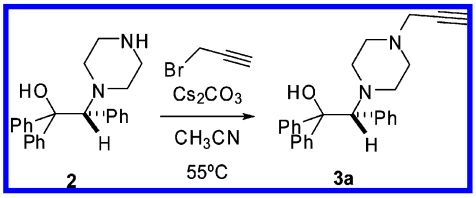


FIGURE 4. Some pharmaceutically active diarylmethanols.

SCHEME 2. Propargylation of Amino Alcohol 2



Results and Discussion

(*R*)-2-Piperazino-1,1,2-triphenylethanol (**2**), whose N-substituted derivatives depict an optimal catalytic profile in solution,[20] has a NH moiety that can allow anchoring onto polymers with minimal steric perturbation of the relevant β-amino alcohol unit.[5b,c] In the present instance, the alkyne handle required for click chemistry was introduced by alkynylation at that site. Thus, treatment of **2** with propargyl bromide in acetonitrile in the presence of cesium carbonate allowed isolation of the desired alkyne-tagged monomer **3a** in 91% yield (Scheme 2).

The complementary azido group for the dipolar cycloaddition was installed onto commercial Merrifield resins (1% DVB, f = 0.74−2.5 mmol Cl/g resin)[21] by reaction with sodium azide.[22] In this way, a set of azido resins with different levels of functionalization (f = 0.74−2.25 mmol N_3/g resin) was prepared.[23] The Cu(I)-catalyzed reaction between **3a** and the polymer-bound azide took place smoothly in 1:1 DMF/THF at 35 °C to lead to resins **1a** (Scheme 3).[24]

The progress of the cycloaddition reaction could be easily controlled by withdrawing resin samples from the reaction vessel at different times and following the disappearance of the azide function by IR spectroscopy (ca. 2100 cm^{-1}) (Figure 5). As a general rule, stirring the reaction mixture (shaker) at 35 °C for

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(21) Product specifications provided by the vendor (Novabiochem).

(22) Harju, K.; Vahermo, M.; Mutikainen, I.; Yli-Kauhaluoma, J. *J. Comb. Chem.* **2003**, *5*, 826−833.

(23) For the nitrogen-containing resins, the degree of functionalization, f [mmol of functional fragment/g of resin] is calculated from the results of elemental analysis with the formula $f = (0.714/n)\%N$, where n is the number of nitrogen atoms in the functional unit and %N is the percent of nitrogen provided by the elemental analysis. For a given resin, the maximum possible substitution level f_{max} [mmol of functional fragment/g of resin] can be calculated with the formula $f_{max} = f_o/[1 + f_o(\Delta M_w)\ 10^{-3}]$, where f_o is the functionalization of the starting resin and ΔM_w is the difference in molecular weight between the final and the initial functional fragments. The yield (%) of the considered step can then be evaluated as $100f/f_{max}$.

(24) Löber, S.; Gmeiner, P. *Tetrahedron* **2004**, *60*, 8699−8702.

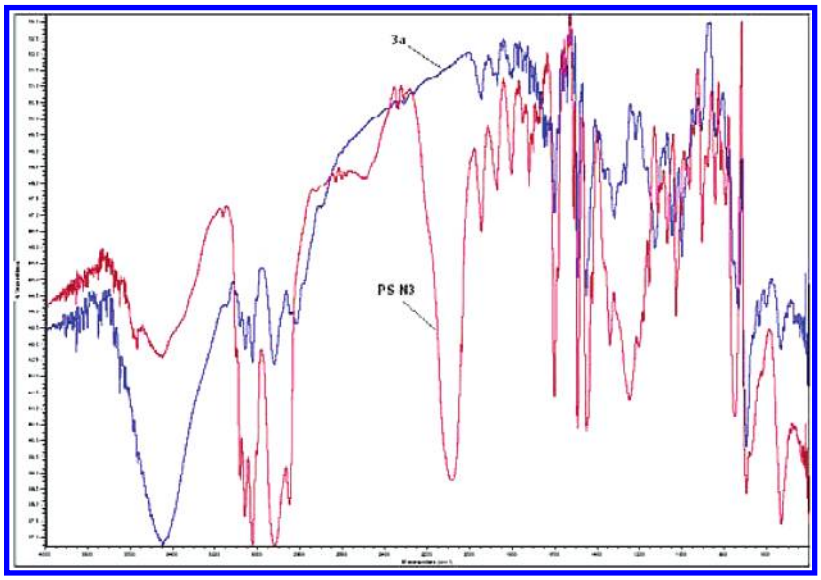
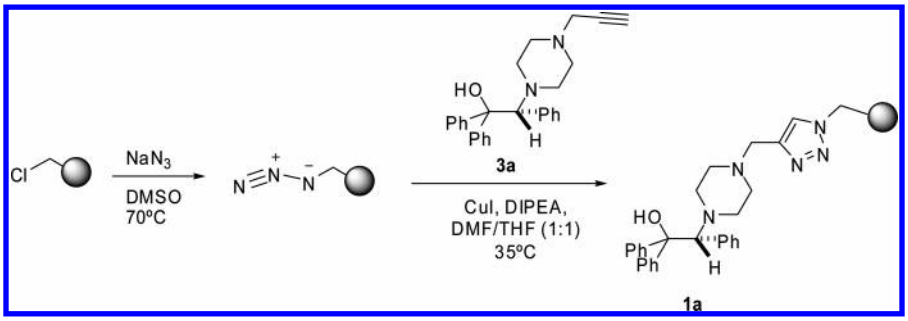


FIGURE 5. Comparison of IR spectra of an azido resin (red line; azide band at 2108 cm^{-1}) and the corresponding click resin **1a** (blue line).

SCHEME 3. Synthesis of Supported Catalysts 1a from Commercial Merrifield Resins



1 day led to complete conversion. Using this procedure a set of resins **1a** with different degrees of ligand functionalization (f = 0.59−1.16 mmol/g resin) could be easily prepared.

Elemental analysis of the final resins[23] in conjunction with high-resolution magic angle spinning (HRMAS) ^{13}C NMR spectroscopy[25] allowed us to establish that the amino alcohol anchors to the resins in quantitative yields. A comparison between the ^{13}C NMR spectra of resin **1a** (HR-MAS) and the model compound **4a**, prepared from benzyl azide and alkyne **3a**, is shown in Figure 6.

With resins **1a** in hand, their use as ligands in the catalytic enantioselective phenylation of aldehydes was explored. Several protocols have been developed for the homogeneous version of the reaction using as aryl transfer agent either $ZnPh_2$,[26] a mixture of $ZnEt_2/ZnPh_2$[27] (presumably giving rise to PhZnEt as the actual phenyl delivering agent),[28] or phenylboronic acid.[29] Use of a mixed ethylphenylzinc reagent, formed in situ from diethylzinc and diphenylzinc (in a 2:1 ratio), has two beneficial effects: first, it allows reducing the amount of diphenylzinc employed in the reaction since both phenyl groups in this reagent can be equally transferred to the carbonyl substrate through the mixed species. On the other hand, since PhZnEt is less reactive than $ZnPh_2$, the non-enantioselective background reaction is efficiently suppressed with its use.

We then tested our novel resins **1a** as catalysts in the asymmetric phenylation of *p*-tolualdehyde and *p*-anisaldehyde using PhZnEt as the phenyl-delivering species. The resins were first allowed to swell in toluene and then treated with the $ZnEt_2/ZnPh_2$ (2:1) mixture. After 1 h, the reaction mixture was cooled to 10 °C and the aldehyde was then added. Table 1 shows that high conversions are obtained after 2 h using only 5 mol % catalyst with enantioselectivities up to 74% (*p*-tolualdehyde) and 77% (*p*-anisaldehyde). Interestingly, a clear dependence of enantioselectivity on the degree of functionalization of resin **1a** is observed: for the phenylation of *p*-tolualdehyde, the corresponding diarylcarbynol is obtained with 74% ee when using a resin with low functionalization (f = 0.59 mmol/g) and with 68% ee for a resin with slightly higher functionalization (f = 0.74 mmol/g). In the limit, when resin **1a** with a larger level of functionality (f = 1.16 mmol/g) was used, the alcohol was obtained in racemic form.[30]

(25) The resins were allowed to swell in C_6D_6 overnight before acquisition of the NMR spectra with the HRMAS probe.

(26) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444−445.

(27) (a) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muniz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465−3467. (b) Bolm, C.; Kesselgruber, M.; Hermanns, N.; Hildebrand, J. P.; Raabe, G. *Angew. Chem., Int. Ed.* **2001**, *40*, 1488−1490.

(28) Fontes, M.; Verdaguer, X.; Solà, L.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 2532−2543.

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(30) On the opposite side, when a low-loading resin (f = 0.29) prepared from a commercial Merrifield resin by reaction with defect sodium azide, capping with MeOH, and cycloaddition with amino alcohol **3a** was used in the reaction, the enantiomeric purity of the resulting carbynol was 60 %. It is thus suggested that functionalization of the resin has an optimal value in the vicinity of f = 0.6 for this particular reaction.

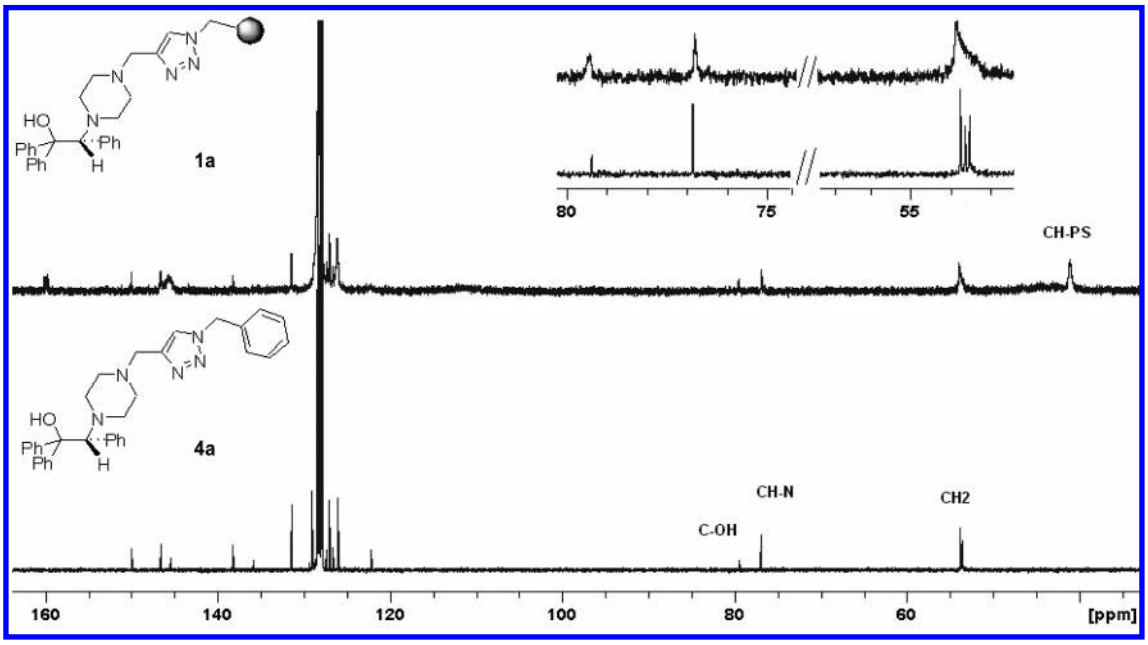
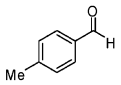
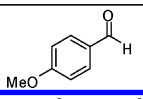


FIGURE 6. Controlling the anchoring of amino alcohol **3a** to an azido resin through click chemistry by HRMAS ^{13}C NMR (**1a**, top). The spectrum of triazole **4a** is included for comparison (bottom). PS: polystyrene.

TABLE 1. Enantioselective Phenylation of Aldehydes with Resins 1a with Variable Degree of Functionalization[a]

entry	aldehyde	*f* [mmol L/g resin][b]	conversion [%][c]	ee [%][d]
1		0.59	95	74
2		0.74	>97	68
3[e]		0.71	89	63
4		1.16	>99	0
5		0.59	64	77
6[f]		0.71	92	71

[a] Reaction conditions: aldehyde (0.25 mmol); ligand (0.0125 mmol; 5 mol %); Ph_2Zn (0.16 mmol); Et_2Zn (0.33 mmol); 7.4 mL of toluene; 10 °C; 2 h. [b] Calculated from %N determined by elemental analysis. [c] Determined by ^1H NMR. [d] Measured by chiral HPLC.[35] The product had the *R* configuration when a ligand of *R* configuration was anchored to the resin. [e] 3.6% catalyst. [f] 10% catalyst.

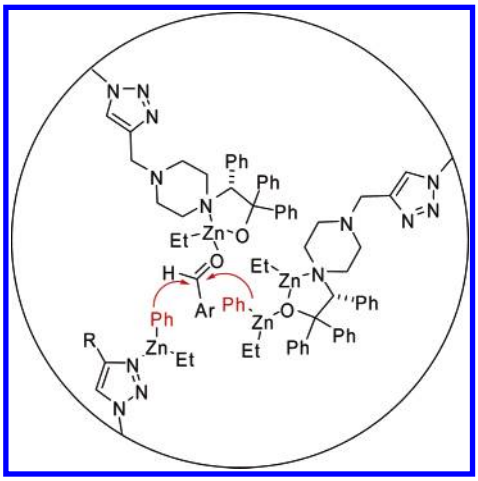


FIGURE 7. Possible non-enantioselective pathways in the phenylation of aldehydes with high-loading resins **1a**.

Although the origin of this behavior has not been investigated in detail, it can be assumed that a high local concentration of Lewis acid/Lewis base sites on the catalytically activated polymer effectively triggers a non-enantioselective reaction pathway (Figure 7). In this context, it is interesting to point out that the catalytic efficiency and enantioselectivity of amino alcohols similar to I (see above) anchored to Merrifield resins is strongly dependent on the functionalization level of the resin.[4b]

Lowering the amount of **1a** employed in the reaction (for entry 3 only 3.6% catalyst was used) provoked a decrease in both conversion and enantioselectivity. On the other hand, an increase to 10 mol % in the amount of **1a** (entry 6) did not lead to any improvement in the enantioselectivity of the process.

As mentioned above, we envisaged that the presence of the triazole ring near the amino alcohol could give rise to some interaction with ethylphenylzinc leading to a detrimental effect in enantioselectivity.[31] To avoid this problem, we decided to insert a linear hydrocarbon spacer between the triazole moiety and the amino alcohol fragment which should coordinate to zinc as a chelate. Two alkyl chains of different length (C_4 and C_8) were used as spacers in an attempt to determine the optimal separation between the two considered fragments. For this purpose, (*R*)-2-piperazino-1,1,2-triphenylethanol (**2**) was reacted with commercially available 6-chloro-1-hexyne and 10-bromo-1-decyne[32] in the presence of cesium carbonate to yield **3b** and **3c**, respectively. The subsequent Cu(I)-mediated cycloaddition of these alkynyl-functionalized amino alcohols with polymer-bound azides led to resins **1b** and **1c** in quantitative yield (Scheme 4). According to the results recorded with **1a**, low-loading azido resins were used in these experiments.

Table 2 shows the results of the comparative phenylation of *p*-substituted benzaldehydes with the polymeric catalysts **1a**−**c**

(31) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850−14851.
(32) For example, phenylation of *p*-tolualdehyde with a Merrifield resin substituted with (*R*)-2-piperazino-1,1,2-triphenylethanol as the ligand (5 %) furnishes the alcohol with 94% ee under similar conditions; see ref 5c.

SCHEME 4. Preparation of Polymer-Supported Ligands 1b,c

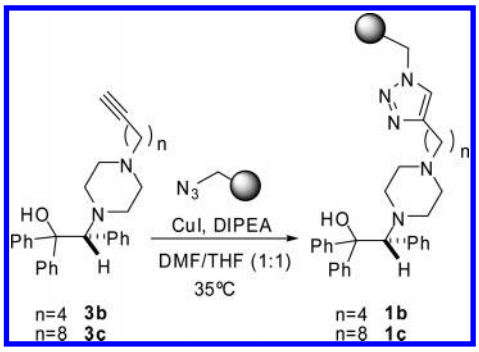


TABLE 2. Catalytic Phenylation of Aldehydes with Resins 1a−c: Effect of the Spacer and Resin Reticulation[a]

entry	catalyst	*f* [mmol L/g resin][b]	aldehyde	conversion [%][c]	ee [%][d]
1	**1a**	0.59		95	74
2	**1b**	0.66		100	66
3[e]	**1b**	0.66		68	66
4	**1b**	0.72		95	76
5	**1b**[f]	0.72		99	78
6	**1c**	0.67		79	75
7	**1a**[f]	0.71		92	71
8	**1b**	0.66		68	77
9	**1b**	0.72		97	82
10	**1c**	0.67		54	76

[a] Reaction conditions: aldehyde (0.25 mmol); ligand (0.0125 mmol; 5 mol %); Ph_2Zn (0.16 mmol); Et_2Zn (0.33 mmol); 7.4 mL of toluene; 10 °C; 2 h. [b] Calculated from %N obtained by elemental analysis. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC.[31] [e] Resin with higher cross-linking (2% divinylbenzene). [f] 10 mol % catalyst used.

containing the different spacers. As it can be readily observed, resins **1a** and **1b** exhibit a higher catalytic activity than **1c** (entries 6 and 10). Since separation of the active center from the polymeric backbone through a longer linker should favor catalytic activity through a better contact with the reagents, observation of an opposite behavior is in favor of some participation of the triazole moiety in the catalytic process. Regarding the enantioselectivity, slight differences were encountered depending on the length of the spacer. As a general trend resin **1b**, containing a four-carbon linker, affords the best results with the two studied aldehydes.

As a final step in this scrutiny, to test the influence of the degree of cross linking of the parent resin on the catalytic behavior of the supported ligands, two types of **1b** resin were prepared with the same functionalization ($f = 0.66$) and different levels of cross-linking (1% and 2% DVB). Both resins behaved similarly in terms of enantioselectivity, but the more reticulated one showed lower catalytic activity as indicated by a lower conversion in the studied reaction (entries 2 and 3).

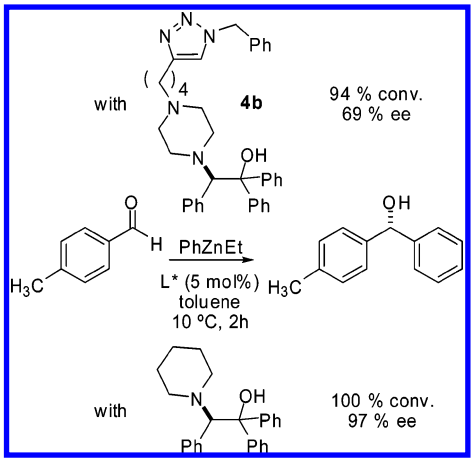
According to these results, resin **1b** containing a C_4 spacer, prepared from a Merrifield resin of low reticulation (1% DVB), and possessing a rather low level of functionalization ($f = 0.72$ mmol/g) appears to be the optimal one (entries 4 and 9).

TABLE 3. Enantioselective Phenylation of Aldehydes with Resin 1b (f = 0.72 mmol/g; 1% DVB)[a]

entry	time [h]	aldehyde	Yield [%][b]	Ee [%][c]
1	2		95	76 (*R*)
2	2		97	82 (*R*)
3	4		100	61 (*R*)
4	4		100	75 (*S*)
5	4		94	64 (*R*)
6	4		46	65 (*R*)

[a] Reaction conditions: 0.25 mmol aldehyde; 5% catalyst; 10 °C. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC.[31]

SCHEME 5. Phenylation of *p*-Tolualdehyde with Reference Ligands



The possibility of resin recycling and reuse was tested with the optimal resin **1b** on *p*-anisaldehyde. After three consecutive runs no change in conversion was detected while the enantiomeric purity of the resulting carbynol showed a very slight decrease (78% vs 82% ee). This is indicative of good stability of the resins under the reaction conditions used.

Once the nature of the optimal resin had been established, polymer **1b** (f = 0.72 mmol/g, 1% DVB) was tested in the phenylation of a set of aromatic and aliphatic aldehydes (Table 3). Using a 5 mol % amount of catalyst and performing the reaction in toluene at 10 °C for 2−4 h the starting aldehydes were cleanly converted in an almost quantitatively manner into the corresponding secondary alcohols with the only exception

(33) Patwardhan, A. P.; Thompson, D. H. *Langmuir* **2000**, *16*, 10340−10350.

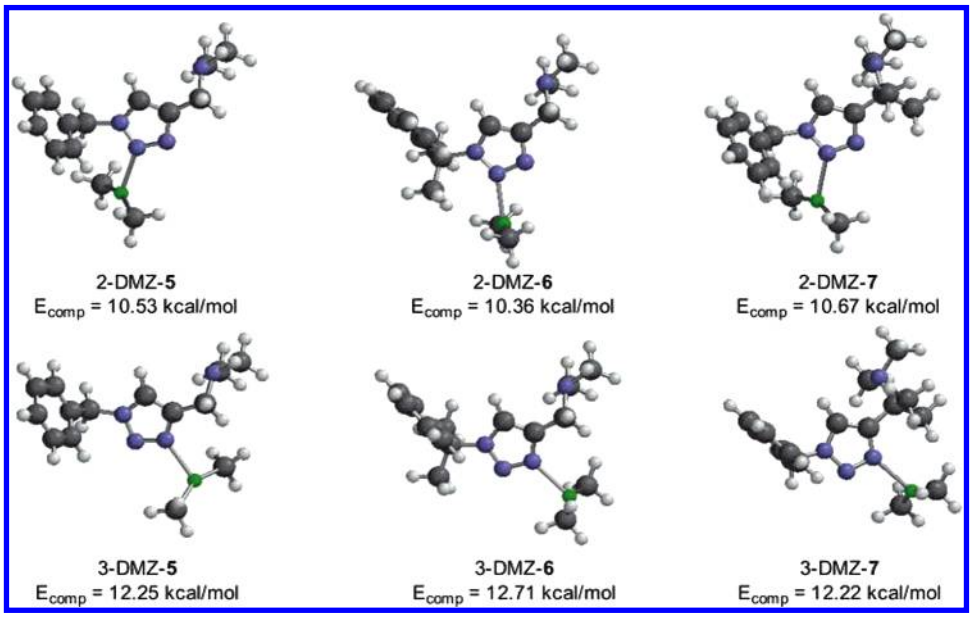


FIGURE 8. DFT-calculated complexation energies for the interaction of dimethylzinc with N-2 and N-3 in the triazole ring of model compounds **5**−**7**.

of 2-naphthaldehyde (entry 6), which was only 46% converted after a 4 h reaction. Interesting to note, 2-ethylbutyraldehyde and α-methylcinnamaldehyde (entries 4 and 5), which showed lower reactivity in reactions mediated by an amino alcohol with the same basic structure supported on a Merrifield resin by nucleophilic substitution,[5c] were completely phenylated with resin **1b**.

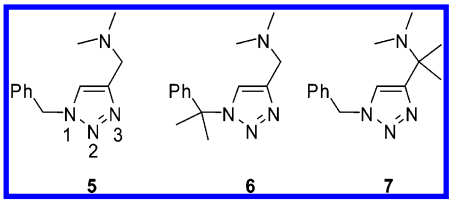
In terms of enantioselectivity, the reaction delivers all diarylcarbynol products in enantioenriched form. Over the family of six studied aldehydes, the mean enantiomeric excess of the carbynol products is 70%. This value is ca. 20% lower than that obtained with a similar supported ligand lacking the 1,2,3-triazole moiety,[5c] and this suggests once again that this unit can be interfering with the asymmetric process by promoting non-enantioselective pathways like those depicted in Figures 2 and 7.

This suggestion is reinforced by the fact that the model compound **4b**, prepared from **3b** by cycloaddition with benzyl azide (66% yield), when used as the ligand under the same reaction conditions yields the alcohol in 94% conversion and 69% ee, this enantioselectivity being much lower than that recorded with simple derivatives of 2-amino-1,1,2-triphenylethanol[28] (Scheme 5).

All available experimental and theoretical evidence on alkyl and aryl transfer from zinc to carbonyl groups suggests that the process is favored by coordination of a Lewis base to the zinc atom from which the group is transferred.[33] Accordingly, the suitability of 1,2,3-triazoles as linkers for immobilization onto polymers of amino alcohols, designed to act as ligands in the considered process, can critically depend on the thermodynamics of the interaction of the zinc reagent with the different electron-rich sites on the ligand molecule.

To gain some insight into these complexation processes, we decided to study complexation of a prototypical zinc reagent (dimethylzinc) with the different Lewis base sites in a molecular system containing the characteristics of ligands **1** from a theoretical point of view.

Molecule **5** could allow evaluation of the interaction of dimethylzinc with the nitrogen atoms in the 1,2,3-triazole moiety exhibiting basic character. Introduction of gem-dimethyl substitution on the two methylene groups adjacent to the triazole (in **6** and **7**) could give an indication of the possibility of modifying the thermodynamics of the complexation with introduction of steric congestion near the 1,2,3-triazole linkers. On the other hand, **5** could also allow evaluation of the stability of chelates involving the participation of nitrogen atoms in the triazole (N-3) and piperazino rings.



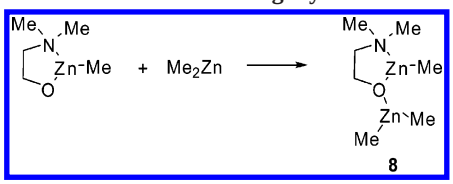
The energy gain associated with all complexation possibilities would be then compared with the one associated with the process shown in Scheme 6, which is representative for one of the pre-equilibrium steps in the catalytic cycle in the amino-alcohol-promoted alkylation/arylation of aldehydes with diorganylzinc reagents.[34]

The calculations were performed using density functional theory (DFT) with the B3LYP functional, as implemented in the Spartan02 suite of programs.[34] Geometry optimization and energy calculations were run using the all-electron 6-31G* basis set.

(34) See, for instance: (a) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028−4036. (b) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327−6335. (c) Kitamura, M.; Oka, H.; Noyori, R. *Tetrahedron* **1999**, *55*, 3605−3614. (d) Rosner, T.; Sears, P. J.; Nugent, W. A.; Blackmond, D. G. *Org. Lett.* **2000**, *2*, 2511−2513. (e) Goldfuss, B.; Steigelmann, M.; Khan, S. I.; Houk, K. N. *J. Org. Chem.* **2000**, *65*, 77−82. (f) Vázquez, J.; Pericàs, M. A.; Maseras, F.; Lledós, A. *J. Org. Chem.* **2000**, *65*, 7303−7309. (g) Rudolph, J.; Rasmussen, T.; Bolm, C.; Norrby, P. O. *Angew. Chem., Int. Ed.* **2003**, *42*, 3002−3005. (h) Jimeno, C.; Vidal-Ferran, A.; Pericàs, M. A. *Org. Lett.* **2006**, *8*, 3895−3898. (i) Rudolph, J.; Bolm, C.; Norrby, P. O. *J. Am. Chem. Soc.* **2005**, *127*, 1548−1552.

(35) *Spartan 02*; Wavefuction, Inc.: Irvine, CA.

SCHEME 6. Pre-equilibrium in the Amino Alcohol-Mediated Addition of Diorganylzincs to Aldehydes



We present graphically in Figure 8 results on the complexation of dimethylzinc with N-2 and N-3 in **5**−**7**. Full details on the complexation partners and complexes are provided in the Supporting Information.

According to the DFT calculations, interaction of dimethylzinc with the triazole ring leads to a significant stabilization. From a general perspective, two aspects of the complexation process should be highlighted: First, complexation of dimethylzinc with N-3 is more favorable than with N-2, in agreement with a higher electron density at that position. Second, introduction of steric congestion near N-3 (compare 3-DMZ-**5** and 3-DMZ-**7** in Figure 8) does not represent any significant variation in the complexation energy.

For reactivity purposes and enantioselectivity discussions, it is important to compare the stability of these complexes with that of the *N*,*N* chelate **9**, derived from **5**, with the usual oxygen-bound complex of dimethylzinc **8** (Scheme 6). Their optimized structures and complexation energies are given in Figure 9. Further details can be found in the Supporting Information.

As expected, the calculations predict that complexation of dimethylzinc with the oxygen atom in the chelated methylzinc alkoxide derived from the amino alcohol moiety (**8**) represents the most favorable situation. However, the difference with the *N*,*N*-chelate **9** that could originate from the simultaneous interaction of dimethylzinc with the triazole ring and the dimethylamino substituent (i.e., the piperazino group in ligands like **1a**) is small (ca. 0.5 kcal·mol^{-1}). In addition, complexation in **8** is only slightly more favorable (ca. 3 kcal·mol^{-1}) than the simple interaction of dimethylzinc with the triazole ring (see Figure 8). It is important to note that this last complexation mode is available for every click-supported ligand.

Although the stability of the considered complexes does not necessarily have to be translated into a parallel order of reactivity for the alkyl or aryl transfer to an aldehyde (in fact, evolution of species like **8** after complexation of the reacting aldehyde to the ring zinc atom should be favored by entropy effects) the predicted tendency of the diorganylzinc reagent to interact with the 1,2,3-triazole moiety in click-supported amino alcohol ligands provides a clue for understanding the limits of enantiocontrol when these ligands are used to promote aryl transfer from zinc to aldehydes.

Conclusions

In summary, the Cu(I)-mediated cycloaddition of terminal alkynes with azides (click chemistry) has been used as an efficient strategy for immobilization of a chiral, properly functionalized amino alcohol ligand onto azidomethyl PS−DVB resins. FTIR spectroscopy can be diagnostically used to follow the progress of the anchoring reaction, while HRMAS ^{13}C NMR spectroscopy allows the unambiguous characterization of the insoluble functional polymers. These polymer-supported ligands have been used as catalysts in the asymmetric phenylation of aldehydes showing high catalytic activity and moderate

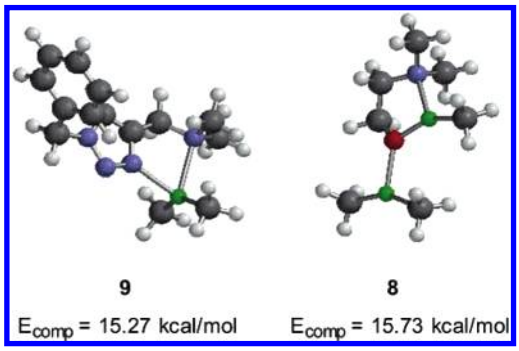


FIGURE 9. Most stable complexes of dimethylzinc with the studied model systems.

to high levels of enantioselectivity (up to 82%). In spite of a thorough optimization of the structure of the polymeric catalyst involving resin parameters (functionalization and reticulation) and ligand parameters (length of a linear hydrocarbon spacer between the triazole linker and the amino alcohol moiety), the levels of enantioselectivity previously achieved with the same amino alcohol anchored on the same resin type by nucleophilic substitution have not been attained. DFT calculations on model compounds have shown that complexation of diorganylzinc species with electron-rich nitrogen atoms in the triazole is energetically favorable and thus suggest that non-enantioselective reaction pathways can be available for aryl transfer.

For future applications the present results should provide caution on the use of click-supported ligands in connection with azaphilic cations.[12] Alternatively, use of this strategy for organocatalysis[13] or in situations where the triazole linker cannot likely interact with the involved metal offers clear promise in view of the ease of ligand design, the ready availability of azido-functionalized resins, and the efficiency of the cycloaddition leading to ligand immobilization.

Experimental Section

1,1,2-Triphenyl-2-(4-(prop-2-ynyl)piperazin-1-yl)ethanol (3a). Amino alcohol **2**[5b] (1.00 g, 2.79 mmol) was reacted with propargyl bromide (0.24 mL, 2.79 mmol) in the presence of Cs_2CO_3 (1.82 g, 5.58 mmol) in acetonitrile (15 mL) at 55 °C for 39 h. After this time the reaction mixture was cooled and washed with water (3 × 5 mL). The organic phase was dried with $MgSO_4$, and the solvent was removed at reduced pressure. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate (4:1) as eluent (R_f = 0.2). The product was obtained as a white solid (1.01 g, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, 2H), 7.29−6.89 (m, 13H), 4.56 (s, 1H), 3.16 (d, ^4J = 2.4 Hz, 2H), 2.42 (m, 6H), 2.20 (t, ^4J = 2.4 Hz, 1H), 2.15 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 149.4, 146.0, 137.5, 131.2, 128.7, 128.3, 128.1, 127.9, 127.6, 127.4, 126.7, 126.6, 125.9, 125.7, 79.0, 78.6, 76.9, 73.3, 52.6, 46.7. IR (ATR) υ_{max}: 3287, 3059, 2802 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{27}H_{28}N_2NaO$, 419.2099; found, 419.2119 [M + Na]$^+$.

2-(4-(Hex-5-ynyl)piperazin-1-yl)-1,1,2-triphenylethanol (3b). Amino alcohol **2**[5b] (0.5 g ,1.39 mmol) was reacted with 6-chloro-1-hexyne (0.17 mL, 1.4 mmol) in the presence of Cs_2CO_3 (1.36 g, 4.2 mmol) in acetonitrile (10 mL) at 70 °C for 68 h. After this time the reaction mixture was cooled and washed with water (3 × 5 mL). The organic phase was dried with $MgSO_4$, and the solvent was removed at reduced pressure. The residue was purified by column chromatography on silica gel with CH_2Cl_2/MeOH (9:1) as the eluent (R_f = 0.7). The product was obtained as a white solid (0.64 g, 48% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, 2H),

7.31−6.90 (m, 13H), 5.57 (br, 1H), 4.58 (s, 1H), 2.43−2.13 (br, 12H), 1.90 (t, ^4J = 2.1 Hz, 1H), 1.47 (br, 4H). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 149.4, 145.9, 137.5, 131.2, 128.6, 128.2, 128.1, 127.8, 127.6, 127.5, 127.2, 126.7, 126.6, 126.5, 125.8, 125.7, 84.4, 78.8, 76.9, 68.6, 57.9, 26.5, 25.9, 18.5. IR (ATR) υ_{max}: 3286, 2945, 2800 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{30}H_{35}N_2O$, 439.2749; found, 439.2762 $[M + H]^+$.

2-(4-(Dec-9-ynyl)piperazin-1-yl)-1,1,2-triphenylethanol (3c). Amino alcohols **2**[5b] (0.5 g, 1.39 mmol) were reacted with 10-bromo-1-decyne[33] (0.36 g, 1.67 mmol) in the presence of Cs_2CO_3 (0.54 g, 1.67 mmol) and NaI (0.01 g, 0.07 mmol) in acetonitrile (10 mL) at 55 °C for 24 h. After this time the reaction mixture was cooled and washed with water (3 × 5 mL). The organic phase was dried with $MgSO_4$, and the solvent was removed at reduced pressure. The residue was purified by column chromatography using hexane/ethyl acetate (4:1) as eluent (R_f = 0.2). The product was obtained as a white solid (0.39 g, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70−6.90 (m, 15H), 5.62 (br, 1H), 4.57 (s, 1H), 2.44−2.14 (br, 10H), 1.90 (t, ^4J = 2.7 Hz, 1H), 1.56−1.24 (br, 14 H). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 149.2, 145.8, 137.4, 131.1, 128.4, 128.0, 127.9, 127.5, 127.3, 127.0, 126.8, 126.5,126.3, 125.6, 125.5, 78.7, 76.8, 68.0, 58.6, 53.9, 29.4, 28.9, 28.6, 28.4, 27.5, 26.8, 18.4. IR (ATR) υ_{max}: 3420, 3155, 2927, 2853 cm^{-1}. HRMS (ES+): *m*/*z* calcd for $C_{34}H_{42}N_2NaO$, 517.3195; found, 517.3201 $[M + Na]^+$.

Synthesis of Click Resins (1a−c). The N_3-functionalized resin[24] was reacted with the corresponding alkyne **3a−c** (1.3 equiv), CuI (0.004 equiv), and DIPEA (0.77 equiv) in a 1/1 mixture of DMF and THF at 35 °C. The progression of the reaction was monitored by IR spectroscopy. After disappearance of the azide signal (t = 20−68 h), the resin was filtrated and successively washed with DMF, water, MeOH, and CH_2Cl_2 to give yellowish materials. The resins were dried under vacuum overnight (50 °C). The cycloaddition yield was calculated from the results of nitrogen elemental analysis (see ref 23).

Resin **1a** (f = 0.71 mmol/g) was obtained from a N_3−PS resin (f = 0.97 mmol/g). A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis: $\%N_{found} = 4.95$; $\%N_{calcd} = 4.91$. ^{13}C NMR (gel, 125. 7 MHz, C_6D_6) δ: 150.0, 146.6, 145.7, 138.2, 131.4, 127.3, 127.0, 126.6, 126.1, 79.5, 76.8, 53.9, 41.0.

Resin **1b** (f = 0.72 mmol/g) was obtained from a N_3−PS resin (f = 1.03 mmol/g). A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis: $\%N_{found} = 5.01$; $\%N_{calcd} = 4.97$. ^{13}C NMR (gel, 125. 7 MHz, C_6D_6) δ: 150.3, 146.8, 138.5, 131.5, 128.3, 127.4, 127.0, 126.6, 126.1, 77.0, 71.1, 58.2, 54.1, 41.1, 27.7, 26.9, 26.2.

Resin **1c** (f = 0.67 mmol/g) was obtained from a N_3−PS resin (f = 1.04 mmol/g). A 97.5% yield of functionalization was calculated on the basis of nitrogen elemental analysis: $\%N_{found} = 4.69$; $\%N_{calcd} = 4.81$. ^{13}C NMR (gel, 125. 7 MHz, C_6D_6) δ: 150.2, 146.7, 138.4, 131.4, 128.3, 127.3, 126.9, 126.5, 126.0, 125.0, 79.3, 76.9, 58.5, 54.1, 41.0, 29.9, 27.8, 27.2, 26.3.

Synthesis of Model Compounds (4a, 4b). To a mixture of the corresponding alkyne **3a** or **3b** (0.29 mmol) and benzyl azide (0.037 μL, 0.29 mmol) in *tert*-butyl alcohol (1 mL), 0.5 mL of an aqueous solution of $CuSO_4 \cdot 5H_2O$ (0.73 mg, 2.94 μmol) and 0.5 mL of an aqueous solution of sodium ascorbate (5.82 mg, 29.4 μmol) were added. The reaction mixture was stirred vigorously for 68 h. The suspended product was filtrated and washed with water. The crude product was purified by column chromatography on silica gel, eluting with hexane/ethyl acetate mixtures of increasing polarity to afford the triazole products (**4a** or **4b**) as white solids.

(*R*)-2-(4-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)piperazin-1-yl)-1,1,2-triphenylethanol (4a): 0.090 g, 59% yield. ^{1}H NMR ($CDCl_3$) δ: 7.67−6.90 (m, 21H), 5.45 (s, 2H), 4.55 (s, 1H), 3.54 (br, 2H), 2.44−2.08 (m, 8H). ^{13}C NMR ($CDCl_3$) δ: 149.3, 145.9, 144.9, 137.4, 134.8, 131.3, 129.3, 128.9, 128.3, 128.2, 127.7, 127.5, 126.7, 126.5, 125.9, 125.7, 122.6, 78.9, 77.4, 54.3, 53.8, 53.3. HRMS-ESI: *m*/*z* calcd for $C_{34}H_{35}N_5NaO$, 552.2739; found, 552.2750 $[M + Na]^+$.

(*R*)-2-(4-(4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,1,2-triphenylethanol (4b): 0.11 g, 66% yield. ^{1}H NMR ($CDCl_3$) δ: 7.69−6.88 (m, 21H, 5.45 (s, 2H), 4.55 (s, 1H), 2.63 (t, J = 7.6 Hz, 2H), 2.39−2.39 (m, 14 H). ^{13}C NMR ($CDCl_3$) δ: 149.4, 148.7, 131.2, 129.2, 128.8, 128.2, 128.1, 127.8, 127.5, 127.2, 126.7, 126.5, 125.8, 125.7, 120.7, 78.8, 77.4, 76.9, 58.3, 54.2, 54.1, 27.4, 26.6, 25.8. HRMS-ESI: *m*/*z* calcd for $C_{37}H_{41}N_5ONa$, 594.3209; found, 594.3183 $[M + H]^+$.

Typical Procedure for Enantioselective Phenyl Transfer to Aldehydes Catalyzed by Resins 1a−c. A mixture of 293 mg (1.33 mmol) of $ZnPh_2$ and 333 mg (2.7 mmol) of pure $ZnEt_2$ was dissolved in 25 mL of anhydrous toluene. Then, the corresponding weight of resin (according to f) was allowed to swell in 1 mL of toluene and then reacted with 6.4 mL of the $ZnPh_2/ZnEt_2$ solution under argon for 1 h at room temperature. After cooling to 10 °C, 0.25 mmol of aldehyde was added. After reacting at 10 °C for 2 h the reaction was quenched with aqueous NH_4Cl. The aqueous phase was extracted with CH_2Cl_2, the combined organic phases were dried ($MgSO_4$), and the solvent was eliminated under reduced pressure. Conversions were determined by ^{1}H NMR, and enantiomeric excess was determined by HPLC.

Acknowledgment. We thank DGI-MCYT (grant no. CTQ2005-02193/BQU), DURSI (grant no. 2005SGR225), Consolider Ingenio 2010 (Grant No. CSD2006-0003), and the ICIQ Foundation for financial support. A.B. is grateful to the Spanish Ministerio de Educación y Ciencia for a "Juan de la Cierva" research contract and D.F. for a predoctoral fellowship. We also thank G. González and K. Gómez (ICIQ support unit) for their help with HRMAS ^{13}C NMR measurements.

Supporting Information Available: General experimental methods, conditions for HPLC analysis, and NMR spectra of new compounds; Cartesian coordinates and energies for the DFT-calculated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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