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Self-Assembly of Bidentate Ligands for Combinatorial Homogeneous Catalysis: Asymmetric Rhodium-Catalyzed Hydrogenation

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Combinatorial methods have recently been introduced to homogeneous metal complex catalysis as a means to accelerate the catalyst discovery process.[1] Many elegant solutions for high-throughput screening have been developed;[2] however, thus far the combinatorial approach to catalyst discovery and optimization suffers from the limited access toward structurally diverse and meaningful ligand libraries. The problem is particularly acute for the important class of bidentate ligands, which has its origin in the complexity of bidentate ligand synthesis. In many cases nontrivial synthetic operations are required, which renders the ligand synthesis unsuited for automation. A particular challenge is the synthesis of nonsymmetric bidentate ligands equipped with two different donor sites.

As one solution to this problem the use of mixtures of two monodentate ligands has been proven to be useful.[3] In these mixtures three potential catalysts are present simultaneously: the two homo-combinations and the hetero-combination. However, only in cases when the hetero-combination is more reactive and at the same time more selective than the homo-dimer, is optimization toward a better catalyst possible.

We recently introduced an alternative to the classical, covalent bidentate ligand synthesis, which relies on self-assembly of monodentate ligands through complementary hydrogen-bonding to give defined heterodimeric bidentate ligands (Scheme 1).[4−6]

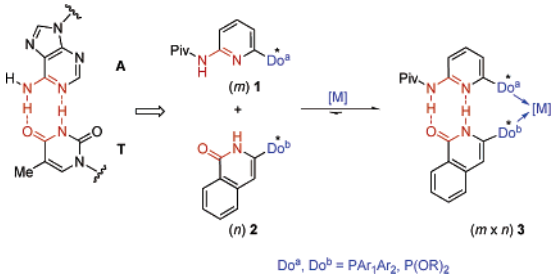
Thus, on the basis of an A−T base pair analogue, the aminopyridine−isoquinolone system, the first achiral bidentate phosphine ligand library was generated and screened against regioselectivity control in the course of the rhodium-catalyzed hydroformylation of terminal alkenes. These studies allowed us to identify a catalyst that operated with excellent activity and regioselectivity in preference for the linear regioisomer.[5]

We herein report on the synthesis[7] of a new library of chiral aminopyridine and isoquinolone systems equipped with phosphine and phosphonite donors and its first application to asymmetric catalysis, the asymmetric rhodium-catalyzed hydrogenation. From this chiral ligand library new heterodimeric combinations emerged, which furnished catalysts performing with enantioselectivities of up to 99% ee (Scheme 2).

In first experiments, we checked whether the ligand self-assembly process via complementary hydrogen-bonding is transferable to a cationic rhodium(I) center. Thus, mixing of one equivalent of the corresponding aminopyridine ligand, and one equivalent of isoquinolone based ligand with one equivalent of $[Rh(COD)_2]BF_4$ gave in all cases the corresponding heterodimer complexes $[RhL^aL^b(COD)]BF_4$ as proven by mass spectrometry as well as NMR spectroscopy.[7]

Original catalyst screening was done for the rhodium-catalyzed hydrogenation of acetamidoacrylate. The most interesting results from the screen of this 10 × 4 library are depicted in Table 1. Thus, replacing the achiral 6-DPPAP ligand (**1** with $Do^a = PPh_2$, Scheme 1) with the P-chiral (−)-**4a** ligand furnished an active hydrogenation catalyst that performed with moderate enantioselectivity (entry 1). However, replacing the achiral 3-DPICon (**2** with $Do^b = PPh_2$) with the chiral phosphonite derivative (*S*)-**6a** led to a

Scheme 1. Self-assembly of Chiral Monodentate to Chiral Bidentate Ligands through Complementary Hydrogen-Bonding on the Basis of an A−T Base Pair Analogue for Combinatorial Asymmetric Catalysis



Scheme 2. Library of Chiral Aminopyridine and Isoquinolone Ligands

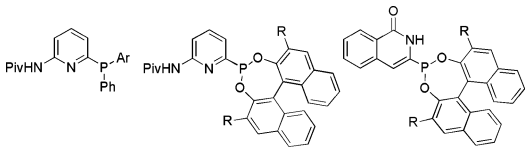
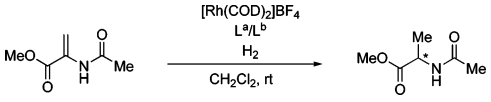


Table 1. Results of Asymmetric Rhodium-Catalyzed Hydrogenation[a] of Acetamidoacrylate



entry	L^a/L^b	conv. [%][b]	ee [%][c]	entry	L^a/L^b	conv. [%][b]	ee [%][c]
1[d]	(−)-**4a**/3-DPICon	quant.	56(*R*)	12[f]	(*S*)-**5a**/(*S*)-**6a**	quant	99(*R*)
2	(−)-**4a**/(*S*)-**6a**	quant.	86(*R*)	13	(*S*)-**5a**/(*S*)-**5a**	quant	98(*R*)
3	6-DPPAP/(*S*)-**6a**	quant.	82(*R*)	14	(*S*)-**6a**/(*S*)-**6a**	quant	94(*R*)
4	(+)-**4a**/(*S*)-**6a**	quant.	92(*R*)	15	(*S*)-**5a**/(*R*)-**6a**	quant.	80(*R*)
5[e]	(+)-**4a**/(*S*)-**6a**	quant.	94(*R*)	16	(*S*)-**5a**/(*S*)-**6b**	quant.	92(*R*)
6	(+)-**4a**/(*S*)-**6b**	12	70(*R*)	17	(*S*)-**5b**/(*S*)-**6a**	quant.	88(*R*)
7	(−)-**4b**/(*S*)-**6a**	94	81(*R*)	18	(*S*)-**5b**/(*R*)-**6a**	quant.	63(*R*)
8	(+)-**4b**/(*S*)-**6a**	quant.	89(*R*)	19	(*S*)-**5b**/(*S*)-**6b**	quant.	59(*R*)
9	(−)-**4c**/(*S*)-**6a**	53	79(*R*)	20	(*S*)-**5c**/(*S*)-**6a**	quant.	33(*R*)
10	(+)-**4c**/(*S*)-**6a**	77	82(*R*)	21	(*S*)-**5c**/(*R*)-**6a**	quant.	83(*R*)
11[e]	(*S*)-**5a**/(*S*)-**6a**	quant.	99(*R*)				

[a] All reactions in CH_2Cl_2, $Rh:L^a:L^b$ = 1:1.1−1.3:1.1−1.3, Rh:olefin = 1:100, 1 bar, 24 h. [b] Determined by NMR. [c] Determined by chiral GC analysis (column Hydrodex-β-TBDAc). [d] 6 bar, 48 h. [e] 0 °C in $ClCH_2CH_2Cl$. [f] Rh:olefin = 1:1000, 1 bar, 24 h.

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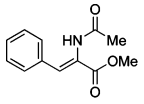
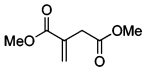
Table 2. Rhodium-catalyzed Hydrogenation[a] of Methyl-α-acetyl-amino Cinnamate (**7**) and Dimethylitaconate (**8**)



7



8

entry	ligands	substrate	*p* [bar]	conv. [%][b]	ee [%]
1	(*S*)-**5a**/(*S*)-**6a**	**7**	1	quant.	90 (*R*)[c]
2	(*S*)-**5a**/(*S*)-**6b**	**7**	1	quant.	94 (*R*)[c]
3	(*S*)-**5a**/(*S*)-**5a**	**7**	1	quant.	93 (*R*)[c]
4	(*S*)-**6b**/(*S*)-**6b**	**7**	1	33	73 (*R*)[c]
5	(*S*)-**5a**/(*S*)-**6a**	**8**	6	quant.	94 (*S*)[d]
6	(*S*)-**5a**/(*S*)-**6b**	**8**	6	quant.	91 (*S*)[d]
7	(*S*)-**5a**/(*R*)-**6a**	**8**	6	quant.	90 (*S*)[d]
8	(*S*)-**5b**/(*S*)-**6a**	**8**	6	quant.	70 (*S*)[d]
9	(*S*)-**5b**/(*S*)-**6a**	**8**	30	quant.	94 (*S*)[d]
10	(*S*)-**5b**/(*S*)-**5b**	**8**	30	22	38 (*S*)[d]
11	(*S*)-**6a**/(*S*)-**6a**	**8**	30	quant.	89 (*S*)[d]

[a] Rh:L[a]:L[b]= 1:1.1−1.3:1.1−1.3, Rh:olefin = 1:100, 24 h. [b] Determined by NMR. [c] Determined by chiral HPLC analysis (column Chiralpak-AD). [d] Determined by chiral GC analysis (column G-TA, trifluoracetyl-γ-cyclodextrin).

catalyst operating with significantly enhanced enantioselectivity (entry 2). Exchanging (−)-**4a** with its enantiomer (+)-**4a** gave an even better catalyst with 92% ee (entry 4) representing the matched ligand combination. This result could be improved to 94% ee when the reaction was run in dichloroethane at 0 °C (entry 5). Any further variation in the phosphine structure of **4** did not provide any better catalyst (entries 7−10). However, exchanging the aminopyridylphosphine monomer **4** by the corresponding phosphonite system (*S*)-**5a** gave the best catalyst (entry 11). Even at catalyst loadings of 0.1 mol % complete conversion and perfect enantioselectivity (99% ee, entry 12) was noted. In a control experiment both homocombinations for ligands **5a** and **6a** were tested separately. Both furnished active hydrogenation catalysts which gave slightly lower enantioselectivities (entries 13 and 14) than the heterocombination, which suggests the heterocombination to be not only the prevalent catalyst but also the kinetically competent species.[8] Interestingly, even the mismatched combination of the two heterodimeric phosphonites (entry 15) furnished 80% ee. This result is in agreement with the rather unsymmetrical P-donor arrangement found in the crystal structure of a square planar platinum complex of the parent 6-DPPAP/3-DPICon system, reported previously.[5] Variation of the ortho-substituents in the BINOL skeleton did not provide any further improvement (entries 16−21).

A small sublibrary based on the bisphosphonite systems was screened against asymmetric hydrogenation of methyl-α-acetyl-amino cinnamate (**7**) and dimethylitaconate (**8**) (Table 2). Interestingly, for substrate **7** the optimal ligand combination was found to be (*S*)-**5a**/(*S*)-**6b** with 94% ee (entry 2). The same ligand combination had provided only mediocre results in case of the parent acetamidoacrylate substrate (Table 1, entry 17). For dimethylitaconate (**8**) both (*S*)-**5a**/(*S*)-**6a** as well as (*S*)-**5b**/(*S*)-**6a** gave the best results (94% ee, Table 2, entries 5,9). In the latter case, control experiments employing the homocombinations clearly showed that the heterocombination provides a catalyst operating with a significantly improved selectivity (entries 9−11). These preliminary examples indicate that catalyst/ligand adjustment to a particular substrate of interest is an important issue, and a combinatorial approach based on self-assembly is in fact a useful technique to rapidly identify an optimal catalyst.

In conclusion, the first chiral bidentate phosphorus donor ligand library based on self-assembly through hydrogen bonding was generated and screened for rhodium-catalyzed asymmetric hydrogenation. Bidentate ligand combinations of phosphine/phosphonites as well as diphosphonite systems were identified that furnished excellent catalysts performing with enantioselectivities of up to 99% ee. Application of this and other chiral ligand libraries to asymmetric catalysis is ongoing in these laboratories.

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Supporting Information Available: Ligand syntheses and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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