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Cyclopropanation of styrenes and stilbenes using lithiomethyl trimethylammonium triflate as methylene donor†

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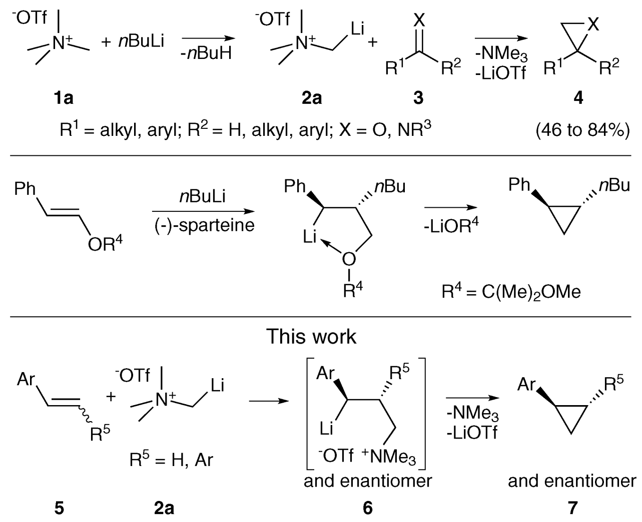
Lithiomethyl trimethylammonium triflate, prepared from tetramethylammonium triflate, cyclopropanates several styrenes and stilbenes with electron-donating and selected electron-withdrawing substituents efficiently. Kinetic data support a stepwise nucleophilic addition–ring closure mechanism for this methylenation.

Naturally occurring and synthetically prepared cyclopropane subunits are prominent in molecules with important biological activities.[1] The synthesis of cyclopropanes,[2] and their subsequent use as intermediates,[3] has been and still is the focus of intensive research. Popular methods for the cyclopropanation of olefins can be divided into three main groups: (1) halomethylmetal-mediated cyclopropanation, *i.e.* Simmons–Smith reaction;[4] (2) transition-metal catalysed decomposition of diazocompounds;[5] and (3) Michael reaction-initiated ring closure (MIRC).[6] Although these methodologies have been improved over the years, problems associated with the formation of (toxic) by-products and safety concerns for the first two groups, or the necessity to use electron poor olefins for the third group, limit the applicability of these methods for cyclopropanation of electron-rich olefins.

An alternative method should ideally use readily accessible materials, be easily scalable, and have a broad substrate scope. For industrial application the first two conditions are of most importance. One alternative method for cyclopropanation of electron rich olefins was reported by Franzen and Wittig in 1960;[7] they used a non-stabilised 'N–C ylide'[8] as methylene donor for the cyclopropanation of cyclohexene. However, later attempts to reproduce their results were unsuccessful.[9] To date, the difficulty of characterising and studying a non-soluble, air sensitive reagent such as lithiomethyl trimethylammonium bromide[8] has limited the applicability of this potential methylenation reagent.

Our group has recently reported[10] the synthesis of soluble lithiomethyl trimethylammonium reagents, *e.g.* **2a**, by deprotonation of tetramethylammonium salts possessing a solubilising anion. This reagent (**2a**) performs methylenation of aldehydes, ketones and imines efficiently (Scheme 1, top).

Nucleophilic addition of organolithium reagents to styrenes has been extensively studied since its discovery[12] for diverse applications,[13] including the formation of heterocycles[14] and the stereoselective formation of cyclopropane derivatives.[11] However, the formation of cyclopropanes *via* carbolithiation was limited to substrates incorporating a leaving group. Potentially, a bigger substrate scope for the cyclopropanation could be obtained when nucleophilic reagents possessing a leaving group, so-called methylene donors as *e.g.* **2a**, are used. Herein, we report our



Scheme 1 Top: generation of soluble lithiomethyl trimethylammonium species and their use for the methylenation of aldehydes, ketones and imines. Middle: previously reported cyclopropanation of styrenes using carbolithiation.[11] Bottom: cyclopropanation of styrenes and stilbenes with **2a**.

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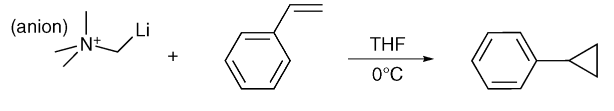
Table 1 Effect of the solubilising anion on the cyclopropanation of styrene[a]

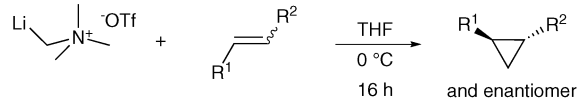


2 (1.1 eqv.) **5a** (1.0 eqv.) **7a**

Entry	Precursor	Anion	Yield of **7a**[c] (%)	Remaining **5a**[c] (%)
1	**1b**	$^{-}\mathrm{BAr^{F}}$[b]	24	76
2	**1c**	$^{-}\mathrm{N(SO_2CF_3)_2}$	19	81
3	**1d**	$^{-}\mathrm{OOC(CH_3)_3}$	30	70
4	**1a**	$^{-}\mathrm{OSO_2CF_3}$	60	40

[a] 0.3 mmol scale. [b] Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate. [c] Determined by GC-FID, see ESI for details.

Table 2 Cyclopropanation of olefins at 1.2 mmol scale with lithiomethyl trimethylammonium triflate



2a (1.1 to 1.5 eqv.) **5** (1.0 eqv.) **7**

Entry	Substrate	R^1	R^2	Product	Yield[a] (%)
1	**5a**	Ph	H	**7a**	71
2	**5b**	4-CH_3Ph	H	**7b**	88
3	**5c**	4-$C(CH_3)_3$Ph	H	**7c**	80
4	**5d**	4-OCH_3Ph	H	**7d**	88
5	**5e**	3-OCH_3Ph	H	**7e**	77
6	**5f**	4-FPh	H	**7f**	17[b]
7	**5g**	4-NO_2Ph	H	**7g**	0[c]
8	**5h**	Ph	*E*-Ph	*trans*-**7h**	92
9	**5i**	Ph	*Z*-Ph	*trans*-**7h**	98
10	**5j**	4-OCH_3Ph	*E*-Ph	*trans*-**7j**	73
11	**5k**	Cyclohexene		**7k**	0[d]

[a] Isolated yields after purification unless otherwise stated, see ESI for details. [b] Estimated from GC data. [c] Exclusively polymeric products were obtained. [d] Unreacted starting material was recovered.

results on the use of lithiomethyl trimethylammonium reagents for the cyclopropanation of styrenes and stilbenes, as well as an investigation of the reaction mechanism using kinetic data.

Lithiated ammonium salts with several counterions were tested for the cyclopropanation of styrene in THF. Deprotonation of the tetramethylammonium salts at 0 °C for 30 min, followed by addition of styrene (**5a**), produced cyclopropylbenzene (**7a**) in all cases. THF-soluble salts tetramethylammonium $\mathrm{BAr^F}$ (**1b**) and triflimide (**1c**) afforded **7a** in 24% and 19% yield respectively (Table 1, entries 1 and 2). Ammonium salts with pivalate (**1d**) and triflate (**1a**) anions were also evaluated. Even though these salts are only sparingly soluble in THF, the resulting lithiomethyl trimethylammonium salts exhibit better solubility. Higher yields of 30% and 60% were obtained when **1d** and **1a** were used respectively (entries 3 and 4). The strong dependence of the reaction yield on the anion might correlate to the ability of the anion to coordinate the lithium cation, *i.e.* this coordination could influence the rate of ring closure from intermediate **6** (*vide supra*).

In our experiments we found that trace amounts of (transition) metals degrade the lithiomethyl trimethylammonium reagent to ethylene and trimethylamine, reducing the efficiency of this methylenation. Consequently, thorough cleaning of all glassware (see ESI†), the use of glass stir bars, and purification of the ammonium salts to ensure sub-ppm concentration of metal impurities (as assessed by ICP-MS) is necessary to achieve high and reproducible yields. The high yield obtained with salt **1d**, as well as its straight-forward synthesis, purification, and its non-hygroscopic character, prompted us to explore the scope of this methylenation using **2a** as methylene source.

At a 1.2 mmol scale styrene could be methylenated by **2a** to produce phenylcyclopropane **7a** in 71% isolated yield (Table 2, entry 1). In a similar fashion, *p*-methyl substituted (**5b**) and *p*-*t*Bu substituted (**5c**) styrenes afforded their corresponding cyclopropanes **7b** and **7c** in 88% and 80% yields, respectively (entries 2 and 3). Styrenes bearing methoxy substituents in the *para*-position (**5d**) as electron-donating group ($\sigma = -0.268$), or in the *meta*-position (**5e**) as electron-withdrawing group ($\sigma = +0.115$), can be methylenated to afford cyclopropanes **7d** and **7e** in 88% and 77% yield (entries 4 and 5). Substitution with electron withdrawing groups in the *para* position leads either to a lower yield (F, entry 6) or to no traces of cyclopropane (NO_2, entry 7). In both of these cases the formation of polymers was observed, for *p*-NO_2 styrene **5g** the polymer was the only product. Methylenation of stilbenes **5h**, **5i** and **5j** afforded *trans*-1,2-bis-substituted cyclopropanes[15] **7h** and **7j** exclusively, in 92, 98 and 73% yields respectively (entries 8 to 10). Finally, reaction of **2a** with the aliphatic olefin cyclohexene (**5k**), the original substrate in Franzen and Wittig's report,[7] did not give the corresponding cyclopropane; instead, unreacted starting material could be recovered after workup (entry 10). This is in agreement with the required forcing reaction conditions reported in literature for the nucleophilic addition of carbanions to nonactivated olefins.[16]

The sharp contrast in reactivity of styrenes and the total inertness of cyclohexene for this methylenation supports a nucleophilic pathway. The addition of the 'N–C ylide' **2** to styrene **5** followed by an intramolecular ring-closure from intermediate **6** is therefore a plausible mechanism for the formation of cyclopropanes **7** (Scheme 1, bottom).

The irreversible nature of carbolithiations,[17] and the supposed irreversible formation of trimethylamine gas in the second step of our mechanism, allows the straightforward kinetic study of this reaction. Monitoring the reaction of **2d** with excess of styrene **5c** using a combination of GC and ESI-MS (electrospray ionization mass spectrometry) analysis (see ESI†) showed first order kinetics for the consumption of **2d** and the formation of cyclopropane **7c**. The pre-exponential factors and kinetic constants found for both curves are statistically very similar (see ESI,† Fig. S2). Assuming the model of two consecutive, irreversible reactions (A → B → C) a kinetic model can be deduced.[18] Our kinetic data strongly support that the first reaction is much slower than the second, *i.e.* the carbolithiation is much slower than the ring-closure, since the concentration of both product and reagent display an apparent first order regime with similar pre-exponential factors and rate constants.

Competitive kinetic measurements[19] showed a marked decrease in reaction rate when electron-donating substituents on the aromatic ring are present (Fig. 1). As expected, nucleophilic

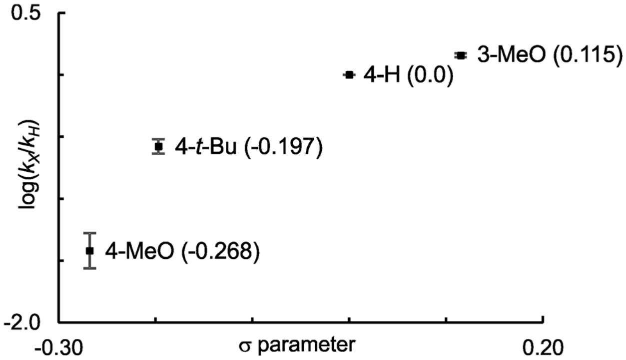


Fig. 1 Hammett plot for the methylenation of styrenes with **2a**. Sigma Hammett parameters are shown in brackets.[22]

attack on the olefin is strongly disfavoured when its electron density is increased, and styrenes bearing electron-withdrawing substituents exhibit a modestly increased methylenation reactivity. Substitution with an electron-withdrawing substituent at the *meta* position influences the olefin inductively but has a minor effect on the resonance stability of intermediate **6**, and therefore only modestly affects the rate of ring closure. For an electron-withdrawing group in the *para* position a much greater influence can be observed; in fact, disappearance of 'N–C ylide' **2d** when reacted with styrene **5h** is instantaneous at 0 °C, however no cyclopropane product is formed. It is likely that the stabilisation of the benzylic carbanion **6h** by the electron-withdrawing group slows down the ring closure enough to kinetically favour polymerisation over cyclopropane formation.[20] The opposing effect of the substituents on the two steps of this mechanism should result in a change of rate limiting step. For electron rich styrenes, addition is rate limiting, whereas for electron poor styrenes, ring closure should be rate limiting. Such changes are normally associated with curved Hammett plots.[21] The measured plot for this system (Fig. 1) deviates from linearity as expected; however, the observed polymerisation does not allow the study of methylenation kinetically dominated by a rate limiting ring closure.

In summary, the soluble, easily accessible lithiomethyl trimethylammonium triflate **2d** was found to cyclopropanate several electron rich styrenes and stilbenes efficiently. Kinetic measurements support the proposed mechanism featuring a nucleophilic addition and a subsequent fast intramolecular ring closure. Our method provides an alternative to traditional methods for cyclopropanation as it uses as a precursor an easily prepared, non-hygroscopic and bench-stable tetramethylammonium salt. Our method makes no use of costly catalysts and it should be well scalable. As long as the electronic requirements on the olefin are fulfilled, our methylenation has a reasonable scope.

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