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Asymmetric synthesis of an aminomethyl morpholine via double allylic substitution

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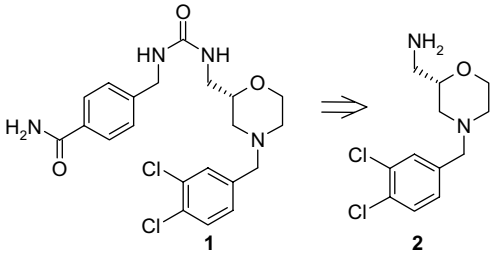
Abstract—The development of an asymmetric route to an aminomethyl morpholine intermediate via palladium-catalysed allylic substitution is described.

Recently we disclosed a series of amido and urea appended morpholine skeletons as potent antagonists of CCR3.[1] These have potential therapeutic applications to asthma and rhinitis, and urea **1** is representative of this series (Scheme 1).

The chiral (dichloro)benzyl aminomethylmorpholine **2** was the key intermediate in the preparation of this series of compounds. Previously, a Mitsunobu diol cyclisation had been utilised to prepare the morpholine core,[2] but as we sought methods for scale-up, alternative routes were examined. We became interested in the work by Hayashi et al. preparing asymmetric vinyl morpholines via palladium-catalysed allylic substitution (Scheme 2).[3] This initial report was followed by work from Achiwa and Yamazaki (83% ee),[4] Ito et al. (81% ee)[5] and notably Nakano et al.,[6] who achieved the highest ee recorded of 94%, with a *P*,*N*-xylofuranose-based ligand (prepared in 3-steps).



Scheme 1.

Keywords: Asymmetric synthesis; Palladium; Allylic substitution.
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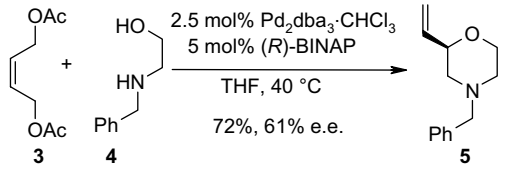
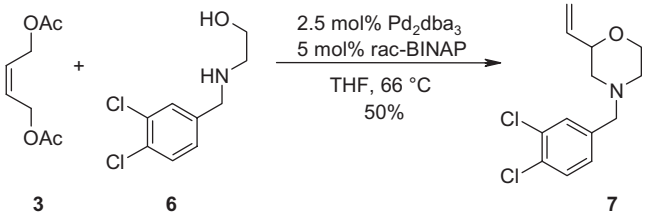


Scheme 2.

In looking to apply this chemistry to an industrial problem, aims for our work would be to increase the ee, lower the metal loading, and find a ligand that was readily accessible on a commercial scale.

The anticipated extension of the literature chemistry for benzylethanolamine to dichlorobenzyl ethanolamine was fortunately trivial. Good conversion was obtained with racemic BINAP which gave us markers for chiral HPLC development (Scheme 3).

We then undertook a ligand screening exercise, as shown in Table 1. We were able to repeat the literature ee values with (*S*)-BINAP, and achieve slight improvements with (*S*)-tol-BINAP. However, we became aware of the commercial availability of the phenyl 'Trost' ligand



Scheme 3.

Table 1. Ligand screening for tandem allylic substitution

Entry	Method[a]	Ligand	Mol% ligand [Pd 2.5 mol%]	ee[c]	% Conversion to **7**
1	A[b]	BINAP	5	65	47
2	A[b]	tol-BINAP	5	70	78
3	A	BIPHEP	5	65	31
4	A	Monophos, **13**	5	30	58
5	A	*P*,*N*-oxazoline, **10**	5	36	30
6	A	*t*-Bu-BOX	5	—	<2
7	B	*t*-Bu-BOX	5	—	<2
8	B	BIPHEP	5	77	24
9	B	Ph Trost, **12**	7.5	89	88
10	B	Quinap	7.5	0	77
11	B	Ph-PyBOX	7.5	—	<5
12	B	MOP	7.5	—	<5
13	B	Chiraphos	7.5	—	<15
14	B	DIOP	7.5	0	67
15	B	DUPHOS	7.5	0	16
16	B	BPE	7.5	'low'	30
17	B	Walphos, **8**	7.5	0	88
18	B	Mandyphos, **9**	7.5	20	37
19	B	Mandyphos, **11**	7.5	0	56
20	B	Monophos, **14**	7.5	30	79

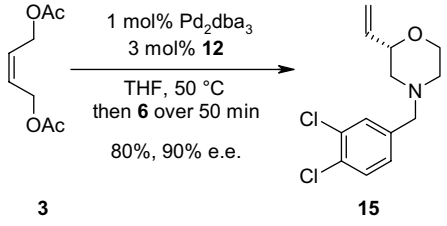
[a] Method A—charge ligand, then THF, then $Pd_2dba_3{\cdot}CHCl_3$, then NEt_3. Stir 1 h, then charge **6**, then **3**, at room temp. Method B—charge THF, degas (vacuum), charge ligand, charge $Pd_2dba_3{\cdot}CHCl_3$, then NEt_3, degas, charge **3**, stir 15 min, charge **6**, at room temp.[7]
[b] Entry 1 reaction at 50 °C, entry 2 reaction at 40 °C.
[c] Determined on Chiralcel OJ column, heptane/IPA eluent.

12 (Scheme 4), which was well precedented for AAA (Asymmetric Allylic Alkylation) reactions.[7] Screening this ligand gave us excellent yields and ee (entry 9). The 'Trost' charging regime was then used for the remainder of our screening experiments.

These conditions from Trost's work had given us a major lead. We also examined iridium catalysis but this was a much slower reaction in refluxing THF.[8] The naphthyl analogue of the 'Trost' ligand was not superior,[7] neither were toluene nor DCM as reaction solvents. We did establish that slow addition of ethanolamine **6** was minimised impurities arising from attack of two benzylic amines on the allylic acetate, and favoured the desired intramolecular cyclisation. We utilised a statistical 'design of experiments' approach to identify rapidly the important factors for improving this reaction. Both conversion and ee benefited from an increase in temperature, so reactions were now run at 50 °C (consistent with an equilibration in the enantiodetermining step).[7] These improvements enabled an increase in the isolated yield to 80% at 90% ee on a 10 g (45 mmol) input, using only 1 mol% of catalyst (Scheme 5).

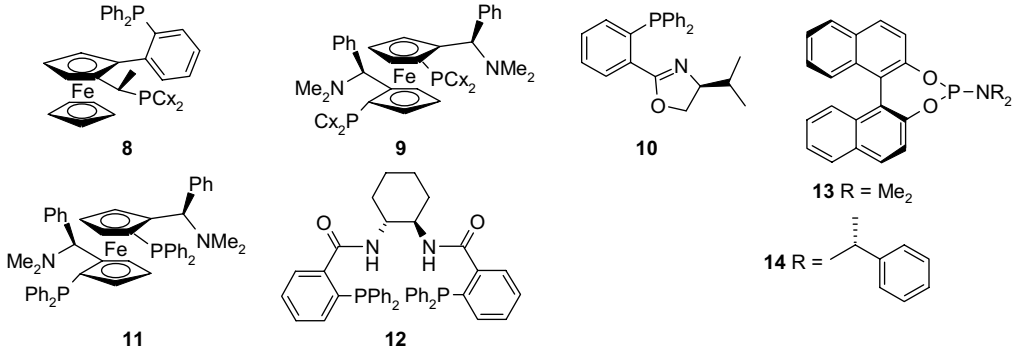
To apply this enantioselective morpholine synthesis to the preparation of urea **1** we were required to transform the vinyl moiety of **15** to the desired aminomethyl group.

This was achieved via dihydroxylation, followed by oxidative cleavage (one pot protocols gave significant



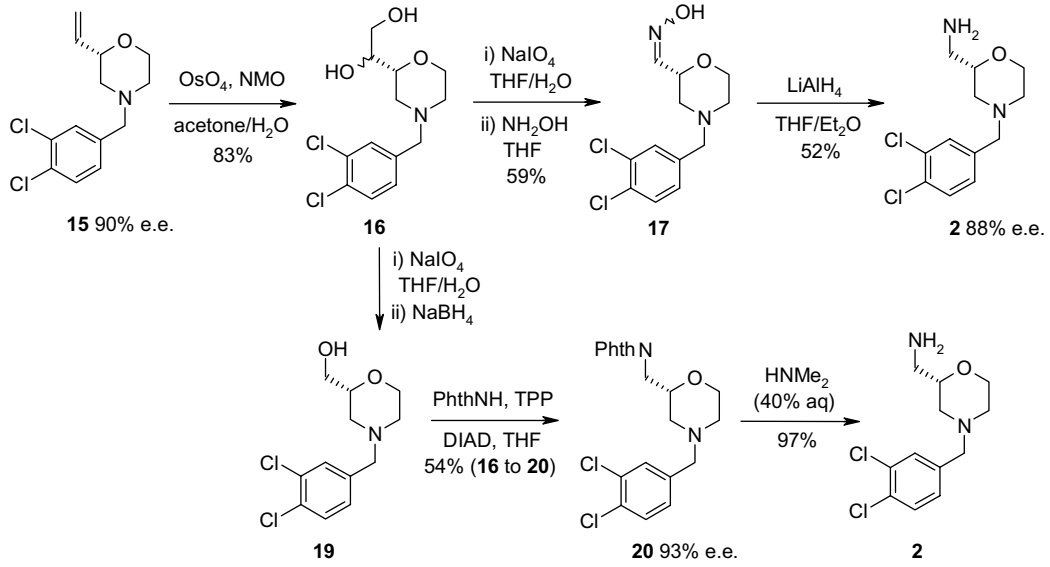
3 **15**

Scheme 5.



8 **9** **10** **11** **12**

Scheme 4.



Scheme 6.

decomposition on this substrate). The oxime **17** was then produced from an intermediate formyl morpholine, and finally reduced to give the desired aminomethyl morpholine **2** with retention of stereochemistry (Scheme 6).

Alternatively, the unisolated formyl morpholine could be reduced to the hydroxymethylmorpholine **19**. Subsequent Mitsunobu reaction using phthalimide as the nucleophile gave phthalimido morpholine **20**, which was an intermediate in our existing route. An apparent slight increase in ee was recorded, perhaps in the crystallisation of highly crystalline **20**. Subsequent deprotection using methylamine was effected to give **2** in excellent yield, and we have demonstrated complete retention of chirality through this deprotection many times on up to 40 kg scale.

In summary, we have demonstrated a catalytic asymmetric route to the key aminomethyl morpholine core of CCR3 antagonist **1** giving up to 35% yield from dichlorobenzyl ethanolamine.

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