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Palladium catalysed mono-*N*-arylation of enantiopure diamines

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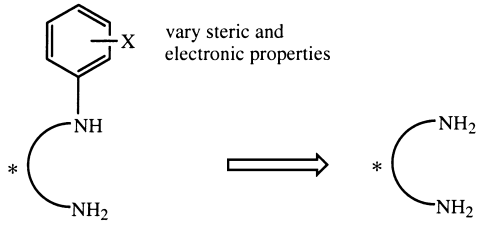
Abstract

The palladium catalysed arylation of amines is employed to prepare selectively a range of new, mono-*N*-arylated, enantiopure diamine ligands. The ligands were tested in the catalytic asymmetric transfer hydrogenation of acetophenone.

The effectiveness of enantiopure amine-based transition metal complexes in asymmetric catalysis is well established.[1] In particular, ligands derived from certain C_2-symmetric enantiopure diamines have been successfully employed in a wide range of asymmetric catalytic transformations including epoxidation,[2] allylic substitution[3] and hydrogenation.[4] As part of an ongoing research programme in the development of new enantiopure ligands for asymmetric catalysis, we required the efficient preparation of mono-*N*-arylated, enantiopure diamines **1**. A flexible protocol that allowed us to incorporate aryl groups with different steric and electronic properties was desired.



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Enantiopure mono-N-arylated diamines

A general aromatic carbon–nitrogen bond forming reaction employing primary amines and aryl bromides as coupling partners was realised independently by the research groups of both Buchwald and Hartwig.[5] We have previously applied this protocol to the iterative coupling of enantiopure amines and aryl bromides in the assembly of new peptidomimetics.[6] Previous studies have revealed that for the reaction to proceed without racemisation the choice of ligand was crucial.[7] The cat-

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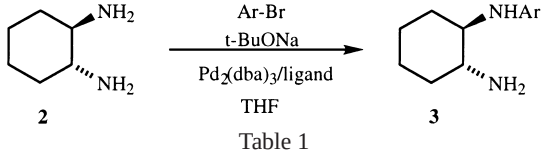
alytic cross-coupling of aryl bromides and enantiopure amines employing Pd(0)/dppf (dppf=1,1′-bis(diphenylphosphino)ferrocene) or Pd(0)/BINAP combinations affords products in good yields with no erosion of enantiopurity. We now wish to report the use of this strategy in the catalytic mono-*N*-arylation of enantiopure diamines.[8]

For the cross-coupling of (1*R*,2*R*)-(−)-1,2-diaminocyclohexane **2** with a range of aryl bromides, we employed the combination of $Pd_2(dba)_3$ and dppf as catalyst. For a typical experiment the aryl halide (1 equiv.) then the diamine (1.4 equiv.) were added to a mixture of *t*-BuONa (1.8 equiv.), $Pd_2(dba)_3$ (6 mol%) and ligand (18 mol%). The mixture was heated to reflux in THF in a sealed tube for approximately 24 hours.



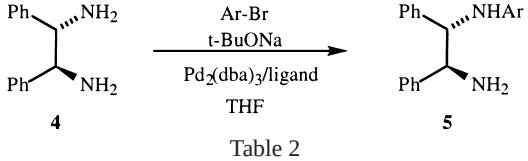
2 **3**

Table 1
Palladium catalysed mono-*N*-arylation

Entry	Ar	Ligand	Product	Yield (%)
1	a-$C_{10}H_7$	dppf	**3a**	43
2	$C_6H_5C_6H_4$	dppf	**3b**	30
3	p-$(PhCH_2N(Ph)SO_2)C_6H_4$	dppf	**3c**	53
4	2-C_5H_5N	dppf	**3d**	19
5	$C_6H_5C_6H_4$	BINAP	**3b**	52
6	p-$(PhCH_2N(Ph)SO_2)C_6H_4$	BINAP	**3c**	70

The mono-*N*-arylated products **3a**–**c** were obtained in moderate yields as indicated in Table 1. For the cross-coupling of **2** with 2-bromopyridine the major product was the bis-*N*-arylated diamine. In each case we observed significant amounts of the reduced product and, in some cases, the starting aryl bromide was not totally consumed. Attempts to optimise the yields by changing reaction parameters such as catalyst loadings, solvent and temperature were largely unsuccessful. However, the use of BINAP as a ligand resulted in a notable increase in efficiency (entries 5 and 6).[9]

Having established that the palladium catalysed arylation protocol could be applied to the mono-*N*-arylation of **2**, we extended this strategy to (1*S*,2*S*)-(−)-1,2-diphenyl-1,2-ethanediamine **4** (Table 2).



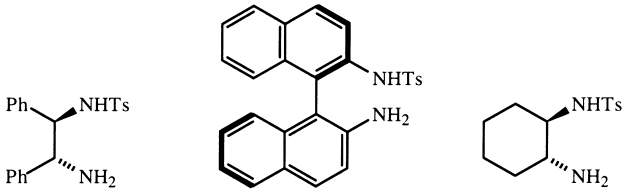
4 **5**

Table 2
Palladium catalysed mono-*N*-arylation

Entry	Ar	Ligand	Product	Yield (%)
1	α-$C_{10}H_7$	BINAP	**5a**	62
2	$C_6H_5C_6H_4$	BINAP	**5b**	40
3	p-$(PhCH_2N(Ph)SO_2)C_6H_4$	BINAP	**5c**	96

With a synthesis of mono-*N*-arylated enantiopure diamines in hand, it was decided to explore their suitability as ligands for asymmetric catalysis. The catalytic, enantioselective transfer hydrogenation of

ketones provides a useful method for obtaining enantiomerically enriched secondary alcohols. Noyori noted a significant rate enhancement in the transfer hydrogenation of acetophenone when ethanolamine was added to a mixture of 2-propanol, potassium hydroxide and catalytic $[RuCl_2(\eta^6\text{-benzene})]_2$.[10] This led to the testing of enantiopure β-amino alcohols as ligands for the enantioselective transformation, and eventually to the development of the enantiopure mono-*N*-tosylated diamine ligands **6** and **7** which allow the highly efficient enantioselective transfer hydrogenation of a wide range of ketones and imines. Knochel has reported that the enantiopure mono-*N*-tosylated diaminocyclohexane **8** is similarly efficient in the same reaction.[11]



6 **7** **8**

Initial results employing the enantiopure mono-*N*-arylated diamines as ligands in the ruthenium catalysed transfer hydrogenation of acetophenone are presented in Table 3.[12] The levels of asymmetric induction obtained were low compared with the enantiopure mono-*N*-tosylated diamine ligand **8**. However, the effect of the electron-withdrawing sulfonamide moiety was significant in terms of activity and enantioselectivity (entries 4 and 7). The enantiomeric bias of the asymmetric reduction is consistent with the Noyori system.[13]

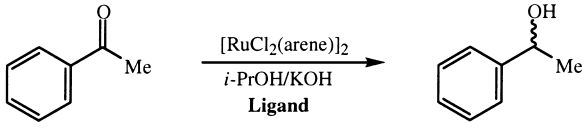


Table 3
Enantioselective transfer hydrogenation of acetophenone

Entry	Ligand	Yield (%)	ee (%)
1	**6**	93	96 (R)
2	**3a**	<5	n.d.
3	**3b**	8	4
4	**3c**	31	6 (R)
5	**5a**	66	21 (S)
6	**5b**	88	7 (S)
7	**5c**	>95	60 (S)

The ligand **5c** was also effective when used in combination with $[Ir(cod)Cl]_2$ to give the product 2-phenylethanol in 67% yield but with lower enantioselectivity (16% ee).

In conclusion, we have shown that the palladium catalysed arylation reaction is effective for the mono-*N*-arylation of enantiopure diamines. This class of compounds has previously been unavailable due to the lack of efficient hetero-aromatic coupling protocols. The compounds are expected to be versatile scaffolds for the assembly of new ligands for asymmetric catalysis, and in this context we have demonstrated a remote electronic effect in the ruthenium catalysed transfer hydrogenation of acetophenone. This has implications in the future design of new ligands for this transformation.

Acknowledgements

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