Direct Copper(I) Iodide Dimethyl Sulfide Catalyzed Conjugate Addition of Alkenyl Groups from Vinylzirconocene Reagents
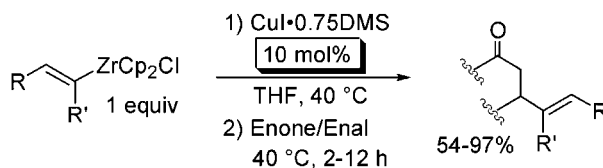
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ABSTRACT

CuI·0.75DMS complex is an excellent catalyst for the direct conjugate addition of alkenyl groups from vinylzirconocene reagents to α,β-unsaturated aldehydes and ketones. The presence of the catalyst with an alkenylzirconocene, at +40 °C in THF, circumvents the need for making discrete alkenylcopper reagents. The catalyst is superior in terms of product yields and alkene flexibility in comparison to other copper(I) sources as well as the nickel(II)-catalyzed conjugate addition. This simple one-pot procedure shows that only 1 equiv of the vinylzirconocene is needed.

Organocopper reagents are some of the most versatile compounds available for creating carbon−carbon bond connections.[1] Specifically, the copper-promoted conjugate addition of vinyl groups to α,β-unsaturated carbonyl compounds is a very useful transformation in organic synthesis.[2] Although organocuprate chemistry routinely takes advantage of milder organometallic nucleophiles,[1d] the vinylcopper reagents commonly originate from the corresponding organolithium and organomagnesium compounds.[1c] These reactive and strongly basic precursors, in the synthesis of the corresponding cuprate reagents, occasionally complicate the experimental procedures and might limit tolerance of other functional groups. Moreover, a stoichiometric quantity of the copper(I) source makes the reaction less appealing, particularly for scale-up. To activate the vinylzirconocene reagent and simultaneously utilize the copper(I) source as the catalyst, Lipshutz[2a] introduced MeLi,[2g] Me$_2$CuLi,[2c] or Me$_3$ZnLi.[2b] Thus, less basic but sufficiently nucleophilic reagents have been required to generate discrete alkenylcuprate reagents.

Hydrozirconation of alkynes, utilizing Schwartz's reagent[3a] {Cp$_2$Zr(H)Cl},[3b] is a superb protocol for making regioselective vinylzirconocene reagents. Although the valuable vinylzirconium intermediates have been used in various coupling reactions,[4] there is no method available for utilizing a combination of the vinylzirconocene and a catalytic amount of copper(I) source directly in the conjugate addition of

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(2) (a) Lipshutz, B. H. *Acc. Chem. Res.* **1997**, *30*, 277−282. (b) Lipshutz, B. H.; Wood, M. R. *J. Am. Chem. Soc.* **1993**, *115*, 12625−12626. (c) Lipshutz, B. H.; Keil, R. *J. Am. Chem. Soc.* **1992**, *114*, 7919−7920. (d) Wipf, P.; Smitrovich, J. H.; Moon, C.-W. *J. Org. Chem.* **1992**, *57*, 3178−3186. (e) Lipshutz, B. H.; Keil, R.; Barton, J. C. *Tetrahedron Lett.* **1992**, *33*, 5861−5864. (f) Lipshutz, B. H.; Kato, K. *Tetrahedron Lett.* **1991**, *32*, 5647−5650. (g) Lipshutz, B. H.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 7440−7441. (h) Babiak, K. A.; Behling, J. R.; Dygos, J. H.; McLaughlin, K. T.; Ng, J. S.; Kalish, V. J.; Kramer, S. W.; Shone, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 7441−7442.

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(4) (a) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853−12910. (b) Negishi, E.; Takahashi, T. *Synthesis* **1988**, 1−19. (c) Negishi, E.; Takahashi, T. *Aldrichimica Acta* **1985**, *18*, 31−48. (d) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340−348.

alkenyl groups.[5] Our results using the copper(I)-based catalysts were inspired from the CuBr·DMS (DMS = dimethyl sulfide)-catalyzed conjugate addition of an alkyl-zirconocene reported by Wipf.[6] Furthermore, our finding that the CuI·0.75DMS complex allows for the conjugate addition of monosilylcopper reagents[7] to occur in THF motivated us to explore the idea of transferring alkenyl groups from vinylzirconocenes directly utilizing CuI·0.75DMS in 1,4-additions.

We now report that by adding 10 mol % of CuI·0.75DMS[8] to 1.0 equiv of an alkenylzirconocene, it is possible to conduct a direct transfer of the vinyl groups to α,β-unsaturated aldehydes and ketones in high yields (54−97%). The process reported herein is a simple protocol having a very good economy of group transfer (Scheme 1).

Scheme 1
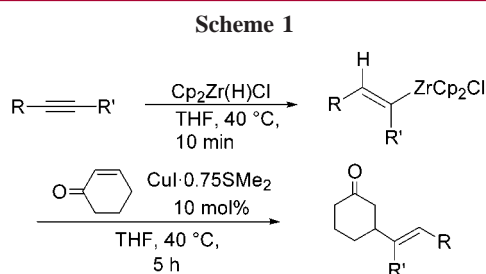
The catalytic efficiency of the CuI·0.75DMS complex prevailed when compared to various other copper sources in the conjugate addition of 1-hexenylzirconocene to benzalacetone (Table 1). The catalytic efficiency is furthermore illustrated from the result using 1 mol % of CuI·0.75DMS (entry 4) and demonstrated in the acquired high yield (entry 2) compared to the yield obtained using the 99.999% grade CuI (entry 5).

Although the yield increased by adding excess DMS to CuI (entry 6), the yield was nonetheless lower than when employing the DMS-purified CuI complex. Replacing DMS with the more basic phosphines (entry 7) or the bulkier diisopropyl sulfide[9] (entry 8) resulted in lower yields. Copper salts purified via their DMS complex render these salts more soluble in THF or diethyl ether, which in turn amplifies reactivity and stability, particularly in neat dimethyl sulfide.[10] Less soluble and less efficient Cu(I) catalysts also included

(5) Loots, M. J.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 8045−8046. For an initial observation that CuOTf facilitates the 1,4-addition of vinyl groups, see ref 3a.

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(7) Dambacher, J.; Bergdahl, M. *Chem. Commun.* **2003**, 144−145.

(8) The CuI·DMS complex is unstable and loses rapidly DMS to form the more stable CuI·0.75DMS stoichiometry, as determined by elemental analysis. For a discussion on the stability of CuI·DMS complex, see: Eriksson, M.; Hjelmencrantz, A.; Nilsson, M.; Olsson, T. *Tetrahedron* **1995**, *51*, 12631−12644. See also: Eriksson, M.; Iliefski, T.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1997**, *62*, 182−187. For CuI purified via its dimethyl sulfide complex, see: House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.*, **1975**, *40*, 1460−1469.

(9) For some initial conjugate additions in the presence of (*i*-Pr)₂S, see: Corey, E. J.; Carney, R. L. *J. Am. Chem. Soc.* **1971**, *93*, 7318−7319. Clark, R. D.; Heathcock, C. H. *Tetrahedron Lett.* **1974**, 1713−1715.

(10) Bertz, S. H.; Dabbagh, G. *Tetrahedron* **1989**, *45*, 425−434.

Table 1. Influence of Copper Source on 1,4-Addition
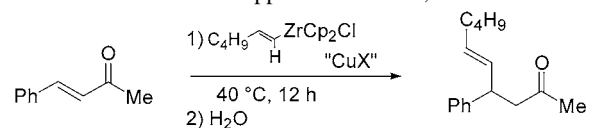
entry[a]	copper(I) source	mol. equiv Cu(I)	yield[b]
1	CuI·0.75DMS	1.00	97
2	CuI·0.75DMS	0.10	97
3	CuI·0.75DMS	0.05	89
4	CuI·0.75DMS	0.01	79
5	CuI[c]	0.10	34
6	CuI·DMS[d]	0.10	68
7	CuI·2PBu₃[e]	0.10	32
8	CuI·2PPh₃[e]	0.10	16
9	CuI·0.75S(*i*-Pr)₂[f]	0.10	52
10	CuBr·DMS	0.10	20
11	None	-	0
12	CuBr	0.10	0
13	LiCuBr₂	0.10	0
14	CuCl	0.10	2
15	CuCN	0.10	10
16	CuCN·2LiCl	0.10	10
17	CuOTf·PhMe	0.10	0

[a] 1.0 equiv of alkyne versus benzalacetone. [b] Based on isolated and purified material (%). [c] Aldrich ultrapure grade (99.999%). [d] 60 equiv of DMS added to 99.999% grade CuI. [e] 2 equiv of PR₃ added to 99.999% grade CuI. [f] CuI purified via CuI·S(*i*-Pr)₂ and used as the solid CuI·0.75S(*i*-Pr)₂ complex.

CuBr, CuCl, CuCN, and CuOTf. It is worth mentioning the formation of copper mirror precipitation in the low yielding reactions, which suggests that the specific alkenylzirconium/copper(I) combinations sometimes were unstable under the conditions specified. Exposing a styrylzirconocene reagent to 100 mol % CuCl[3a] at 20 °C in the absence of enone gave 69% of 1,4-diphenylbutadiene (Scheme 2). Under similar

Scheme 2
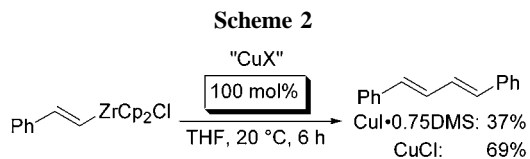
reaction conditions using 100 mol % CuI·0.75DMS, the rate of formation of the coupling product decreased. However, in the presence of 10 mol % CuI·0.75DMS and 1 equiv of 2-cyclohexenone at 40 °C, formation of diene product did not occur,[11] which suggests that the carbonyl group in the enone has a stabilizing effect on the vinylzirconocene copper-(I) complexation in the conjugate addition.

The efficiency of the CuI·0.75DMS complex in conjugate additions is further illustrated for a number of enones and enals (Table 2). Treatment of various alkynes with Schwartz's reagent, Cp₂Zr(H)Cl, in THF at 40 °C for 10 min afforded

(11) Based on ¹H NMR data obtained from crude reaction mixtures.

Table 2. Conjugate Additions of Vinyl Groups

enone	alkyne[a]	cond.[b]	product	yield[c]
Ph—CH=CH—C(O)—Me	C₄H₉—C≡CH	12 h	(1-hexenyl adduct)	97[d]
	Et—C≡C—Et	12 h		86[d]
	Ph—C≡CH	12 h		79[d]
2-methylcyclopentenone	C₄H₉—C≡CH	5 h		54[d] 87[e]
cyclohexenone	Ph—C≡CH	5 h		78[d]
Me—CH=CH—CHO	C₄H₉—C≡CH	2 h		90[d]
BocNH—CH₂—C≡CH		2 h		88[d]
Ph—CH=CH—C(O)—Ph	C₄H₉—C≡CH	10 h		84[d]
	Et—C≡C—Et	10 h		71[d]

[a] 1.0 equiv of alkyne versus enone. [b] 40 °C. [c] Based on isolated and purified material (%). [d] 10 mol % CuI·0.75DMS versus alkyne. [e] 100 mol % CuI·0.75DMS, *trans:cis* ratio 20:1.

the corresponding vinylzirconocenes,[3a] which subsequently were exposed to 10 mol % CuI·0.75DMS and the substrates at 20 °C. Increasing the temperature of the resulting mixture to 40 °C afforded the 1,4-adducts in high yields after the time indicated. The results illustrated exemplify the exceptional capability and synthetic potential of this novel conjugate addition method. Addition of the 1-hexenyl group to crotonaldehyde yielded the corresponding adduct in 90%, which suggests that there is not much oligomerization of the zirconium enolate. The results illustrated show that the catalytic amount of CuI·0.75DMS is a better catalyst compared to the reported[5] nickel(II)-catalyzed conjugate additions of vinylzirconocenes in terms of catalytic efficiency, product yields, and the flexibility of various vinylzirconocene reagents.
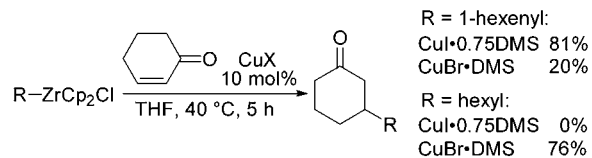
Although the mechanism for the CuI·0.75DMS-catalyzed conjugate addition of alkenyl groups is quite obscure, there seems to be a mechanistic resemblance to the proposed CuBr·DMS-catalyzed conjugate addition of alkyl groups from alkylzirconocenes reported by Wipf.[12] Thus, a simultaneous three-component transition state is postulated partly on the

basis of the lack of formation of diene in the presence of enone (Scheme 3). Furthermore, the π-base complexation

Scheme 3
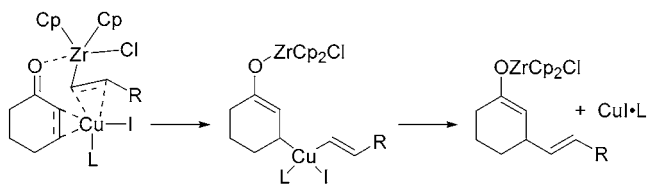
of the Zr-alkene to Cu(I) is more favored with iodide as a π-donor ligand compared to bromide. The formation of a putative alkylvinyl-cuprate[13] intermediate could next undergo a fast reductive elimination step to form the zirconium enolate product. In the case of the alkenylzirconocenes, CuBr·DMS fails to achieve a promising yield whereas CuI·0.75DMS produces a very high yield.

In sharp contrast, the conjugate addition of alkylzirconocenes using CuBr·DMS[6a] produced a high yield of product, but the corresponding conjugate addition employing CuI·0.75DMS did not produce any 1,4-addition product (Scheme 4).

Scheme 4

R–ZrCp₂Cl + (cyclohexenone) → (product)
CuX 10 mol%
THF, 40 °C, 5 h

R = 1-hexenyl:
CuI·0.75DMS 81%
CuBr·DMS 20%

R = hexyl:
CuI·0.75DMS 0%
CuBr·DMS 76%

In summary, a novel method utilizing CuI·0.75DMS as a catalyst in conjugate addition of alkenyl groups derived from vinylzirconocene reagents to α,β-unsaturated aldehydes and ketones has been developed. While the simple CuI·0.75DMS complex is required only in catalytic amounts, no additional transmetalation steps are required in order to obtain high yields in the conjugate addition step. We show that our conjugate addition method works extraordinarily well for internal and terminal alkynes, as well as NHBoc-substituted alkynes. The catalytic efficiency of the CuI·0.75DMS complex is currently being explored with various types of α,β-unsaturated substrates. Further synthetic developments will be reported in due course.

(12) There is no evidence for the formation of a discrete alkenylcopper compound via a Zr → Cu transmetalation step. For an extensive mechanistic study using alkylzirconocenes in conjugate additions, see: Wipf, P.; Xu, W.; Smitrovich, J. H.; Lehmann, R.; Venanzi, L. M. *Tetrahedron* **1994**, *50*, 1935−1954.

(13) A few stable copper(III) species have been isolated, see: (a) Willert-Porada, M. A.; Burton, D. J.; Baenziger, N. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1633−1634. (b) Naumann D.; Roy, T.; Tebbe, K.-F.; Crump, W. *Angew. Chem.* **1993**, *105*, 1555−1556. (c) Naumann D.; Roy, T.; Tebbe, K.-F.; Crump, W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1482−1483. (d) Eujen, R.; Hoge, B.; Brauer, D. J. *J. Organomet. Chem.* **1996**, *519*, 7−20.