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Highly Versatile Pd−Thioether−Phosphite Catalytic Systems for Asymmetric Allylic Alkylation, Amination, and Etherification Reactions

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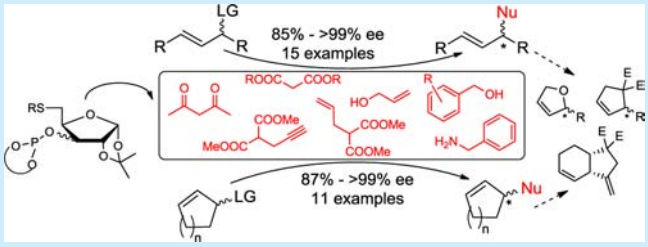
Supporting Information

ABSTRACT: A Pd−furanoside thioether−phosphite catalytic system that can create new C−C, C−N, and C−O bonds in several substrate types using a wide range of nucleophiles in high yields and enantioselectivities has been identified. Of particular note are the excellent enantioselectivities obtained in the etherification of linear and cyclic substrates. The potential application of the new Pd−thioether−phosphite catalytic systems was also demonstrated by the synthesis of the chiral carbo- and heterocycles.



In recent decades, the growing demand for enantiomerically pure compounds for preparing technologically interesting and/or biologically active compounds has encouraged the quest for productive enantioselective catalytic reactions. In particular, transition-metal asymmetric catalysis has become one of the most attractive approaches because of its high selectivity, activity, and sustainability.[1] In this approach, the search for the appropriate enantiopure ligand is crucial if the highest levels of reactivity and selectivity are to be attained.[1] One of the simplest ways of achieving chiral ligands is to derivatize or transform natural chiral products. In this respect, carbohydrates are highly functional compounds with several stereogenic centers. This modular nature offers a wide variety of opportunities for the derivatization and tailoring of synthetic tools in the search for the best ligand for each particular reaction.[2]

The Pd-catalyzed allylic substitution reaction is one of the most powerful and versatile tools for constructing chiral C−C and C−X bonds.[3] Most of the successful ligands developed for this process use either C_2-symmetrical scaffolds, to restrict the number of diastereomeric transition states, or the ability of the ligand to direct the approach to one of the allylic terminal atoms, by means of either a secondary ligand−nucleophile interaction or an electronic differentiation.[3] In this latter strategy, the use of heterodonor ligands allows the ability to electronically distinguish between the two allylic terminal carbons due to the distinct *trans* influences of the donor atoms.[3] All these strategies have led to the discovery of several privileged ligands that provide high levels of enantioselectivity (i.e., DACH-phenyl Trost ligand, PHOX, etc.). However, asymmetric induction is highly dependent on the steric demands of the substrate. Thus, most of the privileged catalytic systems only afford high enantioselectivities for either hindered or unhindered substrates. Recently the use of phosphite containing ligands has been found to have an extremely positive effect on catalytic performance.[4] The π-acceptor capacity of the phosphite moiety increases activities, and the adaptability of phosphite groups enables the catalyst to appropriately tune its chiral pocket to accommodate substrates with different steric requirements.[4] Nevertheless, the success of phosphite-containing ligands is restricted to the allylic alkylation using dimethyl malonate as a nucleophile.[4] More research is needed to expand the range of nucleophiles with the aim to synthesize more complex organic compounds. In this respect, the use of functionalized malonates,[3c] β-diketones,[3c] and alkyl alcohols[5] have hardly been reported. In this context, a small number of catalysts have been efficiently used in the allylic substitution of a broad range of substrates. Substantial improvements are therefore needed in terms of enantioselectivity, chemical yield, and substrate versatility if they are to be of practical interest.

Most heterodonor ligands developed for this process are phosphorus−oxazoline compounds. More recently, the search has moved to the design of heterodonor P−X compounds containing more robust X-groups (i.e., pyridine, thioether, amine, etc.). P,S-ligands have scarcely been evaluated, although some have proved to be potentially useful in this reaction.[6] Notably, Evans and co-workers reported the successful application of phosphinite−thioether ligands derived from chiral β-hydroxysulfoxides. These ligands were effective in the allylic substitution of model substrates **S1** (*rac*-1,3-diphenyl-3-acetoxyprop-1-ene) and **S2** (*rac*-3-acetoxycyclo-hexene) but had low enantioselectivity for such unhindered linear substrates such as **S3** (*rac*-1,3-dimethyl-3-acetoxyprop-1-ene). They also required a low temperature (−20 °C) to achieve high ee. The minor role of thioether-based ligands in this process can be found in the formation of mixtures of diastereomeric thioether complexes (because the S-atom becomes a stereogenic center

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when coordinated to the metal) and the difficulty in controlling their interconversion in solution.[7] Nevertheless, if the ligand scaffold can control the S-coordination, this feature may be extremely beneficial because then the chirality moves closer to the metal. In this respect, we recently found that the furanoside backbone in thioether−phosphite ligands **L1**−**L5** can control the thioether coordination to iridium.[8]

In our search for more versatile and more stable Pd-catalysts, we herein report the successful application of furanoside phosphite−thioether ligands **L1**−**L5** (Figure 1) in the Pd-allylic

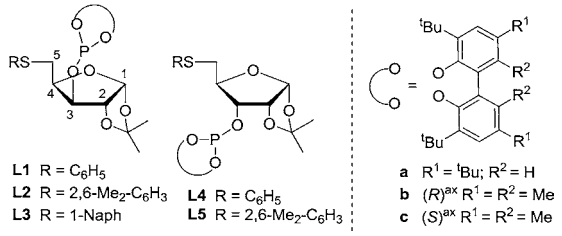
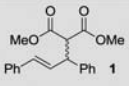
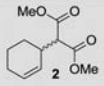


Figure 1. Furanoside thioether−phosphite ligands **L1**−**L5a**−**c**.

substitution of both hindered and unhindered substrates with a large number of nucleophiles, including synthetically useful functionalized malonates, *β*-diketones, and alkyl alcohols. These ligands possess the benefits of the mixed donor groups, the higher stability of thioether groups, and the additional control given by the adaptability of the chiral cavity due to the biaryl-P group. They are also easily prepared in a few steps from cheap D-(+)-xylose. We also demonstrate the potential application of the new Pd−thioether−phosphite catalytic systems by the practical synthesis of chiral carbo- and heterocycles.

Bearing in mind that the stereochemical outcome of this process is highly dependent on the substrate, to make the initial evaluation of thioether−phosphite ligands **L1**−**L5a**−**c**, we chose the allylic alkylation of two model substrates with different steric properties: (a) hindered **S1** and (b) unhindered **S2**, using dimethyl malonate (Table 1). Due to the presence of less bulky *anti* substituents, the enantioselectivity for cyclic substrate **S2** is more difficult to control. There are, therefore,

Table 1. Pd-Catalyzed Allylic Alkylation of Substrates S1−**S2 with Dimethyl Malonate As Nucleophile Using Ligands L1**−**L5a**−**c**[a]

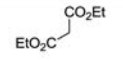
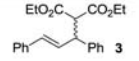
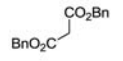
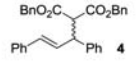
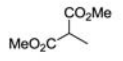
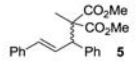
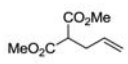
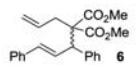
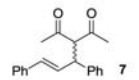
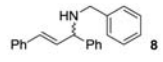
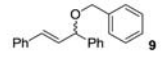
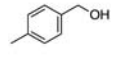
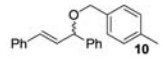
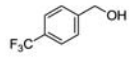
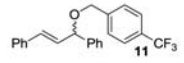
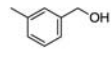
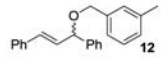
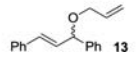
					
		1		2	
entry	L	% yield[b]	% ee[c]	% yield[d]	% ee[e]
1	**L1a**	92	58 (*S*)	89	78 (*S*)
2	**L2a**	96	69 (*S*)	91	63 (*S*)
3	**L3a**	94	78 (*S*)	90	75 (*S*)
4	**L4a**	97	53 (*R*)	89	41 (*R*)
5	**L5a**	93	44 (*S*)	92	66 (*S*)
6	**L3b**	94	33 (*R*)	90	32 (*R*)
7	**L3c**	**95**	**>99 (*S*)**	**91**	**96 (*S*)**

[a]Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), DCM as solvent, ligand (1 mol %), BSA (3 equiv), and KOAc. [b]Full conversions were achieved after 3 h. [c]Determined by chiral HPLC. [d]After 6 h. [e]Determined by chiral GC.

fewer successful catalyst systems for **S2**. We were pleased to identify Pd−**L3c** as one of the very few catalytic systems able to provide excellent enantiocontrol for both types of hindered and unhindered substrates (ee's up to >99% and 96%, respectively) at room temperature. These results compare favorably with those reported in the literature.[3,4]

We then went on to study the allylic substitution of **S1** using a wide range of C, N, and O nucleophiles, among which are the more challenging functionalized malonates, *β*-diketones, and alkyl alcohols (Table 2). Several malonates, including those that

Table 2. Allylic Substitution of S1 with C-, N-, and O-Nucleophiles Using the Pd−L3c Catalytic System[a]

entry	nucleophile	product	% yield[b]	% ee[c]
1		 3	96	99 (*S*)
2		 4	94	99 (*S*)
3		 5	98	98 (*R*)
4		 6	87	92 (*R*)
5		 7	91	99 (*S*)
6		 8	86	>99 (*R*)
7[d]		 9	95	98 (*R*)
8[d]		 10	86	93 (-)
9[d]		 11	97	99 (-)
10[d]		 12	93	>99 (-)
11[d]		 13	52	85 (-)

[a]Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), DCM as solvent, ligand (1 mol %), BSA (3 equiv), and KOAc. [b]Full conversions were achieved after 12 h. [c]Enantiomeric excess determined by chiral HPLC or GC. [d]Reactions carried out using 2 mol % $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 4 mol % ligand, and Cs_2CO_3 (3 equiv). Full conversions were achieved in all cases except for entry 11 (74% conversion).

were *α*-substituted, reacted cleanly with **S1** to afford products **3**−**6** in high yields and enantioselectivities (ranging from 92% to 99% ee). The use of acetylacetone as a nucleophile also provided high enantioselectivities (ee's up to 99%; Table 2, entry 5). Enantiocontrol was also excellent when *N*-nucleophiles were used (compound **8**; 99% ee). Even more interesting are the near-perfect enantioselectivities achieved in the etherification of **S1** using several aliphatic alcohols (compounds **9**−**13**; ee's up to >99%). These results surpass the best results achieved using Pd-(*S*,*R*)-FerroNPS[5i] and Pd-CycloN2P2-Phos[5j] catalytic systems, specifically designed for this purpose.[9]

We also tested Pd−**L3c** in the allylic substitution of cyclic substrate **S2** using a range of C-, N-, and O-nuleophiles (Table

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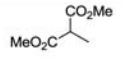
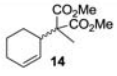
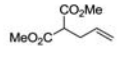
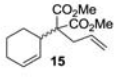
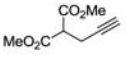
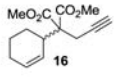
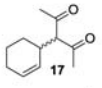
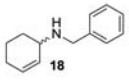
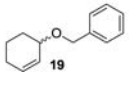
3). In all cases, enantioselectivities were as high as those obtained using dimethyl malonate (ee's up to 98%), except

Table 3. Allylic Substitution of S2 with C-, N-, and O-Nucleophiles Using the Pd−L3c Catalytic System[a]

entry	nucleophile	product	% yield[b]	% ee[c]
1			86	87 (+)
2			69	93 (-)
3			69	98 (*S*)
4			64	96 (-)
5			76	94 (*S*)
6[d]			88	92 (*S*)

[a]Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), DCM as solvent, ligand (1 mol %), BSA (3 equiv), and KOAc. [b]Full conversions were achieved after 12 h. [c]Enantiomeric excess determined by chiral HPLC or GC. [d]Reaction carried out using 2 mol %$[PdCl(\eta^3\text{-}C_3H_5)]_2$, 4 mol % ligand, and Cs_2CO_3 (3 equiv).

when dimethyl methylmalonate was used as the nucleophile, which led to a slightly lower enantioselectivity (compound **14**; 87% ee). Excellent enantioselectivities were therefore obtained using allyl- and propargyl-substituted malonates (compounds **15** and **16**), acetylacetone (compound **17**), and benzylamine (compound **18**). We could also reach high enantioselectivities and yields in the etherification of **S2** (entry 6). Pd−**L3c** is the first catalytic system that can etherificate both substrate types linear **S1** (Table 2, entries 7−11) and cyclic **S2** with high ee's[9] and, therefore, could be used for the synthesis of compounds with ether groups next to a chiral carbon. These compounds are key intermediates for preparing a wide range of biologically active compounds.

The scope of these new catalytic systems was further studied by using other linear substrates with different steric requirements (*rac*-1,3-dimethyl-3-acetoxyprop-1-ene **S3** and *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate **S4**) than those of substrate **S1** (Figure 2, compounds **20**−**22**). We were pleased to see that if ligands are appropriately tuned, high yields and

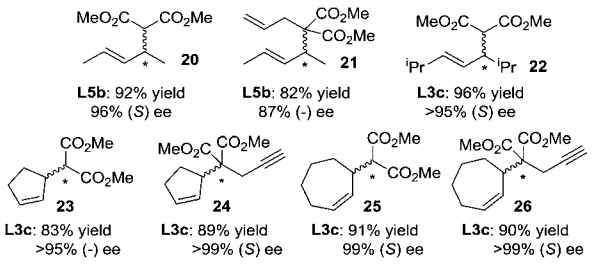
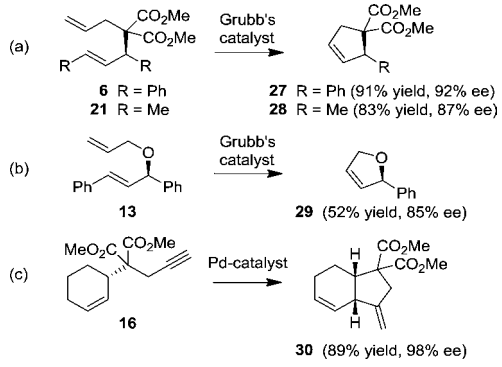


Figure 2. Pd-allylic substitution of **S3**−**S6**. Full conversions were achieved. 0.5 mol % $[PdCl(\eta^3\text{-}C_3H_5)]_2$, CH_2Cl_2 as solvent, ligand (1 mol %), rt, 18 h.

enantioselectivities can also be obtained for the more demanding substrates **S3** and **S4** (ee's up to 96% for **S3** and >95% for **S4**) which usually react with lower yields and enantioselectivities than the corresponding model **S1** substrate. The good performance also extended to the allylic substitution of other cyclic substrates with different ring sizes (*rac*-3-acetoxycyclopentene **S5** and *rac*-3-acetoxycycloheptene **S6**; Figure 2). It should be noted that the enantiocontrol was excellent in both cases, but especially in the allylic substitution of *rac*-3-acetoxycyclopentene (compounds **23** and **24**), which is usually substituted less enantioselectively than the six-membered cyclic substrate **S2**.

The allylic substitution of functionalized nucleophiles can be used in a large variety of synthetic applications, such as the preparation of chiral carbocycles (*R*)-**27** and (−)-**28** by simple tandem reactions, involving the allylic alkylation of the appropriate substrate (**S1** and **S2**) with dimethyl allylmalonate, and a subsequent ring-closing metathesis (Scheme 1a).[10a] In

Scheme 1. Representative Synthetic Applications of Sequential Processes Involving Allylic Substitution of Functionalized Nucleophiles/Cyclation Reactions



both cases, the corresponding carbocycles **27** and **28** were obtained in high yields with no loss in enantiomeric excess. Similarly, the heterocycle (*R*)-**29** is achieved by sequential allylic etherification of **S1** with allyl alcohol and a ring-closing metathesis reaction (Scheme 1b). Another example is the cycloisomerization of the 1,6-enyne **16**, formed from the allylic alkylation of **S2** with dimethyl propargylmalonate, following the methodology described by Uozumi et al.[10b] to yield the carbobicycle hydrindane (3a*R*,7a*S*)-**30** (Scheme 1c).

In summary, a series of furanoside thioether−phosphite ligands **L1**−**L5a**−**c** have therefore been used with success in the Pd-allylic substitution of substrates with different steric requirements by applying a large variety of nucleophiles. These ligands, which are prepared from inexpensive D-xylose, also include the benefits of the heterodonors, the higher stability of thioether groups, and the additional control given by the adaptability of the chiral cavity due to the biaryl-P group. By selecting the ligand components we have been able to identify catalytic systems that can create new C−C, C−N, and C−O bonds, in several substrate types (hindered and unhindered) using a wide range of nucleophiles in high yields and enantioselectivities (ee's up to >99%). Of particular note are the excellent enantioselectivities obtained in the etherification of linear and cyclic substrates, which represent the first example of a successful etherification of both substrate types. So, the exceptional ligand family presented here competes very well with other ligand sets that gave successful selectivities in the

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allylic substitution of substrates using a large variety of C-, O-, and N-nucleophiles, including the much less investigated α-substituted malonates and alkyl alcohols. Furthermore, the potential application of the new Pd−thioether−phosphite catalytic systems has been proven by the stereoselective preparation of carbo- and heterocycles by simple tandem reactions, involving allylic alkylation/ring-closing metathesis or allylic alkylation/cycloisomerization of 1,6-enyne reactions, with no loss in enantiomeric excess. Thus, for the first time, the capacity of an easily accessible and very modular sugar-based thioether-phosphite ligand library in the successful enantioselective Pd-allylic substitution of substrates with a large variety of nucleophiles has been revealed.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(6) Few phosphinite/phosphine−thioether ligands have been successfully applied, and those that do are limited in substrate and nucleophile scope (usually **S1** and dimethylmalonate as the nucleophile). See: (a) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905 (up to 98%, 90%, and 65% ee at −20 °C for **S1**, **S2**, and **S3**, respectively). (b) Nakano, H.; Okuyama, Y.; Hongo, H. *Tetrahedron Lett.* **2000**, *41*, 4615 (up to 94% ee at −30 °C for **S1**). (c) García Mancheño, O.; Priego, J.; Cabrera, S.; Gómez Arrayás, R.; Llamas, T.; Carretero, J. C. *J. Org. Chem.* **2003**, *68*, 3679 (up to 97% ee at −20 °C for **S1**). (d) Enders, D.; Peters, R.; Runsink, J.; Bats, J. W. *Org. Lett.* **1999**, *1*, 1863 (up to 97% ee at −20 °C for **S1**). (e) Guimet, E.; Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2005**, *16*, 959 (up to 93% ee at 0 °C for **S1**). (f) Reference 5k (up to 96% ee at rt for **S1**).

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