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ARTICLE TYPE

Palladium/sulfoxide-phosphine-catalyzed highly enantioselective allylic etherification and amination

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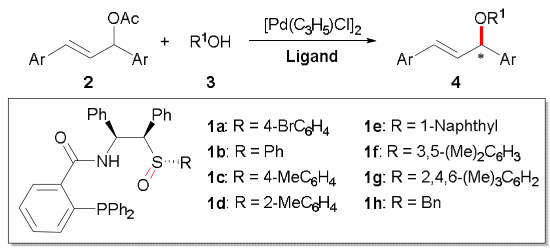
The Pd/sulfoxide-phosphine-catalyzed highly enantioselective allylic etherification and amination with a wide range of *O*- and *N*-nucleophiles have been developed (up to 97% yield, 98.5% ee). The products can also be conveniently transformed into biologically active chiral heterocycles.

Transition-metal catalyzed asymmetric allylic substitution reaction with C-, N-, O-, S- and P-nucleophiles represents one of the most powerful and versatile approaches to the formation of C-C and C-heteroatom bonds, and have attracted a great of attention from chemical community.[1] Over the past decades, however, this field has been mainly dominated by enantioselective allylic alkylation. Recently, the catalytic asymmetric allylic etherification with a diverse set of O-nucleophiles has become the focus of many research groups because of the biological and synthetical significance of the resulted chiral allylic ethers and related derivatives.[2] In this field, many powerful Pd-, Ir-, and Ru-based catalytic systems have been elegantly developed for enantioselective allylic etherification reaction by the use of phenols/alcohols,[3] aryloxides/alkoxides,[4] carboxylic acids/carboxylates,[5] bicarbonate,[6] oximes,[7] silanolates,[8] and water[9] as O-nucleophiles. These works have also resulted in identification of several privileged dienes, P-P, P-N, and P-S ligands, which exhibited broad substrate scope and high functional group tolerance. Despite these impressive advances, it is still highly desirable to develop more efficient catalytic systems for enantioselective allylic etherification by direct utilizing relatively hard aliphatic alcohols as nucleophiles.

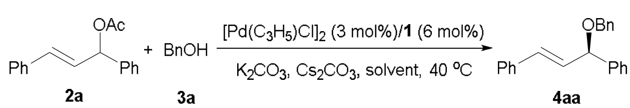
We have been investigating the design and applications of sulfoxide-containing chiral ligands based on the strategy of *rational combination of two privileged backbones into one molecule.*[10,11] And, we have recently documented a new family of chiral sulfoxide–phosphine ligands (Scheme 1), which demonstrated excellent activities and enantioselectivities in Pd-catalyzed asymmetric allylic alkylation reaction.[11b] Notably, the scaffold can be easily prepared from chiral sulfoxide-amino and aryl phosphine units, and such modular features offer great potential for finely tuning the steric and electronic properties of these ligands for each particular chemical reaction. To fully explore the potential of these ligands, we recently extended the scope of nucleophiles to aliphatic alcohols and amines in Pd-catalyzed asymmetric allylic substitution reaction (Scheme 1). Herein, we wish to report our efforts on this subject, and the application of the methodology to the practical synthesis of biologically important enantioenriched oxygen and nitrogen heterocycles.



Scheme 1 Asymmetric allylic substitution and sulfoxide-phosphine ligands.

Based on our previous studies,[11b] we initially screened a representative set of chiral sulfoxide-phosphine ligands **1** in the model reaction between racemic (*E*)-1,3-diphenylallyl acetate **2a** and benzyl alcohol **3a** using K_2CO_3 and Cs_2CO_3 as base in CH_2Cl_2 at 40 °C (Table 1).[12] To our delight, all the sulfoxide-phosphine ligands proved to be suitable for the reaction, giving the desired product **4aa** in generally good yields with excellent enantioselectivities (64-99% yields, 93.7-97.7% ee) (Table 1, entries 1-7). Among them, ligand **1a** provided superior results over others and was chosen for further optimization study. A simple examination of commonly used solvents with ligand **1a** confirmed toluene to be the best of choice in terms of efficiency and enantioselectivity (Table 1, entries 8-11).[13]

Table 1 Condition optimization[a]



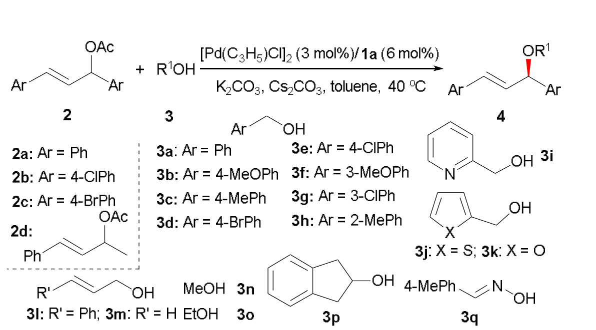
Entry	**Ligand**	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1a**	CH_2Cl_2	24	99	97.7
2	**1b**	CH_2Cl_2	24	97	95.3
3	**1c**	CH_2Cl_2	24	99	93.7
4	**1d**	CH_2Cl_2	24	84	94.3

5	**1e**	CH_2Cl_2	24	99	96.7
6	**1f**	CH_2Cl_2	24	99	96.3
7	**1g**	CH_2Cl_2	24	64	96.5
8	**1a**	DCE	24	87	97.7
9	**1a**	**Toluene**	**4**	**99**	**98.2**
10	**1a**	THF	24	85	97.7
11	**1a**	CH_3CN	24	74	97.1

[a] Unless otherwise noted, reactions were carried out with **2a** (0.2 mmol), **3a** (0.6 mmol), $[Pd(C_3H_5)Cl]_2$ (3.0 mol%), ligand **1** (6.0 mol%), K_2CO_3 (0.3 mmol) and Cs_2CO_3 (0.3 mmol) in solvent (2.0 mL) at 40 °C. [b] Determined by GC using biphenyl as internal standard. [c] Determined by chiral HPLC, the absolute configuration was established as *R* by comparison with literature data.

With the optimized reaction conditions in hand, we then explored the substrate scope of the Pd-catalyzed asymmetric allylic etherification (Table 2). In contrast to Chan's catalytic system,[4c] it was found that the electronic and steric natures of aromatic ring of benzylic alcohols had no obvious effect on the results. For example, a wide variety of benzylic alcohols **3a-3h** bearing electron-donating (MeO, Me) or electron-withdrawing groups (Br, Cl) at *ortho*-, *meta*-, or *para*-positions were well tolerated, and afforded the corresponding products **4aa-4ah** in consistently good yields with excellent enantioselectivities (Table 2, entries 1-8, 82-97% yields, 93.8-98.2% ee). In addition to benzylic alcohols, the potentially problematic heterocycle-substituted alcohols also proved to be suitable as O-nucleophiles. For instance, 2-pyridinyl, 2-thiophenyl and 2-furanyl methanols reacted well to give the corresponding allylic ethers **4ai-4ak** in a range of 81-87% yields with excellent enantioselectivities (Table 2, entries 9-11, 95.5-96.9% ee). Moreover, simple aliphatic alcohols, such as cinnamyl alcohol, allyl alcohol, methanol and ethanol, also participated in the reaction smoothly to give the products **4al-4ao** in a highly enantioselective manner (Table 2, entries 12-15). Importantly, the catalytic system could also be successfully applied to secondary alcohol **3p** and oxime[7] **3q** to provide good yields of corresponding products **4ap** and **4aq** with 80% yield and 94.4% ee, 82% yield and 93.3% ee, respectively (Table 2, entries 16 and 17). As for racemic (*E*)-1,3-diphenylallyl acetate components, both Br and Cl could be incorporated into the aromatic ring without any deleterious effect on the yields or enantioselectivities (Table 2, entries 18-19, 80-81% yields, 96.8-96.9% ee). The reaction with (*E*)-4-phenylbut-3-en-2-yl acetate **2d** also proceeded smoothly to give the corresponding product **4da** in 64% yield, albeit with 52% ee (Table 2, entry 20).

Table 2 Substrate scope of asymmetric allylic etherification[a]

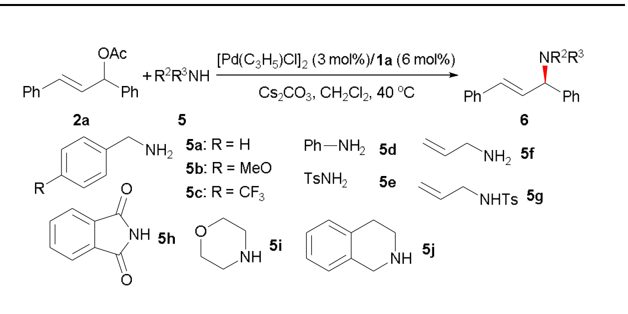


Entry	2	3	Product	Yield[b] (%)	ee[c] (%)
1	**2a**	**3a**	**4aa**	90	98.2
2	**2a**	**3b**	**4ab**	82	98.1
3	**2a**	**3c**	**4ac**	84	97.2
4	**2a**	**3d**	**4ad**	87	96.3
5	**2a**	**3e**	**4ae**	97	93.8
6	**2a**	**3f**	**4af**	85	95.9
7	**2a**	**3g**	**4ag**	87	96.9
8	**2a**	**3h**	**4ah**	83	96.1
9	**2a**	**3i**	**4ai**	82	96.1
10	**2a**	**3j**	**4aj**	87	96.9
11	**2a**	**3k**	**4ak**	81	95.5
12	**2a**	**3l**	**4al**	74	95.5
13	**2a**	**3m**	**4am**	89	95.1
14	**2a**	**3n**	**4an**	87	97.5
15	**2a**	**3o**	**4ao**	84	95.3
16[d]	**2a**	**3p**	**4ap**	80	94.4
17	**2a**	**3q**	**4aq**	82	93.3
18	**2b**	**3a**	**4ba**	81	96.9
19	**2c**	**3a**	**4ca**	80	96.8
20	**2d**	**3a**	**4da**	64	52.0

[a] Unless otherwise noted, reactions were carried out with **2** (0.2 mmol), **3** (0.6 mmol), $[Pd(C_3H_5)Cl]_2$ (3 mol%), ligand **1a** (6 mol%), K_2CO_3 (0.3 mmol) and Cs_2CO_3 (0.3 mmol) in toluene (2.0 mL) at 40 °C for 5 h. [b] Isolated yield. [c] Determined by chiral HPLC, the absolute configuration was established as *R* by comparison with literature data. [d] **3q** (0.24 mmol)

Encouraged by the excellent results achieved in the asymmetric allylic etherification, we next turned our attention to the enantioselective allylic amination by the use of Pd/sulfoxide-phosphine catalytic system. As for the model reaction of racemic (*E*)-1,3-diphenylallyl acetate **2a** with benzyl amine **5a**, a brief investigation of reaction parameters (ligands, bases, and reaction media) resulted in the optimal system: 3 mol% of $[Pd(C_3H_5)Cl]_2$ and 6 mol% of ligand **1a** in the presence of Cs_2CO_3 (3.0 equiv) as base in CH_2Cl_2 at 40 °C.[12,13] And allylic amine **6a** was obtained in 83% yield with 97.1% ee (Table 3, entry 1). In addition to neutral benzyl amine, MeO- and CF_3-substituted benzyl amines **5b** and **5c** also reacted smoothly with **2a**, affording the corresponding products **6b** and **6c** in high yields (83-97%) with excellent enantioselectivities (97.0-98.5% ee) (Table 3, entries 2 and 3). Notably, both phenyl amine **5d** and *p*-toluenesulfonamide **5e** proved to be suitable for the reaction and excellent results were also obtained. It is noteworthy that products **6f** and **6g**, formed by the reaction between allylic amines (**5f** and **5g**) and **2a** with high enantiopurity, would allow for further elaborations for the synthesis of biologically interesting heterocycles (Table 3, entries 6 and 7). The reaction was also successfully extended to secondary amines, such as phthalimide (**5h**), morpholine (**5i**), and tetrahydroisoquinoline (**5j**), with satisfactory results (Table 3, entries 8-10).

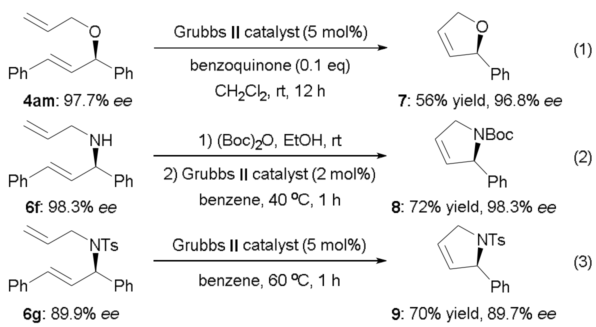
Table 3 Substrate scope of asymmetric allylic amination[a]



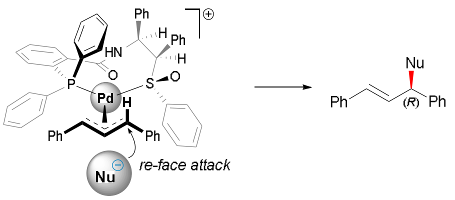
Entry	5	Product	Yield[b] (%)	ee[c] (%)
1	**5a**	**6a**	83	97.1
2	**5b**	**6b**	97	98.5
3	**5c**	**6c**	83	97.0
4	**5d**	**6d**	90	97.3
5[d]	**5e**	**6e**	87	93.9
6	**5f**	**6f**	72	98.3
7[e]	**5g**	**6g**	81	89.9
8	**5h**	**6h**	80	98.3
9	**5i**	**6i**	80	95.3
10[f]	**5j**	**6j**	84	85.1

[a] Unless otherwise noted, reactions were carried out with **2a** (0.2 mmol), **5** (0.6 mmol), $[Pd(C_3H_5)Cl]_2$ (3 mol%), **1a** (6 mol%), Cs_2CO_3 (0.6 mmol) in CH_2Cl_2 (2.0 mL) at 40 °C for 4 h. [b] Isolated yield. [c] Determined by chiral HPLC, the absolute configuration was established as *R* by comparison with literature data. [d] Reaction was conducted at room temperature, 12 h. [e] Na_2CO_3 (0.6 mmol) instead of Cs_2CO_3, 24h. [f] 10 h.

To demonstrate the synthetic potential of the method, we applied the products to the convenient synthesis of biologically important oxygen and nitrogen heterocycles.[14] For example, product **4am** underwent a ring-closing metathesis smoothly to give the corresponding chiral dihydrofuran **7** in good yield with no loss of enantiopurity (eqn (1)). After protection of product **6f** with a easily removable Boc group, a further Grubbs II catalyst-promoted ring-closing metathesis afforded dihydropyrrole derivative **8** in 72% overall yield with 98.3% ee (eqn (2)). Moreover,a direct ring-closing metathesis reaction of **6g** also furnished a good yield of dihydropyrrole **9** with 89.7% ee (eqn (3)).



Based on Evans' transition state model on Pd-phosphine/sulfur complex-catalyzed allylic substitutions,[15] a possible transition state was also proposed to account for the observed stereochemistry of the products. As shown in Scheme 2, a nine-membered chelated intermediary palladium complex, formed by coordination of phosphorus groups and sulfur groups to palladium catalyst, would form M-type allyl system preferentially formed over its W-type counterpart, due to the steric interaction between the two phenyl rings of the phosphine and those of (*E*)-1,3-diphenylallyl acetate. Thus, *O*- and *N*-nucleophiles would attack the allylic site at *Re*-face to afford the corresponding (*R*)-products.



Scheme 2 Proposed transition state.

In summary, we have developed Pd/sulfoxide-phosphine-catalyzed highly enantioselective allylic etherification and amination with a wide range of O- and N-nucleophiles. Successful transformations of the allylic substitution products into the corresponding chiral dihydrofuran and dihydropyrrole derivatives also highlighted the synthetic potential of these sulfoxide-phosphine ligands. Further applications of these ligands to other transition-metal catalyzed asymmetric reactions for the construction of carbon-heteroatom bonds are currently in progress in our laboratory.

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Notes and references

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1 For selected reviews, see: (*a*) B. M.Trost and C. Lee, In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2010, pp 593−649; (*b*) G. Helmchen and A. Pfaltz, *Acc. Chem. Res.*, 2000, **33**, 336; (*c*) L.-X. Dai, T. Tu, S.-L. You, W.-P. Deng and X.-L. Hou, *Acc. Chem. Res.*, 2003, **36**, 659; (*d*) Z. Lu and S. Ma, *Angew. Chem., Int. Ed.*, 2008, **47**, 258; (*e*) B. M. Trost, T. Zhang and J. Sieber, *Chem. Sci.*, 2010, **1**, 427; (*f*) B. M. Trost, *Org. Process Res. Dev.*, 2012, **16**, 185.

2 (*a*) J. Buckingham, *Dictionary of Natural Products*, University Press, Cambridge, Cambridge, MA, 1994; (*b*) B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921; (*c*) A. Lumbroso, M. L. Cooke and B. Breit, *Angew. Chem. Int. Ed.*, 2013, **52**, 1890.

3 (*a*) B. M. Trost and F. D. Toste, *J. Am. Chem. Soc.,* 1998, **120**, 815; (*b*) B. M. Trost, H.-C. Tsui and F. D. Toste, *J. Am. Chem. Soc.*, 2000, **122**, 3534; (*c*) B. M. Trost, H. C. Shen, L. Dong and J. P. Surivet, *J. Am. Chem. Soc.*, 2003, **125**, 9276; (*d*) A. R. Haight, E. J. Stoner, M. J. Peterson and V. K. Grover, *J. Org. Chem.*, 2003, **68**, 8092; (*e*) C. Fischer, C. Defieber, T. Suzuki and E. M. Carreira, *J. Am. Chem. Soc.*, 2004, **126**, 1628; (*f*) C. Welter, A. Dahnz, B. Brunner, S. Streiff, P. Dübon and G. Helmchen, *Org. Lett.*, 2005, **7**, 1239; (*g*) J.-W. Xing, P. Cao and J. Liao, *Tetrahedron: Asymmetry*, 2012, **23**, 527; (*h*) F. Ye, Z.-J. Zheng, L. Li, K.-F. Yang, C.-G. Xia and L.-W. Xu, *Chem. Eur. J.*, 2013, **19**, 15452; (*i*) L. Du, P. Cao and J. Liao, *Acta Chim. Sinica.*, 2013, **71**, 1239.

4 For selected examples, see: (*a*) C.-T. Shu and J. F. Hartwig, *Angew. Chem. Int. Ed.*, 2004, **43**, 4794; (*b*) K. Onitsuka, H. Okuda and H. Sasai, *Angew. Chem. Int. Ed.*, 2008, **47**, 1454; (*c*) F. L. Lam, T. T.-L. Au-Yeung, F. Y. Kwong, Z. Zhou, K. Y. Wong and A. S. C. Chan, *Angew. Chem., Int. Ed.*, 2008, **47**, 1280; (*d*) Z.-Q. Liu and H.-F. Du,

Org. Lett., 2010, **12**, 3054; (*e*) H. He, K.-Y. Ye, Q.-F. Wu, L.-X. Dai and S.-L. You, *Adv. Synth. Catal.*, 2012, **354**, 1084; (*f*) J. Mazuela, O. Pàmies and M. Diéguez, *Chem. Eur. J.*, 2013, **19**, 2416; (*g*) M. Coll, O. Pàmies and M. Diéguez, *Org. Lett.*, 2014, **16**, 1892; (*h*) B.-S. Zeng, X.-Y. Yu, P. W. Siu and K. A. Scheidt, *Chem. Sci.*, 2014, **5**, 2277.

5 (*a*) S. F. Kirsch and L. E. Overman, *J. Am. Chem. Soc.*, 2005, **127**, 2866; (*b*) J. S. Cannon, S. F. Kirsch and L. E. Overman, *J. Am. Chem. Soc.*, 2010, **132**, 15185; (*c*) J.-P. Qu, L. Roßberg and G. Helmchen, *J. Am. Chem. Soc.*, 2014, **136**, 1272.

6 M. Gartner, S. Mader, K. Seehafer and G. Helmchen, *J. Am. Chem. Soc.*, 2011, **133**, 2072.

7 (*a*) H. Miyabe, A. Matsumura, K. Moriyama and Y. Takemoto, *Org. Lett.*, 2004, **6**, 4631; (*b*) H. Miyabe, A. Matsumura, K. Yoshida and Y. Takemoto, *Tetrahedron*, 2009, **65**, 4464; (*c*) Z.-P. Cao, Z.-Q. Liu, Y.-L. Liu and H.-F. Du, *J. Org. Chem.*, 2011, **76**, 6401.

8 I. Lyothier, C. Defieber and E. M. Carreira, *Angew. Chem. Int. Ed.*, 2006, **45**, 6204.

9 N. Kanbayashi and K. Onitsuka, *Angew. Chem. Int. Ed.*, 2011, **50**, 5197.

10 For selected reviews on *S*-chiral sulfoxide ligands, see: (*a*) M. Mellah, A. Voituriez and E. Schulz, *Chem. Rev.*, 2007, **107**, 5133; (*b*) T. Toru and C. Bolm, *Organosulfur Chemistry in Asymmetric Synthesis*, Wiley-VCH: Weinheim, 2008; (*c*) H. Pellissier, *Chiral Sulfur Ligands: Asymmetric Catalysis*, Royal Society of Chemistry: Cambridge, U.K., 2009.

11 (*a*) H.-G. Cheng, L.-Q. Lu, T. Wang, J.-R. Chen and W.-J. Xiao, *Chem. Commun.*, 2012, **48**, 5596; (*b*) H.-G. Cheng, B. Feng, L.-Y. Chen, W. Guo, X.-Y. Yu, L.-Q. Lu, J.-R. Chen and W.-J. Xiao, *Chem. Commun.*, 2014, **50**, 2873.

12 K. Ouyang and Z.-F. Xi, *Acta Chim. Sin.*, 2013, **71**, 13.

13 See ESI†for more detailed optimization studies.

14 (*a*) S. H. Hong, D. P. Sanders, C. W. Lee and R. H. Grubbs, *J. Am. Chem. Soc.*, 2005, **127**, 17160; (*b*) Q. Yang, W.-J. Xiao and Z.-K. Yu, *Org. Lett.*, 2005, **7**, 871; (*c*) M. Gatti, E. Drinkel, L.-L. Wu, I. Pusterla, F. Gaggia and R. Dorta, *J. Am. Chem. Soc.*, 2010, **132**, 15179.

15 D. A. Evans, K. R. Campos, J. S. Tedrow, F. E. Michael and M. R. Gagne, *J. Am. Chem. Soc.* 2000, **122**, 7905.