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Transition metal catalysis in organic synthesis: reflections, chirality and new vistas*

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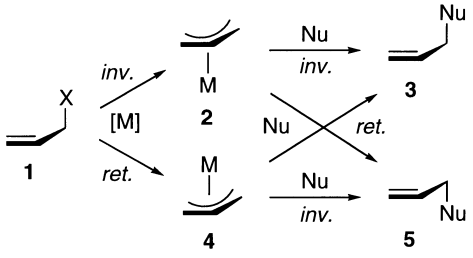
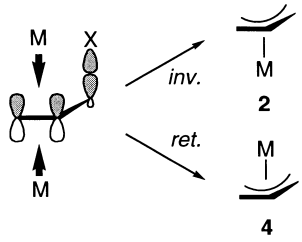
Abstract: The power of transition metal catalysis as a tool in organic synthesis is exemplified by the recent progress in the following areas: (i) diastereocontrol of Pd(0)-, Mo(0)-, and Ni(0)-catalyzed allylic substitution; (ii) Pd(0)-catalyzed asymmetric allylic substitution; (iii) Hartwig–Buchwald amination; and (iv) Suzuki coupling. Development of novel, bidentate binaphthyl ligands (MAP) and their unique mode of P,C_σ-coordination is also described.

DIASTEREOCONTROLLED ALLYLIC SUBSTITUTION CATALYZED BY Pd(0), Ni(0) AND Mo(0) COMPLEXES

In contrast to the generally capricious S_N2' reaction [1] its Pd(0)-catalyzed version [2] is stereospecific and known to occur via the intermediate η^3-complex **2** (M = Pd), arising from allylic esters **1** (X = OAc) via inversion of configuration (Scheme 1) [2]. The subsequent reaction of **2** with malonate anion and other stabilized C-nucleophiles again proceeds with inversion (**2** → **3**) [2] giving overall retention, whereas organometallics and nonstabilized nucleophiles react with retention in the second step (**2** → **5**) [2].



Scheme 1



Scheme 2

Although the Pd(0)-catalyzed reaction is dominated by inversion in the first step (**1** → **2**), retention should also be allowed by purely stereoelectronic effects (Scheme 2), although it may be disfavored by steric hindrance. The first examples of the retention pathway (**1** → **4**) were reported by us [3] and by Kurosawa [4] (Scheme 3); in both cases the reversal was enforced by precoordination of the catalyst to the leaving group (**1** → **6**) [3,4]. Recently, we have extended this methodology to cyclic allylic substrates in which the catalyst approach is directed by precoordination to a neighboring group (**7** → **8**; Scheme 4)

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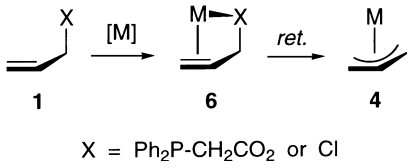
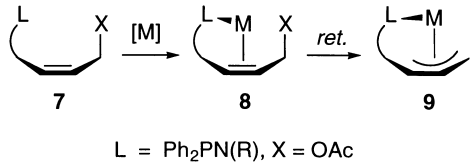


Scheme 3 M = Pd, Mo.



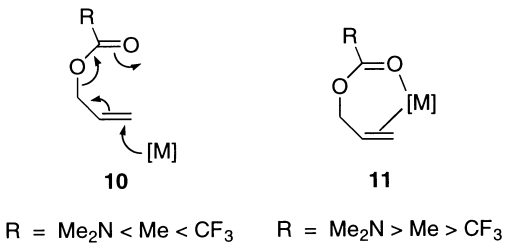
Scheme 4 M = Pd, Ni.

[5–7]. Overall, this whole sequence can be summarized as **1** → **4** → **5** (Scheme 1). Alternatively, using the same protocol (involving **9**), retention in the second step has been obtained for the Ni(0)-catalyzed reaction with a Grignard reagent (**1** → **4** → **3**) [5].

Aside from Pd(0), Group 6 complexes have also been shown to catalyze allylic substitution and to give products of overall retention of configuration (**1** → **3**) [8,9]. Interestingly, there is evidence that the mechanism for the reaction catalyzed by $Mo(CO)_6$ can differ from that for Pd [10–12]: instead of double inversion, we have recently demonstrated a double retention pathway for Mo (**1** → **4** → **3**) [11] The difference between Pd and Mo can be rationalized as follows: while formation of the η^3-Pd complex involves a primary coordination of Pd(0) to the C=C bond followed by extrusion of the leaving group (**10**; Scheme 5) as a result of back-donation [2], the reactivity of Mo(0) complexes can be understood if, instead of coordinating to the C=C bond, Mo is assumed to first associate with the Lewis-basic carbonyl oxygen of the acetate leaving group, followed by coordination to the C=C bond (**11**). [11,12] That $Mo(CO)_6$ acts as a weak Lewis acid is compatible with the effect of altering the Lewis basicity of the carbonyl oxygen by varying the R in the leaving group: thus, an electron-donating nitrogen atom (**11**, R = Me_2N) accelerates the reaction, whereas an electron-withdrawing unit (**11**, R = CF_3) retards the process [11,13]. In stoichiometric reactions, the first step has also been shown to proceed with retention of configuration (**1** → **4**) [10,12] but the isolated η^3-complex **4** is known to react with stabilized nucleophiles via inversion (**4** → **5**) [10,12]. This dichotomy can be attributed to the difference in the nature of the catalyst/reagent: in the stoichiometric reaction, the intermediate complex is first isolated and then reacted with the nucleophile, whereas in the catalytic cycle the nucleophile is present at the time of the complex formation, and may be coordinated to the metal [14].

ENANTIOCONTROLLED ALLYLIC SUBSTITUTION CATALYZED BY Mo(0) AND Pd(0)

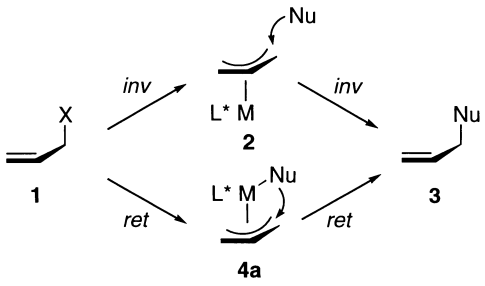
Not surprisingly, in view of the standard double-inversion mechanism (**1** → **2** → **3**; Scheme 6), asymmetric induction in Pd(0)-catalyzed allylic substitution was not straightforward. Note that a chiral ligand adjacent to the metal (**2** in Scheme 6), offers little steric interaction with the approaching nucleophile so that the degree of asymmetric induction can hardly be expected to be high (*vide infra,* however). With Mo(0) catalysts, this scenario may change dramatically: if the double-retention



Scheme 5

mechanism demonstrated above were still operating with a chiral ligand attached to Mo (**4a**; Scheme 6), then the nucleophile approaching from the syn face (presumably, first coordinating to the metal) should experience a direct interaction with the chiral ligand, so that high asymmetric induction could be anticipated.

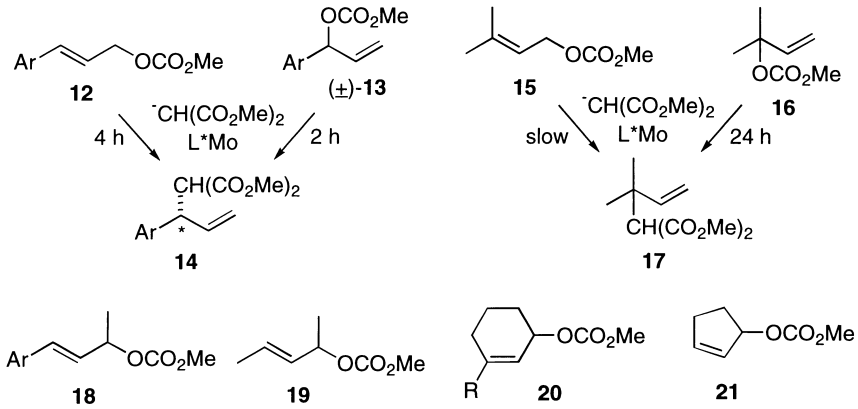
While this work was in progress, Trost reported the first examples of high asymmetric induction in



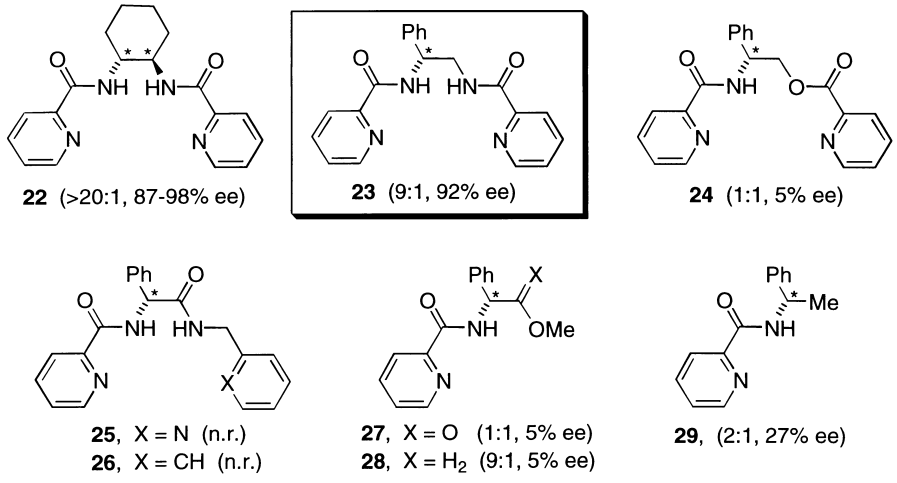
Scheme 6 M = Pd, Mo.

Mo(0)-catalyzed allylic substitution employing cinnamyl carbonate **12**, its allylic isomer **13**, and their aromatic and heteroaromatic counterparts as prototype substrates (Scheme 7): with malonate-type nucleophiles and ligand **22** (Scheme 8), both the regio- and enantioselectivities were excellent. [15]

While Trost's ligand **22** was characterized by two chiral centers and C_2-symmetry [15a], we have investigated ligands such as **23–29,** with just one chiral center. To date, **23** proved to be most successful (with up to 92% enantiomer excess in the model reactions of **12** and **13**), which demonstrates that one chiral center in the scaffold is sufficient to determine the twist of the ligand coordination and effect high asymmetric induction [16]. However, the reaction was sluggish with other substrates (e.g. **15** and **16**) or even failed (**18–21**). We therefore prepared Trost's ligand **22** and screened it with the same substrates. Surprisingly, we found its limitations to be identical to those of **23**, demonstrating that in the use of both ligands, similar mechanisms must be operating.



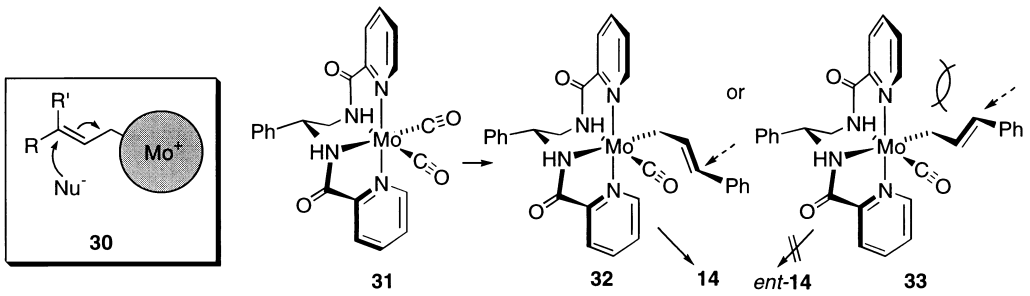
Scheme 7



Scheme 8

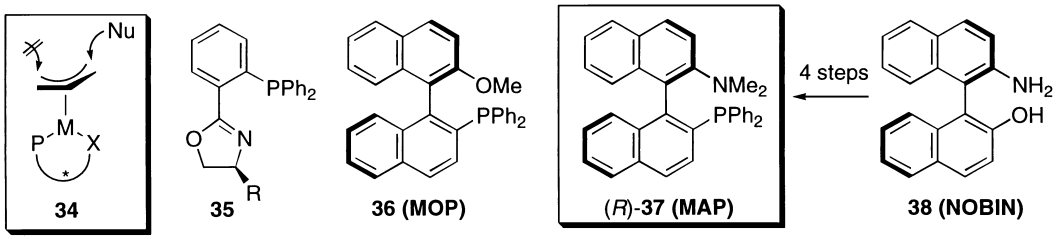
That a number of typical allylic substrates did not react, appears to be inconsistent with the η^3-intermediate and suggests η^1-complex as an alternative (Scheme 9) [17,18]. In this case, the asymmetric induction would then originate from steric bulk within the complex (**30**).

As a working hypothesis, we can propose the *in situ* formation of tetradentate complex **31** from **23** (Scheme 9), which would allow the generation of diastereoisomeric intermediates **32** and **33**, with the former regarded as lower in energy. This model is compatible with the formation of **14** as the major product [19].



Scheme 9

As explained above, attaining enantioselection in Pd(0)-catalyzed substitution, is difficult *a priori* owing to the *inv-inv mechanism*. Thus, even if the catalyst were enantiofacially selective, the two termini of the *n*-allyl system in **2** (Scheme 6) appear not to be sufficiently different to encourage preferential attack by the nucleophile at one of them. [20] By contrast, if the two coordinating groups were of sufficiently different nature, as in **34** (Scheme 10), attack should take place at the *n*-allyl terminus *trans*-related via Pd to the better acceptor atom (e.g. P > N). The first ligands designed according to this hypothesis were phosphinooxazolines **35**, which proved to work extremely well in selected examples [21]. Other ligands, such as **36**, were less efficient [22].



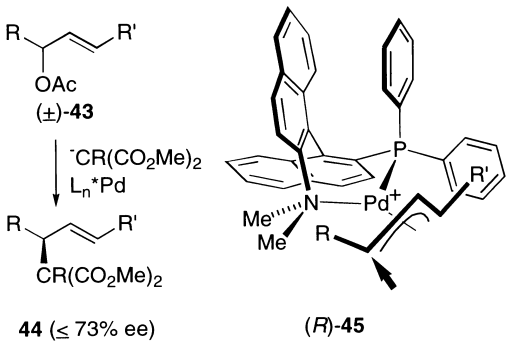
Scheme 10

We set out to design a new class of binaphthyl *P*,*N*-ligands, such as **37** (MAP), that can be regarded as nitrogen analogues of **36**. The synthesis was straightforward, starting with NOBIN (**38**) [23], whose *N*-methylation, followed by the Pd(0)-catalyzed coupling of its triflate with $Ph_2P(0)H$ and reduction, afforded enantiopure **37** in high yield [24–26].

MAP (**37**) proved to be acceptably efficient as chiral ligand in the Pd(0)-catalyzed reaction of allylic acetates **43** with malonate nucleophiles, giving **44** of up to 73% enantiomer excess (Scheme 11). The sense of asymmetric induction was consistent with model **45** assuming preferential attack at that allylic, terminus, which is *trans*-related to phosphorus via Pd [24]; however, see below for further insight.

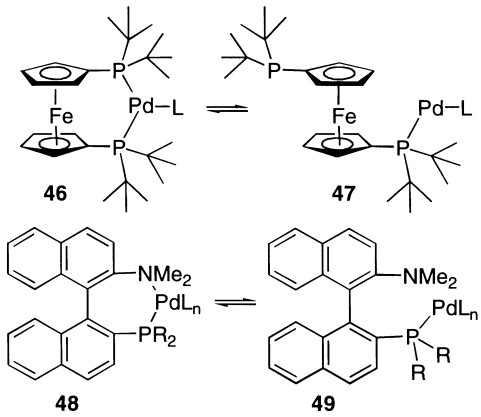
NOVEL LIGANDS IN THE HARTWIG–BUCHWALD AMINATION AND SUZUKI COUPLING

As part of improved ligand design, we aimed at preparation of *N*-aryl derivatives of NOBIN, for which the Hartwig–Buchwald amination [27] appeared to be the method of choice. After the original demonstration of BINAP, DPPF, and related bidentate phosphines as suitable ligands for this coupling (note that Ph_3P is ineffective) [27], Hartwig, Buchwald and Fu have independently developed a series of more efficient bulky phosphines [27–30]. It has been argued that, for instance, chelate **46** can easily expose coordinatively unsaturated Pd (**47**), thereby increasing the catalyst reactivity (Scheme 12) [28].



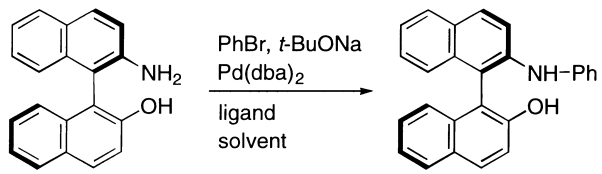
Scheme 11

We reasoned that MAP could mimic this behavior in view of the weaker coordination capability of nitrogen vs. phosphorus so that complex **48** can be expected to generate a sufficient concentration of **49** [25]. A similar approach was pursued by Buchwald, who synthesized biphenyl analogues of MAP [29a] and more recently reported on the binaphthyl MAP ligands with P(*t*-Bu)$_2$ in place of our PPh$_2$ [29b].



Scheme 12

Indeed, MAP/Pd complex proved, e.g. to accelerate dramatically the amination of NOBIN (Scheme 13) [25]. Similar effects have been observed for amination and related coupling reactions (Suzuki coupling and formation of aryl ethers), both by us [25,31] and by Buchwald [29].



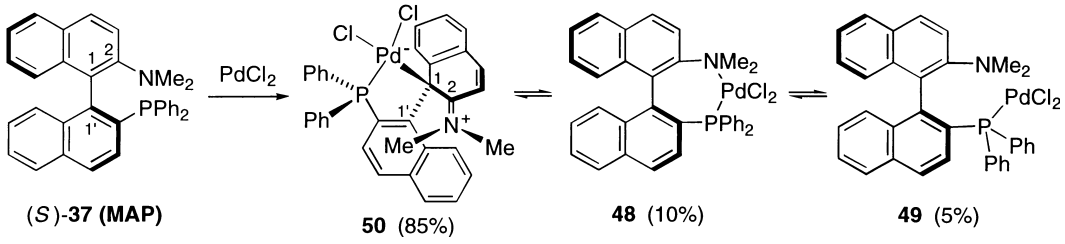
ligand	solvent	temp (°C)	time
BINAP	toluene	60	2 h
MAP	toluene	50	15 min
MAP	THF	50	2 h

Scheme 13

THE UNIQUE MODE OF COORDINATION OF Pd(II) BY MAP AND MOP LIGANDS

In order to shed more light on the mechanism of the Pd/MAP-catalyzed reactions, structural characterization of the complexes involved was required. To this end, we prepared a complex from (PhCN)$_2$PdCl$_2$ and (*S*)-(+)-**37**. Single-crystal X-ray crystallography of the product excluded the expected *P,N*-chelate **48** and revealed its *P,C*$_\sigma$-ligating alternative (*S*)-(+)-**50** (Scheme 14 and Fig. 1) [31] whose formation can be understood in terms of the ligand's enamine-like behavior combined with the known tendency of Pd to form 5-membered palladacycles in preference to other ring-sizes [32]. In solution, an

85:10:5 mixture of three species (**50**, **48** and **49**) has been shown to be present by ^{1}H NMR spectroscopy (Scheme 14). In the NOESY spectrum, exchange cross-peaks between the signals of **50** and **48** indicate a dynamic equilibration.



Scheme 14

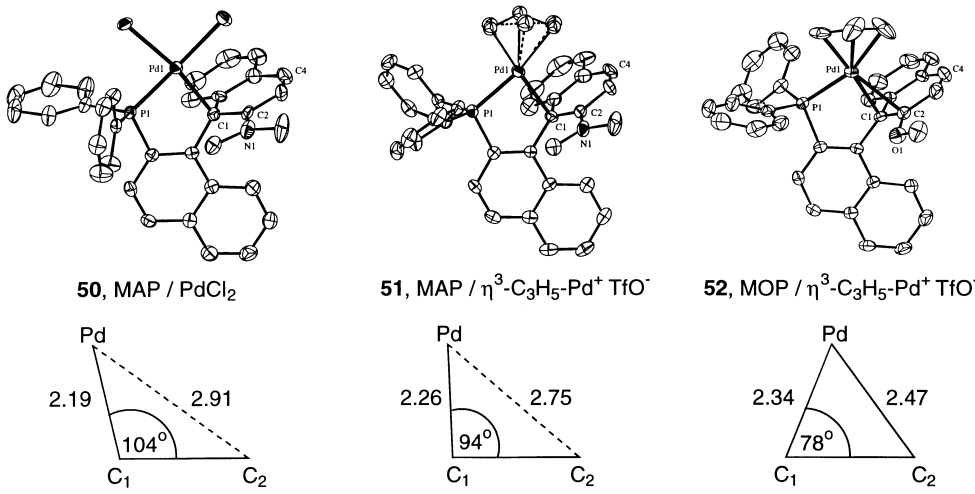
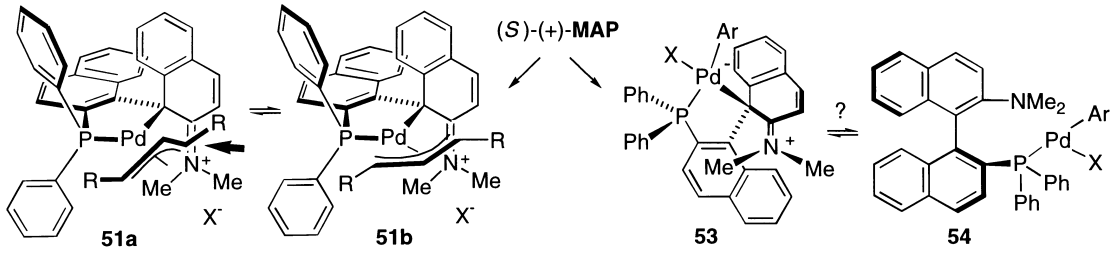


Fig. 1 ORTEP diagrams and bonding parameters for **50**–**52**. Hydrogen atoms and TfO^- are omitted for the sake of clarity.

Crystallographic analysis of the η^3-allyl complex, prepared from (*S*)-(+)-**37** and $[(MeCN)_2Pd(\eta^3\text{-}C_3H_5)]^+$ TfO^-, again revealed the unusual *P,C*$_\sigma$-chelate structure (+)-**51** (Fig. 1) that exists as a ≈3:2 mixture of two diastereoisomers (**51a,b**) resulting from the positioning of the allyl unit (Scheme 15). NMR spectroscopy confirmed the presence of the two latter species in solution (in a ≈1.1:1 ratio), whose interconversion is slower than the NMR time scale at ambient temperature [31]. The sense of asymmetric induction discussed above (Scheme 11) [24] is compatible with model **51a** (note that here we used the opposite enantiomer), assuming preferential nucleophilic attack at the carbon *trans*-related to P via Pd (Scheme 15) [33].



Scheme 15

In contrast to the *P,C*-chelation by **37**, Hayashi's X-ray structure of (**36**)Pd(prenyl)Cl shows that **36** (MOP) is monocoordinated to Pd by P [34]. However, inspection of this structure revealed that Pd is, in

fact, positioned right above the C(1)-C(2) bond with Pd-C(1) and Pd-C(2) distances being 3.38 and 3.50 Å, respectively. Hence, on creation of a vacant coordination site (e.g. by loss of chloride), minimal distortion would permit bonding in a manner analogous to **51**. Indeed, we have now found this to be the case for $[(MOP)Pd(\eta^3\text{-}C_3H_5)]^+$ TfO^- (**52**; Fig. 1), in which Pd-C(1) and Pd-C(2) distances of 2.34 and 2.47 Å were observed by single crystal X-ray analysis, clearly demonstrating η^2-coordination [31].

The enhanced reactivity of the Pd/MAP complexes in the coupling reactions may originate from the presence of the low-abundant P-monocoordinated species **54**, in line with Buchwald's suggestion [29] while the *P,C*-complex would serve as an inactive reservoir. On the other hand, the *P,C*-chelate **53** can also be conjectured as playing a role with the reactivity of Pd/MAP understood in terms of accelerated oxidative addition (the rate-limiting step [27]) owing to the electron richness of the 'palladate' species. The lack of accelerating effect of **36** (MOP) [25,35] (which tends to avoid bidentate coordination in the presence of Cl ligand [34]) seems to support further the importance of *P,c*-coordination of **37** (MAP), at least in some parts of the catalytic cycle [36]. Furthermore, we have recently found the reaction of (±)-(1-^{2}H)-cyclopent-2-enyl pivalate with $NaCH(CO_2Me)_2$ and (*S*)-(+)-**51** (5 mol%) to proceed with 88% regiochemical retention and nearly identical results were observed with **36** (MOP) [31]. This powerful memory effect [31,37] proved to be eroded by the presence of Cl^- (5 mol%), which can be understood in terms of accelerated collapse of an ion-paired [38] intermediate $[\eta^3\text{-}(c\text{-}C_5H_7)\text{-}PdL]^+$ $[O_2C\text{-}t\text{Bu}]^-$ (L = **MAP** or **MOP** in *P,C*-mode) and chloride-catalyzed diastereoisomer equilibration [31b]. Moderate kinetic resolution ($k_R/k_S \cong 4$–7) [31b] and high catalyst stability further support bidentate coordination of MAP and MOP, since a less rigid monodentate ligation would be unlikely to effectively discriminate between enantiomers.

CONCLUSIONS

Our contribution to diastereo- and enantiocontrol in Pd(0)-, Ni(0)-, and Mo(0)-catalyzed allylic substitution has been summarized. New chiral ligands for asymmetric, Mo(0)-catalyzed allylic substitution have been developed and their mode of action discussed. *P,N*-binaphthyls **37** (MAP) have been developed as a new, promising class of chiral ligands to be used, e.g. in Pd(0)-catalyzed allylic substitution, Hartwig– Buchwald amination, Suzuki coupling, and related reactions. Their Pd complexes **50** and **51** have been structurally characterized both in the solid state and in solution, and shown to be P,C_σ- rather than *P,N*-chelates. This unique feature is regarded as an important factor governing the activity of MAP-derived catalysts. Complex **52**, obtained from **36** (MOP), exhibited η^2-chelation of Pd between P and C(1) = C(2).

ACKNOWLEDGEMENT

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REFERENCES

1 (a) R. M. Magid, *Tetrahedron* **36**, 1901 (1980). (b) L. A. Paquette, C. J. M. Stirling, *Tetrahedron* **48**, 7383 (1992).

2 For reviews see: (a) B. M. Trost. *Tetrahedron* **33**, 371 (1977). (b) B. M. Trost. *Acc. Chem. Res.* **13**, 385 (1980). (c) C. G. Frost, L. Howarth, J. M. J. Williams. *Tetrahedron: Asymmetry* **3**, 1089 (1992). (d) L.-E. Backvall. *Acta Chem. Scand.* **50**, 661 (1996). (e) B. M. Trost. *Acc. Chem. Res.* **29**, 355 (1996). (f) J. Tsuji. *Tetrahedron* **42**, 4361 (1986).

3 (a) I. Starý, P. Kočovský. *J. Am. Chem. Soc*. **112**, 4981 (1989). (b) I. Starý, L. Zajíček, P. Kočovský. *Tetrahedron* **48**, 7229 (1992).

4 (a) H. Kurosawa, S. Ogoshi, Y. Kawasaki, S. Murai, M. Miyoshi, I. Ikeda. *J. Am. Chem. Soc.* **112**, 2813 (**1990**).

(b) H. Kurosawa, H. Kajimaru, S. Ogoshi, H. Yoneda, K. Miki, N. Kasai, S. Murai, I. Ikeda. *J. Am. Chem. Soc.* **114**, 8417 (1992).

5 C. N. Farthing, P. Kočovský. *J. Am. Chem. Soc.* **120**, 6661 (1998).

6 This protocol is highly successful with cyclic substrates but fails in non-cyclic series due to the conformational freedom allowing the inversion pathway even for the pre-coordinated catalyst.

7 Retention in the first step has also been reported for cyclic allylic acetates with a neighboring amino group. M. E. Krafft, A. M. Wilson, Z. Fu, M. L. Procter, O. A. Dasse. *J. Org. Chem.* **63**, 1748 (1998).

8 Mo: (a) B. M. Trost, M. Lautens. *J. Am. Chem. Soc.* **104**, 5543 (1982). (b) B. M. Trost, C. A. Merlic. *J. Am. Chem. Soc.* **112**, 9590 (1990) and references given therein. (c) M. P. T. Sjögren, H. Frisell, B. Åkermark, P. O. Norrby, L. Eriksson, A. Vitagliano. *Organometallics* **16**, 942 (1997).

9 W: (a) B. M. Trost, M.-H. Hung. *J. Am. Chem. Soc.* **105**, 7757 (1983). (b) J. Lehmann, G. C. Lloyd-Jones. *Tetrahedron* **51**, 8863 (1995). (c) H. Frisell, B. Akermark. *Organometallics* **14**, 561 (1995).

10 J. W. Faller, D. Linebarrier. *Organometallics.* **7**, 1670 (1988).

11 D. Dvořák, L. Starý, P. J. Kočovský. *Am. Chem. Soc.* **117**, 6130 (1995).

12 Y. D. Ward, L. A. Villanueva, G. D. Allred, L. S. Liebeskind. *J. Am. Chem. Soc.* **118**, 897 (1996).

13 Note that the opposite effect has been observed for the substrates in which the *ret*-mechanism is precluded by a steric bias so that the *inv*-mechanism becomes the only possible pathway (as in **10**) [11].

14 M. E. Krafft, M. L. Procter, K. A. Abboud. *Organometallics* **18**, 1122 (1999).

15 (a) B. M. Trost, I. Hachiya. *J. Am. Chem. Soc.* **120**, 1104 (1998). For the most recent approach and similar results obtained with the bisoxazoline analogue of **22**, see: (b) F. Glorius, A. Pfaltz. *Organic Lett.* **1**, 141 (1999).

16 Most recently, an analogue of **23** proved to give even higher selectivities (>30:1; >98% ee): A. V. Malkov, P. Spoor, V. Vinader, P. Kočovský. Manuscript in preparation.

17 For discussion of the coordination mode in the case of W see [9b].

18 The η^1/η^2-coordination may also be possible. For a similar observation in the case of Rh, see: (a) D. N. Lawson, A. Osborn, G. Wilkinson. *J. Chem. Soc.* 1733 (1966). (b) P. A. Evans, J. D. Nelson. *J. Am. Chem. Soc.* **120**, 5581 (1998).

19 Another high level of enantioselection has been described for a W(0)-phosphinooxazoline catalyst. G. C. Lloyd-Jones, A. Pfaltz. *Angew. Chem, Int. Ed. Engl.* **34**, 462 (1995).

20 A great deal of this problem appears to have been solved by now. B. M. Trost, D. L. Van Vranken. *Chem. Rev.* **96**, 39 (1996).

21 (a) P. von Matt, A. Pfaltz. *Angew. Chem. Int. Eds. Engl.* **32**, 566 (1993). (b) L. Sprinz, G. Helmchen. *Tetrahedron Lett.* **34**, 1769 (1993). (c) C. G. Frost, J. M. J. Williams. *Tetrahedron Lett.* **34**, 2015 (1993). (d) H. Steinhagen, M. Reggelin, G. Helmchen. *Angew. Chem. Int. Eds. Engl.* **36**, 2108 (1997).

22 T. Hayashi, M. Kawatsura, Y. Uozurni. *Chem. Commun*. **561** (1997).

23 (a) M. Smrčina, M. Lorenc, V. Hanuš, P. Kočovský, *Synlett.* 231 (1991). (b) M. Smrčina, M. Lorenc, V., Hanug, P. Sedmera, P. Kočovský. *J. Org. Chem.* **57**, 1917 (1992). (c) M. Smrčina, L. Poláková, Š. Vyskočil, P. Kočovský. *Org. Chem.* **58**, 4534 (1993). (d) M. Smrčina, Š. Vyskočil, B. Máca, M. Polášek, T. A. Claxton, A. P. Abbott, P. Kočovský. *J. Org. Chem.* **59**, 2156 (1994). (e) M. Smrčina, Š. Vyskočil, V. Hanuš, M. Polášek, V. Langer, B. G. M. Chew, D. B. Zax, H. Verrier, K. Harper, T. A. Claxton, P. Kočovský. *J. Am. Chem. Soc.* **118**, 487 (1995). (f) M. Smrčina, Š. Vyskočil, J. Polívková, L. Polívková, P Kočovský. *Collect. Czech. Chem. Commun.* **61**, 1520 (1996). (g) M. Smrčina, Š. Vyskočil, L. Polívková, L. Poláková, J. Sejbal, V. Hanuš, M. Polášek, H. Verrier, P. Kočovský. *Tetrahedron: Asymmetry* **8**, 537 (1997). (h) Š. Vyskočil, M. Smrčina, M. Lorenc, V. Hanuš, M. Polášek, P. Kočovský. *Chem. Commun.* 585 (1998). (i) Š. Vyskočil, L. Jaracz, M. Smrčina, M. Štícha, V. Hanuš, M. Polášek, P. Kočovský. *J. Org. Chem.* **63**, 7727 (1998). (j) K. Ding, Q. Xu, Y. Wang, L. Liu, L. Yu, B. Du, Y. Wu, H. Koshima, T. Matsuura. *Chem. Commun.* 693 (1997). (k) H. Mahmoud, Y. Han, B. M. Segal, L. Cai. *Tetrahedron: Asymmetry* **9**, 2035 (1998). (l) R. A. Singer, S. L. Buchwald. *Tetrahedron Lett.* **40**, 1095 (1999). (m) K. Ding, Y. Wang, H. Yun, J. Lu, Y. Wu, M. Terada, Y. Okubo, K. Mikami. *Chem. Eur. J.* **5**, 1734 (1999).

24 Š. Vyskočil, M. Smrčina, V. Hanuš, M. Polášek, P. Kočovský. *J. Org. Chem.* **63**, 7738 (1998).

25 Š. Vyskočil, M. Smrčina, P. Kočovský. *Tetrahedron Lett.* **39**, 9289 (1998).

26 A practically identical procedure, leading to the same ligand, has appeared this year, [23 m] after the publication of our original paper [24].

27 For a recent review see: J. F. Hartwig. *Angew. Chem. Int.* Eds. **37**, 2046 (1998).

28 (a) M. Kawatsura, J. F. Hartwig. *J. Am. Chem. Soc.* **121**, 1473 (1999). See however a recent discussion in the following: (b) G. Mann, C. Incarvito, A. L. Rheingold, J. F. Hartwig. *J. Am. Chem. Soc.* **121**, 3224 (1999).

29 (a) D. V. Old, J. P. Wolfe, S. L. Buchwald. *J. Am. Chem. Soc.* **120**, 9722 (1998). (b) A. Aranyos, D. W. Old, A. Kiyomori, J. P. Wolfe, J. P. Sadighi, S. L. Buchwald. *J. Am. Chem. Soc.* **121**, 4369 (1999).

30 (a) A. E. Littke, G. C. Fu. *Angew. Chem, Int.* Eds. **37**, 3387 (1998). (b) A. F. Littke, G. C. Fu. *J. Org. Chem.* **64**, 1 (1999).

31 (a) P. Kočovský, Š. Vyskočil, L. Císařová, L. Sejbal, I. Tišlerová, M. Smrčina, G. C. Lloyd-Jones, S. C. Stephen, C. P. Butts, M. Murray, V. Langer. *J. Am. Chem. Soc.* **121**, 7714 (1999). (b) G. C. Lloyd-Jones, S. C. Stephen, M. Murray, C. P. Butts, Š. Vyskočil, P. Kočovský. Manuscript in preparation.

32 (a) G. R. Newkorne, W. E. Puckett, V. K. Gupta, G. E. Kiefer. *Chem. Rev.* **86**, 451 (1986). (b) L. Zhang, E. Zetterberg. *Organometallics* **10**, 3806 (1991). Note, however, that 7-membered chelates are favored by BINAP.

33 In the ^{13}C NMR spectrum of **51a,b**, the allylic carbons *trans*-disposed to C(1) appear at 59.3 and 56.4 p.p.m. whereas those *trans*-disposed to P are located at 89.9 and 93.6 p.p.m. Furthermore, in the solid state structure, the C–Pd bond length at the allylic terminus *trans*-related to P is longer than that trans-related to C (by ≈0.15 Å and 0.16 Å, respectively). Thus, both the NMR and X-ray data demonstrate substantial difference in double bond character and electrophilicity between the two allylic termini.

34 T. Hayashi, H. Iwamura, M. Naito, Y. Matsumoto, Y. Uozurni. *J. Am. Chem. Soc.* **116**, 775 (1994).

35 For accelerating effects of P,O-ligands, see: (a) X. Bei, T. Uno, L. Norris, H. W. Turner, W. H. Weinberg, P. S. Guram, J. L. Petersen. *Organometallics* **18**, 1840 (1999). (b) X. Bei, H. W. Turner, W. H. Weinberg, A. S. Guram, J. L. Petersen. *J. Org. Chem.* **64**, 6797 (1999).

36 Stable, 5-membered P,C_σ- and N,C_σ-chelates of Pd have been shown to accelerate Heck addition, thereby further demonstrating the role of Pd–C. coordination: (a) W. A. Herrmann, C. Brossmer, C.-P. Reisinger, T. H. Riermeier, K. Ofek, M. Beller. *Chem. Eur. J.* **3**, 1357 (1997). (b) M. Beller, T. H. Riermeier. *Eur. J. Inorg. Chem.* **1**, 29 (1998). (c) B. L. Shaw. *New. J. Chem.* 77 (1998). (d) B. L. Shaw, S. D. Perera, E. A. Staley. *Chem. Commun.* 1361 (1998). (e) D. A. Albisson, R. B. Bedford, P. N. Scully *Tetrahedron Lett.* **39**, 9793 (1998). (f) M. Ohff, A. Ohff, D. Milstein *Chem. Commun.* 357 (1999). (g) D. E. Bergbreiter, P. L. Osburn, Y. S. Liu. *J. Am. Chem. Soc.* 121 (1999), in press.

37 For a recent study and detailed analysis of memory effects, see: (a) G. C. Lloyd-Jones, S. C. Stephen. *Chem. Eur. J.* **4**, 2539 (1998). (b) G. C. Lloyd–Jones, S. C. Stephen. *Chem. Commun.* 2321 (1998).

38 C. Amatore, A. Jutand, G. Meyer, L. Mottier. *Chem. Eur. J.* **5**, 466 (1999).