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Effect of Ethers on Reactions of Butylcoppers with α,*β*-Unsaturated Ketones in Toluene

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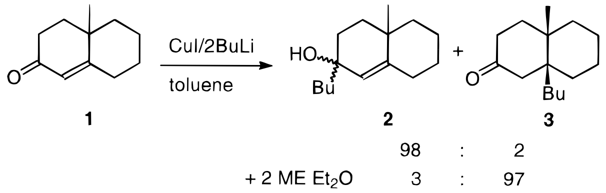
Mixtures of butyllithium and copper iodide prepared in toluene react with α,*β*-unsaturated ketones predominantly in a 1,2-fashion. Addition of various ethers to the system results in some preference for the 1,4-product. The structural characteristics of ethers which influence 1,4-addition have been revealed. Reactions with chiral ethers did not alter the stereochemistry of the product. The results are correlated with the current views on the mechanism of organocuprate reactions.

Introduction

The organocopper-mediated 1,4-(conjugate) addition reaction to α,*β*-unsaturated ketones (enones) is a widely used reaction for selective carbon−carbon bond formation.[1] This extensive synthetic application of organocopper reagents has promoted efforts to understand the mechanism of the reaction[2] and also the effect of external influences such as silyl halides[3−5] and solvents.[5−7] In a previous paper[8] we described the dramatic effect of diethyl ether (Et_2O) on 1,4-addition reactivity of 1:2 CuI/BuLi mixtures prepared in toluene. This procedure is exemplified by the reaction of 4,4a,5,6,7,8-hexahydro-4a-methyl-2(3*H*)-naphthalenone (**1**) to give various amounts of the 1,2- and 1,4-addition products, **2** and **3**, as depicted in Scheme 1.

Scheme 1



In reactions carried out with between 1 and 2 molar equiv (ME) of Et_2O, the amount of **3** which was formed correlated with the amount of Et_2O (Figure 1).

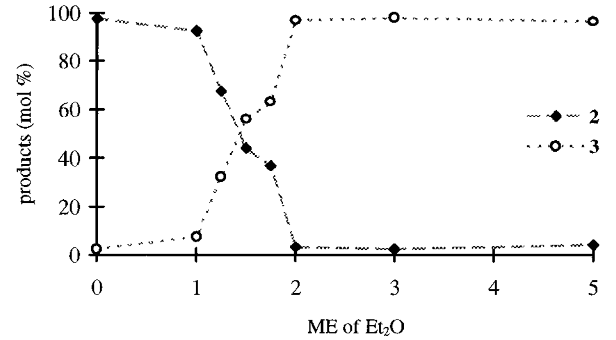
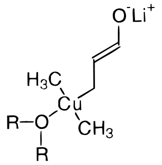


Figure 1. Effect of Et_2O on 1,2-/1,4-addition to **1** with 1:2 CuI/BuLi in toluene.

These findings were in accordance with the theoretical predictions[9,10] that a suitable ligand is required to stabilize a formally copper(III) reaction intermediate (**4**, R = Me,[9] Et[8]) which has been postulated to be on the 1,4-addition reaction mechanistic pathway. It was also suggested that Et_2O could activate an existing organometallic species or facilitate the creation of an entirely new reagent.



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Given that Et_2O does not have any special chemistry, it was anticipated that other ethers could have similar influences on the reaction system. Therefore, studies were undertaken to investigate the effect that variation of ether structure and basicity had on 1,4-addition reactivity. Information gained from these studies was expected to provide further insight into the 1,4-addition mechanism. An additional aim was to identify chiral ethers that affected the 1:2 CuI/BuLi mixture in a manner similar to that of Et_2O. It was envisaged that the use of enantiomerically enriched chiral ethers could provide a stereochemical mechanistic probe and possibly lead to an enantioselective 1,4-addition reaction protocol.

[⊗] Abstract published in *Advance ACS Abstracts,* September 15, 1997.

[1] Recent Reviews: Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135−631. Kozlowski, J. A. In *Comprehensive Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 1.4.

[2] Smith, R. A. J.; Vellekoop, A. S. *Advances in Detailed Reaction Mechanisms, Vol. 3*; Coxon, J. M., Ed.; JAI Press: Greenwich, CT, 1994; pp 79−130 and references therein.

[3] Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019−6022. Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047−1050. Lipshutz, B. H.; James, B. *Tetrahedron Lett.* **1993**, *34*, 6689−6692. Bertz, S. H.; Miao, G.; Rossiter, B. E.; Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11023−11024. Eriksson, M.; Johansson, A.; Nilsson, M. Olsson, T. *J. Am. Chem. Soc.* **1996**, *118*, 10904−10905. Bertz, S. H.; Eriksson, M.; Miao, G.; Snyder, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 10906−10907.

[4] Bertz, S. H.; Smith, R. A. J. *Tetrahedron* **1990**, *46*, 4091−4100.

[5] Christenson, B.; Ullenius, C.; Håkansson, M.; Jagner, S. *Tetrahedron* **1992**, *48*, 3623−3632 and references therein.

[6] House, H. O.; Wilkins, J. M. *J. Org. Chem.* **1978**, *43*, 2443−2454.

[7] Hallnemo, G.; Ullenius, C. *Tetrahedron* **1983**, *39*, 1621−1625.

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[9] Dorigo, A. E.; Wanner, J.; Schleyer, P. von R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 476−478.

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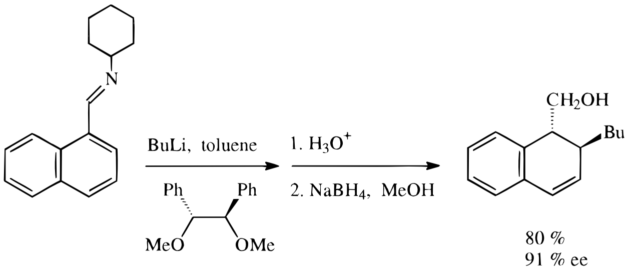
Ethers have previously been used to achieve enantioselectivity in the 1,4-addition reactions of organolithium compounds with α,*β*-unsaturated aldimines.[11] Of particular interest for this work was the high selectivity obtained using (*R*,*R*)-1,2-dimethoxy-1,2-diphenylethane in toluene (Scheme 2).

Scheme 2



Results and Discussion

Various amounts (ME) of ethers were mixed with a 1:2 CuI/BuLi mixture prepared in toluene, and then **1** was added as described previously.[8] The reactions were initially carried out with 2 and 5 ME of each ether. Further investigation of any ether was undertaken if a significant amount of 1,4-addition was noted. The results are tabulated in the Experimental Section.

Acyclic Ethers. 1-Methoxybutane was investigated as it is structurally similar to Et_2O, and the results are summarized in Figure 2.

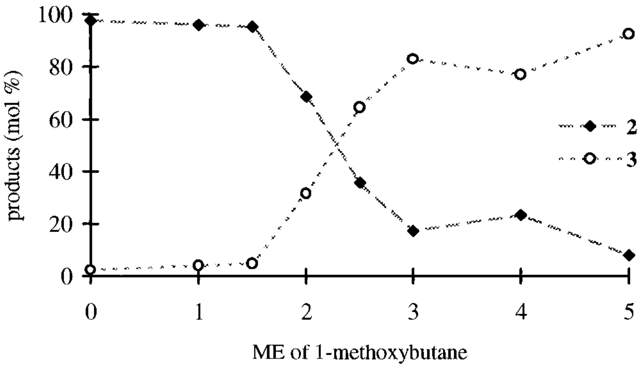


Figure 2. 1,2-/1,4-Addition variation with 1-methoxybutane.

The results were similar to those obtained with Et_2O (Figure 1). Although the increase in the amount of **3** with a ME of 1-methoxybutane was less abrupt than with Et_2O, the ultimate maximum yield was comparable. This indicated that the 1,4-reactivity enhancement was not unique to Et_2O. In contrast, it was surprising to find that reactions containing either 2 or 5 ME of dibutyl ether gave predominantly **2**. Therefore, it appears that the alkyl chain length within the ether ligand plays an important role in promoting 1,4-reactivity.

The effect of alkyl chain branching but without chain length extension was examined with 2-methoxybutane. As 2-methoxybutane is chiral the results were particularly significant for the stereochemical aspects of the research. The product distributions from reactions with 2-methoxybutane were very similar to those obtained with 1-methoxybutane. Hence, it was concluded that small structural changes to the larger alkyl group of the ether appeared to cause no significant reactivity modification.

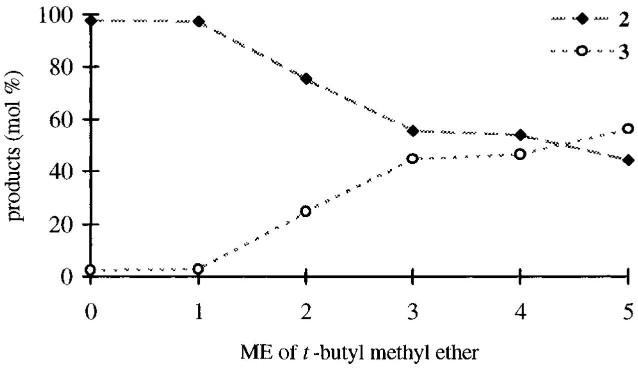


Figure 3. 1,2-/1,4-Addition variation with *tert*-butyl methyl ether.

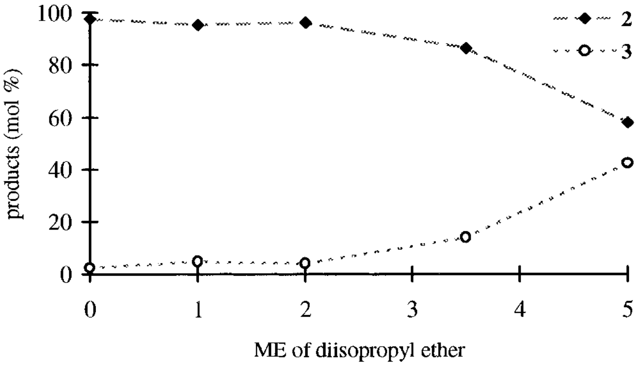


Figure 4. 1,2-/1,4-Addition variation with diisopropyl ether.

To further investigate the effect of alkyl branching, reactions with *tert*-butyl methyl ether and diisopropyl ether were undertaken. The results are outlined in Figures 3 and 4. The amount of **3** produced gradually increased with increasing amounts of *tert*-butyl methyl ether, to a maximum (56%) with 5 ME, which is significantly less than that obtained in reactions with 1- or 2-methoxybutane. Presumably the increased steric hindrance of the *tert*-butyl compared with the 2-butyl component has reduced the effectiveness of the coordination and as a consequence reduced the 1,4-reactivity. The deleterious effect of extensive branching is illustrated in the results from reactions with diisopropyl ether. Although 1,4-addition reactivity was observed, it was less predominant with only 42% of **3** obtained with 5 ME of ligand. The alkyl chain length effect, noted previously with dibutyl ether, may also be a significant factor in this latter set of reactions.

The scope of the effect of chain length was further evaluated by carrying out studies with 2-ethoxybutane and 2-methoxyoctane. The results for these two ethers were very similar, with **2** predominating in the reactions using 2 or 5 ME. These data are in sharp contrast with those obtained with 2-methoxybutane and indicate that the structural “window” of reactivity enhancement is quite narrow with respect to the molecular size of the ether ligand.

The product distributions which were observed can be interpreted in terms of the organometallic system requiring an accessible, ether oxygen, which is only possible using a ligand containing at least one small alkyl group. The relatively strong electron-donating effect of the

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[11] Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266–8268.

methyl group enhances the donor ability of an ether oxygen, and from these considerations methyl ethers were judged to be probably the most useful for further study. On the basis of this premise, a series of aryl-substituted alkyl methyl ethers were prepared and examined. The incorporation of an aryl group makes the ethers more readily recoverable from the reaction and provides an opportunity for ligand recycling which is a desirable feature in asymmetric reactions. Only minor amounts of **3** were detected from the reactions with phenyl methyl ether, and a significant amount of **1** was recovered at high ME. These results presumably reflect the poor coordinating ability of oxygen directly bound to an aromatic ring. Reactions with benzyl methyl ether returned substantial amounts of **1**, indicating severe inhibition of butyl activity, perhaps by preferential direct reaction of the ligand with the organometallic species. Several unidentified products were detected in these reaction product mixtures. The 1,2-/1,4-addition reactivity with phenethyl methyl ether was similar to that observed with *tert*-butyl methyl ether, apart from the occurrence of some recovered **1** at high ME.

In summary, for acyclic ethers, the 1,4-activation is not confined to Et_2O although there are quite narrow structural limits on the types of molecules which are effective. The two major structural requirements for effective 1,4-activation are a relatively unencumbered ether oxygen and a size restriction in terms of allowable alkyl chain length. Cyclic ethers have less conformational mobility than acyclics and hence allow examination of basicity effects without the potential size/conformational complications revealed in the previous section.

Cyclic Alkyl Ethers. Tetrahydrofuran (THF) is a ubiquitous solvent being less conformationally flexible but a considerably stronger Lewis base than dialkyl ethers.[12] It has been well documented that THF and other basic solvents tend to decrease the rate of the diorganocuprate 1,4-addition reaction and also the yield.[6,7] An explanation for these influences is that these solvents effectively compete with the enone for lithium. Coordination of the enone with lithium is a common feature in all cuprate mechanistic scenarios.

Reaction of **1** with a 1:2 CuI/BuLi mixture prepared in THF gave 60 mol % of **2** and 40 mol % of recovered **1**. This product ratio is comparable with that obtained from the related reaction between methyl cuprate and **1**[4] and is consistent with the general inhibiting effect of this solvent on cuprate 1,4-addition reactions. The effect of stoichiometric amounts of THF on the reactivity of the 1:2 CuI/BuLi mixture in toluene was investigated, and the results are presented in Figure 5.

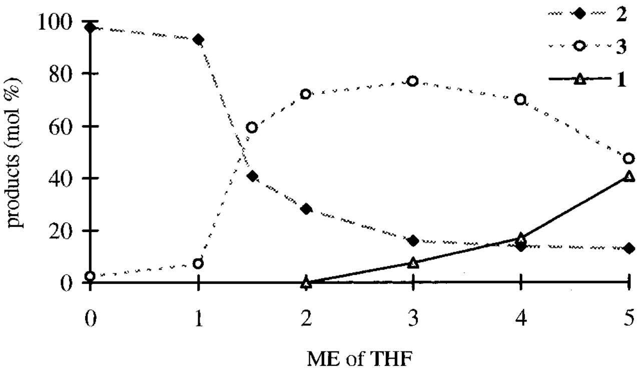

Figure 5. 1,2-/1,4-Addition variation with THF.

There was minimal effect with less than 1 ME of THF. However, the amount of **3** detected rapidly increased with 1 to 2 ME of THF and reached a maximum with 3 ME. Some **1** was recovered from the reactions with amounts greater than 2 ME. With increasing ME of THF the amount of **1** recovered appears linked to a decline in the amount of **3** which is consistent with the notion of preferential lithium coordination by the additional THF as discussed previously. The result with 5 ME of THF illustrates that only minimal additional amounts of strongly Lewis basic solvents are required to disrupt the "usual" cuprate activity observed at loadings of 2−3 ME.

The substituted chiral THF derivative, 2-methyltetrahydrofuran (2-MeTHF) was also examined in detail, and the results are presented in Figure 6. Generally, the amount of **3** obtained from these reactions was greater than that observed with THF. The amount of recovered **1** from reactions with a high ME of 2-MeTHF was also significantly lower than with THF, and this may be associated with the decreased dipolarity−polarizability of 2-MeTHF compared with THF.[13]

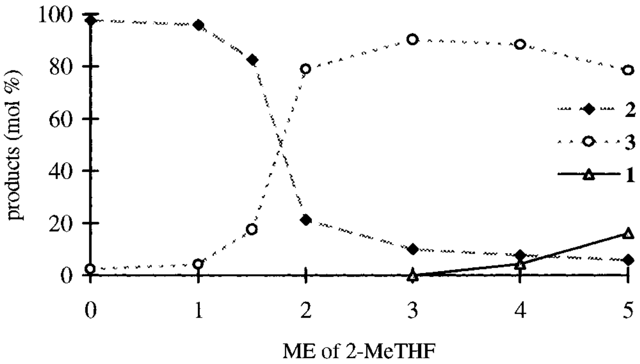

Figure 6. 1,2-/1,4-Addition variation with 2-MeTHF.

These results suggest that the cyclic ethers have a dual role in influencing the 1,4-addition reactivity of the 1:2 CuI/BuLi toluene system. With stoichiometries between 1 and 3 ME, the ligand enhances 1,4-addition, presumably by intermediate stabilization, and behaves similarly to sterically uncluttered acyclic ethers. At higher ME's butyl addition decreases can be related to preferential lithium coordination with the ether. In order to determine the effect of strongly donating ethers on the 1,4-reactivity and especially to probe the necessity of lithium availability for useful levels of reaction, a series of potentially strongly coordinating dialkoxyalkanes was examined.

Dimethoxyalkanes. In all of the above reactions at least 2 ME of an ether was required for maximum 1,4-addition. This implies that the 1:2 CuI/BuLi mixture in toluene requires at least two ether oxygens for effective reaction. Reactions involving dialkoxy compounds introduce two ether oxygens for each ME of additive. 1,2-Dimethoxyethane (DME) can be considered to be comparable in size to 1-methoxybutane and thus allow for comparison of bidentate effects within the size limitation disclosed earlier in this report. DME has been included in studies on the effect of solvent on the ability of methylcuprate to add to various enones.[6] It was found that increased amounts of enone were recovered from reactions performed in 1:5 Et_2O/DME compared with

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(12) Maria, P.-C.; Gal, J.-F. *J. Phys. Chem.* **1985**, *89*, 1296−1304.

(13) Abraham, M. H.; Whiting, G. S.; Doherty, R. M.; Shuely, W. J. *J. Chromatogr.* **1991**, *587*, 213−228.

pure Et_2O and that the product ratios from reactions performed in the Et_2O/DME solvent mixture were similar to that obtained from using 1:5 Et_2O/THF. It has been suggested[14] that the basicity of DME should lie between dioxolane ($\Delta H°(BF_3)$ −68.6 kJ mol^{-1}) and THF ($\Delta H°(BF_3)$ −90.4 kJ mol^{-1}) because of the inductive effect of the second oxygen two carbons removed from the first. Given that the recovery of **1** in reactions containing THF was attributed to Lewis basicity, it was not surprising to find that DME displayed a similar effect (Figure 7). The striking differences between the data for THF and DME are that significant 1,4-activity is noted with less than 1 ME of DME and the amount of **3** reaches a maximum with lower ME of DME compared with THF. Reactions involving 1,2-dimethoxypropane also showed a maximum in the production of **3**; however in this case the maximum yield was only 50% and was obtained with 1 ME. This reactivity difference presumably reflects steric hindrance around the oxygen as noted earlier. The trend of inhibition of 1,4-reactivity with substitution near the ether oxygen was continued with 2,3-dimethoxybutane which gave <30% of **3** and required high ME. Reaction with 1,2-dimethoxy-1,2-diphenylethane gave no detectable amounts of **3**, in concert with the results using phenyl methyl ether. Given the significant production of **3** with 1 ME of DME and the parallel trends in reactivity of the substituted 1,2-dimethoxyalkanes with the acyclic ethers, it seems reasonable to assume that DME is coordinating and possibly as a bidentate chelate ligand.

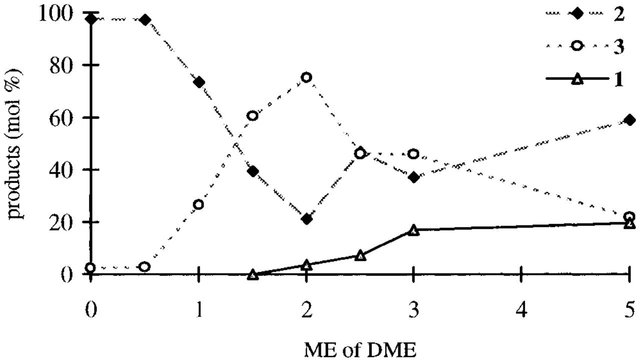

Figure 7. 1,2-/1,4-Addition variation with DME.

The chelation aspect was investigated by using 1,3-dimethoxypropane and 1,4-dimethoxybutane, which are progressively less inclined to offer stable chelation opportunities. The effects of 1,3-dimethoxypropane and 1,4-dimethoxybutane on the reactivity of the 1:2 CuI/BuLi mixture are illustrated in Figures 8 and 9.

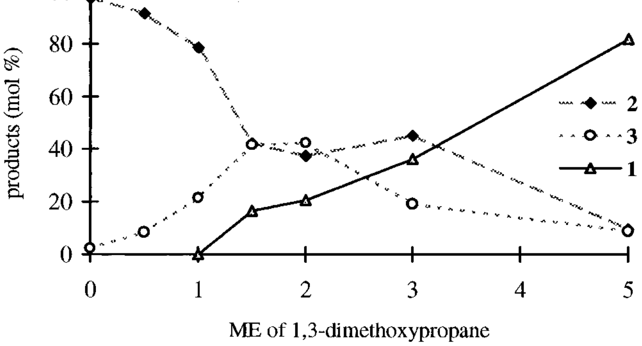

Figure 8. 1,2-/1,4-Addition variation with 1,3-dimethoxypropane.

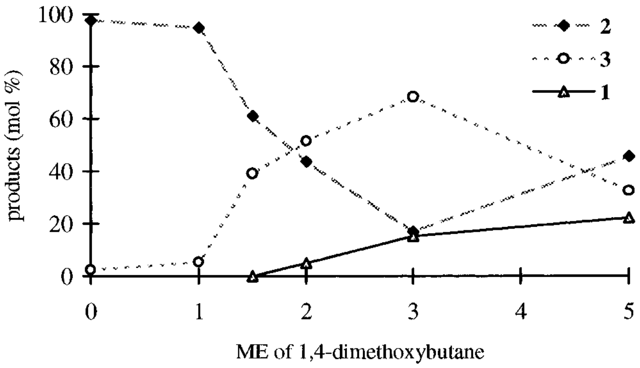

Figure 9. 1,2-/1,4-Addition variation with 1,4-dimethoxybutane.

The influence of 1,3-dimethoxypropane on 1,4-addition is less than that of DME although appreciable 1,4-activity was still noted below 1 ME. The addition of greater than 0.5 ME of 1,3-dimethoxypropane to the black 1:2 CuI/BuLi mixture resulted in the formation of a dense, black precipitate with a colorless supernatant. A yellow solution formed instantly upon the addition of **1**, which quickly darkened to orange and then to black as the precipitate dissolved. The addition of **1** to methylcuprate in Et_2O at −78 °C also immediately produces an orange solution[15] which is considered to be related to the formation of a cuprate(3d) → alkene(π*) complex.[16] Reactions using 1,4-dimethoxybutane, over the 0−3 ME range, gave similar product distributions to that of 1-methoxybutane (Figure 2). At least 1 ME was required for significant production of **3**, and this was interpreted as resulting from effective coordination by only one of the ether oxygens in each molecule of the additive. In summary, the relative reactivity of the 1,ω-dimethoxyalkanes are in accordance with their relative bidentate chelate stability and especially with DME there is strong indications that a bidentate chelation to a metal center is taking place and influencing the 1,4-reactivity.

(*S*)-2-Methoxybutane. Two of the ethers which gave considerable amounts of 1,4-addition over the stoichiometries examined were chiral, and reactions with optically active 2-methoxybutane were undertaken to examine stereochemical outcomes. Prochiral enone substrates were identified for the initial segment of the stereochemical investigation. The influence of Et_2O on the reactions of 1:2 CuI/BuLi in toluene with *trans*-4-phenyl-3-buten-2-one (**5**) or 3,5,5-trimethyl-2-cyclohexen-1-one (**6**) were similar to that observed with **1**.[8] A series of reactions were carried out with **5** and **6** and a 1:2 CuI/BuLi mixture containing appropriate stoichiometric amounts of 2-methoxybutane. The 1,2-/1,4-addition ratios obtained are presented in Table 1 together with the results from reactions with **1** for comparison. Predominant 1,4-addi-

Table 1. Effect of 2-Methoxybutane on 1,2-/1,4-Addition Ratio with Enones

$$\text{CuI} + 2\text{BuLi} \xrightarrow[w(\text{2-methoxybutane})]{\text{toluene}} [\ ] \xrightarrow{\textbf{enone}} \text{products}$$

	1,2-/1,4-addition ratio				
enone	$w = 0$	$w = 2$	$w = 3$	$w = 4$	$w = 5$
1	98/2	63/37	21/79	15/85	10/90
5	91/9	20/80	13/87	3/97	
6	95/5	12/88	9/91	6/94	

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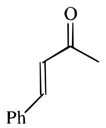
(14) Jackman, L. M.; Petrei, M. M.; Smith, B. D. *J. Am. Chem. Soc.* **1991**, *113*, 3451−3458.



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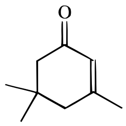

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tion to **5** or **6** was achieved with 2 ME of 2-methoxybutane while a similar selectivity with **1** required about twice the amount of the ether. These results reinforce the view that enone **1** is a severe test of 1,4-addition regioselectivity.

Optically active 2-methoxybutane was prepared from (*S*)-(+)-2-butanol in high yield (83%) of excellent, apparent ee ($\approx$94%)[17] (*cf.* Experimental Section). Reactions of the 1:2 CuI/BuLi mixture and 4 ME of (*S*)-2-methoxybutane with the enones **5** and **6** were carried out and GC analyses of the reaction mixtures indicated that the 1,2-addition products were only minor ($<$10%) components. The ee values for the butyl 1,4-addition products to **5** and **6** were obtained by chiral HPLC and GC analyses, respectively. In both cases the product was found to be racemic. Five ME of (*S*)-2-methoxybutane was added to the 1:2 CuI/BuLi mixture in toluene for the reaction with **1**. A 100% excess of **1** was added to the reaction to allow for the possibility of kinetic resolution. In order to obtain the complete stereochemical profile of this reaction it was necessary to obtain the ee of both the product (**3**) and enone (**1**). Chiral GC separated the enantiomers of **1** while it was necessary to form the silyl enol ether of **3** for satisfactory chiral GC separation of the enantiomers. In this reaction both **1** and the silyl ether from **3** were found to be racemic. These results demonstrate that although some of the ethers studied are highly beneficial for promoting 1,4-addition they do not influence the stereochemical outcome. The overall stereochemistry may well be determined during the formation of the cuprate(3d) $\rightarrow$ alkene(π^*) complex with the ether acting at a later stage in the overall sequence. The formation of mixtures of diastereoisomeric cuprate(3d) $\rightarrow$ alkene(π^*) complexes with **1** has been proposed previously,[16] and it may well be that the high product diastereoselection observed results from one of the complexes being more reactive. These results contrast with those obtained using amino ethers derived from tartaric acid.[18] It may well be that the polydentate features of these chiral solvents/ligands are a key factor in influencing the stereochemistry of the reaction.

Conclusion

The variability in 1,4-/1,2-addition reactivity of the 1:2 CuI/BuLi mixture in toluene with ethers is clearly related to steric and perhaps electronic effects; however the reason for the inhibition with long alkyl chains remains unclear. The proposed 1,4-addition mechanism requires ether involvement at the reactive intermediate stage and clearly from this work the essential coordination places quite definite steric demands on the ligand. Et$_2$O seems to be one of the best ligands for promoting the transformation although it is not unique in this respect. With the benefit of hindsight one can only speculate on how rapidly organocuprate chemistry with applications to organic synthesis would have developed if it had not been carried out with methyllithium in Et$_2$O during its formative stage.

Experimental Section

General experimental conditions have been described previously.[8] Chiral GC analysis was carried out using a 30 m $\times$ 0.25 mm i.d., 0.25 μm film thickness, J&W CYCLODEX-B column, helium carrier gas at 1.1 mL min^{-1}, 25:1 injector split. HPLC analysis was carried out on a Daicel Chiralcel OD 250 $\times$ 4.0 mm column using 10% 2-propanol/hexane, flow rate 0.2 mL min^{-1} and UV detector (220 nm).

All alcohols were obtained commercially except for 1,4-butanediol. Dibutyl ether, *tert*-butyl methyl ether, diisopropyl ether, and 2-methyltetrahydrofuran were distilled from sodium under nitrogen. Phenyl methyl ether was vacuum distilled (95 °C/100 mmHg). THF and DME were freshly distilled from a sodium/potassium amalgam under argon. 1,2-Dimethoxy-1,2-diphenylethane was prepared by Dr A. S. Vellekoop.

1,4-Butanediol. 2-Butyne-1,4-diol (11.62 g, 135 mmol), ethyl acetate (250 mL), and platinum(IV) oxide ($\approx$0.3 g) were shaken under hydrogen (150 psi) for 3 h. The resulting mixture was filtered through a Celite pad, and the solvents were removed under reduced pressure. The resulting brown liquid was distilled using a Kugelrohr apparatus to give 1,4-butanediol (8.81 g, 72%) (bp 120 °C/10 mmHg) (lit.[19] bp 230 °C) as a colorless liquid: ^{1}H NMR δ (ppm) 3.67 (4H, m), 2.98 (2H, broad s, OH), 1.68 (4H, m).

Ether Preparation. The ethers were prepared[20] by the reaction of sodium methylsulfinyl carbanion[21] in dimethyl sulfoxide (DMSO) with the distilled alcohol followed by treatment with a dialkyl sulfate. Ethers with a boiling point above 120 °C were extracted. The DMSO reactions mixture was quenched by slow, dropwise addition of water and then extracted with Et$_2$O. The combined organic phase was washed with brine and water and dried (MgSO$_4$), and the solvents were removed under reduced pressure. The crude reaction product was then vacuum distilled using a Kugelrohr apparatus. Ethers with boiling points lower than 120 °C were recovered in low yields using the above extraction procedure; therefore, an alternate extraction method involving applying a vacuum (0.4 mmHg) to the briskly stirred DMSO reaction mixture was used. The volatile materials were collected in a receiver cooled in liquid nitrogen. Sodium metal was added to the distillate, and after 1 h, the product was vacuum distilled.

The following ethers were prepared and stored over sodium under argon: 1-methoxybutane[19] (68%), 2-methoxybutane[19] (80%), 2-ethoxybutane[19] (77%), 2-methoxyoctane[22] (bp 50 °C/20 mmHg, 43%), benzyl methyl ether[19] (bp 100 °C/100 mmHg, 81%), phenethyl methyl ether[23] (bp 65 °C/16 mmHg, 84%), 1,2-dimethoxypropane[19] (57%), 2,3-dimethoxybutane[24] (87%), 1,3-dimethoxypropane[25] (54%), and 1,4-dimethoxybutane[26] (bp 120 °C/16 mmHg, 45%).

General Method for Organometallic Reactions. (Details of Enone and Ether Are Given with Each Example.) Unless specified otherwise, reactions were as follows: CuI (0.228 g, 1.2 mmol) was weighed into a dry Schlenk tube, which was evacuated for 5 min then filled with argon. Dry, degassed toluene (10 mL) was added, and the resulting white suspension was cooled to −78 °C, with stirring. BuLi (2.2 mmol) was added, and the mixture was stirred for 30 min at −78 °C and

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Chart 1

1-Methoxybutane

w	products (mol %)	
(ME)	**2**	**3**
1.0	96	4
1.5	95	5
2.0	69	31
2.5	36	64
3.0	17	83
4.0	23	77
5.0	8	92

Dibutyl ether

w	products (mol %)	
(ME)	**2**	**3**
2.0	97	3
5.0	95	5

2-Methoxybutane

w	products (mol %)	
(ME)	**2**	**3**
1.0	97	3
1.5	97	3
2.0	63	37
3.0	21	79
4.0	15	85
5.0	10	90

***t*-Butyl methyl ether**

w	products (mol %)	
(ME)	**2**	**3**
1.0	97	3
2.0	75	25
3.0	55	45
4.0	54	46
5.0	44	56

Diisopropyl ether

w	products (mol %)	
(ME)	**2**	**3**
1.0	95	5
2.0	96	4
3.5	86	14
5.0	58	42

2-Ethoxybutane

w	products (mol %)	
(ME)	**2**	**3**
2.0	98	2
5.0	93	7

2-Methoxyoctane

w	products (mol %)	
(ME)	**2**	**3**
2.0	97	3
5.0	92	8

Phenyl methyl ether

w	products (mol %)		
(ME)	**1**	**2**	**3**
2.0	0	83	17
5.0	12	74	14

Benzyl methyl ether

w	products (mol %)		
(ME)	**1**	**2**	**3**
2.0	46	32	22
5.0	97	0	3

Phenethyl methyl ether

w	products (mol %)		
(ME)	**1**	**2**	**3**
2.0	0	62	38
5.0	12	31	57

Tetrahydrofuran

w	products (mol %)		
(ME)	**1**	**2**	**3**
1.0	0	93	7
1.5	0	41	59
2.0	0	28	72
3.0	7	16	77
4.0	17	14	69
5.0	40	13	47

2-Methyltetrahydrofuran

w	products (mol %)		
(ME)	**1**	**2**	**3**
1.0	0	96	4
1.5	0	82	18
2.0	0	21	79
3.0	0	10	90
4.0	4	8	88
5.0	16	6	78

1,2-Dimethoxyethane

w	products (mol %)		
(ME)	**1**	**2**	**3**
0.5	0	97	3
1.0	0	74	26
1.5	0	40	60
2.0	4	21	75
2.5	7	47	46
3.0	17	37	46
5.0	19	59	22

1,2-Dimethoxypropane

w	products (mol %)		
(ME)	**1**	**2**	**3**
0.50	0	86	14
1.00	10	40	50
1.50	23	34	43
1.75	29	37	34
2.00	30	42	28
5.00$^{\#}$	37	42	21

2,3-Dimethoxybutane

w	products (mol %)		
(ME)	**1**	**2**	**3**
1.0	0	88	12
2.0	18	6	19
3.0	23	55	22
4.0	21	55	24
5.0	13	59	28

1,2-Dimethoxy-1,2-diphenylethane

w	products (mol %)		
(ME)	**1**	**2**	**3**
2.0	8	92	0
5.0	9	91	0

1,3-Dimethoxypropane

w	products (mol %)		
(ME)	**1**	**2**	**3**
0.5	0	92	8
1.0$^{\#}$	0	79	21
1.5$^{\#}$	17	42	41
2.0$^{\#}$	21	37	42
3.0$^{\#}$	36	45	19
5.0$^{\#}$	82	9	9

1,4-Dimethoxybutane

w	products (mol %)		
(ME)	**1**	**2**	**3**
1.0$^{\#}$	0	95	5
1.5$^{\#}$	0	61	39
2.0	5	44	51
3.0	15	17	68
5.0	22	46	32

then for 15 min at −20 °C. Over this period the suspension darkened through grey to black. The mixture was then cooled to −40 °C, inoculated with various amounts of **ether**, and stirred for 10 min. This mixture was cooled to −78 °C; then **enone** (1.0 mmol) and GC internal standard (1.0 mmol) were added by syringe over 5−10 s. The mixture was stirred for 30 min at −40 °C and then quenched at −40 °C with an aqueous mixture of saturated ammonium chloride/ammonia (NH_4^+/NH_3). The resulting biphasic mixture was allowed to warm to room temperature when two aliquots (≈0.5 mL) were removed from the organic phase and were added to separate sample tubes, each containing NH_4^+/NH_3 (≈0.5 mL), and diluted with hexane (2 mL). The mixtures were shaken until all solid had dissolved and was allowed to settle, and the organic phase was analyzed by GC.

Reactions of 1:2:*w* CuI/BuLi/Ether Mixtures with 1. All reactions were run using the General Method, **ether** (*w*(ME)), **1** (155 μL, 1.0 mmol), and *n*-C_{12} as the GC internal standard (227 μL, 1.0 mmol). A black precipitate was obtained after the addition of some diethers, indicated by $^\#$ (Chart 1).

Reaction of a 1:2 CuI/BuLi Mixture with 1 in THF. The procedure was followed as for the General Method, except freshly distilled, dry degassed THF (10 mL) was used as the solvent and the entire reaction was carried out at −78 °C. The reaction mixture went black 30 min after BuLi addition. GC analysis of the reaction product showed **1** (40 mol %) and **2** (60 mol %).

Reactions of 1:2:*w* CuI/BuLi/2-Methoxybutane Mixture with 5 or 6. All reactions were carried out using the General Method, 2-methoxybutane (*w*(ME)) added directly, and **5** (0.146 g, 1.0 mmol, in toluene (2 mL)) or **6** (150 μL, 1.0 mmol).

n-Dodecane (*n*-C_{12}) (227 μL, 1.0 mmol) was used as the GC internal standard for reactions with **5**. The GC column was programmed 90 → 175 °C, 15 °C min^{-1}. Retention times (t_R) and response factors (R_f) for **5**, 1,2-[27] and 1,4-addition[28] products were

compd	t_R (min)	R_f
n-C_{12}	2.0	
5	2.9	1.35
1,2-	5.1	0.99
1,4-	4.3	0.95

n-Tetradecane (*n*-C_{14}) (260 μL, 1.0 mmol) was used as the GC internal standard for reactions with **6**. The GC column was programmed 90 → 130 °C, 7.5 °C min^{-1}. Under these conditions the retention times (t_R) and response factors (R_f) for **6**, 1,2-[8] and 1,4-addition[29] products were

compd	t_R (min)	R_f
n-C_{14}	4.9	
6	1.6	1.70
1,2-	2.0−3.8	1.25
1,4-	4.6	1.17

The results are given in Table 1.

(*S*)-(+)-2-Butanol. 2-Butanol was resolved with brucine *via* the hydrogen phthalate ester according to published procedures[30,31] in a 34.5% yield, $[\alpha]^{22}_D = +13.1°$ (neat) (lit.[30] $[\alpha]^{27}_D = +13.5°$ (neat), 97% ee). The ee was also determined by NMR analysis of the (*R*)-(−)-*O*-methylmandelic acid ester (98 ± 2%) and by GC analysis using a β-cyclodextrin column (98 ± 1%) (*cf.* Supporting Information).

(*S*)-(+)-2-Methoxybutane. This compound was prepared from (*S*)-(+)-2-butanol by following the standard volatile ether preparation method described above and gave (*S*)-(+)-2-methoxybutane (83%) (≈94% ee (*vide infra*)), $\alpha_D = +1.668°$, neat, 0.1 dm length, which based on density = 0.742 g mL^{-1}, gives $[\alpha]^{22}_D = +22.5°$. (lit.[17] $\alpha_D = +12.2°$ (neat) from 2-butanol $\alpha_D = +7.5°$ (neat), *i.e.* 69% ee). The estimated specific rotation for pure (*S*)-(+)-2-methoxybutane, assuming no racemization during alkylation, is $[\alpha]_D = +23.8°$.

***cis*-8a-Butyl-3,4,4a,5,6,7,8,8a-octahydro-4a-methyl-2-((trimethylsilyl)oxy)naphthalene.** The General Method for Organometallic Reactions using Et_2O (230 μL, 2 ME) and **1** (155 μL, 1.0 mmol) was followed except that after 30 min at −40 °C the reaction mixture was not quenched but cooled to −78 °C. Et_2O (10 mL) was added dropwise over 10 min, and the solution was warmed to −40 °C when chlorotrimethylsilane (382 μL, 3.0 mmol) and triethylamine (418 μL, 3.0 mmol) were added. The mixture was removed from the bath, stirred for 2 h, and then quenched with NH_4^+/NH_3 as usual. The total reaction mixture was poured into a separatory funnel, and the reaction Schlenk tube was washed consecutively with NH_4^+/NH_3 (10 mL) and hexane (10 mL) and shaken until a deep blue developed and all solids had dissolved. The layers were then separated. The aqueous layer was extracted with hexane (2 × 20 mL), and the combined organic extracts were washed with water (50 mL) and then dried ($MgSO_4$). The mixture was filtered after approximately 15 min, and solvents were evaporated under reduced pressure to give the product (0.292 g, 99%) as a colorless oil. Anal. Calcd for $C_{18}H_{34}OSi$: C, 73.40; H, 11.64. Found: C, 73.56; H, 11.96. IR: ν_{max} (cm^{-1}) (film) 1666 (C=C). ^{1}H NMR (300 MHz) δ (ppm): 4.63 (1H, broad s, H-1), 2.1−1.0 (18 H, m), 0.87 (6H, m, H-9 and H-13), 0.19 (9H, s, Si-Me_3). ^{13}C NMR (75 MHz) δ (ppm): 148.3 (C-2), 113.6 (C-1), 39.7, 34.3, 33.8, 32.5, 27.0, 26.3, 24.1, 23.2, 22.6, 22.1, 14.3, 0.54 (Si-CH_3).

Reactions of 1:2:*w* CuI/BuLi/(*S*)-2-Methoxybutane Mixtures. All reactions were performed using the General Method for Organometallic Reactions. GC internal standards were not added as in all reactions the 1,4-addition product was the major component (>90%).

Reaction with 5. (*S*)-2-Methoxybutane (523 μL, 4 ME), **5** (0.146 g, 1.0 mmol), and chiral HPLC analysis gave racemic 1,4-addition product (48.3:51.7) (t_R 24, 25 min).

Reaction with 6. (*S*)-2-Methoxybutane (523 μL, 4 ME), **6** (150 μL, 1.0 mmol), and chiral GC analysis gave racemic 1,4-addition product (50.2:49.8) (90 °C/95 min, 5 °C min^{-1} → 150 °C, t_R 103.2, 103.5 min).

Reaction with 1. (*S*)-2-Methoxybutane (654 μL, 5 ME) and **1** (310 μL, 2.0 mmol) were reacted as described for the preparation of *cis*-8a-butyl-3,4,4a,5,6,7,8,8a-octahydro-4a-methyl-2-((trimethylsilyl)oxy)naphthalene. Chiral GC analysis showed racemic recovered **1** (49.9:50.1) (150 °C, t_R 20.9 (*R*) and 21.2 (*S*) min), and silyl enol ether (49.2:50.8) (110 °C/30 min, 0.5 °C min^{-1} → 145 °C, t_R 99.4, 100.4 min).

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Supporting Information Available: Ee determination of (*S*)-(+)-2-butanol (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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