SUPRAphos-based palladium catalysts for the kinetic resolution of racemic cyclohexenyl acetate†

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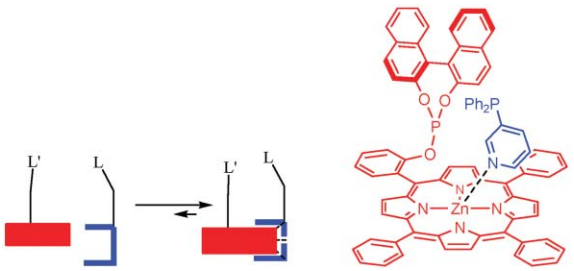
High-throughput screening of the SUPRAphos library revealed a palladium catalyst based on supramolecular ligands that gave fast and highly efficient kinetic resolution of cyclohexenyl acetate with an *S*-value up to 12.

The palladium catalyzed asymmetric allylic alkylation for the formation of C–C and C–heteroatom bonds is an intensively explored reaction that finds application in organic synthesis.[1] Numerous chiral catalysts reported in the literature provide the product in high enantioselectivities (ee's), especially when 1,3-diphenylpropenyl acetate is used as the model substrate.[1] Interestingly, for other substrates such as 1,3-dimethylpropenyl acetate and cyclic ones (5–7 membered rings), there is only a limited number of chiral catalysts available that induce high enantioselectivity.[1,2]

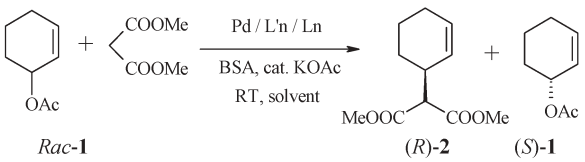
Palladium catalysts can also be used for kinetic resolution,[3] a process in which one of the enantiomers of the racemic starting material is converted to the desired product while the other enantiomer is recovered unchanged. Kinetic resolution can be very powerful because extremely high enantiopurities can be achieved, albeit at the cost of the yield in less favourable cases.[3] In most examples in which metal catalysts are used both enantiomers of the substrate show some reactivity towards the catalyst.[3–6] While the palladium catalyzed allylic substitution reaction has been widely studied, relatively few catalysts have been reported in the literature for kinetic resolution.[7–9] A plausible mechanism for the kinetic resolution of cyclohexenyl acetate using palladium bisphosphine ligands was reported in 1998.[8]

We,[10,11] and others,[12] have recently introduced a new class of bidentate ligands which form *via* self-assembly of two monodentate ligands (Scheme 1). We have used the zinc(II)porphyrin–pyridine interaction as an assembly motif to generate bidentate phosphorus-based ligands. With the use of a small number of building blocks a large library of (hetero-)bidentate phosphorus ligands[10b,d] was generated that was successfully used in hydroformylation,[10a,b,c] asymmetric hydrogenation,[10d] and asymmetric allylic alkylation.[10c,d] Here we report for the first time a combinatorial approach to search for novel catalysts for the kinetic resolution of cyclohexenyl acetate *rac*-**1** (Scheme 2), using the SUPRAphos ligand library (building blocks **L′1–L′4**, Fig. 1 and **L1–L15**, Fig. 2).

We screened the catalysts library based on SUPRAphos ligands **L′1–L′4** (Fig. 1) and **L1–L15** (Fig. 2) in the palladium catalyzed



Scheme 1 Schematic representation of a supramolecular bidentate ligand and a typical example from the SUPRAphos library that forms *via* a zinc(II) porphyrin–pyridyl interaction.



Scheme 2 Schematic representation of kinetic resolution of *rac*-**1**.

kinetic resolution of *rac*-**1** (Table 1). We simultaneously monitored the conversion, the ee of substrate **1**, and that of product **2**. Hot spots for high conversions and ee's are displayed in red in Table 1. It should be noted that for kinetic resolution we aim for 50% conversion (100% of one enantiomer).

The SUPRAphos library contains phosphine–phosphite as well as bisphosphite type ligands and in control experiments we also used **L′1–L′4** as chiral, monodentate ligands (the last column of Table 1). Inspection of Table 1 reveals that a few catalysts based on heterobidentate supramolecular ligands give rise to kinetic resolution of *rac*-**1**; four catalysts provide substrate **1** in 99% ee at a

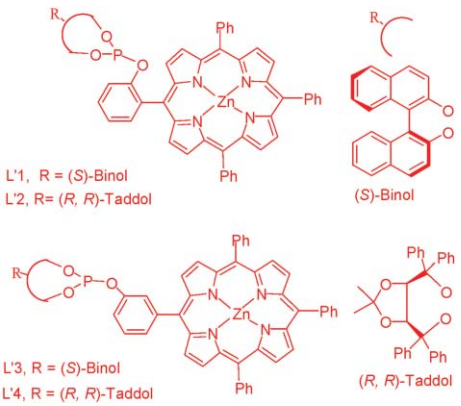


Fig. 1 Structures of porphyrin functionalized phosphites (**L′*n***).

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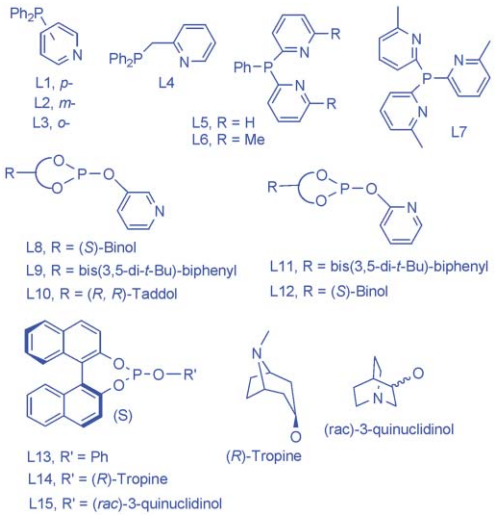
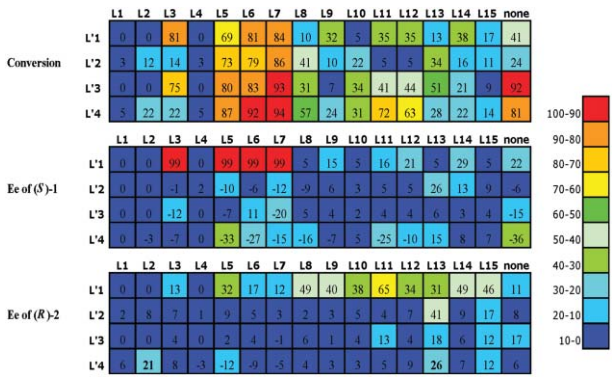


Fig. 2 Structures of N-containing phosphorus ligands (**L*n***).

conversion between 69 and 84%. As second best result we obtained 36% ee only for the substrate. The four best catalysts had in common that the ligand consisted of **L′1** and an *ortho*-pyridyl functionalized phosphine and we decided to study these in more detail.

We monitored the progress of the reaction with time at room temperature in CH_2Cl_2 using SUPRAphos ligand **L′1/L5** and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as the palladium precursor (1 mol%), *rac*-**1** as the substrate and dimethyl malonate as the nucleophile. We obtained curves that are typical of kinetic resolution; the ee of unreacted

Table 1 Kinetic resolution of *rac*-**1** using palladium catalysts based on various SUPRAphos ligands **L′*n*/L*n***[a]



[a] General conditions: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 1 mol% Pd, Pd/**L′*n*/L*n*** = 1/1.5/1.2 with respect to Pd, 20 eq. dipea (diisopropylethylamine), 1 mmol (0.25 mM) of *rac*-**1** in CH_2Cl_2, unless otherwise noted, 3 mmol dimethyl malonate, 3 mmol BSA,[13] catalytic amount of KOAc, RT, inert conditions (dried N_2). The ee of the substrate and conversion of the reaction were determined by ultra fast GC on a chiral column (Diethyl Terbutyl Silyl Beta in PS086), Interscience®, t_S **1** = 8.5 min, t_R = 9.1 min, the absolute configuration was compared with the literature.[7f,8] The ee (%) of the product was determined by chiral GC, β-Dex column, t_R = 69.9 min, t_S = 70.8 min, the absolute configuration was compared with the literature.[7f,8] $S = K_R/K_S = \ln(1 - C)(1 - E)/\ln(1 - C)(1 + E)$, C = conv%/100, E = ee%/100. In the last column the results of control experiments are displayed in which the ligands have been used as monodentates (**L′*n*** : Pd = 2.2).

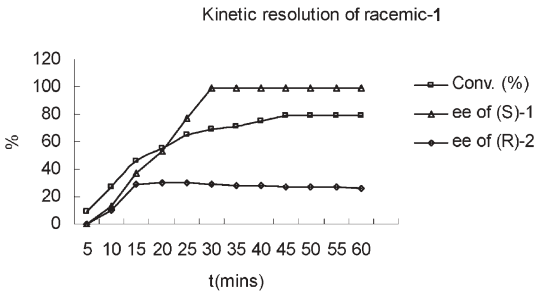


Fig. 3 Kinetic resolution of *rac*-**1** with Pd(**L′1/L5**) in CH_2Cl_2. For general conditions see footnote.

substrate increases with time (and conversion) whereas that of the product remains the same (Fig. 3). After 30 min the conversion reached 69%, and the ee of the remaining 31% substrate (*S*)-**1** reached 99%, equivalent to an *S*-value of 12. In contrast to what is usually found for kinetic resolution experiments, the ee of the product (*R*)-**2** is only moderate (31%) and, as usual, of the opposite enantiomeric form.

We have explored various reaction conditions to optimize the selectivity and activity of the system. In other solvents such as THF, EtOAc and CH_3CN the kinetic resolution was lower than that found in CH_2Cl_2 and the reaction times required in THF, EtOAc and CH_3CN are much longer (16 h). A result comparable to that in CH_2Cl_2 was found in toluene (see supporting information for details). The lower rates may be due to (1) the much lower solubility of porphyrin–phosphite **L′1** in these solvents compared to CH_2Cl_2 or (2) to solvent coordination to palladium or zinc.

Upon changing the metal/ligands ratios of Pd/**L′1/L5**, the reactivity and enantioselectivity varied substantially, but results could not be improved (see supporting information for details). A ratio of 1/1.5/1.2 gave the highest kinetic resolution. In the presence of an excess of achiral ligand **L5**, catalysis by the complexes of Pd(**L5**)$_2$ species becomes dominant and no enantioselectivity is obtained. With substoichiometric amounts of ligands, *e.g.* a ratio of 1/0.5/0.45, the reaction becomes extremely slow and non-enantioselective. Lower temperatures did not lead to better results. Elevating the temperature to 40 °C accelerated the reaction and after 10 min the conversion reaches 75% with 99% ee of (*S*)-**1** (TOF 450 mol·mol^{-1}·h^{-1}). We also investigated the influence of the palladium precursors on the kinetic resolution (see supporting information for details). $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ gave the fastest reaction and the highest resolution. The use of Pd(0) species led to formation of the active catalyst, but, due to slow exchange of dba by phosphorus ligands and substrate, the reaction is much slower. The combination of $Pd(COD)Cl_2$ and **L′1/L5** did not lead to any conversion.

We also studied the scope of nucleophiles that can be used; the size of the nucleophiles has been varied systematically by replacing the methyl groups of the malonate ester for larger ones (Me, Et, *i*-Pr, *t*-Bu, Bn). The palladium catalyst based on **L′1/L5** was reasonably tolerant to these changes as with all nucleophiles, except for the *t*-butyl ester (60% ee at 70% conversion), a high ee (99%) for the substrate was observed at conversions between 69 and 80%. An increase of the steric bulk of the nucleophiles (Me, Et, *i*-Pr, *t*-Bu, Bn) leads to a small decrease of the resolution and a lower rate of reaction was observed (see supporting information

for details). We assume that for more bulky groups the approach of the nucleophile to the substrate is more hindered, resulting in lower reaction rates.

Compared to *m*-pyridyl phosphine **L2**, that in combination with **L′1** provides a palladium catalyst that shows no kinetic resolution, the *o*-pyridyl phosphines **L3, L5–7** (providing selective catalysts with **L′1**) interact more weakly with Zn-porphyrin. Indeed, UV–Vis measurements for the complexes of Pd/**L′1**/**L3**, **L5**–**L6** and Pd/**L′1** and Pd/**L′1**/**L2** showed that pyridyl coordination of **L3**, **L5** and **L6** to the zinc porphyrin of **L′1** is not complete, leaving the pyridyl function partly in the free state. The weaker interaction, and thus the partly free pyridyl, may be responsible for the peculiar enantioselective behaviour of the catalysts described in this paper that give rise to kinetic resolution. It is important to note that the palladium catalyst based on PPh_3 and **L′1** gives rise to low ee of the substrate and the product, demonstrating that the weak interaction between the two ligands in Pd(**L′1**)(**L3**) is important for its performance.

The kinetic resolution (*S*-factor 12) is acceptable, yielding high ee's of the *S* enantiomer above conversions of 60% at high rates (TOF 450 $mol \cdot mol^{-1} \cdot h^{-1}$), but the ee of the product is low (30%) and opposite, albeit constant during the reaction. The combination of a high kinetic resolution and a low ee of the product is remarkable as usually a catalyst will lead to acceptable ee's of the product and a poor kinetic resolution. The currently accepted view is that the transition state for the oxidative addition is similar to that of the nucleophilic attack, explaining why usually high kinetic resolution is accompanied by high ee of the product. The main difference between the current system and those previously reported is the dynamic character of the ligand, enabling the catalyst to change its coordination sphere during the various reaction steps. For instance, a decoordination of the achiral pyridylphosphine ligands from the zinc is envisaged, which could either result in coordination to palladium or cause deracemization of the substrate attached to the palladium. Future research will study these processes in more detail and we will explore this type of adaptive supramolecular catalysts in other reactions to see if this principle can be generalized.

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Notes and references

1 For recent reviews, see: (*a*) A. Pfaltz and M. Lautens, in *Comprehensive Asymmetric Catalysis I–III*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer, Berlin, 1999, Vol. **II**, ch. 24, p. 833; (*b*) L. Acemoglu and J. M. J. Williams, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E.-I. Negishi, John Wiley, Hoboken, NJ, 2002, Vol. **2**, pp. 1689, 1945; (*c*) A. Heumann, in *Transition Metals for Organic Synthesis*, ed. M. Beller and C. Bolm, Wiley-VCH, Weinheim, 2nd edn, 2004, Vol. **1**, p. 307.

2 Recent breakthroughs in palladium catalyzed asymmetric allylic alkylation for cyclic substrates, see: (*a*) M. Dieguez, O. Pamies and C. Claver, *J. Org. Chem.*, 2005, **70**, 3363; (*b*) O. Pamies, M. Dieguez and C. Claver, *J. Am. Chem. Soc.*, 2005, **127**, 3646.

3 (*a*) H. Pellissier, *Tetrahedron*, 2003, **59**, 8291; (*b*) F. F. Huerta, A. B. E. Minidis and J.-E. Backvall, *Chem. Soc. Rev.*, 2001, 321; (*c*) S. Caddick and K. Jenkins, *Chem. Soc. Rev.*, 1996, 447; (*d*) E. N. Jacobsen, *Acc. Chem. Res.*, 2000, **33**, 421; (*e*) J. R. Dehli and V. Gotor, *Chem. Soc. Rev.*, 2002, **31**, 365.

4 Recent reviews on kinetic resolution with enzymes, see: (*a*) A. Archelas and R. Furstoss, *Curr. Opin. Chem. Biol.*, 2001, **5**, 112; (*b*) A. Steinreiber and K. Faber, *Curr. Opin. Chem. Biol.*, 2001, **5**, 552; (*c*) M. T. Reetz, *Angew. Chem., Int. Ed.*, 2001, **40**, 284; (*d*) H. Groger, *Adv. Synth. Catal.*, 2001, **343**, 547; (*e*) A. Ghanem and H. Y. Aboul-Enein, *Chirality*, 2005, **17**, 1; (*f*) N. J. Turner, *Curr. Opin. Chem. Biol.*, 2004, **8**, 114.

5 Recent reviews on non-enzymatic catalysts in kinetic resolution, see: (*a*) E. Vedejs and M. Jure, *Angew. Chem., Int. Ed.*, 2005, **44**, 3974; (*b*) D. E. J. E. Robinson and S. D. Bull, *Tetrahedron: Asymmetry*, 2003, **14**, 1407; (*c*) M. Keith, J. F. Larrow and E. N. Jacobsen, *Adv. Synth. Catal.*, 2001, **343**, 5; (*d*) G. R. Cook, *Curr. Org. Chem.*, 2000, **4**, 869; (*e*) A. H. Hoveyda and M. T. Didiuk, *Curr. Org. Chem.*, 1998, **2**, 489.

6 Reviews on the use of enzymes and transition metal in tandem, see: (*a*) O. Pamies and J.-E. Backvall, *Curr. Opin. Biotechnol.*, 2003, **14**, 407; (*b*) R. Sturmer, *Org. Synth. Highlights IV*, 2000, 172; (*c*) R. Azerad and D. Buisson, *Curr. Opin. Biotechnol.*, 2000, **11**, 565; (*d*) P. M. Dinh, M. T. El Gihani, J. M. J. Williams and W. Harris, *Chim. Oggi*, 1998, **16**, 42; (*e*) M. T. El Gihani and J. M. J. Williams, *Curr. Opin. Chem. Biol.*, 1999, **3**, 11; (*f*) R. Sturmer, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1173.

7 Examples of palladium mediated kinetic resolution of cyclic substrates *via* allylic alkylation, see: (*a*) H.-J. Gais, H. Eichelmann, N. Spalthoff, F. Gerhards, M. Frank and G. Raabe, *Tetrahedron: Asymmetry*, 1998, **9**, 235; (*b*) M. Frank and H.-J. Gais, *Tetrahedron: Asymmetry*, 1998, **9**, 3353; (*c*) A. Bohme and H.-J. Gais, *Tetrahedron: Asymmetry*, 1999, **10**, 2511; (*d*) H.-J. Gais, N. Spalthoff, T. Jagusch, M. Frank and G. Raabe, *Tetrahedron Lett.*, 2000, **41**, 3809; (*e*) B. Dominguez, N. S. Hodnett and G. C. Lloyd-Jones, *Angew. Chem., Int. Ed.*, 2001, **40**, 4289; (*f*) J. M. Longmire, B. Wang and X. Zhang, *Tetrahedron Lett.*, 2000, **41**, 5435; (*g*) T. Okauchi, K. Fujita, T. Ohtaguro, S. Ohshima and T. Minami, *Tetrahedron: Asymmetry*, 2000, **11**, 1397; (*h*) G. C. Lloyd-Jones and S. C. Stephen, *Chem. Commun.*, 1998, 2321; (*i*) B. M. Trost, J. Dudash, Jr. and E. J. Hembre, *Chem.–Eur. J.*, 2001, **7**, 1619; (*j*) B. M. Trost, D. E. Patterson and E. J. Hembre, *Chem.–Eur. J.*, 2001, **7**, 3768; (*k*) B. M. Trost and E. J. Hembre, *Tetrahedron Lett.*, 1999, **40**, 219; (*l*) B. M. Trost and M. G. Organ, *J. Am. Chem. Soc.*, 1994, **116**, 10320; (*m*) T. Hayashi, A. Yamamoto and Y. Ito, *J. Chem. Soc., Chem. Commun.*, 1986, 1090.

8 S. Ramdeehul, P. Dierkes, R. Aguado, P. C. J. Kamer, P. W. N. M. van Leeuwen and J. A. Osborn, *Angew. Chem., Int. Ed.*, 1998, **37**, 3118.

9 Examples of palladium mediated kinetic resolution of acyclic substrates *via* allylic alkylation, see: (*a*) B. M. Trost, R. C. Bunt, R. C. Lemoine and T. L. Calkins, *J. Am. Chem. Soc.*, 2000, **122**, 5968; (*b*) M. T. Reetz and S. Sostmann, *J. Organomet. Chem.*, 2000, **603**, 105; (*c*) G. R. Cook and S. Sankaranarayanan, *Org. Lett.*, 2001, **3**, 3531; (*d*) S. R. Gilbertson and P. Lan, *Org. Lett.*, 2001, **3**, 2237; (*e*) T. Hayashi, A. Yamamoto and Y. Ito, *J. Chem. Soc., Chem. Commun.*, 1986, 1090; (*f*) S. Jansat, M. Gomez, K. Philippot, G. Muller, E. Guiu, C. Claver, S. Castillon and B. Chaudret, *J. Am. Chem. Soc.*, 2004, **126**, 1592.

10 (*a*) V. F. Slagt, P. W. N. M. van Leeuwen and J. N. H. Reek, *Chem. Commun.*, 2003, 2474; (*b*) V. F. Slagt, P. W. N. M. van Leeuwen and J. N. H. Reek, *Angew. Chem., Int. Ed.*, 2003, **42**, 5619; (*c*) V. F. Slagt, M. Röder, P. C. J. Kamer, P. W. N. M. van Leeuwen and J. N. H. Reek, *J. Am. Chem. Soc.*, 2004, **126**, 4056; (*d*) J. N. H. Reek, M. Röder, P. E. Goudriaan, P. C. J. Kamer, P. W. N. M. van Leeuwen and V. F. Slagt, *J. Organomet. Chem.*, 2005, **690**, 4505; (*e*) X.-B. Jiang, L. Lefort, P. E. Goudriaan, A. H. M. de Vries, P. W. N. M. van Leeuwen, J. G. de Vries and J. N. H. Reek, *Angew. Chem., Int. Ed.*, 2006, **45**, 1223; (*f*) L. K. Knight, Z. Freixa, P. W. N. M. van Leeuwen and J. N. H. Reek, *Organometallics*, 2006, **24**, 954; (*g*) M. Kuil, P. E. Goudriaan, P. W. N. M. van Leeuwen and J. N. H. Reek, *Chem. Commun.*, 2006, 4679; (*h*) A. J. Sandee, A. M. van der Burg and J. N. H. Reek, *Chem. Commun.*, 2007, 864.

11 For recent reviews on this subject see: (*a*) M. J. Wilkinson, P. W. N. M. van Leeuwen and J. N. H. Reek, *Org. Biomol. Chem.*, 2005, **3**, 2371; (*b*) B. Breit, *Angew. Chem., Int. Ed.*, 2005, **44**, 6816; (*c*) A. J. Sandee and J. N. H. Reek, *Dalton Trans.*, 2006, 3385.

12 (*a*) B. Breit and W. Seiche, *J. Am. Chem. Soc.*, 2003, **125**, 6608; (*b*) B. Breit and W. Seiche, *Angew. Chem., Int. Ed.*, 2005, **44**, 1640; (*c*) B. Breit and W. Seiche, *J. Am. Chem. Soc.*, 2003, **125**, 6608; (*d*) F. Chevallier and B. Breit, *Angew. Chem., Int. Ed.*, 2006, **45**, 1599; (*e*) J. M. Takacs, D. S. Reddy, S. A. Moteki, D. Wu and H. Palencia, *J. Am. Chem. Soc.*, 2004, **126**, 4494; (*f*) P. A. Duckmanton, A. J. Blake and J. B. Love, *Inorg. Chem.*, 2005, **44**, 7708; (*g*) M. Weis, C. Waloch, W. Seiche and B. Breit, *J. Am. Chem. Soc.*, 2006, **128**, 4188.

13 BSA = *N*,*O*-bis(trimethylsilyl)acetamide.