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Organotellurides as a source of organometallics: application in the synthesis of (+/−)-frontalin

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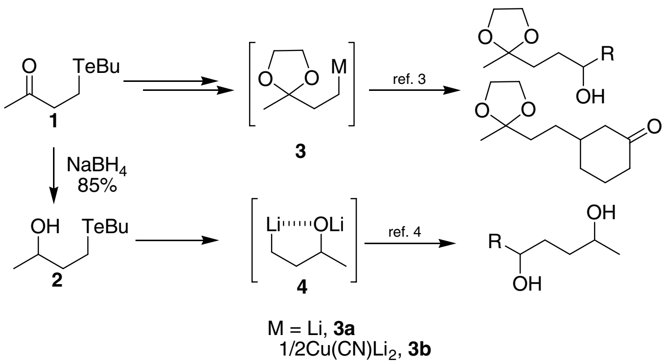
Abstract—A masked lithium homoenolate, generated by tellurium/lithium exchange, was reacted with epoxides. The lithium compound was also converted into other organometallics such as Grignard, and cuprates and the reactivity of those organometallics with epoxides was evaluated. The same building block was employed in the synthesis of (+/−)-frontalin.

Acting as bases or nucleophiles, organolithium compounds are probably the most popular organometallics commonly used in organic synthesis. Upon transmetallation they may serve for the preparation of many other organometallics.[1] This also includes the tellurium/lithium exchange reaction.[2] This is fast and clean, leading to useful organolithium building blocks.

Recently, we employed this strategy to generate β-masked metal homoenolates (**3**)[3] and 1,4-*C*,*O*-dianions (**4**).[4] The lithium salts were reacted with carbonyl compounds and **3** was also converted into the higher order cyanocuprate **3b**, which was submitted to reaction with Michael acceptors. Hydroxytelluride **2**, precursor of dianion **4**, was recently resolved into its enantiomers by enzymatic kinetic resolution,[5] which opens the way for its use in asymmetric synthesis (Scheme 1).

In this letter we present a systematic study on the reaction of several organometallics of type **3** with epoxides and with an allylic tosylate aiming at the synthesis of (+/−)-frontalin, an aggregation pheromone of pine bark beetles, *Dendroctonus* spp.[6] in order to demonstrate the synthetic applicability of functionalized alkyltellurides.

A retrosynthetic analysis reveals that (+/−)-frontalin (**5**) can be obtained by an intramolecular acid-catalyzed ketalization of the key intermediate **6**, which could be



Scheme 1.

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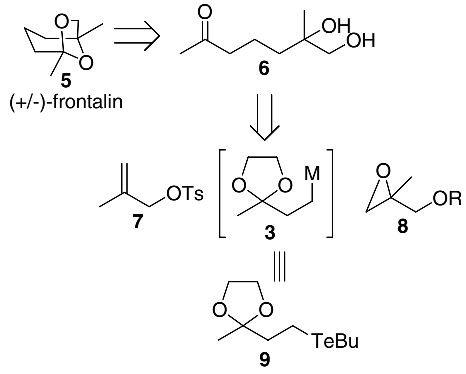
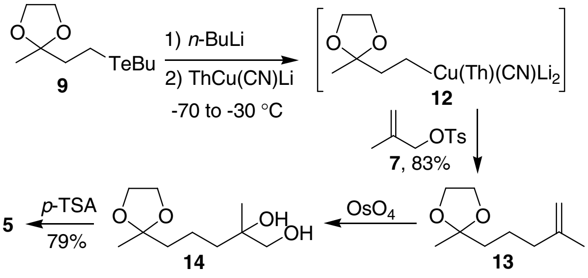


Scheme 2.

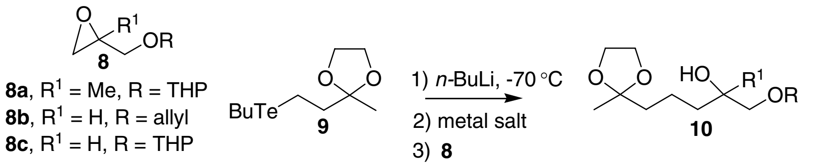
prepared by reacting **3** with epoxide **8**, similar to Murahashi's approach.[7] Alternatively, **6** could be prepared by reacting **3** with allylic tosylate **7** followed by the functionalization of the double bond (Scheme 2).

We prepared telluride **1** in 86% yield, by hydrotelluration of methyl vinyl ketone using *n*-butyltellurol, generated in situ from elemental tellurium and *n*-butyllithium, followed by a proton source such as water.[3,8] Telluride **9** was prepared in 96% isolated yield by refluxing a benzene solution of **1** and ethylene glycol in the presence of a catalytic amount of Amberlist® in a Dean–Stark apparatus.[3,8] The addition of 1 equiv of *n*-butyllithium to a solution of **9** in THF at −70 °C, produced **3a** instantaneously (Scheme 1), which can be directly used in reactions with electrophiles or converted into other organometallics[3] by reaction with appropriate metal salts. Scheme 3 and Table 1 summarize the results concerning the reaction of **3** with epoxides (**8a–c**).

Epoxide **8a** did not react with **3** as lithium or copper specie (Table 1, entries 1–8), but the corresponding Grignard reagent, obtained by transmetallation of **3** with $MgBr_2$, opened the epoxide in an acceptable yield (Table 1, entry 9). Epoxide **8a** is unreactive also towards (trimethylsilyl)ethynylcuprate (Table 1, entry 10). However, the same cuprate opened epoxide **8b**, while 1-hexynylcuprate reacted with epoxide **8c** (Table 1, entries 11 and 12). These experiments show that the lack of reactivity can be attributed to epoxide **8a**. In view of the



Scheme 4.



Scheme 3.

Table 1.

Entry	Metal salt	Additive	Epoxide **8**	Yield (%) **10**[a]
1	RLi[b]	—	**8a**	0
2	1/2CuBr·DMS[c]	—	**8a**	0
3	1/2CuCN·2LiC[d]	—	**8a**	0
4	1/2CuCN·2LiC[d]	$BF_3·Et_2O$	**8a**	0
5	1/2CuCN·2LiC[d]	$BF_3·Et_2O$/TMSCl	**8a**	35
6	1/2CuCN·2LiC[d]	HMPA	**8a**	<10
7	1CuCN·2LiCl[d]	—	**8a**	0
8	1CuCN·2LiCl[d]	$BF_3·Et_2O$/TMSCl	**8a**	<10
9	$MgBr_2$	—	**8a**	52
10	TMS–C≡C–Cu[e]	—	**8a**	0
11	TMS–C≡C–Cu[e]	—	**8b**	60
12	Bu–C≡C–Cu[f]	—	**8c**	62

[a] Isolated yield.

[b] Used directly as THF solution at −70 °C; the use of **3** in association with HMPA, $BF_3·Et_2O$, TMSCl, $BF_3·Et_2O$ or TMSCl/$BF_3·Et_2O$ was also unfruitful.

[c] Used as a suspension in THF.

[d] Freshly prepared as 1 mol/L solution in THF.

[e] Prepared in situ from lithium (trimethylsilyl)acetylide and copper(I) iodide in THF.

[f] Prepared in situ from hexynyllithium and copper(I) iodide in THF.

poor yields in the epoxide opening step of the proposed synthesis (Scheme 2), a second route was attempted. Allylic tosylate **7** was reacted with Lipshutz cuprate **12**. The expected olefin **13**[9] was obtained in 83% isolated yield, which was transformed into **14** by osmium tetroxide oxidation. Acidic quenching of the reaction mixture gave (+/−)-frontalin (**5**) in 79% overall yield (Scheme 4).

In conclusion, the synthesis of (+/−)-frontalin (**5**) was accomplished in 65% overall yield, featuring a tellurium/lithium exchange in its key step and demonstrating the synthetic potential of the functionalized alkyltellurides.

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