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Easy selective generation of (lithiomethyl)cyclopropane or homoallyllithium by a chlorine–lithium exchange

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Dedicated to Professor Rioyi Noyori on occasion of his 70th birthday

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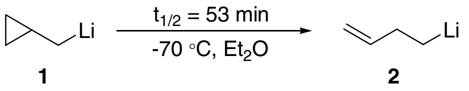
S_E reaction
Lithium

ABSTRACT

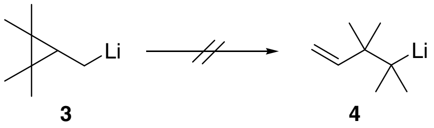
The reaction of (chloromethyl)cyclopropane **5** with lithium and a catalytic amount of DTBB (5 mol %) in the presence of different carbonyl compounds [Et_2CO, *n*-Pr_2CO, (*c*-$C_3H_5)_2CO$, $(CH_2)_5CO$, PhCOMe, *t*-BuCHO, *i*-PrCHO, PhCHO] as electrophiles in THF at −78 °C leads, after hydrolysis with water, to the corresponding cyclopropyl alcohols **6**. However, when the same starting material is lithiated using naphthalene as the arene catalyst in ether at 0 °C and then reacts with the same series of electrophiles, the final hydrolysis with water yields the corresponding unsaturated alcohols **7**.

Lithiomethylcyclopropane **1** is an unstable intermediate that even at −70 °C leads to the corresponding thermodynamically more stable homoallyllithium **2** in a period of a couple of hours (Scheme 1).[1]

The ways to generate intermediates of type **1**/**2** include iodine–lithium exchange (using an organolithium reagent such as EtLi, *n*-BuLi/TMEDA or *s*-BuLi),[1,2] mercury–lithium transmetallation (with lithium metal),[3] selenium–lithium exchange (with *t*-BuLi)[4] or a silicon–lithium rearrangement (in a Brook-type process).[5] Normally, except in few cases,[1] even working at low temperatures, organolithium reagents of type **1** undergo partial or total transformation into the corresponding homoallyllithium derivative of type **2**.[6] To our best knowledge, the only report described in the literature preparing an intermediate of type **1** by chlorine–lithium exchange was described by Maercker et al.[3] These authors prepared intermediate **3**, which was stable enough to give suitable crystals for X-ray determination: in this case, the energy gained by the release of the ring strain upon opening of the cyclopropane is not enough to compensate the instability of the tertiary organolithium intermediate **4** (Scheme 2).



Scheme 1.



Scheme 2.

In this Letter we report the selective generation of intermediate **1** or **2** by an arene-catalysed lithiation[7] starting from the corresponding (chloromethyl)cyclopropane.

Commercially available (chloromethyl)cyclopropane **5** was treated with a slight excess of lithium powder (1:3.6 molar ratio; theoretical 1:2 molar ratio) and a catalytic amount of an arene [4,4′-di-*tert*-butylbiphenyl (DTBB) or naphthalene; 5 mol %] in the presence (Barbier-type conditions[8]) or absence (Grignard-type conditions: two-step process) of 3-pentanone as the electrophile under different reaction conditions to give, after hydrolysis with water, the expected mixture of alcohols **6a** and **7a**, resulting from intermediates **1** and **2**, respectively (Table 1).

The optimal conditions to obtain the cyclopropyl derivative **6a** were −78 °C, THF as the solvent, DTBB as the electron carrier agent and performing the process in the presence of the electrophile (Table 1, entry 1). Any change in the temperature (Table 1, entry

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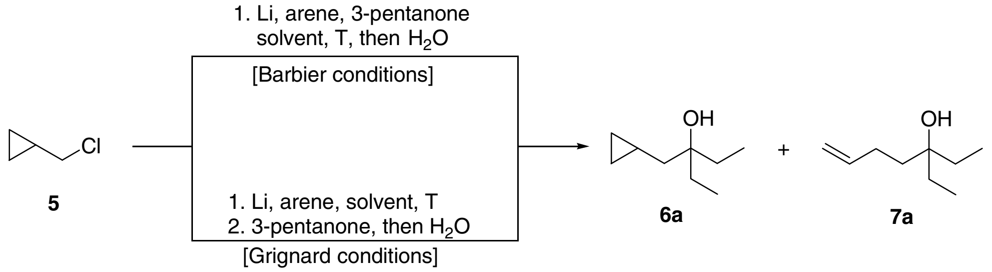
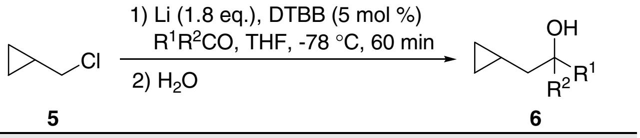
Table 1
Arene-catalysed lithiation of (chloromethyl)cyclopropane and reaction with 3-pentanone[a]

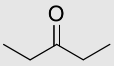
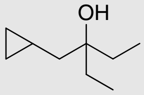
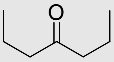
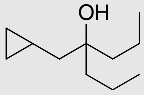
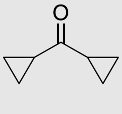
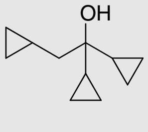
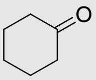
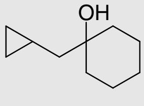
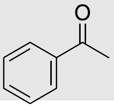
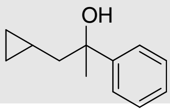
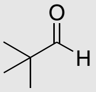
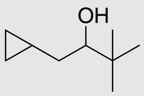
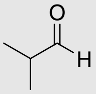
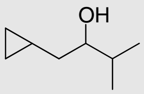
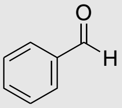
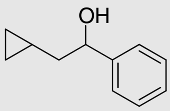


Method	Entry	*T* (°C)	Time[b] (min)	Arene	Solvent	Yield[c] (%)		
						6a	**7a**	Total
Barbier-type conditions	1	−78	60	DTBB	THF	87	0	87
	2	−5	60	DTBB	THF	4	85	89
	3	−78	60	$C_{10}H_8$	THF	65	0	65
	4	−78	60	$C_{10}H_8$	Et_2O	1	0	1
Grignard-type conditions	5	−78	60 + 30	DTBB	THF	19	53	72
	6	−78	90 + 30	DTBB	THF	3	66	69
	7	−78	180 + 30	DTBB	THF	1	50	51
	8	−45	60 + 30	DTBB	THF	4	90	94
	9	−5	60 + 30	DTBB	THF	0	84	84
	10	−78 to −5	60 + 30	DTBB	THF	0	87	87
	11	−5	60 + 30	DTBB	THP	7	44	51
	12	−5	60 + 30	$C_{10}H_8$	THF	0	54	54
	13	−5	60 + 30	$C_{10}H_8$	Et_2O	0	97	97
	14	−5	60 + 30	$C_{10}H_8$	THP	0	51	51
	15	−78	60 + 30	$C_{10}H_8$	Et_2O	2	3	5

[a] Reactions performed with (chloromethyl)cyclopropane (2 mmol), Li (7.1 mmol), arene (0.1 mmol), solvent (10 mL) and 3-pentanone (2.2 mmol).
[b] Under Grignard conditions, the given times correspond to the two steps (lithiation and reaction with the electrophile).
[c] Yields of compounds **6a** and **7a** were calculated by GLC using an internal standard (1-decanol).

Table 2
Preparation of cyclopropyl alcohols **6**[a]



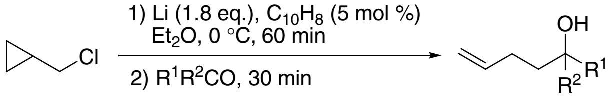
Entry	Electrophile	Product[b]		
		No.	Structure	Yield[c] (%)
1		**6a**		67
2		**6b**		61
3		**6c**		53
4		**6d**		71
5		**6e**		63
6		**6f**		53
7		**6g**		52
8		**6h**		62

[a] Reactions were performed with (chloromethyl)cyclopropane (4 mmol), Li (14.2 mmol), DTBB (0.2 mmol) THF (15 mL) in the presence of electrophile (4.4 mmol).
[b] All compounds **6** were fully characterised by spectroscopic means (IR, 1H and ^{13}C NMR, and MS).
[c] Isolated yield of pure (>95%) products **6** after column chromatography (silica gel, hexane/ethyl acetate).

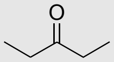
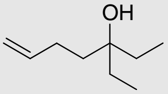
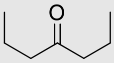
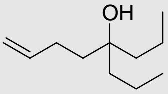
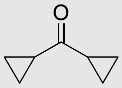
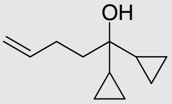
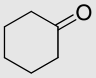
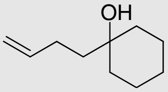
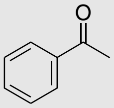
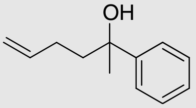
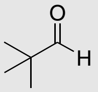
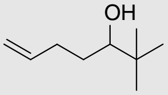
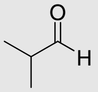
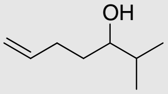
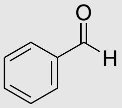
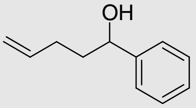
2), arene (Table 1, entries 3 and 4) or solvent (Table 1, entry 4) gave poorer results. On the contrary, the best result in achieving the unsaturated alcohol **7a** was obtained by working under Grignard-type conditions at −5 °C and using naphthalene as the arene catalyst and ether as the solvent (Table 1, entry 13). At lower temperatures (Table 1, entries 5–8, 10 and 15), using DTBB as the electron carrier (Table 1, entries 5–11) or other solvents (Table 1, entries 5–12 and 14), we did not improve the mentioned optimal result.

Once the best conditions to generate (lithiomethyl)cyclopropane **1** were established (DTBB, THF, −78 °C and Barbier condi-

Table 3
Preparation of unsaturated alcohols **7**[a]



5 **7**

Entry	Electrophile	Product[b]		
		No.	Structure	Yield[c] (%)
1		**7a**		77
2		**7b**		70
3		**7c**		51
4		**7d**		65
5		**7e**		63
6		**7f**		51
7		**7g**		63
8		**7h**		50

[a] Reactions performed with (chloromethyl)cyclopropane (4 mmol), Li (14.2 mmol), naphthalene (0.2 mmol), Et_2O (15 mL) and then added electrophile (4.4 mmol).

[b] All compounds **7** were fully characterised by spectroscopic means (IR, 1H and ^{13}C NMR, and MS).

[c] Isolated yield of pure (>95%) products **7** after column chromatography (silica gel, hexane/ethyl acetate).

tions) the scope of the process was studied applying the reaction to different carbonyl compounds as electrophiles as it is shown in Table 2.[9] As it can be seen, the reaction is general for aldehydes and ketones giving compounds **6** in satisfactory isolated yields, the corresponding unsaturated alcohols **7** being not detected in any case.

Also in the case of generating intermediate **2**, we applied the optimal conditions as shown in Table 1 (naphthalene, ether, 0 °C and Grignard conditions). Thus, using the same carbonyl compounds as for intermediate **1**, the corresponding unsaturated alcohols **7** were also obtained in satisfactory isolated yields (Table 3).[10] Also in this case, no cyclopropyl derivatives **7** were detected in the reaction mixtures.

In summary, we have described herein the easy selective generation of both (lithiomethyl)cyclopropane **1** and homoallyllithium **2** using a very simple methodology, the DTBB- or naphthalene-catalysed lithiation of commercially available (chloromethyl)cyclopropane **5**. These organolithium compounds react with different carbonyl compounds as electrophiles affording the expected cyclopropyl or unsaturated alcohols **6** or **7**, respectively, under mild reaction conditions. Work is in progress in order to study the scope of the reaction concerning differently substituted cyclopropyl derivatives as well as cyclobutyl systems.

Acknowledgements

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6. The ring opening reaction is avoided when the cyclopropylcarbinyl carbanion is stabilized by the presence of a phenylthio or silyl propargyl moieties. See, for instance: (a) Chen, F.; Mudryk, B.; Cohen, T. *Tetrahedron* **1999**, *55*, 3291–3304; (b) Lorthiois, E.; Marek, I.; Normant, J. F. *Tetrahedron Lett.* **1995**, *37*, 6693–6694.
7. For reviews, see: (a) Yus, M. *Chem. Soc. Rev.* **1996**, *25*, 155–161; (b) Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225–237; (c) Yus, M. *Synlett* **2001**, 1197–1205; (d) Yus, M.; Ramón, D. J. *Lat. J. Chem.* **2002**, 79–92; (e) Ramón, D. J.; Yus, M. *Rev. Cubana Quim.* **2002**, *14*, 75–115; (f) Yus, M. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; J. Wiley & Sons: Chichester, 2004; 1,. Part 2, Chapter 11 For mechanistic studies, see: (g) Yus, M.; Herrera, R. P.; Guijarro, A. *Tetrahedron Lett.* **2001**, *42*, 3455–3458; (h) Yus, M.; Herrera, R. P.; Guijarro, A. *Chem. Eur. J.* **2002**, *8*, 2574–2584; (i) Yus, M.; Herrera, R. P.; Guijarro, A. *Tetrahedron Lett.* **2003**, *44*, 1309–1312; (j) Yus, M.; Herrera, R. P.; Guijarro, A. *Tetrahedron Lett.* **2003**, *44*, 1313–1316; (k) Yus, M.; Herrera, R. P.; Guijarro, A. *Tetrahedron Lett.* **2003**, *44*, 5025–5027; (l) Melero, C.; Guijarro, A.; Baumann, V.; Pérez-Jiménez, A. J.; Yus, M. *Eur. J. Org. Chem.* **2007**, 5514–5526; (m) Melero, C.; Herrera, R. P.; Guijarro, A.; Yus, M. *Chem. Eur. J.* **2007**, *13*, 10096–10107; For a polymer supported arene-catalysed version of this reaction, see: (n) Gómez, C.; Ruiz, S.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1397–1400; (o) Gómez, C.; Ruiz, S.; Yus, M. *Tetrahedron* **1999**, *55*, 7017–7026; (p) Yus, M.; Candela, P.; Gómez, C. *Tetrahedron* **2002**, *58*, 6207–6210; (q) Alonso, F.; Gómez, C.; Candela, P.; Yus, M. *Adv. Synth. Catal.* **2003**, *345*, 275–279; (r) Candela, P.; Gómez, C.; Yus, M. *Russ. J. Org. Chem.* **2004**, *40*, 795–801.
8. For a review on Barbier-type reactions, see: Alonso, F.; Yus, M. *Recent Dev. Org. Chem.* **1997**, *1*, 397–436.
9. *General procedure for the preparation of compounds* **6**: (Chloromethyl)-cyclopropane (**5**, 0.38 mL, 4 mmol) and the electrophile (4.4 mmol) were added to a suspension of lithium powder (100 mg, 14.2 mmol) and DTBB (53.2 mg, 0.2 mmol) in dry THF (15 mL) at −78 °C, and stirred for 1 h. The reaction mixture was quenched with water (10 mL), and then the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The resulting organic phase was washed with brine (10 mL), dried over anhydrous $MgSO_4$ and the solvent was evaporated under vacuum (15 Torr). The cyclopropyl alcohol **6** was purified by column chromatography (silica gel, mixtures of ethyl acetate and hexane).
10. *General procedure for the preparation of compounds* **7**: (Chloromethyl)-cyclopropane (**5**, 0.38 mL, 4 mmol) was added to a suspension of lithium powder (100 mg, 14.2 mmol) and naphthalene (26 mg, 0.2 mmol) in dry Et_2O (15 mL) at 0 °C, and stirred for 60 min. Then, the electrophile (4.4 mmol) was added and the reaction mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched with water (10 mL), and then the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The resulting organic phase was washed with brine (10 mL), dried over anhydrous $MgSO_4$ and the solvent was evaporated under vacuum (15 Torr). The unsaturated alcohol **7** was purified by column chromatography (silica gel, mixtures of ethyl acetate and hexane).