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Asymmetric Tsuji–Trost substitution in 3-acetoxy-1,3-diphenylpropene under phase-transfer conditions

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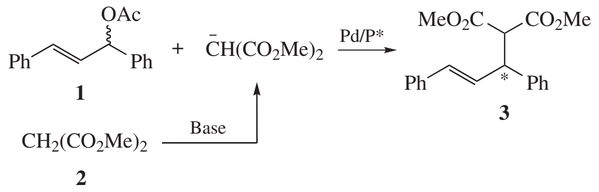
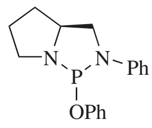
P*-Chiral diamidophosphite ligand-assisted Pd-catalyzed Tsuji–Trost reaction between dimethyl malonate and prochiral 3-acetoxy-1,3-diphenylpropene in organic solvents using potassium carbonate as the base affords the substitution product in quantitative yields and with enantioselectivities up to 99% *ee*.

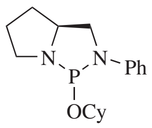
Asymmetric Tsuji–Trost reaction of prochiral substrates using chiral catalysts is nowadays a well-recognized methodology to access non-racemic molecules.[1] Replacement of acetoxy group of prochiral 3-acetoxy-1,3-diphenylpropene **1** (1,3-diphenylallyl acetate) by dimethyl malonate **2** fragment is mostly employed as a model reaction for testing new catalysts, ligands and reaction conditions (Scheme 1). Excellent yields and *ee* values have been currently achieved.[1(*c*)] However, the best ligands are usually poorly accessible, and most of standard procedures are based on generation of malonate carbanion using highly flammable or expensive bases such as NaH or BSA–AcOK system. This brings certain restrictions to wide use of such a promising type of reaction.



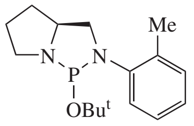
Scheme 1



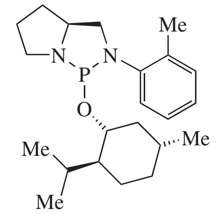
L1



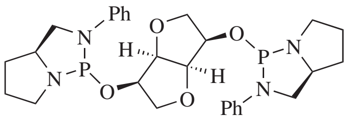
L2



L3



L4



L5

Recently, we have shown[2] that phase-transfer methodology for generation of CH-acid carbanion using cheap and safe bases such as alkali carbonates or phosphates (*cf.* ref. 3) can be successfully employed in the Tsuji–Trost reaction even in the case of problematic substrates. Based on this principle, we pioneered in carrying out reaction between the reactants **1** and **2** in supercritical carbon dioxide thus providing reasonable yields and *ee* values of the product **3**.[4] Herein, we report our latest results on this reaction in conventional organic solvents using potassium carbonate as the base and readily accessible P*-chiral diamidophosphite ligands **L1**–**L5**. Such ligands proved to be very efficient in various versions of Pd-catalyzed allylic substitution.[5]

Experiments using the simplest ligand **L1** with $\mathrm{Pd_2dba_3}$ (two P atoms per one Pd, Pd:L = 1:2) showed (Table 1, entry 1) that quantitative yield and very good enantiomeric purity of the product **3** can be truly achieved in DMF using potassium carbonate as the base.[†] Apparently, the carbonate basicity is not sufficient to fully deprotonate malonate **2**, however, it is enough to maintain necessary steady-state concentration of the carbanion thus allowing the reaction to proceed. Low concentration of reacting species is usually recognized as an important factor providing high enantioselectivity. We suppose that both reacting species, namely, π-allylic Pd complex and carbanion, are generated during the course of the reaction and definitely are present in low concentrations. On carrying out the process in less polar solvents such as THF and $\mathrm{CH_2Cl_2}$ (entries 2 and 3), application of phase transfer catalyst, for example $\mathrm{Bu_4NBr}$, was required. Although yield of product **3** remained quantitative, *ee* values were somewhat lower.

Testing of other diamidophosphites **L2**–**L5** (Table 1, entries 4–7) showed that bidentate dianhydromannitol-tethered one **L5** was the ligand of choice. Interestingly, L-menthol-derived ligand **L4** also containing additional chiral centers proved to be inefficient in view of enantioselectivity (entry 6). Further optimization of reaction conditions (entries 8–10) by varying solvent and palla-

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[†] A Schlenk tube equipped with a stirring magnet and charged with dimethyl malonate **2** (0.3 mmol), an appropriate solvent (0.7 ml) and $\mathrm{Bu_4NBr}$ (0.025 mmol, if necessary) was three times deaerated by evacuation and filling with argon (special care should be taken in case of volatile solvents). Diamidophosphite **L1**–**L4** (0.01 mmol) or **L5** (0.005 mmol) and $\mathrm{Pd_2dba_3}$ or $\mathrm{[Pd(C_3H_5)Cl]_2}$ (0.0025 mmol) were added, and the mixture was stirred for *ca.* 5 min until change in the colour occurred. Then (*E*)-3-acetoxy-1,3-diphenylpropene **1** (50 mg, 0.25 mmol) was added, and the mixture was stirred for 10 min, followed by addition of finely powdered potassium carbonate (69 mg, 0.5 mmol). Each opening of the Schenk tube was carried out under argon flushing. The mixture was stirred at ambient temperature for 18 h, after which it was treated with water, extracted with benzene and dried with $\mathrm{CaCl_2}$. To determine conversion of substrate **1** and enantiomeric excess (*ee*) of product **3**, an aliquote was analyzed by chiral HPLC (Daicel Chiralcel OD-H column) as described previously.[6]

Table 1 Enantioselective Tsuji–Trost substitution in 3-acetoxy-1,3-diphenylpropene **1** under phase-transfer conditions.[a]

Entry	Ligand	Solvent	Conversion (%)	*ee* (%)[b]
1	**L1**	DMF	100	90
2	**L1**	THF (+ Bu_4NBr)	100	84
3	**L1**	CH_2Cl_2 (+ Bu_4NBr)	100	77
4	**L2**	DMF	100	76
5	**L3**	DMF	100	68
6	**L4**	DMF	100	30
7	**L5**	DMF	100	92
8	**L5**	THF (+ Bu_4NBr)	100	95
9	**L5**	CH_2Cl_2 (+ Bu_4NBr)	100 (100)[c]	96 (99)[c]
10	**L5**	toluene (+ Bu_4NBr)	95 (100)[c]	94 (97)[c]

[a] Reaction conditions: 0.25 mmol of 3-acetoxy-1,3-diphenylpropene **1**, 0.3 mmol of dimethyl malonate **2**, 0.5 mmol of K_2CO_3, 0.7 ml of solvent, 0.025 mmol of Bu_4NBr (if specified), 1 mol% of Pd_2dba_3 (2 g-at% Pd per **1**), 4 mol% of ligand (or 2 mol% of bidentate ligand **L5**), 20 °C, 18 h. [b] Major isomer had (*S*)-configuration. [c] Parentheses are related to when $[Pd(C_3H_5)Cl]_2$ was used as the Pd source.

dium source {Pd_2dba_3 or $[Pd(C_3H_5)Cl]_2$} revealed that the use of $[Pd(C_3H_5)Cl]_2$, CH_2Cl_2, Bu_4NBr (cat.) and K_2CO_3 provided excellent enantioselectivity (99% *ee*) and complete conversion of **2** within 18 h at ambient temperature (entry 9). Note that the use of $[Pd(C_3H_5)Cl]_2$ as the palladium source brought about slightly better results under the same reaction conditions (see entries 9–10).

The results obtained are superior to previous not only for excellent yields and enantioselectivities, but also for availability and easiness-to-handle of the ligands, low price and safety of the base and room temperature processing. Several precedents of using alkali carbonates in asymmetric Tsuji–Trost substitution in 3-acetoxy-1,3-diphenylpropene **1** were documented, though. With aqueous K_2CO_3, cetyltrimethylammonium hydrosulfate, $[Pd(C_3H_5)Cl]_2$ and R-BINAP at 25 °C, the product **3** was obtained quantitatively with 91% *ee*.[7] Without phase transfer catalyst, analogous to **3** ethyl diester of 80% *ee* was formed in 21% yield on heating at 70 °C for 12 h.[8] In ionic liquids, 74–86% *ee* values were achieved at yields of 27–81% on using of very expensive chiral ferrocene phosphine ligands.[9] It is worth noting that diamidophosphite ligands **L1** and **L5** on conventional manner of **1**+**2** coupling (BSA–AcOK system as the base, ambient temperature) provided 74–98% *ee* of the product **3**, with the conversion having never reached its completion (72–90%) even upon 48 h of the processing.[5(*a*),(*g*),(*h*)]

To conclude, we believe that our findings will promote wider application of the Tsuji–Trost allylic substitution in the total synthesis of useful biologically active compounds.

References

1 (*a*) B. M. Trost, *Acc. Chem. Res.*, 1996, **29**, 355; (*b*) B. M. Trost and D. L. Van Vranken, *Chem. Rev.*, 1996, **96**, 395; (*c*) Z. Lu and S. Ma, *Angew. Chem. Int. Ed.*, 2008, **47**, 258.

2 (*a*) A. A. Vasil'ev, S. E. Lyubimov, E. P. Serebryakov, V. A. Davankov and S. G. Zlotin, *Mendeleev Commun.*, 2009, **19**, 103; (*b*) A. A. Vasil'ev, S. E. Lyubimov, E. P. Serebryakov, V. A. Davankov, M. I. Struchkova and S. G. Zlotin, *Izv. Akad. Nauk, Ser. Khim.*, 2010, 592 (*Russ. Chem. Bull., Int. Ed.*, 2010, **59**, 605).

3 (*a*) S. A. Lebedev, L. F. Starosel'skaya and E. S. Petrov, *Zh. Org. Khim.*, 1986, **22**, 1565 [*J. Org. Chem. USSR* (*Engl. Transl.*), 1986, **22**, 1410]; (*b*) S. A. Lebedev, Yu. P. Leonova, S. S. Berestova and E. S. Petrov, *Zh. Org. Khim.*, 1988, **24**, 1112 [*J. Org. Chem. USSR* (*Engl. Transl.*), 1988, **24**, 1005].

4 (*a*) S. E. Lyubimov, I. V. Kuchurov, A. A. Vasil'ev, A. A. Tyutyunov, V. N. Kalinin, V. A. Davankov and S. G. Zlotin, *J. Organomet. Chem.*, 2009, **694**, 3047; (*b*) S. E. Lyubimov, I. V. Kuchurov, A. A. Vasil'ev, S. G. Zlotin and V. A. Davankov, *Mendeleev Commun.*, 2010, **20**, 143.

5 (*a*) V. N. Tsarev, S. E. Lyubimov, A. A. Shiryaev, S. V. Zheglov, O. G. Bondarev, V. A. Davankov, A. A. Kabro, S. K. Moiseev, V. N. Kalinin and K. N. Gavrilov, *Eur. J. Org. Chem.*, 2004, 2214; (*b*) K. N. Gavrilov, V. N. Tsarev, A. A. Shiryaev, O. G. Bondarev, S. E. Lyubimov, E. B. Benetsky, A. A. Korlyukov, M. Yu. Antipin, V. A. Davankov and H.-J. Gais, *Eur. J. Inorg. Chem.*, 2004, 629; (*c*) S. E. Lyubimov, V. A. Davankov and K. N. Gavrilov, *Tetrahedron Lett.*, 2006, **47**, 2721; (*d*) S. E. Lyubimov, V. A. Davankov, M. G. Maksimova, P. V. Petrovskii and K. N. Gavrilov, *J. Mol. Catal. A: Chem.*, 2006, **259**, 183; (*e*) K. N. Gavrilov, S. E. Lyubimov, O. G. Bondarev, M. G. Maksimova, S. V. Zheglov, P. V. Petrovskii, V. A. Davankov and M. T. Reetz, *Adv. Synth. Catal.*, 2007, **349**, 609; (*f*) K. N. Gavrilov, S. E. Lyubimov, S. V. Zheglov, E. B. Benetsky, P. V. Petrovskii, E. A. Rastorguev, T. B. Grishina and V. A. Davankov, *Adv. Synth. Catal.*, 2007, **349**, 1085; (*g*) K. N. Gavrilov, S. V. Zheglov, P. A. Vologzhanin, E. A. Rastorguev, A. A. Shiryaev, M. G. Maksimova, S. E. Lyubimov, E. B. Benetsky, A. S. Safronov, P. V. Petrovskii, V. A. Davankov, B. Schäffner and A. Börner, *Izv. Akad. Nauk, Ser. Khim.*, 2008, 2266 (*Russ. Chem. Bull., Int. Ed.*, 2008, **57**, 2311); (*h*) K. N. Gavrilov, S. V. Zheglov, P. A. Vologzhanin, M. G. Maksimova, A. S. Safronov, S. E. Lyubimov, V. A. Davankov, B. Schäffner and A. Börner, *Tetrahedron Lett.*, 2008, **49**, 3120.

6 H. Kodama, T. Taiji, T. Ohta and I. Furukawa, *Tetrahedron: Asymmetry*, 2000, **11**, 4009.

7 (*a*) D. Sinou, C. Rabeyrin and C. Nguefack, *Adv. Synth. Catal.*, 2003, **345**, 357; (*b*) C. Rabeyrin and D. Sinou, *Tetrahedron: Asymmetry*, 2003, **14**, 3891.

8 F.-X. Felpin and Ya. Landais, *J. Org. Chem.*, 2005, **70**, 6441.

9 (*a*) Š. Toma, B. Gotov, I. Kmentová and E. Solčániová, *Green Chem.*, 2000, **2**, 149; (*b*) I. Kmentová, B. Gotov, S. E. Solčániová and Š. Toma, *Green Chem.*, 2002, **4**, 103.

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