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The first series of chiral 2,2′:6′,2″-terpyridine tri-*N*-oxide ligands for Lewis base-catalyzed asymmetric allylation of aldehydes

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Received 27th May 2004, Accepted 27th May 2004
First published as an Advance Article on the web 9th June 2004

The first series of chiral 2,2′:6′,2″-terpyridine tri-*N*-oxide ligands have been developed; They were showed to be active Lewis base-catalysts for asymmetric allylation of aldehydes using allyltrichlorosilane with optimal results at 0 °C for electron-deficient aromatic aldehydes (yields up to 97% and enantioselectivities up to 86% ee).

Asymmetric catalysis has been an attractive synthetic approach among chemists since it can in principle provide the most convenient, economical and general route to optically pure compounds.[1] In the pass few decades, various catalytic systems based on oxophilic metals in combination with oxygen-containing ligands have been studied intensively and some of them have been showed to be highly efficient catalysts for asymmetric synthetic transformations.[2] Among the salient examples, Noyori's group developed 2,2′-binaphthol for asymmetric reduction of ketones.[3] Sharpless and Katsuki demonstrated the utilities of diethyl tartrate in asymmetric epoxidation of allylic alcohols.[4] Besides alcohols and phenols, aromatic amine *N*-oxides have recently become a popular choice of oxygen donors for developing new chiral oxygen-containing ligands. Some of these ligands have exhibited good reactivity and selectivity in asymmetric catalysis, which include Nakajima's planar-chiral biquinoline *N*,*N*-dioxides for allylation of aldehydes[5] and conjugate additions of thiols[6] and enolates,[7] Fu's planar-chiral pyridine *N*-oxides for desymmetrization of *meso*-epoxides,[8] Hayashi's axially chiral bipyridine *N*,*N*′-dioxide for allylation of aldehydes,[9] Denmark's chiral bipyridine *N*,*N*-dioxides for aldol additions,[10] and Kočovský's bipyridine mono-*N*-oxides[11] and planar-chiral quinoline-type *N*-oxide[12] for allylation of aldehydes. In spite of the usefulness of this new generation of oxygen-containing monodentate and bidentate ligands, reports on neutral polydentate pyridine *N*-oxide ligands for asymmetric catalysis are rare. The development of such a system should be a significant addition to the field of asymmetric catalysis.

Polydentate ligands containing the pyridine *N*-oxide moiety have been of interest due to their interesting coordination properties.[13,14] Recently, Amoroso and co-workers reported the coordination studies of 2,2′:6′,2″-terpyridine tri-*N*-oxide ($tpyO_3$) (Fig. 1) with nickel(II) perchlorate. The X-ray crystallographic data of $[Ni(tpyO_3)_2][ClO_4]_2$ revealed the distorted pseudooctahedral geometry of the complex, in which two $tpyO_3$ ligands were coordinated with the metal center in the facial coordination mode *via* seven-membered chelate rings.[14]

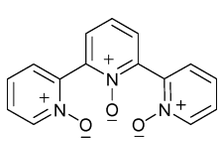
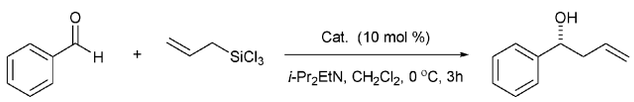


Fig. 1 2,2′:6′,2″-Terpyridine tri-*N*-oxide ($TpyO_3$).

Table 1 Allylation of benzaldehyde using allyltrichlorosilane with **2a**–**e** as the catalyst[a]



Entry	Ligand	Yield (%)[b]	% ee[c]	Configuration[d]
1	**2a**	89	74	*R*
2	**2b**	97	64	*R*
3	**2c**	87	67	*R*
4	**2d**	85	44	*R*
5	**2e**	85	34	*R*

[a] The general procedure was followed. [b] Isolated yield. [c] Determined by chiral HPLC analysis using a Daicel Chiral-Cel OD column according to reported procedures.[5,11] [d] Absolute configurations were assigned by comparing the retention time with the known compounds.[5,11]

This unique conformation and highly coordinated metal center should lead to the activity and selectivity that are of interest. Herein, we report the synthesis of the first series of chiral neutral *O*,*O*,*O*-tridentate ligands (**2a**–**e**) based on the framework of $tpyO_3$. Their utility in asymmetric catalysis have been demonstrated in asymmetric allylation of aldehydes.

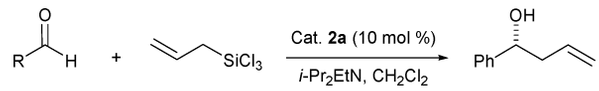
Terpyridine (tpy) tri-*N*-oxides **2a**–**e** can be readily obtained from *m*-CPBA oxidation of the parent tpy ligands **1a**–**e**[15] (Scheme 1).† The structures of **2a**–**e** were assigned unambiguously by ^1H and ^{13}C NMR, ESI-MS, IR and elemental analysis. With this new class of tri-*N*-oxide ligands prepared, we first examine their catalytic activity and enantioselectivity in the Lewis base-catalyzed asymmetric allylation of aldehydes using allyltrichlorosilane.‡

Allylations of benzaldehyde using allyltrichlorosilane with 10 mol% of **2a**–**e** as the catalyst went to completion in 3 hours at 0 °C in dichloromethane. As shown in Table 1, all the new tri-*N*-oxide ligands afforded good to excellent isolated yields of the allylation product (85–97%) and moderate to good enantioselectivities (34–74% ee). Ligand **2a** gave the best enantioselectivity (74% ee) and ligand **2b** gave the best yield (97%) of the homoallylic alcohol. Ligands **2d** and **2e** gave only moderate enantioselectivities (44% ee for **2d** and 34% ee for **2e**). These results may be due to the fact that the chiral groups of these ligands are too bulky for good coordination between the ligands and allyltrichlorosilane.

To study the temperature effects, ligand **2a** was employed for the allylation conditions at different reaction temperatures (Table 2). Surprisingly, the ee values of the allylation product decreased as the temperature decreased from 0 °C to −10 or −40 °C. The optimal temperature for allylation was found to be 0 °C, which provided 89% of the isolated homoallylic alcohols in 74% ee. This trend is quite different from other allylation systems. In fact, all the reported allylation systems were carried

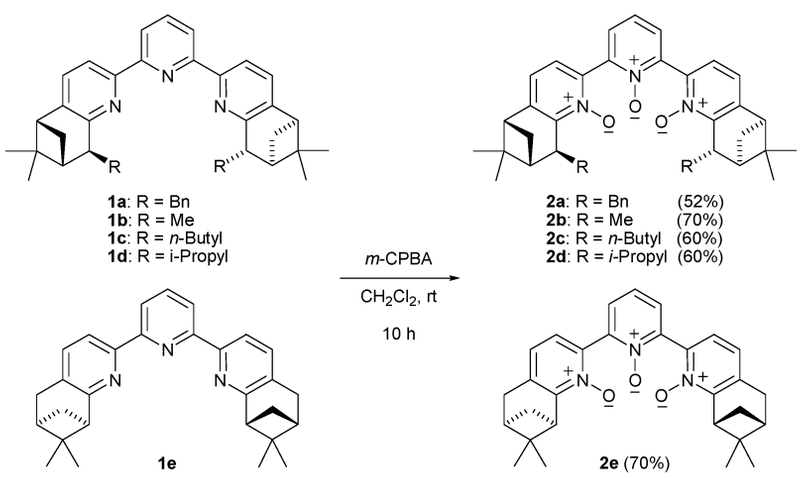
DOI: 10.1039/b407933g

Table 2 Allylation of aldehydes using allyltrichlorosilane with **2a** as the catalyst[a]



Entry	R	Temp./°C	Time/h	Yield[b] (%)	% ee[c]	Configuration[e]
1	Ph	25	2	85	66	*R*
2	Ph	0	3	89	74	*R*
3	Ph	−10	7	68	70	*R*
4	Ph	−40	7	56	70	*R*
5	4-$MeOC_6H_4$	0	3	94	65	*R*
6	4-$NO_2C_6H_4$	0	3	91	86	*R*
7	1-Naphthyl	0	3	95	74	*R*
8	2-Naphthyl	0	3	86	78	*R*
9	5-Methylfurfuryl	0	3	82	44	*R*[f]
10	Octyl	0	3	80	20[d]	*S*[f]

[a] The general procedure was followed. [b] Isolated yields. [c] Determined by chiral HPLC analysis using a Daicel Chiral-Cel OD column according to reported procedures.[5,11,16,17] [d] Determined by chiral GC using a column Chrompack WCOT Fused Silica, CP-Chirasil-Dex CB according to reported procedures.[18] [e] Absolute configurations were assigned by comparing the retention time with the known compounds.[5,11] [f] Assigned by analogy.



Scheme 1 Synthesis of chiral tpy tri-*N*-oxides **2a**–**e**.

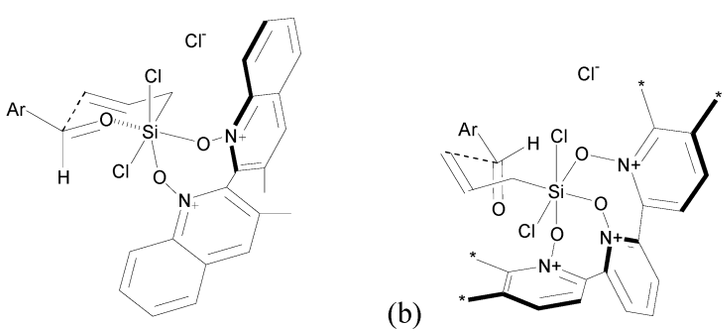


Fig. 2 Proposed transition states for allylation with (a) Nakajima's planar-chiral biquinoline *N*,*N*-dioxides,[5] and (b) our chiral tpy tri-*N*-oxides (* = chiral groups).

out at low reaction temperature (below −40 °C) for good enantioselectivity.

The utility of **2a** was further studied using different substrates including aromatic and aliphatic aldehydes, and the results are summarized in Table 2. An electron-donating group at the *para*-position of benzaldehyde exhibited a negative impact on the enantioselectivity (entry 5), while the substrate bearing an electron-withdrawing group at the *para*-position remarkably improved the enantioselectivity to 86% ee with 91% isolated yield (entry 6). This interesting trend was only observed in Kočovský's quinoline-type *N*-oxide system, which gave 73% yield with 89% ee for 4-nitrobenzaldehydehyde at −40 °C.[12] In addition, the two naphthaldehydes with different steric environment gave very similar results (entries 7 and 8), which indicated that the steric influence of the aromatic aldehydes was not significant in this system. Replacing the benzene ring with a furan ring led to significant decrease in enantioselectivity (entry 9) and straight chain aliphatic aldehyde gave only 20% ee (entry 10).

Previous studies by other groups suggested that the transition state of the allylation reaction involve a cyclic 6-membered chair-liked structure (Fig. 2a), which could be generated *via* the coordination between the *N*-oxide ligands and allyltrichlorosilane.[5,11] This coordination mode may not be favorable for the highly sterically demanding tri-*N*-oxide ligands. Based on the facts that achiral $tpyO_3$ can act as a tridentate ligand[14] and similar enantioselectivity results were obtained with 1- and 2-naphthaldehydes, which have very different steric environments, an acyclic transition state with the tri-*N*-oxide acting as tridentate ligand was proposed

(Fig. 2b). Work is in progress to investigate the mechanism of the reaction and the utility of this new series of chiral tpy tri-*N*-oxide ligands in different catalytic systems.

In summary, we have prepared the first series of *O*,*O*,*O*-tridentate ligands (**2a**–**e**) based on the frame work of $tpyO_3$. These novel ligands have been showed to be active Lewis base catalysts for asymmetric allylation of aldehydes using allyltrichlorosilane with yields up to 97% and enantioselectivities up to 86%. The optimal results were obtained with electron-deficient aromatic aldehydes at 0 °C.

Acknowledgements

Financial support for this research project from the Hong Kong Research Grants Council CERG grant (CityU 1095/01P), the Area of Excellence Scheme established under the University Grants Committee of the Hong Kong SAR, China (Project No. AoE/P-10/01), and the City University of Hong Kong are gratefully acknowledged.

Notes and references

† Preparation of **2a**–**e**: To a stirred solution of tpy ligands **1** (0.40 mmol) in dry CH_2Cl_2 (1 mL) was added a solution of *m*-CPBA (2.6 mmol) in CH_2Cl_2 (3 mL) slowly. The mixture was stirred at room temperature for 10 h and then quenched with aqueous $NaHCO_3$ (10 mL) followed by CH_2Cl_2 (15 mL). The organic layer was separated and washed with water until the aqueous washing was neutral. Then the organic layer was dried over $MgSO_4$, filtered and concentrated. Recrystallization of the residue from diethyl ether afforded **2** (52–70%).
‡ A general procedure for allylation of aldehydes with allyltrichlorosilane using **2** as the catalyst: To a stirred solution of **2** (0.10 mmol), freshly distilled aldehyde (1.0 mmol) and dry diisopropylethylamine (1.4 mL) in dry CH_2Cl_2 (1 mL) was added allyltrichlorosilane (1.2 mmol) at the desired temperature. The resulting mixture was stirred at this temperature until the aldehyde was consumed. The reaction was then quenched with aqueous $NaHCO_3$ (1 mL) followed by H_2O (10 mL). The aqueous layer was extracted with diethyl ether (1 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography.

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