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Chiral palladium-pincer complex catalyzed asymmetric condensation of sulfonimines and isocyanoacetate

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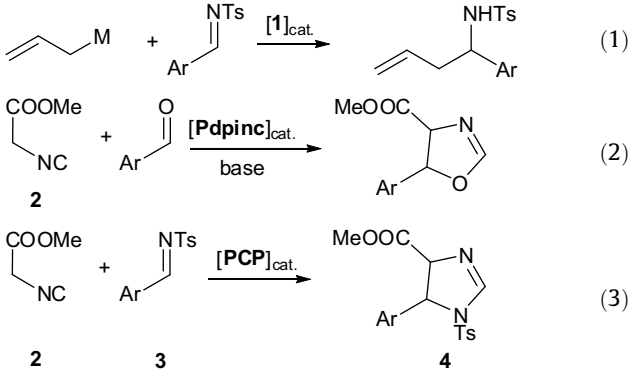
ABSTRACT

The asymmetric condensation of isocyanoacetate and sulfonimines was studied. Chiral BINOL and biphenantrol-based palladium-pincer complexes proved to be efficient catalysts affording 2-imidazoline derivatives with up to 86% ee. The level of enantioselectivity was clearly dependent on the γ-substituents of the BINOL ring. The best results were obtained by using biphenantrol-based pincer-complex catalysts. Some of the complexes induced the selective formation of the *anti*-diastereomer of the 2-imidazoline. The diastereo- and enantioselectivity showed an interesting solvent dependence as well. It was found that the application of diglyme as a solvent instead of THF leads to preferential formation of the *anti* product with a slight decrease of the enantioselectivity.

1. Introduction

Chiral-pincer complexes represent a promising new tool in asymmetric catalysis.[1–8] These species are characterized by strong metal to ligand bonding and a well-defined stoichiometry, which allows an efficient fine-tuning of the catalytic properties and rational ligand design.[9–21] In previous studies, we have systematically developed a series of BINOL and biphenantrol-based palladium-pincer complexes, in which the substituents were varied at the γ-position of the BINOL unit (Fig. 1).[9,10] These complexes could be employed in the asymmetric allylation[22–27] of various imine substrates (Eq. 1). It was found that γ-substitution of the BINOL units has a high influence on the enantioselectivity of the allylation reaction. For the allylation of sulfonimines, the best results were achieved using catalyst **1a** to afford the corresponding homoallylamine with 85% ee. Another important area of application of palladium-pincer complexes is the aldol reaction of aldehydes with isocyanides affording oxazoline derivatives (Eq. 2).[12–16] The oxazoline derivatives obtained in these reactions can be hydrolyzed to non-natural α-aminoacids. The possibility of obtaining enantiomerically pure α-aminoacids by this process has stimulated the development of the asymmetric version of this reaction using chiral-pincer complexes.[12–16] In these studies, the best results (up to 75% ee) were presented by Nishiyama et al.[14] using phebox derived pincer complexes.



Recently, we have shown that using pincer complex catalysis, a similar condensation reaction (Eq. 3) can be performed for isocyanides **2** and sulfonimines **3** to obtain imidazoline derivatives **4**.[28] The resulting imidazoline derivatives **4** can be readily hydrolyzed to α,β-diaminoacids, which are important bioactive compounds.[29,30] Condensation reactions of **2** and **3** affording imidazoline derivatives **4** have previously been performed using gold,[31–33] ruthenium,[34] and copper[35] catalysis; however, common palladium catalysts[31] performed poorly. On the other hand, palladium-pincer complex catalysis is very efficient[28] and highly selective compared to simple mono- and bidentate palladium catalysts. Accordingly, we decided to develop an asymmetric version of the palladium catalyzed condensation of **2** and **3** using chiral-pincer complex catalysts **1**. In these studies we have investigated the role of the substituent pattern and chirality of the BINOL/biphenantrol ligands[9] on the stereo- and enantioselectivity of the reactions. The

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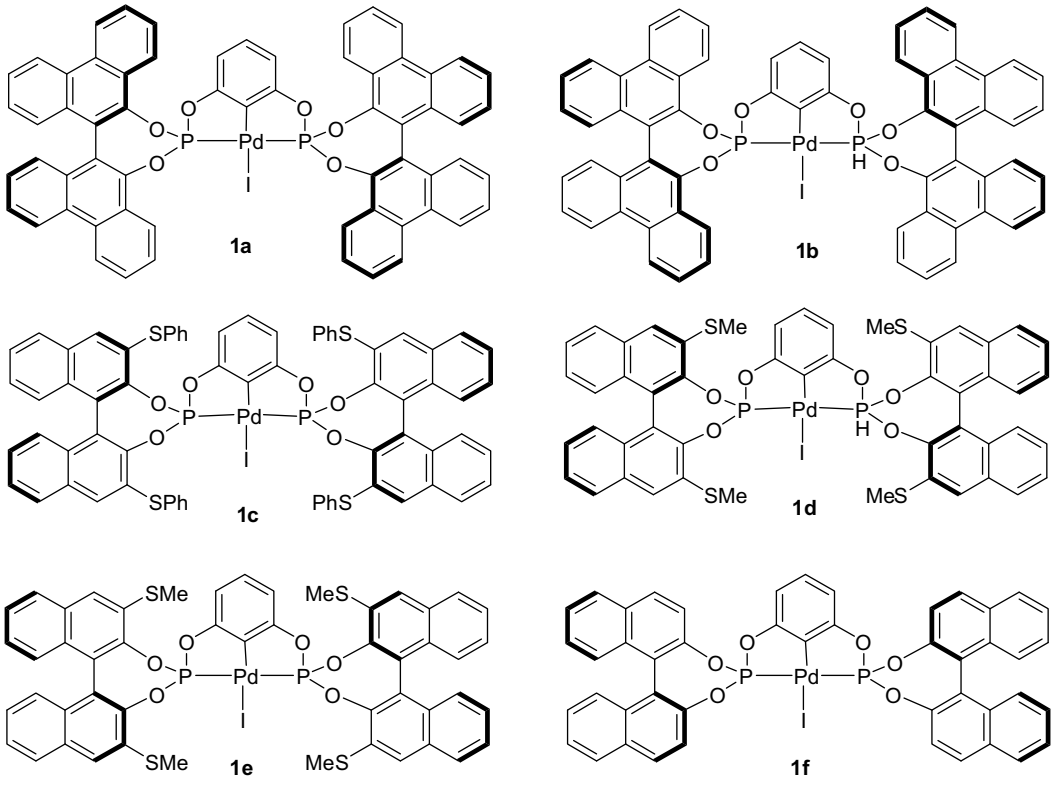


Figure 1. Chiral pincer complexes used as catalysts (5 mol %) in the condensation reactions of **2** and **3**.

enantioselective synthesis of the *anti*-products *anti*-**4** and *anti*-**5** is particularly interesting, as these species are not accessible by gold-ferrocenyl complex catalyzed asymmetric condensation of **2** and **3** as reported by Lin et al.[32,33]

2. Results and discussion

The condensation reaction of **2** and **3** is very efficiently catalyzed by complexes **1a**–**f** (Fig. 2, Table 1) using THF and other ether-based solvents (such as dioxane and diglyme). According to ^{31}P NMR spectroscopy of the final reaction mixtures, the chiral palladium catalysts remained completely unchanged in the reactions studied. This suggests that **1a**–**f** can be completely recycled after the completed catalytic processes. The formed imidazoline products **4** can be readily hydrolyzed to the corresponding α,β-diaminoacid derivatives **5**. As the partial hydrolysis of **4** can take place under the HPLC analysis of the products, we performed a complete hydrolysis of the imidazoline derivatives **4** obtained, and the ee was determined for **5**. Similarly to the allylation studies (Eq. 1), the highest ee, 86%, was obtained with biphenantrol complex **1a** (entry 1). This enantiomeric excess is somewhat higher than the corresponding value (up to 75%) obtained for the pincer complex catalyzed condensation of **2** with aldehydes.[13,14] Furthermore, the selectivity achieved with **1a** is almost as high (88%) as in the gold-ferrocenyl complex catalyzed reaction by Lin et al.[32,33] On the other hand, the stereoselectivity of the **1a** catalyzed process (dr *syn*/*anti* = 1:1) is clearly inferior to the gold catalyzed (dr *syn*/*anti* = 94:6) asymmetric catalysis.

Changing the chirality of the biphenantrol-based catalyst leads to change of the enatioselectivity of the condensation reaction. Accordingly, using **1a** as catalyst the major enantiomer is (2*S*,3*S*)-**4**-*syn* (entry 1); however, when **1b** is used under identical reaction conditions the major enantiomer is (2*R*,3*R*)-**4**-*syn* (entry 4) with slightly lower ee (72%). Interestingly, change of the solvent from

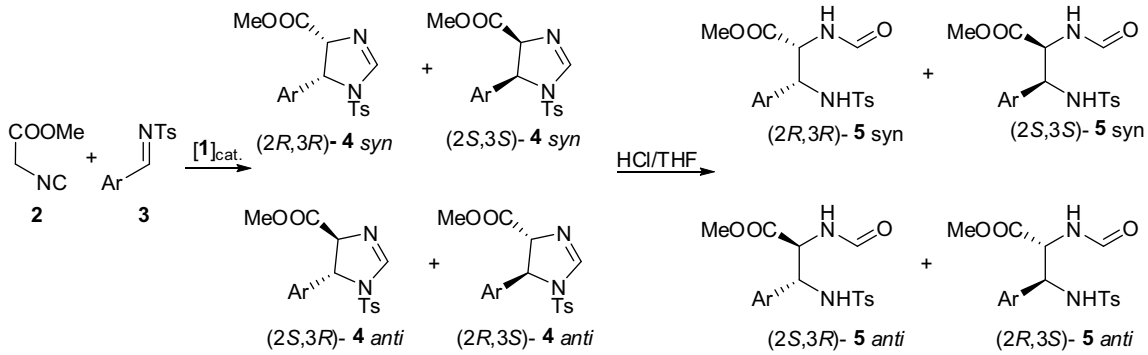
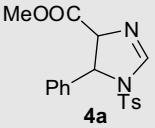
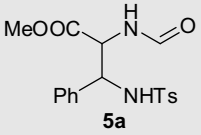
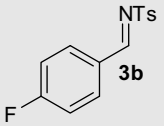
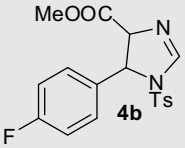
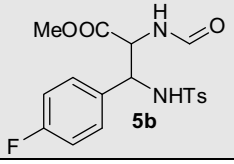


Figure 2. Direct products (**4**) of the condensation of **2** and **3** and the corresponding α,β-diaminoacid derivatives **5** obtained by hydrolysis.

Table 1
Product distribution in palladium-pincer complex (**1**) catalyzed condensation of **2** and **3**[a]

Entry	Catalyst	Imine	Product **4**	Product **5**	Yield **4**[b]	*Syn*/*anti*[c]	ee *syn*[d]	ee *anti*[d]
1	**1a**	 **3a**	 **4a**	 **5a**	98	1:1	86 (2*S*,3*S*)	28 (2*R*,3*S*)
2[e]	**1b**	**3a**	**4a**	**5a**	98	1:4	25 (2*R*,3*R*)	75 (2*S*,3*R*)
3[f]	**1b**	**3a**	**4a**	**5a**	98	1:1	73 (2*R*,3*R*)	68 (2*S*,3*R*)
4	**1b**	**3a**	**4a**	**5a**	98	1:1	72 (2*R*,3*R*)	18 (2*S*,3*R*)
5[e]	**1b**	**3a**	**4a**	**5a**	98	1:2.5	20 (2*S*,3*S*)	62 (2*R*,3*S*)
6	**1c**	**3a**	**4a**	**5a**	98	1:4	37 (2*S*,3*S*)	64 (2*R*,3*S*)
7	**1d**	**3a**	**4a**	**5a**	98	1:2	10 (2*S*,3*S*)	46 (2*R*,3*S*)
8	**1e**	**3a**	**4a**	**5a**	98	1:2	44 (2*R*,3*R*)	12 (2*S*,3*R*)
9	**1f**	**3a**	**4a**	**5a**	98	1:4	14 (2*R*,3*R*)	46 (2*S*,3*R*)
10	**1e**	 **3b**	 **4b**	 **5b**	98	1:2	35 (2*R*,3*R*)	7 (2*S*,3*R*)

[a] Unless stated otherwise, **3a**–**b** (0.2 mmol), **2** (0.2 mmol) and the corresponding catalyst **1a**–**f** (1 mol %) were reacted in THF at 20 °C for 18 h.
[b] Isolated yield [%].
[c] Diastereomer ratio determined by ^{1}H NMR.
[d] Enatiomeric excess [%].
[e] Diglyme was used as solvent.
[f] Dioxane was used as solvent.

THF to dioxane (entry 3) leads to only minor change of the enantioselectivity of the formation of the *syn* diastereomer; however, the ee of the *anti*-diastereomer is increased to 68% (c.f. entries 3 and 4).

The enantioselectivity for the formation of the *anti*-isomer can be further increased to 75% (entry 2), when diglyme is employed as the solvent instead of THF or dioxane. Gratifyingly, the diastereoselectivity (dr *syn*/*anti* = 1:4) of the condensation reaction could also be improved upon by using diglyme as a solvent (c.f. entries 2 and 4). Thus application of **1b** as catalyst in diglyme can be considered as a complement to the gold-ferrocenyl complex catalyzed reaction, which is *syn*-selective (dr *syn*/*anti* = 94:6).[32] Complex **1a** performed similarly to **1b** in diglyme by increasing the *anti* selectivity and the ee of the *anti* form; however, the extent of the effect was less pronounced (c.f. entries 1 and 5).

The enantioselectivity with BINOL-based pincer complexes **1c**–**f** proved to be lower than with the biphenantrol analogues (**1a**–**b**). However, in the presence of bulky thioether substituents at the γ-position of the BINOL unit, the enantioselectivity is clearly higher than with the parent system **1f**. Accordingly, using the SPh derivative **1c** (entry 6) the enantioselectivity is higher (64%) than with the SMe derivatives (entries 7 and 8) **1d** or **1e** (up to 46%) or with BINOL derivative (entry 8) **1f** (46%). Interestingly, these reactions are also selective for the formation of the *anti*-product (dr *syn*/*anti* up to 1:4).

We also performed limited studies with substituted sulfonimine derivatives, such as **3b**. The *para*-fluoro substitution of the sulfonimine led to an increase of the reactivity in the condensation process, but a decrease in the diastereo- and enatioselectivity when compared to **3a**.

As can be seen from the above studies, the enantio- and diastereoselectivity of the coupling reaction are strongly dependent on the structure of the pincer complex catalysts and also modified by solvent effects. Our previous mechanistic studies[28] indicate that the stereo- and enantioselectivity of the process are probably determined in the same reaction step. However, an exact description of the steric and electronic effects determining the selectivity can only be given on the basis of in depth DFT modeling studies, which are currently in progress.

3. Conclusions

Palladium-pincer complexes based on BINOL and biphenantrol-based ligands **1** are efficient catalyst for the condensation of isocyanoacetate **2** and sulfonimines **3** in up to 86% ee. The reactions proceed with higher enantioselectivity, when the biphenantrol **1a**–**b** based systems are employed instead of BINOL derivatives. For BINOL based complexes the selectivity is higher in the presence of bulky SPh substituents **1c** at the γ-position of the BINOL ring than with SMe substituent **1d**–**e** or with the parent system **1f**. The catalytic condensation reaction shows a tendency for the selective formation of the *anti* diastereomer, and thus it may complement the gold-ferrocenyl complex catalyzed method published by Lin et al.[32]

4. Experimental

All experiments were conducted under an argon atmosphere employing standard manifold techniques. The enantiomerically pure chiral palladium-pincer complexes **1a**–**f** were prepared from enantiopure BINOL and biphenantrol derivatives using our previously published[9,10] procedures. All solvents used in the reactions were freshly distilled prior to use. HPLC chromatograms were obtained using an Acquity™ Ultra Performance LC and Daicel Chiracel OD-H or AD-H columns with the parameters given in the experimental part. For column chromatography, Merck Silica Gel 60 (230–400 mesh) was used.

4.1. General procedure for the synthesis of 2-imidazoline derivatives 4a–b and α,β-diaminoacid derivatives 5a–b

A mixture of *N*-sulfonylimine **3a**–**b** (0.2 mmol), methyl isocyanoacetate **3** (0.02 g, 0.2 mmol), and the corresponding catalyst **1a**–**f** (0.002 mmol, 1 mol %) was stirred in THF (1.0 ml) at 20 °C for 18 h. After filtration through a thin pad of Celite, the solvent was removed to yield a *syn*/*anti* mixture of 2-imidazoline derivative **4a**–**b**. The *syn*/*anti* ratio was determined from crude ^{1}H NMR

spectra. The NMR data obtained for **4a–b** are identical with the literature values.[28] For the determination of the ee values, 2-imidazoline derivatives **4a–b** were hydrolyzed to **5a–b** by stirring a mixture of water (0.022 g, 1.4 mmol), HCl (37%, 0.004 g, 0.11 mmol), THF (1.5 ml), and 2-imidazoline **4** (0.195 mmol) for 3 h at 20 °C. Thereafter, the crude mixture was purified by chromatography using CH_2Cl_2/$CHCl_3$/MeOH (50:50:1) as eluent to yield **5a–b**.

4.2. Methyl 2-formylamino-3-[(4-methylphenyl)sulfonyl]-amino-3-phenylpropanoate 5a

This compound was obtained by the above general procedure. The NMR data obtained for **5a** are identical with the literature values.[28] The enantiomeric excess of **5a** was determined by chiral phase HPLC (Daicel Chiralcel OJ-H, hexane/*i*PrOH 85:15, flow rate 1.0 ml/min). The retention times are the following: *syn* diastereomer t_r (2*R*,3*R*) = 33 min; t_r (2*S*,3*S*) = 62 min. *anti* diastereomer t_r (2*S*,3*R*) = 16 min; t_r (2*R*,3*S*) = 23 min. Specific rotation: $[\alpha]_D^{20} = +32$ (*c* 1.1, THF); corresponding to a *syn*:*anti* ratio of 1.6:1 for which the enantiomeric excess was *syn* 86% and *anti* 28%. The absolute configuration of the major product was determined by comparison of the observed specific rotation to literature data.[32]

4.3. Methyl-3-(4-fluorophenyl)-2-formylamino-3-[(4-methylphenyl)sulfonyl]amino-propanoate 5b

This compound was obtained by the above general procedure. The NMR data obtained for **5b** are identical with the literature values.[28] The enantiomeric excess of the *syn* diastereomer of **5b** was determined by chiral phase HPLC (Daicel Chiralcel AD-H, hexane/*i*PrOH 70:30, flow rate 0.7 ml/min). The retention times are the following: *syn* enantiomers t_r (2*S*,3*S*) = 26 min; t_r (2*R*,3*R*) = 30.7 min. The enantiomeric excess of the *anti* diastereomer of **5b** was determined by chiral phase HPLC (Daicel Chiralcel OD-H, hexane/*i*PrOH 70:30, flow rate 1.0 ml/min). The retention times are the following: *anti* enantiomers t_r (2*R*,3*S*) = 32.7 min; t_r (2*S*,3*R*) = 41.9 min.

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