Regio- and Enantioselective Iridium-Catalyzed Intermolecular Allylic Etherification of Achiral Allylic Carbonates with Phenoxides

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Transition metal-catalyzed allylic substitution is a powerful tool for the controlled formation of carbon–carbon and carbon–heteroatom bonds.[1] Most enantioselective versions of these reactions with carbon nucleophiles have been reported with Pd,[2] but enantioselective allylic alkylation has also been reported with Mo,[3,4] W,[5] and, most recently, Ir catalysts.[6] Despite the importance of optically active allylic ethers and amines, fewer enantioselective allylic aminations and etherifications by reactions of heteroatom nucleophiles have been described. We recently reported a general regio- and enantioselective amination of allylic carbonates catalyzed by an iridium–phosphoramidite complex.[7,8] We now describe an enantioselective and regioselective iridium-catalyzed reaction of terminal allylic electrophiles with phenoxides to give optically active, branched allylic ethers.

Aryl ethers are common subunits of biologically active molecules. Apart from their use as precursors for the Claisen rearrangement,[9,10] aryl allyl ethers have not been used extensively as building blocks for natural product synthesis because methods for their enantioselective construction are limited. Two reports of stereospecific allylic etherification of branched carbonates catalyzed by Ru[11] and Rh[12,13] were reported recently, and a few enantioselective palladium-catalyzed examples have been reported.[14–16] Elegant applications of the palladium-catalyzed chemistry for the synthesis of natural products demonstrate the potential of asymmetric allylic etherification in organic synthesis.[17–20] Thus, new, more general, enantioselective methods for the construction of allylic ethers would be synthetically valuable.

Under the appropriate conditions, iridium complexes of phosphoramidite (R_a,R_c,R_c)-**3**[21] (Scheme 1) catalyzed allylic etherification of linear achiral electrophiles to form the branched product **4** with high enantioselectivity. Choice of base and solvent and matching of the phenoxide nucleophile with the appropriate allylic carbonate derivative were crucial to observe high yields, regioselectivities, and enantioselectvities for formation of **4**.

The base used to generate the phenoxide influenced selectivities. To avoid transesterification, we tested tertiary amines as bases for the reactions of the model substrate (*E*)-cinnamyl methyl carbonate (**1a**) (Table 1, entries 1–3). The highest regio- and enantioselectivities were obtained with Et_3N as base at 50 °C (entry 1). Reactions conducted with a more hindered amine (entry 2) occurred more slowly and less enantioselectively. Reactions conducted with a less hindered amine (entry 3) occurred faster, but with lower yields, regioselectivities, and enantioselectivities.

Alkali metal phenoxides as nucleophiles proved to be superior to the combination of phenol and amine base. Sodium phenoxide furnished the corresponding allylation product with high regio- and enantioselectivity (entries 4–6). Reaction of sodium phenoxide (**2a**) with methyl carbonate **1a** formed the alkylation product at room temperature in a modest 40% yield because of competing transesterification (entry 4), but reactions with the more hindered and less reactive (*E*)-cinnamyl ethyl carbonate (**1b**) occurred without
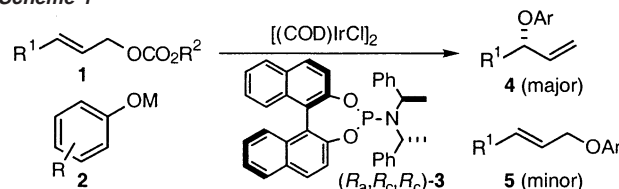
Scheme 1

Table 1. Effect of Nucleophile on the Ir-Catalyzed Enantioselective Allylic Etherification of (*E*)-Cinnamyl Carbonates $(R^1 = Ph)^a$

entry	R^2	1	M–OPh	temp (°C)	time (h)	4/5[b]	yield (%)[c]	% ee[d]
1	Me	**1a**	PhOH/Et₃N	50	15	93/7	76	84
2	Me	**1a**	PhOH/*i*-Pr₂NEt	50	45	89/11	66	78
3	Me	**1a**	PhOH/Me₂NEt	50	11	53/47	31	45
4	Me	**1a**	NaOPh **2a**[e]	23	22	97/3	40	92
5	Et	**1b**	NaOPh **2a**[e]	23	35	99/1	76	94
6	Et	**1b**	NaOPh **2a**[e]	50	17	95/5	78	92
7	Me	**1a**	LiOPh **2b**[f]	50	20	96/4	86[g]	96
8	Me	**1a**	LiOPh/CuCl[f]	50	12	96/4	73	37

^{a} All reactions were carried out with 1 mmol of **1** and 2.0 mmol of MOPh in THF (0.5 mL) in the presence of 0.01 mmol of [(COD)IrCl]₂ and 0.02 mmol of (R_a,R_c,R_c)-**3** (L/Ir = 1) unless otherwise noted. ^{b} Ratios of regioisomers were determined by ^{1}H NMR of crude reaction mixtures. ^{c} Isolated yields of the combined regioisomers. ^{d} Enantiomeric excess was determined by chiral HPLC. ^{e} Reactions were conducted in 1 mL of THF. ^{f} Reactions were conducted in 2 mL of THF. ^{g} Isolated yield of pure **4**.

significant competing transesterification. This combination of phenoxide and carbonate gave the branched ether in good yields with excellent regio- and enantioselectivities after 35 h at room temperature or 17 h at 50 °C (entries 5 and 6).

However, the highest yield and enantioselectivity from reaction of an electron–neutral phenol derivative with carbonate **1a** occurred with the less basic lithium phenoxide (**2b**). Reactions of this substrate combination occurred smoothly at 50 °C to provide after 20 h 86% yield of ether **4** with 96:4 regioselectivity and 96% enantioselectivity (entry 7). Reaction of the allylic carbonate with a phenoxide generated by transmetalation of the LiOPh with CuCl[13] to soften the alkoxide occurred with much lower enantioselectivities.

Other (*E*)-cinnamyl alcohol derivatives reacted in lower yields or with lower enantioselectivities. Reactions of LiOPh with the corresponding *tert*-butyl carbonate were slow, but gave the branched ether in 97% ee. (*E*)-Cinnamyl acetate did not react, even at 50 °C. (*E*)-Cinnamyl diethyl phosphate underwent complete reaction with LiOPh after only 10 h at 50 °C to form the allylic ethers **4** and **5** in a 91:9 ratio and in an 83% combined yield. However, the ee was only 60%.

Similar to the previously reported Ir-catalyzed allylic amination,[7] regioselective formation of **4** required careful selection of the reaction conditions. In THF, the iridium phosphoramidite complex catalyzed allylic transposition of branched **4** to form linear **5**. Thus, long reaction times led to lower selectivities. For example, the

Table 2. Enantioselective Allylic Etherification with Aryloxides Catalyzed by Ir-(R_a,R_c,R_c)-**3** (Scheme 1)[a]

entry	R^1, R^2 (**1**)	metal–aryloxide (**2**)	time (h)	**4/5**[b]	yield (%)[c]	ee (%)
1	Ph, Me (**1a**)	2-MeC$_6$H$_4$OLi **2c**	14	96/4	87	95 (R)[d]
2	Ph, Me (**1a**)	4-MeC$_6$H$_4$OLi **2d**	22	98/2	91	95
3	Ph, Me (**1a**)	4-MeOC$_6$H$_4$OLi **2e**	8	98/2	88	97
4	Ph, Me (**1a**)	3-MeOC$_6$H$_4$OLi **2f**	17	95/5	84[e]	96
5	Ph, Me (**1a**)	3-PhC$_6$H$_4$OLi **2g**	13	96/4	76	95
6	Ph, Me (**1a**)	2-PhC$_6$H$_4$OLi **2h**	10	96/4	65	93
7	Ph, Me (**1a**)	3-Me$_2$NC$_6$H$_4$OLi **2i**	14	99/1	56	97
8	Ph, Me (**1a**)	3,4-(OCH$_2$O)C$_6$H$_3$OLi **2j**	18	99/1	65	94
9	Ph, Me (**1a**)	2,4-Me$_2$C$_6$H$_3$OLi **2k**	11	98/2	85[e]	95
10	Ph, Me (**1a**)	2,4,6-Me$_3$C$_6$H$_2$OLi **2l**	22	93/7	82[e]	93
11	Ph, Et (**1b**)	4-BrC$_6$H$_4$ONa **2m**[f]	8	96/4	91	90
12	Ph, Et (**1b**)	4-ClC$_6$H$_4$ONa **2n**[f]	20	93/7	86	92
13	Ph, Et (**1b**)	4-Br,3-MeC$_6$H$_3$ONa **2o**[f]	8	95/5	89	87
14	Ph, Et (**1b**)	4-CF$_3$C$_6$H$_4$ONa **2p**[f]	10	90/10	92	80 (R)[d]
15	2-MeOC$_6$H$_4$, Me (**1c**)	PhOLi **2b**	41	98/2	79	75
16	4-MeOC$_6$H$_4$, Me (**1d**)	PhOLi **2b**[g]	13	97/3	70	86
17	n-Pr, Me (**1e**)	PhOLi **2b**	14	92/8	93	92
18	n-Pr, Me (**1e**)	2-MeC$_6$H$_4$OLi **2c**	20	87/13	86	90
19	n-Pr, Me (**1e**)	4-MeOC$_6$H$_4$OLi **2e**	14	90/10	73	85

[a] All reactions were carried out with 1 mmol of **1a** and 2.0 mmol of M−OAr (isolated from the reaction of aryl alcohols and n-BuLi or NaH) in the presence of 0.01 mmol of [(COD)IrCl]$_2$ and 0.02 mmol of (R_a,R_c,R_c)-**3** unless otherwise noted. [b] Ratios of regioisomers were determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [c] Isolated yields of **4** and **5** unless otherwise noted. [d] Absolute configuration of the products was established by correlation with known compounds.[11] [e] Yield of isolated **4**. [f] The reaction was conducted with 1 M **1b**. [g] Three equivalents of LiOPh.

reaction of LiOPh (2 equiv) with **1a** in THF gave complete conversion and excellent regio- and enantioselectivity after 20 h at 50 °C, but lower ratios of **4** to **5** and lower ee's were observed at times significantly longer than 20 h.[22]

Solvent also influenced the reactivity, regioselectivity, and enantioselectivity. Reactions of 2.0 equiv of LiOPh with **1a** at 50 °C in various solvents followed the order DME (10 h) > THF (20 h) > 1,4-dioxane (36 h) > Et$_2$O (48 h). Reactions in each solvent, except DME, occurred with high regioselectivities and ee's from 92 to 96%. Reactions in THF displayed the most suitable balance of rate, regio-, and enantioselectivity.

Reactions were also conducted with lithium phenoxide generated in situ. LiOPh generated from n-BuLi (hexanes) or Cy$_2$NLi provided **4** with equally high yields and enantioselectivities. However, LiOPh generated from LDA reacted with lower regioselectivities, and LiOPh generated from LiN(SiMe$_3$)$_2$ did not completely convert the allylic carbonate after 72 h.

The scope of the allylic etherification catalyzed by [(COD)IrCl]$_2$ and (R_a,R_c,R_c)-**3** is summarized in Table 2. Reactions of **1a** with lithium aryloxides containing a single substituent at the ortho, meta, or para position (entries 1−7) gave the corresponding branched allylic ethers **4** with high selectivity over the achiral linear ether **5** and with enantioselectivities ranging from 93 to 97%. Methyl, phenyl, methoxy, or dialkylamino substituents were tolerated on the aryloxide. Lithium sesamolate (**2j**), lithium 2,4-dimethyl-phenoxide (**2k**), and the more sterically hindered 2,4,6-trimethyl-phenoxide (**2l**) (entries 8−10) also reacted to give the chiral phenyl ethers in good yields and with enantioselectivities between 93 and 95%.

High yields from reactions of aryloxides with electron-withdrawing groups were obtained from reactions of the sodium aryloxides

and ethyl carbonate **1b** (entries 11−14). Enantioselectivities ranged from 80 to 92%. Aryloxides containing stronger electron-withdrawing groups, such as nitro and cyano, in the para position failed to react under these conditions.

The scope of the carbonate encompassed both aromatic and aliphatic derivatives. Ortho- and para-substituted methoxycinnamyl carbonates (**1c** and **1d**) reacted in high yield, with high regioselectivities, and with enantioselectivities between 75 and 86% (entries 15 and 16). The combination of [(COD)IrCl]$_2$ and (R_a,R_c,R_c)-**3** also catalyzed etherification of the straight-chain aliphatic (E)-2-hexenyl carbonate (**1e**) to give predominantly the branched ether (entries 17−19). Carbonate **1e** reacted with unsubstituted, ortho-substituted, or electron-rich phenols to give the branched ether with 85−92% ee. Reactions of branched allylic carbonates have occurred, thus far, with low enantioselectivities after full conversion.

In summary, we developed a new catalytic process to produce branched allylic ethers in high yields with excellent enantioselectivity from achiral allylic carbonates. Mechanistic understanding and further evaluation of substrate scope will be the subject of further studies.

Supporting Information Available: Experimental procedures and spectroscopic data of the reaction products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) **4/5** = 90/10 after 36 h, 80/20 after 76 h, and 70/30 after 240 h. ee = 90% after 36 h, 86% after 76 h, and 70% after 240 h.

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