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Chiral Diketimines as Ligands in Pd-Catalyzed Reactions: Prediction of Catalyst Activity by the AMS Model

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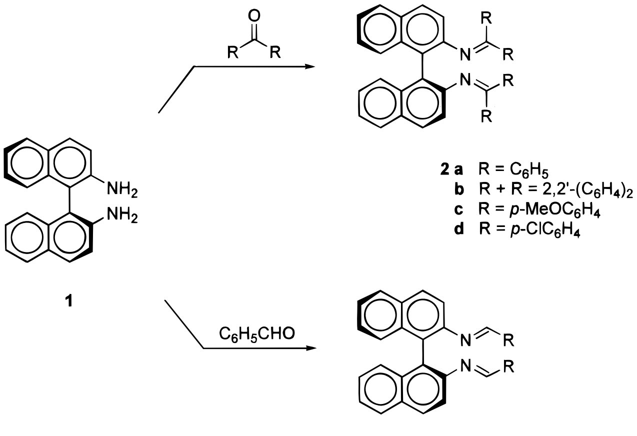
Whereas C_2-symmetric dialdimines constitute a well-known class of chiral ligands in a number of transition metal catalyzed reactions,[1] the corresponding diketimines have not been described to date. We report here the synthesis of the C_2-symmetric diketimines **2a**−**e** and their use as chiral ligands in Pd-catalyzed C−C bond forming reactions. Included is a comparison with the known dialdimine **3**[2] as well as a theoretical analysis of the relative catalyst activity of the entire homologous series of Pd complexes derived from these ligands.

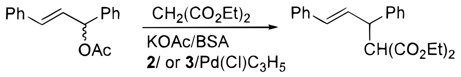


1

2 a R = C_6H_5
b R + R = 2,2'-$(C_6H_4)_2$
c R = *p*-$MeOC_6H_4$
d R = *p*-ClC_6H_4

3 R = C_6H_5

While the preparation of dialdimine **3** is straightforward simply by mixing the diamine **1** with benzaldehyde, the synthesis of the diketimines requires the presence of molecular sieves as well as considerably longer reaction times (2−3 d) in order to achieve yields of >95%. Upon performing the Pd-catalyzed allylic substitution **4**→**5** as a model reaction,[3] the Pd complex derived from the diketimine **2a** turned out to be a reasonably active catalyst, affording product **5** in 78% yield after a reaction time of 72 h with an ee-value of 92%. Surprisingly, the Pd complex derived from dialdimine **3** showed no activity whatsoever, even after 4 days of reaction time. Catalyst decomposition was not observed.



4 **5**

Why does a sterically encumbered catalyst show dramatically higher activity than the seemingly less shielded homologue? To shed some light on this unexpected finding, we applied the AMS model,[4] a special type of molecular modeling in which the *a*ccessible *m*olecular *s*urface at the active site in a homologous series of transition metal catalysts is calculated and correlated with catalyst activity. On the basis of a molecular fragment of the proposed transition metal catalyst, the following steps are performed: (1) Exploration of the conformational space within defined energy limits (3 kcal/mol) using force field calculations;[5] (2) combining all of the generated conformers into a single "pseudo-molecule" after superimposition of their fixed structural fragments; and (3) determining the size and orientation of the AMS at the metal at coordination distance (similar to the method of Connolly[6] in which the solvent accessible surface at the active site of enzymes is calculated). The AMS method was originally applied to the Rh-catalyzed hydrogenation of CO_2 in which the coordination number is lowered upon passing through the transition state, low AMS values therefore correlating with high catalyst activities.[4] In the present case the opposite is to be expected, that is, a large AMS should lead to high catalyst activity due to steric reasons. Upon applying the model to **2a**/Pd, rotational freedom was allowed for the four σ-bonds between the phenyl groups and the respective C-atoms of the imine moieties, whereas the actual metallocycle was assumed to be static. This gave rise to 33 conformers, the superimposition of which generates the respective pseudo-molecule which is shown in Figure 1a together with the calculated AMS (13.7 Å^2). Whereas a single analysis of this type is of little value, the comparison with analogous calculations of the homologous series is in fact illuminating. Thus, in the case of the Pd-catalyst derived from the dialdimine **3**, a dramatically different steric picture evolves (Figure 1b). In this case the AMS is only 7.3 Å^2. Moreover, since the free coordination sites are not even on the accessible molecular surface, complexation with substrates should be difficult, in contrast to the situation in **2a**/Pd (cf. orange markers in Figure 1a versus those in Figure 1b).

A small AMS and an unfavorable position of the free coordination sites are both expected to decrease catalyst activity. It is clear that the metal in **2a**/Pd is sterically much more accessible for coordination than in **3**/Pd. This can be traced to a "locking-in" effect of the phenyl groups in **2a**/Pd. In contrast, the phenyl groups of **3**/Pd rotate much more freely, resulting in considerably enhanced steric shielding. The analysis was also performed for the fluorenone-derived catalyst **2b**/Pd, in which only a single conformer is relevant, leading to an AMS of 9.9 Å^2 with the coordination sites being on the edges of the accessible surface (Figure 1c). Thus, catalyst activity is predicted to decrease in the series **2a**/Pd > **2b**/Pd ≫ **3**/Pd. Of course, possible electronic effects are not considered in this simple model, which is the reason the *para*-substituted catalysts **2c**-**d**/Pd were not subjected to the analysis.

The above prediction concerning relative rates should pertain to other Pd-mediated reactions as well. We therefore tested the Pd-catalyzed alternating copolymerization[7] of *p-tert*-butylstyrene (**6a**) with carbon monoxide leading to polyketones **7a**. The stereoselectivity of this type of process has been studied previously by several groups using various prochiral olefins, Pd complexes of chiral ligands such as unsymmetrical phosphine−phosphites,[8]

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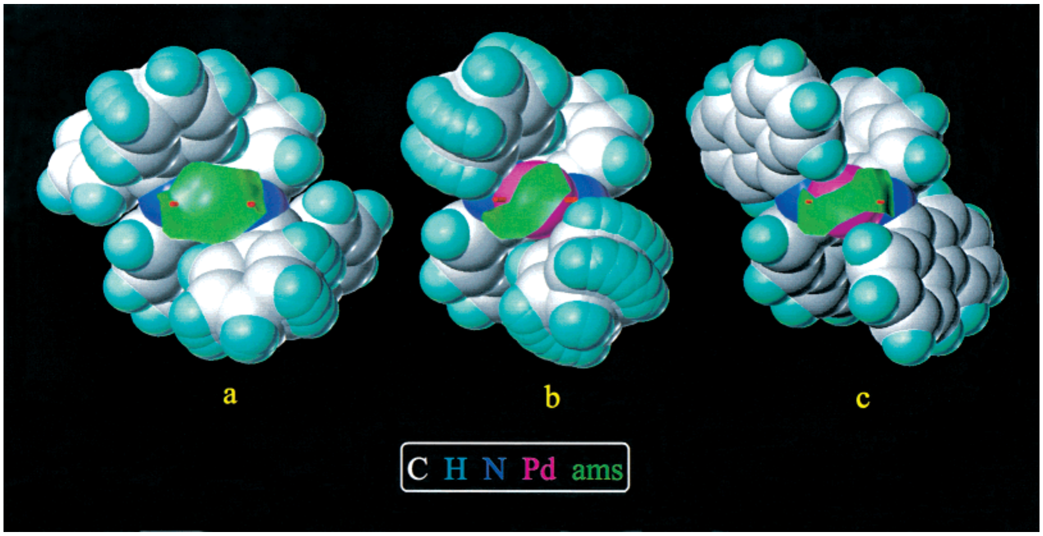
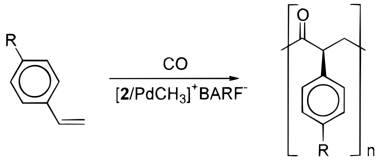


Figure 1. AMS model of **2a**/Pd (a), **3**/Pd (b), and **2b**/Pd (c). Orange markers denote coordination sites.

bisoxazolines,[9] phosphine−oxazolines,[10] phosphine−phosphinites,[11] or diphosphines[12] affording more or less isotactic polymers.



6 a R = *t*-Bu
b R = H
7

In the present case isotacticity of the polymers **7a** following the use of cationic Pd complexes of appropriate chiral diketimines **2** turned out to be >97% with formation of polymers in the molecular weight range of $M_n = 40\,000-50\,000$ ($M_w/M_n = 1.2$ by GPC). Tacticity was determined by integration of the ^{13}C NMR signals of the methylene C-atoms. The absolute configuration of **7** is unkonwn. Significantly, catalysts derived from fluorenone and benzaldehyde (**2b** and **3**, respectively) showed no activity whatsoever. In complete contrast, those catalysts prepared from **2a**, **2c**, and **2d** led to productivities of 20, 16, and 40 kg (polymer)/mol Pd, respectively. Under optimized conditions even activities of up to 110 kg (polymer)/mol Pd could be achieved, applying $[\mathbf{2a}/\mathrm{PdCH_3}]^+\mathrm{BARF}^-$ which is comparable or better than those reported previously using other chiral ligands.[8−12] Similar results were obtained in the case of styrene itself (**6b**). Thus, the qualitative predictions made on the basis of the AMS model are fully substantiated.[13]

In summary, we have prepared a new class of chiral ligands **2** for Pd-catalyzed C−C bond forming reactions. Extreme differences in catalyst activity within the diketimine series **2** and the dialdimine **3** are readily understood by applying the AMS model. We expect that this type of theoretical treatment, although rather crude, can be of substantial use in predicting catalyst activity in a homologous series of other transition metal mediated reactions as well. Thus it may turn out to be helpful in designing transition metal catalysts.

Acknowledgment. This paper is dedicated to Professor Günther Wilke on the occasion of his 75th birthday.

Supporting Information Available: Experimental Data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) In spite of the crudeness of the AMS model, it is in line with the experimental results. Nevertheless, knowledge of transition states and rate-determining steps will in general be required to make predictions about catalyst activity. For example, in the copolymerization the insertion of the olefin in the Pd−acyl bond, which is believed to be the rate-determining step, requires an open and accessible site for the olefin. Extremely open catalysts species, however, may form very stable intermediates, such that the subsequent CO insertion could then become the rate-limiting step for those catalysts, making comparisons difficult. The AMS concept is a computationally fast and intuitive way to distinguish between active and less active catalysts in a homologous series, provided that they react in a similar way. It can be applied even to molecular systems in which the size of the species considered prohibits the use of sophisticated methods. Because of the modeling type of approach, the results obtained by the AMS concept should be applied with the appropriate care.