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Regio- and Enantiospecific Rhodium-Catalyzed Allylic Etherification Reactions Using Copper(I) Alkoxides: Influence of the Copper Halide Salt on Selectivity

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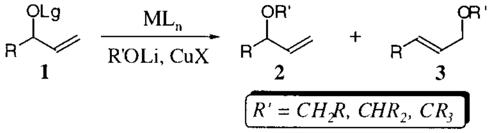
The transition metal-catalyzed allylic substitution with alcohols represents a fundamentally important cross-coupling reaction for the construction of allylic ethers.[1] Despite the enormous synthetic potential for the construction of allylic ethers, many of the current approaches utilize *intra*molecular or proximal effects to circumvent poor regioselectivity with *unsymmetrical* allylic alcohol derivatives.[2,3] Furthermore, the *inter*molecular metal-catalyzed allylic etherification has, for the most part, been limited to reactions with primary alcohols due to the challenges associated with the corresponding secondary and tertiary alcohols. This may be attributed to poor regioselectivity, and the propensity for metal alkoxides to promote elimination of the metal−allyl intermediate or hydrolysis of the leaving group in the allylic alcohol precursor. Hence, the ability to facilitate a regioselective metal-catalyzed allylic etherification, using substituted alcohols, would provide an important cross-coupling reaction for target directed synthesis.

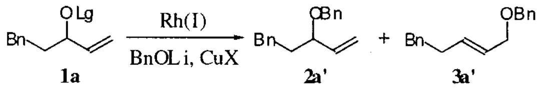


1 **2** **3** (1)

We envisioned that the rhodium-catalyzed allylic substitution would facilitate the regioselective etherification as a result of its propensity to undergo selective alkylation through a configurationally stable *distorted* π-allyl or *enyl* ($\sigma + \pi$) organorhodium intermediate.[4,5] The main problem anticipated with this approach was the necessity to employ a hard alkali metal salt of the alcohol to promote alkylation. Hence, we decided to examine the transmetalation of the alkali metal alkoxide with a copper(I) salt,[6,7] with the expectation this would soften the basic character of the metal alkoxide. Herein, we now describe the rhodium-catalyzed *inter*molecular allylic etherification of acyclic *unsymmetrical* secondary alcohol derivatives **1** using copper(I) alkoxides of primary, secondary, and tertiary alcohols to afford the *secondary allylic ethers* **2** with excellent regioselectivity (eq 1).

Preliminary studies confirmed that alkali metal alkoxides would not be suitable nucleophiles for the rhodium-catalyzed allylic etherification owing to extensive side-reactions. Table 1 summarizes the optimization of this reaction using various copper(I) salts and leaving groups. Treatment of the allylic carbonate **1a** (Lg = CO_2Me) with the trimethyl phosphite *modified* Wilkinson's catalyst, followed by the copper(I) alkoxide derived using copper cyanide, furnished the allylic ethers **2a′**/**3a′** in good yield, albeit with no selectivity (entry 1). Gratifyingly, the addition of a copper(I) halide salt led to significant improvement in the regioselectivity, in which there was a pronounced halide effect (I > Br > Cl) on the selectivity (entries 2−4).[8] Additional improvements were obtained by changing the leaving group to suppress competitive transacylation, in which the *tert*-butyloxycarbonate proved optimum (entry 6).

Table 1. Effect of Copper(I) Salts and Leaving Groups on the Regioselective Rhodium-Catalyzed Allylic Etherification



1a **2a′** **3a′**

entry	leaving group Lg[a]	CuX	2°:1° **2a′:3a′**[b]	yield (%)[c]
1	CO_2Me	CuCN	1:1	73
2	”	CuCl	44:1	58
3	”	CuBr	72:1	66
4	”	CuI	≥99:1	73
5	CO^tBu	CuI	≥99:1	42
6	$\boldsymbol{CO_2{}^tBu}$	**CuI**	≥***99:1***	***96***

[a] All reactions were carried out on a 0.5 mmol reaction scale using 10 mol % of $RhCl(PPh_3)_3$ *modified* with 40 mol % $P(OMe)_3$, 1.9 equiv of the lithium alkoxide, and 2.0 equiv of CuX. [b] Ratios of regioisomers were determined by capillary GLC on aliquots of the crude reaction mixture. [c] GLC yields.

Table 2. Scope of the Regioselective Rhodium-Catalyzed Allylic Etherification Reaction (eq 1)[a]

entry	allylic carbonate **1** (Lg = $CO_2{}^tBu$) R=	R′=		2°:1° **2**: **3**[b,c]	yield (%)[d]
1	$Ph(CH_2)_2$	$^iPr_2CH-$	**a**	≥99:1	73
2	Me	”	**b**	≥99:1	65
3	^nPr	”	**c**	≥99:1	67
4	$CH_2{=}CH(CH_2)_3$	”	**d**	≥99:1	70
5	$(CH_3)_2CH(CH_2)_2$	”	**e**	≥99:1	71
6	$BnOCH_2$	”	**f**	18:1	50
7	$CH_2{=}CH$	”	**g**	13:1	46
8	Ph	”	**h**	22:1	70
9	Npth	”	**i**	28:1	73

[a] All reactions were carried out on a 0.5 mmol reaction scale. [b] Ratios of regioisomers were determined by capillary GLC on the crude reaction mixture. [c] The primary products **3** were prepared for comparison using the copper(I) cyanide additive (Table 1, entry 1). [d] Isolated yields.

Although our initial studies utilized a copper(I) alkoxide derived from a primary alcohol, we anticipated a *secondary alcohol* would provide a more challenging and useful nucleophile to determine the scope and limitations of this transformation. Table 2 summarizes the application of the optimized reaction conditions (Table 1, entry 6) to a variety of racemic *secondary* allylic carbonates, using the copper(I) alkoxide derived from 2,4-dimethyl-3-pentanol (*vide supra*). The allylic etherification is clearly tolerant of linear alkyl substituents (Table 2, entries 1−4), while branched derivatives proved challenging in terms of selectivity and turnover.[9] Indeed, the γ-position appears to be the first point at which branching does not interfere with the substitution (entry 5). The allylic etherification

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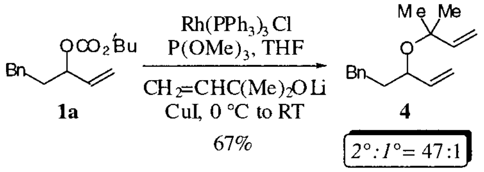
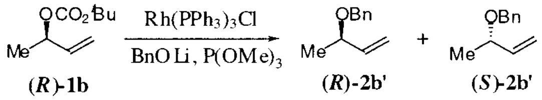
also proved feasible for hydroxymethyl, alkene, and aryl substituents, albeit with lower selectivity (entries 6−9). This transformation is remarkably tolerant, given that the classical alkylation of a hindered metal alkoxide with a *secondary* alkyl halide would undoubtedly lead to elimination. *Hence, the regioselective rhodium-catalyzed allylic etherification with a secondary copper(I) alkoxide provides an important new method for the synthesis of allylic ethers.*



1a **4** (2)

Encouraged by the results in Table 2, we anticipated that the rhodium-catalyzed allylic etherification could be extended to tertiary alcohols (eq 2). Preliminary attempts revealed that, although the alkylation was indeed feasible, the reaction required increased catalyst loading. Treatment of the allylic carbonate **1a** with the copper(I) alkoxide derived from lithium anion of 3-methyl butene-3-ol and the trimethyl phosphite *modified* Wilkinson's catalyst (20 mol %), furnished the allylic ether **4** in 67% yield (*2*°:*1*° = 47:1 by GLC).

Table 3. Exploring the Influence of the Copper(I) Halide Salt on Enantiospecificity



entry	copper halide salt[a]	temp	*2*°:*1*° **2b′: 3b′**[b]	*cee* (%)[c]	yield (%)[d]
1	CuI	0 °C to rt	≥99:1	41	84
2	CuBr	0 °C to rt	91:1	85	86
3	CuCl	0 °C to rt	≥99:1	88	81
4	***CuCl***	***−10 °C***	**≥*99:1***	***96***	***81***

[a] All reactions were carried out on a 0.5 mmol reaction scale. [b] Ratios of regioisomers were determined by capillary GLC on the crude reaction mixture. [c] Enantiomeric excess was determined by chiral capillary GLC.[d] GLC yields.

The excellent enantiospecificity obtained in the previous rhodium-catalyzed allylic substitution reactions prompted the examination of the enantiomerically enriched allylic carbonate **(*R*)-1b** with a copper(I) alkoxide (Table 3). Treatment of **(*R*)-1b** (94% *ee*) under the optimized reaction conditions, furnished the allyl ether **2b′** in 84% yield (*2*°:*1*° ≥ 99:1), albeit with poor enantiospecificity (41% *cee*) which was a significant departure from our earlier studies (entry 1).[4] The low specificity prompted the reexamination of the effect of the copper halide salt. Treatment of the allylic carbonate **(*R*)-1a** with the copper(I) alkoxide derived from benzyl alcohol using copper(I) chloride or bromide, furnished the allylic alkylation adducts **(*R*)-2b′** with significantly improved chirality transfer (entries 2 and 3). Interestingly, the trend for enantiospecificity is the reverse of that for the regiospecificity, illustrating that they are independent (*cf*. Table 1, entries 2−4). Although the origin of the erosion of enantiospecificity with copper(I) iodide is unclear, it is most likely the result of the equilibration of the rhodium−allyl intermediate prior to etherification through a dissociative-type mechanism. The trend in regiospecificity is tentatively attributed to the *in situ* exchange (I for Cl) of the counterion on the metal, which results in a more selective catalyst.[10]

In conclusion, we have developed a new regio- and enantiospecific rhodium-catalyzed allylic etherification of acyclic *unsymmetrical* allylic alcohol derivatives using copper(I) alkoxides derived from primary, secondary, and tertiary alcohols. This study demonstrates that the choice of copper(I) salt is crucial for obtaining high stereospecificity, providing another example of the effect of halide ions in asymmetric transition metal-catalyzed reactions. Finally, the ability to modify alkali metal alkoxides in this manner may provide a useful method for related cross-coupling reactions.

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Supporting Information Available: Representative experimental procedure and spectral data for **2a−i** and **4** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Although the exact composition of a copper(I) alkoxide prepared through the transmetalation of a lithium alkoxide is not known, it has been proposed to consist of an associated lithium halide salt.[6]

(8) For a recent review on halide effects in transition-metal catalysis, see: Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26.

(9) The α- and β-branched derivatives significantly lead to reduced *secondary* selectivity and turnover rates.

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