Highly versatile Pd-thioether-phosphite catalytic systems for asymmetric allylic alkylation, amination and etherification reactions.

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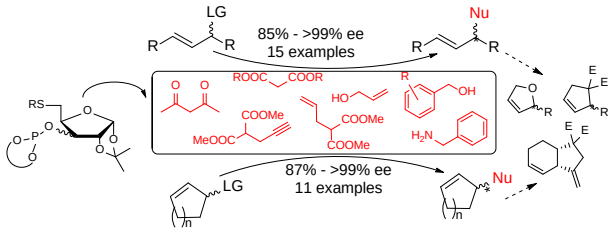
Supporting Information Placeholder



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 stimulated the search for highly efficient asymmetric catalytic processes. 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 design of the chiral ligand is perhaps the most crucial step 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] This latter strategy uses heterodonor ligands to electronically discriminate between the two allylic terminal carbon atoms because of the different *trans* influences of the donor groups.[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. More recently, we have shown that the introduction of biaryl-phosphite moieties into the ligand design is highly advantageous.[4] The benefits have been attributed, on the one hand, to the larger π-acceptor ability of the phosphite groups, which increases reaction rates and, on the other hand, to the flexibility of the phosphite moieties, which allows the catalyst chiral pocket to adapt to both hindered and unhindered substrates.[4] Despite this success, the potential of phosphite-containing ligands is limited to the use of dimethyl malonate as nucleophile.[4] Greater effort has to be made to enlarge the scope of nucleophiles, and increase their chances of being used in the synthesis of more complex chiral organic molecules. In this respect, the use of functionalized malonates,[3c] β-diketones[3c] and alkyl alcohols[5] have hardly been reported. Few catalytic systems, then, provide high enantioselectivities and those that do are limited in substrate scope. Substantial improvements are therefore needed in terms of enantioselectivity, chemical yield and substrate versatility if they are to be of practical interest.

Mixed phosphorus-oxazoline ligands have played a dominant role among heterodonor ligands in this process.[3,4] However, in recent years the range of heterodonor P-X ligands has been extended to include more robust X-donor groups (i.e. amine, pyridine, thioether, etc.). P,S-ligands have scarcely been evaluated, although some have proved to be potentially useful in this reaction.[6] Notably, Evans and coworkers 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 substrate as **S3** (*rac*-1,3-dimethyl-3-acetoxyprop-

1-ene). They also required 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 when coordinated to the metal) and the difficulty of 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]

Because we are interested in discovering more versatile and more robust Pd-catalytic systems, we report herein the successful application of furanoside phosphite-thioether ligands **L1**-**L5** (Figure 1) in the Pd-allylic substitution of both hindered and unhindered substrates with a wide range of nucleophiles, including synthetically useful functionalized malonates, β-diketones and alkyl alcohols. These ligands incorporate the advantages of the heterodonor, the robustness of the thioether moiety and the extra control provided by the flexibility of the chiral pocket through the presence of a biaryl phosphite 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.

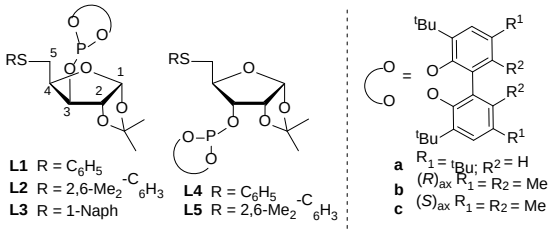
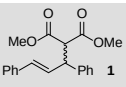
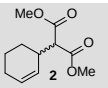


Figure 1. Furanoside thioether-phosphite ligands **L1**-**L5a-c**

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). Enantioselectivity is more difficult to control for cyclic **S2** mainly because of the presence of less sterically demanding *anti* substituents. There are, therefore, fewer successful catalyst systems for **S2**. We were pleased to identify Pd-**L3c** as one of the very few catalytic system 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 the best ones reported in the literature.[3,4]

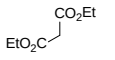
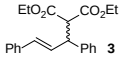
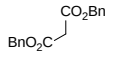
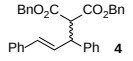
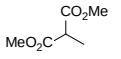
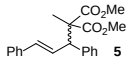
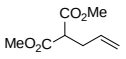
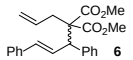
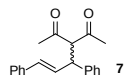
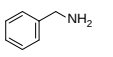
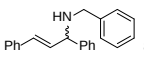
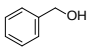
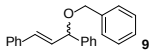
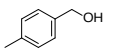
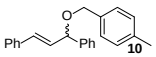
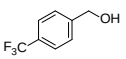
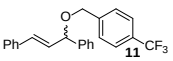
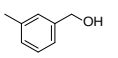
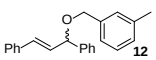
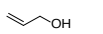
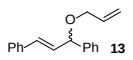
We then went on to study the allylic substitution of **S1** using a wide range of C, N and O nucleophiles, among which are the more challenging functionalized malonates, β-diketones, and alkyl alcohols (Table 2). Several malonates, including those that were α-substituted, reacted cleanly with **S1** to afford products **3**-**6** in high yields and enantioselectivities (ranging from 92% to 99% ee).

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), KOAc. [b] Full conversions were achieved after 3 h. [c] Determined by chiral HPLC. [d] After 6 h. [e] Determined by chiral GC.

Table 2. Allylic substitution of S1 with other several C-, N- and O-nucleophiles using the Pd-L3c catalytic system[a]

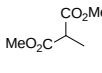
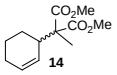
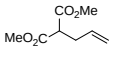
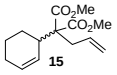
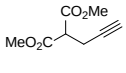
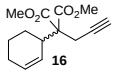
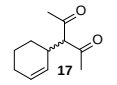
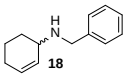
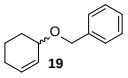
entry	nucleophile	product	% yield[b]	% ee[c]
1		 3	96	99 (*S*)
2		 4	94	99 (*S*)
3		 5	98	98 (*R*)
4		 6	87	92 (*R*)
5		 7	91	99 (*S*)
6		 8	86	>99 (*R*)
7[d]		 9	95	98 (*R*)
8[d]		 10	86	93 (-)
9[d]		 11	97	99 (-)
10[d]		 12	93	>99 (-)
11[d]		 13	52	85 (-)

[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), 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, Cs_2CO_3 (3 equiv). Full conversions were achieved in all cases except for entry 11 (74% conversion).

The use of acetylacetone as nucleophile provided enantioselectivity that was as high as any observed when dimethyl malonate was added (Table 2, entry 5). Enantiocontrol was also excellent when *N*-nucleophiles were used (compound **8**; 99% ee). Even more interesting are the almost 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 3). In all cases, enantioselectivities were as high as those obtained using dimethyl malonate (ee's up to 98%), except when dimethyl methylmalonate was used as nucleophile, which led to 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**). High yields and enantioselectivities were also achieved 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 stereoselective construction of an ether linkage adjacent to a stererogenic carbon center, which is of great importance for the synthesis of many biologically active targets.

Table 3. Allylic substitution of S2 with other several C-, N- and O-nucleophiles using the Pd-L3c catalytic system[a]

entry	nucleophile	product	% yield[b]	% ee[c]
1		 **14**	86	87 (+)
2		 **15**	69	93 (-)
3		 **16**	69	98 (*S*)
4		 **17**	64	96 (-)
5		 **18**	76	94 (*S*)
6[d]		 **19**	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), 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, Cs_2CO_3 (3 equiv).

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 substrate **S1** (Figure 2, compounds **20**-**22**). We were pleased to see that if ligands are appropriately tuned, high yields and 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 size (*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 6-membered cyclic substrate **S2**.

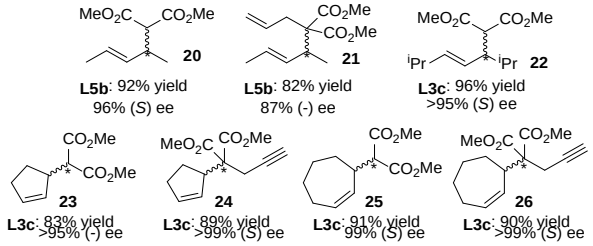
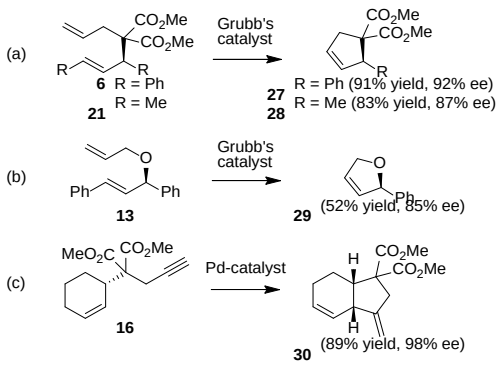


Figure 2. Pd-allylic substitution of **S3**-**S6**. Full conversions were achieved. 0.5 mol % $[PdCl(\eta^3\text{-}C_3H_5)]_2$, CH_2Cl_2 as solvent, ligand (1 mol %), rt, 18 h.

A wide range of synthetic applications can be envisaged for the allylic substitution using functionalized nucleophiles. One example is the practical synthesis of the chiral carbocycles (*R*)-**27** and (-)-**28** by a simple sequential allylic alkylation of the corresponding substrate (**S1** and **S2**), with dimethyl allylmalonate, and ring-closing metathesis reactions (Scheme 1(a)).[10a] In 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 1(b)). 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 1(c)).

Scheme 1. Representative synthetic applications of sequential processes involving allylic substitution of functionalized nucleophiles/cyclation reactions



In summary, a series of furanoside thioether-phosphite ligands **L1**-**L5a-c** have been successfully applied for the first time in the Pd-catalyzed allylic substitution reactions of several substrate types using a wide range of nucleophiles. These ligands, which are prepared from inexpensive D-xylose, also incorporate the

advantages of the heterodonor, the robustness of the thioether moiety and the extra control provided by the flexibility of the chiral pocket through the presence of a biaryl phosphite 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 successful etherification of both substrate types. So, the exceptional ligand family presented here competes very well with a few other ligand series that also provide high ee in several substrate types using a wide range of C-, N- and O-nucleophiles, among which are the little studied α-substituted malonates and alkyl alcohols. Furthermore, the potential application of the new Pd-thioether-phosphite catalytic systems has been demonstrated by the practical synthesis of the chiral carbo- and heterocycles using a simple sequential allylic alkylation/ring-closing metathesis or allylic alkylation/cycloisomerization of 1,6-enyne reactions, with no loss in enantiomeric excess. These results open up the asymmetric Pd-catalyzed allylic substitution of several substrate types with a wide range of nucleophiles to the potential effective use of readily available and highly modular furanoside thioether-phosphite ligands.

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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REFERENCES

[1] a) Asymmetric Catalysis in Industrial Scale: Challenges, Approaches and Solutions; 2nd Ed; Blaser, H. U.; Federsel, H.-J. Eds.; Wiley: Weinheim, Germany, 2010; b) Catalytic Asymmetric Synthesis; 3rd Edition; Ojima, I., Ed.; John Wiley & Sons, Inc.: Hoboken, 2010; c) Comprehensive Asymmetric Catalysis; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999.

[2] a) Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189; b) Woodward, S.; Diéguez, M.; Pàmies, O. *Coord. Chem. Rev.* **2010**, *254*, 2007; c) Boysen, M. M. K. *Chem. Eur. J.* **2007**, *13*, 8648; d) Benessere, V.; Del Litto, R.; De Roma, A.; Ruffo, F. *Coord. Chem. Rev.* **2010**, *254*, 390.

[3] For recent reviews, see: a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. c) Lu, Z.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 258.

[4] a) Pàmies, O.; Diéguez, M. *Acc. Chem. Res.* **2010**, *43*, 312. b) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Claver, C.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2011**, *111*, 2077.

[5] Few examples on the Pd-catalyzed etherification of allylic substrates have been reported. The reason can be found in the low nucleophilicity of alcohols, which usually results in moderate yields. In addition, most of the etherification reactions use phenols as nucleophiles, being the aliphatic ethers much less studied. For representative examples using phenols, see: a) Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J.-P. *J. Am. Chem. Soc.* **2003**, *125*, 9276. b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815; c) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545; d) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 11262; e) Haight, A. R.; Stoner, E. J.; Peterson, M. J.; Grover, V. K. *J. Org. Chem.* **2003**, *68*, 8092; f) Uozumi, Y.; Kimura, M. *Tetrahedron: Asymmetry* **2006**, *17*, 161; g) Tietze, L. F.; Lohmann, J. K.; Stadler, C. *Synlett* **2004**, 1113. For alkyl alcohols, see: h) Iourtchenko, A.; Sinou, D. *J. Mol. Catal. A* **1997**, *122*, 91. i) Lam, F. L.; Au Yeung, T. T.-L.; Kwong, F. Y.; Zhou, Z.; Wong, K. Y.; Chan, A. S. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 1280. j) Ye, F.; Zheng, Z.-J.; Li, L.; Yang, K.-F. ; Xia, C. G.; Xu, L.-W. *Chem. Eur. J.* **2013**, *19*, 15452. k) Caldentey, X.; Pericàs, M. A. *J. Org. Chem.* **2010**, *75*, 2628; l) Liu, Z.; Du, H. *Org. Lett.* **2010**, *12*, 3054. m), Kato, M.; Nakamura, T.; Ogata, K.; Fukuzawa, S. *Eur. J. Org. Chem.* **2009**, 5232. For a recent report based on Ir-catalysts, see: n) Ueno, S.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 1928.

[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 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) ref. 5k (up to 96% ee at rt for **S1**).

[7] Masdeu-Bultó, A. M.; Diéguez, M.; Martin, E.; Gómez, M. *Coord. Chem. Rev.* **2003**, *242*, 159.

[8] Coll, M.; Pàmies, O.; Diéguez, M. *Chem. Commun.* **2011**, *47*, 9215.

[9] The etherification reactions using alkyl alcohols are restricted to **S1**-type substrates with a maximum ee of 96%. There is only one report using cyclic substrate **S2** (ref. 5h).

[10] a) Dugal-Tessier, J.; Dake, G. R.; Gates, D. P. *Org. Lett.* **2010**, *12*, 4667. b) Nakai, Y.; Uozumi, Y. *Org. Lett.* **2005**, *7*, 291.

An exceptional Pd/thioether-phosphite catalytic system has been identified for the highly enantioselective construction of C-C, C-N and C-O bonds. Of particular note are the high yields and enantioselectivities achieved in the substitution of several substrates types (with different steric properties) using the little studied α-substituted malonates and alkyl alcohols. We also report the first successful etherification of both linear and cyclic substrates using alkyl alcohols. The potential application of the new catalytic systems was also demonstrated by the synthesis of the chiral carbo- and heterocycles.