

Kinetic resolution of chiral aminoalkenes *via* asymmetric hydroamination/cyclisation using binaphtholate yttrium complexes†

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Received (in Cambridge, UK) 11th December 2003, Accepted 26th January 2004

First published as an Advance Article on the web 20th February 2004

Chiral binaphtholate yttrium aryl complexes are highly active and enantioselective catalysts for the asymmetric hydroamination of aminoalkenes, as well as the kinetic resolution of  $\alpha$ -substituted 1-aminopent-4-enes to give *trans*-2,5-disubstituted pyrrolidines with good enantiomeric excess and high  $k_{rel}$ .

The hydroamination reaction in general<sup>1</sup> and its asymmetric variant in particular<sup>2</sup> constitute an important goal in current research due to their relevance to the synthesis of nitrogen-containing fine chemicals and pharmaceuticals. Rare earth metal catalysts have proven to be competent catalysts in various hydroamination reactions. However, chiral catalysts based on planar chiral cyclopentadienyl ligands were hampered by facile catalyst epimerisation.<sup>3</sup> Only recently have new chiral rare earth metal catalysts based on non-cyclopentadienyl ligands evolved.<sup>4</sup> However, enantioselectivities have not been improved markedly compared to lanthanocene catalysts and catalyst activity was unsatisfactory. In a previous study<sup>4b</sup> we observed the first example of a kinetic resolution of 2-aminohex-5-ene, albeit with a rather low  $k_{rel}$  value of only 2.6. Herein we communicate the synthesis of new binaphtholate yttrium aryl complexes which show significantly improved catalytic activity for aminoalkene hydroamination/cyclisation with unprecedented enantioselectivities, which are also capable of promoting efficient kinetic resolution of  $\alpha$ -substituted 1-aminopent-4-enes.<sup>5</sup>

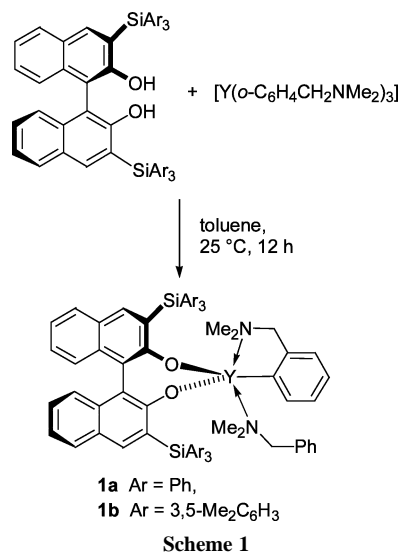
Our previous study had shown that steric bulk in the 3- and 3'-positions of the biphenolate or binaphtholate is an indispensable requirement for a monomeric catalyst structure and effective asymmetric induction. We anticipated that a further increase in steric bulk of these substituents would increase the enantioselectivity. We decided that 3,3'-bis(tris(aryl)silyl)-substituted binaphtholate ligands<sup>6</sup> would be suitable candidates to provide sufficient steric bulk. Although analogous binaphtholate lanthanum alkyl complexes have been reported,<sup>7</sup> their catalytic activity remains unexplored. Suitable yttrium complexes were prepared by arene elimination starting from  $[Y(o-C_6H_4CH_2NMe_2)_3]$ <sup>8</sup> (Scheme 1). Complexes **1a** and **1b** retain one equivalent of *N,N*-dimethylbenzylamine.

Initial experiments with a few hydroamination/cyclisation benchmark substrates (Table 1) showed that the two binaphtholate yttrium complexes display good catalytic activity at room temperature of comparable magnitude to that of lanthanocene catalysts.<sup>3,9</sup> The rate is only slightly depressed in the presence of THF (3.2 h<sup>-1</sup> for substrate **2** using **1a** plus 3 equivalents of THF, compared with 8 h<sup>-1</sup> in the absence of THF). Although enantioselectivities for 2,2-dimethyl-pent-4-enylamine (**2**) are rather moderate, higher enantioselectivities were observed for 1-aminopent-4-ene (**4**). Additionally, enantioselectivities using catalyst **1b** are up to 14% higher than those observed with sterically less hindered **1a**. Complex **1b** delivers 2-methylpyrrolidine (**5**) in unprecedented 83% ee, the highest enantioselectivity observed with a chiral rare earth metal catalyst to date.<sup>2-4</sup> The remote methyl groups on the aromatic substituents of silicon clearly increase the efficiency of the

binaphtholate ligand to transmit its chirality onto the substrate during the cyclisation step. Cyclisation of 2-allyl-2-methyl-pent-4-enylamine (**6**) proceeded with almost identical enantiomeric excess for both catalysts, although **1a** gave a slightly better diastereomeric ratio.

We then began to investigate the kinetic resolution of  $\alpha$ -substituted 1-aminopent-4-enes (Scheme 2, Table 2). Both catalysts show moderate (Table 2, entries 1 and 2) to high (Table 2, entries 3 and 4) *trans* selectivity depending on the steric bulk of the substituent  $\alpha$  to the amino group. Cyclisation of 2-aminohex-5-ene (**8**) is known to yield predominantly *trans*-2,5-dimethylpyrrolidine (**9**),<sup>9,10</sup> which can be explained with minimal 1,3-diaxial interactions in the cyclisation transition state.<sup>11</sup>

The sterically more hindered catalyst **1b** gave a good  $k_{rel}$  for sterically less hindered substrate **8**, but inferior selectivity for more bulky substrates **10** and **12**, for which catalyst **1a** gave better values.

Table 1 Catalytic hydroamination/cyclisation reactions<sup>a</sup>

Entry	Substrate	Cat.	t/h	Conv. (%)	TOF/h <sup>-1</sup>	ee (%)
1	<b>2</b>	<b>1a</b>	3	≥98	8	43
2	<b>2</b>	<b>1b</b>	2	≥98	14	53
3	<b>4</b>	<b>1a</b>	24	≥98	1.2	69
4	<b>4</b>	<b>1b</b>	20	≥98	2.2	83
5	<b>6</b>	<b>1a<sup>b</sup></b>	1	≥98	75	63, 53 <sup>c</sup>
6	<b>6</b>	<b>1b<sup>b</sup></b>	1.2	≥98	70	65, 65 <sup>d</sup>

<sup>a</sup> Reaction conditions: 4 mol% cat., C<sub>6</sub>D<sub>6</sub>, Ar atm, 22 °C. <sup>b</sup> 2 mol% cat. <sup>c</sup> dr = 1.8:1. <sup>d</sup> dr = 1.4:1.

† Electronic supplementary information (ESI) available: experimental procedures and characterisation data for all new complexes and substrates. See <http://www.rsc.org/suppdata/cc/b3/b316096c/>

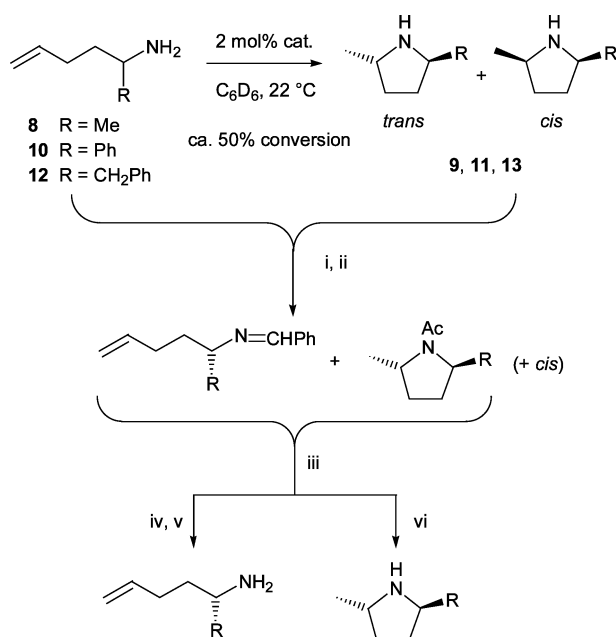
**Table 2** Catalytic kinetic resolution of chiral aminopentenes<sup>a</sup>

Entry	Substrate	Cat.	<i>t</i> /h	Conv. (%)	<i>trans</i> : <i>cis</i>	% ee of recovered reactant	% ee of product <sup>b</sup>	<i>k</i> <sub>rel</sub> <sup>c</sup>
1	<b>8</b>	<b>1a</b>	25.5	53	11:1	72	68	9.5
2	<b>8</b>	<b>1b</b>	26	52	13:1	80	78 (–) <sup>d</sup>	16
3	<b>10</b>	<b>1a</b>	95	50	≥50:1	74	— <sup>e</sup> (+)	15
4	<b>10</b>	<b>1b</b>	18 <sup>f</sup>	52	≥50:1	63	— <sup>e</sup>	7
5	<b>12</b>	<b>1a</b>	9	50	20:1	42	40 (–)	3.6
6	<b>12</b>	<b>1b</b>	27	52	20:1	38	34	2.9

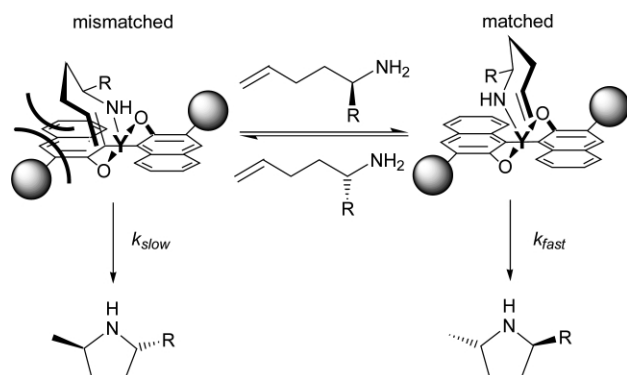
<sup>a</sup> Reaction conditions: 2 mol% cat., C<sub>6</sub>D<sub>6</sub>, Ar atm, 22 °C. <sup>b</sup> Sign of optical rotation given in parentheses. <sup>c</sup> Based on starting material. <sup>d</sup> (2*S*,5*S*) absolute configuration. <sup>e</sup> Not determined. <sup>f</sup> At 40 °C.

A simple protocol allowed the convenient separation of the aminoalkene starting material and pyrrolidine product by aqueous extraction of the secondary amine acetate from the primary amine benzimine (Scheme 2).

A working model for the observed stereodifferentiation explaining the preferred formation of (2*S*,5*S*)-**9** is depicted in Fig. 1. Efficient kinetic resolution is only possible if the initial exchange of matching and mismatching substrates is significantly faster than



**Scheme 2** Reagents and conditions: i, 0.55 equiv. AcOH; ii, 0.6 equiv. PhCHO, 25 °C, 2 h; iii, extraction with benzene/hexanes/water (1:1:2); iv, organic layer: 2 N HCl, Et<sub>2</sub>O, 25 °C, 24 h; v, aq. NaOH; vi, aqueous layer: aq. NaOH.



**Fig. 1** Proposed stereochemical model for the kinetic resolution of  $\alpha$ -substituted 1-aminopent-4-enes.

cyclisation. Slower cyclisation of (*R*)-**8** results from sterically unfavourable interactions of the vinylic methylene protons with one triphenylsilyl substituent in the seven-membered transition state.

In conclusion, the synthesis of chiral *trans*-2,5-disubstituted pyrrolidines *via* kinetic resolution of  $\alpha$ -substituted 1-aminopent-4-enes represents a new promising application of asymmetric hydroamination in organic synthesis. We are confident that this general route can be applied to other chiral aminoalkenes allowing the facile synthesis of enantiopure nitrogen-containing heterocycles. Modification of the substitution pattern of the binaphtholate ligands as well as the ionic radius of the rare earth metal can be expected to result in even more active and enantioselective hydroamination catalysts.

Generous financial support by the Deutsche Forschungsgemeinschaft (DFG) and the Fonds der Chemischen Industrie is gratefully acknowledged. K. C. H. is a DFG Emmy Noether fellow and thanks Professor John A. Gladysz for generous support.

## Notes and references

$\ddagger k_{\text{rel}}$  denotes the relative ratio between the faster and slower reacting enantiomer of the substrate. See: H. B. Kagan and J. C. Fiaud, *Top. Stereochem.*, 1988, **18**, 249.

- T. E. Müller and M. Beller, *Chem. Rev.*, 1998, **98**, 675; M. Beller, C. Breindl, M. Eichberger, C. G. Hartung, J. Seayad, O. R. Thiel, A. Tillack and H. Trauthwein, *Synlett.*, 2002, 1579; F. Pohlki and S. Doye, *Chem. Soc. Rev.*, 2003, **32**, 104.
- P. W. Roesky and T. E. Müller, *Angew. Chem., Int. Ed.*, 2003, **42**, 2708; P. W. Roesky and T. E. Müller, *Angew. Chem.*, 2003, **115**, 2812.
- M. A. Giardello, V. P. Conticello, L. Brard, M. Gagné and T. J. Marks, *J. Am. Chem. Soc.*, 1994, **116**, 10 241; M. R. Douglass, M. Ogasawara, S. Hong, M. V. Metz and T. J. Marks, *Organometallics*, 2002, **21**, 283; S. Hong and T. J. Marks, *J. Am. Chem. Soc.*, 2002, **124**, 7886.
- (a) P. N. O'Shaughnessy, P. D. Knight, C. Morton, K. M. Gillespie and P. Scott, *Chem. Commun.*, 2003, 1770; (b) D. V. Gribkov, K. C. Hultsch and F. Hampel, *Chem. Eur. J.*, 2003, **9**, 4796; (c) P. N. O'Shaughnessy and P. Scott, *Tetrahedron: Asymmetry*, 2003, **14**, 1979; (d) S. Hong, S. Tian, M. V. Metz and T. J. Marks, *J. Am. Chem. Soc.*, 2003, **125**, 14 768.
- This method for the preparation of *trans*-2,5-disubstituted pyrrolidines complements the synthesis of *cis*-2,5-disubstituted pyrrolidines *via* enantioselective hydrogenation of pyrrolines, see: A. Viso, N. E. Lee and S. L. Buchwald, *J. Am. Chem. Soc.*, 1994, **116**, 9373.
- K. Maruoka, T. Itoh, Y. Araki, T. Shirasaka and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 2975; L.-Z. Gong and L. Pu, *Tetrahedron Lett.*, 2000, **41**, 2327.
- C. J. Schaverien, N. Meijboom and A. G. Orpen, *J. Chem. Soc., Chem. Commun.*, 1992, 124.
- M. Booi, N. H. Kiers, H. J. Heeres and J. H. Teuben, *J. Organomet. Chem.*, 1989, **364**, 79.
- M. R. Gagné, C. L. Stern and T. J. Marks, *J. Am. Chem. Soc.*, 1992, **114**, 275.
- Y. K. Kim and T. Livinghouse, *Angew. Chem., Int. Ed.*, 2002, **41**, 3645; Y. K. Kim and T. Livinghouse, *Angew. Chem.*, 2002, **114**, 3797; Y. K. Kim, T. Livinghouse and Y. Horino, *J. Am. Chem. Soc.*, 2003, **125**, 9560.
- J.-S. Ryu, T. J. Marks and F. E. McDonald, *Org. Lett.*, 2001, **3**, 3091.