Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 1849–1851

BIOORGANIC &
MEDICINAL
CHEMISTRY
LETTERS

Polymer-Bound 1-Aryl-3-alkyltriazenes as Modular Ligands for Catalysis. Part 2: Screening Immobilized Metal Complexes for Catalytic Activity

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Received 13 December 2001; accepted 31 January 2002

Abstract—A range of polymer-supported triazenes and their metal-bound analogues were screened for use in catalysis. Fe, Cu and Zr complexes were, together with the polymer-supported triazene ligand alone, screened in the addition of Et_2Zn to benzaldehyde. A supported Pd triazene complex was screened for activity in Suzuki and Sonogashira reactions and a supported Ru triazene complex screened for transfer hydrogenation. © 2002 Elsevier Science Ltd. All rights reserved.

There is increasing interest in the development of polymer-bound metal catalysts and reagents for organic synthesis that maintain high activity and selectivity.[1,2] As transition metal complexes are often expensive to purchase or prepare, the immobilization on a support thereby enabling simple extraction and re-use makes for commercial advantage as well as ease of manipulation.

In the previous letter,[3] we presented the synthesis of a number of novel solid-supported triazenes of general structure **1** (Fig. 1) and showed that these co-ordinate metal complexes. We reported the syntheses of polymer-supported palladium and ruthenium triazene complexes **8** and **9**. In this letter, the findings on the activity of these and other supported metal complexes in catalysis of a range of reactions are described.

The initial reaction chosen for assessing the activity of the polymer-supported triazenes and metal complexes derived from them was the addition of diethyl zinc to benzaldehyde, **5**, to yield enantiomerically enriched 1-phenylpropanol, **6** (Scheme 1). This reaction was chosen because product analysis is straightforward to perform, efficient ligands are known for comparison[4] and intensive mechanistic investigations reveals the origin of enantioselectivity. In addition, with this reaction there is a competing slow reaction giving rise to racemic 1-phenylpropanol and benzyl alcohol. The latter is normally produced in small

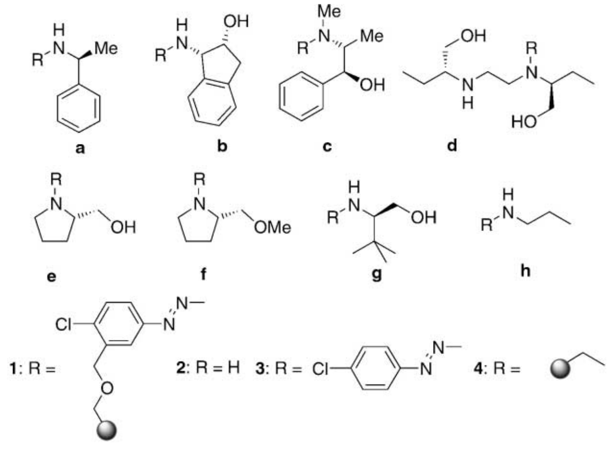

Figure 1.

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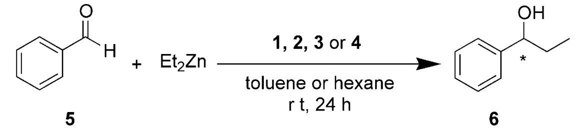
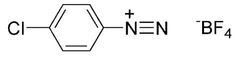
PII: S0960-894X(02)00279-2



Scheme 1.

amounts (under 2%) using efficient catalysts however, larger amounts (up to 39%) are observed with inefficient or in the absence of catalysts. This therefore would give an indication as to the efficiency of our catalyst candidates.

We also were keen to assess the activity of the amines used to make the triazenes, **2a**–**h** in the asymmetric diethyl zinc addition reaction and also representative examples of their immobilized analogues **4c** and **4g**. It was therefore firstly necessary to prepare a solution-phase library of the 4-chloroaryltriazene derivatives of **1**, namely **3e**,**f** and also to prepare **4c** and **4g**. The solution-phase analogues **3e**,**f** was prepared by treating the amines **2e**,**f** with the diazonium salt **7**.[5] The resins **4c** and **4g** were prepared by treating a THF suspension of Merrifield's resin with the sodium salts of **2c** and **2g** respectively. Loading was determined with CHN analysis and the results indicated $>95\%$ conversion.



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A range of amines **2a**–**g** were screened in the diethyl zinc addition reaction to determine the efficiency of the precursors. Reactions were performed at room temperature in both dichloromethane and in toluene using 5 mol% amine, for 24 h. Care was taken to ensure that every reaction was performed under identical conditions.[6] After aqueous workup, the yield and enantioselectivity was determined using chiral GLC. Results are shown in Table 1. Not surprisingly, ephedrine **2c** was an efficient catalyst for the addition in terms of yield and enantioselectivity. As previously reported in the literature, *tert*-leucinol is a poor catalyst for the reaction resulting in low enantioselectivity. Aminoindanol was far superior to this; however, etambutol displayed nearly no enantioselectivity.[7] To develop the investigations, the efficiency of the polymer-supported amines **4c** and **4g** in the diethyl zinc addition reaction was assessed.[8]

Using **4c** and **4g**, excellent yields of 1-phenylpropanol were obtained. The enantioselectivity observed was very similar to that using the liquid-phase analogues **2c** and **2g**.

Next, the immobilized triazene catalysts **3a**–**g** were screened for catalytic activity using dichloromethane as a solvent. While the conversion to the desired product was good and in some cases exceeded that obtained with either the complexed or uncomplexed amines **2c**, **4c**, **2g**, and **4g**, the enantioselectivity was low. All the triazenes led to (*S*)-1-phenylpropanol being yielded. Using toluene as the solvent, the conversion was more efficient, but the products were again obtained with low enantiomeric purity.

Selected metal complexes based on amines **2**, prepared in our initial screening experiments, were assessed for activity in the diethyl zinc addition reaction to determine whether the coordination of a transition metal to the triazene has a beneficial effect on yield or enantioselectivity of reaction. Complexes derived from Cu(OTf)$_2$, Zr(acac)$_4$ and FeCl$_2$ were screened. Generally a diminished enantioselectivity was observed with the notable exceptions of the zirconium and iron complexes of **1a**, which gave slightly better results than the uncomplexed triazene **3a**. Of significant interest is that the copper complex of **3c** resulted in the formation of the opposite enantiomer to all the other metal bound triazenes, only the resin-bound amines **4c** and **4g** showing similar results.

In related studies, the characterized polymer-supported palladium and ruthenium triazene complexes **8** and **9** were screened for catalytic activity in transition-metal catalyzed reactions, comparing results obtained with those from solution-phase complexes and also, in the case of **9**, with another polymer-supported catalyst candidate. (Scheme 2).

Using 50 mg of **8** (loading of Pd of approximately 0.1 mmol/g resin; 5 μmol, 3 mol%) the supported triazene complex was found to be active as a catalyst in con-

Table 1. Catalysis results for various resins and liquid-phase experiments: relative yield of 1-phenylpropanol according to GLC[a,b]

Entry	Amine **2**[c]	**1** in CH$_2$Cl$_2$	**1** in toluene	Cu complex of **1**	Zr complex of **1**	Fe complex of **1**	**3**	**4**
1	Phenylethylamine: n.d.	88 (−4)		69 (rac)	n.d. (−10)	86 (−8)		
2	Aminoindanol: 63 (−59)	100 (−10)	94 (−8)	75 (rac)				
3	Ephedrine: 98 (+73)	78 (−9)	94 (−7)	74 (+9)	n.d. (rac)	n.d. (rac)		98 (+71)
4	Etambutol[g] 69 (rac)	62 (−5)	96 (rac)	71 (−5)				
5	Prolinol: n.d.[d]	39 (−9)		75 (rac)			70 (−32)	
6	SMP: n.d.						n.d. (−6)	
7	Leucinol: 95 (+15)[e,f]	70 (−6)		77 (−5)				95 (+32)

[a] Values in parenthesis represent ee of the product '−' for (*R*)-enantiomer, '+' for the (*S*)-enantiomer.

[b] General conditions: 0.1 g of resin (~0.07 mmol amine or triazene), 1.0 mmol of PhCHO, 2.7 mmol of Et$_2$Zn in hexane, 24 h, rt; aqueous workup.

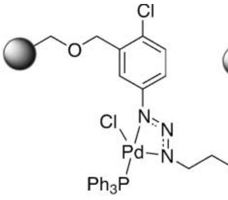
[c] Also represents amine used to prepare triazene (e.g., **2a** forms **1a**).

[d] n.d., not determined.

[e] *N*-Methyl leucinol used.

[f] Et$_2$Zn was added neat.

[g] (*S*,*S*)-1,2-Bis((1-hydroxybut-2-yl)amino)ethane.



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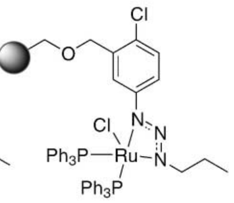

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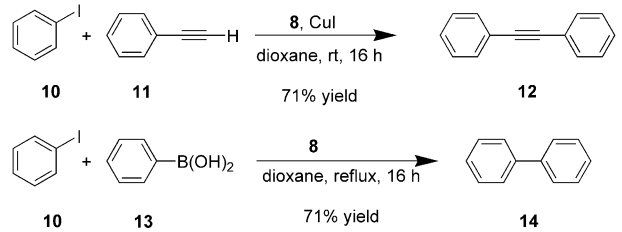
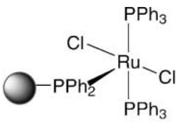


Scheme 2.

junction with CuI in the reaction of iodobenzene (1.79 mmol) with phenylacetylene (2.28 mmol), diphenylacetylene being formed in 86% yield. In an attempt to determine the extent, if any, of leaching of the palladium complex off the support during the course of the reaction, after filtration and removal of the solvent the entire crude reaction mixture was dissolved in CDCl$_3$ (400 mg in 1 mL) and analyzed by ^{31}P{^{1}H}NMR. There were no peaks observed in the range from δ +300 →−300 ppm. Also, the UV–vis spectrum of the product mixture showed no absorptions due to Pd (II) complexes. This was taken as a preliminary indication that there was no leaching of the catalyst from the polymer support to this level of detection. Similar results both in terms of activity and leaching were obtained on re-use of the same batch of **8** indicating that it is recyclable. The supported complex was also active in the Suzuki reaction; the reaction of benzene boronic acid (**13**, 0.1 mmol) and iodobenzene (**10**, 0.09 mmol) giving biphenyl in 71% yield using 30 mg (3 μmol, 3 mol%) of **8**. Although recyclable, the yields on subsequent uses were substantially lower than on the first use indicating some deactivation of the catalyst. As with the Sonogashira reaction, there was no leaching of the catalyst from the polymer support to the level of NMR and UV–vis detection.

We have recently shown that transfer hydrogenation is a suitable reaction for adaptation to solid-phase conditions using a polymer supported analogue **17** of Bäckvall's catalyst RuCl$_2$(PPh$_3$)$_3$.[9] To build on this, we screened **9** for activity in transfer hydrogenation but found that this was not successful.



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In conclusion, a range of triazene supported metal complexes as well as the free triazenes have been screened for activity in the enantioselective addition of diethyl zinc to benzaldehyde; however, the enantiomeric excess achieved was low. The best results were obtained using a simple triazene based on prolinol, this resulting in 32% enantiomeric excess. Polymer-supported palladium triazene complex **8** was shown to have good activity in both Sonogashira and Suzuki reactions with no leaching to the level analyzed and with similar results obtained when recycled. Polymer-supported ruthenium triazene complex **9** was found not to be a suitable catalyst for transfer hydrogenation reactions with little activity.

Acknowledgements

The British Council and the DAAD are thanked for a British-German Academic Research Collaboration grant (ARC 1119.00). Our work was supported by the Deutsche Forschungsgemeinschaft (SFB 380, BR1750–1), the Fonds der Chemischen Industrie and King's College London. The Royal Society is thanked for a University Research Fellowship (N.E.L.). We thank the BASF AG, Bayer AG and NovaBioChem for the donation of chemicals.

References and Notes

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5. In a general reaction, **7** was added slowly to a THF solution of **2** cooled to −10 °C. After stirring at −10 °C for 15 min, the reaction mixture was warmed to room temperature, the mixture stirred for a further 30 min then the product isolated by flash chromatography and characterized by NMR spectroscopy and CHN analysis.
6. Comparisons of data produced by asymmetric catalysis (yields and enantioselectivity) should only be performed using identical conditions.
7. Enantioselectivity below 2.5% *ee* was regarded as racemic.
8. For similar systems investigated before, see for example: Hodge, P.; Kell, R. J.; Ma, J. B.; Morris, H. *Aust. J. Chem.* **1999**, *52*, 1041. Hodge, P.; Sung, D. W. L.; Stratford, P. W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2335.
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