

Allylic Etherification via Ir(I)/Zn(II)
Bimetallic Catalysis

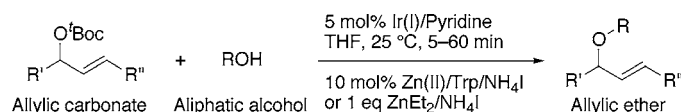
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Received April 15, 2005

ABSTRACT



An efficient allylic etherification of aliphatic alcohols with allylic carbonates has been achieved by an iridium catalysis using stoichiometric zinc alkoxides or a two-component bimetallic catalytic system where the Ir(I) catalyst acts on allylic carbonates to generate electrophiles while aliphatic alcohols are separately activated by Zn(II) coordination to function as nucleophiles. This reaction occurs with complete regioselectivity and tolerates a wide range of functional groups.

Development of catalysts that mobilize otherwise inert substrates to engage in chemical reactions continues to be a major theme in organic chemistry. While the majority of catalytic reactions are typically mediated by a single catalyst, opportunities for further development arise from employing a two-component catalyst system in which the nucleophilic and electrophilic components of the reactant are activated independently by respective catalysts.¹ Such approaches, though uncommon, have demonstrated high potential for the discovery of new reactions, particularly in the processes involving a η^3 -allylmetal species.²

Recently, the scope of the transition metal-catalyzed allylic alkylation has been extended to include the allylic etherification of aliphatic alcohols by using copper(I)³ and zinc(II)⁴ alkoxides as nucleophiles. These discoveries have stimulated the emergence of powerful strategies for the synthesis of ether linkages conjoining chiral carbons, as

exemplified by the stereodivergent approach to oxacycle⁵ and glycosidic bond formations.^{4b} While investigating the palladium-catalyzed allylic etherification,⁴ we wondered whether the zinc effect might also be operative in the context of other transition metal catalysts. In particular, it was of interest to examine these catalyst systems which could give different stereo- and regiochemical outcomes vis-à-vis the Pd(0)/Zn(II) system, thus broadening the utility of the zinc alkoxide protocol.⁶ Moreover, the facile ligand exchange process of zinc(II) complexes was envisaged to be exploited for the catalytic activation of the alcohol,⁷ whereby the etherification could be achieved through catalysis mediated by two separate transition metal complexes. This approach would provide a unique opportunity to modulate the reactivity of each reactant and/or to achieve asymmetric induction by independent tuning of each metal coordination sphere. We report here an iridium-catalyzed allylic etherification of aliphatic alcohols that proceeds with high regioselectivity in the presence of a stoichiometric or catalytic zinc alkoxide.

To assess the feasibility of the proposed bimetallic catalytic process, the etherification was first examined with allylic carbonate **1a** using a stoichiometric zinc benzyloxide and a

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Table 1. Iridium-Catalyzed Allylic Etherification of Alcohol **2a** with Carbonate **1a** Using a Stoichiometric Zinc Reagent^a

entry	catalyst ^b	ligand ^c	salt	time	yield ^d	3aa:4aa ^e
1	[Ir(COD)Cl] ₂	P(OPh) ₃	NH ₄ I	48 h	39%	2:3
2	[Ir(COD)Cl] ₂	P(OAr) ₃	NH ₄ I	2 h	90%	22:1
3	[Ir(COD)Cl] ₂	pybox	NH ₄ I	0.25 h	74%	>50:1
4	[Ir(COD)Cl] ₂	pyridine	NH ₄ I	0.25 h	96%	>50:1
5	[Ir(COE) ₂ Cl] ₂		NH ₄ I	48 h	0%	
6	Ir(CO)(dppe)Cl		NH ₄ I	48 h	0%	
7	Ir(CO)(PPh ₃) ₂ Cl		NH ₄ I	48 h	4%	5:1
8	Ir(PCy ₃)(COD)(Py)PF ₆		NH ₄ I	48 h	46%	>50:1
9	[Ir(COD)Cl] ₂	pyridine		48 h	0%	
10	[Ir(COD)Cl] ₂	pyridine	NH ₄ OAc	48 h	0%	
11	[Ir(COD)Cl] ₂	pyridine	NH ₄ BF ₄	48 h	50%	2:1
12	[Ir(COD)Cl] ₂	pyridine	NH ₄ F	12 h	80%	1:1
13	[Ir(COD)Cl] ₂	pyridine	NH ₄ Cl	48 h	14%	1:2
14	[Ir(COD)Cl] ₂	pyridine	NH ₄ Br	48 h	11%	15:1
15	[Ir(COD)Cl] ₂	pyridine	NMe ₄ I	24 h	95%	1:2
16 ^f	Pd(PPh ₃) ₄			1.5 h	40%	<1:50

^a All reactions were carried out in THF (1.0 M) with 1.0 equiv of **1a** and 1.1 equiv of **2a** at 25 °C in the presence of 5 mol % [M]/ligand, 0.55 equiv of Et₂Zn, and 1.0 equiv of salt. ^b COD = 1,5-cyclooctadiene; COE = cyclooctene. ^c P(OAr)₃ = tris(2,4-di-*tert*-butylphenyl)phosphite; pybox = 2,6-bis[(4*R*)-(+)-isopropyl-2-oxazolin-2-yl]pyridine; DTBBP = di(*tert*-butyl)-2-biphenylphosphine. ^d Isolated yields. ^e Determined by ¹H NMR. ^f Ref 4.

variety of iridium catalysts (Table 1). Guided by literature precedents in which the Ir-catalyzed allylic alkylation reactions with a substrate of type **1a** generated a branched product such as **3aa** in preference to the linear isomer **4aa**, our studies were focused on the identification of catalyst systems viable with a zinc alkoxide and analysis of their regiochemical outcome.^{8,9} Initial experiments performed in THF using 2.5 mol % [Ir(COD)Cl]₂ and 5 mol % P(OPh)₃ resulted in a poor yield of allylic ethers **3aa** and **4aa** as an inseparable 1:1.5 isomeric mixture (entry 1). Notably, a considerable amount of benzaldehyde (ca. 10%) was formed presumably through a β-H elimination of an iridium benzyloxide. It was thus reasoned that the addition of more steric bulk to the ligand would minimize such a process occurring at the iridium center. Accordingly, the employment of a *tert*-butyl-substituted ligand substantially increased both the yield and the regioselectivity (entry 2). Further improvement came surprisingly from the use of nitrogen ligands.¹⁰ In the presence of pybox and pyridine, the reactions were complete in 15 min to furnish **3aa** as a single product, whereas no

reaction occurred without these ligands (entries 3 and 4). The screening of various precatalysts, however, proved to be less fruitful, as COE- and CO-bound Ir complexes performed poorly (entries 5–8). Only Crabtree's catalyst exhibited modest results, highlighting the critical role of 1,5-cyclooctadiene (COD) as a requisite bidentate ligand in this catalyst system (entry 8).¹¹ Also noteworthy were the significant salt effects, which proved to be most beneficial when NH₄I was used (entry 4 vs entries 9–15).¹² Both the ammonium and iodide components of NH₄I were required for high turnover and regioselectivity. The regiochemical outcome could be reoriented by using Pd(PPh₃)₄, which led to the exclusive formation of the linear isomer **4aa** (entry 16).^{4a}

Having established an optimized set of conditions for the Ir (catalytic)–Zn (stoichiometric) protocol, we then set out to screen ligands for the zinc center and probed the prospect of achieving bimetallic catalysis (Table 2). In control experiments performed without an additional ligand, the yield of the allylation products was roughly proportional to the amount of Et₂Zn employed. Hence, attempts were first made using common zinc(II) ion ligands derived from sp²-hybridized nitrogens (entries 1–4).¹³ These ligands indeed promoted turnover of the zinc catalyst but led to prolonged

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Table 2. Screening of Ligands for the Zn(II) Center in the Ir(I)/Zn(II)-Catalyzed Allylic Etherification^a

$ \begin{array}{c} \text{2.5 mol\% [Ir(COD)Cl]}_2 \\ \text{5 mol\% pyridine} \\ \hline \text{1a} + \text{2a} \longrightarrow \text{3aa} + \text{4aa} \\ \hline \text{10 mol\% Et}_2\text{Zn/NH}_4\text{I} \\ \text{10 mol\% Ligand} \end{array} $									
entry	ligand ^b	time	yield ^c	3aa:4aa ^d	entry	ligand ^b	time	yield ^c	3aa:4aa ^d
1	BIPY	48 h	8%	11:1	9	L-His	0.5 h	73%	>50:1
2	TRPY	48 h	36%	22:1	10	L-Trp	0.25 h	89%	>50:1
3	Tpm	48 h	59%	47:1	11 ^e	L-Trp	0.5 h	70%	>50:1
4	KTp	48 h	29%	>50:1	12	L-Asn	0.75 h	68%	>50:1
5	NME	0.5 h	65%	34:1	12	L-Tyr	0.25 h	68%	>50:1
6 ^e	NME	0.5 h	80%	>50:1	14	L-Ser	0.5 h	70%	>50:1
7	Gly	0.75 h	67%	>50:1	15	L-Cys	0.5 h	68%	>50:1
8	L-Glu	0.5 h	74%	>50:1					

^a All reactions were performed with 1.0 equiv of **1a** and 1.5 equiv of **2a** in THF (1.0 M) at 25 °C unless otherwise noted. ^b BIPY = 2,2'-bipyridine; TRPY = 2,2',6',2''-terpyridine; Tpm = tris(pyrazol-1-yl)methane; KTp = potassium hydrotris(pyrazol-1-yl)borate; NME = (1R,2S)-(-)-N-methylephedrine. ^c Isolated yields. ^d Determined by ¹H NMR. ^e Reactions were performed in the absence of pyridine.

reaction times. In contrast, marked acceleration of the reaction rate was brought about when a β -amino alcohol (NME)¹⁴ (entries 5 and 6) and various α -amino acids (entries 7–15) were employed as ligands. In these cases, all reactions proceeded rapidly with complete regioselectivity in the presence of these N,O-chelators, among which L-tryptophan displayed superior results (entries 10 and 11). An additional

finding was that pyridine was not required when the reactions were carried out with these ligands (entries 6 and 10), although the use of pyridine led to a shorter reaction time and a higher yield (entry 10 vs entry 11).

With the two iridium-catalyzed protocols viable under stoichiometric or catalytic zinc conditions, we examined the scope of the new processes. As shown in Table 3, a variety

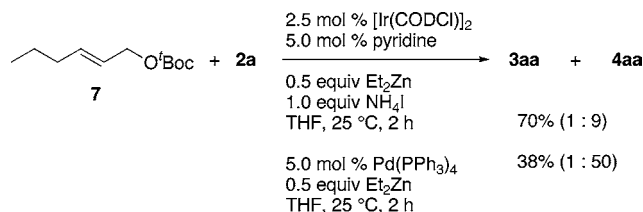
Table 3. Iridium-Catalyzed Allylic Etherification Using Stoichiometric and Catalytic Zinc Alkoxides^a

entry	carbonate	alcohol	ether (yield) ^b	entry	carbonate	alcohol	ether (yield) ^b
1			 3ab (77%, 66%)	8			 3di (34%, 73%)
2			 3ac (62%, 71%)	9			 3dj (62%, 80%)
3			 3bd (97%, 81%)	10			 3dk (58%, 73%)
4			 3ce (78%, 75%)	11			 3el (94%, 0%) ^d
5			 3cf (40%, 61%)	12			 3fl (52%, 0%) ^d
6			 3cg (30%, 46%)	13			 3gm (50%, 0%) ^d
7			 3ch (73%, 69%) ^c	14			 6 (96%, 50%) ^c

^a Method A: 1.0 equiv of **1**; 1.1 equiv of **2**; 2.5 mol % [Ir(COD)Cl]₂; 5 mol % pyridine; 0.55 equiv of Et₂Zn; 1.0 equiv of NH₄I; 25 °C; THF (1.0 M). Method B: 1.0 equiv of **1**; 1.5 equiv of **2**; 2.5 mol % [Ir(COD)Cl]₂; 5 mol % pyridine; 10 mol % Et₂Zn; 10 mol % L-Trp; 10 mol % NH₄I; 25 °C; THF (1.0 M). ^b First and second numbers refer to the isolated yields from methods A and B, respectively. ^c Diastereomeric mixture (1:1). ^d Single isomer.

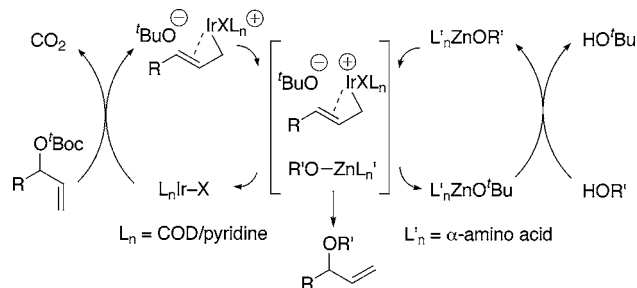
of allylic ethers could be prepared with complete regiocontrol from the reactions of structurally diverse aliphatic alcohols and allylic carbonates. Notable from these examples was the high chemoselectivity manifested through exceptional tolerance of a wide range of functional groups. Both mono- and disubstituted carbonates participated well in the etherification process under the standard conditions using stoichiometric zinc reagents (conditions A), whereas the catalytic zinc conditions (conditions B) failed to induce a reaction when applied to disubstituted allylic substrates **1e–g**. It was worthy of note, however, that the catalytic zinc conditions proved to be more effective in many cases with monosubstituted allylic substrates. Reaction rates of the stoichiometric and catalytic methods were comparable, with slightly longer reaction times for the latter (5–20 vs 15–60 min). As demonstrated by the formation of single isomers as the products, the reactions of disubstituted allylic substrates proceeded with complete retention of regio- and stereochemistry (entries 11–13). In particular, a high level of selectivity was maintained in the reaction of dimethylallyl system **1e**, in which the scrambling of regiochemistry via a symmetric irido- π -allyl intermediate would constitute loss of stereochemistry (entry 11). In contrast, a disparity between the regio- and stereochemical outcomes was noted in reactions of monosubstituted allylic systems. For example, when optically enriched (*S*)-**1b** (98% ee) was reacted with **2d** under conditions A, ether **3bd** was produced as a single regioisomer but only in 57% ee (cf. entry 3). These results indicated that with the present catalytic system, the putative “enyl” iridium intermediate undergoes slow allylic isomerization but fast enantiofacial interconversion processes relative to the intermolecular nucleophilic addition reaction with a zinc alkoxide.^{15,16} The regiospecific nature of the present Ir protocol was also manifested in the reaction of the linear substrate **7** (Scheme 1), whereas the Pd-catalyzed method proved to be regioselective (cf. entry 16, Table 1).

Scheme 1. Regiospecificity of Allylic Etherifications



The mechanism for the Ir/Zn two-component bimetallic catalytic allylic etherification is proposed in Scheme 2, in which the allylic carbonate and aliphatic alcohol are activated

Scheme 2. Proposed Mechanism for the Ir(I)/Zn(II) Bimetallic Catalytic Allylic Etherification



catalytically and independently by the respective iridium(I) and zinc(II) catalysts. Under both stoichiometric and catalytic zinc conditions, the iridium catalyst acts on the allylic carbonate to generate the requisite cationic η^3 -allyl iridium intermediate (left catalytic cycle). Critical to the bimetallic catalytic mechanism is an alkoxide exchange at the zinc center (right catalytic cycle). In light of the well-known pK_a -dependent equilibrium between a free alcohol and its corresponding zinc alkoxide,⁷ it is believed that alcohols with a higher acidity than *tert*-butyl alcohol are capable of undergoing the exchange and subsequent nucleophilic addition processes. An additional important feature that renders the dual catalytic cycles feasible is the poor reactivity of zinc *tert*-butoxide toward the iridium-bound cationic intermediate, whereby the requisite deprotonation process is effectively mediated by zinc *tert*-butoxide. While a detailed understanding awaits further studies, the pronounced effect of NH₄I may be due to the combination of the high affinity of the iodide anion for the iridium center and a subtle proton-transfer process required for the reaction.¹⁷

In summary, we have demonstrated that “softening-the-alkoxide approach” via zinc(II) coordination is viable for the regiospecific *O*-allylation of aliphatic alcohols under iridium(I) catalysis. High chemo- and regioselectivities and operational simplicity are important features of the new protocol. Our studies have also led to the development of a two-component catalyst system that achieves the allylic etherification through the separate yet cooperative action of the iridium and zinc complexes on the respective allylic carbonate and alcohol substrates. On the basis of the present findings, future investigations will be directed at the development of related catalytic reactions and their asymmetric variants, particularly by crafting the ligands independently for each metal center.

Acknowledgment. We thank Princeton University for generous support of this research. We would also like to thank Merck for the donation of compound **2m**.

Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL0508328

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