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# Asymmetric hydrogenation of indene carboxylic acids: stereochemistry of hydrogen addition

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**Abstract**

The stereochemistry of hydrogen addition to α,β-unsaturated carboxylic acids was studied by means of hydrogenation of indene carboxylic acids and their derivatives. Experiments were carried out over $Pd/Al_2O_3$ in the presence and absence of cinchonidine as a chiral modifier. In all cases hydrogenation occurred via bottom side *syn* addition of two hydrogen atoms to the chemisorbed substrate. Formation of *trans* isomers, up to 72%, was observed due to C=C bond isomerization in the substrate, and to adsorption and hydrogenation of the unsaturated molecule in a sterically unfavourable position. Adsorption in 'upside down' position was promoted by N-bases. Hydrogenation of 3-methylindene-2-carboxylic acid provided up to 45% ee. Due to the high activity of Pd in C=C bond migration, a good ee can be achieved only when isomerization is negligible. 

## 1. Introduction

Asymmetric hydrogenation of C=C bonds is an important synthetic method in the laboratory and industry. Considerable effort has been expended in the past decades for the enantioselective hydrogenation of α,β-unsaturated carboxylic acids, in particular with homogeneous metal complexes possessing chiral ligands, and excellent enantiomeric excesses (ees) have been reached.[1–4] Unfortunately, heterogeneous enantioselective hydrogenation is far less successful, although it would be preferable due to its advantageous technical aspects, such as catalyst separation, handling and reuse.

To date, supported palladium modified with strongly adsorbing cinchona or vinca type alkaloids are the most promising heterogeneous enantioselective catalysts for the hydrogenation of functionalized olefins.[5,6] Examples are the hydrogenation of *E*-α-phenylcinnamic acid (72% ee),[7] and aliphatic α,β-unsaturated carboxylic acids (20–53% ee).[8,9]

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Previously, we have reported an empirical rule developed to predict the configuration of the major enantiomer formed in the enantioselective hydrogenation of alkenoic acids over cinchonidine-modified palladium.[8,10] According to our present understanding, the chiral modifier cinchonidine interacts with an alkenoic acid dimer on the metal surface, involving both the quinuclidine nitrogen and the OH group of cinchonidine in hydrogen bonding. It is assumed that the alkenoic acid dimer is in *trans* position and one of the C=C double bonds points toward the quinoline moiety of cinchonidine.[8] In this model we assumed the stepwise bottom side *syn* addition of two hydrogen atoms to the chemisorbed species, which is the mostly accepted mechanism for metal-catalyzed hydrogenations (Langmuir–Hinshelwood mechanism).[11] However, a large number of examples are described even in recent literature on the *anti*, or 'top side–bottom side', addition of hydrogen[12] and these examples also include asymmetric hydrogenation reactions.[13]

The formation of *trans* isomers in liquid phase reactions is interpreted mainly by the following two mechanisms: (i) C=C double bond migration followed by desorption and readsorption on the other face of the molecule (classical, mostly accepted mechanism);[14] and (ii) by an ionic mechanism (*anti* addition of hydrogen) involving a solvent molecule in the liquid phase.[15]

Very recently, we have detected the formation of *trans* isomers in the enantioselective hydrogenation of 3-methylindene-2-carboxylic acid **1** over cinchonidine-modified palladium. This observation would question the validity of the assumption of bottom side *syn* addition of hydrogen, if the appearance of the *trans* product in considerable amounts can be attributed to direct *anti* addition of hydrogen to the C=C bond. Moreover, it could explain the moderate enantioselectivity of the Pd–cinchona alkaloid system in the hydrogenation of functionalized olefins.[5] The importance of this observation prompted us to reinvestigate the stereochemistry of hydrogen addition to unsaturated compounds over palladium. The asymmetric hydrogenation of indene carboxylic acids and derivatives over $Pd/Al_2O_3$, in the absence and presence of cinchonidine as a chiral modifier, are used as test reactions.

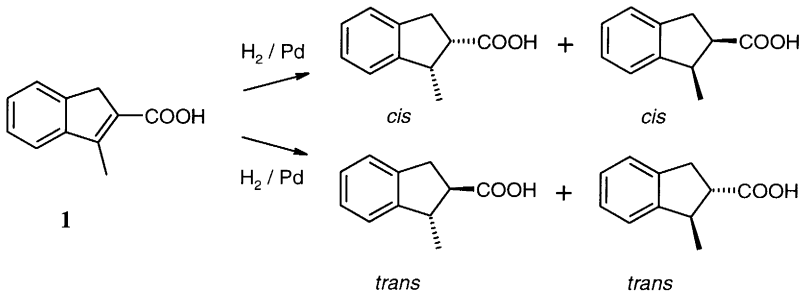
## 2. Results and discussion

### *2.1. Hydrogenation of 3-methylindene-2-carboxylic acid **1***

Hydrogenation of **1** furnished mainly *cis* isomers, but a small amount of the *trans* isomer was also detected by gas chromatography (Scheme 1). More astonishingly, the presence of cinchonidine favoured the formation of isomers with *trans* configuration (Fig. 1). Furthermore, the enantioselectivity — which corresponds to the enrichment of one of the *cis* enantiomers — diminished rapidly above a cinchonidine/reactant molar ratio of 0.017. This correlation contrasts with the general observation that in the enantioselective hydrogenation of α,β-unsaturated acids the ee increases linearly with increasing amounts of cinchonidine.[7,9] Note that determination of the ee of one of the *trans* isomers was uncertain due to their small quantity.

The reaction medium had a remarkable effect on both *cis*/*trans* ratio and ee (Table 1). No clear correlation between solvent polarity, ee and *cis*/*trans* ratio could be established. Excluding the reaction where EtOH was used as solvent, the presence of the N-base cinchonidine favoured the formation of *trans* isomers, whereas addition of a strong acid (TFA) in excess related to the base had the opposite effect. Employing the methyl ester of **1** barely changed the *cis*/*trans* ratio.

According to the classical mechanism, C=C double bond isomerization prior to hydrogenation is responsible for the presence of *trans* isomers. C=C double bond shift around the cyclopentene ring of **1** would lead to intermediate 1-methylindene-2-carboxylic acid **2** (Scheme 2). Direct hydrogenation




Scheme 1. Hydrogenation of **1** over $Pd/Al_2O_3$ providing both *cis* and *trans* isomers

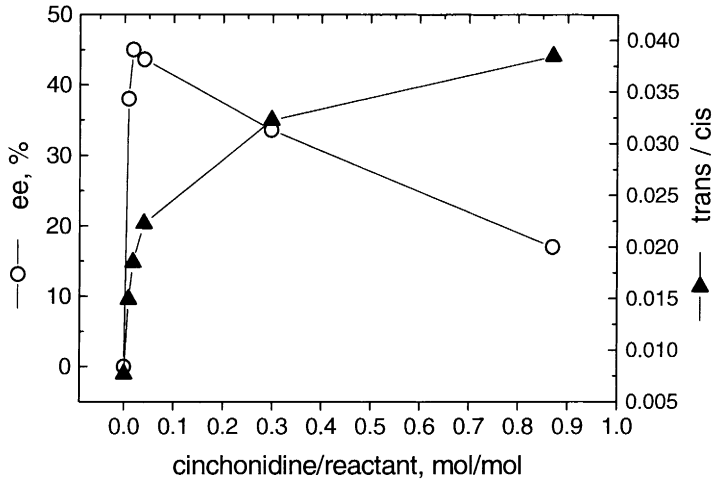



Fig. 1. Enantiomeric excess and formation of *trans* isomers as a function of cinchonidine/reactant ratio in the hydrogenation of **1**. Standard reaction conditions (not optimized): 20 ml toluene, 100 mg **1**, 50 mg cat., 1 bar hydrogen, reaction time: till full conversion

of **2** affords *cis* isomers, but desorption followed by its readsorption on the sterically more hindered side (with the methyl group facing the catalyst surface, i.e. 'upside down') and hydrogenation would furnish *trans* isomers, still assuming *syn* addition of hydrogen atoms to the adsorbed face. Note that **2** was not detectable during hydrogenation of **1**, which can be attributed to the fact that hydrogenation of isomeric trisubstituted compounds is much faster than that of tetrasubstituted olefins.[16] Besides, diffusional limitations in the pores or strong adsorption of the isomerized olefin can hinder the detection of the isomerized compound in the liquid phase. The proposed mechanism shown in Scheme 2 is supported by the following two sets of experiments (I and II).

### *2.1.1. Experiment I.* trans-*Indane-carboxylic acid via preceding isomerization*

In the first experiment the hydrogenation of the suggested isomer **2** was carried out (Scheme 2). The results are shown in Table 2. A large amount of *trans* isomer was formed without any modifier, while cinchonidine enhanced further the *trans*/*cis* ratio. The fraction of *trans* isomers increased remarkably with increasing conversion over cinchonidine modified catalyst, as illustrated by entries 2 and 3. When cinchonidine was substituted by quinuclidine the *trans/cis* ratio barely changed. Hence, the enhanced rate of formation of *trans* isomers over the Pd–cinchonidine system cannot be attributed to the chirality of cinchonidine, but presumably to an acid-based interaction between the quinuclidine nitrogen of cinchonidine and **2**. Apparently, the presence of the bulky N-base favours the hydrogenation of **2** in the 'upside down' position.

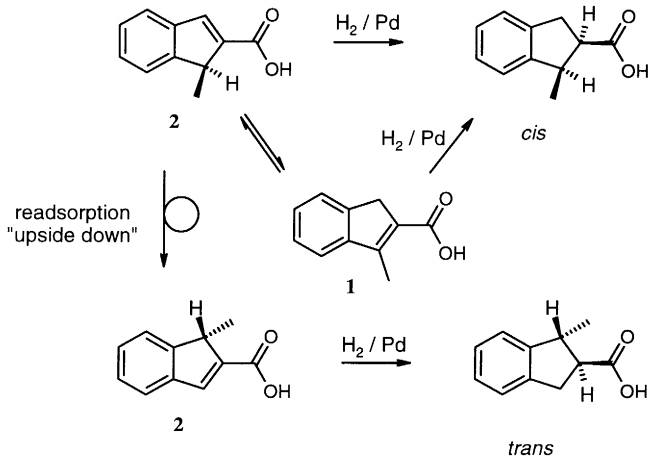
Table 1
Solvent effect on the ee and *cis*/*trans* ratio in the enantioselective hydrogenation of **1** according to Scheme 1 (100 mg **1**, 50 mg cat., 6.8 mg cinchonidine, 20 ml solvent, 1 bar hydrogen, reaction time: 2.5 h)

| Solvent | ε[a] | ee, % | *cis* / *trans* | |
|---|---|---|---|---|
| | | | without CD | with CD |
| **Cyclohexane** | 2.0 | 8 | only *cis* | 50 |
| **Toluene** | 2.3 | 41 | 130 | 75 |
| **EtOH** | 24.3 | 32 | only *cis* | only *cis* |
| **DMF** | 36.7 | 15 | 78 | 30 |
| **Toluene** [b] | - | - | only *cis* | - |
| **Toluene** [c] | 2.3 | - | 140 | - |

[a] dielectric constant at 20°C

[b] $3.4\times10^{-2}$ g TFA was added, ε of the mixture is not known

[c] methyl ester of **1** was the reactant



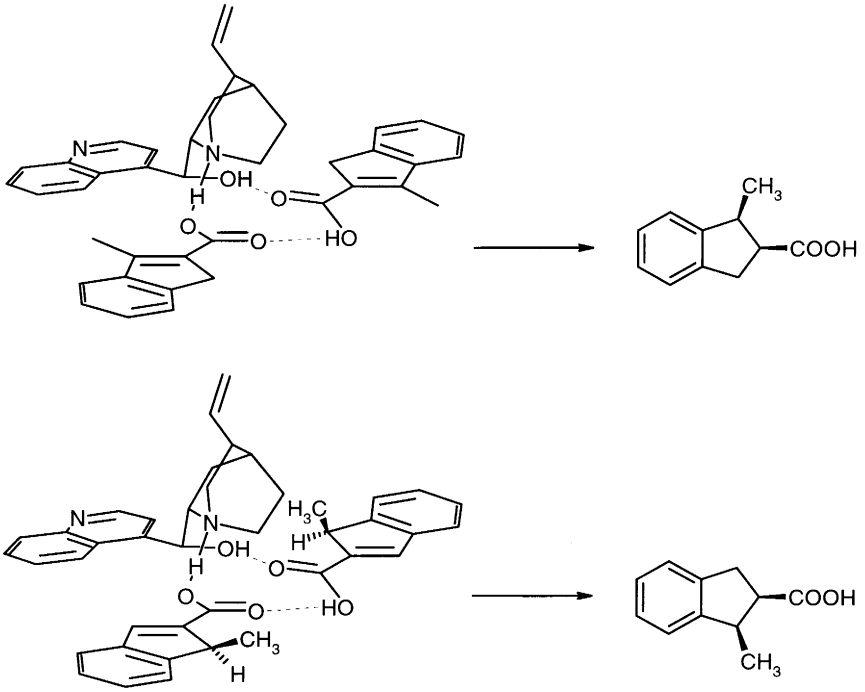

Scheme 2. Possible formation of *trans* isomers via an 'upside down' adsorption of the isomerized reactant **2**

Isomerization of the C=C double bond in **2** resulted in the formation of the thermodynamically more stable **1**, which could always be detected in the liquid phase. The tetrasubstituted isomer **1** was present even after complete disappearance of **2** in the reaction carried out without any modifier (neither cinchonidine nor quinuclidine). In cinchonidine-modified hydrogenations, **2** furnished the opposite enantiomer to **1** with moderate enantioselectivity. This observation is in full agreement with our former mechanistic model,[8] which predicts different enantiomers in excess for the hydrogenation of **1** and its isomer **2** (Scheme 3). Based on this model one C=C bond in the acid dimer points toward the quinoline ring of cinchonidine.[10] Recently, we have demonstrated the crucial role of C=C bond migration in the hydrogenation of 2-ethyl propenoic acid over $Pd/Al_2O_3$.[17] Isomerization and subsequent hydrogenation

Table 2
Product distribution and enantioselectivity in the hydrogenation of **2** according to Scheme 2 (20 ml toluene, 100 mg **2**, 10 mg catalyst, 2 mg cinchonidine (0.75 mg quinuclidine), 1 bar hydrogen)

| Entry | Modifier | Conversion of 2, % | Selectivity to, % | | | ee, % | |
|---|---|---|---|---|---|---|---|
| | | | **1** | *cis* | *trans* | *cis* | *trans* |
| **1** | – | 100 | 2 | 66 | 32 | – | |
| **2** | CD | 67 | 8 | 32 | 60 | 17 | 17 |
| **3** | CD | 92 | 1 | 27 | 72 | 16 | 13 |
| **4** | quinuclidine | 95 | 4 | 27 | 69 | – | |

of the two isomer alkenoic acids explain the relatively large differences in the ee as a function of substrate structure (20–53%).

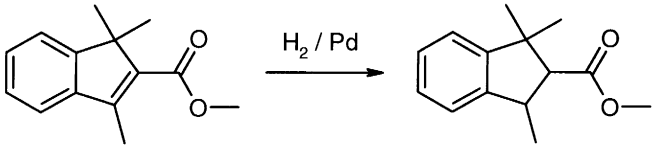



Scheme 3. Model for the explanation of the formation of opposite enantiomers in the hydrogenation of **1** and **2** (only the sterically favoured adsorption mode is shown)

Obviously, isomerization of **2** to the thermodynamically more stable tetrasubstituted **1** and their hydrogenation occurred parallel (Scheme 2). It is known that palladium is the most active catalyst for C=C double bond isomerization.[12] During hydrogenation of **2**, those molecules which are adsorbed on palladium with the methyl group pointing away from the surface (sterically less hindered adsorption), afford *cis* isomers, but obviously a facile isomerization to **1** occurs as well. This transformation is energetically favoured over the reverse reaction due to the thermodynamic stability of the tetrasubstituted olefin. Sterically hindered adsorption of **2**, namely adsorption with the methyl group pointing to the catalyst, is a feasible assumption.[18] Species adsorbed on the sterically hindered side provide *trans* isomers upon *syn* addition of two hydrogen atoms.

*2.1.2. Experiment II. Hydrogenation of 1,1,3-trimethyl-2-carboxylic acid methyl ester **3***

Hydrogenation of **3** was chosen as another control experiment because in this compound migration of the double bond along the ring system is excluded (Scheme 4). Note that hydrolysis of **3** to the corresponding carboxylic acid was not successful even with 'anhydrous hydroxide' which is otherwise a suitable reagent for the hydrolysis of hindered esters.[19] The hydrogenation of **3** provided only the two corresponding *cis* isomers identified by GC–MS, equipped with a chiral column, and NMR analysis. Hence, no *trans* isomer is formed when the isomerization is excluded.




**3**

Scheme 4. Hydrogenation of **3** over $Pd/Al_2O_3$

*2.2. Hydrogenation of indene derivatives: ionic or atomic mechanism?*

In the hydrogenation of some bicyclic olefins, strong acids (TFA, $HClO_4$) favoured the formation of *trans* isomers.[20] It was concluded that the hydrogenation involved the participation of the solvent and a 'top side attack' of the protonated solvent at the chemisorbed reactant took place (ionic mechanism of hydrogenation). As is usually the case with electrophilic addition, ionic hydrogenation is essentially accompanied by *anti* addition of the proton and the hydride ion to the multiple bond.[21] Addition of a proton from the top side to adsorbed species could explain the appearance of *trans* isomers in the Pd–catalyzed hydrogenation of some indene derivatives.

Two different methods were applied to test whether the C=C bond in indene derivatives can undergo ionic hydrogenation. In the first the well known $TFA/SiHEt_3$ system was used as the source of $H^+$ and $H^-$ ions.[15] Conversions of <2% could be detected in 10 h using **1** and **2** as reactants. It has already been demonstrated that C=C double bond with electron-donor and -acceptor substituents may undergo ionic hydrogenation, but the reaction rate is remarkably reduced by the electron-acceptor substituent, and α,β-unsaturated carboxylic acids are not reduced by this reagent.[15]

Secondly, a dissolving metal reduction using the $Zn/H^+$ system was applied. Here the considerable overpotential of atomic hydrogen on Zn surface provided adequate conditions for ionic hydrogenation. No detectable hydrogenation of **1** or **2** occurred.

The failure of the reduction by the $TFA/SiHEt_3$ and $Zn/H^+$ systems demonstrates that hydrogenation of **1** and **2** obeys an atomic mechanism.

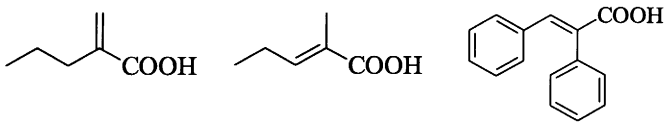
## 3. Conclusions

Investigation of the asymmetric hydrogenation of several indene derivatives revealed that an adsorption mode, which is usually rejected as sterically hindered, can rationalize the formation of the *trans* isomer even as a dominant hydrogenation product. It seems that *syn* addition of two hydrogen atoms from the metal surface is a reasonable assumption for describing the stereochemistry of (asymmetric) hydrogenations of unsaturated compounds over Pd.

A further implication from our results is that due care is necessary in interpreting the influence of reaction conditions on the catalytic performance of chirally modified Pd. Facile isomerization of the

reactant over Pd, followed by the competitive hydrogenation of the isomers can remarkably confuse the effect of some reaction parameters on the overall reaction rate and enantioselectivity. Our findings indicate that only those substrates which possess a tetrasubstituted C=C bond (e.g. *E*-α-phenylcinnamic acid, ee ~72%) can be hydrogenated with good stereoselectivity. Hydrogenation of unsaturated acids possessing a trisubstituted or a terminal C=C bond, where isomerization is a significant side reaction, provides only moderate ees. Examples, besides the reduction of indene carboxylic acids **1** and **2**, are the hydrogenation of 2-methyl-2-pentenoic acid (ee=52%) and 2-ethyl propenoic acid (ee=20%)[8] (Table 3).

Table 3
Influence of isomerization on ee in the enantioselective hydrogenation of α,β-unsaturated acids over cinchonidine modified palladium




| | | | |
|---|---|---|---|
| Isomerization: | fast | slow | no |
| ee, %: | 20 | 52 | 72 |

## 4. Experimental

$^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker Advance DPX 300 operating at 300 and 75 MHz, respectively, with chemical shifts related to TMS ($\delta$=0). 3-Methylindene-2-carboxylic acid (Aldrich) was used as received.

### *4.1. (±)-1-Methylindene-2-carboxylic acid **2***

To a suspension of NaH (1.4 g, 58.3 mmol) and dimethyl carbonate (13.1 g, 145 mmol) in anhydrous benzene (50 ml), 3-methyl-1-indanone (5 ml, 34 mmol) in dry benzene (50 ml) was added via a dropping funnel during 20 min at 75–80°C under a nitrogen atmosphere. The mixture was kept at 80°C for an additional 4 h then cooled to 0°C, acidified by AcOH (50 ml) and poured into an ice-cold aqueous HCl solution (300 ml, 6 M). After extractive work-up followed by washing with aqueous bicarbonate and brine, the distillation of the solvent furnished a reddish dense oil which was distilled bulb to bulb under reduced pressure (0.5 torr) to give 1-methyl-3-oxo-indan-2-carboxylic acid methyl ester (5.9 g, 28,8 mmol) in 85% yield. The reduction of the ketone with equimolar amount of $NaBH_4$ in methanol during 4 h provided the corresponding alcohol in practically quantitative yield (GC). The alcohol was dehydrated by azeotropic distillation with benzene in the presence of *p*-toluenesulfonic acid monohydrate (0.5 g) and trace amounts of hydroquinone during 4 h. The extractive work-up of the solution and drying over $MgSO_4$ was followed by filtration through silica gel (hexane:ether, 6:1) and bulb to bulb distillation in vacuo (0.5 torr). The colourless ester crystallized on standing.

Hydrolysis with trichloromethylsilane/sodium iodide system in dry acetonitrile[22] yielded the free acid. $^{1}H$ NMR ($CDCl_3$): 1.50 (d, $CH_3$), 3.78 (q, H), 7.30–7.55 (m, Ar-H), 7.82 (d, H). $^{13}C$ NMR ($CDCl_3$): 16.1, 44.4, 123.3, 123.8, 127.0, 128.3, 140.7, 141.4, 142.9, 151.7, 170.18.

### 4.2. 1,1,3-Trimethylindene-2-carboxylic acid methyl ester[23] **3**

To a stirred solution of NaH (0.7 g, 29 mmol, 55–60% dispersion in mineral oil) in dry DMF (10 ml), a solution of 3-methyl-indene-2-carboxylic acid methyl ester (2.8 g, 14.8 mmol, in 10 ml DMF) was added through a syringe under an atmosphere of nitrogen. The temperature was kept below 40°C. The violet coloured solution was stirred for a further 15 min, cooled to 0°C and treated dropwise with $CH_3I$ (3.5 ml) in DMF (20 ml) keeping the temperature below 5°C. The reaction mixture was stirred at room temperature for 4 h then poured onto ice. Extractive work-up followed by distillation under reduced pressure furnished the title compound (2.55 g, 79.6%), b.p. 84–85°/0.1 mmHg. $^1$H NMR ($CDCl_3$): 1.43 (s, 2×$CH_3$), 2.50 (s, $CH_3$), 3.85 (s, $COOCH_3$), 7.25–7.5 (m).

### 4.3. Preparation of trans-3-methylindan-2-carboxylic acid methyl ester as authentic sample for GC-analysis

Isomerization of *cis*-3-methylindan-2-carboxylic acid methyl ester in a basic environment furnished the thermodynamically more stable *trans* isomers.[24] To a solution of NaOMe (0.5 g) in methanol (5 ml) *cis*-3-methylindan-2-carboxylic acid methyl ester (100 mg) was added and refluxed for 3 h. Acidification and extractive work-up furnished a 6:1 *trans*:*cis* isomer mixture.

### 4.4. Catalytic hydrogenation

Pd/alumina (5 wt%) (Engelhard 40692, dispersion=0.21 as determined by TEM) was used for hydrogenations in a 100 ml glass autoclave equipped with magnetic mixing. If not otherwise stated, the following standard conditions were used: 100 mg acid, 10 mg catalyst, 2 mg cinchonidine, 20 ml toluene, at room temperature and 1 bar, reaction time: 1.5–2 h. A CP-cyclodextrin-2,3,6-M-19 (Chrompack) capillary column was used for GC analysis. Indene carboxylic acids were converted into their methyl esters before analysis ($MeOH/BF_3$, Fluka).[25]

### 4.5. Ionic hydrogenation

*Method A:* TFA (0.56 mmol) was slowly added to a mixture of 3-methylindene-2-carboxylic acid methyl ester (50 mg, 0.26 mmol) and triethylsilane (0.26 mmol) in dichloromethane. The solution was kept at room temperature for 10 h, poured into water and neutralized with aqueous $NaHCO_3$ solution, extracted with Me$O^t$Bu ether and analyzed by GC.

### 4.6. Dissolving metal reduction

*Method B:* Indene derivative (50 mg) was dissolved in 5 ml EtOH, then 0.1 g Zn powder was added and the slurry was treated with ~10 ml aqueous HCl solution. The mixture was then refluxed for 10 min, cooled down, neutralized ($NaHCO_3$), extracted and analyzed by GC.

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