Transition-Metal Catalysis

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Nickel-Catalyzed Cyclopropanation with NMe_4OTf and *n*BuLi

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Abstract: *Nickel was identified as a catalyst for the cyclopropanation of unactivated olefins by using in situ generated lithiomethyl trimethylammonium triflate as a methylene donor. A mechanistic hypothesis is proposed in which the generation of a reactive nickel carbene explains several interesting observations. Additionally, our findings shed light on a report by Franzen and Wittig published in 1960 that had been retracted later owing to irreproducibility, and provide a rational basis for the systematic development of the reaction for preparative purposes as an alternative to diazomethane or Simmons–Smith conditions.*

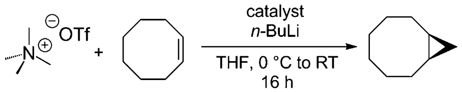
In 1960, in a short Communication in *Angewandte Chemie*, Franzen and Wittig reported the cyclopropanation of cyclohexene with tetramethylammonium bromide (**1**) to give norcarane (**2**).[1] Dropwise addition of an ethereal solution of phenyllithium/phenylsodium (1:10) to a suspension of **1** in neat cyclohexene resulted in the formation of **2** in 5–18% yield. Franzen and Wittig proposed the decomposition of trimethylammonium methylide into a free carbene that is trapped by cyclohexene to give **2**. In 1964, in *Liebigs Annalen*, Wittig and Krauss reported that the 1960 cyclopropanation could not be reproduced under any conditions, and explicitly retracted the earlier claim.[2] Since then, this verdict has seemingly remained unchallenged; there have been no published reports of any attempts to use tetramethylammonium salts as methylene donors and no citations of the work.[3] Herein, we report the nickel-catalyzed cyclopropanation of unactivated olefins with tetramethylammonium triflate and *n*BuLi, which suggests that Franzen's work on cyclopropanation might have worked after all, albeit with the unsuspected influence of a metal catalyst. Moreover, we report unusual features of the reaction that would have hindered reproduction of the original work.

There are only a few methods for the cyclopropanation of electron-rich olefins known, especially for simple methylenation. The Simmons–Smith reaction is the method of choice in industry but has the drawback of generating a large amount of waste.[4] The decomposition of diazomethane with transition metals, although very versatile, is limited to small-scale reactions owing to the inherent hazards of the reagent itself.[5,6] A safe, scalable, and cost-effective method for these substrates would therefore be highly desirable.

Our group recently reported the addition of lithiomethyl trimethylammonium triflate to unsaturated bonds to give aziridines, epoxides, and cyclopropanes.[7,8] Even though styrenes and stilbenes could be cyclopropanated in good to excellent yields, the substrate scope was limited to these activated alkenes; attempts to cyclopropanate an unactivated olefin, cyclohexene, resulted only in recovery of the starting material.

We report now that a variety of nickel complexes catalyze the cyclopropanation of unactivated olefins. In the absence of catalyst, no reaction takes place (Table 1, entry 1). Different nickel sources, with and without added phosphine ligands, proved to be effective (Entries 2 to 4), with $[(PPh_3)_2NiBr_2]$ giving bicyclo[6.1.0]nonane (**3**) from cyclooctene, for example, in 23% yield based on the ylide (Entry 3). Interestingly, there seems to be no major difference between employing a Ni^0 or Ni^{II} complex (Entry 3 vs. 4). Surprisingly, no other metal catalyst (Fe, Co, Cu, Zn, Rh, Pd, Re) tested yielded any significant cyclopropanation product, which suggests that nickel is unique in this reaction. (Table S2 in the Supporting Information).

Table 1: Screening of catalysts.



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Entry[a]	Catalyst	Yield [%][b]
1	None	0[c,d]
2	0.5 mol% $[(dme)NiBr_2]$	16
3	1 mol% $[(PPh_3)_2NiBr_2]$	23 (25)[d,e]
4	1 mol% $[Ni(cod)_2]$/2 mol% PPh_3	19[d]

[a] Conditions: NMe_4OTf (1 equiv, 0.1 mmol), BuLi (1.05 equiv), COE (5 equiv) in THF (0.05 M). COE = cyclooctene, dme = dimethoxyethane, cod = 1,5-cyclooctadiene. [b] Calibrated GC yields with undecane as internal standard. Average of two independent runs. [c] 15 equiv COE used. [d] Single run only. [e] Slow addition of *n*BuLi over 5.5 h, 0.5 mmol scale.

Table 2 shows that the yield for the cyclopropanation of electron-rich olefins parallels the proclivity of the substrates for forming olefin π-complexes.[9] Based on our previous observations,[7,8] one would expect direct carbolithiation for electron-poor olefins. As noted previously,[8] we found that the lithiomethyl trimethylammonium reagent decomposes when the reaction vessel is open to an argon line, which allows gas exchange. The same decomposition occurs when using Ni as a catalyst. When the flask is open to an argon line, a distinct

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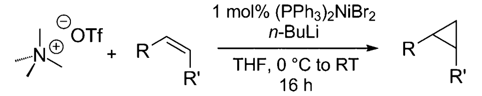
Table 2: Cyclopropanation yield for other alkenes.



Entry[a]	Alkene	Yield [%][b]
1	Norbornene	79
2	4-Phenyl-1-butene	40
3	Cyclohexene	8
4	3,4-Dihydro-2*H*-pyrane	0[c,d]
5	α-Pinene	0[c,d]

[a] For conditions, see Table 1; 5 equiv alkene. [b] Calibrated GC yields with undecane as internal standard. Average of two independent runs. [c] Single run only. [d] Only starting material observed.

Table 3: Difference between open and closed reaction vessels for the cyclopropanation of cyclooctene.

Entry[a]	Catalyst	Open/closed[b]	Yield [%][c]
1	0.5 mol% [(dme)NiBr$_2$]	Open	<1
2	0.5 mol% [(dme)NiBr$_2$]	Closed	16
3	1 mol% [(PPh$_3$)$_2$NiBr$_2$]	Open	16
4	1 mol% [(PPh$_3$)$_2$NiBr$_2$]	Closed	23

[a] For conditions see Table 1. [b] Open/closed refers to whether the reaction was run in a closed vessel or open to an argon line. [c] Calibrated GC yields with undecane as internal standard. Average of two independent runs.

decrease in the cyclopropanation yield is obtained (Table 3, entry 1 vs. 2, 3 vs. 4) relative to the case where an identical flask is kept closed after the addition of *n*BuLi. Interestingly, with catalytic amounts PPh$_3$, there is a much reduced dependence on whether the flask is open or closed.

Despite this finding, no or very little influence on product yield has been observed for the addition of NMe$_3$ (Table S5), at least in the molar excesses we tried. This holds true for catalysts with and without phosphine ligands. We note that the reaction catalyzed by [(dme)NiBr$_2$] alone is unpredictable and yields between 2% and 20% were obtained under otherwise identical conditions, whereas [(PPh$_3$)$_2$NiBr$_2$] catalyzed the reaction reproducibly and reliably.[10] Especially for catalysts with no phosphine ligand, this seems surprising given the marked influence on yield of whether the flask is open or closed (Table 3).

A third, important observation was made based on the catalyst loading. With no catalyst, there is no cyclopropanation. With 5 mol% catalyst, there is also no cyclopropanation. A maximum in the cyclopropanation yield is obtained with a catalyst loading of between 0.1 and 1.0 mol% (Figure 1).[11] Importantly, no other products were observed that correspond to alternative CH$_2$ insertions (e.g. methylenecyclooctane or 1-methylcyclooctene from cyclooctene)[12] or Stevens rearrangement of the lithiomethyl trimethylammonium to *N*,*N*-dimethylethylamine.[13] The only identifiable byproducts were a polymer, identified as polyethylene by GPC, IR, ^{1}H and ^{13}C NMR spectroscopy (Figures S14–S19), which was isolated in 17% yield, and cyclopropane, presumably from the cyclopropanation of ethylene, which was also observed in significant amounts by ^{13}C NMR (Figure S12).

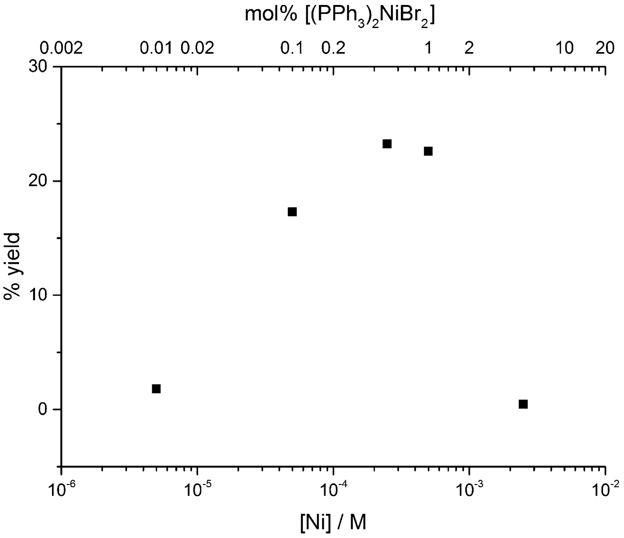
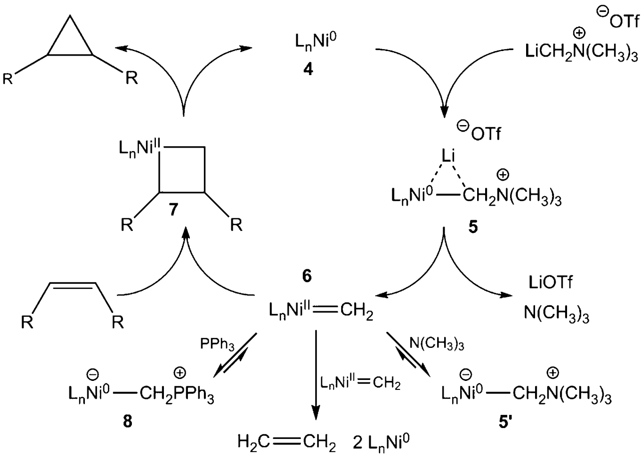


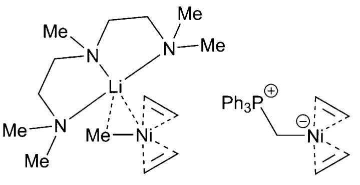
Figure 1. Dependence of the yield of the reaction cyclooctene→**3** on [(PPh$_3$)$_2$NiBr$_2$] loading. Each point represents the average of two independent runs.



Scheme 1. Proposed catalytic cycle for the nickel-catalyzed cyclopropanation with lithiomethyl trimethylammonium triflate as a methylene donor.

A proposed schematic catalytic cycle is shown in Scheme 1. Under the reaction conditions, the precatalyst is likely first reduced by the alkyllithium species RLi (R = Bu or CH$_2$NMe$_3$) that are present in solution since Ni^{II} halides are known to be reduced to Ni^0 by *n*BuLi.[9] The active Ni^0 catalyst **4** (L = PPh$_3$ or COE) then adds lithiomethyl trimethylammonium triflate to give the niccolate **5**. After the elimination of NMe$_3$, nickel carbene **6** is formed, which can react further to an intermediate nickelacyclobutane **7** (inner-sphere mechanism) or react directly via a transition state (outer-sphere mechanism; not shown) with an olefin to give the cyclopropane product and regenerate **4**. A DFT study by Geng et al. indicated that both cyclopropanation pathways could be plausible for Ni carbenes.[14] Reversible trapping by a nucleophile present in solution, either NMe$_3$ or PPh$_3$, leads to **5’** and **8**, respectively, thereby reducing the steady-state concentration of carbene intermediate **6**. Given the volatility (b.p. 3 °C) of NMe_3, this proposed trapping might also explain why reactions with catalytic PPh_3 in addition to Ni are less susceptible to whether the flask is open to an argon line or closed (Table 3). Stoichiometric methylenation of PPh_3 had been observed by Franzen and Wittig.[1] While the catalytic cycle proposed in Scheme 1 is admittedly speculative at this time, it does account adequately for the oddities of the reaction, which may have been the cause of the difficulties encountered 50 years ago. Moreover, each individual step in Scheme 1 has reasonable precedent in the literature.

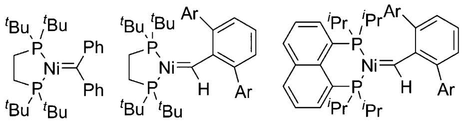
Although, to our knowledge, there are no reported adducts of trimethylammonium methylides to nickel, the formally isoelectronic Zn^{II} and Hg^{II} adducts have been synthesized. They are ill-characterized in the literature, and no attempts were made to cyclopropanate alkenes.[15] In situ prepared allyl ammonium ylide adducts of Cu and Zn have been used in [2,3] rearrangements, but no cyclopropanation derived from the ylides was observed.[16] Nevertheless, the behavior of Ni^0 as a weak Lewis acid (the L_2Ni^0 fragment is isolobal to $:CH_2$) has been studied in detail. Pörschke et al. reported the addition of MeLi and Ph_3PCH_2 to Ni^0 to give the corresponding niccolates(0) (Figure 2).[17] The compound $[(PMDTA)(LiMe)Ni(C_2H_4)_2]$ (**9**; PMDTA = *N,N,N′,N′,N″*-pentamethyldiethylenetriamine) was characterized by X-ray crystallography and is analogous to our proposed intermediate **5**. The P-ylide adduct $[(Ph_3PCH_2)Ni(C_2H_4)_2]$ (**10**) was identified in solution by NMR spectroscopy. Complex **10** is stable in solution under 0 °C and stable in the solid state at room temperature for several hours. Under an atmosphere of ethylene at higher temperature, **10** decomposes to give cyclopropane (not quantified), which led the authors to propose a carbenoid character for the methylene group in **10**.



9 **10**

Figure 2. Structurally characterized niccolates(0) relevant to this study. Compound **9** has been identified by X-ray crystallography and compound **10** has been studied in solution by NMR spectroscopy.[17]

There are only a few terminal nickel carbene complexes (non-Fischer) known in the literature (Figure 3). Hillhouse et al. reported the synthesis of nickel carbene complexes **11**, **12**, and **13** through decomposition of the appropriate diazo precursor.[18] Heating complex **11** under an atmosphere of ethylene resulted in the formation of 1,1-diphenylcyclopropane (**14**) in 85 % yield of isolated product.[19] Additionally, catalytic cyclopropanation was observed with 10 mol % **11** and $N_2{=}CPh_2$ under an atmosphere of ethylene to give **14** in 41 % yield. A [2+2] cycloaddition of ethylene to the nickel carbene was proposed to explain the formation of **14**.



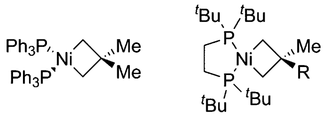
11 **12** **13**

Ar = 2,4,6-$(CH_3)_3C_6H_2$

Figure 3. Nickel carbenes isolated and structurally characterized (non-Fischer) by Hillhouse et al.[18]

Even though we have not detected the formation of ethylene under the conditions where we observe cyclopropanation, we had previously observed the decomposition of lithiomethyl trimethylammonium to give ethylene.[8] A homocoupling of two nickel carbenes can be expected to be second-order with respect to the carbene, as had been shown by Gladysz et al. for an electrophilic rhenium carbene and by Schrock et al. for a nucleophilic Ta carbene,[20] while cyclopropanation is first-order, thereby accounting for the strongly non-monotonic dependence on catalyst loading (Figure 1), in analogy to the persistent radical effect.[21] Additionally, the formation of polymer and the lack of ethylene could be explained by a subsequent polymerization and/or cyclopropanation of ethylene by nickel.[22] While ethylene in our reaction could, in principle, derive from decomposition of THF induced by *n*BuLi, this decomposition has been reported under conditions involving higher temperature and longer reaction times than we employed.[23] Moreover, in our previous work, we observed C_2H_4 in a closed NMR tube experiment where the solvent was $[D_8]$THF. Finaly, the decomposition of THF by *n*BuLi was reported to produce, besides ethylene, the lithium enolate of acetaldehyde, which was trapped by benzophenone. We found no evidence for this adduct in our previous work, in which our lithiomethyl trimethylammonium triflate was prepared in situ and reacted with benzophenone.[7] Accordingly, we consider it most probable that the polyethylene and cyclopropane side products in our reaction derive from homocoupling of nickel carbene **6**.

Nickelacyclobutanes formed by the reaction of a nickel carbene and an alkene have been invoked as reactive intermediates in cyclopropanation reactions to explain the observed stereochemistry.[24] Grubbs and Miyashita published a series of papers on the synthesis and reactivity of nickelacyclobutanes of the type $[(R_3P)_nNi(CH_2C(Me)_2CH_2)]$, for example, **15** (R = Ph, $n = 2$; Figure 4).[25] These complexes are stable at low temperature. Thermal decomposition of **15** or oxidation with O_2 results in the formation of 1,1-dimethylcyclopropane in 47 %[25b] and 80 %[25c] yield, respectively. Experimental observations indicate that nickelacyclobutane **15** might be in equilibrium with the corresponding carbene- and alkene-containing complex. Thermal decomposition of **15** in the presence of cyclohexene produced norcarane (**2**) in 10 % yield.[25d] In the present case, labeling studies with ^{13}C-enriched NMe_4OTf showed no scrambling of the label. Only enriched NMe_3 and isotopic incorporation into the CH_2 of the cyclopropane product were observed, that is, there is no indication for metathesis (see the Supporting Information). Hillhouse et al. reported on the similar complexes **16a** and



15 **16a** R = Me **16b** R = Ph

Figure 4. Isolated nickelacyclobutanes that undergo reductive elimination to form cyclopropanes.[25,26]

16b (Figure 4).[26] Both undergo facile reductive elimination to form the corresponding cyclopropanes in quantitative yield.

Each individual step in the proposed mechanism has precedent in analogous stoichiometric reactions, although the present report is the first to demonstrate catalytic turnover. While the best present cyclopropanation yields are admittedly only modest to good, we have identified the main side reactions that consume the lithiomethyl trimethylammonium triflate in an otherwise very clean reaction. The side reactions limit the chemical yield of the desired cyclopropane product, which for the better substrates already corresponds to turnover numbers on the order of 10^2 when the catalyst loading is near or slightly above 0.1 mol %.

In conclusion, we have shown that nickel catalyzes the cyclopropanation of unactivated olefins with lithiomethyl trimethylammonium triflate as the methylene donor, albeit in modest to good chemical yield. Based on our experimental observations and the presented literature, we propose a plausible mechanistic hypothesis involving a nickel carbene as a reactive intermediate. Our findings offer a potential explanation for the original 1960 report by Franzen and Wittig, and identify odd features of the reaction that might have made its reproduction difficult at the time. The mechanism furthermore provides a rational basis for the systematic development of the reaction for preparative purposes. Detailed mechanistic studies are ongoing.

Experimental Section

General procedure for cyclopropanation: An oven-dried 5 mL Schlenk flask was charged with NMe_4OTf (22.3 mg, 0.1 mmol), cyclooctene (65 μL, 0.5 mmol), catalyst in anhydrous THF, and anhydrous THF (total volume 2 mL, 0.05 M) inside the glove box. The flask was removed and cooled to 0 °C, and *n*BuLi (66 μL, 0.105 mmol) was added dropwise. The flask was sealed and the reaction was allowed to warm to RT overnight. After 16 h, undecane was added as an internal standard and the yield was determined by GC–FID.

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Keywords: carbenes · cyclopropanation · nickel · ylides

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