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The Remarkable Ability of Lithium Ion To Reverse the Stereoselectivity in the Conjugate Addition of Li[BuCuI] to a Chiral *N*-Crotonyl-2-oxazolidinone

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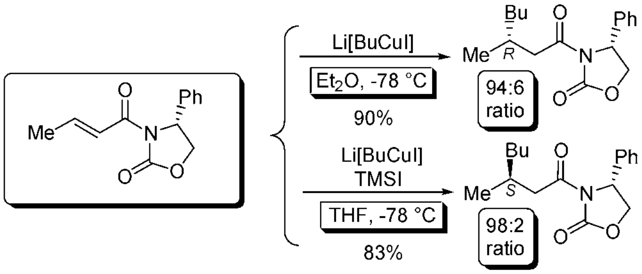
ABSTRACT



The influence of lithium ions on the conjugate addition of the monoorganocuprate reagent, Li[BuCuI], to a chiral crotonate has been investigated. The results show that iodotrimethylsilane (TMSI) is crucial for the asymmetric conjugate addition of the copper reagent, but only in THF or when 12-crown-4 is used. The reaction is thought not to involve any halosilane in any critical steps in the organocopper mechanisms conducted in Et$_2$O.

Organocopper reagents are among the most powerful reagents available for carbon−carbon bond formations.[1] The applications of organocopper chemistry started in 1966 when House[2a] demonstrated the Gilman reagents, LiR$_2$Cu, in conjugate addition reactions. However, one major disadvantage with the LiR$_2$Cu reagents is that one has to employ at least 2 equiv of the lithium reagent for each equivalent of Cu(I) source, which becomes more of an acute problem if expensive R groups are employed. The monoorganocuprate reagents, RCu·LiX or Li[RCuX],[2b] possess an excellent economy of group transfer, but their inherent lower reactivity and solubility have limited their widespread use in conjugate addition reactions. Such problems can be circumvented by taking advantage of nontransferable ligands[3] or Lewis acids[4] in the conjugate addition process. Chlorotrimethylsilane (TMSCl) is probably the most common additive employed with Gilman-type reagents.[5]

Several contradicting theories on the precise role of TMSCl in the addition of LiR$_2$CuLi have appeared,[5f−u] but it seems most likely TMSCl is responsible for a rate-limiting silylation of an intermediate copper π-complex.[5d,e] This mechanistic

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(1) (a) *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH GmbH: Weinheim, 2002. (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. (c) Taylor, R. J. K.; Casy, G. In *Organocopper Reagents—A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: New York, 1994. (d) Nakamura, E.; Mori, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3750−3771.

(2) (a) House, H. O.; Respess, W. L.; Whitesides, G, M. *J. Org. Chem.* **1966**, *31*, 3128−3141. (b) That the iodide ion is an important ligand for the transfer of the R group in "R" was recognized by House. See: House, H. O.; Fischer, W. F. *J. Org. Chem.* **1968**, *33*, 949−956.

(3) (a) Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 3911−3912. (b) Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1968**, *90*, 5615−5616. (c) Bertz, S. H.; Dabbagh, G.; Villacorta, G. M. *J. Am. Chem. Soc.* **1982**, *104*, 5824−5826. (d) Bertz, S. H.; Dabbagh, G. *J. Org. Chem.* **1984**, *49*, 1119−1122.

(4) Ibuka, T.; Yamamoto, Y. In *Organocopper Reagents—A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: New York, 1994.

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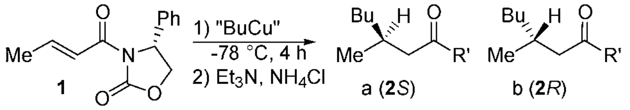
insight regarding organocuprate reactions was supported by determination of kinetic isotope effects for the TMSCl-mediated reactions of Li[Bu_2Cu] to enones in ether and THF.[5v] Because of the uncertainty of many variables in the organocopper reactions (e.g., cuprate structures, solvent, additives, reaction conditions, and substrate, as well as the cuprate cluster at each stage of the reaction pathway), a detailed mechanistic explanation has not yet emerged. However, it is generally accepted that the initial lithium−carbonyl coordination is a critical factor in the conjugate addition in the absence of additives, which seems to be a sufficient activator for highly reactive α,β-unsaturated systems. On the other hand, butylcopper prepared from BuLi and CuI in Et_2O, washed free from LiI, has been reported to undergo conjugate addition to a chiral enoate in the presence of iodotrimethylsilane (TMSI).[6c] Hence, even in absence of lithium, there is evidence that electrophiles more powerful than TMSCl, e.g., TMSI[6] and trimethylsilyl triflate,[6d] can facilitate the conjugate addition of butylcopper.

We have encountered two dramatically different solvent-dependent reaction pathways for the conjugate addition of Li[BuCuI]/TMSI to *N*-crotonyl-2-oxazolidinone (**1**)[7] (Table 1). Conducting the addition to (**1**) in THF afforded 96% de of product **2***S* (entry 1). On the other hand, conducting the conjugate addition in Et_2O, employing the same copper reagent system, gave 88% de of the other (**2***R*) diasteromer in 90% yield (entry 4). Due to the radical turn in diastereomeric ratio, several mechanistic questions for the iodosilane-promoted conjugate addition of Li[BuCuI] became apparent. The lithium ion is proposed to initially coordinate one or both carbonyl groups in the imide employing Et_2O, while a rapid silylation by TMSI of the copper π-complex is more likely the case in THF.

Table 1. Asymmetric 1,4-Additions



entry	Cu(I)[a]	reagent	additive(s)[b]	ratio (a:b)	yield[c]
1	**A**	Li[BuCuI]/THF	TMSI	98:2	83
2	**A**	Li[BuCuI]/THF	-	24:76	60(30)
3	**A**	Li[BuCuI]/THF	TMSCl	14:86	12(85)
4	**A**	Li[BuCuI]/Et_2O	TMSI	6:94	90
5	**A**	Li[BuCuI]/Et_2O	-	6:94	90
6	**A**	Li[BuCuI]/Et_2O (2 h)	TMSI	6:94	75(20)
7	**A**	Li[BuCuI]/Et_2O (2 h)	-	6:94	75(20)
8	**A**	Li[BuCuI]/Et_2O	TMSI/12♛4[d]	72:28	80
9	**A**	Li[BuCuI]/Et_2O	TMSI/12♛4[e]	96:4	80
10	**A**	Li[BuCuI]/Et_2O	12 ♛4[e]	-	0(90)
11	**B**[f]	Li[BuCuI]/THF	TMSI	90:10	50(45)
12	**B**	Li[BuCuI]/THF	-	44:56	12(85)
13	**B**	Li[BuCuI]/THF	TMSI	-	0(95)
14	**A**	Li[Bu_2Cu]LiI/THF	TMSCl	69:31	55(40)
15	**A**	Li[Bu_2Cu]LiI/Et_2O	TMSCl	45:55	85

[a] "RCu" (1.5 equiv) vs **1**. **A** = CuI purified via DMS and used as the $(CuI)_4(DMS)_3$ complex. **B** = 99.999% grade CuI. [b] Halosilane (1.0 equiv) vs copper reagent. [c] Based on isolated and purified material (a + b)%. Recovered **1** in brackets. [d] 12-Crown-4 (1.0 equiv) vs lithium. [e] 12-Crown-4 (2 equiv) vs lithium. [f] DMS (0.75 equiv) was added to CuI.

The presence of TMSI is crucial for high stereoselectivity and yield, but only in THF. Avoiding TMSI in the addition of Li[BuCuI] in THF not only decreased the rate of the reaction but also provided an excess of diastereomer **2***R* (entry 2). This same major diastereomer was obtained in much greater excess and yield in Et_2O (entry 4). As the initial lithium carbonyl interaction seems stronger in Et_2O compared to THF, the imide is allowed to more readily undergo a conjugate addition via the proposed lithium-chelated syn-s-cis conformation rather than the anti-s-cis conformer. This same syn-s-cis chelated metal complex has been proposed for the $MgBr_2$-promoted addition of Li[BuCuI] to **1**.[7f,8]

Surprisingly, we found that the presence of TMSI for the addition of Li[BuCuI] to **1** in Et_2O was unnecessary (entry 5). The results, including rates, yields, and selectivities, were identical independently of the presence of TMSI in the conjugate addition of Li[BuCuI] to **1** in Et_2O (entry 6). By quenching the Li[BuCuI] reactions after 2 h instead of the standard 4 h reaction time, the same yield as well as stereoselectivity was obtained with or without the presence of TMSI (entry 7). Employing 1 equiv of 12-crown-4 relative to Li[BuCuI]/TMSI in Et_2O increased the influence of the iodosilane as the silylating agent (entry 8). Increasing the amount of crown ether to 2 equiv afforded an increased stereoselectivity in favor of product **2***R* (entry 9). 12-Crown-4

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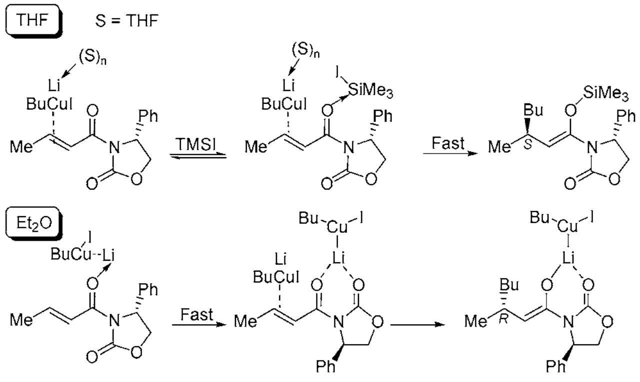
(5) (a) Chuit, C.; Foulon, J. P.; Normant, J. F. *Tetrahedron* **1980**, *36*, 2305−2310. (b) Chuit, C.; Foulon, J. P.; Normant, J. F. *Tetrahedron* **1981**, *37*, 1385−1389. (c) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc*. **1984**, *106*, 3368−3370. (d) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett*. **1985**, *26*, 6015−6018. (e) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett*. **1985**, *26*, 6019−6022. (f) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett*. **1986**, *27*, 1047−1050. (g) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett*. **1986**, *27*, 4025−4028. (h) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett*. **1986**, *27*, 4029−4032. (i) Linderman, R. J.; Godfrey, A. *Tetrahedron Lett*. **1986**, *27*, 4553−4556. (j) Johnson, C. R.; Marren, T. J. *Tetrahedron Lett*. **1987**, *28*, 27−30. (k) Lindstedt, E.-L.; Nilsson, M.; Olsson, T. *J. Organomet. Chem*. **1987**, *334*, 255−261. (l) Smith, A. B.; Dunlap, N. K.; Sulikowski, G. A. *Tetrahedron Lett*. **1988**, *29*, 439−442. (m) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349−362. (n) Corey E. J.; Hannon, F. J.; Boaz, N. W. *Tetrahedron* **1989**, *45*, 545−555. (o) Horiguchi, Y.; Komatsu, M.; Kuwajima, I. *Tetrahedron Lett*. **1989**, *30*, 7087−7090. (p) Alexakis, A.; Sedrani, P.; Mangeney, P. *Tetrahedron Lett*. **1990**, *31*, 345−348. (q) Sakata, H.; Aoki, Y.; Kuwajima, I. *Tetrahedron Lett*. **1990**, *31*, 1161−1164. (r) Bertz, S. H.; Smith, R. A. J. *Tetrahedron* **1990**, *46*, 4091−4100. (s) Lipshutz, B. H.; Dimock, S. H.; James. B. *J. Am. Chem. Soc*. **1993**, *115*, 9283−9284. (t) Bertz, H. B.; Miao, G.; Rossiter, B. E.; Snyder, J. P. *J. Am. Chem. Soc*. **1995**, *117*, 11023−11024. (u) Lipshutz, B. H.; Aue, D. H.; James, B. *Tetrahedron Lett*. **1996**, *37*, 8471−8474. (v) Frantz, D. E.; Singleton, D. A. *J. Am. Chem. Soc*. **2000**, *122*, 3288−3295.

(6) (a) Bergdahl, M.; Lindstedt, E.-L.; Nilsson, M.; Olsson, T. *Tetrahedron* **1988**, *44*, 2055−2062. (b) Bergdahl, M.; Lindstedt, E.-L.; Olsson, T. *J. Organomet. Chem*. **1989**, *365*, c11−14. (c) Bergdahl, M.; Nilsson, M.; Olsson, T.; Stern, K. *Tetrahedron* **1991**, *47*, 9691−9702. (d) Bergdahl, M.; Iliefski, T.; Nilsson, M.; Olsson, T. *Tetrahedron Lett*. **1995**, *36*, 3227−3230.

(7) (a) Nicolás, E.; Russel, K. C.; Hruby, V. J. *J. Org. Chem*. **1993**, *58*, 766−770. (b) Lou, B.-S.; Li, G.; Lung, F.-D.; Hruby, V. J. *J. Org. Chem*. **1995**, *60*, 5509−5514. (c) Qian, X.; Russel, K. C.; Boteju, L. W.; Hruby, V. J. *Tetrahedron* **1995**, *51*, 1033−1054. (d) Andersson, P. G.; Schink, H. E.; Österlund, K. *J. Org. Chem*. **1998**, *63*, 8067−8070. (e) Williams, D. R.; Kissel, W. S.; Li, J. J. *Tetrahedron Lett*. **1998**, *39*, 8593−8596. (f) Schneider, C.; Reese, O. *Synthesis* **2000**, 1689−1694.

(8) Pollock, P.; Dambacher, J.; Anness, R.; Bergdahl, M. *Tetrahedron Lett*. **2002**, *43*, 3693−3697.

Scheme 1. Proposed Influence of the Lithium Ion



Gilman-type reagents have been characterized by crystallography, where it was shown that each lithium ion is coordinated to two 12-crown-4 molecules.[9] We propose that the lithium−carbonyl coordination in Et_2O is kinetically favored over TMSI−carbonyl interaction, even though the iodosilane is highly electrophilic.[10] The results reported show that TMSI appears to coordinate very favorably to the carbonyl group in THF or in the presence of 12-crown-4.[11] When Li[BuCuI] is added to **1** in the absence of TMSI either in THF (entry 2) or in the presence of 2 equiv of 12-crown-4 (entry 10), the initial lithium carbonyl interaction decreases, as shown by the significant drop in yield.

Scheme 1 depicts the different proposed mechanisms of the conjugate addition reaction conducted in THF relative to Et_2O that rationalize the shift in stereoselectivity. TMSI is proposed to rapidly silylate an initial copper π-complex in THF, thus allowing the copper reagent to add to **1** via the most available π-face of the s-cis enone with the imide carbonyls adopting an anti nonchelated conformation. The rapid silylation of an initial copper π-complex has been proposed not only for the Me_2CuLi/TMSCl[5d,e,v] combination but also for Li[BuCuI]/TMSI in additions to cyclohexenone,[12] a process that is shown here to be favored only in THF.[13] In Et_2O, a lithium species is believed to chelate the carbonyl groups preceding the formation of the copper π-complex,[14,15] thereby allowing the addition to occur with the most available π-face of the imide in an s-cis conformation, yielding an excess of the other diastereomer (**2***R*). Although formation of an α-cuprioketone[16] has been reported for Gilman-type reagents as a favored intermediate, it cannot be neglected as one possible intermediate also for the Li[BuCuI] reagent. The nature of the monoorganocopper species forming the π-complex[17] depicted is unknown, but there is the possibility for dimers[18] and higher oligomers.[19]

Quite surprisingly, employing 1 equiv TMSCl relative to lithium has a retarding effect on the conjugate addition of Li[BuCuI] (entry 3). Compared to the more electrophilic TMSI (entry 1), TMSCl is proposed to inhibit the reactivity of the Li[BuCuI] reagent either via a chlorine−copper or chlorine−lithium interaction. As expected, when 1 equiv of TMSCl was employed in combination with the more reactive Gilman reagent, $Li[Bu_2Cu]LiI$ showed a moderate solvent dependence; a slower reaction was observed in THF[20] (entry 14) relative to Et_2O (entry 15).

As a final point, the Li[RCuI] reagent is a versatile reaction system that provides a more economical use of the "R" groups compared with the Gilman-type reagents. It was instrumental to use the CuI−dimethyl sulfide complex (CuI·0.75DMS)[21] instead of the high-purity-grade CuI. Entries 10−12 demonstrate the effect of DMS, either by precomplexation[22a] or subsequent addition,[22b] on the solubility and reactivity of the copper reagent.

In summary, this paper shows that monoorganocuprate reagents react at −78 °C as long as the CuI·0.75DMS is employed.[23] Even though the exact mechanistic details of the organocopper reactions are still quite elusive, a qualitative pattern using the Li[RCuI] reagent system is emerging.

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Supporting Information Available: Experimental procedures and spectral data (^1H NMR, ^{13}C NMR, MS, and IR) for pertinent compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] Hope, H.; Olmstead, M.; Power, P. P.; Sandell, J.; Xu, X. *J. Am. Chem. Soc.* **1985**, *107*, 4337−4338.

[10] (a) Bergdahl, M.; Eriksson, M.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1993**, *58*, 7238−7244. (b) Eriksson, M.; Iliefski, T.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1997**, *62*, 182−187.

[11] Lithium ion solvation energies and bond lengths have been reported: Li−carbonyl (1.746 Å), Li−THF (1.798 Å), and Li−ether (1.807 Å). See: Jarek, R. L.; Miles, T. D.; Trester, M. L.; Denson, S. C.; Shin, S. K. *J. Phys. Chem. A* **2000**, *104*, 2230−2237.

[12] Eriksson, M.; Johansson, A.; Nilsson, M.; Olsson, T. *J. Am. Chem. Soc.* **1996**, *118*, 10904−10905.

[13] TMS−ketene amide intermediates are observed in the ^1H NMR spectra if anhydrous Et_3N is added; see ref 10a.

[14] For the influence of polar solvent to alter the chemoselectivity using the $LiMe_2Cu$ reagent, see: House, H. O.; Lee, T. V. *J. Org. Chem.* **1978**, *43*, 4369−4371.

[15] THF is an exceptional ligand for lithium ions; see: (a) Remenar, J. F.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5567−5572. (b) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448−454.

[16] (a) Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11025−11026. (b) Dorigo, A. E.; Wanner, J.; von Ragué Schleyer, P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 476−478. See also ref 1d.

[17] For a recent NMR study on π-complex formation, see: Bertz, S. H.; Carlin, C. M.; Deadwyler, D. A.; Murphy, M. D.; Ogle, C. A.; Seagle, P. H. *J. Am. Chem. Soc.* **2002**, *124*, 13650−13651.

[18] $MeCu(LiCl)_2$ has been reported to be favorable, see: Nakamura, E.; Mori, S.; Morokuma, K. *J. Am. Chem. Soc.* **1998**, *120*, 8273−8274.

[19] Olmstead, M.; Power, P. P. *J. Am. Chem. Soc.* **1990**, *112*, 8008−8014.

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

[21] For a discussion on the stability of CuI/DMS complex, see: Eriksson, M.; Hjelmencrantz, A.; Nilsson, M.; Olsson, T. *Tetrahedron* **1995**, *51*, 12631−12644.

[22] (a) House, H.; Chu, C.; Wilkins, J.; Umen, M. *J. Org. Chem.* **1975**, *40*, 1460−1469. (b) Bertz, S.; Dabbagh, G. *Tetrahedron* **1989**, *45*, 425−434.

[23] For corresponding monosilylcopper reagents in asymmetric conjugate additions, see: Dambacher, J.; Bergdahl, M. *Chem. Commun.* **2003**, 144−145.