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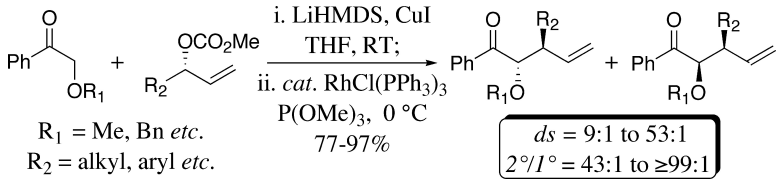

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Regio- and Diastereoselective Rhodium-Catalyzed Allylic Substitution with Acyclic α-Alkoxy-Substituted Copper(I) Enolates: Stereodivergent Approach to 2,3,6-Trisubstituted Dihydropyrans

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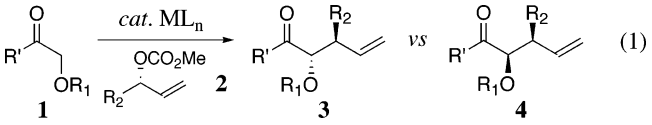
The regio- and diastereoselective transition metal-catalyzed allylic alkylation with α-substituted ketone enolates represents both a challenging and important synthetic transformation.[1−3] Although significant advances have been accomplished with enolates derived from α-heteroatom-substituted carboxylic acid derivatives, the reactions are generally limited to electronically biased or symmetrical metal−allyl fragments to reduce or circumvent regiochemical infidelity.[4,5] Hence, the ability to facilitate the regio- and diastereoselective allylic alkylation of unsymmetrical allylic alcohol derivatives with an *acyclic* α-heteroatom-substituted ketone enolate would constitute a significant advance for this type of sp^3-sp^3 cross-coupling reaction.

We envisioned that the copper(I) enolate derived from an α-alkoxy-substituted ketone would provide a general approach to *acyclic* diastereocontrol, due to its propensity to form the *Z*-chelated enolate (Figure 1). Furthermore, the stereoelectronic nature of the alkoxy substituent could be tailored to accomplish optimal selectivity. Herein, we now describe the regio- and diastereoselective rhodium-catalyzed allylic alkylation of enantiomerically enriched unsymmetrical secondary allylic alcohol derivatives **2**, with the copper(I) enolate of an *acyclic* α-alkoxy ketone **1**, to furnish the secondary allylic alkylation adducts **3**/**4** in excellent yield, favoring **3** (eq 1).[6]



(1)

Preliminary studies tested our hypothesis through examination of the effect of the α-alkoxy substituent on the regio- and diastereoselectivity (Table 1). This study demonstrated that, although these reactions are highly regioselective, the nature of the alkoxy substituent has a dramatic effect on the level of stereocontrol. Interestingly, the unsubstituted hydroxyl and the bulky *tert*-butyldimethylsilyl ether furnished poor diastereoselectivity (entries 1 and 5), while the alkyl-substituted derivatives afforded very good to excellent stereocontrol (entries 2−4).[7] The observed diastereoselectivity is consistent with the open transition structure outlined in Figure 1, involving a distorted π-allyl or *enyl*[8] ($\sigma + \pi$) organorhodium intermediate with a chelated *Z*-copper(I) enolate. In the favored transition structure, the substituent (R_2) is flanked by the proton and planar phenyl group of the enolate. Alternatively, the disfavored transition structure has the copper(I) enolate eclipsed by this substituent, as a consequence of the bidentate binding and the relative orientation of the ether substituent. The relative size of the ether substituent (Bn > Me ≫ H) in conjunction with bidentate coordination appears to be crucial for good stereocontrol, since the proton in the hydroxyl group clearly diminishes the ability to distinguish between the transition structures, while the lower basicity of trialkylsilyl ethers presumably reduces chelation.[9]

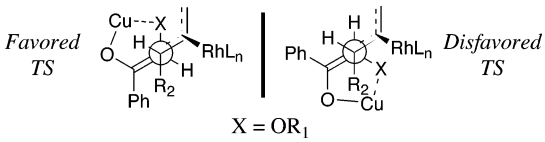


Figure 1. Proposed transition structures for the observed diastereoselectivity with α-alkoxy-substituted copper enolates.

Table 1. Effect of the α-Alkoxy Substituent on the Regio- and Diastereoselective Rhodium-Catalyzed Allylic Alkylation Reaction Using Copper(I) Enolates (eq 1; **1**, R′ = Ph, *rac*-**2a**; R_2 = $Ph(CH_2)_2$)[a]

entry	α-alkoxy ketone **1**, R_1 =	2°:1°[b,c]	ds **3**/**4**[b]	yield (%)[d]
1	H	≥19:1	2:1	92
2	Me	≥19:1	17:1	85
3	CH_2═$CHCH_2$	≥19:1	35:1	70
4	$PhCH_2$	≥19:1	37:1	90
5	^{t}BuMe$_2$Si	≥19:1	3:1	75

[a] All reactions were carried out on a 0.25 mmol reaction scale using 10 mol % $RhCl(PPh_3)_3$ *modified* with 40 mol % $P(OMe)_3$, and 1.5 equiv of the lithium enolate transmetalated with an equivalent amount of CuI. [b] Regio- and diastereoselectivity was determined by 400 MHz NMR and/or capillary GLC on the crude reaction mixtures. [c] The primary products were prepared using copper(I) cyanide.[3] [d] Isolated yields.

Table 2. Scope of the Regio- and Diastereoselective Rhodium-Catalyzed Allylic Alkylation Reaction with a α-Alkoxy Copper(I) Enolate (eq 1; **1**, R′ = Ph, R_1 = $PhCH_2$)[a]

entry	allylic carbonate R_2 =		2:1°[b,c]	ds **3**/**4**[b]	yield (%)[d]
1	$Ph(CH_2)_2$	**a**	≥99:1	37:1	90
2	Me	**b**	≥99:1	24:1	97
3	^{n}Pr	**c**	≥99:1	37:1	92
4	^{i}Pr	**d**	91:1	10:1	93
5	^{i}Bu	**e**	43:1	15:1	94
6	$(CH_3)_2CH(CH_2)_2$	**f**	≥99:1	53:1	96
7	CH_2═$CH(CH_2)_3$	**g**	≥99:1	36:1	94
8	Bn	**h**	≥99:1	9:1	77
9	$BnOCH_2$	**i**	≥99:1	44:1	77
10	$TBSOCH_2$	**j**	≥99:1	28:1	84
11	Ph	**k**	≥99:1	14:1	91
12	naphthyl	**l**	≥99:1	12:1	92

[a] All reactions were carried out on a 0.25 mmol reaction scale. [b] Regio- and diastereoselectivities were determined by capillary GLC or HPLC analysis on the crude reaction mixtures. [c] The primary products were prepared using copper(I) cyanide,[3] with the exception of entries 11 and 12 which were prepared via cross-metathesis. [d] Isolated yields.

Table 2 summarizes the application of the copper(I) enolate derived from α-benzyloxy acetophenone (Table 1, entry 4) to a variety of racemic secondary allylic carbonates (vide infra). The regioselectivity in the allylic alkylation is tolerant of a wide array of allylic alcohol derivatives, whereas the diastereoselectivity is significantly affected by the relative size of the allylic substituent. For example, linear and branched alkyl substituents afford excellent diastereocontrol (Table 2, entries 1−3, 6−7, and 9−10), provided

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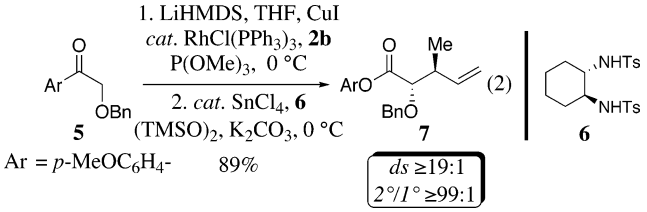
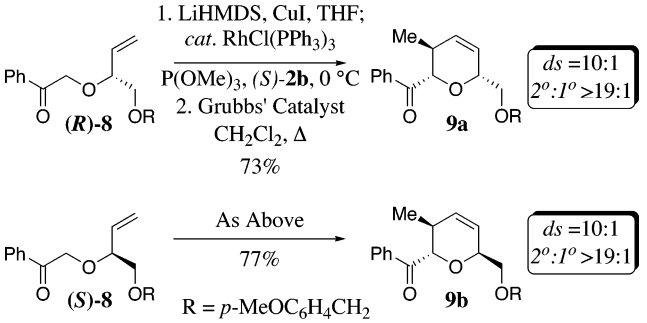
branching is beyond the β-position. Nonetheless, the α- and β-branched alkyl (entries 4 and 5) and benzyl (entry 8) and aryl substituents (entries 11 and 12) afford synthetically useful levels of stereocontrol. Additional studies examined the enantiospecificity of this transformation.[10] Treatment of the allylic carbonate (*S*)-**2b** (R_2 = Me, 97% *ee*) with the trimethyl phosphite *modified* Wilkinson's catalyst and the copper(I) enolate, derived from transmetalation[11] of the lithium enolate of **1** (R' = Ph, R_1 = Bn) with copper(I) iodide at 0 °C, furnished the enantiomerically enriched alkylation products *anti*-**3b**/*syn*-**4b** in 94% yield (≥99% *cee*), with excellent regio- and diastereoselectivity (*2°:1°* ≥ 99:1, *ds* = 24:1), favoring *anti*-**3b**. *Hence, the excellent regio- and diastereoselectivity coupled with the enantiospecificity makes this an important new method for the construction of acyclic adjacent ternary stereogenic centers*. The versatility and synthetic utility of this potentially important transformation was further demonstrated by the allylic alkylation using the aryl ketone **5**, followed by a Baeyer−Villiger oxidation to afford the corresponding ester **7** in 89% yield with excellent regio- and diastereoselectivity (eq 2).[12,13]



5 **7** **6**

The stereocontrolled construction of trisubstituted cyclic ethers remains an important area of investigation, primarily due to the ubiquity of this structural motif in biologically important natural and unnatural products.[14] We envisioned that the combination of the regio- and diastereoselective rhodium-catalyzed allylic alkylation reaction with ring-closing metathesis would provide a stereodivergent approach to 2,3,6-trisubstituted dihydropyrans. Interestingly, treatment of the allylic carbonate (*S*)-**2b** (R_2 = Me, 97% *ee*), under the analogous reaction conditions with the copper(I) enolate derived from the ketones (*R*)- and (*S*)-**8**,[15] furnished the corresponding α,β-disubstituted ketones, which upon ring-closing metathesis furnished the cyclic ethers **9a** and **9b** in 73 and 77% overall yield, respectively (*2°:1°* ≥ 19:1, *ds* = 10:1).[16] The relative configurations of **9a** and **9b** were confirmed with the aid of an NOE experiment and X-ray crystallography, respectively.

Scheme 1



In conclusion, we have developed a regio- and diastereoselective rhodium-catalyzed allylic alkylation reaction utilizing copper(I) enolates derived from *acyclic* alkyl-protected α-alkoxy ketones. This study suggests that the ability to form a chelated enolate intermediate is crucial for obtaining high diastereoselectivity, whereas excellent regioselectivity is obtained regardless of this substituent. Finally, the synthetic utility of this method was highlighted through the conversion of the aryl ketone to the ester and the development of a stereodivergent approach to 2,3,6-trisubstituted dihydropyrans (Scheme 1).

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Supporting Information Available: Experimental procedures and spectral data for **3a**−**l**, **7**, and **9a/b**. X-ray crystallographic file in CIF format for **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Tsuji, J. In *Palladium Reagents and Catalysts*; Wiley: New York, 1996; Chapter 4, pp 290−404. (b) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 8, pp 593−649.
(2) For examples of enantio- and diastereoselective metal-catalyzed allylic alkylations using α-alkyl ketone enolates, see: (a) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759. (b) Braun, M.; Laicher, F.; Meier, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 3494.
(3) For an example of a regio- and diastereoselective allylic alkylation reaction using an *acyclic* α-alkyl-substituted copper(I) enolate, see: Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2003**, *125*, 8974.
(4) For examples of diastereoselective allylic alkylation reactions using cyclic ester and amide enolates, see: (a) Trost, B. M.; Dogra, K. *J. Am. Chem. Soc.* **2002**, *124*, 7256. (b) Trost, B. M.; Dogra, K.; Franzini, M. *J. Am. Chem. Soc.* **2004**, *126*, 1944.
(5) For examples of allylic alkylation reactions using *acyclic* α-amino ester enolates, see: (a) Kazmaier, U.; Zumpe, F. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 802. (b) Kanayama, T.; Yoshida, K.; Miyabe, H.; Kimachi, T.; Takemoto, Y. *J. Org. Chem.* **2003**, *68*, 6197.
(6) For the challenges associated with obtaining the regio- and diastereoselectivity in the rhodium-catalyzed allylic alkylation with ketones and ester enolates, see: Muraoka, T.; Matsuda, I.; Itoh, K. *Tetrahedron Lett.* **2000**, *41*, 8807.
(7) The unmodified lithium enolate results in poor conversion (22%) and diminished selectivity (*2°:1°* = 34:1, ds = 8:1).
(8) For an example of an *enyl* ($\sigma + \pi$) organorhodium intermediate, see: Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581 and pertinent references therein.
(9) Shambayati, S.; Schreiber, S. L.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1990**, *112*, 697.
(10) For an explanation of the effect of copper(I) halide salts on the stereospecificity of the rhodium-catalyzed allylic alkylation reaction with copper(I) enolates, see: Evans, P. A.; Leahy, D. K.; Slieker, L. M. *Tetrahedron: Asymmetry* **2003**, *14*, 3613.
(11) For an example of the transmetalation of a lithium enolate with a copper(I) halide salt, see: Posner G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934.
(12) (a) Gottlich, R.; Yamakoshi, K.; Sasai, H.; Shibasaki, M. *Synlett* **1997**, *8*, 971. (b) Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 10521.
(13) Although the phenyl ketones **3** undergo the analogous Baeyer−Villiger oxidation, the yields are approximately 20% lower as compared to those for the *p*-methoxy phenyl ketone derivative.[12b]
(14) For a recent review on the stereoselective construction of cyclic ethers, see: Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913 and pertinent references therein.
(15) Stoltz, B. M.; May, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 12426.
(16) For recent reviews on ring-closing metathesis, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012 and pertinent references therein.

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