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Synthesis of xanthene-derived diimine and iminophosphine compounds as potential chiral bidentate ligands

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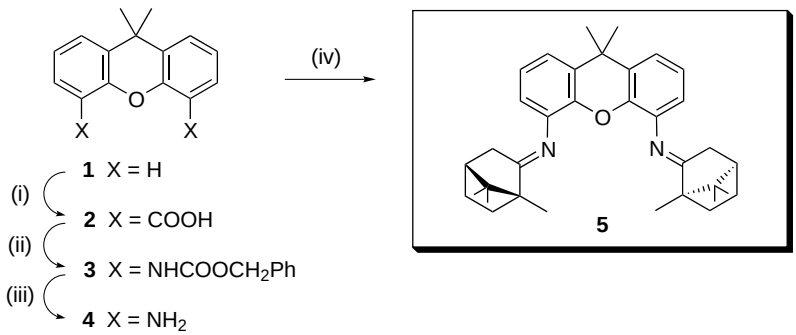
Abstract—The synthesis of one diimine and two iminophosphine chiral ligands bearing a xanthene backbone in, respectively, four and five steps is described. The diimine is characterised by X-ray crystallography. A preliminary test in palladium-catalysed asymmetric allylic alkylation is reported.

The search for new ligands in asymmetric catalysis,[1] and particularly in palladium-catalysed asymmetric allylic alkylation,[2] has been a topic of intensive research for past decades. C_2-symmetric diphosphines have met great success, but high ee levels have also been reached with mixed-P,N-donor bidentate ligands, especially phosphinooxazolines.[3]

Recently, wide bite angle duxantphospholanes have proved to be very efficient and versatile P,P ligands for asymmetric allylic alkylation.[4] Besides, bidentate achiral ligands with xanthene backbones bearing donor atoms other than phosphorus have been reported.[5] Therefore, we have planned to extend the family of chiral xanthene-based ligands to P,N and N,N ligands. In analogy with reported iminophosphines[6] or diimines,[7] we have employed (1*R*)-camphor and (1*S*)-fenchone as chiral sources, and we describe hereafter the synthesis of three new chiral iminophosphine or diimine ligands with a rigid xanthene scaffold.

The diimine **5** was prepared in four steps by double functionalisation of the commercial 9,9-dimethylxanthene **1** (Scheme 1). The carboxylation of **1** was achieved following a reported procedure;[8] we noticed that the yield was unchanged (49%) although the reaction was run at lower temperature without TMEDA. Umezawa et al. have reported the conversion of a *tert*-butyl-substituted analogue of **2** to a diamine.[9] Following their procedure, we obtained the dicarbamate **3**



Scheme 1. (i) (a) *n*BuLi (2.5 equiv.), THF, −78°C→rt; (b) CO_2, −78°C→rt; (ii) diphenylphosphorylazide (2.2 equiv.), $PhCH_2OH$ (2.2 equiv.), NEt_3 (2.2 equiv.), $PhCH_3$, 100°C; (iii) KOH, EtOH, 100°C; (iv) (1*R*)-camphor (3 equiv.), $TiCl_4$ (5 equiv.), NEt_3 (20 equiv.), $PhCH_3$, reflux.

Keywords: chiral ligands; xanthene backbone; imines; phosphines.

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from **2** via a Curtius rearrangement with an increased yield (64 instead of 22%). Basic hydrolysis of **3** led to the diamine **4** (53% yield).

Titanium tetrachloride is a convenient reagent to condense sterically encumbered ketones like camphor or fenchone with aromatic amines,[6] but often a large excess of diamine is required.[10] To convert **4** to the expected diimine **5**, we adapted the procedure by using a default of amine and adding triethylamine to the reaction mixture. Refluxing a solution of **4** for 18 h in toluene with an excess of (1*R*)-camphor, $TiCl_4$ and NEt_3, led to **5** with a 43% yield.

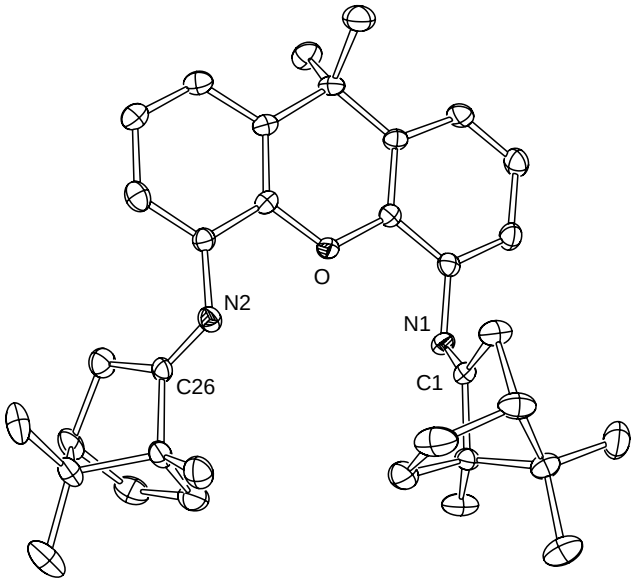
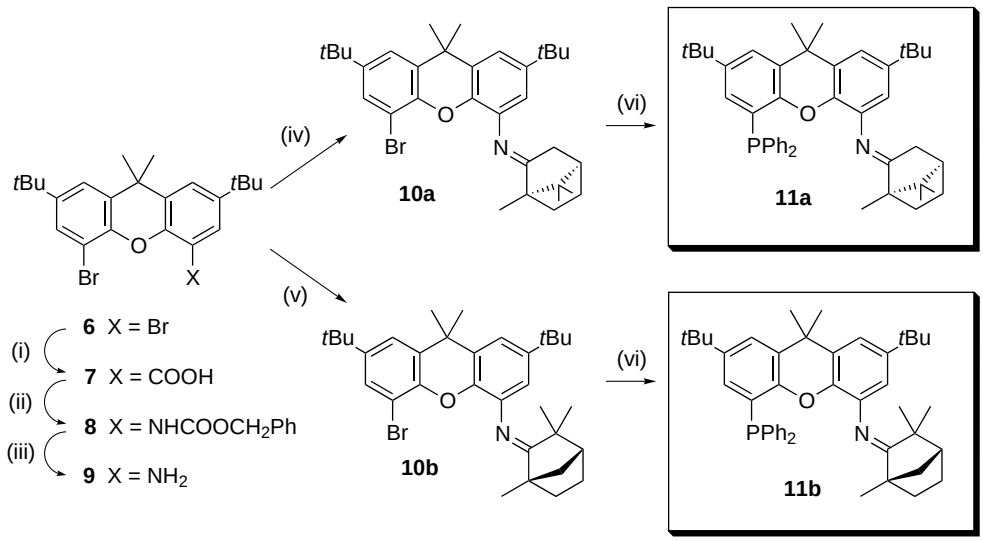


Figure 1. ORTEP drawing of compound **5**, showing 30% probability thermal ellipsoids.

Crystals of compound **5** suitable for X-ray crystallographic analysis have been obtained by slow diffusion of water in an ethanol solution.‡ The solid-state structure is represented Fig. 1. Both imines display a *E* configuration in which steric interactions between the xanthene backbone and camphor are minimised. The C1–N1 and C26–N2 bond distances (respectively 1.258(4) and 1.268(4) Å) are in the normal range for carbon–nitrogen double bonds.

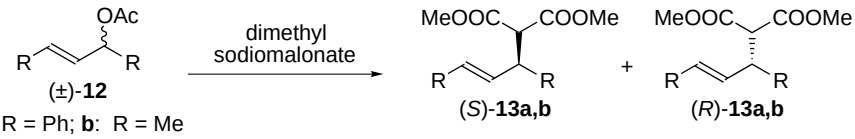
We tried to prepare an iminophosphine ligand starting from **1**. For that purpose, we monofunctionalised **1** with an imine through a pathway similar to the synthesis of **5**. We then planned to graft a PPh_2 function by deprotonating with *n*BuLi at room temperature and treating with PPh_2Cl; unfortunately, this led to complete decomposition. An alternative pathway starting from the commercially available 4,5-dibromo-2,7-di-*tert*-butyl-9,9-dimethylxanthene **6** was preferred, because bromide–lithium exchange takes place in softer conditions than deprotonation of xanthene by *n*BuLi (−78°C instead of rt), which might prevent degradation.

Thus **11a** and **11b** were synthesised in five steps with good overall yields (respectively, 48 and 35%), as shown in Scheme 2. Compound **6** was converted to the monolithiated derivative by reaction with 1 equiv. *n*BuLi at −78°C, and then to the bromoacid **7** by bubbling CO_2 (85% yield). Conversion of the related dibromobenzofuran to a monoacid with PhLi has been reported,[11] but in our case using that reagent instead of *n*BuLi led to a



Scheme 2. (i) (a) *n*BuLi (1 equiv.), THF, −78°C; (b) CO_2, −78°C→rt; (ii) diphenylphosphorylazide (1.1 equiv.), $PhCH_2OH$ (1.1 equiv.), NEt_3 (1.1 equiv.), $PhCH_3$, 100°C; (iii) KOH, EtOH, 100°C; (iv) (1*R*)-camphor (1.5 equiv.), $TiCl_4$ (2.5 equiv.), NEt_3 (10 equiv.), $PhCH_3$, reflux; (v) (1*S*)-fenchone (1.5 equiv.), $TiCl_4$ (7.5 equiv.), NEt_3 (30 equiv.), $PhCH_3$, reflux; (vi) (a) *n*BuLi (1.3 equiv.), THF, −78°C; (b) PPh_2Cl (1.3 equiv.), −78°C→rt.

‡ Crystallographic data (excluding structure factors) for **5** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-160449. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].



Scheme 3.

lower yield (43%). The Curtius rearrangement and following hydrolysis were conducted with respective yields of 82 and 92%. Addition of the resulting amine **9** to (1*R*)-camphor in conditions similar to those of the synthesis of **5** led to the imine **10a** with excellent yield (93%). The yield dropped to 15% when (1*R*)-camphor was replaced with (1*S*)-fenchone (preparation of **10b**); it could however be increased to 70% by periodic addition of $TiCl_4$ and NEt_3 over 4 days. Use of $SnBu_2Cl_2$ as a Lewis acid catalyst[12] for the condensation of fenchone with **9** did not lead to any product. Finally, the bromide of **10a,b** was exchanged with lithium by reaction with *n*BuLi at −78°C, and the resulting organolithium species made to react with PPh_2Cl to give the iminophosphines **11a,b** with good yields (respectively, 80 and 78%). It was observed by 1D and 2D (NOESY) ^1H NMR spectroscopy that the configuration of **11a** is *E* as in **5**, whereas for **11b** the *Z* (represented Scheme 2) and *E* isomers are in equilibrium (*Z*/*E* ratio = 91:9 at 298 K).

As a preliminary catalytic study, we have applied the P,N ligands to palladium-catalysed enantioselective allylic alkylation of racemic *O*-acetyl-1.3-diphenylprop-1-en-2-ol **12a** and *O*-acetylpent-2-en-3-ol **12b** (Scheme 3). Making **12a** react with 2 equiv. nucleophile in THF in the presence of 0.005 equiv. $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ and 0.012 equiv. ligand **11b** afforded (*R*)-**13a** in 80% yield with 17% ee, whereas with ligand **11a** the alkylation product was obtained quantitatively, but was racemic. Surprisingly, using substrate **12b**, which is usually more difficult to alkylate enantioselectively,[2] led to better ee's with ligands **11a** and **11b** (respectively 20 and 36%, in 82 and 62% yields). According to preliminary NMR studies, those results can be explained by the formation of mixtures of Pd complexes upon coordination by the ligands. Better ee's are expected with silver-catalysed reactions, as silver(I) complexes were cleanly synthesised with our ligands. Work in this direction is still in progress and will be reported in due course.

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