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Copper(I) iodide dimethyl sulfide catalyzed 1,4-addition of alkenyl groups from alkenyl-alkylzincate reagents

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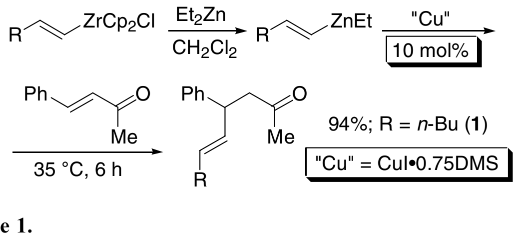
Abstract—The presence of catalytic quantities of the copper(I) iodide dimethyl sulfide complex $\{(CuI)_4(SMe_2)_3\}$ with alkenyl-alkylzincate reagents allows for the complete chemoselective 1,4-addition of various alkenyl groups to a number of α,β-unsaturated carbonyl compounds in CH_2Cl_2 at +35 °C. The 1,4-addition of the mixed vinylzincate reagent is more efficient than the corresponding vinylzirconocene reagent in CH_2Cl_2 or THF. By employing CH_2Cl_2 as a medium, the asymmetric copper-catalyzed addition of the vinyl groups to α,β-unsaturated imides is facilitated by the presence of TMSOTf to give excellent yields and up to 95:5 diastereomeric ratios (dr).

The use of Schwartz's reagent[1a–c] $\{Cp_2Zr(H)Cl\}$[1d] in the regioselective hydrozirconation of alkynes is a versatile method for making synthetically useful organometallic reagents. Although organozirconocenes have been used in many applications in organic chemistry,[2] the transmetalation from zirconium to zinc has been demonstrated to be a more efficient subsequent procedure toward the creation of carbon–carbon bonds.[3] In a sharp contrast to the more reactive organolithium or Grignard reagents, the corresponding organozinc reagents have distinguished themselves to be more compatible with various functional groups.[4] The process to form such sufficiently nucleophilic alkenylzincate intermediates and their subsequent 1,2-addition reactions to aldehydes was introduced by Wipf,[3g] and more recently the enantioselective 1,2-vinylation of ketones was reported by Walsh.[5]

Copper(I) catalysis in promoting the 1,4-addition of alkenyl groups is not only a very useful transformation in synthetic chemistry,[6] but it is also a complementary resource to the use of more reactive discrete alkenylcuprate reagents. Moreover, applying a stoichiometric quantity of the copper(I) source makes the reaction less appealing, particularly for scale-up. In order to maintain the catalytic efficiency of Cu(I), reagents such as Me_3ZnLi,[2e] Me_2CuLi,[2f] or MeLi[2g] have been reported necessary for the activation of the vinylzirconocene reagents to be able to undergo conjugate addition reactions. We recently reported[7] the direct conjugate addition of the vinyl group in high yields from the corresponding alkenylzirconocene reagent in the presence of the CuI·0.75DMS catalyst (DMS = dimethyl sulfide) in THF conducted at 40 °C. We now report that the CuI·0.75DMS complex is also a good catalyst for selective and high yield 1,4-additions of vinyl groups using mixed alkenyl-alkylzincate reagents in CH_2Cl_2 at 35 °C.

The simple protocol reported herein is initiated by the hydrozirconation of an alkyne using $Cp_2Zr(H)Cl$ in CH_2Cl_2, followed by in situ transmetalation with Et_2Zn (Scheme 1).[8] The corresponding alkenylzincate reagent is subsequently exposed to 10 mol % of the CuI·0.75DMS catalyst and the enone. The reaction of the 1-hexenylzincate with benzalacetone utilizing the CuI·0.75DMS complex to give the 1,4-product in 94% illustrates the efficiency of this Cu(I) catalyst.[9] Not only is the formation of the 1,2-addition product completely circumvented in this process, but also the 1,4-addition of



Scheme 1.

Keywords: Copper catalyzed; Conjugate addition; 1,4-Addition.

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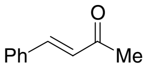
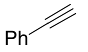
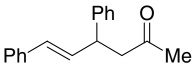
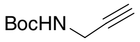
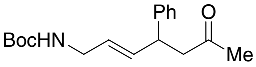
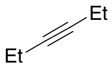
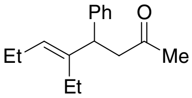
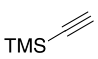
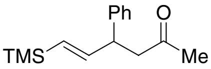
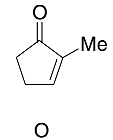
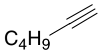
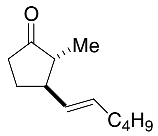
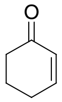
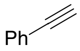
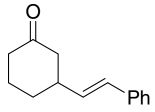
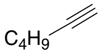
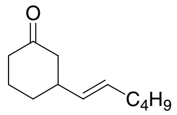
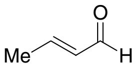
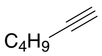
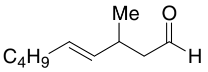
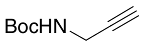
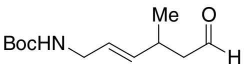
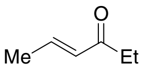
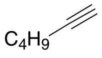
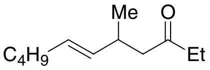
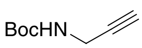
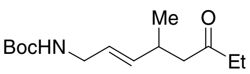
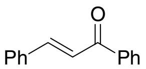
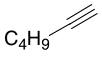
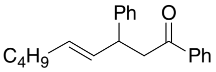
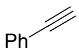
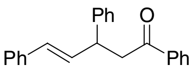
the vinylzincate reagent is faster than the corresponding vinylzirconocene reagent in CH_2Cl_2. Moreover, the copper-catalyzed addition of vinylzincate reagent in CH_2Cl_2 is not only faster, but the yield of the 1,4-addition product is higher than the corresponding copper-catalyzed 1,4-addition of vinylzirconocene reagents in THF.[7]

The unique efficiency of the dimethyl sulfide-containing copper(I) iodide complex[10] in the conjugate addition of alkenylzinc reagents is demonstrated using a number of enals and enones (Table 1). The results exemplify the capability and the synthetic potential of this protocol. It is important to note the efficiency of the Et_2Zn reagent

Table 1. CuI·0.75DMS-catalyzed 1,4-additions of vinyl groups to enals and enones in CH_2Cl_2

Entry	Substrate	Alkyne[a]	Reaction time[b]	Product	Yield[c,d]
1			6 h	 **2**	82[e] 33[f]
2			6 h	 **3**	89[e] 29[f]
3			6 h	 **4**	82[e]
4			6 h	 **5**	84[e]
5			2 h	 **6**	67[e,g] 27[f]
6			2 h	 **7**	74[e]
7			2 h	 **8**	83[e] 39[f]
8			30 min	 **9**	88[e] 41[f]
9			30 min	 **10**	82[e]
10			4 h	 **11**	95[e] 39[f]
11			4 h	 **12**	93[e]
12			6 h	 **13**	91[e] 51[f]
13			6 h	 **14**	79[e]

[a] 1.0 equiv alkyne versus enone.

[b] 35 °C in CH_2Cl_2.

[c] Isolated and purified material (%).

[d] 10 mol % CuI·0.75DMS versus alkyne.

[e] Reaction conducted with vinylzincate reagent.

[f] Reaction conducted with vinylzirconocene reagent (absence of Et_2Zn).

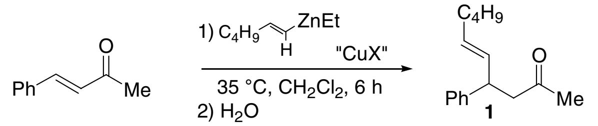
[g] Trans–cis ratio, ~20:1.

in CH_2Cl_2. Attempts to conduct the reaction using the vinylzirconocene intermediate directly in CH_2Cl_2, without in situ transmetalation with the dialkylzinc reagent, resulted in lower yields of the desired products and recovered starting materials (e.g., entry 1). The Cu(I) catalyst promotes the selective 1,4-addition transfer of the vinyl group over the ethyl group[11] from the mixed alkenyl-alkylzinc reagent, which presumably is due to the pre-formation of a more favorable sp^2-hybridized carbon to copper bond. Our results show that not only terminal alkynes, but also internal alkynes are favored in the 1,4-addition of vinyl groups. Functional groups such as TMS and NHBoc, do not create drawbacks. The fact that good chemical yields are obtained with enones and enals implies that there is little, if any, oligomerization occurring. Normally, this is a common side reaction between aldehydes and the enolates generated from conventional Gilman type organocopper reagents.

The catalytic efficiency of the CuI·0.75DMS complex is unique when it is compared to other complementary copper(I) and copper(II) sources in the 1,4-addition of a vinyl group utilizing a mixed vinylzincate reagent (Table 2). It is not entirely surprising that the mixed alkenyl-alkylzinc reagent displays both 1,4- and 1,2-addition pathways with benzalacetone in CH_2Cl_2 in the absence of a Cu(I) catalyst (entry 10), but it is unexpected that both these reaction pathways are shut down in the presence with most of the scrutinized copper catalysts. Moreover, the amount of the diene coupling product suggests that the Cu(I) species maintains its role as a catalyst in those side reactions. On the other hand, the presence of only 10 mol % of the CuI·0.75DMS complex (entry 1) circumvents the formation of this 'Glaser-type' coupling product and provides in its place a high yield of the conjugate addition product from benzalacetone.

The CuI·0.75DMS catalyzed 1,4-addition of the alkenylzincate reagent is more efficient compared to the corresponding alkenylzirconocene using CH_2Cl_2 as a medium (Table 1). In terms of solvent efficiency, it is worth mentioning that the CuI·0.75DMS catalyzed 1,4-addition of the vinylzincate reagent in solvents such as THF or toluene gave at best 60% of the conjugate product **1** after 6 h at 35 °C, while the yield is considerably higher in CH_2Cl_2 using the same reaction conditions.

Table 2. Influence of Cu and Ni additives on the 1,4-addition



Entry[a]	Additive	mol. equiv 'CuX'	Yield[b]
1	CuI·0.75DMS	0.10	94 (0)
2	CuI[c]	0.10	64 (30)
3	CuBr·DMS	0.10	32 (60)
4	CuCl	0.10	0 (95)
5	CuOTf·PhMe	0.10	0 (95)
6	CuCN·2LiCl	0.10	10 (85)
7	$Cu(acac)_2$	0.10	0 (95)
8	$Cu(OTf)_2$	0.10	0 (95)
9	$Ni(acac)_2$	0.10	21 (70)
10	None	—	55[d] (0)

[a] 1.0 equiv alkyne versus substrate.

[b] Isolated and purified material. Recovered substrate in brackets (%).

[c] Aldrich ultrapure grade (99.999%).

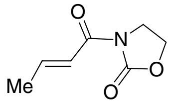
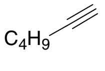
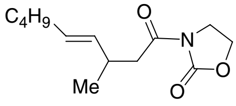
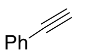
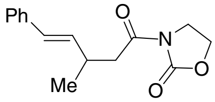
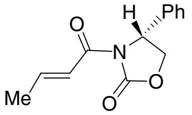
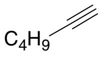
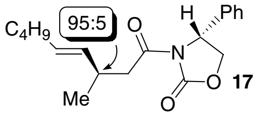
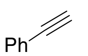
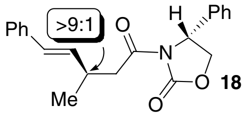
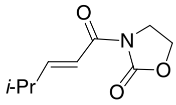
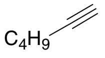
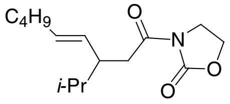
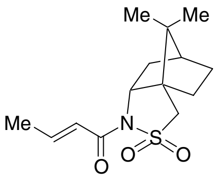
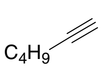
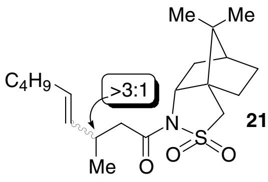
[d] 24% of 1,2-addition product.

Because of the increased efficiency of the mixed vinylzincate reagent using CH_2Cl_2, we broadened the scope of this copper-catalyzed reaction methodology to include α,β-unsaturated imides. We found that the presence of TMSOTf[12] not only safeguards the efficiency of the CuI·0.75DMS as a catalyst in 1,4-addition type reactions of the vinyl group using the mixed alkenyl-alkylzincates to the *N*-enoyl derived oxazolidinones,[13–15] but TMSOTf also achieves 1,4-products in high yields as well as diastereomeric ratios up to 95:5 (Table 3). In the absence of TMSOTf, the reaction using the vinylzincate reagents to the imides requires stoichiometric quantities of the CuI·0.75DMS in order to sustain a respectable yield of the 1,4-addition products. The results suggest that TMSOTf is a more efficient Lewis acid with the imides than the corresponding vinylzincate species. In the absence of Et_2Zn, the intermediate *vinylzirconocene* reagent is too unreactive to undergo Cu(I)-catalyzed 1,4-transfer of the vinyl group to the imides in THF, even in the presence of 1 equiv of TMSOTf (entries 1, 3, and 6). Nor is the TMSOTf powerful enough to assist in the 1,4-addition of the *vinylzincate* reagent[16] in the absence of the CuI·0.75DMS catalyst, which then underscores the crucial role of Cu(I) in these reactions.

Based on our previous work utilizing the same chiral *N*-enoyl amides exposed to TMSOTf-promoted copper reactions, the major diastereomer is formed via the non-chelating conformational (*anti-s-cis*) transition state (entry 3).[17] The same major diastereomer obtained in the absence of TMSOTf or Et_2Zn (entry 3) suggests that the zinc reagent is not acting as a chelating agent in these reactions. The presence of powerful chelating agents (e.g., $MgBr_2$) influence the diastereomeric ratio in the direction[17b] opposite to the TMSOTf-promoted 1,4-additions of the alkenyl-alkylzinc reagents reported herein. Thus, the *anti-s-cis* conformation is favored over the chelated form (*syn-s-cis*) for the *N*-enoyl amides (Scheme 2).

Although the presence of TMSOTf was crucial to achieve good results in the conjugate addition process, its precise role remains uncertain. Even more elusive is the role of the CuI·0.75DMS catalyst in the addition of the vinyl groups. Since there is no evidence for the formation of a discrete alkenylcopper species via the zinc to copper transmetalation, it is proposed that the reaction proceeds via an alkenyl-alkyl copper(III) intermediate as indicated in Scheme 3.[18,19] A subsequent reductive elimination would then provide the zinc enolate of the 1,4-addition product and regeneration of the essential Cu(I). We have previously rationalized the greater efficiency of the CuI·0.75DMS complex in comparison to the CuBr·DMS complex in the conjugate additions of vinyl groups from alkenyl zirconocenes.[7] Also in the case for the alkenyl zincates, it appears as

Table 3. TMSOTf-promoted Cu(I) catalyzed 1,4-additions of vinyl groups to α,β-unsaturated imides

Entry	Substrate	Alkyne[a]	Reaction time[b] (h)	Product	Yield[c,d]
1			10	 **15**	92[e] (23)[e,f] 89[g]
2			12	 **16**	84[e]
3			10	 **17**	86[e] (27)[e,f] 87[g]
4			12	 **18**	89[e]
5			12	 **19**	85[e]
6			12	 **21**	54[e] (0)[e,f]

[a] 1.0 M ratio of alkyne:substrate:TMSOTf.

[b] 35 °C in CH_2Cl_2.

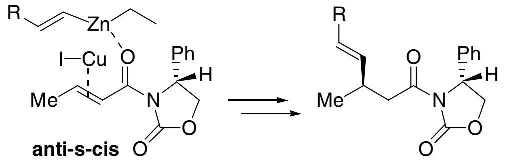
[c] Based on isolated and purified material (%).

[d] Diastereomeric ratio (dr) determined on the crude material using ^1H NMR spectroscopy.

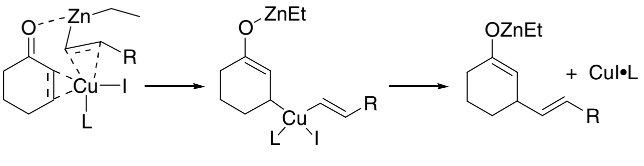
[e] 10 mol % CuI·0.75DMS versus alkyne.

[f] Reaction conducted with vinylzirconocene reagent (absence of Et_2Zn).

[g] Without TMSOTf. 100 mol % CuI·0.75DMS versus alkyne.



Scheme 2.



Scheme 3.

the π-base complexation of the Zn-alkene to Cu(I) is more favored with iodide present as a π-donor in comparison to the bromide. Obviously, solubility differences of the distinct copper reagents or intermediates should not be disregarded as important variables.

In conclusion, the experimentally convenient methodology of in situ hydrozirconation–transmetalation to zinc can be extended to the 1,4-addition of alkenyl groups to various α,β-unsaturated carbonyl compounds. The unique behavior of the CuI·0.75DMS complex and the role of TMSOTf in asymmetric 1,4-additions are currently being explored into further synthetic developments and will be reported in due course.

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Supplementary data

Supplementary data (experimental procedures and spectral data (^{1}H, ^{13}C NMR, IR, and MS/HRMS) for pertinent compounds) associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2007.01.041.

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