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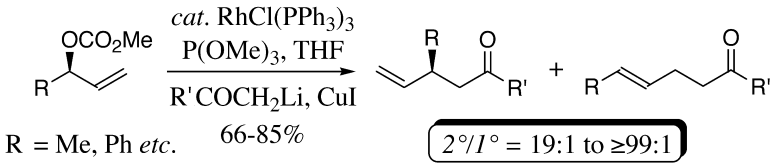

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Regioselective and Enantiospecific Rhodium-Catalyzed Allylic Alkylation Reactions Using Copper(I) Enolates: Synthesis of (−)-Sugiresinol Dimethyl Ether

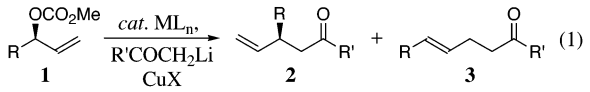
P. Andrew Evans* and David K. Leahy

Department of Chemistry, Indiana University, Bloomington, Indiana 47405

Received May 6, 2003; E-mail: paevans@indiana.edu

The stereocontrolled construction of carbon−carbon bonds *via* transition metal-catalyzed allylic alkylation represents a fundamentally important process for target-directed synthesis.[1] Despite significant advances with stabilized carbon nucleophiles, as exemplified by malonates, β-keto esters, etc., the analogous reactions with enolates are limited to symmetrical or stereoelectronically biased allyl fragments to circumvent problems associated with regiochemical infidelity.[2−4] Hence, the ability to facilitate a stereospecific allylic alkylation with an acyclic ketone enolate would circumvent the need for further functionalization of the allylic alkylation adduct, and thereby provide an important sp^3-sp^3 cross-coupling protocol, which would expand the current repertoire of unstabilized nucleophiles.

We envisioned that the rhodium-catalyzed allylic substitution would facilitate the regio- and enantiospecific alkylation of ketone enolates, owing to its propensity to undergo a selective alkylation through a configurationally stable *distorted* π-allyl or *enyl* ($\sigma + \pi$) organorhodium intermediate.[5,6] The nature of the ketone enolate was expected to be crucial in overcoming some of the inherent limitations associated with this transformation, namely elimination of the metal−allyl intermediate, polyalkylation, and poor regio- and stereocontrol. In light of these concerns, we decided to examine the transmetalation of the alkali metal enolate salt with a copper(I) halide, with the expectation that this would soften the basic character of the enolate.[7] Herein, we now describe the rhodium-catalyzed *inter*molecular allylic alkylation of enantiomerically enriched acyclic unsymmetrical secondary alcohol derivatives **1**, using a copper(I) enolate, to afford the secondary allylic alkylation adducts **2** with excellent stereospecificity (eq 1).



(1)

Preliminary studies examined the effect of the transmetalation of a lithium enolate with the requisite copper(I) halide salt. This study demonstrated that although the transmetalation is crucial for efficient conversion the nature of the copper(I) halide salt was inconsequential to the stereospecificity (I ∼ Br ∼ Cl), which is in sharp contrast to the previous studies with copper alkoxides.[5f] Additional studies demonstrated that dialkylation could be minimized at 0 °C (≤5%), making this an extremely tolerant transformation. Hence, the treatment of the enantiomerically enriched secondary allylic carbonate **1a** (R = $Ph(CH_2)_2$; ≥99% *ee*) with the lithium enolate of acetophenone, transmetalated with copper(I) iodide using trimethyl phosphite-*modified* Wilkinson's catalyst at 0 °C, furnished the alkylation products **2a/3a** in 87% yield, with excellent regioselectivity and enantiospecificity (*2°:1°* ≥ 99:1, *cee* = 100%), favoring the secondary product **2a**.

Table 1. Scope of the Regioselective Rhodium-Catalyzed Allylic Alkylation Reaction Using Copper(I) Enolates (eq 1; R′ = Ph)[a]

entry	R in allylic carbonate *rac*-**1**		*2°:1°* *rac*-**2**:**3**[b,c]	yield (%)[d]
1	$Ph(CH_2)_2$	**a**	≥99:1	83
2	Me	**b**	≥99:1	85
3	^{n}Pr	**c**	≥99:1	74
4	$CH_2{=}CH(CH_2)_3$	**d**	≥99:1	80
5	^{c}Hex	**e**	≥99:1	83
6	^{i}Pr	**f**	≥99:1	76
7	^{i}Bu	**g**	19:1	75
8	$(CH_3)_2CH(CH_2)_2$	**h**	≥99:1	82
9	Ph	**i**	≥99:1	84
10	Npth	**j**	≥99:1	73
11	Bn	**k**	76:1	80
12	$CH_2{=}CH$	**l**	28:1	66
13	$TBSOCH_2$	**m**	50:1	75[e]
14	$BnO(CH_2)_2$	**n**	83:1	78

[a] All reactions were carried out on a 0.5 mmol reaction scale using 10 mol % $RhCl(PPh_3)_3$ *modified* with 40 mol % $P(OMe)_3$.[8] [b] Ratios of regioisomers were determined by capillary GLC on the crude reaction mixtures. [c] The primary products **3** were prepared for comparison using the copper(I) cyanide to transmetalate the enolate, with the exception of **3j** and **3k**, which were prepared using crossed metathesis. [d] Isolated yields. [e] Reaction run at −10 °C.

Table 1 summarizes the application of the optimized reaction conditions to a variety of racemic secondary allylic carbonates using the copper enolate derived from acetophenone (*vide supra*). The alkylation is tolerant of linear and branched alkyl substituents (Table 1, entries 1−8), in which the excellent selectivity for the α-branched derivatives is contrary to our previous studies. The allylic alkylation is also feasible for aryl, benzyl, and vinyl substituents, providing comparable results (entries 9−12). The benzyl-protected hydroxymethyl substituent proved unsatisfactory due to low chemical yield and extensive side products. However, the *tert*-butyldimethylsilyl-protected hydroxymethyl and benzyl-protected hydroxyethyl substituents afforded the alkylation products in excellent yield (entries 13 and 14). *The excellent regioselectivity and enantiospecificity, coupled with the synthetic utility of enolates, makes this an important method for the stereospecific allylic alkylation of acyclic ketone enolates.*

Encouraged by the results in Table 1, we anticipated that the rhodium-catalyzed allylic alkylation could be extended to α-substituted enolates, and thereby facilitate the introduction of an additional stereogenic center.[2,3] Interestingly, treatment of the allylic carbonate **1o** (R = $BnOCH_2$), which had proven problematic in the previous study, under analogous reaction conditions with the copper enolate derived from the ketone **4** furnished the α,β-disubstituted ketone, which was then subjected to ring-closing metathesis to furnish the 1,2-cyclohexenes **5a/5b** in 75% overall yield, favoring the *trans*-diastereoisomer **5a** (eq 2, *2°:1°* = 30:1, *ds* = 10:1).[9] Overall, this reaction sequence provides an alternative approach to an *exo*-selective Diels−Alder

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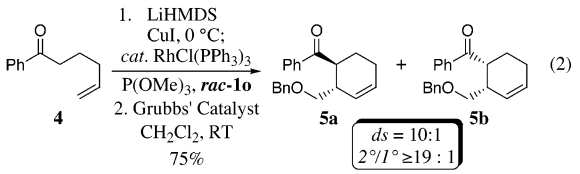
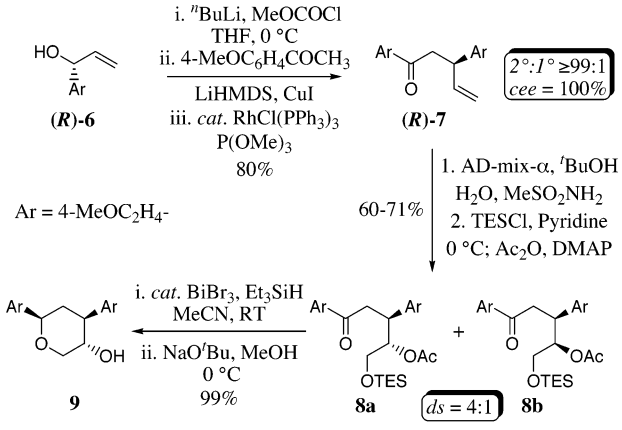
cycloaddition, and indicates that substituted enolates are more tolerant nucleophiles.



(−)-Sugiresinol, a norlignan isolated from heartwood of *Cryptomeria japonica* by Funaoka *et al*., has potent antifungal activity and inhibits cyclic AMP phosphodiesterase in addition to the growth of *C. shiitake* hyphae.[10] We envisioned that the rhodium-catalyzed allylic alkylation, in combination with a reductive etherification, would provide an expeditious synthesis of the dimethyl ether of this biologically important agent.[11] Preliminary studies demonstrated that the allylic carbonate derived from **(*R*)-6** was unstable due to facile ionization. To circumvent this problem, an *in situ* activation/allylic alkylation protocol was devised. Treatment of the allylic alcohol with *n*-butyllithium followed by methyl chloroformate furnished the allylic carbonate, which was then treated in a manner analogous to that described earlier, to afford the β-substituted ketone **(*R*)-7** in 80% yield (*2°:1°* ≥ 99:1, *cee* ≥ 99%). Sharpless asymmetric dihydroxylation, followed by a one-pot differential protection, led to the cyclization precursor **8a/b** in 60−71% yield over two steps, albeit as a 4:1 mixture of diastereoisomers.[12] The mixture was separated, and the desired isomer **8a** was subjected to reductive etherification using bismuth bromide and triethylsilane, followed by an *in situ* deprotection of the acetyl group, to afford (−)-sugiresinol dimethyl ether **9** in 99% yield, with ≥19:1 diastereoselectivity.[13] The combination of the rhodium-catalyzed allylic alkylation with a diastereoselective reductive etherification reaction provides the most expeditious asymmetric synthesis of (−)-sugiresinol dimethyl ether developed to date, which was accomplished in four steps in 45% overall yield from the enantiomerically enriched allylic alcohol **(*R*)-6**.

Scheme 1



In conclusion, we have developed a regioselective and enantiospecific rhodium-catalyzed allylic alkylation of acyclic *unsymmetrical* allylic alcohol derivatives using copper(I) enolates to prepare β-substituted ketones. This protocol represents a convenient asymmetric Claisen rearrangement surrogate in which substituted enolates permit the introduction of an additional stereogenic center. The synthetic utility of this transformation was highlighted in the construction of a *trans*-1,2-disubstituted cyclohexene and the total synthesis of (−)-sugiresinol dimethyl ether. Finally, we anticipate that copper(I) enolates may prove useful nucleophiles in related metal-catalyzed reactions.

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Supporting Information Available: Experimental procedures for **5**−**9**, and spectral data for **2a**−**n** and **5**−**9** (PDF). X-ray crystallographic file in CIF format for **5a**. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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(8) *Representative experimental procedure:* Trimethyl phosphite (24 μL, 0.20 mmol) was added directly to a suspension of Wilkinson's catalyst (46.0 mg, 0.05 mmol) in anhydrous THF (2.0 mL) at 0 °C, and the mixture then stirred under an atmosphere of argon. The catalyst was allowed to form over *ca*. 15 min, resulting in a light yellow homogeneous solution. Lithium hexamethyldisilazide (950 μL, 0.95 mmol, 1.0 M solution in THF) was added dropwise to a suspension of copper(I) iodide (189.6 mg, 1.00 mmol, dried *in vacuo* at 160 °C) and acetophenone (120 μL, 1.03 mmol) in anhydrous THF (3.0 mL), and the anion was allowed to form over ca. 2 min until a light yellow homogeneous solution was obtained. The catalyst and the enolate solutions were then cooled with stirring to 0 °C, and the former was then added *via* Teflon cannula to the copper enolate solution. The allylic carbonate ***rac*-1a** (110.3 mg, 0.50 mmol) was then added via a tared 500-μL gastight syringe to the catalyst/enolate mixture, and the reaction was allowed to warm slowly to room temperature over *ca*. 4 h (tlc control), resulting in a tan heterogeneous solution. The reaction mixture was then quenched with NH_4Cl solution (1 mL) and partitioned between diethyl ether and saturated aqueous NH_4Cl solution. The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 1% ethyl acetate/hexanes), followed by additional flash chromatography (eluting with 15% methylene chloride/hexanes), furnished the β-substituted ketone ***rac*-2a** (109.7 mg, 83%) as a colorless oil.

(9) The relative configuration was proven through X-ray crystallographic analysis of the 4-nitrobenzoate derived from **5a** after debenzylation.

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