Iridium-Catalyzed Intermolecular Allylic Etherification with Aliphatic Alkoxides: Asymmetric Synthesis of Dihydropyrans and Dihydrofurans**

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Elimination and racemization limit the synthesis of sterically hindered ethers,[1] such as α-chiral ethers, by the Willamson synthesis. Enantioselective transition-metal-catalyzed allylic substitution[2–6] could be used to prepare these materials from achiral or racemic allylic electrophiles, but intermolecular enantioselective reactions of allylic acetates or carbonates with alkoxides are limited. Enantioselective reactions of phenoxides are well documented,[7–9] but no metal catalyzes intermolecular enantioselective allylations of alkoxides with broad scope.[10–13]

Lee and Kim[14] as well as Evans and Leahy[15] demonstrated that zinc and copper alkoxides were more reactive for allylic substitution with achiral palladium and rhodium catalysts than alkali metal alkoxides. The palladium-catalyzed reactions generated achiral ethers, but the rhodium-catalyzed reactions formed branched chiral ethers. Reactions of primary alkoxides with optically active allylic acetates occurred with predominant retention of configuration, but reactions of secondary and tertiary alkoxides were conducted with racemic allylic electrophiles. Because the products from reactions of primary alkoxides can be formed by alkylation of an optically active alcohol, but products from reactions of secondary alkoxides cannot, a catalyst that forms optically active products from hindered alkoxides and allylic carbonates is synthetically valuable. We report herein enantioselective reactions of primary, secondary, and tertiary alkoxides with achiral allylic carbonates to form branched chiral allylic ethers in high yields and with high stereoselectivity in the presence of an iridium catalyst containing a phosphoramidite ligand (Scheme 1).[16–22]

To optimize the conditions for the allylation of aliphatic alkoxides with iridium–phosphoramidite catalysts, we studied the reactions of cinnamyl carbonate with benzyloxides (Table 1). Careful selection of carbonate, alkoxide counterion, and nitrogen substituents in the ligand was essential for high yields. Cinnamyl carbonates with small alkyl groups underwent transesterification in competition with etherification, but *tert*-butyl cinnamyl carbonate (**1a**) provided the

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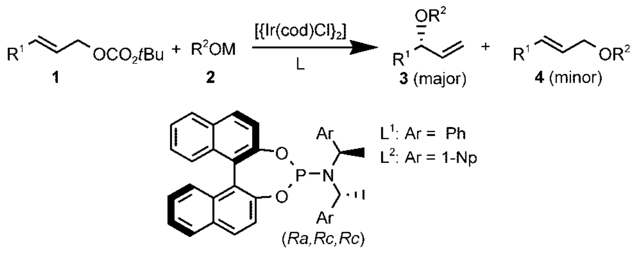


Scheme 1. The synthesis of chiral allylic ethers. The ratio L/Ir was 1:1. cod = cycloocta-1,5-diene, 1-Np = 1-naphthyl.

Table 1: Effect of ligands and nucleophiles on the regio- and enantioselective allylic etherification with aliphatic alkoxides (Scheme 1).[a]

Alkoxide **2**	L (mol %)	Yield [%]	**3**/**4**	*ee* [%]
$Zn(BnO)_2$ (**2a**)	L^1 (4)	45	75:25	93
LiOBn + CuCl (**2b**)	L^1 (4)	56	92:8	70
LiOBn + CuBr (**2c**)	L^1 (4)	65	96:4	73
LiOBn + CuI (**2d**)	L^1 (4)	68	95:5	93
$Zn(BnO)_2$ (**2a**)	L^2 (2)	72	90:10	94
LiOBn + CuI (**2d**)	L^2 (2)	92	99:1	94

[a] In all cases *tert*-butyl cinnamyl carbonate (**1a**, R^1 = Ph) was used.

desired product in high yields. Alkali metal alkoxides did not form the ether, but zinc[14] and copper[15] alkoxides did; reactions in the presence of copper iodide furnished the products in the highest yields.[23] Reactions conducted with an iridium catalyst generated from [{Ir(cod)Cl}$_2$] and phosphoramide L^1 found the branched ethers in low yields, but reactions conducted with the catalyst bearing L^2,[24,25] which contains a bis(naphthethylamino) group instead of the bis(phenethylamino) group (Scheme 1), formed this ether in high yields. With this catalyst and the above conditions, LiOBn (Bn = benzyl) and CuI reacted with *tert*-butyl cinnamyl carbonate to form the allylic ether in 92 % yield with a branched-to-linear regioselectivity of 99:1 and 94 % *ee*.[26]

The scope of the allylation of copper alkoxides in the presence of [{Ir(cod)Cl}$_2$] and L^2 is summarized in Table 2. Allylic ethers were formed in high yield and enantioselectivity from reactions of primary alkoxides. For example, methyl-substituted allylic carbonate **1b** reacted with alkoxide **2d** to afford the branched ether, with a branched-to-linear (B/L) ratio of 95/5, in 80 % yield and 97 % *ee* (entry 1).

More important, secondary alkoxides reacted with a variety of allylic carbonates in the presence of 4 mol % iridium to form allylic ethers with excellent regio- and enantioselectivities. Reaction yields varied from moderate to excellent (entries 2–8). Copper alkoxides derived from simple secondary alcohols (**2e, 2f**) reacted with cinnamyl carbonate (**1a**) to give the branched ethers in high yields, as well as high regio- and enantioselectivities (entries 2, 3). Reactions of secondary alkoxides containing an accompanying tert-butoxycarbonyl (Boc) group formed the allylic ether in lower yield, but the regio- and enantioselectivities remained high (entry 4). The etherification with secondary alkoxides encompassed both aromatic and aliphatic carbonates. The reactions between alkyl-substituted allylic carbonates **1b**, **1c**, and alkoxide **2g**, and the reactions between aryl-substituted allylic carbonates **1d**, **1e**, and alkoxide **2f** all proceeded with excellent regio- and enantioselectivities.

Reactions with tertiary alkoxides also formed the allylic ether products in good yields. However, the reactions were slower and the enantioselectivities were lower than for reactions of secondary alkoxides (entry 9). Although the reason for the lower enantioselectivity is not clear at this time, slow attack of a tertiary alkoxide may allow epimerization of the allyl intermediate and erosion of stereoselectivity established during the addition of the allylic carbonate.

Optically active ethers with two chiral centers adjacent to the central oxygen atom are important structural motifs in a number of biologically important natural products.[27] A metal-catalyzed diastereoselective addition of chiral, non-racemic secondary alcohols to allylic carbonates could provide a versatile route to these compounds. An achiral catalyst would be unlikely to generate the product diastereoselectively because of the distance between the newly forming and existing stereocenters. However, a catalyst for enantioselective allylic etherification of allylic carbonates could provide diastereocontrol in the formation of chiral ethers with two stereocenters.

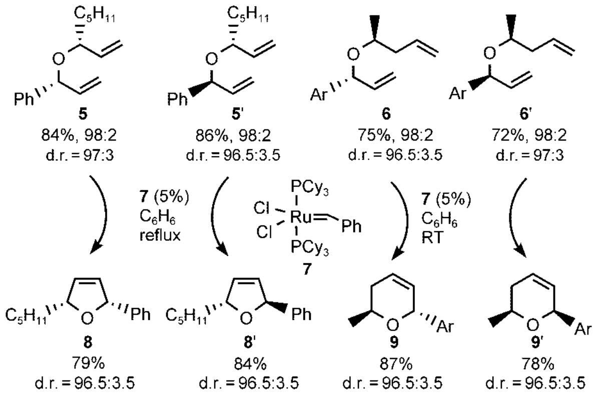
Table 2: Enantioselective allylic etherification of allylic carbonates with aliphatic copper alkoxides catalyzed by the complex formed from [{Ir(cod)Cl}$_2$] and L^2 (Scheme 1).[a]

Entry	R^1 (**1**)	R^2 (**2**)	**3**/**4**[b]	Yield [%][c]	*ee* [%][d]
1[e]	Me (**1b**)	Bn (**2d**)	95:5	80	97
2	Ph (**1a**)	*i*Pr$_2$CH (**2e**)	99:1	86	96
3	**1a**	1-cyclohexyl (**2f**)	97:3	79	94
4	**1a**	*N*-Boc-4-piperidinyl (**2g**)	98:2	70[f]	95
5	**1b**	**2g**	97:3	56[f]	94
6	*n*Pr (**1c**)	**2g**	92:8	66[f]	93
7[g]	*p*-$NO_2C_6H_4$ (**1d**)	**2f**	94:6	59	86
8[g]	*p*-$MeOC_6H_4$ (**1e**)	**2f**	99:1	86	95
9[h]	**1a**	*t*Bu (**2h**)	96:4	80	63
10	**1a**	(*S*)-1-(2-Np)-1-ethyl (**2i**)	99:1	90	95 de
11[i]	**1a**	**2i**	99:1	91[j]	93 de
12	*E*-$CH_3CH{=}CH$ (**1f**)	**2i**	98:2	90	96 de
13[i]	**1f**	**2i**	98:2	88[j]	96 de

[a] All reactions were conducted with 0.5 mmol of **1** and 1.0 mmol of **2** (prepared by treating LiOR^2 with 1.05 equiv of CuI) in THF (2.0 mL) in the presence of 0.010 mmol of [{Ir(cod)Cl}$_2$] and 0.020 mmol of (R_a,R_c,R_c)-L^2 (L:Ir = 1) for 12–16 h unless specified otherwise. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [c] Average of two yields of isolated **3** and **4** unless specified otherwise. [d] Determined by chiral HPLC. [e] The reaction was conducted with 0.005 mmol of [{Ir(cod)Cl}$_2$] and 0.01 mmol of (R_a,R_c,R_c)-L^2. [f] Average of two yields of isolated **3**. [g] The reactions were conducted with 3.0 mL THF. [h] The reaction time was 48 h. [i] The ligand (S_a,S_c,S_c)-L^2 was used. [j] The major product is the opposite diastereomer of that from the reaction conducted with (R_a,R_c,R_c)-L^2.

Indeed, reactions of the alkoxide derived from (*S*)-1-(2-naphthyl)ethanol (**2i**) with allylic carbonates (**1a, 1f**) catalyzed by iridium complexes containing opposite enantiomers of ligand L^2 formed the opposite diastereomers of the allylic ether with excellent yields, regio- and diastereoselectivities (entries 10–13). The reaction was not constrained by a match and mismatch of the substrate and catalyst chirality.

The control of enantio- and diastereoselectivity is applicable to the synthesis of *cis*- and *trans*-2,5-disubstituted dihydrofurans and *cis*- and *trans*-2,6-disubstituted dihydropyrans[28,29] with control of absolute and relative stereochemistry with readily available, enantioenriched allylic[30,31] and homoallylic alcohols[32,33] (Scheme 2). For example, **1a** and **1e** reacted with alkoxides derived from (*R*)-1-octen-3-ol and (*S*)-4-penten-2-ol, respectively, in the presence of catalysts derived from the two enantiomers of L^2 to form the branched allylic ethers **5, 5′** and **6, 6′** with excellent yields and regio- and diastereoselectivities. Ring-closing metathesis[34] with the Grubbs catalyst **7**[35] proceeded smoothly to give the corresponding cyclic ethers **8, 8′** and **9, 9′** in high yields and with retention of configuration.[36]



Scheme 2. Synthesis of disubstituted dihydrofurans and dihydropyrans. Ar = *p*-$MeOC_6H_4$, Cy = cyclohexyl.

In summary, we have developed the first general and highly selective allylic etherification with both primary and secondary aliphatic alkoxides. The ability of the catalyst to control the new stereocenter generated from the reaction of chiral secondary alkoxides makes possible highly enantioselective and diastereoselective routes to ethers and oxygen heterocycles that have been challenging to prepare in uncatalyzed reactions.

Experimental Section

Representative procedure. In a drybox, lithium alkoxide (1.00 mmol) and CuI (200 mg, 1.05 mmol) were mixed in a screw-capped vial. THF (1.0 mL) was added, and the suspension was stirred for 30 min. To this suspension was added a solution of [{Ir(cod)Cl}$_2$] (3.4 mg, 0.0051 mmol for primary alkoxides; 6.7 mg, 0.010 mmol for secondary and tertiary alkoxides) and (*Ra,Rc,Rc*)-L^2 (6.4 mg, 0.010 mmol for primary alkoxides; 12.8 mg, 0.020 mmol for secondary and tertiary alkoxides) in THF (0.5 mL for primary alkoxides; 1.0 mL for secondary and tertiary alkoxides). A magnetic stir bar was added, and the vial was sealed with a cap containing a PTFE septum and removed from the drybox. The vial was placed in an ice-water bath, and *tert*-butyl carbonate (0.50 mmol) was added to the reaction mixture by syringe. The reaction mixture was slowly warmed to room temperature over 4 h. After the reaction was complete (determined by GC and TLC) the crude mixture was passed through a pad of silica gel (EtOAc/hexanes 10:90), and the resulting solutions were concentrated. The ratio of regioisomers was determined by ^1H NMR spectroscopy of the crude sample. The mixture was then purified by flash column chromatography on silica gel to give the desired product.

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[1] H. Feuer, J. Hooz in *The Chemistry of Ether Linkage* (Ed.: S. Patai), Interscience, London, UK, **1967**, p. 445.
[2] B. M. Trost, C. Lee in *Catalytic Asymmetric Synthesis 2nd Edition* (Ed.: I. Ojima), Wiley-VCH, New York, **2000**, Ch. 8.
[3] B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921.
[4] J. Tusji, *Palladium Reagents and Catalysis*, Wiley, New York, **1996**.
[5] L. Acemoglu, J. M. J. Williams in *Handbook of Organopalladium Chemistry for Organic Synthesis*, *Vol. 2* (Ed.: E.-I. Negishi), Wiley, New York, **2002**, p. 1945.
[6] A. Pfaltz, M. Lautens in *Comprehensive Asymmetric Catalysis I-III*, *Vol. 2*, Springer, New York, **1999**, p. 833.
[7] A. Iourtchenko, D. Sinou, *J. Mol. Catal. A* **1997**, *122*, 91.
[8] B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **1998**, *120*, 815.
[9] C. Fisher, C. Defieber, T. Suzuki, E. M. Carreira, *J. Am. Chem. Soc.* **2004**, *126*, 1628.
[10] C. Thorey, J. Wilken, F. Henin, J. Martens, T. Mehler, J. Muzart, *Tetrahedron Lett.* **1995**, *36*, 5527.
[11] B. M. Trost, E. J. McEachern, F. D. Toste, *J. Am. Chem. Soc.* **1998**, *120*, 12702.
[12] L. Jiang, S. D. Burke, *Org. Lett.* **2002**, *4*, 3411.
[13] E. Keinan, M. Sahai, Z. Poth, A. Nudelman, J. Herzig, *J. Org. Chem.* **1985**, *50*, 3558.
[14] H. Kim, C. Lee, *Org. Lett.* **2002**, *4*, 4369.
[15] P. A. Evans, D. K. Leahy, *J. Am. Chem. Soc.* **2002**, *124*, 7882.
[16] T. Ohmura, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 15164.
[17] F. Lopez, T. Ohmura, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 3426.
[18] C. A. Kiener, C. Shu, C. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 14272.
[19] J. P. Janssen, G. Helmchen, *Tetrahedron Lett.* **1997**, *38*, 8025.
[20] B. Bartels, G. Helmchen, *Chem. Commun.* **1999**, 741.
[21] B. Bartels, C. Garcia-Yebra, G. Helmchen, *Eur. J. Org. Chem.* **2003**, 1097.
[22] G. Lipowsky, G. Helmchen, *Chem. Commun.* **2004**, 116.
[23] P. A. Evans, D. K. Leahy, L. M. Slieker, *Tetrahedron: Asymmetry* **2003**, *14*, 3613.
[24] L. A. Arnold, R. Imbos, A. Mandoli, A. H. M. De Vries, R. Naasz, B. L. Feringa, *Tetrahedron* **2000**, *56*, 2865.
[25] A. Alexakis, S. Rosset, J. Allamand, S. March, F. Guillen, C. Benhaim, *Synlett* **2001**, 1375.
[26] The absolute configuration of the product was established by comparison with the *R* configured ether prepared from commercial (*R*)-1-phenylpropanol.
[27] J. Buckingham, *Dictionary of Natural Products*, University Press, Cambridge, MA, **1994**.
[28] W. Friedrichsen in *Comprehensive Heterocyclic Chemistry*, *Vol. 2* (Ed.: C. W. Bird), Elsevier, Oxford, UK, **1996**, p. 386.

[29] J. D. Hepworth, C. D. Gabbutt, B. M. Heron in *Comprehensive Heterocyclic Chemistry II*, *Vol. 5* (Ed.: A. McKillop), Elsevier, Oxford, **1996**, p. 382.

[30] Y. Gao, J. M. Klunder, R. M. Hanson, H. Masamune, S. Y. Ko, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765.

[31] K. Burgess, L. D. Jennings, *J. Am. Chem. Soc.* **1990**, *112*, 7434.

[32] W. R. Roush, K. Ando, D. B. Powers, A. D. Palkowitz, R. L. Halterman, *J. Am. Chem. Soc.* **1990**, *112*, 6339.

[33] W. R. Roush, A. D. Palkowitz, K. Ando, *J. Am. Chem. Soc.* **1990**, *112*, 6348.

[34] A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012.

[35] P. Schwab, M. B. France, J. W. Ziller, R. H. Grubbs, *Angew. Chem.* **1995**, *107*, 2179; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039.

[36] M. T. Crimmins, A. L. Choy, *J. Org. Chem.* **1997**, *62*, 7548.