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Asymmetric synthesis of α-aminoamides by Pd-catalyzed double carbohydroamination†

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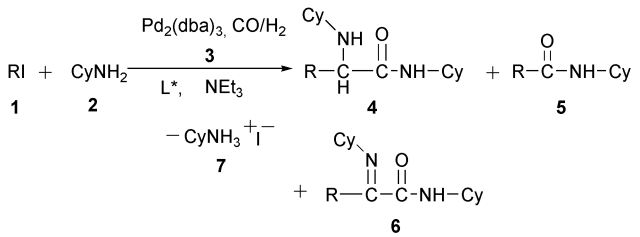
Tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] catalyzed asymmetric double carbohydroamination of iodoarenes in the presence of a chiral ligand (Trost ligand and Me-DuPHOS are most effective) is an excellent method for the chiral synthesis of α-aminoamides in up to 99% ee.

Asymmetric synthesis, using enantioselective catalysts, is a powerful and commonly used method for the preparation of chiral molecules. Typically in the pharmaceutical industry, only one of the enantiomers is responsible for the desired biological activity, while the other is either inactive or may cause adverse side effects. Recent developments in homogeneous asymmetric hydrogenation, by means of transition metal catalysts, have been extremely promising. In contrast to the high enantioselectivities observed in both catalytic olefin and keto group hydrogenations, only limited success has been achieved thus far in the catalytic asymmetric hydrogenation of the C=N functionality in compounds such as imines. In addition to Rh[1–3] complexes, there are many examples employing Ir[4–6] and Ti[7,8] for the asymmetric hydrogenation of imines. The first commercially feasible enantioselective hydrogenation of imines was developed by a team at Ciba-Geigy.[9] The ability to enantioselectively reduce the C–N double bond could lead to a useful reductive amination procedure for the conversion of prochiral ketones into optically active amino derivatives.

In 2001, one of us reported a novel one-pot synthesis of α-aminoamides from iodoarenes and amines *via* a Pd-catalyzed double carbohydroamination.[10] The ability to effect the double carbohydroamination reaction in an asymmetric manner would be highly significant, since it would provide a one-pot chiral preparation of amino acid derivatives. Our initial strategy to use 10% Pd/C with added chiral ligands was unproductive. Consequently we first had to develop a homogeneous variant of the double carbohydroamination reaction.

Experiments were first conducted by using iodobenzene (**1**, R = Ph), cyclohexylamine (**2**), carbon monoxide (800 psi; 55 atm), hydrogen (100 psi, 7 atm), and the chloroform adduct of tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] (**3**) as the catalyst with different chiral ligands (L*) in the presence of triethylamine and 4 Å molecular sieves (Scheme 1). This reaction proceeded well at 120 °C to form α-cyclohexylamino amide (**4**, R = Ph) as the major product (83% yield) while cyclohexylamide (**5**, R = Ph) was obtained as the by-product



Scheme 1 Pd catalyzed asymmetric double carbohydroamination.

† Electronic Supplementary Information (ESI) available: spectral data. See http://www.rsc.org/suppdata/cc/b3/b306879j/

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(13%), and traces of α-*N*-cyclohexylimino amide (**6**, R = Ph) were also detected in the reaction mixture. The role of molecular sieves is to absorb water produced during the reaction. Note that $Pd(OAc)_2$ gave inferior results, while $Pd(PPh_3)_4$ afforded the imine.

We investigated the extent of asymmetric induction in triethylamine with a variety of commercially available chiral ligands including BINAP (*S* or *R*),[11,12] *S*-Tol-BINAP,[13] *R*,*R*-Me-DuPHOS,[14] and (1*R*,2*R*)-(+)-1,2-diaminocyclohexane-*N*,*N*′-bis(2′-diphenylphosphinobenzoy)l (Trost ligand).[15,16] The results are presented in Table 1.

R,*R*-Me-DuPHOS (entries 5, 6), *S*-Tol BINAP (entry 7) and the Trost (entry 8) ligand were found to be the best chiral ligands for this reaction, giving 93–99+% ee, while *R* and *S*-BINAP (entries 1 and 2) afforded the α-aminoamides in less than 50% ee. Interestingly, although *S*-BINAP and *S*-Tol-BINAP are very similar in structure, these ligands show very different enantioselectivities.

Several different *para*-substituted iodobenzenes were reacted with cyclohexylamine in order to determine the influence of the substituent on the asymmetric double carbohydroamination reaction, and the results are presented in Table 2.

Interestingly, the Trost ligand (Table 2, entries 5, 10, 16, 23) and *R*,*R*-Me-DuPHOS (entries 3, 8, 13, 21, 22) gave excellent % ee values. However, the product yields were moderate in several cases, while *S*,*S*-Me-DuPHOS (entries 18, 19) and *S*-Tol-BINAP (entries 4, 9, 15) were inferior to the Trost ligand and *R*,*R*-Me-DuPHOS. *R*- and *S*-BINAP gave results similar to those using iodobenzene as the reactant.

Use of methanol as the solvent instead of triethylamine appreciably affected the % ee. When 4-iodobenzene was employed as a reactant, the % ee decreased markedly using *R*,*R*-Me-DuPHOS or the Trost ligand in methanol compared with triethylamine (Table 2, entries 14, 17). Interestingly, in the case of *S*,*S*-Me-DuPHOS , the α-aminoamide **4**, R = $CH_3C_6H_4$, was obtained in comparable % ee using either triethylamine or methanol as the solvent (Table 2, entries 18, 19). In addition, it is northworthy that,while use of *R*- or *S*-BINAP afforded products in comparable % ee in Et_3N, *R*,*R*- and *S*,*S*-Me-

Table 1 Asymmetric double carbohydroamination of iodobenzene[a]

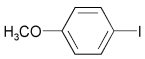
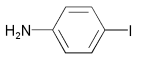
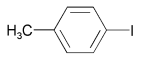
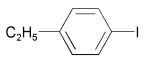
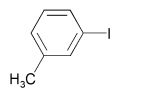
Entry	Ligand	Yield of **4**, R = Ph [%][c]	ee [%][d]
1	*R*-BINAP	83	43
2	*S*-BINAP	55	40
3	*R*-BINAP[b]	43	41
4	*S*-BINAP[b]	20	36
5	*R*,*R*-Me-DuPHOS	31	> 99
6	*R*,*R*-Me-DuPHOS[b]	15	93
7	*S*-Tol-BINAP	37	> 99
8	TROST	49	98

Reaction conditions:[a] PhI (1 mmol), cyclohexylamine (10 mmol), Et_3N (3 ml), 4 Å MS (1 g), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.02 mmol), ligand (0.04 mmol), CO (800 psi), and H_2 (100 psi) were employed at 120 °C for 24–42 h. [b] Ligand (0.06 mmol). [c] Yields determined based on GC and ^1H NMR spectroscopy. [d] % ee determined by chiral HPLC using a Chiralcel OD column.

DuPHOS gave products in similar % ee (69–73%) using methanol as the solvent, but in quite different ee's using Et_3N (92, 73%)

When 3-iodotoluene was used as the substrate with *R*,*R*-Me-DuPHOS or the Trost ligand similar results were obtained in comparison to the *para*-substituted iodobenzenes (Table 2, entries 22, 23) When 2,6-dimethyliodobenzene was used as the substrate in the double carbohydroamination reaction, no α-aminoamide products were observed in the reaction mixture, possibly due to steric hindrance. Bromobenzene, benzyl-bromide and vinyl iodide did not undergo the double carbohydroamination reaction, thus giving trace amounts of the product.

Table 2 Asymmetric double carbohydroamination of aromatic iodides[a] with cyclohexylamine

Entry	ArI	Ligand	Solvent	Yield [%]	ee [%]
1		*R*-BINAP	Et_3N	51	40
2		*S*-BINAP	Et_3N	42	36
3		*R*,*R*-Me-DuPHOS	Et_3N	41	75
4		*S*-Tol-BINAP	Et_3N	46	69
5		TROST	Et_3N	44	> 99
6		*R*-BINAP	Et_3N	43	32
7		*S*-BINAP	Et_3N	32	28
8		*R*,*R*-Me-DuPHOS	Et_3N	33	89
9		*S*-Tol-BINAP	Et_3N	41	72
10		TROST	Et_3N	45	90
11		*R*-BINAP	Et_3N	46	39
12		*S*-BINAP	Et_3N	38	35
13		*R*,*R*-MeDuPHOS	Et_3N	45	92
14		*R*,*R*-MeDuPHOS	MeOH	51	73
15		*S*-Tol-BINAP	Et_3N	65	84
16		TROST	Et_3N	41	91
17		TROST	MeOH	68	68
18		*S*,*S*-Me-DUPHOS	Et_3N	36	72
19		*S*,*S*-Me-DUPHOS	MeOH	43	69
20		*R*-BINAP	Et_3N	47	44
21		*R*,*R*-Me-DuPHOS	Et_3N	46	94
22		*R*,*R*-Me-DuPHOS	Et_3N	43	93
23		TROST	Et_3N	51	90

[a] Reaction conditions were the same as those described in Table 1.

In conclusion, the $Pd_2(dba)_3$ catalyzed asymmetric double carbohydroamination reaction was effected with different iodoarenes and cyclohexylamine, in the presence of a chiral ligand, to form α-aminoamides. Outstanding results were attained using *R*,*R*-Me-DuPHOS and the Trost ligand. The asymmetric double carbohydroamination reaction thus constitutes a facile chiral synthesis of α-amino acid derivatives.

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