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S_N2' Alkylation of Cyclopropanols via Homoenolates**

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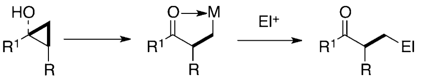
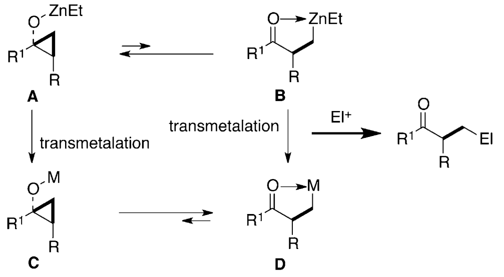
Metal homoenolates are characterized by the juxtaposition of an organometallic species β to a carbonyl group. These bifunctional reagents require a delicate balance between stability and reactivity for applications in C−C bond formations. A particularly useful class of homoenolates is zinc homoenolates. It is not surprising that known zinc and related metal homoenolates are limited primarily to those bearing weakly electrophilic esters, amides, and nitriles.[1,2] In contrast, little is known about zinc homoenolates of ketones and aldehydes because of the known proclivity of metal homoenolates to cyclize into the corresponding cyclopropoxides.[3] An attractive synthesis of cyclopropanols by treatment of α,β-epoxy ketones with $CH_2(ZnI)_2$ indeed corroborates facile cyclization of zinc keto homoenolates to the corresponding cyclopropoxides.[4] Nonetheless, we hypothesized that subsequent transmetalation with a suitable metal could shift the otherwise unfavorable equilibrium to generate β-keto homoenolates for subsequent elaboration [Eq. (1); M = metal]. As



(1)

part of research programs on synthetic applications of the Kulinkovich cyclopropanation,[5,6] we report herein the preparation and in situ S_N2' alkylation of mixed zinc/copper keto homoenolates.

Treatment of cyclopropanol with diethylzinc should result in formation of the zinc alkoxide **A** and ethane (Scheme 1). **A** could be in equilibrium with the homoenolate **B**, where the former is expected to be strongly favored. In situ trapping of **B** by transmetalation could afford **D** for subsequent reactions. Depending on the nature of the metal, an alternate sequence of transmetalation/ring opening (**A**→**C**→**D**) cannot be ruled out.[7] Among extensive prior art in the reactions of mixed zinc/copper reagents, as well as organocopper chemistry,[8,9] we chose to asses allylation in this C−C bond-forming reaction.[10]



Scheme 1. A working hypothesis on the generation of β-keto homoenolates.

Upon addition of diethylzinc to a THF solution of the (racemic) cyclopropanol (±)-**1**, vigorous gas evolution was observed (Table 1). CuCN·2 LiCl and allyl bromide (**2a**) were then added successively to the mixture, which had been cooled to −30 °C. The reaction mixture was slowly warmed to room temperature to afford the allylation product **3a** in 84 % yield (entry 1).[11,12] GC/MS analysis of the crude reaction mixture indicated the absence of the allylation product arising from the ethyl-group transfer. A cursory survey of other metal alkoxides revealed that a zinc alkoxide is particularly effective, probably because of its softness compared to other metals (e.g., Na^+, Li^+, Mg^{+2}, and Ti^{+4}).

We next examined the allylation reactions of (±)-**1** with other allylating reagents under identical reaction conditions to determine regioselectivity (S_N2 versus S_N2'). A broad range of allylic halides gave the products **3a**–**h** in good yields (Table 1, entries 1–8). Most importantly, exclusive formation of the S_N2' products was clearly seen from the results in entries 5–8, independent of the substitution pattern (with no deleterious influence by substituents at the 3-position). Thus, the products involving formation of a quaternary center were obtained in comparable yields (entries 7 and 8). These remarkably selective S_N2' reactions are noteworthy, especially because zinc homoenolates of esters were reported to require polar additives (such as HMPA or DMF) for high levels of S_N2' selectivity, as well as good yields.[1b] Both terminal and internal propargylic halides or sulfonates displayed the identical regiochemical outcome to yield the corresponding allenes (entries 9–12). Different cyclohexenyl derivatives were evaluated to assess nucleofugality and the following trend was found in both rates and yields: bromide **2m** > phosphate **2n** > pentafluorobenzoate **2o** (entries 13–15).

A survey of the literature disclosed two closely related precedents by the groups of Knochel[10a,d] and Matsubara[4c]: regiochemistry was not addressed, except for only two examples; surprisingly, the opposite S_N2 regioselectivity was reported with geranyl bromide (**2h**)[10a] and prenyl chloride (**2g′**),[4c] which contrasts this work (Table 1, entries 5–8). The origin for the striking reversal in regioselectivity between the two procedures is unclear and must await further studies.

Alkylation of *cis*- and *trans*-1,2-dialkyl-substituted cyclopropanols with the allyl bromides **2a** and **2g** was carried out

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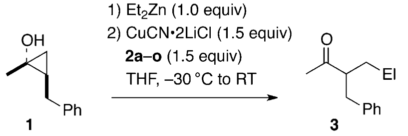
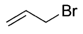
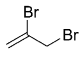
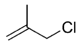
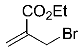
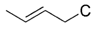
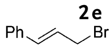
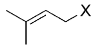
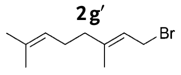
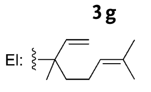
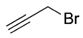
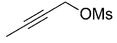
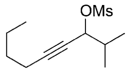
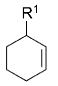
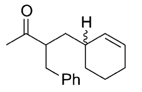
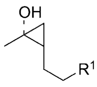
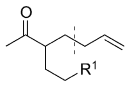
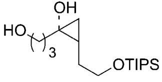
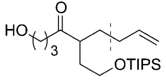
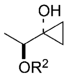
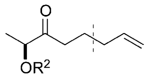
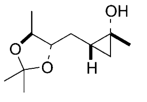
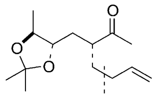
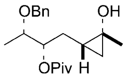
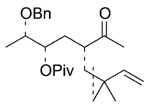
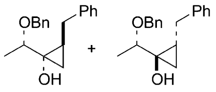
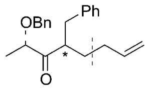
Table 1: S_N2' Alkylation of Cyclopropanol (±)-**1**.



Entry	El-LG[a]	Product	Yield [%][b]
1	 **2a**	El: $CH_2CH{=}CH_2$ **3a**	84
2	 **2b**	El: $CH_2C(Br){=}CH_2$ **3b**	74
3	 **2c**	El: $CH_2C(Me){=}CH_2$ **3c**	85
4	 **2d**	El: $CH_2C(CO_2Et){=}CH_2$ **3d**	87
5	 **2e**	El: $CH(Me)CH{=}CH_2$ **3e**	84[c]
6	 **2f**	El: $CH(Ph)CH{=}CH_2$ **3f**	80[c]
7	 **2g** **2g′**	El: $CMe_2CH{=}CH_2$ **3g**	80 78
8	 **2h**	El:  **3h**	76[c]
9	 **2i**	El: $CH{=}C{=}CH_2$ **3i**	82
10	 **2j**	El: $C(TMS){=}C{=}CH_2$ **3j**	81
11	 **2k**	El: $CMe{=}C{=}CH_2$ **3k**	85
12	 **2l**	El: C*n*Bu=C=CH*i*Pr **3l**	79
			
13	**2m**		90[c]
14	**2n**	**3m**	60[c]
15	**2o**		55[c]

[a] LG = Leaving group. [b] Yields are those of isolated products. [c] Diastereomeric ratio: 1:1. THF = tetrahydrofuran, TMS = trimethylsilyl.

Table 2: Additional examples with **2a** and **2g**.[a,b]

Entry	Cyclopropanol	Product	Yield [%][c]
			
1	**4a**: R^1 = OBn	**5a**: R^1 = OBn	92
2	**4b**: R^1 = N(Boc)Ts	**5b**: R^1 = N(Boc)Ts	63
3[d]	 **6**	 **7**	82
			
4	**8a**: R^2 = H	**9a**: R^2 = H	30,[a] 82[d]
5	**8b**: R^2 = OTBS	**9b**: R^2 = OTBS	72
6	 **10**	 **11**	49
7[b]	 **12**	 **13**	73
8[e]	 **14**	 **15**	93

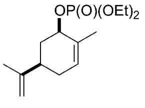
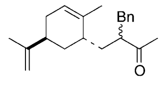
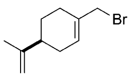
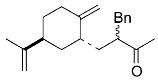
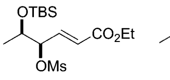
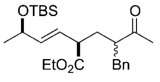
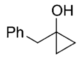
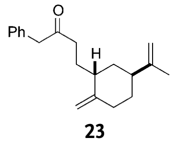
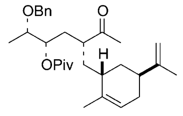
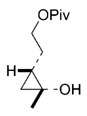
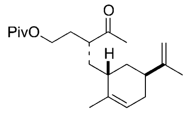
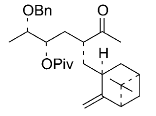
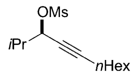
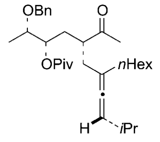
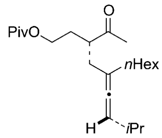
[a] Reaction conditions: Et_2Zn (1.0 equiv), CuCN·2 LiCl (1.5 equiv), **2a** or **2g** (1.5 equiv). [b] Reaction conditions: THF, −30 °C to RT. [c] Yields are those of the isolated product. [d] Used 2.0 equiv of Et_2Zn. [e] A 2:1 diastereomeric mixture of **14** was used and yielded **15** in an identical ratio of diastereomers. Bn = benzyl, Boc = *tert*-butoxycarbonyl, Piv = pivaloyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl, Ts = 4-toluenesulfonyl.

under identical reaction conditions to establish the scope and limitations of the method (Table 2). A wide range of cyclopropanols bearing common functional groups underwent allylation in moderate to good yields, and clean S_N2' regioselectivity was again confirmed for **12**→**13** (entry 7). With cyclopropanols containing a free hydroxy group (e.g., **6** and **8a**), an extra equivalent of Et_2Zn was necessary to obtain higher yields (entries 3 and 4). The α-hydroxyketone **9a** was thus isolated in 82 % yield, free from tautomerization, which is indicative of mild reaction conditions. Additional examples involved the use of nonracemic allylating reagents (Table 3). A rapid increase in molecular complexity was made possible by employing nonracemic compounds,[13] as exemplified by the results in entries 5–9, wherein the allylation products were obtained as single diastereomers. Also included was the preparation of attractively functionalized allenes **29** and **30** (entries 8 and 9).

A characteristic preference for S_N2' over S_N2 regioselectivity is apparent in exclusive formation of **19**, **21**, **23**, and **27** (Table 3). The stereochemical configuration of **23** was determined by one- and two-dimensional NMR experiments to reveal the exclusive axial attack by **22** at **18** (entry 4). Diastereofacial selectivity was anticipated to be *anti* by analogy to ample literature precedents on the S_N2' reactions of mixed zinc/copper reagents.[8,10,14] The dihydropyrans **32** and **33** were obtained as additional examples, and their stereochemical assignment was made by comparison with **34a** (Scheme 2).[15] Notably, the phosphates **35** and **36**, which are epimeric to **31** and **16**, respectively, were recovered unreacted.

In conclusion, we have developed a stereoselective method for S_N2' alkylation of cyclopropanols via mixed zinc/copper homoenolates of ketones. Cyclopropanols can be viewed as a new class of enantiopure and attractively functionalized β-keto alkylzinc reagents. Mechanistic studies are currently in progress.

Table 3: Additional examples with nonracemic El$^+$.[a]

Entry	Cyclopropanol	El-LG	Product	Yield [%][b]
1	(±)-**1**	 **16**	 **17**	70
2	(±)-**1**	 **18**	 **19**	74
3	(±)-**1**	 **20**	 **21**	62
4	 **22**	**18**	 **23**	58
5	**12**	**16**	 **24**	62
6	 **25**	**16**	 **26**	65
7	**12**	(1*R*)-myrtenyl bromide	 **27**	65
8	**12**	 **28**	 **29**	60
9	**25**	**28**	 **30**	70

[a] Reaction conditions: Et_2Zn (1.0 equiv), CuCN·2 LiCl (1.5 equiv), El$^+$ (1.5 equiv), THF, −30°C to RT. [b] Yields are those of the isolated product. Ms = methanesulfonyl.

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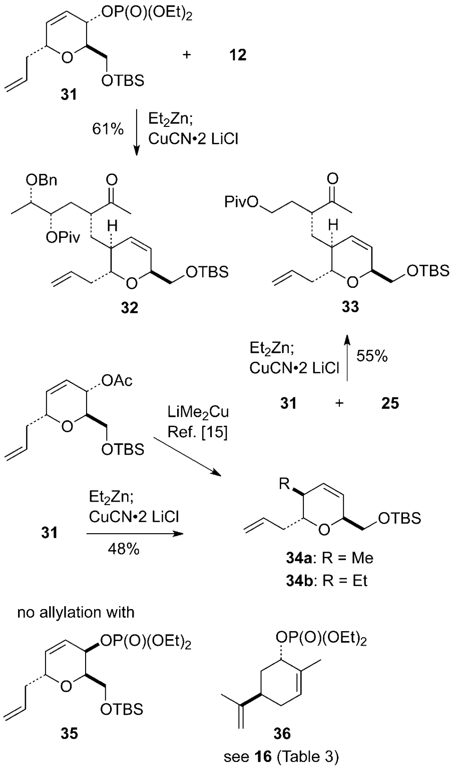

Scheme 2. Additional examples.

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[1] a) E. Nakamura, H. Oshino, I. Kuwajima, *J. Am. Chem. Soc.* **1986**, *108*, 3745; b) E. Nakamura, S. Aoki, K. Sekiya, H. Oshino, I. Kuwajima, *J. Am. Chem. Soc.* **1987**, *109*, 8056; c) I. Kuwajima, E. Nakamura, *Top. Curr. Chem.* **1990**, *155*, 1.

[2] M. T. Crimmins, P. G. Nantermet, *Org. Prep. Proced. Int.* **1993**, *25*, 41.

[3] Previous examples were limited to mercury, tin, silver, and copper species: a) I. Ryu, K. Matsumoto, M. Ando, S. Murai, N. Sonoda, *Tetrahedron Lett.* **1980**, *21*, 4283; b) I. Ryu, M. Ando, A. Ogawa, S. Murai, N. Sonoda, *J. Am. Chem. Soc.* **1983**, *105*, 7192; c) I. Ryu, S. Murai, N. Sonoda, *J. Org. Chem.* **1986**, *51*, 2389.

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[7] Depending on metals, direct attack by **A** or **B** at electrophilic transition metal complexes may also be possible.

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[11] Use of diethylzinc was prerequisite for allylation. No reaction was observed in the absence of diethylzinc. Ethylzinc iodide and zinc carbenoids were ineffective.

[12] Zinc carbenoid-promoted ring opening of cyclopropanols gave the regioselective preparation of α-methyl substituted ketones: P. P. Das, B. B. Parida, J. K. Cha, *ARKIVOC* **2012**, *Part (ii)*, 74.

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[14] Cf. For previous alkylation of cyclohexenyl derivatives with dialkylcuprates, see: a) H. L. Goering, V. D. Singleton, Jr., *J. Org. Chem.* **1983**, *48*, 1531; b) A. Kreft, *Tetrahedron Lett.* **1977**, *18*, 1035.

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Communications

Synthetic Methods

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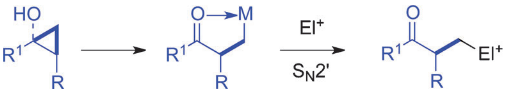
S_N2' Alkylation of Cyclopropanols via Homoenolates



Reining in reactivity: Stereoselective S_N2' alkylation of cyclopropanols has been devised under the control of mixed zinc/copper reagents. This method provides convenient access to enantiopure keto homoenolates which react with electrophiles (El^+) to form C–C bonds. M = metal.