

PROCESS FOR THE CYCLOPROPANATION OF OLEFINS USING N-METHYL-N-NITROSO COMPOUNDS

Field of the Invention

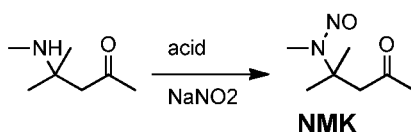
5 This disclosure relates to a method of cyclopropanating alkenes.

Background to the Invention

The conversion of a carbon-carbon double bond to a cyclopropane ring is a chemical trans-
10 formation used commonly in the synthesis of organic chemical compounds. Cyclopropana-
tion on a laboratory scale is commonly performed with the aid of a diazo compound, for
example, diazomethane (DAM), and transition metal catalyst typically comprising a copper
or palladium complex. Diazo compounds such as DAM are prepared from an N-alkyl-N-
nitroso compound, more particularly a N-methyl-N-nitroso compound (MNC), and still
15 more particularly with an MNC having the general formula $R(N(NO)Me)_x$. In order to
make such a process useful in industry, it would be highly desirable if both the MNC and
the DAM could be formed in-situ, and further reacted without isolation, in order to avoid
the hazards associated with handling these toxic materials. Such a process is described in
WO 2015059290, wherein an N-alkyl-N-nitroso compound is generated in a liquid phase
20 from a mixture of an amine $HNRR'$, water, $NaNO_2$ and an acid. An organic solvent can be
added to the N-alkyl-N-nitroso compound once it is formed to facilitate phase separation.
The N-alkyl-N-nitroso compound partitions into the organic solvent provided for that pur-
pose. A biphasic mixture is formed, and the organic phase can be separated from the aque-
ous phase in a phase separation step. Thereafter, the organic phase containing the N-alkyl-
25 N-nitroso compound is added to an alkene substrate, without having first to isolate it in
pure form. As the N-alkyl-N-nitroso compound is in an organic solvent, it can be cleanly
and simply transferred into a reaction vessel containing an alkene substrate.

A particularly suitable N-alkyl-N-nitroso compound is N-nitroso- β -methyaminoisobutyl methyl ketone NMK (sometimes referred to as "Liquizald") which can be prepared from the methylamine mesityloxide adduct through nitrosation in the presence of an acid.

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NMK was first prepared by E.C.S.Jones and J.Kenner (*JCS* 363, 1933) and used for the preparation of diazomethane in the presence of base. Nitrosation (with 2 mol eq NaNO₂) was carried out in the presence of HCl (> 1 mol eq) and NMK was distilled after extraction from the organic phase. Decomposition of NMK in the presence of base gave DAM which was distilled before being used for the methylenation of benzoic acid.

NMK was also prepared by nitrosation of the methylamine mesityloxide adduct by using 2.5 mol-eq acetic acid and NaNO₂ (2.35 mol-eq) in aqueous phase. Treatment of the crude NMK with base gave DAM, which was, once again, distilled before being used for the methylation of an acid (D.W.Adamson, J.Kenner *JCS* 1553 (1937)).

The same method was later on used by C.E.Redemann, F.O.Rice, R.Roberts and H.P.Ward (*Org.Synth.Coll.Vol.3*, 244, 1955) employing less acetic acid (HOAc) (1.7 mol-eq) and NaNO₂ (1.2 mol-eq) per mol mesityl oxide for the preparation of NMK. The crude NMK was treated with base and DAM was distilled. References for further derivatization of DAM were given, however, the transition metal catalyzed methylenation of double bonds with DAM was unknown at that time.

From these prior art references one can conclude that although NMK and DAM can be efficiently generated from the methylamine mesityloxy adduct by nitrosation in the presence of acetic acid, the NMK and/or DAM were purified and isolated by distillation before being used in any subsequent reactions. Indeed, distillation was deemed necessary to separate

5 NMK and/or DAM from acetic acid as methylation of acetic acid would occur as soon as DAM is generated. In other words, acetic acid is a competitive substrate in any methylation reaction and would thus decrease the yield of any desired methylenated product. The reaction of DAM with acetic acid is well documented in the art, see for example WO 0147869.

10 The transition metal catalyzed methylenation of alkenes with diazomethane formed from NMK has been described in WO 2013110932. In this reference, NMK is formed by the nitrosation of methylamine mesityl oxide adduct, in the presence of a tribasic acid, notably H_3PO_4 . The tribasic acid is compared favourably over acetic acid because it reduces or even eliminates acid contamination in the NMK. After phase separation of the organic NMK

15 phase, this procedure produces a 60 – 80% aqueous H_3PO_4 waste solution, and it is emphasized that phase separation is improved by the fact that sodium phosphate salts produced as a by-product of the reaction are close to saturation in the aqueous phase, and that the high level of salt saturation reduces the solubility of NMK in the aqueous phase, ensuring high yields and clean separation of NMK. It is emphasized that the use of the tribasic acid results

20 in a cheaper process and a cleaner (less acidified) product than could be produced using prior art methods. In fact, comparative experiments in WO 2013110932 show that whereas the yields of NMK are similar whether one uses the tribasic acid H_3PO_4 or the mono-basic acetic acid, in the latter case the NMK product is contaminated by significant amounts of HOAc (6.4% w/w), which would indicate that using the NMK to subsequently generate

25 DAM in order to methylate a substrate would not be appropriate without first purifying the NMK by distillation.

The use of the method described in WO 2013110932, e.g. preparation of NMK using acidification with H_3PO_4 , to generate diazomethane for the $\text{Pd}(\text{OAc})_2$ -catalyzed cyclopropanation of a 1,1-disubstituted alkene has been described by Markus Baenziger (31th International Conference, Organic Process Research and Development, September 29 – October 1, 2014, Cologne, Germany).

WO 2015059290 discloses an efficient $\text{Pd}(\text{acac})_2$ -catalyzed cyclopropanation of a terminal-ly mono-substituted alkene producing diazomethane directly (without nitrogen sparging) in a biphasic reaction mixture consisting of catalyst, substrate, aqueous base and NMK. As stated in Example 7, NMK was prepared as described in WO 2013110932, using H_3PO_4 for acidification.

When investigating this route for the purpose of assessing its potential as an industrially scalable process, applicant found however, that generating NMK (and by extension, any N-alkyl-N-nitroso compound) using a tribasic acid such as H_3PO_4 , decomposing it to form DAM *in-situ* without purification or isolation of either NMK or DAM, and reacting the DAM with an alkene substrate to cyclopropanate that substrate, resulted in a poorly reproducible reaction.

Applicant believes - without intending to be bound by any particular theory - the poor reproducibility may have as its cause, the generation of high levels of nitrous gases during NMK formation, which could contaminate both the NMK and the DAM, and poison the catalyst used in the cyclopropanation step.

In addition to this empirical observation, the relatively high price of H_3PO_4 , sustainability issues related to future supply of limited phosphorus resources, and generation of phosphorus waste from the reaction, particularly when using stoichiometric amounts of H_3PO_4 , led

the applicant to conclude that the use of a tri-basic acid and in particular H_3PO_4 , contrary to suggestions in the prior art, was not a viable, industrially scalable route.

There remains a need to address the deficiencies in the prior art and to provide a method of
5 cyclopropanating alkene functionality on a substrate that is safe, cost effective, and can reliably produce industrial quantities of product in high yields.

Summary of the Invention

10 The disclosure provides in a first aspect a method of converting a carbon-carbon double bond on a substrate into a cyclopropane ring, which method comprises the step of treating the substrate with a N-alkyl-N-nitroso compound, a transition metal catalyst and an aqueous base, wherein the N-alkyl-N-nitroso compound is formed by reacting an alkyl amine and NaNO_2 in the presence of a mono-basic or di-basic acid or mixtures of said acids, more
15 particularly a mono-basic carboxylic acid such as acetic acid or a di-basic inorganic acid such as sulfuric acid, and wherein the N-alkyl-N-nitroso compound is not distilled before it is mixed with the substrate, catalyst and base for the purpose of cyclopropanation in this mixture.

20 Detailed description of the Invention

Although the preparation of a N-alkyl-N-nitroso compound, and its subsequent use, without purification or isolation, in the conversion of a carbon-carbon double bond to a cyclopropane ring is known in the art, there is a clear prejudice in the art to do this if the acid
25 employed in the preparation of the N-alkyl-N-nitroso compound is an acid which can be methylated, such as a mono basic carboxylic acid and more particularly acetic acid.

The applicant was surprised to find, therefore, that the cyclopropanation reaction proceeded to produce reliably high yields of cyclopropanated product on an industrial scale. Furthermore, the use of these acids is relatively inexpensive compared with the use of tribasic acids such as H_3PO_4 . Further still, the reaction is advantageous from a sustainability point of view due to the generation and degradation of carboxylic acids in the biosphere.

In exercising the present invention the preferred mono- or di-basic acids are sulphuric acid, or mono- or di-basic carboxylic acids, such as $\text{C}_1\text{-C}_{20}$ carboxylic acids, which may be linear, branched or cyclic, and which may be saturated, or contain saturation, and may or may not be substituted with functional groups. Of course, for reasons related to economy, it is preferred to use low-cost carboxylic acids with low molecular weight such as formic acid, acetic acid or propionic acid, most preferably acetic acid. $\text{C}_1\text{-C}_{20}$ mono-, bis, tri and polyacids are also an option as well as mixtures of carboxylic acids or mixtures of carboxylic acids and inorganic acids such as dibasic sulfuric acid or mixtures of mono- and dibasic inorganic acids.

In a particular embodiment of the invention mixtures of a carboxylic acid, e.g. acetic acid, with stronger (i.e. lower pKa) organic and inorganic acids can be employed in the formation of N-alkyl-N-nitroso compounds. Typical solutions might include 5 to 50 % solutions of said stronger acid in said carboxylic acid, and more particularly 5 to 20 % is preferred, as higher levels of the stronger acid in the carboxylic acid can be detrimental to phase separation, yield and purity of N-alkyl-N-nitroso compounds, as well as produce high levels of nitrous gases, which as stated above, can poison the catalyst in the subsequent cyclopropanation step. An exception to this appears to be use of H_2SO_4 as the acidification reagent in the nitrosation reaction. In contrast to other strong acids, such as HCl , HNO_3 and methyl sulphonic acid for example, H_2SO_4 can be used without a carboxylic acid, although

it can also be employed 0.1 – 1.5 eq, more preferably with 0.5 – 1 eq., in combination with acetic acid.

These findings were all the more surprising given that from the literature, one would predict, substantially reduced yields both of N-alkyl-N-nitroso compound and the final cyclopropanated substrate if mono- or di-basic acids, and in particular acetic acid is employed instead of the favoured tribasic acids, and in particular H_3PO_4 . In fact, applicant found that the yields of cyclopropanated product were comparable irrespective of whether one employs acetic acid or other mono- and dibasic acids in the acidification step or H_3PO_4 . As stated above, although the use of H_3PO_4 may carry with it certain advantages, the applicant believes that the generation of nitrous gases may play a negative role, and it was observed that lower levels of nitrous gases were formed when using acetic acid compared with the use of H_3PO_4 . In the case of the acidification with acetic acid less nitrous gases were generated, based on the observation that the less brownish coloration of the N-alkyl-N-nitroso compound layer and less brown vapors in the nitrogen waste stream, compared with a process wherein acidification was carried out using H_3PO_4 .

Any of the N-alkyl-N-nitroso compounds disclosed in WO 2015059290 may be employed in the present invention. The N-alkyl-N-nitroso compounds may be made in accordance with prior art methods, in which an alkyl amine, alkyl amide, alkyl urethane or alkyl urea HNRR' is reacted with an acid and an alkali metal nitrite, such as NaNO_2 . The alkyl amine may be commercially available material, or it may be formed by reacting an aliphatic amine H_2NR with a suitable starting material reactive with the aliphatic amine, such as an α,β -unsaturated ketone. Preparative methods are set out in WO 2015059290. A particularly preferred N-alkyl-N-nitroso compound is N-nitroso- β -methyaminoisobutyl methyl ketone (NMK). This particular material may be prepared when methylamine is reacted with the α,β -unsaturated ketone - mesityl oxide - to form a methylamine mesityl oxide adduct (cor-

responding to HNRR', above). The adduct can then be further reacted with NaNO₂ and an acid to provide NMK. Methods of forming NMK are described in WO2013110932, which is hereby incorporated by reference.

- 5 The reaction to produce the N-alkyl-N-nitroso compounds may be carried out in a biphasic mixture. Before, during, or after the reaction is completed, one can add an organic solvent, which is a solvent for the alkyl-N-nitroso compound, and the organic layer, containing the crude N-alkyl-N-nitroso compound can be separated and used in the subsequent cyclopropanation reaction without further purification, for example by distillation. Optionally, how-
- 10 ever, the organic layer containing the N-alkyl-N-nitroso compound may be washed with an aqueous washing procedure known in the art, for example washing with a salt solution, provided no further acidification takes place or any basification does not increase the pH above a level of moderate basicity, e.g. 7 to 8.5, to prevent liberation of diazomethane. Such a washing procedure ideally removes nitrous gases, traces of acid, e.g. acetic acid, and
- 15 other impurities. In a further optional procedure, one may subject the organic layer to a degassing procedure using inert gas (e.g. nitrogen) to remove any traces of nitrous gases.

The cyclopropanation reaction is carried out in a biphasic mixture, in which the organic phase is a solvent for the N-alkyl-N-nitroso compound. Suitable solvents include ethers and

20 toluene, and more particularly tetrahydrofuran, dimethoxyethane, dioxane and dimethylisobutyl ether. In a first step, the organic phase containing the N-alkyl-N-nitroso compound is added to a mixture containing the substrate to be converted, aqueous base and catalyst. The aqueous base decomposes the N-alkyl-N-nitroso compound to form the diazoalkane, which in the presence of the catalyst converts the carbon-carbon double bond into a cyclopropyl

25 group. Upon completion of the cyclopropanation reaction, the mixture is phase separated and the organic phase, containing the target cyclopropanated compound is obtained.

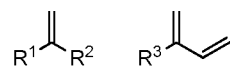
The methods herein described may be carried out under flow conditions in a flow reactor. Methods and apparatus for carrying out flow chemistry are well known in the art and do not require further elaboration here.

- 5 Details of the cyclopropanation process, as well as the reagents, solvents and reaction conditions and work-up conditions employed are set forth in WO 2015059290, which is hereby incorporated by reference for this purpose.

Catalysts useful in the present invention are transition metal catalysts, more particularly
10 palladium catalysts, still more particularly the palladium catalysts, Pd(acac)₂, Pd(OAc)₂ or PdCl₂.

Any double bond-containing substrate may be converted in accordance with the method of the present invention, to form all manner of useful and desirable cyclopropanated target
15 compounds. Suitable double bond-containing substrates and the target cyclopropanated compounds, especially useful in fragrance, cosmetic and flavour applications are set forth and described in WO 2015059290, which is hereby incorporated by reference for this purpose.

- 20 Particular substrates include terminal (i.e. mono-substituted) alkenes. More particularly, compounds according to the general formulae



- wherein R¹ and R² may, independently, represent H, alkyl, alkylidene, or aryl, which
be branched or unbranched and substituted or unsubstituted; and R³ may be an alkyl,
25 alkylidene, or aryl, which may be branched or unbranched and substituted or unsubstituted.

Still more particularly, the substrate may be an isoprenoid, such as alpha or beta farnesene.

Target compounds that may be formed by a method according to the present invention include compounds of the formula



in which $n = 0, 1, 2$ or 3 .

In a particular embodiment the target compound is



In another particular embodiment the target compound is



Target compounds according to the present invention are useful precursors to compounds that are useful ingredients in perfumery.

There now follows a series of examples serving to further illustrate the invention.

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Examples

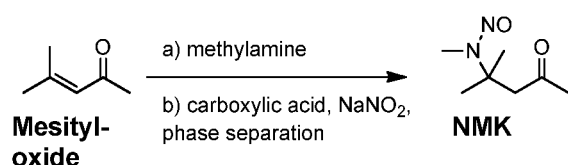
¹H-NMR: The reported NMR spectra were measured in CDCl₃ at 400 MHz if not stated otherwise. The chemical shifts are reported in ppm downfield from TMS. The quantification of Liquizald was performed using an internal standard (anisaldehyde) with known puri-

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ty in d₆-DMSO. Additionally, to guarantee full relaxation of the signals, the relaxation time d1 was set to 56s.

Example 1

- 5 Preparation of (N-methyl-N-nitroso)-4-amino-4-methyl-2-pentanone (NMK) by nitrosation in the presence of carboxylic acids



- 10 Mesityl oxide (10 g, 0.1 mol) is added dropwise over 15 min to methylamine (40 % in water, 8.3 g, 0.11 mol) at 5 - 15 °C under external cooling and stirring. The resulting orange solution is stirred for one hour at room temperature and cooled to 10 °C where formic acid (98%, 8.4 g, 0.18 mol) is added dropwise over 15 min at 10 - 20 °C. Then a 30% solution of sodium nitrite (8.85 g, 0.125 mol) in water (21 g) is added dropwise over 10 min at 10 -
- 15 15 °C. The biphasic mixture is left under stirring and at room temperature overnight (16 h). After phase separation (1 h) 15.25 g (68% based on mesityl oxide) of an organic layer is obtained consisting mainly of (N-methyl-N-nitroso)-4-amino-4-methyl-2-pentanone (NMK) with a purity of 72% according to ¹H-NMR with internal standard.
- 20 The following table shows results from the variation of this procedure using different carboxylic acids:

run	acid	acid conc	mol-eq acid / mesityl oxide	formation of NOx gases ^b	purity ^a	yield ^c
comparison	phosphoric	75% in H ₂ O	0.9	insignificant	77%	73%
1	formic	pure	1.75	weak	72%	68%
2	acetic	pure	1.75	insignificant	69%	66%

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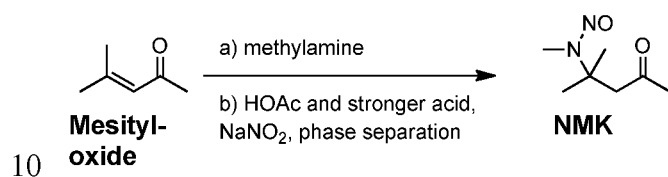
3	acetic	pure	1.6	insignificant	70%	62%
4	α -hydroxy-isobutyric	75% in H ₂ O	1.75	middle	59%	38%
5	lactic	pure	1.75	insignificant	71%	62%
6	glycolic	pure	1.75	insignificant	74%	61%

Conditions: Addition of carboxylic acids to the methyl amine / mesityl adduct followed by NaNO₂ addition and phase separation as described above. a) determination of the purity by ¹H-NMR with internal standard anisaldehyde. b) brown coloration of reaction mixture, brown vapors over reaction surface and in the exhaust tube. c) based on quantity of organic phase and purity.

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Example 2

Preparation of (N-methyl-N-nitroso)-4-amino-4-methyl-2-pentanone (NMK) by nitrosation in the presence of acetic acid and stronger acids



Mesityl oxide (10 g, 0.1 mol) is added dropwise over 15 min to methylamine (40 % in water, 8.5 g, 0.11 mol) at 5 - 15 °C under external cooling and stirring. The resulting orange solution is stirred for one hour at room temperature and cooled to 10 °C where acetic acid (100%, 10 g, 0.1 mol) is added dropwise over 15 min at 10 - 20 °C. Then a 30% solution of sodium nitrite (8.85 g, 0.125 mol) in water (21 g) is added dropwise over 10 min at 10 - 15 °C. The biphasic mixture is left under stirring and at room temperature overnight (16 h). After phase separation (1 h) 14.25 g (62% based on mesityl oxide) of an organic layer is obtained consisting mainly of (N-methyl-N-nitroso)-4-amino-4-methyl-2-pentanone (NMK) with a purity of 70% according to ¹H-NMR with internal standard.

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The following table shows results from the variation of this procedure using acetic acid in combination with different stronger acids

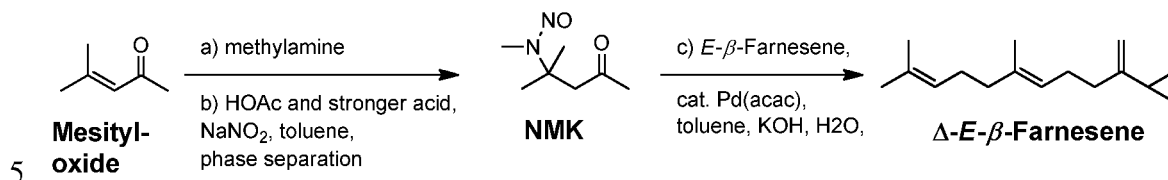
run	HOAc and stronger acid	mol-eq HOAc ^c	mol-eq stronger acid ^c	formation of NOx gases ^b	purity ^a	yield ^e
comparison	./.	1.6	./.	insignificant	70%	62%
1	65% HNO ₃	1.8	0.1	insignificant	69%	64%
2	65% HNO ₃	1.3	0.3	insignificant	76%	66%
3	65% HNO ₃	0.5	0.8	intermediate	much less organic phase	
4	65% HNO ₃	./.	1.75	significant	much less organic phase	
5	32% HCl	1.6	0.1	insignificant	72%	68%
6	32% HCl	1.3	0.3	insignificant	74%	68%
7	32% HCl	0.5	0.8	intermediate	much less organic phase	
8	32% HCl	./.	1	significant	63%	32%
	32% HCl	./.	1 + 1 ^d	intermediate	61%	39%
9	98% H ₂ SO ₄	1.6	0.1	insignificant	69%	64%
10	98% H ₂ SO ₄	1.3	0.3	intermediate	65%	71%
11 ^c	80% H ₂ SO ₄	./.	0.65	insignificant	63%	58%
12 ^d	80% H ₂ SO ₄	./.	1	intermediate	69%	50%
13	80% H ₂ SO ₄	./.	2	significant	no phase separation	
14	CF ₃ SO ₃ H	1	0.1	insignificant	66%	65%
15	75% MeSO ₃ H	1	0.1	insignificant	71%	68%
16	75% MeSO ₃ H	./.	1.75	significant	much less organic phase	

Conditions: Addition of pure acetic acid (and stronger acid) to the methyl amine / mesityl adduct followed by

- 5 NaNO₂ addition and phase separation as described above. a) Determination of the purity by ¹H-NMR with internal standard anisaldehyde. b) brown coloration of reaction mixture, brown vapors over reaction surface and in the exhaust tube. c) stronger acid dissolved in acetic acid. d) method described in *JCS* 363, 1933. e) based on quantity of organic phase and purity.

Example 3

Diazomethane cyclopropanation with (N-methyl-N-nitroso)-4-amino-4-methyl-2-pentanone (NMK) made through nitrosation in the presence of HOAc

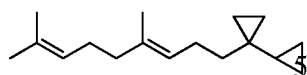


Mesityl oxide (68.8 g, 0.7 mol) is added dropwise over 1 h to methylamine (40 % in water, 58.1 g, 0.75 mol) at 5 - 15 °C under external cooling and stirring. The resulting orange solution is stirred for one hour at room temperature. Water (140 ml) and toluene (70 ml) are added, followed by dropwise addition of acetic acid (100%, 115 g, 1.9 mol) over 1 h at 10 - 20 °C. Then a 30% solution of sodium nitrite (49.8 g, 0.7 mol) in water (116 g) is added dropwise over 60 min at 20 – 25 °C. The biphasic mixture is left under stirring and at room temperature overnight (16 h). After phase separation (1 h) 155.23 g of an organic layer is obtained consisting mainly of (N-methyl-N-nitroso)-4-amino-4-methyl-2-pentanone (NMK) which is flushed with nitrogen through a sintered tube for 1 h which turns the opaque organic phase into a clear solution.

Pd(acac)₂ (0.1 g, 0.33 mmol) are added to a solution of *E*- β -Farnesene 98% (51.5 g, 0.25 mol) in toluene (150 ml), followed by KOH (49.9 g, 0.76 mol) in water (208.5 g) under strong stirring. The (N-methyl-N-nitroso)-4-amino-4-methyl-2-pentanone layer (155.2 g) is added over 2 h at 25 °C. GC after 0.5 h shows *E*- β -Farnesene (4%), Δ -*E*- β -Farnesene (88%), and Δ_2 -*E*- β -Farnesene (8%). After 17 h (same GC profile) the phases are separated. The water phase is washed with toluene (100 ml), the organic phase is washed with water (250 ml), acetic acid (250 g), water (250 ml), 10% NaOH (250 ml) and water (2 x 250 ml). The combined organic layers are dried over MgSO₄, filtered and the solvent is removed under reduced pressure giving 63.6 g of crude Δ -*E*- β -Farnesene which is purified by flash

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distillation giving 0.73 g of *E*- β -Farnesene (0.5%), 48.12 g of Δ -*E*- β -Farnesene (89%) and 3.1 g Δ_2 -*E*- β -Farnesene (5%) whose analytical data are identical to the ones described in WO 2015059290.

 Δ_2 -*E*-Farnesene

The following table shows results from the variation of this procedure using different amounts of catalyst and / or dibasic acid H₂SO₄.

run	mol-eq ^a acid	mol-eq ^a NaNO ₂	mol% ^a Pd(acac) ₂	con-version	Δ_1	Δ_2	isolated yield ^b
comparison	2.8 H ₃ PO ₄	2	0.13 %	100%	91%	8%	86%
1	7.6 HOAc	2.8	0.13 %	96%	88%	8%	87%
2	7.6 HOAc	2.8	0.05%	81%	76%	3%	n.d.
3	7.6 HOAc	2.8	0.02%	67%	57%	1%	n.d.
4	1.5 H ₃ PO ₄	2.1	0.02%	68%	53%	2%	n.d.
5	1.75 H ₂ SO ₄	2.8	0.02%	52%	40%	./.	n.d.
6	1.75 H ₂ SO ₄	3	0.13%	100%	90%	10%	87%

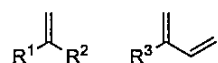
Conditions: Cyclopropanation at 25 °C. a) mol-eq or mol% based on farnesene. b) After short-path distillation

10 and corrected by purity of *E*- Δ_1 -Farnesene. n.d. = not determined.

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Claims:

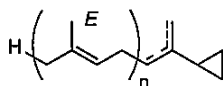
1. A process of converting a carbon-carbon double bond on a substrate into a cyclopropane ring, which method comprises the step of treating the substrate with N-nitroso- β -methylaminoisobutyl methyl ketone, a transition metal catalyst and an aqueous base,
 - 5 wherein the N-nitroso- β -methylaminoisobutyl methyl ketone is formed by reacting β -methylaminoisobutyl methyl ketone with an alkali metal nitrite in the presence of formic acid and wherein the N-nitroso- β -methylaminoisobutyl methyl ketone is not distilled before it is mixed with the substrate, catalyst and base.
- 10 2. A process according to any of the preceding claims wherein the substrate is a compound according to the general formulae



- wherein R^1 and R^2 may, independently, represent H, alkyl, alkylidene, or aryl, which may be branched or unbranched and substituted or unsubstituted; and R^3 may be an alkyl, alkylidene, or aryl, which may be branched or unbranched and substituted or unsubstituted.
- 15 3. A process according to claim 2 wherein the substrate is an isoprenoid, more particularly alpha farnesene or beta farnesene.

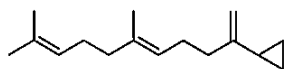
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4. A method of forming a compound of the formula



- 25 in which $n = 0, 1, 2$ or 3 , according to any of the claims 1 through 3.

5. A method of forming a compound of the formula,



- 5 according to any of the claims 1 through 4.