# Synthesis of Alkali Metal Carboxylates and Carboxylic Acids Using "Wet" and "Anhydrous" Alkali Metal Hydroxides

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*Received October 23, 2009*

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## 1. Hydroxide Anion and Organic Synthesis

### 1.1. Typical Reactivity of Hydroxide Anion

Hydroxide ion has been used in a large number of important organic reactions in which it plays the role of either nucleophile or base.[1,2] This is inter alias the case of (i) the hydrolysis of esters, amides, nitriles, carbonates, carbamates, and ureas,[1−3] (ii) Haller−Bauer-type scission of non enolizable ketones,[4] (iii) Favorskii rearrangement,[1,5] (iv) Cannizaro disproportion reaction of non enolizable aldehydes,[6] (v) carbenes synthesis,[7] especially dihalogeno carbenes,[7,8] (vi) alkylation reactions[8−10] including C alkylations,[9] (vii) aldol and related reactions, especially those involving malonates and nitroalkanes,[1] (viii) elimination reactions,[1] and marginally (ix) fission of unsaturated acid.[11]

Potassium hydroxide is known from ancient time when it was produced by leaching water through hardwood ashes; it produced crude soap ("soft soap") and glycerol on "saponification" of animal fat.[3i,j] A related reaction can be also achieved by sodium hydroxide but produces a "hard soap" instead.[3]

Alkaline hydroxides are quite cheap compounds as compared to other nucleophiles and bases. They have been often indistinctly used for synthetic purpose. However, (i) potassium hydroxide is believed to be "more reactive" than lithium hydroxide and possesses a higher propensity to epimerize the $\alpha$-carbon of carboxyl derivatives, (ii) lithium hydroxide is the choice reagent to transform oxazolidinones to carboxylic acids,[12] and (iii) cesium hydroxide is particularly

10.1021/cr9003506 
Published on Web 04/05/2010

Prof. Alain Krief (French and Tunisian) was born in Tunis in 1942. He studied chemical sciences at the University "Pierre et Marie Curie" in Paris where he completed his Ph.D. in 1970 under the supervision of the late Professor Jacqueline Ficini. He move to Harvard University in 1970 for a postdoctoral stay in the laboratory of Professor Elias J. Corey (CNRS & NSF fellowships). In 1972, he was appointed Associate Professor at the "Facultés Universitaires Notre-Dame de la Paix" (FUNDP) in Namur, Belgium, and was then promoted to Full Professor in 1975. From the beginning, Professor Krief has focused his research on several different topics all related in a broad sense to organic synthesis. They include the elucidation of the mechanism of sterol biosynthesis as well as the use of antibodies as catalysts, the synthesis of pyrethroid insecticides and chrysanthemic acid in particular, use of α-heterosubstituted organometallics in connection with the synthesis of three membred cyclic compounds, and the reactivity of organoselenium compounds as well as inorganic reagents such as $BrN_3$, $P_2I_4$, $OsO_4$, and more recently KOH. He has been involved in a collaborative work with Dr. Paul Janssen (CMD, Beerse Belgium) in the discovery of very efficient antiaid drugs as well as virucides. Ten years ago, he initiated a project aimed at the development of an electronic encyclopedia of organic syntheses freely accessible on the Web, which differentiates it from, for example, Wikipedia, being built collaboratively but under strict editorial policy. He has been involved in that context in creating original communication tools using the Grid technologies for services (in collaboration with Prof. S. Cerri, University of Montpellier II), an electronic chemistry dictionary with unusual properties, original search engines, chemical ontologies using Protégé tool (in collaboration with Prof. M. Musen, Stanford University), and an original chemical editor (ChemEd), which tends to perceived chemical structures, in selected contexts, as the most experienced chemists and to report in computer understandable language (XML) as well as in natural language understandable by the chemist (in collaboration with Prof. P. Sankar, Pondicherry Engineering College, and Prof. G. Aghila, Pondicherry University). Prof. A. Krief spent 9 months on sabbatical leave in ICI, plant division at Bracknell, UK (Now Syngenta), and has been for 3 years head of a small research unit of ACROS Organic. He has been visiting professor at the HEJ Research Institute; University of Karachi (Pakistan, 2005); JSP-fellow (Japan, 1996); Technion Haifa (Israel, 1995 and 1983); Universities of Stuttgart and Honeheim (Germany, 1991); Universities of Geneva, Neuchâtel, Fribourg, Lausanne, (Switzerland, 1991 and 1981); University of Reims (France, 1990 and 1977), University of Strasbourg (France, 1991); University of Hamburg (Germany, 1989); Université Libre de Bruxelles (Belgium, 1984); University of Bochum (Germany, 1980); and University of Giessen (Germany, 1979). He is the author of over 350 original scientific publications including patents and review articles. He has organized and been chairman of several congresses of international renown such as the "Belgian Organic Synthesis Symposium or BOSS" or the "European Symposium on Organic Chemistry" and was chairman of the 40th Bürgenstock Conference in 2005. He is Emeritus Professor at FUNDP since September 2008 and a member of the Laboratoire de Chimie des Matériaux Organiques Supramoléculaires (CMOS) and Laboratoire de Chimie des Matériaux Inorganiques (CMI). Since 2009, he is the 2009 Executive director of IOCD (International Organization for Chemical Sciences in Development), a nonprofit organization aimed at supporting international collaboration in the chemical sciences to benefit the health, agricultural, and economic sectors of developing countries.

efficient[10] to favor, by template effect, S-alkylation especially for the synthesis of crown thioethers.

Dr. Adrian Kremer (Belgian and Swiss) was born in Charleroi (Belgium) in 1979. He studied chemical sciences at the University of Namur. He has also been a teaching assistant at this university. He has carried out his master and Ph.D. theses under the supervision of Prof. A. Krief on the asymmetric dihydroxylation of olefins and on the synthesis of pyrethroid insecticides, respectively. He has developed novel synthetic methods for the construction of the cyclopropane ring and has found that "anhydrous potassium hydroxide" prepared from potassium *t*-butoxide and water often, but not always, offers substantial advantages over commercial potassium hydroxide for fragmentation of non enolizable-cyclopentenones bearing a leaving group in the β-position.

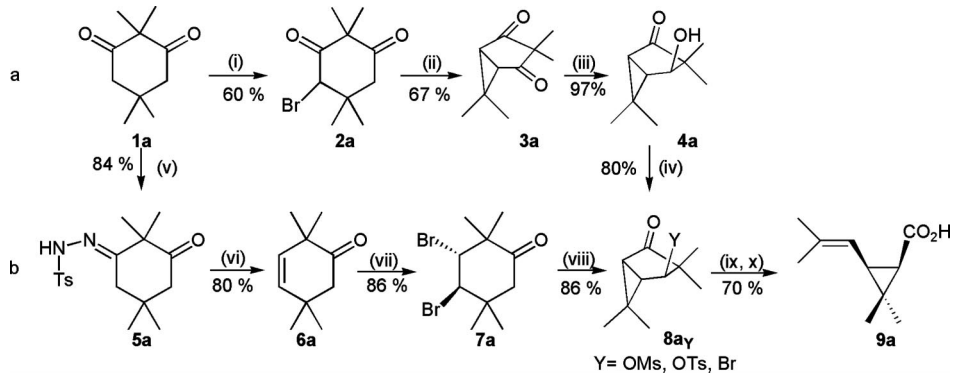
The reactivity of hydroxide ion depends not only on the nature of the counterion (usually an alkali metal or an onium salt[8a−f,9]) but also on the solvent used (hydroxylic, apolar aprotic, polar aprotic).[13b] Reactions implying alkaline hydroxides have been carried out also (i) at high temperature in water (HT-$H_2O$),[13c] (ii) neat up to 350 °C (alkaline fusion),[68c] (iii) neat without[14a] or with sonication,[14b,c] and (iv) under phase-transfer catalysis (PTC)[8,9] in liquid−liquid or liquid−solid phases,[8c,f,g] using catalytic amounts of quaternary onium salts,[8a−f] or macrocyclic and open chain polyethers.[8c,h,15] Thus, cyclodextrins and their derivatives act as inverse phase-transfer catalysts in the hydrolysis of carboxylic acid esters. They are particularly efficient for lipophilic esters, which are hydrolyzed more efficiently than under classical phase-transfer catalysis (PTC).[15a] Reactions of reagents delivering hydroxide ion have been also performed in capillary flow reactors under phase-transfer catalysis and sonication.[14d]

Hydrolysis of esters, amides, and nitriles has been carried out by hydroxide ion in the presence of hydrolytic enzymes such as lipases, esterases, amidases, and nitrilases that allow in nature related transformations. They have been successfully used for hydrolysis of unnatural substrates, allowing rate acceleration, kinetic resolution of racemates, and enantioselective conversion of meso-derivatives.[16a,b] Finally, the concept of transition-state binding[17] has led to the design of transition-state analogues used in eliciting (i) monoclonal antibodies[18] that catalyze esters,[19] carbamates,[20a] and carbonates[20b] hydrolysis or (ii) imprinted polymers that catalyze enantioselective hydrolysis of esters.[21]

## 1.2. Reactivity of Hydroxide Anion in the Context of *cis*-Chrysanthemic Acid Synthesis

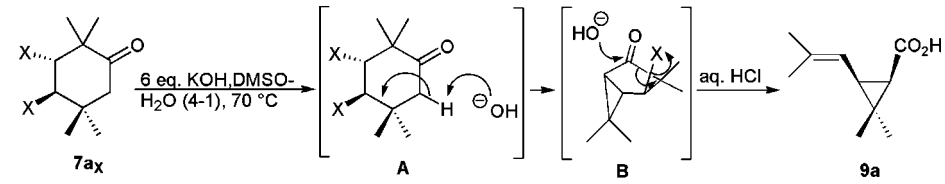
Several years ago, we devised two routes to *cis*-chrysanthemic acid **9a**,[22] a valuable precursor of pyrethroids, the most potent insecticides commercially available for indoor and outdoor uses,[23] whose key step is a potassium hydroxide monitored Grob-type fragmentation. The latter allows in a single step one to build the carboxylic acid and the vinyl

**Scheme 1**[a]

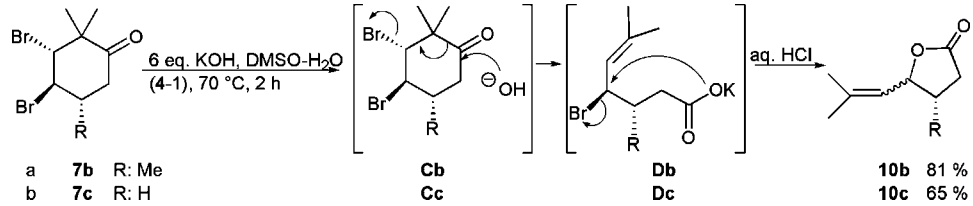



[a] (i) 1 equiv of $Br_2$, $CCl_4$; (ii) 1.1 equiv of *t*-BuOK, THF, −78 to 20 °C; (iii) $NaBH_4$−$CeCl_3$, methanol, −78 °C; (iv) MsCl or TsCl, pyr., $CH_2Cl_2$, 20 °C; (v) 1 equiv of $TsNHNH_2$, EtOH, 20 °C; (vi) 5 equiv of $HOCH_2CH_2ONa$, ethyleneglycol, 180 °C; (vii) 1 equiv of $Br_2$, 0.1 equiv of $AcNH_2$, $CCl_4$, 0 °C; (viii) 1 equiv of LDA, THF, −78 °C; (ix) 6 equiv of KOH, DMSO−$H_2O$ (4:1), 70 °C, 2−4 h; (x) aq HCl.

**Scheme 2**




**Scheme 3**




moieties from β-sulfonyloxy $\mathbf{8a_{OSO2R}}$ or β-bromo $\mathbf{8a_{Br}}$ ketones (Scheme 1).

We found[22e] that the transformation of **7a** to **9a** is even more conveniently achieved using aqueous potassium hydroxide ("WPH") in DMSO instead of potassium *t*-butoxide because both steps can be realized in the same pot. In such case, potassium hydroxide acts sequentially as a base, and then as a nucleophile (Scheme 2).

The method disclosed in Scheme 1, entry b has been successfully applied to the synthesis of desmethyl and didesmethyl analogues **9b** and **9c**.[22e] However, the variant described in Scheme 2 does not apply because the lactones **10b**, **10c** resulting from a competing reaction are instead formed (Scheme 3).[22e] This reaction probably involves the attack of the hydroxyl ion onto the carbonyl group of **7**, leading to the intermediate formation of **D**, which then collapses to **10** via a SN1-type substitution reaction.[22e]

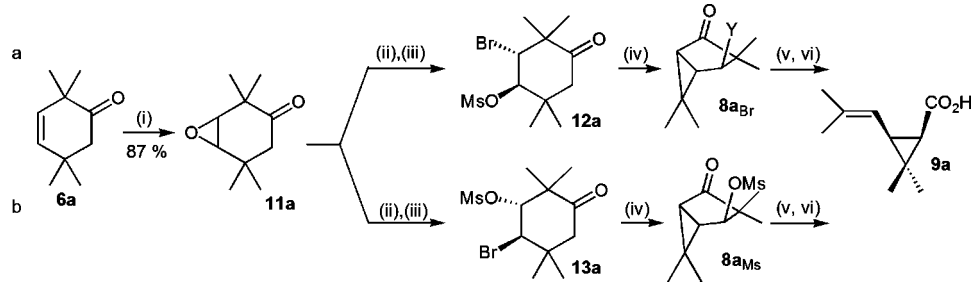
In a more recent work, disclosed in Scheme 4,[24a] we have been able to synthesize $\mathbf{12a_{Br}}$ and $\mathbf{13a_{Br}}$ in a two-step sequence from **6a**. Reaction with KHMDS produces a mixture of the *exo*-bromide $\mathbf{8a_{Br}}$ and the *exo*-mesylate $\mathbf{8a_{OMs}}$, which were particularly easily separated by chromatography on silica gel due to the different polarities of their respective functional groups.[24a]

Transformation of the β-bromo ketone $\mathbf{8a_{Br}}$ to *cis*-chrysanthemic acid **9a** was efficiently achieved using potassium hydroxide in DMSO, according to the protocol we already published (6 equiv of KOH, DMSO−$H_2O$ (4:1), 70 °C, 2−4 h, then aq HCl, Scheme 4, entry a).[22e]

It was tempting to perform the transformation of the bromomesylate $\mathbf{12a_{Br}}$ to *cis*-chrysanthemic acid **9a** in one pot in an approach that parallels the one that we already disclosed for the dibromide **7a** (Scheme 2).[24b] We were rather surprised to find that $\mathbf{12a_{Br}}$ possesses a much higher propensity to produce the lactone **10** than the dibromide **7a** (Scheme 5, entry a, compare to Scheme 2, entry b) and that the amount of **10a** increases by lowering the temperature (Scheme 5, entry b, compare to entry a). The chloro derivative $\mathbf{12a_{Cl}}$ possesses a different behavior toward KOH in aqueous DMSO because it produces selectively the β-chloroketone $\mathbf{8a_{Cl}}$ when the reaction is carried out at room temperature (Scheme 5, entry c, compare to entry b)[24b] and to *cis*-chrysanthemic acid **9a** if it is performed at higher temperature (Scheme 5, entry d, compare to entry c).[24b] On the contrary, the iodo compound $\mathbf{12a_I}$ leads almost exclusively to the lactone **10** whatever is the temperature at which the reaction is performed (Scheme 5, entry e).[24b]

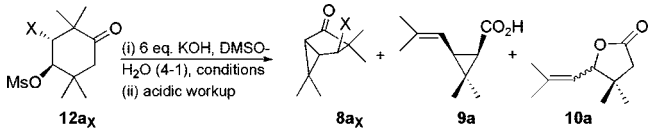
We were even more surprised to be unable to perform the transformation of the β-keto mesylate $\mathbf{8a_{OMs}}$ to *cis*-chrysanthemic acid that we described 20 years ago (6 equiv of KOH, DMSO−$H_2O$ (4:1), 70 °C, 2−4 h, then aq HCl, Scheme 4, entry b).[22b] Chrysanthemic acid **9a** is effectively produced

**Scheme 4**[a]




[a] (i) 2 equiv of *m*-CPBA, 4 equiv of $NaHCO_3$, $CH_2Cl_2$, 20 °C, 84 h; (ii) 0.5 equiv of $TiBr_4$, $CH_2Cl_2$, 20 °C, 96%: **12a/13a** 43/57; (iii) 1.2 equiv of MsCl, 1.5 equiv of $NEt_3$, $CH_2Cl_2$, −10 to 0 °C, 5 h, 83%; (iv) 1.2 equiv of KHMDS, THF, 0 °C, 1 h, 78%; (v) 6 equiv of KOH, DMSO−$H_2O$ (4:1), 70 °C, 2−4 h; (vi) aq HCl.

**Scheme 5**




| | X | Conditions | Overall | 8a$_X$ | 9a | 10a |
|---|---|---|---|---|---|---|
| a | Br | 70 °C, 1 h | 79 % | - | 33 % | 67 % |
| b | Br | 20 °C, 8 h | 68 % | - | 10 % | 90 % |
| c | Cl | 20 °C, 8 h | 70 % | 100 % | 0 % | - |
| d | Cl | 70 °C, 6 h | 63 % | 10 % | 90 % | - |
| e | I | 20 °C, 3 h | 71 % | - | 5 % | 95 % |

but in less than 7% (instead of 70%) beside large quantities of polymer **14a**. This led us to suspect that **14a** results from a competing reaction of the hydroxyl ion on the electrophilic sulfur atom of the sulfonate, leading to the potassium 4-*exo*-oxy-3,3,6,6-tetramethyl-bicyclo[3.1.0]hexan-2-one **E** intermediate, which then polymerizes via a tandem retroaldol-*cis*/*trans*-isomerization reaction as tentatively disclosed in Scheme 6.[24c]

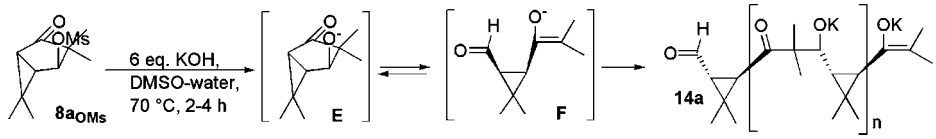
Similarly, reaction of 7-trimethylsilyl-3,3,6,6-tetramethyl-4-oxobicyclo[3.1.0]hexan-2-yl methanesulfonate **15a** with potassium hydroxide at 70 °C for 2 h (Scheme 7) produces chrysanthemic acid **9a** in less than 10% beside large quantities of polymeric material **14a**. Again, this was not due to the presence of the silyl group on **15a** because desylilation occurs smoothly when the reaction is performed at lower temperature (22 °C, 0.75 h, Scheme 7) producing **8a$_{OMs}$** in good yield (93%, Scheme 7).[24c]

We successfully prevented the attack of the hydroxide ion onto the sulfur atom of the sulfonate by increasing steric hindrance there. This proved to be effectively the case because increasing yields of chrysanthemic acid **9a** (up to 50%) have been observed on reaction of potassium hydroxide with 2,4,6-trimethyl benzenesulfonate **8a$_{MB}$** (R = 2,4,6-$(Me)_3$−Ph, Scheme 8, entry a) or better 2,4,6-triisopropyl benzenesulfonate **8a$_{PB}$** (R = 2,4,6-$(i\text{-}Pr)_3$−Ph, Scheme 8, entry b).[24c]

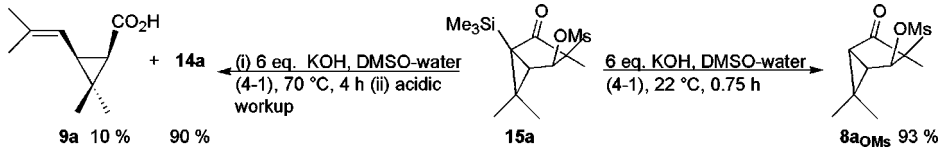
The whole process is nevertheless of poor synthetic value because the access to those "sterically hindered sulfonates **8a**" from the ketoalcohol **4a** was far from easy (Scheme 8). Therefore, another more practical solution would have to be envisioned.

We have been unable to carry out the fragmentation of **4a** after activation of the hydroxyl group as acetate, benzoate, and phosphinate using potassium hydroxide as a reagent under various experimental conditions, and because we were unable also to perform the fragmentation of **8a** using metal alcoholates[4c] and trimethysilanolate,[25] we decided to perform an extensive literature survey with the contradictory objectives to find an alternative "hydroxyl-based reagent".

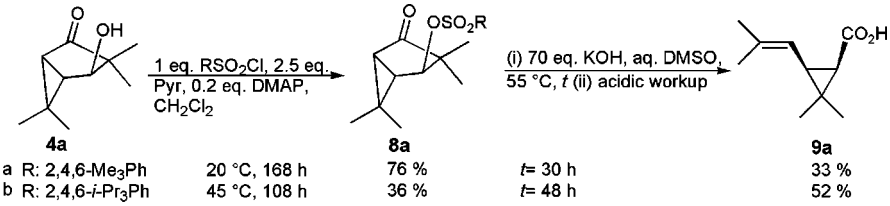
**Scheme 6**




**Scheme 7**




**Scheme 8**



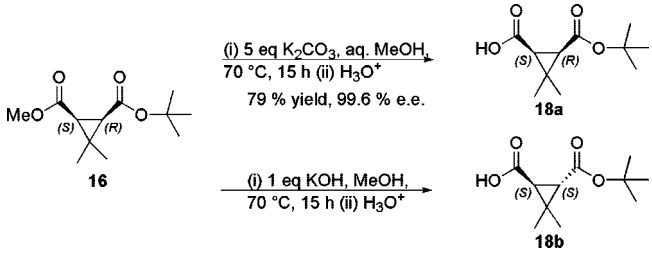
This reagent should possess an enhanced (i) nucleophilicity toward the carbonyl group, to perform the transformation of **8** to **9**, and (ii) basicity toward the hydrogen α to the carbonyl group of **7**, **12**, and **13** so the bicyclic derivatives **8** could be produced at the expanses of the formation of lactones **10** (Schemes 3 and 5). The more challenging problem remained the direct transformation of **12** to **9** because the reagent should have both "incompatible features" sequentially.

We decided to perform a large literature survey to tackle the potential reagents able to transfer a hydroxyl ion to perform successfully the desired transformations.

We report in this Review our finding concerning the reactivity of reagents able to deliver their hydroxyl moiety in reactions related to those involved in the transformation of **8** to **9**, such as: (i) Haller−Bauer and Grob fragmentation reactions of non enolizable carbonyl compounds; (ii) basic hydrolysis of esters because both reactions produce a carboxylate by substitution reaction (are there reagents able to hydrolyze "sterically hindered" esters when hydrolysis cannot be achieved by conventional methods?); (iii) basic hydrolysis of amides and carbamates, which involves a poorly electrophilic carbonyl group and the substitution of the amino group possessing a poor leaving group aptitude; and (iv) basic hydrolysis of oxazolidinone and camphor sultame derivatives, which often suffers from competing heterocycle ring-opening.

Transfer of the hydroxide species has been achieved with variable success not only by alkali metal or ammonium hydroxides under a large variety of conditions involving different solvents or additives but also by using in situ generated potassium hydroxide. The aim of this Review is to compare such reagents, to point out the behavior of the most efficient ones, and to disclose their limitations.

**Scheme 9**




## 2. Available Sources of Hydroxide Anion

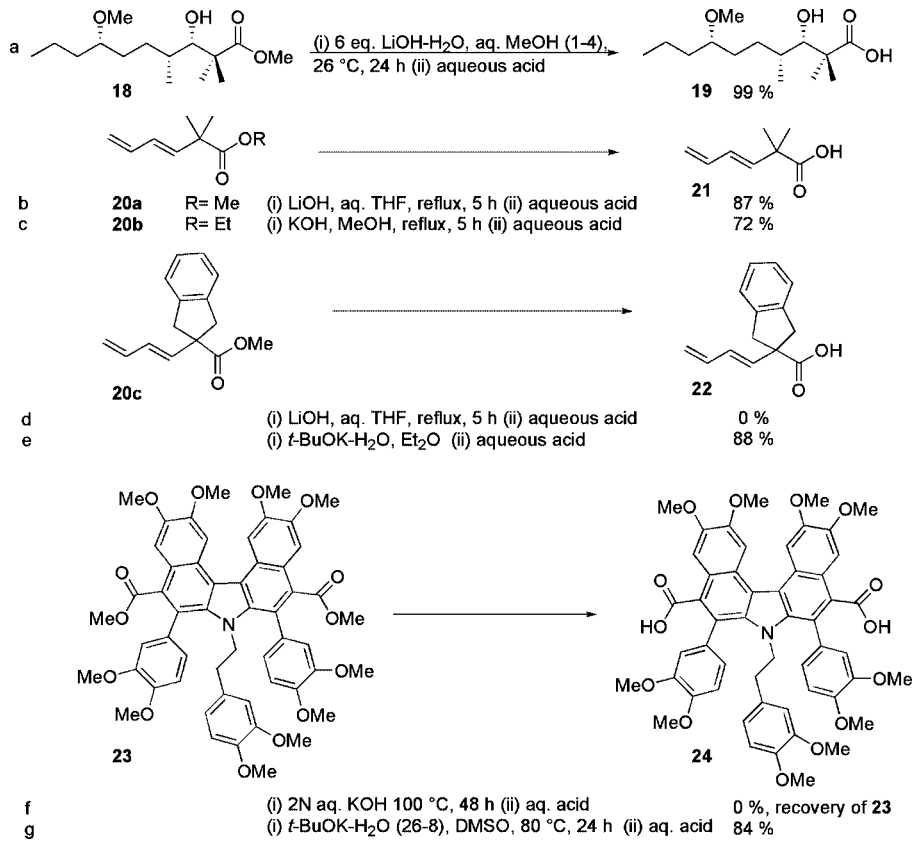
### 2.1. Alkali Metal Hydroxides as a Source of Hydroxide Anion

#### 2.1.1. Reactivity of Alkali Metal Hydroxides toward Carboxylates and Carboxamides (Overview)

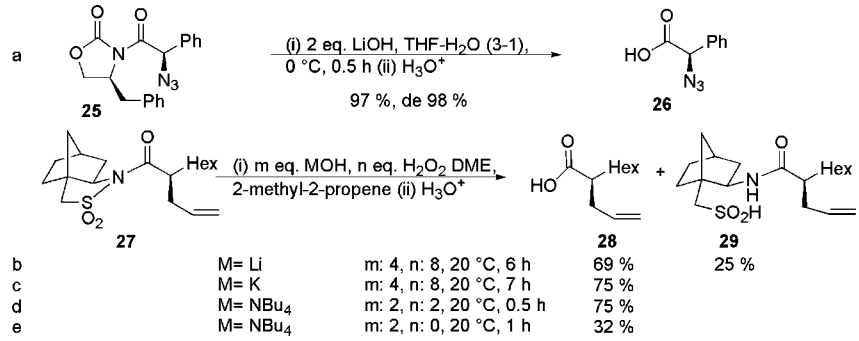
Lithium, sodium, potassium, and cesium hydroxides, in hydroxylic solvents, have been used indistinctively to perform various reactions described above. Potassium hydroxide is usually highly reactive toward the carbonyl group of esters but often possesses a high propensity at the same time to epimerize at the α carbon (Scheme 9).[26]

Lithium hydroxide offers often the advantage to avoid concomitant epimerization α to the carboxyl group in saponification reactions especially when a retro-aldol reaction can compete (6 equiv of LiOH, aq MeOH, 26 °C, 24 h, Scheme 10, entry a).[27] It allows as well as potassium hydroxide the hydrolysis of methyl and ethyl esters **20a** and **20b** bearing a quaternary carbon atom α to the carbonyl carbon substituted by a 1-butadienyl moiety and two methyl

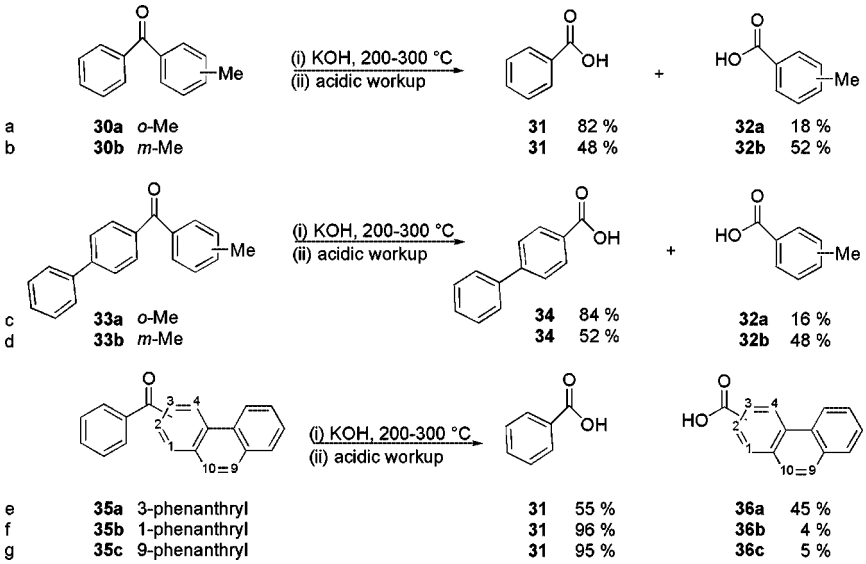
**Scheme 10**



**Scheme 11**




**Scheme 12**




or two benzyl groups (Scheme 10, entries b,c).[28] They are, however, unable to hydrolyze either the related more hindered ester **20c** (Scheme 10, entry d)[28] or the diester **23** (Scheme 10, entry f).[29]

Lithium hydroxide is recommended alone or in the presence of hydrogen peroxide (as precursor of more nucleophilic lithium hydroperoxide) for the hydrolysis of oxazolidinones to lithium carboxylates avoiding competing ring-opening (Scheme 11, entry a);[12b,30] potassium and tetrabutylammonium hydroxides in the presence of hydrogen peroxide proved to be quite effective for the transformation of compound **27** bearing the Oppolzer camphor sultame chiral auxiliary to the carboxylic acid **28** without the competing formation of **29** resulting from the ring-opening of the camphor sultame functional group (Scheme 11 entry d, compare to entries b,e).[31a]

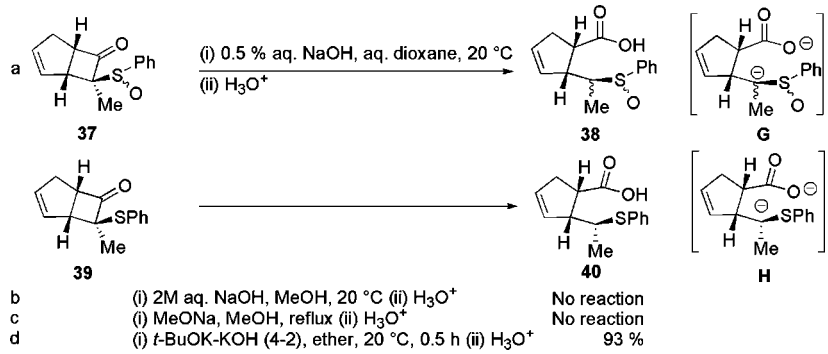
Hydroxide ion has been used in different reactions under a variety of experimental conditions. For example, alkaline fusion requires heating an organic compound with solid potassium hydroxide up to 350 °C. It has been extensively used to transform esters such as poly(methyl acrylate), poly(isobutyl methacrylate), and poly(butyl methacrylate) to the corresponding carboxylic acids, which are reluctant to be hydrolyzed using conventional methods.[32a] A variant of this method uses concomitantly a small amount (0.5%) of sodium acetate, which acts as a flux in the fusion and permits one to lower the melting temperature. This reaction coupled with gas chromatography allows the identification and the measurement of the alcohols liberated by hydrolysis of esters[32a] and has been also used for the determination of compounds bearing an amide, urea, nitrile, or acetanilide functional group including *N*,*N*-dimethyl acetanilide, Nylon 66, polyacrylamide, and polyacrylonitrile.[32b]

### *2.1.2. Reactivity of Alkali Metal Hydroxides toward Ketones (Overview)*

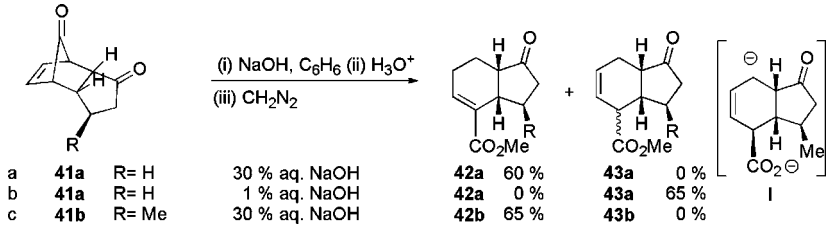
Alkaline fusion has been used among others for the fission of unsaturated acids[11] and the Haller−Bauer-type scission of diaryl ketones leading to the aryl carboxylates (Scheme 12).[33] It is surprising that even at that extreme temperature some regioselective fragmentations can be achieved in the latter case (Scheme 12, entries a,c,f,g).[33]

Haller−Bauer-type scission of the cyclobutanone **37** bearing a sulfinyl group in α position leading to **38** has been achieved[34a] at much lower temperature (Scheme 13, entry a), and this accounts for the stabilization of the incipient carbanion by the phenylsulfinyl group in **G**. Similar fragmentation has been observed with α,α-diphenyl cyclobutanones probably for the same reasons. The related cyclobutanone **39**, which bears a phenylsulfanyl group, is, however, insensitive to sodium hydroxide (Scheme 13, entry b) or even to sodium methoxide in methanol at reflux (Scheme 13, entry c).[34a] It has been, however, efficiently achieved using "anhydrous potassium hydroxide" (Scheme 13, entry d),[34a] but this will be discussed in more detail in the next paragraph.

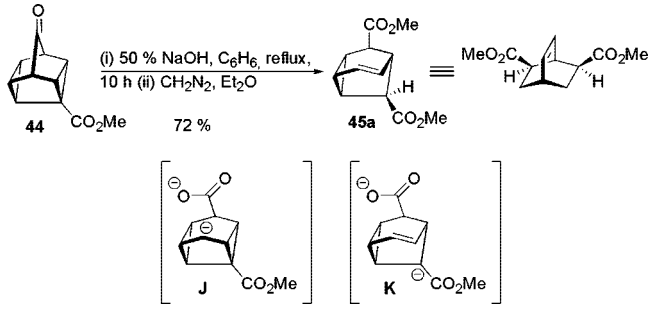
**Scheme 13**



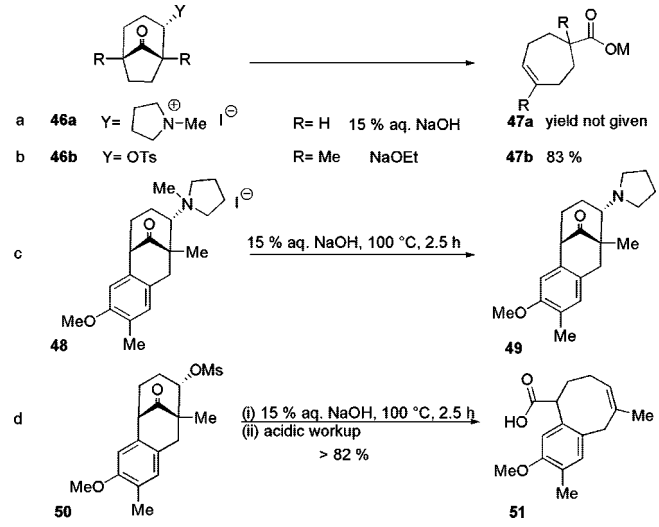

**Scheme 14**




**Scheme 15**




**Scheme 16**




Tricyclic compounds **41** incorporating the 7-norbornanone moiety, conveniently accessible via a Diels−Alder reaction involving cyclopentadiene, provide on reaction in a biphasic media of aqueous sodium hydroxide in benzene a *cis*-hydrindane skeleton by regioselective cleavage of the C1−C10 bond leading to the allylic stabilized intermediate **I** (Scheme 14).[35] Aqueous sodium hydroxide (30%) reacts with **41** and provides regioselectively **42** in which the double bond expected to be at the C5−C6 position has migrated to the C4−C5 position (Scheme 14, entries a,c).[35a] Performing the reaction on **41a** with a 1% aqueous sodium hydroxide instead avoids the isomerization of the double bond and delivers **43a** with complete regiocontrol but as a diastereoisomeric mixture (Scheme 14, entry b).[35b]

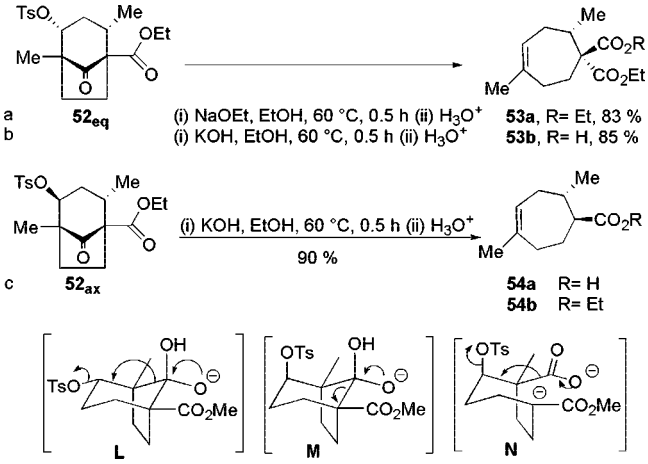
The case of the $\gamma$-keto ester **44** is worthwhile to mention because it produces when heated in the presence of 50% sodium hydroxide in benzene the diester **45a**. This transformation should involve a cascade Haller−Bauer scission−fragmentation reaction schematized in Scheme 15. This process leads to the formation of the reasonably well-stabilized enolate **K** intermediate (Scheme 15, compare to **J**).[36]

Related reactions closer to the one we have not been able to repeat (Scheme 6)[24c] have been carried out using hydroxide ion on non enolizable ketones[37,38] and aldehydes[39] bearing a leaving group in the $\beta$ position such as an ammonium,[37a] a halide, or a sulfonate[37−39] (Scheme 16). Haller−Bauer scission−Grob fragmentation reaction leading to $\delta,\omega$-unsaturated carboxylic acids **47** and **51** after acidic workup has been successfully achieved (Scheme 16, entries a,b,d) except on the compound **48**, which suffers demethylation of the ammonium moiety leading to the $\beta$-amino ketone derivative **49** instead (Scheme 16, entry c).[37b]

Fragmentation occurs on reacting the $\beta$-tosyloxy ketone $\mathbf{52_{eq}}$ bearing an α carboethoxy group on the α carbon and a tosyl group in the equatorial position on the $\beta'$ carbon atom with sodium ethylate or potassium hydroxide in ethanol. It delivers the $\delta,\omega$-unsaturated diethyl malonate **53a** (Scheme 17, entry a)[38b] or the related mono malonic acid **53b** (Scheme 17, entry b),[38b] respectively. It is believed to occur through the process depicted in **L** (Scheme 17) in which the alkoxy moiety, the leaving group, and the carbon framework lie in an antiperiplanar arrangement, which is the most suitable for a concerted fragmentation reaction.[38b]

Fragmentation also occurs on reacting the related ketone $\mathbf{52_{ax}}$ bearing instead the tosyloxy group in axial position with potassium hydroxide in the same solvent, but it leads instead to $\delta,\omega$-unsaturated carboxylic acid **54a** and its ester **54b** (Scheme 17, entry c),[38b] whose formation does not involve

**Scheme 17**




the same mechanism because the antiperiplanar arrangement cannot be attained this time and should proceed in a nonconcerted manner through intermediates **M** and **N** (Scheme 17).[38b]

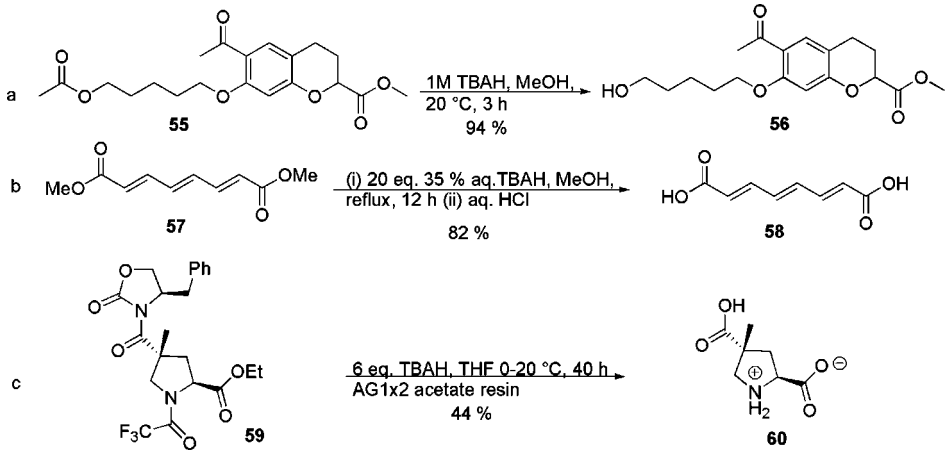
## 2.2. Ammonium Hydroxide Reactivity toward Carboxylic Esters and Carboxamides (Overview)

Tetrabutylammonium hydroxide (TBAH) has often proved to be more efficient than alkaline hydroxides, especially when used as an anhydrous reagent.[31a,c] The reactions have been usually carried out with an aqueous commercially available solution of TBAH (40%) in methanol or THF.[31a,40−43] "Dry TBAH", prepared by azeotropic removal of water from the commercial aqueous solution of TBAH, with DME proved to be far superior.[31a,c] It has been also reported that TBAH−$H_2O_2$ is even more efficient than ammonium- or tetradecyl ammonium hydroxides[31a] especially toward camphor sultame **27** (Scheme 11, entry d, compare to entry e).[31a]

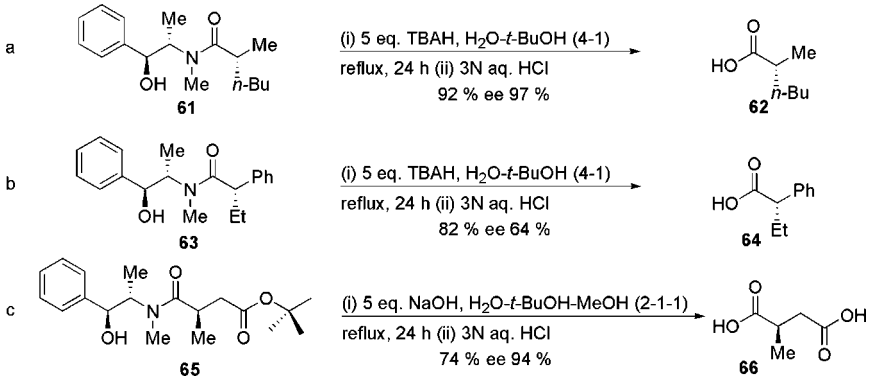
An aqueous solution of tetrabutylammonium hydroxide (TBAH) in methanol, *t*-butanol, and THF allows the efficient hydrolysis of various esters[40−43] and *N*,*N*-disubstituted amides.[44] The method proved to be efficient every time the resulting acid is soluble in diethyl ether because it facilitates the separation of the ammonium salt, which is insoluble in this solvent. TBAH (i) allows, under mild conditions, the chemoselective transformation of **55** to **56** by selective cleavage of the acetate derived from a long chain alcohol leaving untouched the methyl ester attached on the 2-position of the pyran ring (Scheme 18, entry a),[40] (ii) efficiently saponifies the polyunsaturated diester **57** (Scheme 18, entry b),[41] and (iii) allows the hydrolysis of the highly functionalized ester **59** to produce in reasonable yield the α-amino acid **60** (Scheme 18, entry c),[42] but it concomitantly removes both the oxazolidino- and the trifluoroacetamido groups.[42]

TBAH in THF or better in acetonitrile−water (2:1) efficiently hydrolyzes polypeptide esters such as Boc-Leu-Phe-OBzl and Boc-Leu-Leu-Leu-Leu-Lys(Z)-OBzl. The reaction proceeds rapidly (0.2−1 h) at 0 °C, with extremely little epimerization.[43] This reagent is far more efficient than the one involving NaOH in acetone, which is comparatively very slow at 0 °C and only occurs at a reasonable rate at 20 °C.[43]

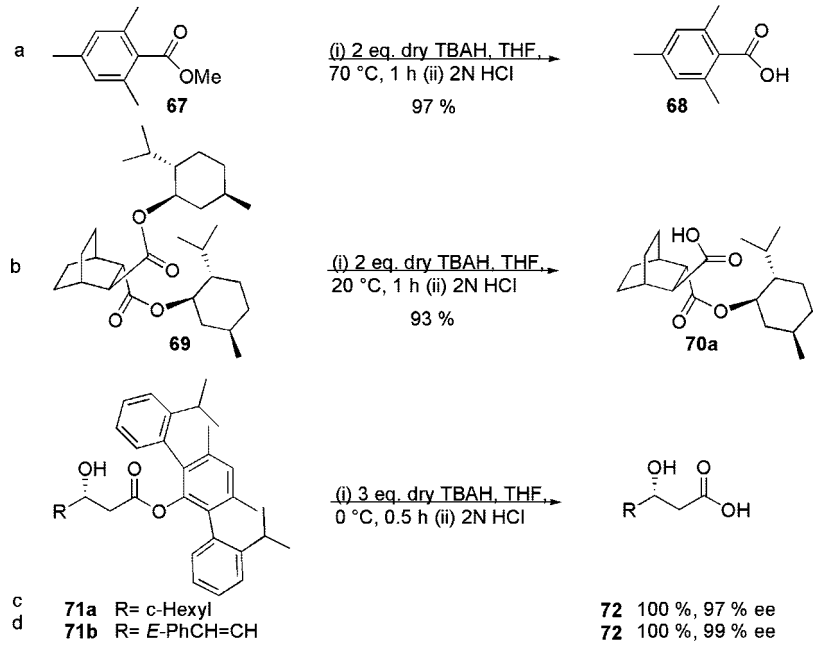
**Scheme 18**




**Scheme 19**



**Scheme 20**



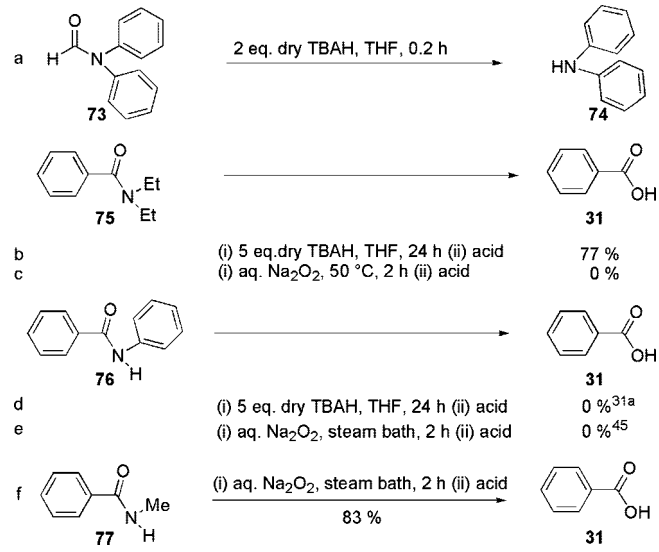

TBAH has been successfully used in the basic hydrolysis of tertiary amides derived from pseudoephedrine (Scheme 19).[44] Carboxylic acids are usually produced in excellent yields and with high stereocontrol even from amides possessing an epimerizable α chiral center such as **61**. In the case of the amide **63**, which bears an aromatic ring α to the carboxamide group, epimerization, however, occurs to a quite large extent (Scheme 19, entry b).

The reaction proved to be superior to that which uses instead aqueous sodium hydroxide in the presence of *t*-butanol or methanol.[44] The latter conditions have been nevertheless successfully used with compound **65** (Scheme 19, entry c), which is highly insoluble under conditions used with TBAH.[44] It allows the simultaneous hydrolysis of both the *t*-butyl ester and the tertiary amide functional groups.

Anhydrous tetrabutylammonium hydroxide, "dry TBAH", is one of the rare reagents that allows the hydrolysis of extremely hindered esters,[31] which are unreactive toward alkaline hydroxides (Scheme 20). It has been, however, reported that hydrolysis of the C-2 unsymmetrical substrate **69** occurs regioselectively on the *exo*-ester group,[31c] but that racemization is predominant unless a single equivalent of "dry TBAH" is instead used (THF, 20 °C, TBAH: 1 equiv, 70% **70a**, 91% ee; 2 equiv, 93% **70a**, 74% ee).[31c]

The transformation of the diester **69** to the half ester **70a** is probably caused by (i) electronic repulsion of the naked carboxylate anion intermediate[31a] formed under the anhydrous conditions used or by (ii) steric hindrance around the intermediate monocarboxylate resulting from the close contact with the bulky tetrabutylammonium counterion.[31c] Anyhow, the reaction proved to be by far superior to that involving instead (i) "wet TBAH" (DME, 20 °C, 1 h, 9% **70a**, 91% recovery of **69**),[31c] (ii) 4 N aqueous sodium hydroxide (DME, 20 °C, 16 h or reflux, 2 h, no reaction),[31c] (iii) 2 N potassium hydroxide (DMSO−DME, 20 °C, 31 h, 21% **70a**, 77% recovery of **69**), and (iv) "anhydrous potassium hydroxide" in DME, which is so reactive that it directly produces, by hydrolysis of the two ester groups, the diacid **70b** in good yield but with extremely poor ee (*t*-BuOK−water (9:2), 20 °C, 1 h, 89% **70b**, ee, 8%; see paragraph on "anhydrous potassium hydroxide").[31c]

**Scheme 21**




This transformation is useful because the syntheses of the scalemic bicyclic diester **69** and related compounds have been efficiently achieved by asymmetric Diels−Alder reactions involving dimenthyl fumarate.[31c] Thus, several chiral dimenthyl esters whose structures are related to **69** have been converted successfully to the corresponding half esters at room temperature by using 2 equiv of "dry TBAH", and interestingly the menthol concomitantly formed has been recovered in high yield.[31c] Hydrolysis using "dry TBAH" of the extremely hindered scalemic β-hydroxy-aroyl esters **71** to the corresponding acids **72** is remarkable because it occurs without epimerization arising from a retro-aldol reaction (Scheme 20).[31b]

"Dry TBAH" efficiently hydrolyzes tertiary amides such as *N*,*N*-diphenyl formamide **73** and *N*,*N*-diethyl benzamide **75** to the corresponding amines and carboxylic acids (2−5 equiv of "dry TBAH", THF, 20 °C, 2−24 h, Scheme 21).[31a] The method is milder and superior for tertiary amides (Scheme 21, entry b, compare to entry c) to that found by the researchers of Procter and Gamble, which uses instead

aqueous sodium peroxide.[45] The latter conditions efficiently hydrolyze primary, secondary, and tertiary carboxylic amides under mild conditions (50 °C, 1 h) to the corresponding carboxylic acids and involve peroxycarboxylates.[45]

Unfortunately, however, both methods do not allow hydrolysis of the *N*-phenyl benzamide **76**, which bears a quite acidic hydrogen on the nitrogen atom, which is deprotonated by the hydroxide ion acting as a base (Scheme 21, entries d,e).[31a] The least acidic *N*-methyl benzamide **77** has been, however, successfully hydrolyzed (Scheme 21, entry f).[45]

## 3. Tracking the Reactivity of Hydroxide Anion Generated from Different Sources

### 3.1. Hydrolysis of Alkyl Benzoates Using Various Reagents Delivering the Hydroxyl Anion under Different Conditions

#### 3.1.1. Hydrolysis Involving Alkali Metals under "Normal Conditions"

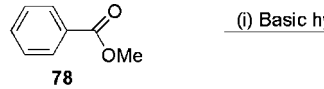
We have gathered in Schemes 22, 23, and 24 results involving hydrolysis of benzoates under different conditions. They include quite hindered esters such as methyl 2,4,6-trimethyl benzoate **67** (methyl mesitoate, Scheme 23),[8g−j,13b,14c,15c−e,31,47] *tert*-butyl benzoate **82b** (Scheme 24, entries c−f),[8i,j,15c,46,47] and *tert*-butyl mesitoate **82a** (Scheme 24, entries a,b),[15c] in which the steric hindrance is (i) part of the carboxylate or of the alkoxy group or is (ii) present at both sites. We also disclosed for comparison purpose related results involving methyl benzoate **78** (Scheme 22).[8g,i,j,13b,14c,46,47]

The hydrolysis of (i) methyl mesitoate **67**, which possesses a hindered carbonyl group, is far more difficult than that of methyl benzoate **78**. Thus, **67** is not hydrolyzed with 20% aqueous sodium[13a] or potassium hydroxides[14c] even when the reaction is carried out at reflux (Scheme 23, entries a,b), whereas methyl benzoate **78** is almost quantitatively hydrolyzed under the same conditions (Scheme 22, entry b).[14c]

The hydrolysis of (ii) methyl 2,6-dimethylbenzoate ($k = 3.8 \times 10^{-7}$ L mol$^{-1}$ s$^{-1}$) and 4-substituted-2,6-dimethylbenzoates (4-$NH_2$, 4-Br, 4-$NO_2$) by sodium hydroxide in dioxane−water (60:40) solution is very slow even when performed at 120 °C and mainly proceeds by alkyl-oxygen fission.[13b]

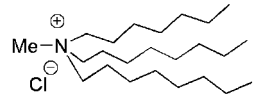
The hydrolysis of (iii) esters is efficiently achieved in DMSO. Thus, basic hydrolysis of ethyl benzoate in aqueous

**Scheme 22**




78 31

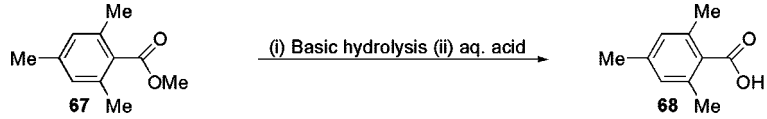
| | | | |
|---|---|---|---|
| a | 20 % aq. NaOH, 20 °C,1 h | 12 % | 8g |
| b | 20 % aq. KOH, 100 °C, 1.5 h | 97 % | 14c |
| c | 20 % aq. KOH, ultrasound application, 0.2 h | 98 % | 14c |
| d | 50 % aq. NaOH, 1 % aliquat 336 **79**, pentane, 20 °C, 1 h | 34 % | 8g |
| e | 2 % aq. KOH, 200 °C, 0.5 h | 98 % | 13b |
| f | KOH (powder)-$Al_2O_3$, ether, 20 °C, 4 h | 85 % | 8i |
| g | 60 % aq. KOH-Polyethyleneglycol-grafted copolymer, toluene, 25 °C, 5 h | 88 % | 8j |
| h | *t*-BuOK-$H_2O$-**78** (8.8-2.2-1), ether, 20 °C, 0.5 h | 44 % | 47 |
| i | *t*-BuOK-$H_2O$-**78** (8.8-2.2-1), ether, 20 °C, 2 h | 100 % | 47 |




79

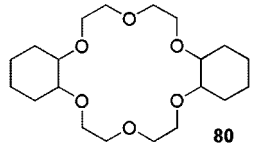
Aliquat 336
Methyl tri-octylammonium chloride

**Scheme 23**



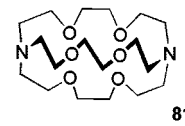

67 68

| | | | |
|---|---|---|---|
| a | 20 % aq. NaOH, 100 °C, 1 h | 0 % | 13b |
| b | 20 % aq. KOH, 100 °C, 1.5 h | 0 % | 14c |
| c | excess KOH, 1-propanol, reflux, 5 h | 0 % | 15c |
| d | 20 % aq. KOH, ultrasound application, 1 h | 0 % | 14c |
| e | 50 % aq. NaOH, 1 % aliquat 336 **79**, pentane, 20 °C, 1 h | 9 % | 8g |
| f | 2 % aq. KOH, 300 °C, 0.5 h | 90 % | 13b |
| g | 2 % aq. KOH, 250 °C, 0.5 h | 57 % | 13b |
| h | 1 eq. KOH, dicyclohexyl-18-crown-6 **80**, toluene, 73.6 °C, 31 h | 58 % | 15c,d |
| i | 2.5 eq. KOH, dicyclohexyl-18-crown-6 **80**, toluene, 109 °C, 5 h | 93 % | 15c |
| j | KOH (anhydrous powder), 1 eq. 222-kryptate **81**, toluene 25 °C, 12 h | 70 % | 15e |
| k | 5 eq. KOH (anhydrous powder), 2 % Aliquat 336 **79**, 85 °C, 5 h | 93 % | 8h |
| l | KOH (powder)-$Al_2O_3$, toluene, 20 °C, 45 h | 60 % | 8i |
| m | 60 % aq. KOH-Polyethyleneglycol-grafted copolymer, neat, 70 °C, 72 h | 81 % | 8j |
| n | Tetrabutyl ammonium hydroxide "dry", THF, 70 °C, 1 h | 97 % | 31a |
| o | *t*-BuOK-$H_2O$-**67** (8.8-2.2-1), ether, 20 °C, 72 h | 72 % | 47 |



80

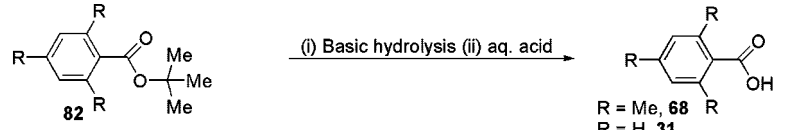
Dicyclohexyl-18-crown-6



81

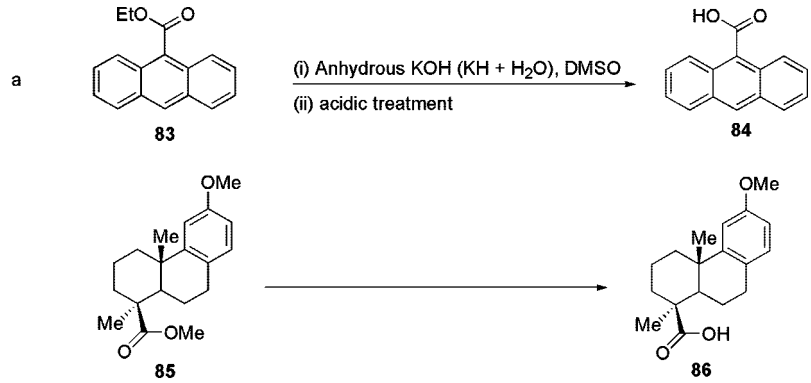
Kryptan 222

**Scheme 24**




| | R | | | | Ref |
|---|---|---|---|---|---|
| a | Me | **82a** | 2.5 eq. KOH, dicyclohexyl-18-crown-6 **80**, benzene, 80 °C, 5 h | 22 % | 15c |
| b | Me | **82a** | 2.5 eq. KOH, dicyclohexyl-18-crown-6 **80**, toluene, 109 °C, 5 h | 94 % | 15c |
| c | H | **82b** | KOH (powder)-$Al_2O_3$, toluene, 21 h | 90 % | 8i |
| d | H | **82b** | 60 % aq. KOH-Polyethyleneglycol-grafted copolymer, neat, 70 °C, 17 h | 91 % | 8j |
| e | H | **82b** | *t*-BuOK-$H_2O$-**82b** (3-1-1), ether, 20 °C, 16 h | 72 % | 46 |
| f | H | **82b** | *t*-BuOK-$H_2O$-**82b** (8.8-2.2-1), ether, 20 °C, 5 h | 100 % | 47 |

**Scheme 25**




| | | |
|---|---|---|
| b | (i) Anhydrous KOH (KH + $H_2O$), DMSO (ii) acidic treatment | 0 % |
| c | (i) Excess *t*-BuOK, 56 °C, 2 h (ii) acidic treatment | 97 % |
| d | (i) Excess *t*-BuOK, 20 °C, 24 h (ii) acidic treatment | 0 % |

DMSO (water−DMSO 15:85) is 300 times faster than that carried out in aqueous ethanol (water−ethanol 15:85).[48c] Furthermore, the reaction rate is twice as high when carried out with potassium hydroxide in the presence of kryptant (222) **81**, and this has been related to the larger amount of potassium hydroxide soluble in DMSO (0.8 M instead of $10^{-3}$ M).[15c]

The hydrolysis of (iv) esters is even better achieved with a fine suspension of anhydrous sodium hydroxide in DMSO, generated by titration using water and dimsyl sodium[48a] or sodium hydride.[48b] The reaction not only proceeds faster with a rate enhancement of $4 \times 10^5$, but also its mechanism is completely different. The hydroxide ion no longer reacts on the alkyl group of the ester as reported earlier for highly hindered esters leading to their hydrolysis by alkyl-oxygen cleavage,[13b] but attacks their carbonyl group and leads instead to the acyl-oxygen cleavage.[48b]

Anhydrous potassium hydroxide in DMSO is able to hydrolyze methyl as well as ethyl benzoates,[48b] and as expected the reaction rate of methyl mesitoate **67** ($10^{-2}$ L $mol^{-1}$ $s^{-1}$) is higher than that of its ethyl homologue ($4 \times 10^{-3}$ L $mol^{-1}$ $s^{-1}$).[48b] This reagent is able to hydrolyze ethyl 9-anthranoate **83** (Scheme 25, entry a).[48b] The most highly hindered methyl *O*-methyl podocarpate **85** whose carboxyl group lies in a particularly hindered axial position is not hydrolyzed under the latter conditions. Notice that it has been described that its rate of hydrolysis is more than 200 times slower than that of methyl mesitoate (Scheme 25, entry b).[48b] Transformation of methyl *O*-methyl podocarpate **85** to *O*-methyl podocarpic acid **86** has been successfully achieved using potassium *t*-butoxide in anhydrous DMSO.[49]

### 3.1.2. Hydrolysis Involving Alkali Metals under Sonication

Ultrasound efficiently enhances the reactivity of potassium hydroxide toward methyl benzoate **78** (Scheme 22, entry c, compare to entry b) as well as aromatic esters possessing a more hindered carbonyl group such as methyl 2,4-dimethyl- and 3,6-dimethyl benzoates.[14c] Methyl mesitoate **67**, which possesses an even more hindered carbonyl group due to the presence of the two methyl groups at 2- and 5-positions on the aromatic ring, remains, however, unaffected even after 1 h of sonication (Scheme 23, entry d, compare to Scheme 22, entry c).[14c]

### 3.1.3. Hydrolysis Involving Alkali Metals under "HT Conditions"

Both methyl benzoate **78** and the more hindered methyl mesitoate **67** have been efficiently hydrolyzed with potassium hydroxide (2%)[13c] if the reactions are performed at high temperature (HT) for one-half hour. The reaction already occurs at 200 °C for methyl benzoate **78** but requires a higher temperature when carried out on methyl mesitoate **67** instead (Scheme 23, entries f,g, compare to Scheme 22, entry e).[13c] It has been successfully extended to methyl 2,4-dimethyl-, 4-amino-, 4-methoxy-, 4-nitro-, and 4-trifluoromethyl benzoates.[13c] In the latter case, the reaction is best achieved using either potassium or ammonium hydroxides (2%) at temperature not higher than 200 °C; otherwise, *p*-phthalic acid is concomitantly formed (4-trifluoromethyl benzoic acid/*p*-phthalic acid 41:20, under supercritical conditions (375 °C)) by competing hydrolysis of the trifluoromethyl group.[13c]

Hydrolysis of esters can also be carried out without base added, but decarboxylation occurs as a competing reaction.[13c]

### 3.1.4. Hydrolysis Involving Alkali Metals under "Phase-Transfer Catalysis"

Phase-transfer catalysis protocols using onium salts as catalyst do not usually allow efficient esters hydrolysis, and although rate acceleration up to 5 times has been observed

in pentane (decreasing from pentane > benzene or ether > dichloromethane) as compared to the reaction performed under similar conditions but without catalyst,[8g] the yields of the corresponding acids are usually modest.[8g] This could be due to the ability of the liberated lipophilic anions to tend to pair with the catalyst cation, thus inhibiting the transfer of hydroxide ion into the organic phase.[8g]

Thus, hydrolysis of methyl benzoate **78** and methyl mesitoate **67** using 50% aqueous sodium hydroxide in the presence of methyl trioctylammonium chloride **79** provides the corresponding carboxylic acids in poor and symbolic yields, respectively (Scheme 22, entry d; Scheme 23, entry e).[8g] Those and related conditions[7c] have been used with a series of aliphatic esters including dialkyl adipates.[8g] Thus, whereas hydrolysis of neat dimethyl adipate proceeds exothermically, that of methyl tetradecanoate is rather inefficient.[7c]

The outcome is, however, completely different if methyl mesitoate **67** is instead reacted neat with solid potassium hydroxide (5 equiv, containing 15% water) in the presence of methyl trioctylammonium chloride because **68** is formed in up to 93% yield when the reaction is carried out at 85 °C for 5 h (Scheme 23, entry k; 80% **68** after 2 h).[8h] Mesitoic acid **68** is also formed in up to 87% yield besides 1-octanol (83%) when those conditions are applied to 1-octyl mesitoate.[8h]

Hydrolysis of methyl mesitoate **67** has been also carried out with 2.5 equiv of potassium hydroxide−dicyclohexyl-18-crown-6 **80** complex in toluene at 110 °C for 5 h (Scheme 23, entry h as compared to i).[15c] Those conditions are also efficient for the hydrolysis of extremely hindered *t*-butyl- (Scheme 24, entry b) and neopentyl mesitoates.[15c]

Lehn (222) Kryptant **81** has successfully replaced dicyclohexyl-18-crown-6 **80** for the hydrolysis of methyl mesitoate **67** (Scheme 23, entry j).[15e] The control experiment shows[15e] that hydrolysis is not observed if **81** is missing. It has been suggested that the reaction involves potassium hydroxide particles covered superficially by a layer of kryptant rather than a kryptated species $[(222),K^+]\ OH^-$.[15e]

Polyethyleneglycols grafted to cross-linked polystyrene are an active and stable triphase catalyst for saponification of methyl- **78** (Scheme 22, entry g) and *tert*-butyl- **82b** (Scheme 24, entry d) benzoates and methyl mesitoate **67** (Scheme 23, entry m).[8j] The reaction is best achieved using 60% aq KOH and polyethyleneglycol-grafted copolymer polystyrene (1%) divinyl benzene (200−400 mesh) containing 52% ring substitution, neat or in a solvent such as benzene, toluene, or hexane at room temperature or at 70 °C for the least reactive esters or lactones.[8j] These conditions also allow quantitative hydrolysis at room temperature of amyl acetate and ethyl decanoate as well.[8j]

This reagent offers over the conventional soluble quaternary ammonium salts the advantages (i) to be stable toward bases (quaternary ammonium salts have a half-life typically on the order of 0.5 h at 70 °C),[8d,j] (ii) to not be subjected to deactivation by ion pairing (see above),[8g] and (iii) to be easily recovered by filtration and reused without lost of activity (up to three times tested).[8j]

### 3.1.5. Saponification Involving "Dry Potassium Hydroxide on Alumina"

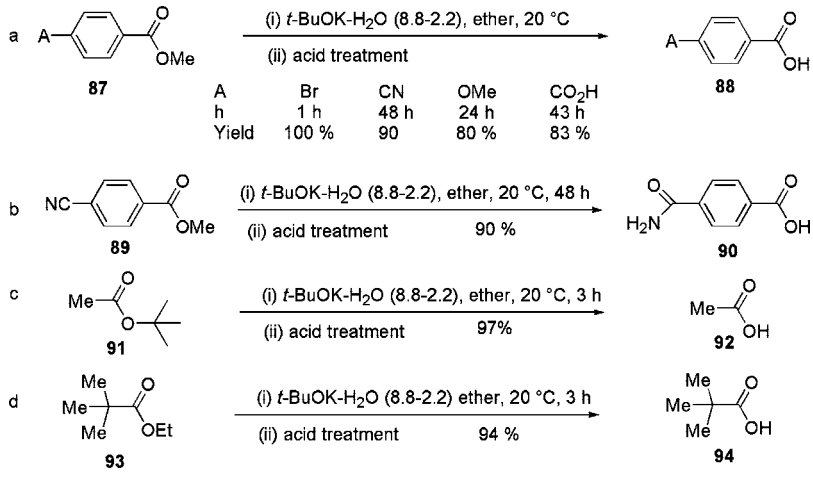
It has been also reported that potassium hydroxide crushed together with neutral alumina efficiently allows the hydrolysis of methyl (Scheme 22, entry f), *tert*-butyl (Scheme 24, entry c) benzoates, and methyl mesitoate **67** (Scheme 23, entry l) at ambient temperature.[8i] It requires a small but finite quantity of water for high hydrolytic activity because a mixture of potassium hydroxide and alumina dried at 100 °C for 24 h does not exhibit the hydrolytic activity reported above.[8i]

The reaction is usually carried out indistinctly in ether or toluene for 4 h for methyl benzoate **78** to up to 45 h for the more hindered methyl mesitoate **67** (Scheme 23, entry l; compare to Scheme 22, entry f and to Scheme 24, entry c).[8i] The method offers the advantages already described for the triphase catalyst disclosed above[8j] and the ready access of commercially available low cost neutral alumina for which recycling is useless. Hydrolysis of *n*-decyl benzoate (toluene, 48 h, 89% yield), methyl 4-bromo and 4-methoxy benzoates (22−23 h, 75−100% yield), amyl and decyl acetates (4 h, quantitative), and ethyl octanoate (18 h, quantitative) using solid KOH−neutral alumina has been also successfully achieved.[8i] This method is by far superior to a related one that uses instead an aqueous solution of potassium hydroxide and alumina, which hydrolyzes rapidly 3,5-dinitro benzoic esters but is far more slower with less reactive esters.[50]

### 3.1.6. Hydrolysis of Esters Involving "Anhydrous Potassium Hydroxide" from Potassium t-Butoxide

Finally, it has been first reported by Swan[46] that a potassium *t*-butoxide and water (3:1) mixture ("anhydrous

**Scheme 26**



potassium hydroxide" = "APH") hydrolyzes, at room temperature, *t*-butyl benzoate **82b** smoothly (Scheme 24, entry e). Those results have been confirmed later by Gassman[47] who monitored this reaction (Scheme 24, entries f, see also Scheme 27, entry a).[47] He extends it[47] to methyl benzoate **78** (Scheme 22, entry i), methyl mesitoate **67** (Scheme 23, entry o), and methyl 4-substituted benzoates **87** (Scheme 26, entry a) as well as to *t*-butyl acetate **91** (Scheme 26, entry c) and ethyl pivaloate **93** (Scheme 26, entry d). "Anhydrous potassium hydroxide" ("APH") is also able to hydrolyze the ester moiety present on methyl 4-cyano benzoate **89** to produce after acid hydrolysis the carboxylic acid **90** bearing an amido group in place of the cyano group at the 4-position. Therefore, those conditions also affect the nitrile functional group, which is at the same time transformed to the primary amide (Scheme 26, entry b).

This reaction probably involves a complex reagent, which still contains potassium *t*-butoxide and potassium hydroxide often quoted as "anhydrous potassium hydroxide" ("APH").

## 4. "Anhydrous Potassium Hydroxide" in Organic Synthesis

Since its rediscovery by Gassman,[47,51,52] "APH" has been widely used to generate particularly nucleophilic "naked hydroxide ion". More than 350 papers relate the use of this reagent, often comparing the results with those from related reagents, and therefore we can reasonably trust the scope and limitations presently available on the many transformations this reagent is able to perform.

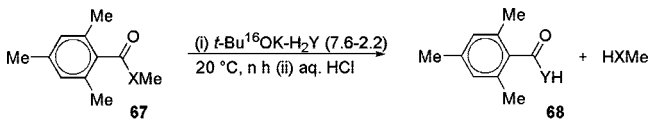
"APH" has been prepared by addition of a limited amount of water to potassium *t*-butoxide suspended in diethyl ether,[46,47,51,52] THF,[52] dioxane,[46] dimethoxyethane,[53] glyme,[51b] hexane,[51b] pyridine,[46] DMSO,[51] and HMPA[51b] and indistinctly used in these solvents. However, diethyl ether has been used because the reaction often takes place at room temperature and the workup is easy.[51b] However, it has been reported that it is inefficient in hydroxylic solvents[46] and that even a trace amount of added *t*-butanol is deleterious.[46]

Ester hydrolysis is, among the various transformations that "APH" is able to achieve, the one on which substantial work including mechanistic one has been achieved. Furthermore, it is possible to compare the results involving "APH" to those we have already gathered.

The mechanism of ester hydrolysis has been described by Gassman[47] on the basis of labeling experiment involving $^{18}O$ methyl mesitoate and $^{16}O$ water as well as $^{16}O$ methyl mesitoate and $^{18}O$ water (Scheme 27, entries b,c).

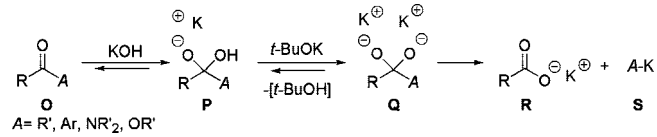
It is expected to involve the attack of the highly nucleophilic "naked hydroxide ion" onto the carbonyl group of the ester **O** (A = OR) leading to the "tetrahedral intermediate" **P** (A = OR), which, on reaction with the excess of potassium *t*-butoxide or of the complex *t*-BuOK−KOH, could produce the putative extremely reactive dianion **Q** (A = OR), which

**Scheme 27**




| | X | Y | |
|---|---|---|---|
| a | O | O | 50 % (24 h), 63 % (48 h), 72 % (72 h) |
| b | $^{18}O$ | $^{16}O$ | $^{16}O$ acid 49 % (24 h) |
| c | $^{16}O$ | $^{18}O$ | $^{18}O$ acid -- (24 h) |

**Scheme 28**




tends to collapse to the carboxylate **R** and the alcoholate **K** (A = OR, Scheme 28).[47]

Related intermediates have been also proposed in reactions that also produce potassium carboxylates in spectacularly high yields by cleavage of (i) the C,C bond of non enolizable ketones related to the Haller−Bauer reaction discussed above (Scheme 28, **Q**: A = R′, Ar)[46,51] and of (ii) the C,N bond in tertiary amides (Scheme 28, **Q**: A = $NR'_2$).[52] Amines are also produced in the last case as well as on reaction of "anhydrous potassium hydroxide" with carbamates (Scheme 28, R = $NR'_2$, **Q**: A = OR′, see below) and ureas (Scheme 28, R = $NR'_2$, **Q**: A = $NR'_2$, see below).

The reactions are usually carried out at room temperature,[46,47,51,52] and in only rare cases do they require to be heated up to 85 °C.[53] The nature of the counterion of the tertiobutylate used, its ratio to the carbonyl compound, and the amount of water used seem to be much more important for the success of the reaction than the nature of the solvent used.

It was found that potassium *t*-butoxide is by far better than its sodium or lithium analogues and that an excess of about 3[46] to 10 equiv[51a] of potassium *t*-butoxide and 1.2[46] to 3[51a] equiv of water is usually a good compromise.

"Anhydrous potassium hydroxide" has been also prepared from potassium hydride, *t*-butanol, and water in DMSO,[51a] and the best results have been obtained with a KH/*t*-BuOH/water ratio 10/10/3, which is expected to produce a potassium *t*-butoxide/KOH mixture of 10/3.[51a] Increasing the amount of water is deleterious especially if the potassium *t*-butoxide/water mixture reaches 1/1.[51a] On the contrary, the reagent that involves potassium *t*-butoxide in anhydrous DMSO obtained by mixing both compounds[49a] or prepared in situ from potassium hydride and *t*-butanol,[49b] in which potassium hydroxide is missing, hydrolyzes, contrary to "APH", methyl *O*-methylpodocarpate **85** to the corresponding acid **86** (Scheme 25, entry c). The latter reaction implies the alkyl-O cleavage because it also produces *t*-butyl methyl ether[49b] and therefore involves a mechanism completely different from that reported by Gassman[47] for the hydrolysis of esters using "APH" (Schemes 27, 28).

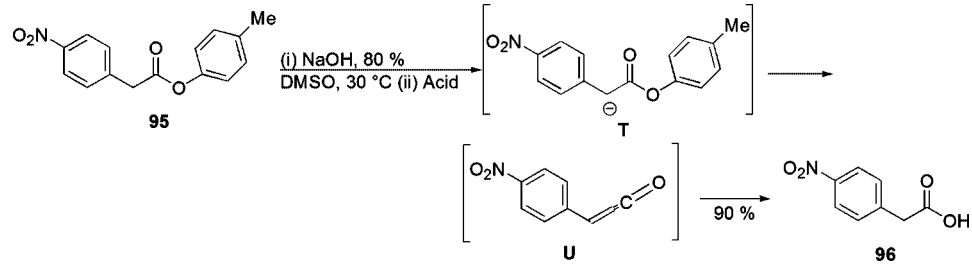
"Anhydrous potassium hydroxide" has only a limited propensity to react as a base. For example, only rarely does ester hydrolysis by "APH" lead to the corresponding carboxylates with an epimerized α-carbon arising from the metalation of either the starting ester or the resulting carboxylate. Therefore, the event described in Scheme 29 has never been reported using "APH".[54]

### 4.1. "Anhydrous Potassium Hydroxide" Acting as a Base

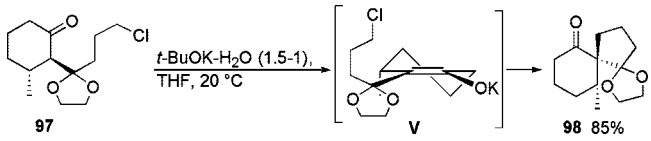
#### 4.1.1. Typical Reactivity of "Anhydrous Potassium Hydroxide" Acting as a Base

Only few papers report the use of "APH" as a base. It has been nevertheless used as "the most reliable base" to promote the high yield spiroannulation of a series of cyclohexanones bearing in the α-position a 3- or 4-carbon side chain bearing

**Scheme 29**




**Scheme 30**




an acetal moiety and a leaving group at the terminus such as **97** (Scheme 30).[55]

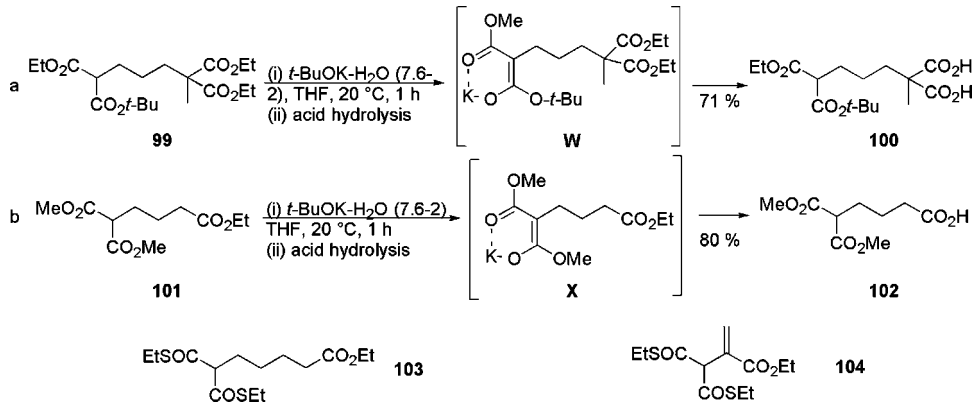
"APH" has been ingeniously used to transform the compound **99** bearing two malonyl ester moieties differently substituted at their α-carbon atoms to **100** bearing the malonic acid moiety exclusively at the fully alkyl-substituted carbon, leaving intact the malonyl ester attached to an enolizable carbon (Scheme 31, entry a).[56]

Similarly, the triester **101** has been selectively hydrolyzed by "APH" to **102** bearing the monocarboxylic acid, still bearing intact the malonyl ester attached to an enolizable carbon (Scheme 31, entry b).[56] These selective transformations have been attributed to the metalation of the malonates leading to the intermediates **W**, **X**, respectively deactivating therefore the two related ester groups and allowing thus the excess of reagent to act as a nucleophile on the more electrophilic ester groups (Scheme 31, entries a,b). Compounds **103** and **104** behave similarly toward "APH" (Scheme 31).[56]

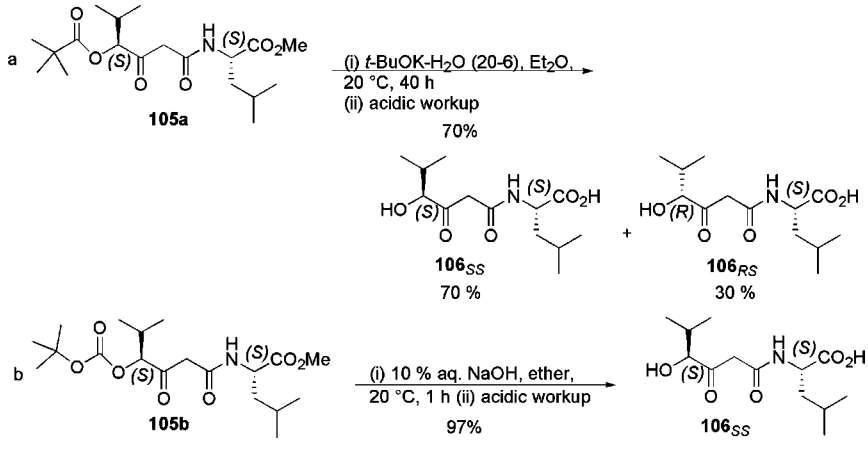
Epimerization α to the carboxyl[57] or the carboxamido[58] groups has been rarely observed. In the case of highly functionalized **105a**, however, hydrolysis with "APH" of the methyl carboxylate and the pivaloyl group generates the related carboxylic acid possessing the α-hydroxy-ketone moiety **106**, as a mixture of diastereoisomers due to epimerization α to the keto group bearing the pivaloyloxy or the hydroxy moiety (Scheme 32, entry a).[57] Surprisingly, no epimerization was reported when the related carbonate **105b** was transformed with sodium hydroxide to the same compound **106** (Scheme 32, entry b).[57]

Epimerization has been observed during the hydrolysis of the amide **107**, whose nitrogen is part of an indole and the α carbon is substituted by an alkoxy group part of an

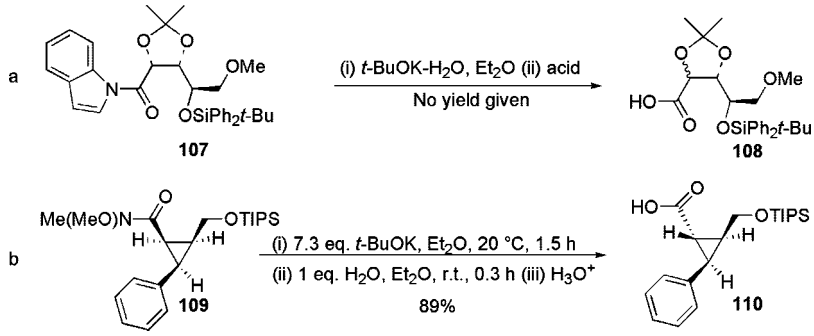
**Scheme 31**



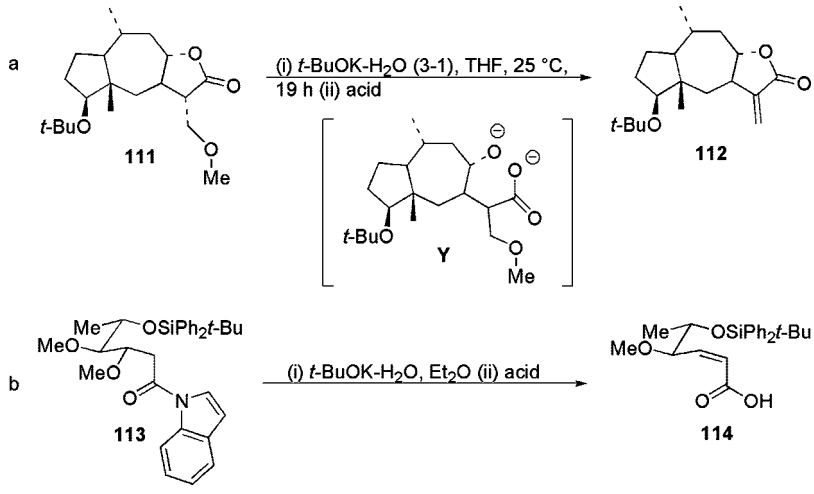

**Scheme 32**



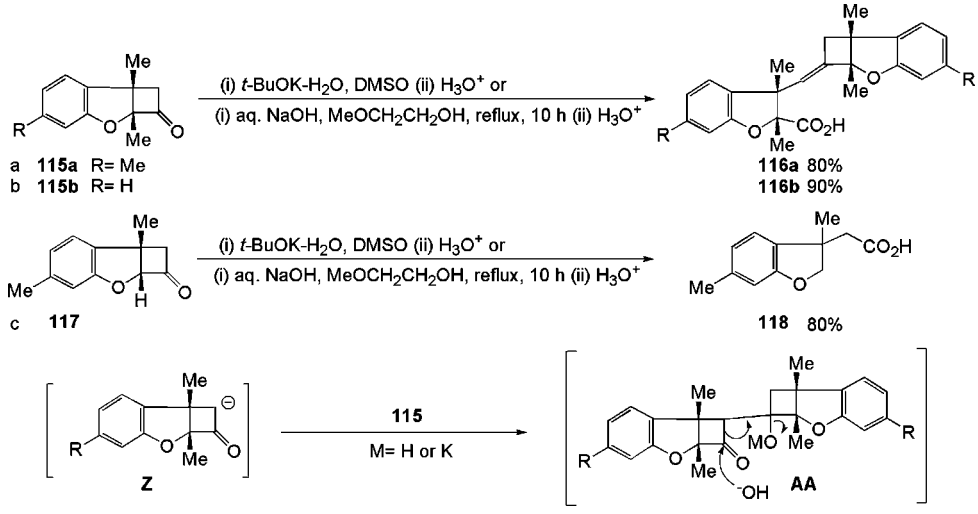
**Scheme 33**




**Scheme 34**




**Scheme 35**

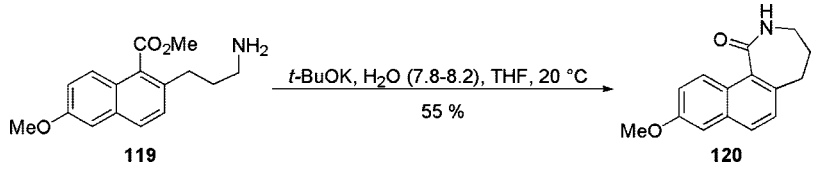



acetonide (Scheme 33, entry a),[58] as well as on reaction of Weinreb amides such as **109** with "APH".[60] The "unconventional" way the reagent is generated (in situ and after a prolonged reaction of **109** with potassium *t*-butoxide) could be responsible for epimerization prior to amide hydrolysis leading to the cyclopropane carboxylic acid **110** (Scheme 33, entry b).[60]

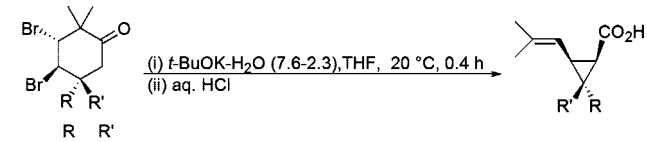
In rare cases such as the $\beta$-methoxy lactone **111**[61a,b] (Scheme 34, entry a) and the indol derived amide **113**[58] (Scheme 34, entry b), a $\beta$-elimination reaction leading to the methylene lactone **112** or to the insaturated carboxylic acid **114** has been reported, which implies a metalation step (Scheme 34). In the former case, the reaction can be also carried out in two steps. The first one involves the reaction of **111** with methanolic potassium hydroxide and leads to the intermediate **Y**. Removal of the solvent and reaction of anhydrous potassium *t*-butoxide in THF again produces **112** (Scheme 34, entry a).[61b]

Attempting Haller−Bauer-type scission of the enolizable cyclobutanones **115** with "APH" leads instead to the carboxylic acids **116** whose structures are composed of twice the carbon framework of **115** (Scheme 35, entries a,b).[59] It has been proposed that "APH" enolizes the cyclobutanones **115** rather than reacting on its carbonyl carbon. The resulting enolate **Z** reacts on **115** to produce **AA** on which "APH"

**Scheme 36**




**Scheme 37**




| | | R | R' | | |
|---|---|---|---|---|---|
| a | **7a** | Me | Me | **9a** | 94 % |
| b | **7b** | Me | H | **9b** | 92 % |
| c | **7c** | H | H | **9c** | 86 % |
| d | **7b'** | H | Me | **9b'** | 94 % |

reacts to produce **116** via a tandem Haller−Bauer-scission followed by elimination of the oxy group.[59]

Finally, the naphtoic ester **119**, bearing a primary amino group at the terminus of a 3-carbons side chain lying in the ortho position of the benzene ring, proved to be reluctant to hydrolysis with "APH". However, if stirred for a long period, intramolecular cyclization resulting from the substitution of the methoxy group of the ester by the primary amido group intermediate generates the lactame **120** (Scheme 36).[62] The same transformation has been also achieved using anhydrous potassium *t*-butoxide in THF instead.[62]

[It will be also reported in a forthcoming section that "APH" (i) hydrolyzes the *t*-butyl ester **280b** bearing a nitrogen atom part of a carbamate in the $\beta$-position to deliver the $\alpha,\beta$-unsaturated acid **282** resulting from the concomitant $\beta$-elimination reaction (Scheme 55, entry b),[99] (ii) metallates triphenylmethyl ketone **320** bearing a C,C triple bond in the $\gamma,\delta$-position (Scheme 65, entry a)[115] but not the related **322** (Scheme 65, entry b),[115] and (iii) epimerizes the $\alpha$-carbon of the carboxylic acid **301a** under drastic conditions (Scheme 61).[51c] Finally, it has been reported that "APH" is unable to generate benzyne from chlorobenzene and is therefore unable to metalate it (DME, 20 °C, 2 h).[107]]

### *4.1.2. "Anhydrous Potassium Hydroxide" for Chrysanthemic Acid Synthesis from Cyclohexanones Bearing Leaving Groups in $\gamma$- and $\delta$-Positions*

We were delighted to observe[24b] that "APH" in DMSO behaves toward $\mathbf{7a_{Br}}$ as aqueous potassium hydroxide ("WPH", Scheme 2, entry b), producing after acid hydrolysis *cis*-chrysanthemic acid **9a** in lower yield (65% instead of 86%) but under much milder conditions (20 °C instead of 70 °C; 0.5 h instead of 2 h, Scheme 2, entry b). We were even more satisfied when we discovered, and that was unexpected, that an extremely high yield of **9a** (94%) can be obtained, under such mild conditions, if the reaction is instead carried out in THF (Scheme 37, entry a).[24b] We also found that "APH" in THF behaves similarly toward the dichloro derivative $\mathbf{7a_{Cl}}$ than toward $\mathbf{7a_{Br}}$, delivering **9a** in 80% yield after 1 h of reaction at 20 °C.[24b]

The case of **7b** and **7c** is even more interesting[24b] because, whereas they almost exclusively produce the lactone **10b** and **10c** on reaction with "wet potassium hydroxide" in DMSO (Scheme 3),[22e] they provide desmethyl *cis*-chrysanthemic **9b** and didesmethyl *cis*-chrysanthemic **9c** almost quantitatively on reaction with "anhydrous potassium hydroxide" in THF (20 °C, 0.4 h, Scheme 37, entries b,c). The reaction is stereospecific because the dibromide **7b′** stereoisomer of **7b** produces the desmethyl *cis*-chrysanthemic **9b′** (Scheme 37, entry d).[24b]

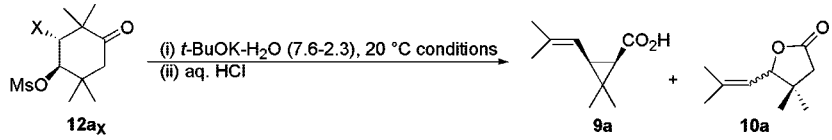
"APH" exhibits also a high propensity to transform mesyloxy bromo- and iodo- ketones $\mathbf{12a_{Br}}$ and $\mathbf{12a_{I}}$ to *cis*-chrysanthemic acid **9a** especially when the reaction is performed in THF (Scheme 38, entries a,c).[24b] Those ketones generate lactone **10a** if "wet potassium hydroxide" is instead used (Scheme 5; compare Scheme 38, entry a to Scheme 5, entry a, and Scheme 38, entry c to Scheme 5, entry e).[24b]

Both "wet" and "anhydrous" potassium hydroxides produce chrysanthemic acid **9a** from mesyloxy chloro-ketone $\mathbf{12a_{Cl}}$, but the latter reagent is by far more reactive especially if the reaction is carried out in THF (Scheme 38, entry b).[24b]

For comparison purposes, the synthesis of chrysanthemic acid **9a** from $\mathbf{12a_{Cl}}$ is achieved in 2 h at 20 °C with "APH" and requires more than 6 h at 70 °C with "wet potassium hydroxide" in the same solvent (Scheme 5, entry d).[24b] The latter conditions performed at 20 °C instead produce after 8 h the bicyclic[3.1.0]$\beta$-chloroketone $\mathbf{8a_{Cl}}$ (compare Scheme 5, entry c to Scheme 38, entry b).[24b]

All of these reactions deliver *cis*-chrysanthemic acids **9** possessing the *cis*-stereochemistry (Schemes 37, 38), and therefore these results support the idea that the formation of the *trans*-cyclopropane carboxylic acid **110** from the *cis*-Weinreb amide **109** involves a cis/trans isomerization, which takes place prior to hydrolysis (Scheme 33).[60]

**Scheme 38**




| | X | Conditions | Overall | 9a (10a) % | Conditions | Overall | 9a (10a) % |
|---|---|---|---|---|---|---|---|
| a | Br | THF, 0.6 h | 89 % | 100 | DMSO, 2 h | 81 % | 94 (6) |
| b | Cl | THF, 0.6 h | 90 % | 80 | DMSO, 2 h | 75 % | 100 |
| c | I | THF, 0.6 h | 93 % | 96 (4) | DMSO, 2 h | 41 % | 88 (12) |

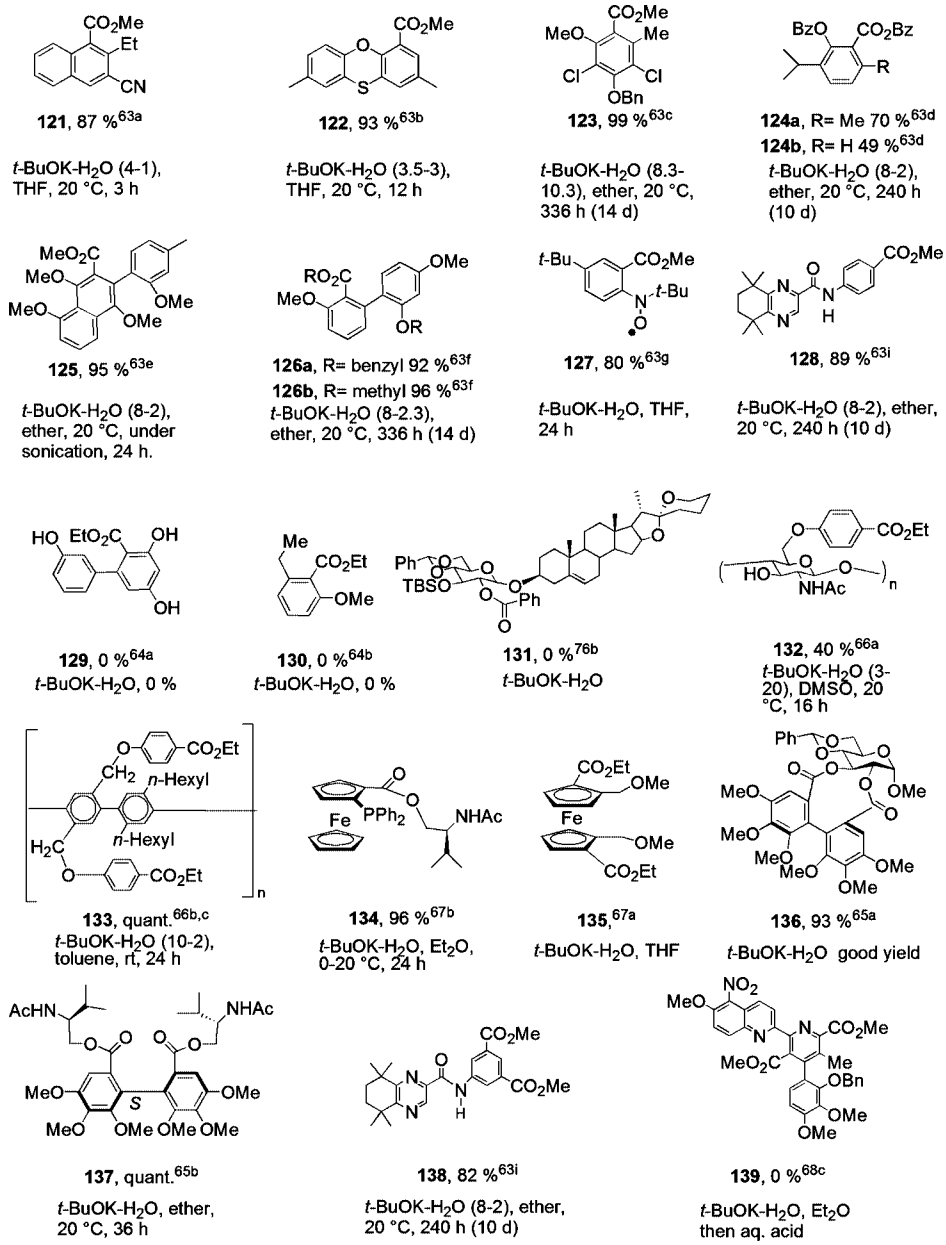



**Figure 1.** "APH" monitored transformation of aromatic and heteroaromatic carboxylic esters to the corresponding aromatic and heteroaromatic carboxylic acids.

## 4.2. "Anhydrous Potassium Hydroxide" Acting as a Nucleophile

### *4.2.1. Reactivity of "Anhydrous Potassium Hydroxide" toward Carboxylic Esters*

"APH" has been widely used for the hydrolysis of carboxylic esters to the corresponding carboxylic acids especially for the hindered ones (Figures 1−3) such as aromatic esters (Schemes 22, 23, 24, 25, entry a; Scheme 26, entries a,b; Scheme 27; Figure 1, **121**−**131**, **134**; Scheme 43, entries d−f)[46,47,63,64,67b,76b] and polyesters (Scheme 10, entry g; Figure 1, **135**−**139**),[29,63i,65,67a,68c] polymeric aromatic esters (Figure 1, **132**, **133**),[66] ferrocenyl esters (Figure 1, **134**, **135**),[67] heteroaromatic esters (Scheme 39),[68] and α,β-unsaturated esters (Figure 2, **166**, **167**),[69] enolizable "aliphatic" esters (Scheme 32, entries a,b; Figure 2, **146**, **147**, **148**, **156**−**163**),[57,70a−c,e,71c−f 72l,n] and non enolizable "aliphatic" esters (Scheme 10, entry e; Figure 2, **140**−**145**, **149**−**155**),[28,72] "aliphatic" polyesters (Figure 2, **164**, **165**, Figure 3, Schemes 40, 41),[31c,70b,71b,73] as well as polymeric "aliphatic" esters (Scheme 42, entries a,b).[74a,75a]

"APH" does not allow hydrolysis of long chain esters attached to a silica surface because it damages the monolayer structure of the surface (Scheme 42, entry c).[75c] It has been successfully used for hydrolysis of compounds bearing one or several ester groups (acetates and benzoates), allowing isolation of the corresponding alcohols by deprotection (Figure 2, **157**, Scheme 43).[63j,k,70b,76] Hydrolysis of protected pivaloyl steroid **157** is remarkable but requires a large amount of "APH" to be successful (Figure 2).[70b]

**4.2.1.1. Reactivity of "Anhydrous Potassium Hydroxide" toward Aromatic and Heteroaromatic Carboxylic Esters.** Most of the reactions have been carried out on methyl aromatic and heteroaromatic carboxylates (Scheme 10, entry g; Scheme 22, entries h,i; Scheme 23, entry o; Scheme 26, entries a,b; Scheme 27, Figure 1, **121**−**123**, **125**−**128**, **138**;

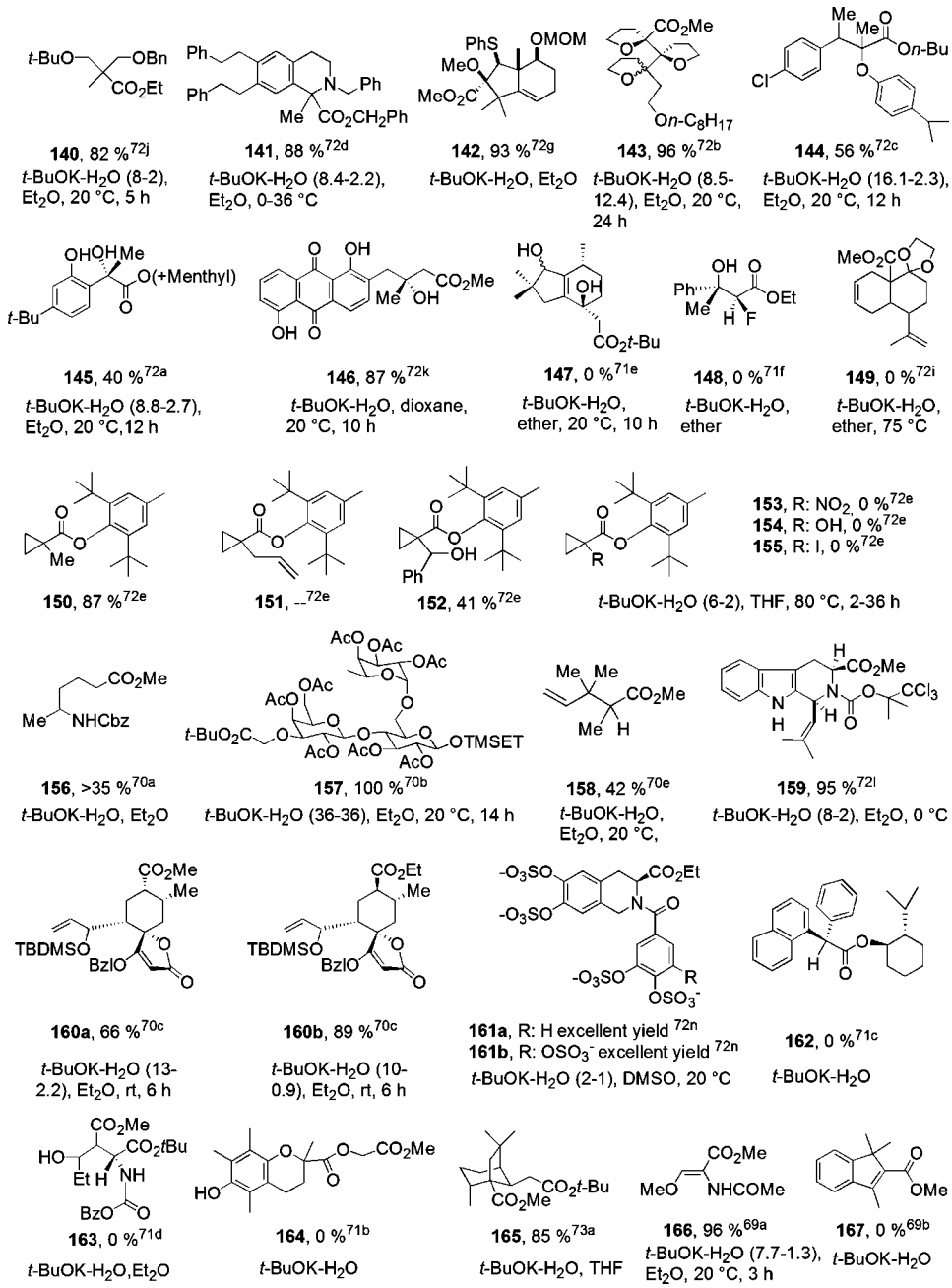



**Figure 2.** "APH" monitored transformation of aliphatic carboxylic esters to the corresponding aliphatic carboxylic acids.

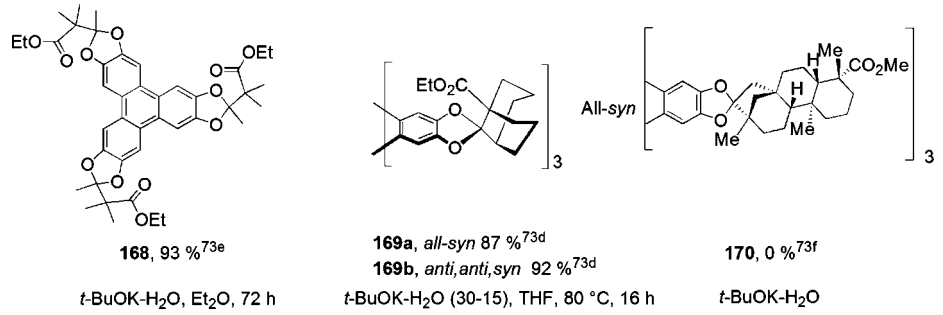
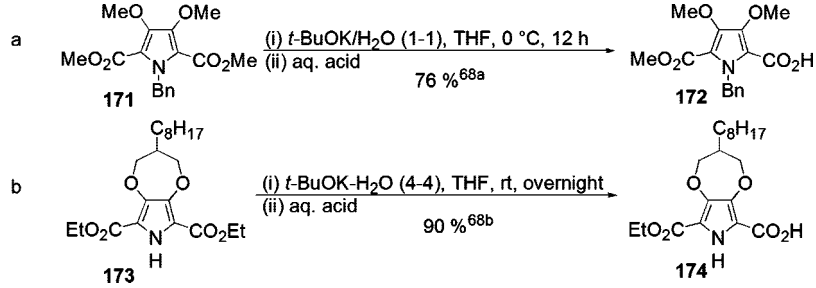



**Figure 3.** "APH" monitored transformation of polyaliphatic carboxylic esters to the corresponding polyaliphatic carboxylic acids.

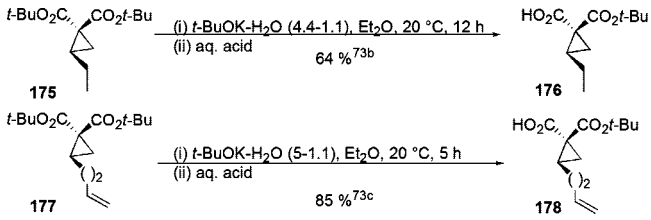
Scheme 39, entry a), but hydrolysis has also been carried out on ethyl esters (Figure 1, **129**, **130**, **132**, **133**, **135**; Scheme 39, entry b), *t*-butyl esters (Scheme 24, entries e,f), and more rarely benzyl esters (Figure 1, **124**, **126**) as well as esters derived from $\beta$-amino alcohols (Figure 1, **134**, **137**), sugars (Figure 1, **136**), or taxane derivatives possessing several hydroxyl groups protected as acetates (Scheme 43, entries d−f).

The reaction was successfully achieved on very hindered aromatic esters especially methyl and *t*-butyl mesitoates

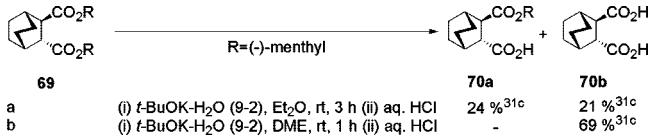
**Scheme 39**




**Scheme 40**




**Scheme 41**




(Scheme 23, entry o; Scheme 24, entries e,f) and occurs on benzoates bearing in the *para*-position a bromine, methoxy, or carboxyl group (Scheme 26, entry a) or an amino group part of a secondary amide (Figure 1, **128**); however, it has been reported once that after 48 h the nitrile also present on **88** reacts to lead finally to the *p*-amido-benzoic acid instead of the expected *p*-cyano-benzoic acid (Scheme 26, entry b). Interestingly, it seems feasible to keep the nitrile untouched by properly tuning the conditions (Scheme 26, entry b, as compared to Figure 1, **121**). Hydrolysis has been successfully performed on methyl aromatic esters bearing on the aromatic ring in the *ortho*-position aryl (Scheme 10, entry g; Figure 1, **125**, **126b**, **136**, **137**), alkoxy (Figure 1, **122**−**126b**), or nitroxyl groups (Figure 1, **127**).

In most of the cases, aromatic diesters are transformed to the corresponding diacids (Scheme 10, entry g; Figure 1, **135**−**138**), but in only a few cases can selective monohydrolysis be achieved (Scheme 39).

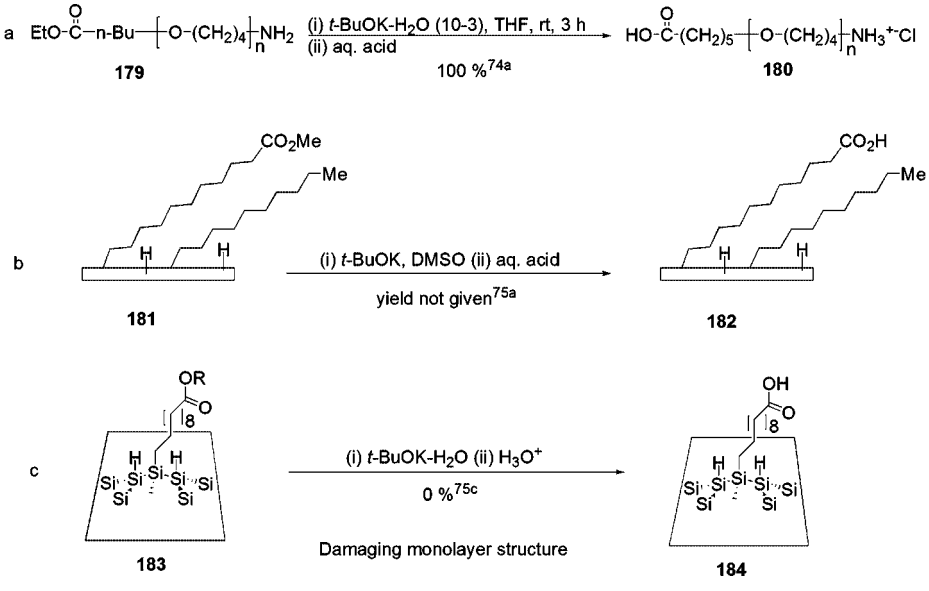
In some cases, other methods have been tried, which proved to be less efficient than "APH". This is the case, for example, of the methyl naphtoate **125**, which is so efficiently hydrolyzed[63e] on reaction with "APH" under sonication (Figure 1) and is inert to "WPH".[63e] This is also the case of the dimethyl diester **23** (Scheme 10, entry g as compared to entry f)[29] and the biphenyl dimethyl diester **136** (Figure 1),[65a] which do not react or provide extremely low yields of the corresponding acids using aqueous LiOH, NaOH, or KOH instead.[29,65a] Remarkable differences can be observed on **23**, which remains unchanged when reacted with aqueous hydroxide at 100 °C for 48 h[29] and is hydrolyzed efficiently to the corresponding dicarboxylic acid **24** in up to 84% yield at 80 °C using "APH" in DMSO (Scheme 10, entries f,g).[29]

The ester **129** (Figure 1) is apparently hydrolyzed with "APH", but the resulting carboxylate, whose structure can be viewed as a $\beta$-ketocarboxylate, decarboxylates easily.[64a] **129** behaves similarly toward sodium hydroxide.

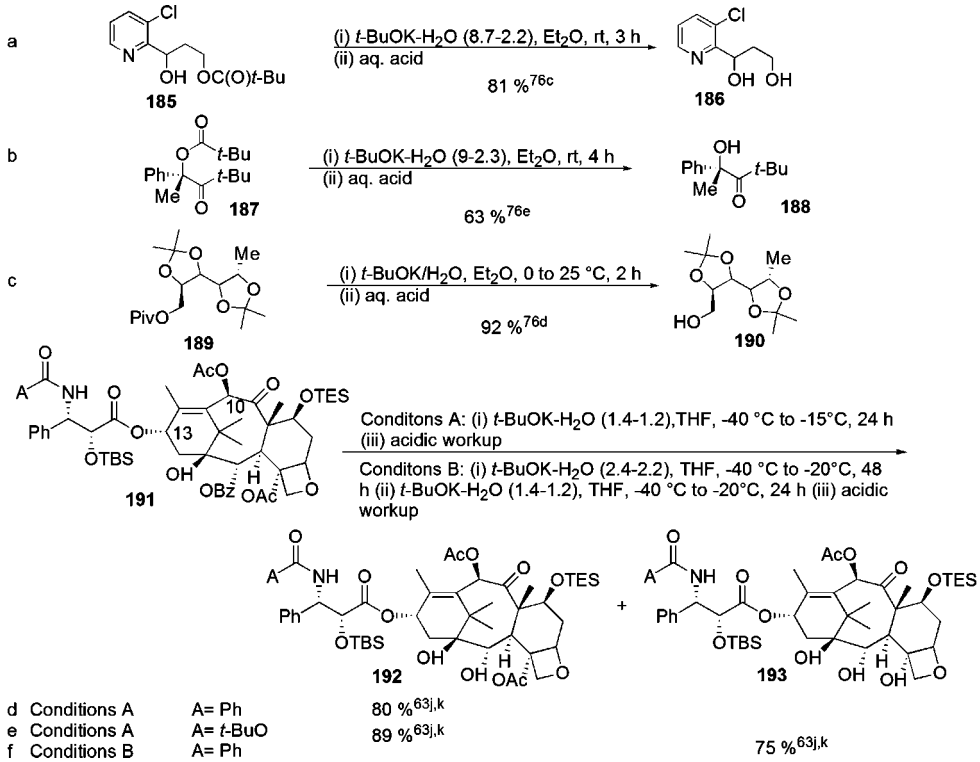
In few cases, other methods proved to be more efficient to perform the hydrolysis of esters. This is the case of the mono ester **130** (Figure 1)[64b] and the diester **139** (Figure 1),[68c] which cannot be hydrolyzed by "APH" but are efficiently transformed to the corresponding acids by a dealkylative process involving instead lithium *t*-butylthiolate[64b] or sodium phenylselenolate.[68c] In both cases, those reagents also effect the demethylation of methoxy group present on the aromatic or heteroaromatic cycles.[64b,68c]

**4.2.1.2. Reactivity of "Anhydrous Potassium Hydroxide" toward Aliphatic Carboxylic Esters.** Hydrolysis of

**Scheme 42**



**Scheme 43**




aliphatic esters proved to be extremely successful with "APH" especially with esters whose α carbon is fully substituted and whose carbonyl group is expected to be difficult to access by nucleophilic reagents.

For example, it has been reported that esters **20c** (Scheme 10), **140**, and **143**−**145** (Figure 2) are hydrolyzed far more better with "APH" than with lithium hydroxide (THF, **20c**,[28] **144**,[72c] no reaction), sodium hydroxide (1 M aq, ethanol, **140**,[72j] **144**,[72c] no reaction; 10% aqueous and **145**, degradation[72a]), or potassium hydroxide (50% aqueous, MeOH, **145**, 38%).[72a]

Carboxylic esters possessing hydrogens on the α-carbon such as **156**−**161** (Figure 2) have been successfully hydrolyzed with "APH", and interestingly the reaction occurs without concomitant epimerization when carried out on scalemic amino ester **159** and on the two epimeric methyl cyclohexane carboxylates **160a** and **160b**.[70c,72l] The ester **156** is transformed to the corresponding acid in modest yield,[70a] and although a nitrogen atom is present on the δ-carbone as on the related **119** (Scheme 36),[62] the formation of the lactame ring no longer takes place probably due to the presence of a protected amino group.[70a]

"APH" effects the hydrolysis of highly sterically crowded cyclopropane carboxylic esters **150**−**152** bearing alkyl-, alkenyl-, or hydroxyalkyl groups on the α-carbon, but (i) partial migration of the terminal C,C double bond of the allyl cyclopropyl carboxylate **151** concomitantly takes place to produce the related cyclopropane carboxylic acid possessing the more substituted and therefore the more stable α,β-disubstituted C,C double bond,[72e] (ii) retro-aldol reaction occurs concomitantly to hydrolysis on the β-hydroxy cyclopropane carboxylic ester **152**,[72e] and (iii) hydrolysis of related cyclopropane carboxylic esters **153**−**155**, bearing a nitro or a hydroxy group or an iodine atom in α-position, cannot be achieved under similar conditions.[72e]

"APH" efficiently transforms[72k] the β-hydroxy ester **146** (Figure 2) to the corresponding acid with no stereochemical lost at the carbon bearing the hydroxyl group. This suggests that, at least in this case, no competing retro-aldol reaction is taking place (compare to **152**).[72k] A retro-Claisen reaction, however, occurs with the ester **147**,[71e] and degradation has been reported for the ester **148**,[71f] which both possess a hydroxy group on β-carbon of the ester group (Figure 2).

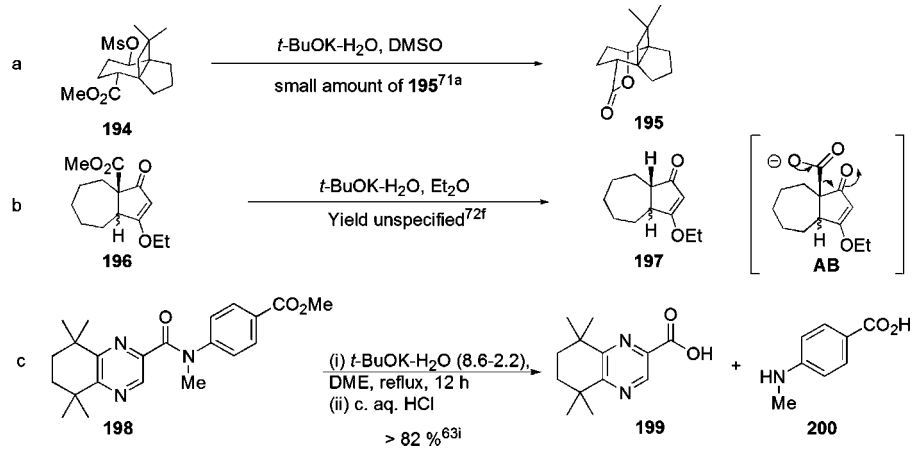
Hydrolysis of those esters **147** and **148** has been, however, successfully achieved using instead potassium carbonate in aqueous methanol at room temperature[71e] or sodium hydroxide (0.2 M, 5 °C, 2 h, 90% yield),[71f] respectively. It is not therefore always necessary to use the strongest reagent to achieve what can be done under smoother conditions.

It has been also reported that alternative reagents can achieve the transformation of esters to acids that cannot be achieved by "APH". Thus, transformation of **149**, which proved to be unsuccessful with "APH",[72i] lithium hydroxide,[72i] sodium phenylselenolate in THF−HMPA at reflux,[72i] and lithium iodide−sodium cyanide mixture in DMF at reflux,[72i] could be achieved in an impressive yield using instead lithium ethylthiolate in HMPA (100 °C, 2 h, 91% yield).[72i]

"APH" did not afford products resulting from hydrolysis of sterically crowded scalemic menthyl-naphtyl phenylacetate **162** (Figure 2),[71c] which resists acidic as well as alkaline hydrolysis including under phase-transfer catalysis or using lithium hydroxide in aqueous tetrahydrofurane.[71c] Even lithium aluminum hydride followed by oxidation produces the corresponding acid in low yield and as a racemate.[71c] Trimethylsilyl iodide did not afford the desired product.[71c] Transformation of **162** to the corresponding scalemic acid has been surprisingly successfully performed in good chemical and optical yield using trifluoromethanesulfonic acid-coated silica (neat, 125 °C, 0.2 h, 76% yield),[71c] but menthol cannot be recovered because it is believed to suffer dehydratation under those drastic conditions.[71c]

The case of methyl α-heterosubstituted acetate **163** whose oxygen atom is part of a carboxy group (Figure 2)[71d] is

**Scheme 44**




exceptional because transformation to the corresponding acid cannot be achieved either with "APH" or using conventional methods such as (i) lithium hydroxide (LiOH, $H_2O$−MeOH), (ii) 5-diazabicyclo[4.3.0]non-5-ene (DBN), a strong non-nucleophilic base (*o*-xylene, reflux),[71d] or (iii) reagents that usually produce carboxylate via deakylative processes such as lithium iodide and sodium cyanide (LiI, pyridine, or DMF, reflux; 90% NaCN, HMPA).[71d] Hydrolysis of the triester **170** whose α carbon is fully alkyl substituted and part of a cyclohexyl group also cannot be achieved using "APH" (Figure 3).[73f]

Finally, "APH" indistinctly hydrolyzes at the same rate the different ester groups present on compounds bearing two or triester groups such as the (i) diester **165** (Figure 2),[73a] which bears not only a particularly sterically hindered carbomethoxy group but also a *t*-butyl carboxylate moiety, (ii) dimenthyl ester **69**[31a,c] when the reaction is carried out at room temperature in DME leading to the diacid **70b** (Scheme 41, entry b),[31c] whereas it provides a 1/1 mixture of the monoacid-monoester **70a** and the diacid **70b** when the reaction is even performed under the same condition but in ether (Scheme 41, entry a as compared to entry b and to Scheme 20, entry b),[31c] (iii) the triesters **168**, **169**, which possess sterically hindered α-carbon (Figure 3),[73d,e] and we have to recall the hydrolysis of both ester groups of the malonate **99** (Scheme 31).[56]

Monohydrolysis of one of the ester groups of a polyester has been nevertheless achieved (i) regioselectively on the diesters **171** and **173** bearing two methyl- or ethyl- carboxyl groups on the 2- and 5-positions of symmetrical pyrolle derivatives (Scheme 39)[68a,b] and (ii) stereoselectively on the carboxy group of the di-*t*-butyl cyclopropanemalonates **175** and **177**, which is trans to the alkyl/alkenyl group present on the *β*-carbon of the cyclopropane ring (Scheme 40).[73b,c]

In a few cases, "APH" allows the hydrolysis of the ester group, but the resulting carboxylate reacts further as is the case of the esters **194**, **196**, and **198** (Scheme 44). Thus, hydrolysis using "APH" in DMSO of the quite hindered methyl carboxylate **194** bearing a mesyloxy group in the *δ*-position does not produce the corresponding carboxylic acid but instead a small amount of the lactone **195** resulting from the substitution of the mesyloxy group by the carboxylate intermediate (Scheme 44, entry a).[71a] The lactone **195** has been, however, obtained in better yield (65%) if lithium methylthiolate in HMPA is instead used.[71a] Deprotection of the methyl carboxylate **196** can be achieved, but the resulting carboxylate **AB** is unstable under the conditions used and decarboxylates to produce instead **197** (Scheme 44, entry b).[72f]

Reaction of the methyl benzoate **198** bearing in the *p*-position a nitrogen atom part of a *N*-methyl carboxamide delivers the pyrazine carboxylic acid **199** and *p*-*N*-methyl-amino-benzoic acid **200** resulting from the cleavage of both the ester C,O bond and the amide carbonyl C,N bond (Scheme 44, entry c).[63i] It is interesting to compare the reactivity of the methyl benzoate **198** to the related ester **128**, which possesses the same framework but misses the *N*-methyl group and leads instead to the corresponding carboxylic acid, leaving intact the amide group (compare **128**, Figure 1, to **198**, Scheme 44, entry c).[63i]

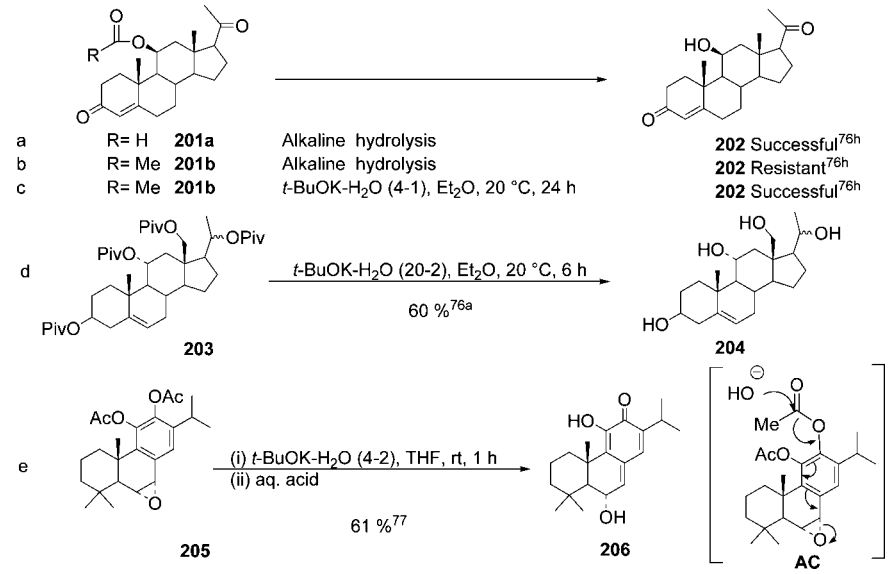
The difference of reactivity between **128** and **198** results from the propensity of tertiary amides to be cleaved by "APH", whereas it does not take place with secondary or primary amide, which are instead *N*-metalated (see section 4.2.2). This lowers the electrophilicity of such amide carbonyl groups, preventing their cleavage.[52]

**4.2.1.3. Deprotection of Carboxylic Esters Using "Anhydrous Potassium Hydroxide"** "APH" has been used to deprotect several esters, allowing isolation of the resulting alcohols and polyols in high yields (Schemes 43, 45).

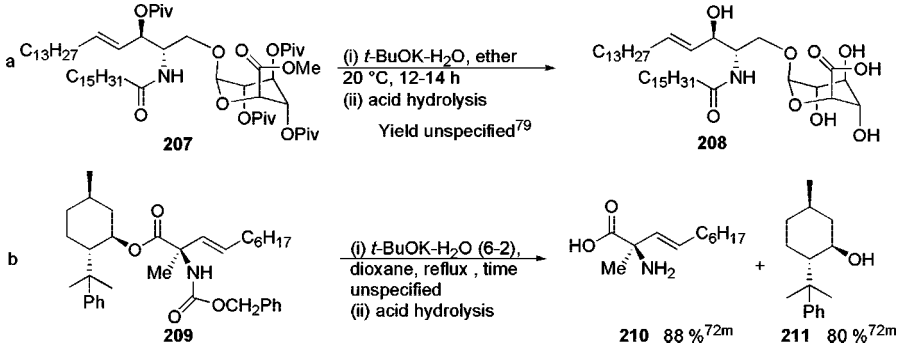
Transformation of **191** (Scheme 43, entries d−f) to **192** or **193** can be achieved by performing the reactions at quite a low temperature for quite a long time. The amount of "APH" used (1.2 or 4 equiv) and the reaction time dictate its outcome.[63j,k] It is interesting to note that (i) neither the benzamido- or the carbamato- functional group present on **191a** (A = Ph) or **191b** (A = *t*-BuO) nor the functionalized carboxy group attached at C-13 and the acetoxy group attached at C-10 are saponified by "APH", (ii) nor the ketone functional group whose carbonyl group lies at C-9 on **191** is affected by a Haller−Bauer reaction, which could have taken place (see section 4.2.7).[63j,k]

Otherwise, "APH" efficiently reacts on (i) the formyl,[76f] acetyl,[76f] and pivaloyl[76a] groups attached to the particularly hindered C-11 carbon of steroids **201a**, **201b**, and **203** to deliver the corresponding alcohols **202** and **204** (Scheme 45, entries a−e). In the case of the tetrakispivalate **203**,[76a] a large excess of "APH" (>20 equiv) is required to allow the deprotection of all of the ester groups present on the tetrakispivalate **203** (Scheme 45 entry d),[76a] but it has been reported that a complex mixture of compounds resulting from partial hydrolysis is observed if the reaction is carried out with a stoichiometric amount "APH".[76a]

**Scheme 45**




**Scheme 46**




Finally, "APH" as well as sodium hydroxide and sodium methylate are unable to hydrolyze the benzoate **131** (Figure 1).[76b]

"APH" efficiently reacts with the diacetoxy derivative **205** in THF at 0 °C and provides **206** by deprotection and concomitant oxirane ring-opening as disclosed in **AC** (Scheme 45, entry d).[77a,b] Subsequent reactions of the alkoxides generated from "APH" and $\beta$-acetoxy carboxamides[78] and related lactones[78] have also been reported (see for example Scheme 51). It is important to mention that **205** is particularly resistant to hydrolysis when reacted with potassium carbonate in THF, and potassium hydroxide in the presence of 18-crown-6 in benzene and reducing agent such as super hydride, DIBAL-H, and Selectride gives poor results.[77a,b]

"APH" in ether efficiently cleaves[79] the three pivaloyl groups and the methyl carboxylate present on the tri-*O*-pivaloyl $\beta$-glucoronic acid methyl ester of **207** and leads to **208**, which still possesses the *N*-acyl group (Scheme 46, entry a).[79] Performing the reaction of "APH" on menthyl ester **209**, bearing a *N*-protected α-amino group (as a carbamate) in the α position under harsher conditions (dioxane at reflux), allows not only the hydrolysis of the ester group but also of the carbamate moiety producing the $\beta,\gamma$-unsaturated amino acid **210** and menthol **211** in good yields (Scheme 46, entry b).[72m]

**4.2.1.4. Carboxylic Esters Basic Hydrolysis by "APH" in the Synthesis of Bioactive Compounds.** "APH" has been used in a key step of the synthesis of isocrotocaudin,[72h] (+)-anamarine,[76d] ningalin D (**24**, Scheme 10, entry g),[29] neurokinin antagonists ZM374979 (**121**, Figure 1),[63a] dichloroisoeverninic acid (**123**, Figure 1),[63c] phenanthrovirin Aglycon (**125**, Figure 1),[63e] fluorenone dengibsinin and azafluorenthene alkaloid imeluteine (**126**, Figure 1),[63f] pyrazinylcarboxamidobenzoates with retinoidal activity (**128**, **138**, Figure 1),[63i] C-6 substituted chitin derivatives (**132**, Figure 1),[66a] ellagitannin (see **137**, Figure 1),[65b] A,B,C rings of terreulactone A (**142**, Figure 2),[72g] fridamycin E (**146**, Figure 2),[72k] *rac*-monomorine I (**156**, Figure 2),[70a] demethoxy fumitremorgin C (**159**, Figure 2),[72l,p] chlorotricolide (top half, **160**, Figure 2),[70c] scalemic isishippuric acid B (**165**, Figure 2),[73a] peptide bases inhibitors of hepatitis C virus protease (**176**, **178**, Scheme 40),[73b,c] 4-substituted taxol analogues and Paclitaxel metabolites (**191**, Scheme 43),[63j,k] *rac*-taxodone (**206**, Scheme 45),[77a,b] ceramide-$\beta$-D-glucuronide (**208**, Scheme 46),[79] and quaternary (*E*)-vinylglycine (**210**, Scheme 46).[72m]

### *4.2.2. Reactivity of "Anhydrous Potassium Hydroxide" toward Carboxylic Amides*

Basic hydrolysis of carboxylic amides to carboxylic acids, especially those that possess a dialkyl amino group, is usually extremely difficult to achieve. That accounts for the poor electrophilicity of their carbonyl carbon, which disfavors the first step of the reaction leading to the tetrahedral intermediate **P** (Scheme 28, A = $NR'_2$, step **O** to **P**) and the lower propensity of the amido group to be expelled as compared to the hydroxide anion from **P**. Therefore, carboxylic amides are far more difficult to hydrolyze than are the corresponding esters.

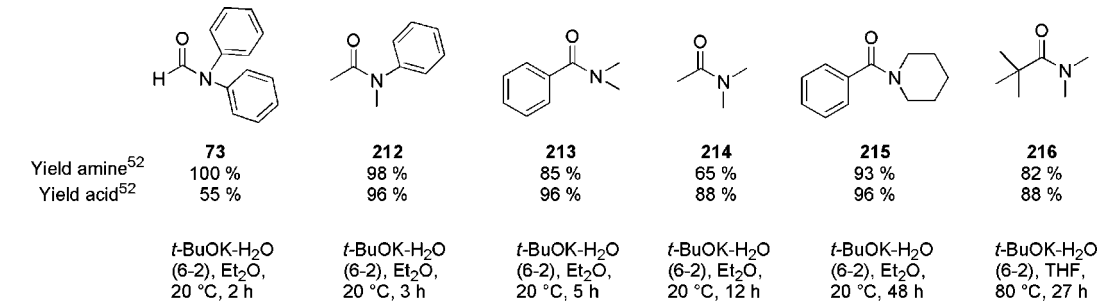



**Figure 4.** Transformation of tertiary carboxylic amides to carboxylic acids and secondary amines using "APH".

It has been reported, however, by Gassman[52] that "APH" efficiently hydrolyzes tertiary amides under mild conditions (Figure 4), whereas primary and secondary amides remain untouched even under forcing conditions.[52]

The reactions are usually carried out at room temperature in ether (Figure 4, **73**, **212**−**216**) and only in the case of the hindered *N*,*N*-dimethyl pivaloyl amide **216**, which requires heating to reflux of THF to achieve the hydrolysis (Figure 4, **216**). Furthermore, the results disclosed in Figure 4 show the relative reactivity of a series of aliphatic and aromatic tertiary amides possessing a *N*-alkyl or *N*-aryl group attached to their carbonyl group.

The success of this transformation has been related to the capacity of "APH" to produce the putative dianion "tetrahedral intermediate" **Q** (A = $NR'_2$), generated from the alcoholate **P** (A = $NR'_2$) by potassium *t*-butoxide still present in excess in the medium beside the anhydrous potassium hydroxide (Scheme 28).[52]

The fact that this reaction cannot be achieved on primary and secondary carboxylic amides supports the previous hypothesis because in those cases the *N*-metalation competes and leads to an even worse *N*-leaving group.

Reaction of "APH" with carboxamide produces, after hydrolysis, amines and potassium carboxylates, which can be in turn transformed to the corresponding carboxylic acids.[52] Except in rare cases, however,[52] the results concerning only one of the two products generated (the acid,[80] Figure 5, or the amine,[81] Figure 6) have been reported due to the context. In the former case, the amino group can be viewed as the protecting group of the acid, whereas in the second one the acyl group plays the role of a protecting group of the amine.

This method offers an attractive counterpart to the procedure of White for cleavage of secondary amides in the presence of the tertiary ones.[82]

The ideal case involves the benzolactames **243**, which on reaction with "APH" produce **244** that bears a carboxyl group and an amino group part of an indole ring (Scheme 47),[83] whereas the same transformation cannot been achieved if instead carried out with sodium hydroxide in aqueous methanol.[83]

The reactivity of various amides toward "APH" is disclosed in Figure 4.[52] As expected, *N*,*N*-diphenyl formamide **73** is the more reactive (20 °C, 2 h) of the series disclosed in Figure 4. This is due to the accessibility of its carbonyl group and the good leaving group ability of the diphenylamino moiety.[52] *N*,*N*-Dimethyl pivaloylamide **216**, which possesses the bulky *tert*-butyl group on its carbonyl group and the relative strongly basic *N*,*N*-dimethylamino moiety, is the least reactive and requires heating at reflux of THF to reach similar results (80 °C, 27 h).[52]

The results disclosed in Scheme 48 allow comparisons between "APH" and other more conventional reagents toward the particularly hindered amides **245** possessing the good indolyl leaving group (Scheme 48).[84] This transformation applied to **245a** is achieved in less than 0.1 h using "APH" (Scheme 48, entry a), whereas it requires up to 30 h using instead aqueous sodium hydroxide in ethanol (Scheme 48, entry d).[84] "APH" even allows hydrolysis of related derivatives **245b** and **245c** whose carbonyl group is hindered by the presence of a phenylthio group or a bromine atom on the benzene ring (Scheme 48, entries e,f).[84]

"APH" successfully hydrolyzes amides, especially those (i) whose α-carbonyl carbon is part of an aromatic ring such as **213**, **215** (Figure 4), **220**, **228**, **229** (Figure 5), **235**−**238**, **242** (Figure 6), **243** (Scheme 47), and (ii) aliphatic amides **107** (Scheme 32, entry c), **117** (Scheme 35), **73**, **212**, **214**, **215** (Figure 4), **217**−**226** (Figure 5), **230**−**234**, **239**−**241** (Figure 6), **245** (Scheme 48), including α,*β*-unsaturated amides **218** whose *E*-isomers have been transformed stereoselectively to the corresponding *E*-α,*β*-unsaturated carboxylic acids (Figure 5).

Those belong to the *N*,*N*-dialkyl family **213**−**216** (Figure 4), **217**, **218**, **220**, **225**−**229** (Figure 5), **236**−**241** (Figure 6); *N*-alkyl, *N*-aromatic family **212** (Figure 4), **242** (Figure 6); *N*,*N*-diaromatic family **73** (Figure 4), **230**−**234** (Figure 6); indol derivatives **107** (Scheme 32, entry c), **113**[58] (Scheme 34), **219** (Figure 5), **235** (Figure 6), **243** (Scheme 47), **245** (Scheme 48); and Weinreb amide bearing a nitrogen atom substituted by an alkyl and an alkoxy group such as **109**[60] (Scheme 33), **221**, and **222** (Figure 5).[80e−i] This reaction is particularly efficient, but in the case of cyclopropaneamide **109**,[60] in which the amide group is cis to an adjacent phenyl group, epimerization takes place producing exclusively the *trans*-cyclopropane carboxylic acid **110** (Scheme 34, see section 4.1.1).

Several carboxylic amides whose structures have been disclosed above have been successfully transformed to carboxylic acids.[58,80a−d,81a−m,83−85] This is particularly the case for *N*,*N*-diaryl acetamide **230** (Figure 6), which bears, on each of its two phenyl groups, a *o*-methoxy group that hinders its carbonyl group and a long alkyl chain on the *meta*-position, which increases its hydrophobicity. Its hydrolysis to the corresponding anisidine occurs quantitatively with "APH"[81a] but fails using potassium hydroxide even under very rude conditions.[81a]

This is also the case of related *N*-acyl dibenz[*b*,*f*]-azepines[81b−d] **231**−**233**, which proved difficult to hydrolyze by conventional methods such as refluxing 6 N aqueous

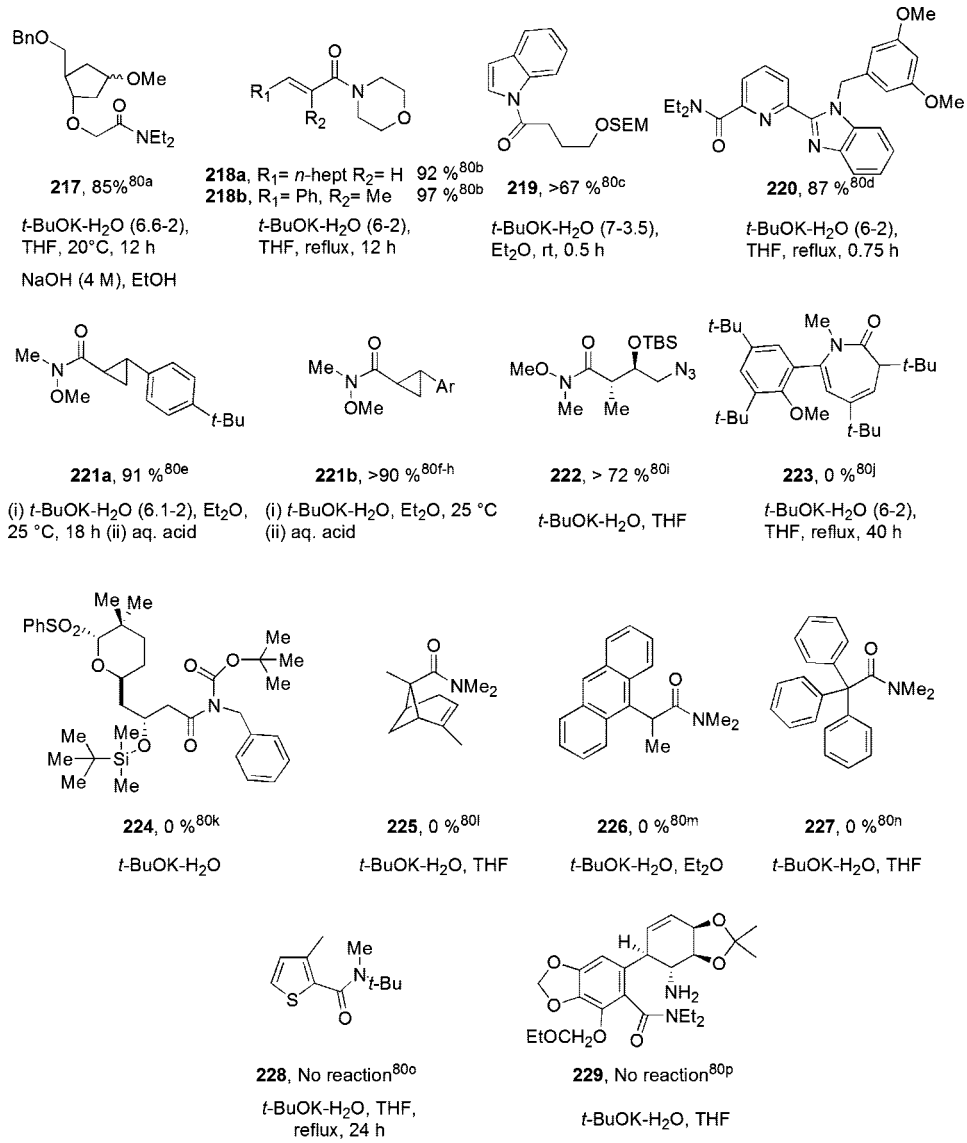



**Figure 5.** "APH" monitored transformation of carboxylic amides to the corresponding carboxylic acids.

hydrochloric acid,[81b] but which have been easily *N*-deacetylated using instead "APH".[81b−d] The yields are excellent from **231a** and **232** but poorer with **231b**.[81b−d] In the case of **233**, partial retro Diels-Alder reaction occurs competitively, producing the tribenz[*b*,*f*]-azepine in modest yield when carried out at 80 °C in THF and in much better yield if performed at reflux of DME instead (Figure 6).[81b] Tribenz[*b*,*f*]-azepine compound has been also obtained on reaction of **231a** with "APH" at reflux of THF.

"APH" allows the removal of the *N*-benzoyl protection of a large variety of polyaza macrocycles such as **236**[81g−i] and **237**[81j] (Figure 6). It has been used on many occasions to hydrolyze indolyl amides, taking advantage of the good leaving group aptitude of the indolyl moiety, which favors amides hydrolysis (**107**, Scheme 32, entry c; **117**, Scheme 35, entry b), and has been used as the key step in the synthesis[81f,83,84,87] of several indole alkaloids (**243**,[83] Scheme 47; **245**,[84] Scheme 48, entry a; **249**,[87] Scheme 49, entry b; **235**,[81f] Figure 6).

Although in all of the cases, successful transformation of the amides to the acids has been achieved, in some cases it has been reported that competing (i) epimerization reaction (**107**, **109** Scheme 33), (ii) elimination reaction (**113**, Scheme 34, entry b, **249**[87] Scheme 49, entry b), or even (iii) oxidation reaction, whose origin is still unclear, leads to **254** from **253**[85] (Scheme 49, entry d).

The reaction of the poly functionalized *N*-benzoyl derivative **251** under Gassman conditions provides a low yield of **252**,[88] whereas it proved successful using a related reagent implying a mixture of *t*-BuOK and sodium hydroxide in THF−DMSO.[88b] An alternative procedure using triethyloxonium salt proved also successful.[88a]

Selective debenzoylation takes place at the dihydroxyindolylbenzoyl position of **253**, leading to **254** regioselectively and in good yield leaving untouched the *N*-benzoyl dihydropiperidine moiety also present in **253**.[85]

"APH" has been successfully used for the hydrolysis of imidazol-5-*N*-methyl carboxamides **238** (Figure 6)[81k] and **247** (Scheme 49, entry a).[86]

In the first case, hydrolysis leaves unaffected the cyano groups also present on **238b**, **238c** (compare to Scheme 26, entry b),[46] whereas epimerization has been reported concomitantly to the deprotection of each of the two diastereoisomeric camphanic amides **247a** and **247b**, which leads to the racemate **248**. This epimerization could have taken place before the deprotection (Scheme 49, entry a).

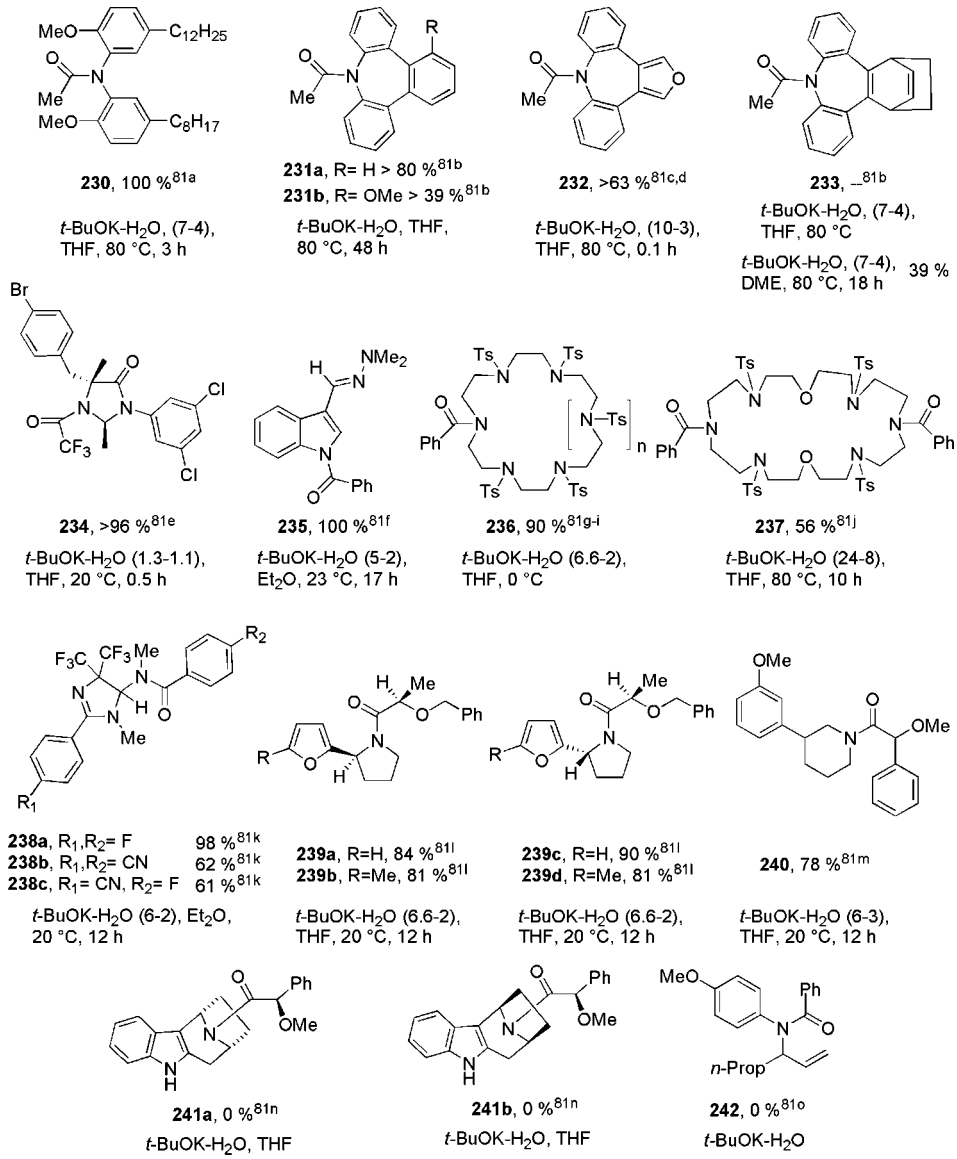
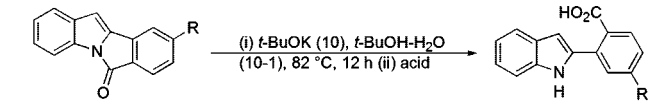


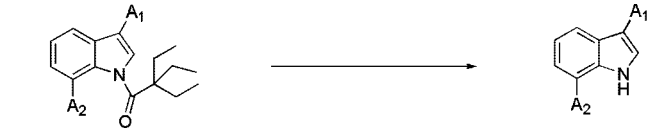

**Figure 6.** "APH" monitored transformation of carboxylic amides to the corresponding secondary amides.

**Scheme 47**




| | | |
|---|---|---|
| a | **243a** R= H | **244a** 75 %[83] |
| b | **243b** R= Me | **244b** 74 %[83] |
| c | **243c** R= Cl | **244c** 70 %[83] |

**Scheme 48**



| | | | |
|---|---|---|---|
| a | **245a** $A_1$, $A_2$= H | *t*-BuOK-$H_2O$ (9-2), THF, 0.1 h | **246a** 84% |
| b | **245a** $A_1$, $A_2$= H | $K_2CO_3$, MeOH, 24 h | **246a** 97% |
| c | **245a** $A_1$, $A_2$= H | NaOEt, EtOH, 24 h | **246a** 87% |
| d | **245a** $A_1$, $A_2$= H | aq. NaOH, EtOH, 30 h | **246a** 90% |
| e | **245b** $A_1$= Me $A_2$= SPh | *t*-BuOK-$H_2O$ (9-2), THF, 0.5 h | **246b** 96% |
| f | **245c** $A_1$= Me $A_2$= Br | *t*-BuOK-$H_2O$ (9-2), THF, 2 h | **246c** 85% |

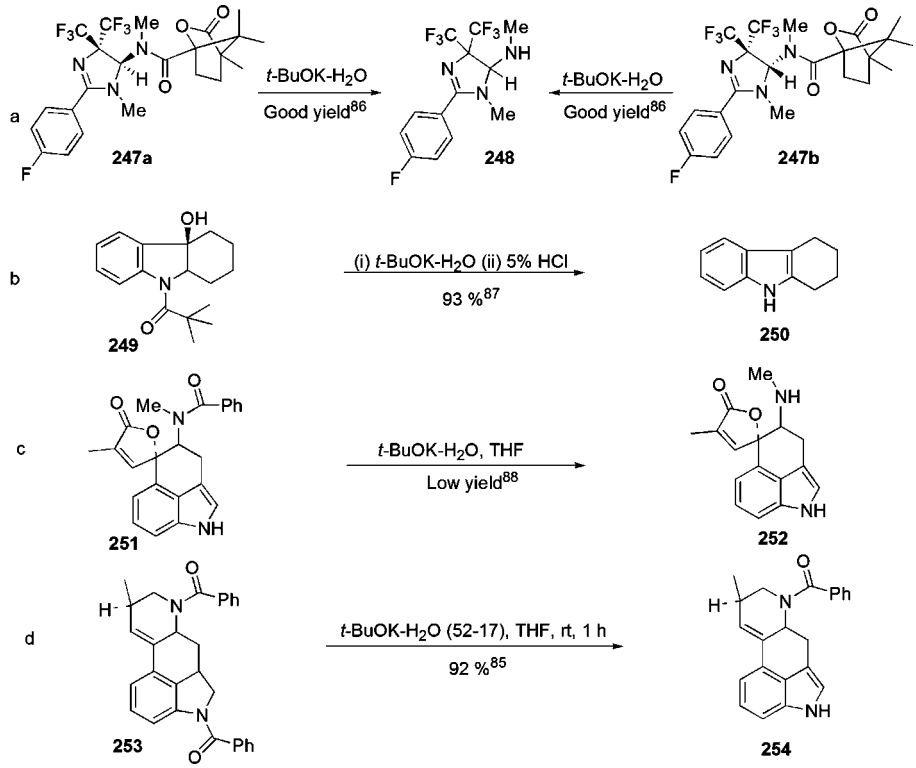
The "APH" method has been used as (i) the last step of a tandem metalation-*N*-alkylation-saponification of *N*-aryl secondary benzamides **255** producing a tertiary benzamides **256**, leading finally to the *N*-aryl (a) -*N*-methyl amines **257a**, **257b**, and **257c**, and (b) -*N*-allyl amines **257d** and **257e** (Scheme 50).[89] This method formally allows the selective mono *N*-methylation or *N*-allylation of anilines (Scheme 50).[89]

It has also been used as (ii) one of the key steps of the resolution of racemic amines.[81l–n,86] However, although successful for the chiral 2-benzyloxy-propioamide **239** series (Figure 6),[81l] "APH" is unable to remove the *O*-methylmandeloyl group from the amides **241** (Figure 6),[81n] and epimerization was observed from **247** (Scheme 49, entry a).[86]

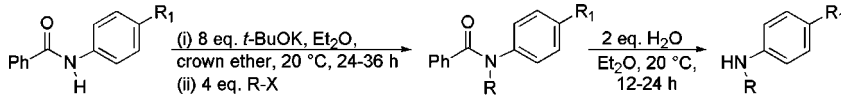
Hydrolysis of the related scalemic amide **240** has been successfully achieved after resolution of the racemate (Figure 6),[81m] but epimerization occurs on the *O*-methylmandelic acid concomitantly produced after acidic workup.[81m]

It has been surprisingly reported that this reaction does not follow the usual steps disclosed in Scheme 28 (A = $NR'_2$).[52] It produces mainly the *N*-formyl intermediate, which then collapses to the amine with complete stereocontrol.[81m] Isolation of the *N*-formyl derivative (3-(3-methoxyphenyl)-piperidine-1-carbaldehyde), as intermediate, suggests that "APH" cleaves first the carbonyl benzylic carbon bond of **240**.[81m]

**Scheme 49**

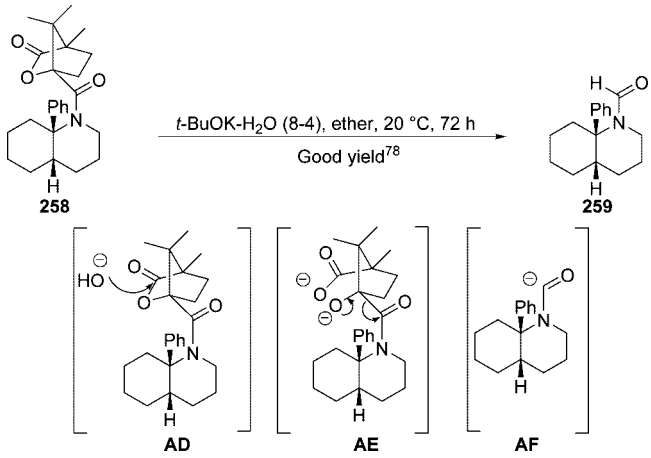



**Scheme 50**




| | $R_1$ | RX | R | | | | |
|---|---|---|---|---|---|---|---|
| **255a** | H | MeI | Me | **256a** | 96 % | **257a** | 87 % |
| **255b** | Cl | MeI | Me | **256b** | 90 % | **257b** | 83 % |
| **255c** | OMe | MeI | Me | **256c** | 91 % | **257c** | 90 % |
| **255b** | Cl | $CH_2$=$CHCH_2Br$ | $CH_2$=$CHCH_2$ | **256d** | 86 % | **257d** | 86 % |
| **255c** | OMe | $CH_2$=$CHCH_2Br$ | $CH_2$=$CHCH_2$ | **256e** | 89 % | **257e** | 85 % |

**Scheme 51**

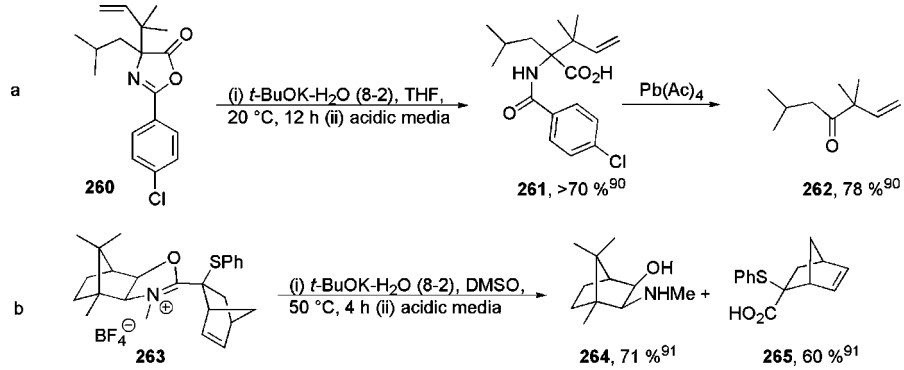



A related process could take place from the camphanic carbamide **258**, which produces[78] on reaction with "APH" the formamide **259** and the related deuteroformyl derivative on reaction with *t*-BuOK−$D_2O$ in ether (Scheme 51).

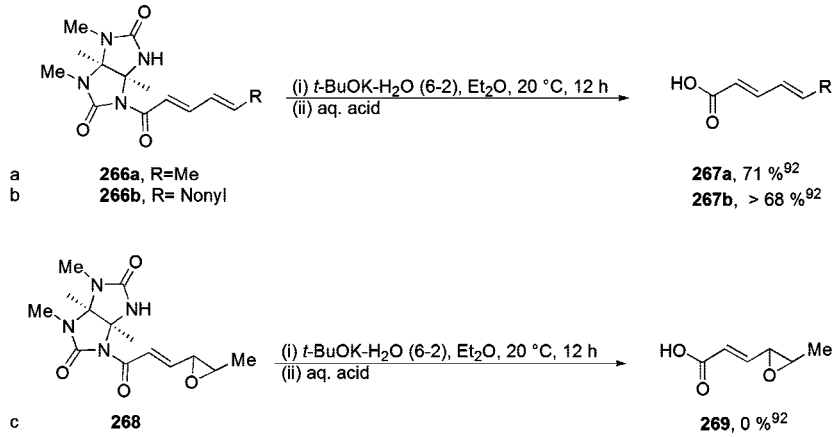
It has been suggested[78] that the naked hydroxide ion reacts at the lactone carbonyl group rather than on the hindered amide carbonyl group (intermediate **AD**). The resulting alkoxide anion released in this process (intermediate **AE**) initiates C,C bond cleavage to generate the carbamoyl anion **AF**, which is subsequently protonated to produce **259** (Scheme 51).

As was already pointed out above, some carboxamides are not cleaved by "APH".[80j−p,81n,o,88] This is the case of the amides **224**,[80k] **225**,[80l] **226**,[80m] **227**,[80n] **228**,[80o] **229**[80p] (Figure 5), **241**[81n] and its diastereoisomer,[81n] **242**[81o] (Figure 6), and the dienyl lactame **223**[80j] (Figure 5). This is probably due to the presence of (i) the complex structure of **224**,[80k] which possesses a *t*-BOC group on the nitrogen atom of the amide group; reaction with "APH" leads to decomposition of the substrate, whereas efficient hydrolysis leading to the corresponding carboxylic acid has been achieved using instead milder reagents such as lithium hydroxide (25 °C, 14 h, 70%)[80k] or $LiO_2H$ (25 °C, 12 h, 94%);[80k] (ii) the severe steric environment of the amide carbonyl carbon in *N*,*N*-dimethyl carboxamide **225**[80l] possessing a neopentyl center with one face completely shielded by the three-carbon bridge of the bicyclic skeleton expected to preclude formation of the tetrahedral intermediate **P** (Scheme 28) necessary for hydrolysis;[52] (iii) the large 9-anthranyl moiety on the α-carbon of *N*,*N*-dimethyl propanamide **226**;[80m] (iv) the three phenyl groups on the α carbon of the *N*,*N*-dimethyl triphenylacetamide **227**;[80n] (v) *ortho*-methyl group on the furan ring as well as the *N*-methyl and the large *N*-*t*-butyl group on the

**Scheme 52**




**Scheme 53**




furylamine of **228**;[80o] (vi) large groups in both *ortho*-positions of the *N*,*N*-diethyl benzamide **229**;[80p] (vii) *O*-methylmandeloyl amides derived from bridged carbolines **241a** and **241b**;[81n] and (viii) large *N*-aryl and *N*-3-hex-1-enyl groups on the benzamide **242**.[81o]

Other methods known to break the amide linkage proved unsuccessful in many of those cases, as follows:

(i) **226** is not hydrolyzed with concentrated solutions of sodium hydroxide in ethanol, refluxing hydrochloric-, perchloric-, methanesulfonic-, or glacial propionic acid.[80m] Related propionamide bearing instead 9-phenanthranyl or 2-anthranyl moieties has been successfully hydrolyzed using aqueous hydrochloric acid (reflux, 18 h)[80m] or an aqueous methanolic solution of potassium hydroxide (reflux, 36 h),[80m] respectively, and even those conditions proved to be efficient for the hydrolysis of *N*,*N*-dimethylacetamide bearing 9-anthranyl moiety.[80m]

(ii) **227** is unreactive toward trifluoroacetic acid−water (9:1), lithium aluminum hydride in THF, reflux 18 h, 6 M methyllithium, lithium, or sodium in liquid ammonia in the presence of ammonium acetate.[80n]

(iii) **228** is resistant to 40% potassium hydroxide in aqueous methanol (1:1), reflux, 12 h, as well as "APH", THF, reflux 24 h, and degradation occurs on further heating.[80o]

(iv) **229** does not react with lithium aluminum hydride, DIBAL-H/*t*-butyllithium, sodium bis(methoxyethoxy)-aluminum hydride, and lithium triethylborohydride.[80p]

(v) **241a** and **241b** are not cleaved by superhydride. However, **241a** could be cleaved by methyllithium in THF at 0 °C to produce the related bridged carboline, but the same reagent is unable to cleave its diastereoisomer **241b**.[81n]

(vi) **242** is not hydrolyzed with sodium ethylate, potassium hydroxide in methanol, hydrochloric acid, or hydrobromic acid in acetic acid and does not react with DIBAL-H.[81o]

### *4.2.3. Reactivity of "Anhydrous Potassium Hydroxide" toward Oxazolin-5-one and Oxazoliniums*

"APH" proved suitable for hydrolysis of sterically hindered thermolabile oxazolinone **260**, which produces after acid hydrolysis *N*-acyl protected α-amino acid **261** (Scheme 52, entry a).[90] Reaction of the latter with lead tetra-acetate effects the oxidative decarboxylation, leading to the ketone **262** (Scheme 52, entry a).[90]

*N*-Methyl oxazolinium salt **263**, derived from an asymmetric Diels−Alder reaction, also reacts with "APH" and leads to the β-amino alcohol **264** as well as the carboxylic acid **265** after acid hydrolysis (Scheme 52, entry b).[91]

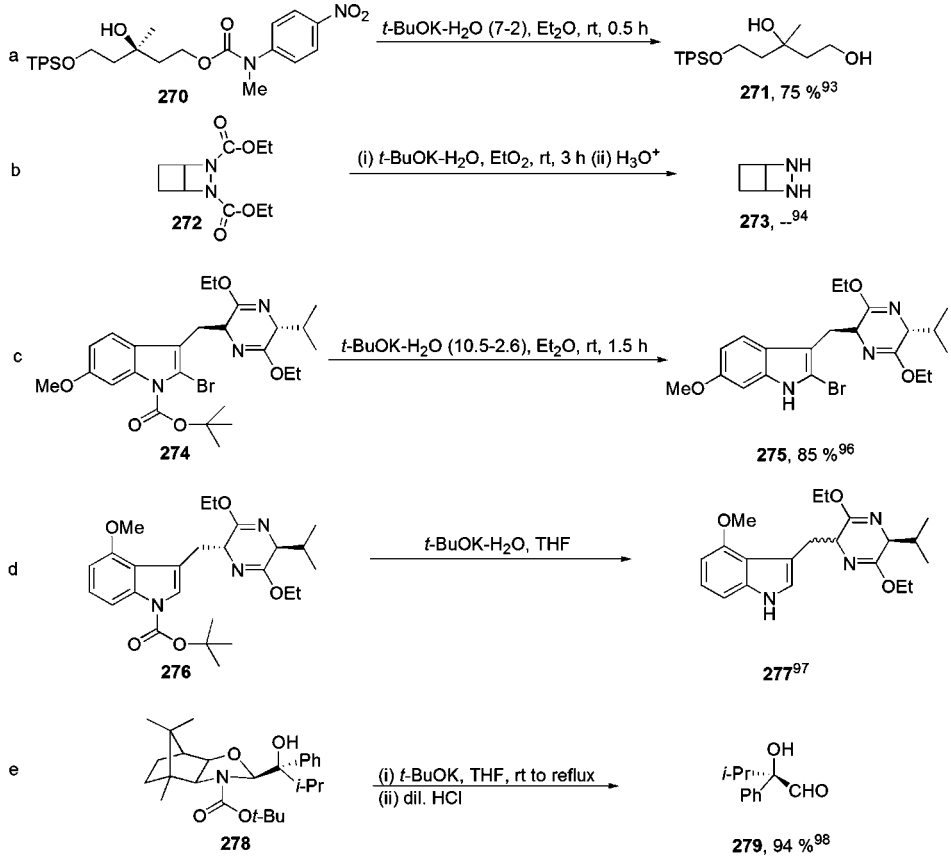
### *4.2.4. Reactivity of "Anhydrous Potassium Hydroxide" toward Imides*

"APH" efficiently and regioselectively hydrolyzes the amide function part of the acyl-glucoril moiety of **266** to produce the dienyl acids **267** (Scheme 53, entries a,b),[92] but however fails to generate the carboxylic acid **269** from the related acyl-glucoril compound **268** bearing a vinyl epoxy instead of the dienyl moiety (Scheme 53, entry c).[92] Lithium hydroxide, lithium methoxide, or lithium benzyloxide all also fail to produce **269** from **268**.[92]

### *4.2.5. Reactivity of "Anhydrous Potassium Hydroxide" toward Carbamates*

Hydrolysis of the carbamate **270** (Scheme 54, entry a) to the corresponding alcohol **271**, precursor of the mevalonolactone, has been achieved using "APH" in ether in less than 1 h at room temperature.[93] Similarly hydrolysis of the biscarbamate **272** has been performed by "APH" in a little more

**Scheme 54**




time (3 h, Scheme 54, entry b) and provides the strained hydrazine **273** precursor of the corresponding diazene.[94] Attempts to perform hydrolysis using potassium hydroxide in ethylene glycol at high temperature[95] were unsuccessful, resulting in complete destruction of the compound, and acid-catalyzed hydrolysis is similarly unproductive.[94]

"APH" has been used to remove the Boc protecting group of the *N*-Boc indolo derivatives **274** and **276** bearing a bislactims group and leads to indol alkaloids **275**[96] and **277**[97] (Scheme 54, entries c,d). The reaction proceeds with complete control of the stereochemistry with the 2-bromo derivative **274**,[96] but epimerization takes place to an extent of 20% with the unsubstituted analogue **276** (Scheme 54, entry d).[97] Other alternative methods for removal of the Boc group such as TMSOTf/lutidine and silicagel mediated reaction also produce **277** as a mixture of diastereoisomers.[97]

"APH" also remove the Boc group of the *N*-Boc protected scalemic 1,3-oxazolidine **278** producing scalemic hydroxy-aldehyde **279** in almost quantitative yield after acid hydrolysis (Scheme 54, entry e).[98] Attempts to cleave the Boc group by acid treatment under various conditions have been unsuccessful due to extensive decomposition.[98]

"APH" has been used for hydrolysis of the five-membered oxazolidinones **280**[99] and **283**[100] (Scheme 55, entries a−d) and the six-membered 1,3-oxazine **287**[101] (Scheme 55, entry i), which produce the corresponding 2-amino- **281**, **284**, and the 3-amino- **288** alcohols, respectively.

Several *N*-benzyloxazolidinones whose structures are related to **280** have been hydrolyzed successfully except **280b**, which affords with "APH" as well as under a variety of acidic and basic conditions the cinnamic acid derivative **282** by elimination reaction (Scheme 55, entry b).[99]

It has been also reported that epimerization takes place at the thioaminal carbon of the thiazoline ring during the hydrolysis of oxazolidinones **283**, which are fused to a thiazoline ring (Scheme 55, entries c,d).[100] "APH" is, however, unable to hydrolyze **285a** (Scheme 55, entry g).[103] This is also the case of cesium carbonate[102] or 3 M ethanolic sodium hydroxide at reflux (Scheme 55, entries e,f).[102] Ethanolic sodium hydroxide, however, efficiently reacts on the related oxazolidinone **285b** to produce the aminoalcohol **285b** in reasonably good yield (Scheme 55, entry h).[103]

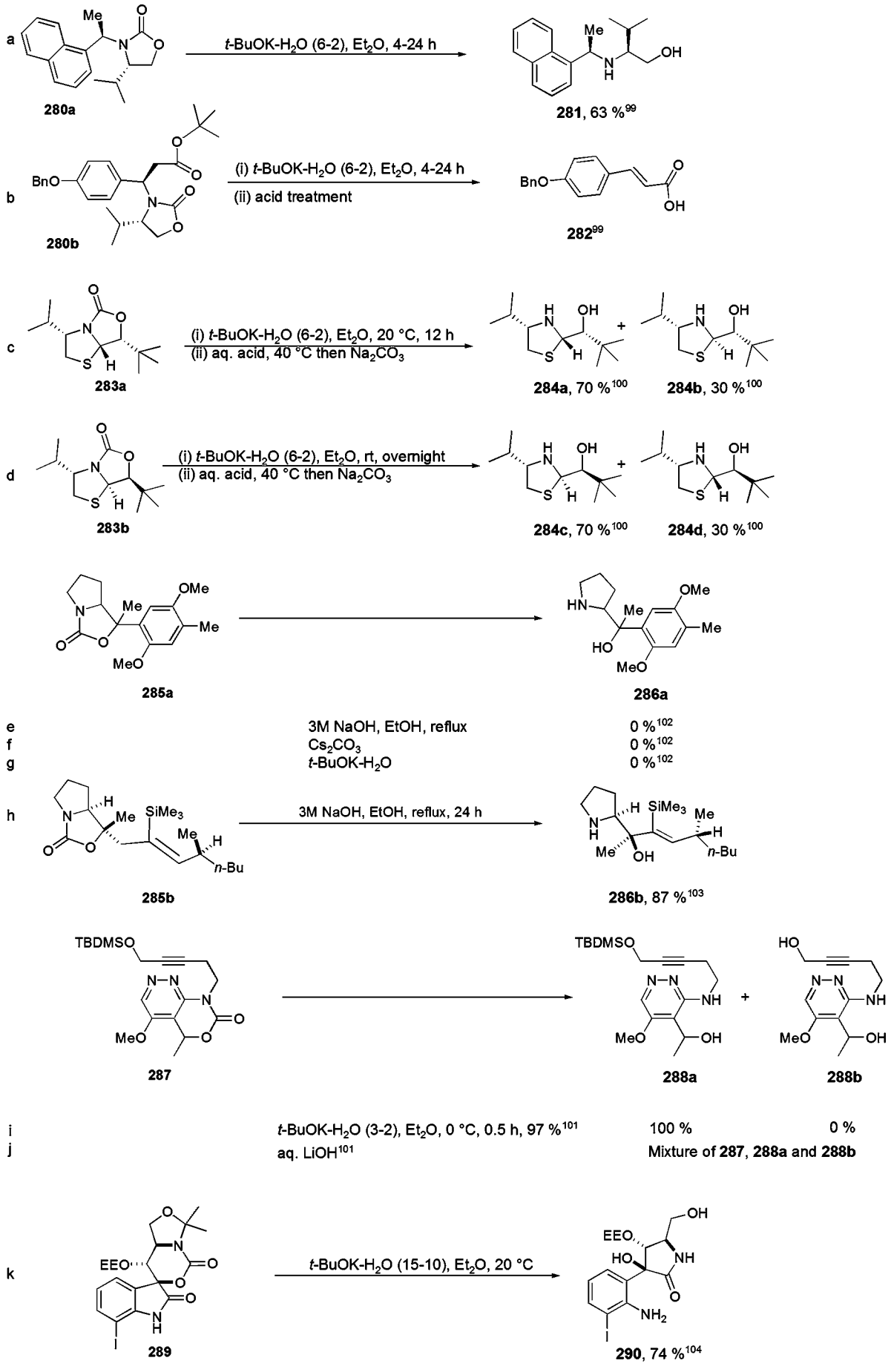
The reaction of **287** with "APH" affords **288a** in high yield (Scheme 55, entry i), whereas lithium hydroxide, if instead used, produces a mixture of **288a** as well as the *O*-desilylated derivative **288b** (Scheme 55, entry i).[101]

Finally, the highly functionalized compound **289**, which proved to be extremely resistant under a variety of conditions,[104] has been successfully hydrolyzed using "APH" and produces, whether an acidic treatment is performed or not, the hydroxy-oxazolidone **290** in which the carbamate and the acetonide have been both hydrolyzed (Scheme 55, entry k).[104] A reaction mechanism has been postulated to rationalize this unusual tandem reaction.[104]

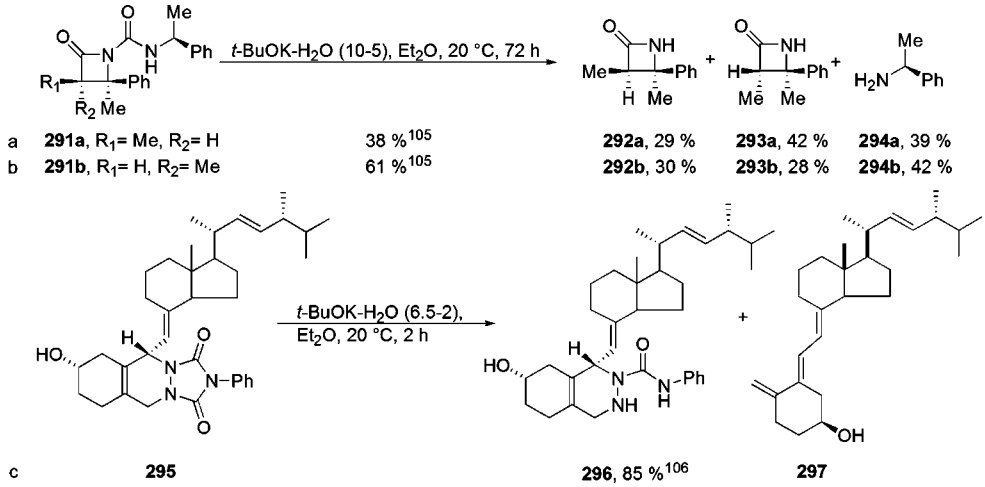
### *4.2.6. Reactivity of "Anhydrous Potassium Hydroxide" toward Ureas*

"APH" has been also used to hydrolyze ureas **291** and **295**, which possess an *N*-acetylated nitrogen atom, and therefore an imide functional group. The former reaction proceeds regioselectively, but epimerization takes place to produce a stereoisomeric mixture of the azetidinones **292** and **293** without competing decomposition of the strained azetidinone functional group[105] (Scheme 56, entries a,b).

**Scheme 55**


a
t-BuOK-H2O (6-2), Et2O, 4-24 h
280a
281, 63 %99
b
(i) t-BuOK-H2O (6-2), Et2O, 4-24 h
(ii) acid treatment
280b
28299
c
(i) t-BuOK-H2O (6-2), Et2O, 20 °C, 12 h
(ii) aq. acid, 40 °C then Na2CO3
283a
284a, 70 %100
284b, 30 %100
d
(i) t-BuOK-H2O (6-2), Et2O, rt, overnight
(ii) aq. acid, 40 °C then Na2CO3
283b
284c, 70 %100
284d, 30 %100
285a
286a
e
3M NaOH, EtOH, reflux
0 %102
f
Cs2CO3
0 %102
g
t-BuOK-H2O
0 %102
h
3M NaOH, EtOH, reflux, 24 h
285b
286b, 87 %103
287
288a
288b
i
t-BuOK-H2O (3-2), Et2O, 0 °C, 0.5 h, 97 %101
100 %
0 %
j
aq. LiOH101
Mixture of 287, 288a and 288b
k
t-BuOK-H2O (15-10), Et2O, 20 °C
289
290, 74 %104

**Scheme 56**




Reaction of "APH" with **295** generates the *N*-carbamoyl hydrazine **296** in extremely good yield, suggesting that it generates a charged intermediate that would be resistant to further nucleophilic attack (Scheme 56, entry c).[106]

Reaction of **295** with sodium hydroxide in refluxing methanol, potassium hydroxide in refluxing butanol, aqueous ethylene glycol, or refluxing toluene in the presence of dibenzo-18-crown-6 leads to the same *N*-carbamoyl hydrazine **296** along with 5,6-*trans*-vitamin $D_2$ **297** (15%).

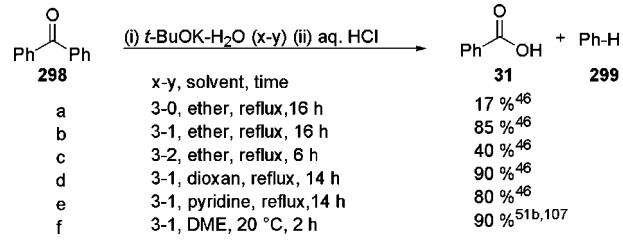
### *4.2.7. Reactivity of "Anhydrous Potassium Hydroxide" toward Ketones*

"APH" efficiently cleaves, under mild conditions, the carbonyl,α-carbon carbon bond of ketones in a reaction related to (i) the Haller−Bauer reaction ["APH" mediated Haller−Bauer reaction (APH-HB reaction)], which normally uses sodium amide instead, and (ii) the haloform reaction, which involves the reaction of a hydroxide ion with trihalomethyl ketones.

**4.2.7.1. Reagents and Conditions for Carbonyl-α Carbon C,C Bond Fission of Ketones.** The "APH-HB" reaction has been first reported by Swan[46] who described that wet potassium *t*-butoxide (*t*-butoxide−water 6:1), in various non hydroxylic solvents such as benzene, diethyl ether, dioxane, and pyridine, has the exceptional property to produce under mild conditions, much milder than the alkaline fusion reported[33] earlier (Scheme 12), benzoic acid **31** from benzophenone **298** after acidic workup (Scheme 57 as compared to Scheme 12). Isolation of a small amount of triphenylcarbinol (9%) suggests that phenyl potassium, which is produced as intermediate, reacts on the benzophenone reactant **298**.[46,107]

It has been also reported[46,51] that the best results are obtained when at least 3 molar equiv of potassium *t*-butoxide are used as compared to the ketone so the recommended ratio of reactant is ketone/potassium *t*-butoxide/water: 1/10/3. The reactions have been also carried out successfully with different ratios of "APH" and even in some cases without water added, but it has been stressed that water could have been introduced inadvertently.

**Scheme 57**



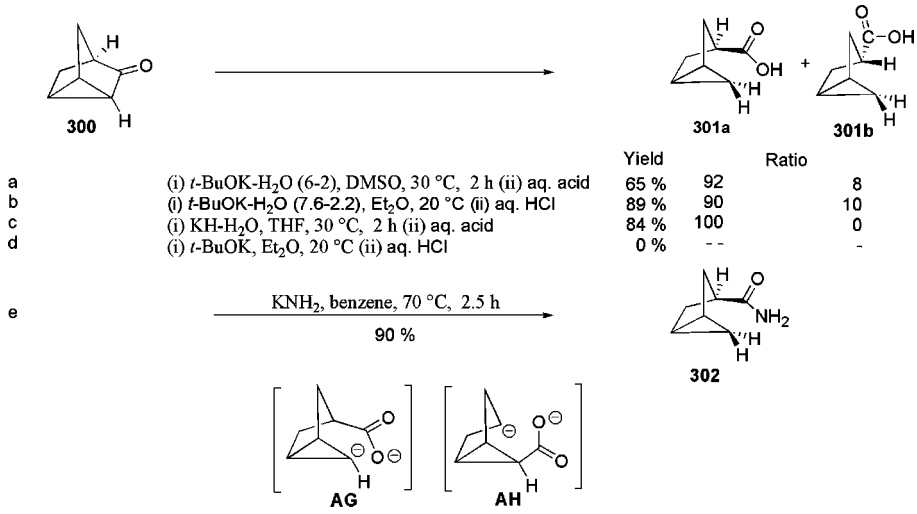

The "APH-HB" reaction proceeds at room temperature[51] or more rarely at reflux of the solvent[46,51] in aprotic solvents such as dimethyl sulfoxide,[51] hexamethylphosphoramide,[51b] glyme especially dimethoxyethane (DME),[51b,107] and even in hexane,[51b] but diethyl ether[46,51b] is the most desirable solvent from an experimental point of view.[51b] It does not, however, occur in protic solvents such as *t*-butanol.[46] It has been reported[46] that addition of *t*-butanol has an inhibiting effect on the reaction involving benzophenone **298** performed in ether lowering the yield of benzoic acid **31** from 90% to 50% if as little as 1% mol of *t*-butanol is present and to 17% by adding 3% molar equiv. This effect is much less if the reaction is carried out in dioxane instead.[46]

The amount of water is crucial for the success of this reaction. It usually does not proceed in its absence, and the yield drops dramatically if a too large amount is used; for example, it has been reported that the reaction of "APH" with benzophenone requires the presence of water. In its absence, the yield of benzoic acid **31** is low (Scheme 57, entry a as compared to entry b).[46] In ether, the yield increases to 90% when water is present (1.2 molar equiv) and then falls as more water is added (75% 1.5 molar equiv; 40% 2.0 molar equiv).[46] Similar results have been described when the reaction is performed in DMSO on nortricyclanone (**300**, Scheme 58).[51]

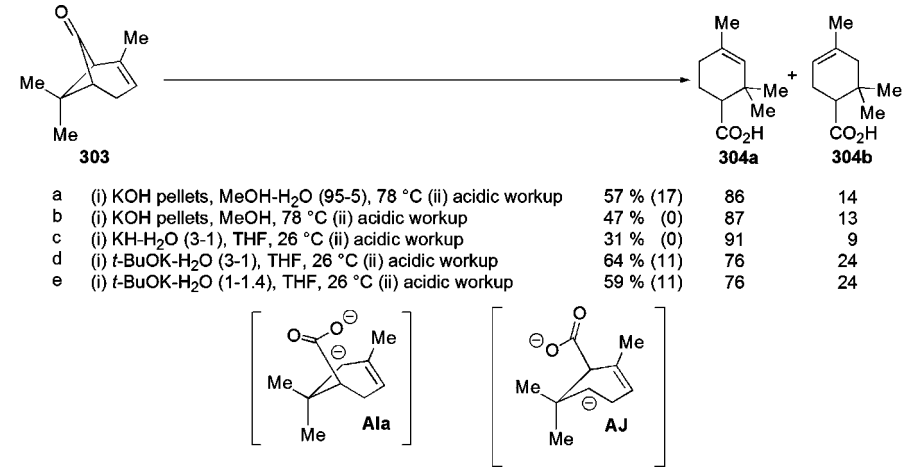
Cleavage of diaromatic ketones including benzophenone **298** has been also achieved neat with potassium hydroxide and without water added.[108] It requires much more drastic conditions (145 °C, 3.5 h), which relates them to the alkaline fusion (Scheme 12),[33] and delivers benzoic acid **31** and benzene **299** in poor yield (26% and 24%, respectively) with recovered benzophenone **298** (42%).[108] It offers no advantages over the "APH" method discussed in this Review.

Related reactions have been successfully achieved using "APH" generated from potassium hydride and a stoichiometric amount of water (Scheme 58, entry c, Scheme 59, entry c),[51b,109] and therefore the role of the excess of potassium *t*-butoxide and of the *t*-butanol produced in situ by reaction of water on potassium *t*-butoxide in the scission reaction is questionable.[51b]

**Scheme 58**




**Scheme 59**




It has been reported[46] that the behavior of potassium *t*-butoxide is unique among the alkoxides: aluminum *t*-butoxide and potassium phenoxide do not achieve the scission reaction reported above, and potassium ethoxide and isopropoxide in ether reduce benzophenone **298** to benzhydrol in a process related to the Meerwein−Pondorf−Verley reaction.[110]

*4.2.7.1.1. About the Mechanism of the "APH"-Mediated Haller−Bauer ("APH-HB") Fission of Ketones to Carboxylic Acids.* Several mechanisms have been proposed to explain the scission reaction, but because the nature of the reagent that really affects the process is still unknown, only speculation can be proposed.[46,51,108]

Swan[46] suggested that potassium *t*-butoxide is the reactive species, which adds to the carbonyl group of ketones leading to tetrahedral intermediates. The latter collapse then to the corresponding *t*-butyl esters, which are in turn hydrolyzed to carboxylates and carbanions. This mechanism has been ruled out by Gassman (Scheme 58).[51b]

Gassman showed by quenching the reaction of nortricyclanone **300**, potassium *t*-butoxide, and water with deuterated water that no deuterium was incorporated on the bicyclo[3.1.0]-hexane-3-carboxylic acid **301** and conclude that the placement of the hydrogen at C-6 takes place before the workup.[51b] He also observed that the reaction produces **301** in which a deuterium atom is inserted (61% deuterium incorporation; (**301c** + **301d**)/(**301a** + **301b**); 61/39) when nortricyclanone **300** is reacted in ether with potassium *t*-butoxide and deuterium oxide ("APD").[51b] Similar results have been observed by Hodge[107] on performing the reaction of "APD" with 4,4′-dimethoxybenzophenone in DME (reflux, 5 h), which produces 4-methoxy benzoic acid (88%) and anisole (27%) deuterated at the 4-position to an 84% extent.

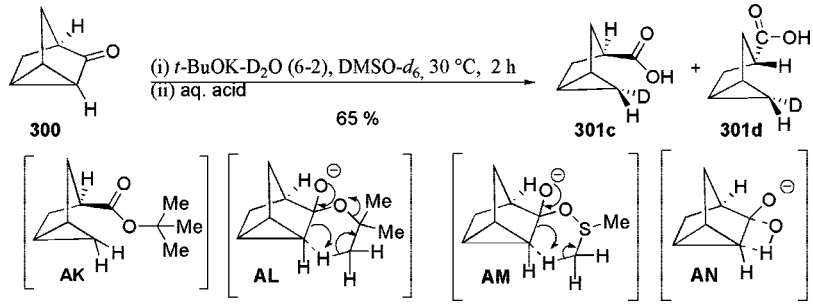
Gassman also showed that deuteration takes place exclusively at C-6 cis to the acid function in **301** (related to Scheme 58, entry a),[51b] when performing the labeling experiment using nortricyclanone **300**, perdeuterated DMSO, and deuterated water.

This tends to suggest that the cyclopropyl carbanion resulting from the fission of the carbonyl−carbon cyclopropane−carbon bond retains its stereochemistry until deuteration occurs, as is often described for such a carbanion.[111]

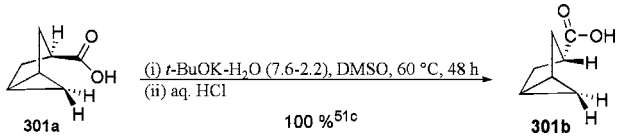
Intermediates such as **AK**, **AL**, **AM**, and **AN** have been ruled out[51b] for (i) **AK** because it proved independently to hydrolyze at a much lower rate than **300** and has never been observed even at the early stage (10%) of the reaction, for (ii) **AL** because isobutylene is not formed in the process, for (iii) **AM** because DMSO is not required for the cleavage to occur (Scheme 58, compare entry b to a), and for (iv) **AN** because the cleavage does not occur when potassium *t*-butoxide is saturated with water.

Gassman proposed[51b] that anhydrous and unsolvated hydroxide ion generated by hydrolysis of potassium *t*-butoxide attacks the carbonyl group of ketones, leading to

**Scheme 60**




**Scheme 61**




the tetrahedral intermediate **P** (Scheme 28, R = alkyl, aryl, or heteroaryl), which reacts with the 2-fold excess of potassium *t*-butoxide to produce the intermediate **Q** precursor of the carboxylate **R** (Scheme 28).

The reaction of "APH" with nortricyclanone requires further comments because epimerization of the corresponding caboxylate **301a** takes place, leading to a small amount (8%) of the more stable **301b** (Scheme 58). This is not a general trend because epimerization of **301a** to **301b** requires harsher conditions to be complete (Scheme 61).[51c]

The efficiency of the scission of nortricyclanone **300** has been attributed to (i) the relief of the particularly high steric strain (*I* strain) present on **300** during the process and (ii) the formation of a cyclopropyl carbanion **AG**, which is reasonably well stabilized.[51b,c] The higher stability of **AG** over **AH** is responsible for the extremely high regiocontrol, which exclusively produces **301**.[51]

Access of the reagent to the carbonyl group of the ketone, release of the strain, and formation of a well-stabilized carbanion are usually the factors responsible for the success of this process and account for the regiocontrol observed when the reaction is performed on unsymmetrical ketones.

The "APH-HB" reaction possesses all of the features described for the Haller−Bauer reaction using more conventional reagents.[4] For example, as reported in the case of nortricyclanone **300**, the reaction proceeds with retention of the configuration, the carbon substituant being stereospecifically replaced by hydrogen after carbon−carbon bond cleavage.[4b] The radiolabeled experiments reported above (Scheme 60) tend to suggest that the scission involves a tight ion pair producing a carbanion that remains strongly coordinated to the metal counterion and the leaving group with a proton source in close environment.[4b]

*4.2.7.1.2. Scope and Limitation of "APH-BH" Fission of Ketones to Carboxylic Acids.* The "APH-HB" reaction has been mainly carried out on non enolizable ketones, and although some enolizable ones have been successfully

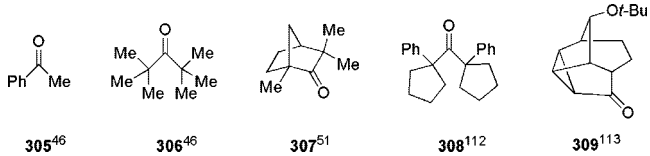
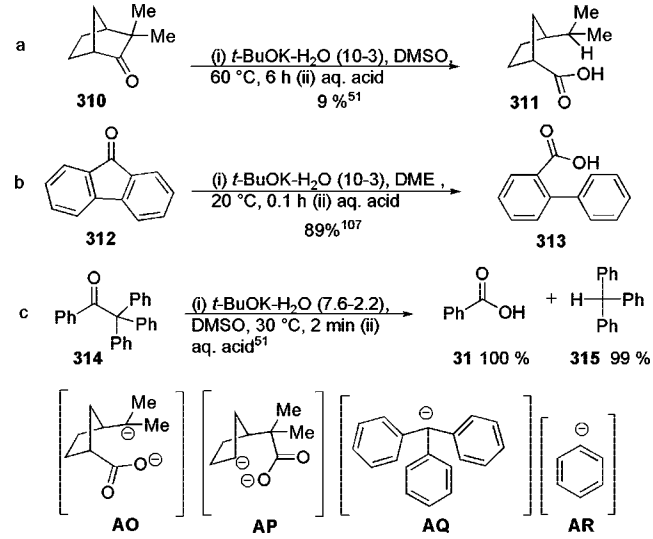



**Figure 7.** Ketones that remain intact or almost after treatment with "APH".

**Scheme 62**



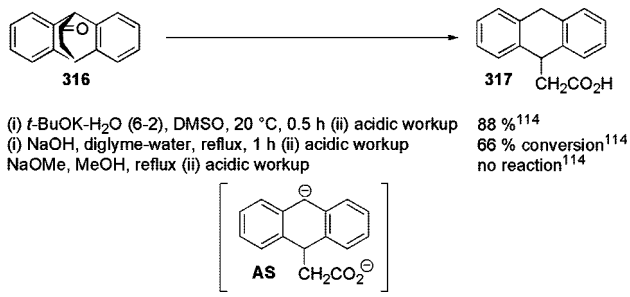

cleaved, competing metalation is an important limitation as it is the case, for example, for acetophenone **305** (Figure 7), which is not cleaved by "APH" and is recovered,[46] or the ketone **320** (Scheme 65, entry a), but other enolizable ketones are transformed to carboxylic acids with "APH" as will be described in section 4.2.7.2.

"APH" is unable to promote the fission of the non enolizable ketones whose carbonyl group is very hindered such as di-*tert*-butyl ketone **306** (ether or even in dioxane at reflux, recovery, Figure 7)[46] or fenchone **307** (DMSO, 60 °C, 6 h, inert, Figure 7),[51b] and although the presence of a carbanion stabilizing group on the ketone alpha-carbon is known to promote the "APH-HB" reaction, the hindered di(1-phenylcyclopentyl) ketone **308** is reluctant to cleavage, which would have produced a benzylic carbanion[112] (DMSO, 90% recovery; inert to hot aqueous KOH in dioxane, $NaNH_2$ in refluxing toluene, cold concentrated sulfuric acid, Figure 1).[112] This is also the case of the hindered cyclopropyl cyclopentanone **309**, which does not react with "APH", although release of strain and formation of a reasonably well-stabilized cyclopropyl carbanion would have been expected to favor the "APH-HB" reaction (Figure 7, compare to the successful cleavage of the more strained nortricyclanone **300**, Scheme 58).[51b]

Camphelinone **310** missing the methyl group at bridgehead reacts with "APH" but provides[51] camphocenic acid **311** after 6 h of reaction in DMSO at 60 °C with a miserable 9% yield beside some camphelinone−DMSO adduct[51] (Scheme 62, entry a).

Less strained benzophenone **298** (Scheme 57)[46,51] and fluorenone **312** (Scheme 62)[107] produce, under mild conditions, aryl carboxylates and arenide anions (DME, 30 °C,

**Scheme 63**




2 h, Scheme 57, entry f; DME, 20 °C, 0.1 h, Scheme 62, entry b). Benzopinacolone (phenyl triphenylmethyl ketone) **314**, which produces the highly stabilized triphenyl carbanion **AQ**, extremely easily (DMSO, 20 °C, < 2 min) produces benzoic acid **31** and triphenylmethane **315** in almost quantitative yields (Scheme 62, entry c).[46,51]

The reaction proceeds in all of the cases cited regioselectively and produces, except for **310** (**AO** instead of **AP**, Scheme 62), the most stable of the two possible carbanion intermediates (**AG** instead of **AH** for **300**, Scheme 58; **AIa** instead of **AJ** for **303**, Scheme 53; **AQ** instead of **AR** for **314**, Scheme 62).

*4.2.7.1.3. Reactivity of "Anhydrous Potassium Hydroxide" toward Ketones As Compared to Other Reagents Able To Perform the Same C,C Bond Scission.* "APH" has been widely used since its rediscovery by Gassman for the transformation of ketones to carboxylic acids.[4c] In a few cases, this method has been compared to others that are able to achieve the same C,C bond scission of ketones, such as (i) KOH under alkaline fusion, aqueous potassium hydroxide, alcoholic potassium, and sodium hydroxides leading to carboxylic acids after acid treatment; (ii) sodium ethylate, which leads to ethyl carboxylates; and (iii) potassium amide, which instead produces the carboxylic amide.[4]

Thus, anhydrous potassium hydroxide prepared from (i) potassium *t*-butoxide−water (6:1) in DMSO[51a] (Scheme 58, entry a) or ether (Scheme 58, entry b)[51b] or (ii) potassium hydride and a stoichiometric amount of water in ether (Scheme 58, entry c)[51b] cleaves the carbonyl,carbon−cyclopropane carbon bond of nortricyclanone **300** to produce the carboxylic acid **301** under milder conditions than required by potassium amide to produce the corresponding amide **302** (Scheme 58, entries c,d; compare to Scheme 58, entry e).[51]

"APH" in DMSO cleaves faster and under milder conditions (20 °C, 0.5 h, 100% conversion) the bicyclo[2.2.2]cyclooctanone **316** (Scheme 63, entry a) to produce **317** than does aqueous sodium hydroxide in diglyme (reflux, 1 h, 66% conversion, Scheme 63, entry b).[114] Interestingly, cleavage fails to occur using refluxing methanolic sodium methoxide or 6 N hydrochloric acid diglyme solution.[114]

It has been also described that "APH" allows the cleavage of (i) the α-phenylsulfanyl-cyclobutanone **39** (Scheme 13, entry d),[34a] which neither sodium hydroxide nor sodium methylate is able to achieve even under more drastic conditions (Scheme 13, entries b,c),[34a] and (ii) the α,α-dimethyl cyclobutanone **318** fused to the cyclopentene ring, to the mixture of isomeric cyclopentenecarboxylic acids whose α-carbon is fully alkyl-substituted **319** (Scheme 64, entry c) under milder conditions[109] and in better yield than when potassium hydroxide pellets in anhydrous or aqueous methanol are instead used (Scheme 64, compare entry c to entries a,b).[109]

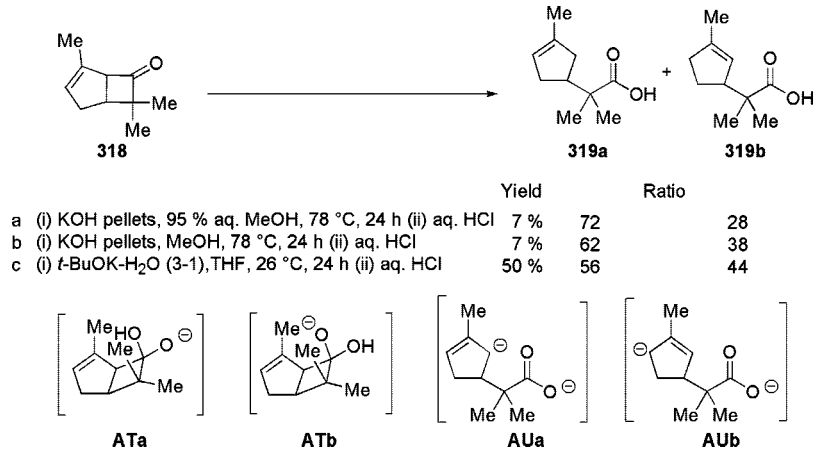
Similarly, "APH" cleaves the cyclobutanone present in the bicyclo[3.1.1]cyclohexanone **303** (Scheme 59, entries c−e) under milder conditions than potassium pellets (Scheme 59, entries a,b, as compared to entries c−e)[109] and more efficiently than using "anhydrous potassium hydroxide" prepared from potassium hydride instead (Scheme 59, entry c, as compared to entries d,e).[109]

**4.2.7.2. Reactivity of "Anhydrous Potassium Hydroxide" toward Enolizable Ketones.** The "APH" scission of ketones has been carried out on diaromatic ketones including anthraquinones and xanthones as well as on poorly enolizable ketones in which the carbonyl group is attached to a bridgehead position or to a fully alkyl-substituted methyl group.

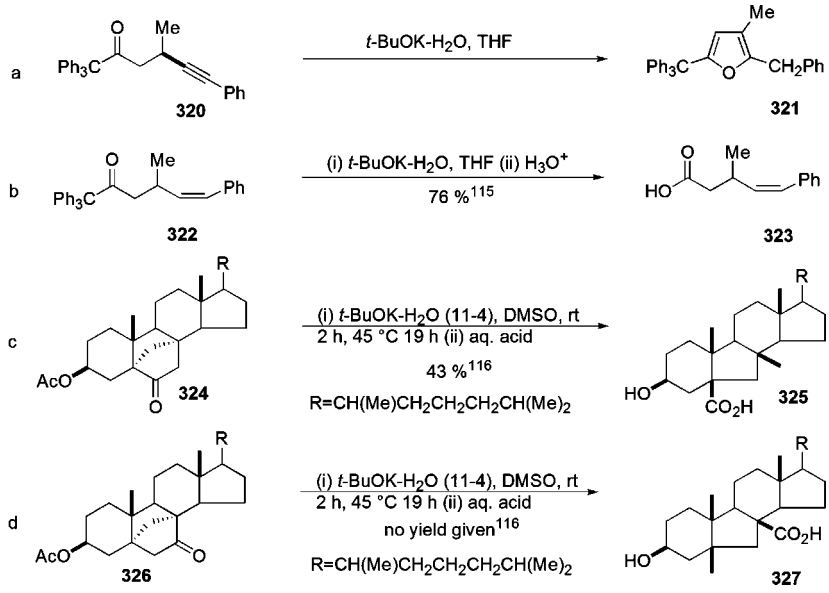
Enolizable ketones have been rarely subjected to "APH". For example, acetophenone is recovered unchanged on admixing with "APH" in ether,[46] and scission does not take place with the β-alkynyl triphenylmethyl ketone **320**, which instead leads[115] to the furan derivative **321**.[115] Its formation probably involves metalation of **320** α to its carbonyl group (Scheme 65, entry a).[115] However, the scission efficiently takes place on the related triphenylmethyl ketone **322**,[115] which only differs from **320** by the presence at the same position on the chain of a *cis*-disubstituted C,C double bond instead of C,C triple bond (Scheme 65, entry b).

Successful fission has been also achieved with the two regioisomeric bridged steroids **324** and **326** possessing a bicyclo[2.2.1] ring B system (Scheme 65, entries c,d)[116] and with norbornenones **328**[51a,117] and **331**[118] bearing a methylene or an isobutylidene moiety on their bridge, respectively

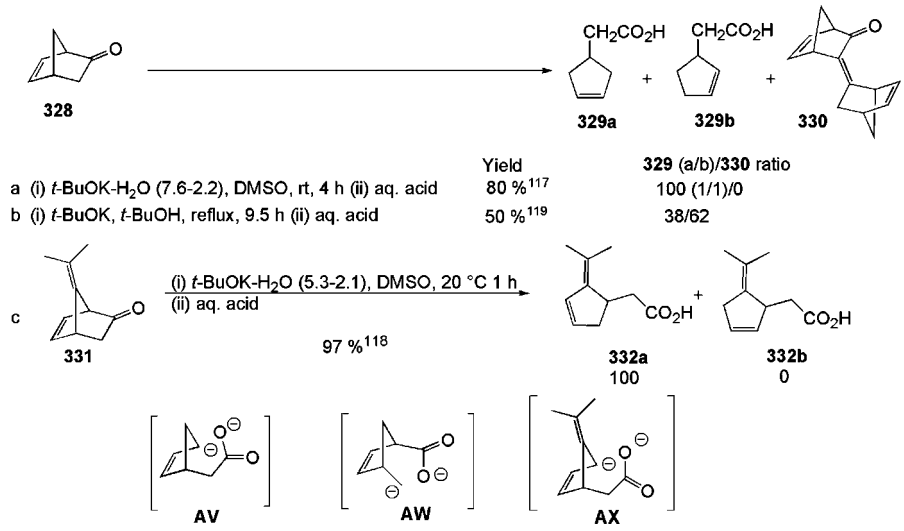
**Scheme 64**



**Scheme 65**




**Scheme 66**




(Scheme 66, entries a,c). It is worthwhile to notice the particularly high nucleophilicity of "APH" in DMSO toward **328**, which provides the isomeric carboxylic acids **329** in 80% yield (20 °C, 4 h). Reacting **328** with potassium *t*-butoxide in *t*-butanol requires much more drastic conditions (reflux of *t*-butanol, 9.5 h, Scheme 66, entry b) and delivers **329**[51a,119] in poorer yield (38%) along with the enone **330** resulting from competing intermolecular aldolization and crotonization reactions, which implies competing metalation of **328**.

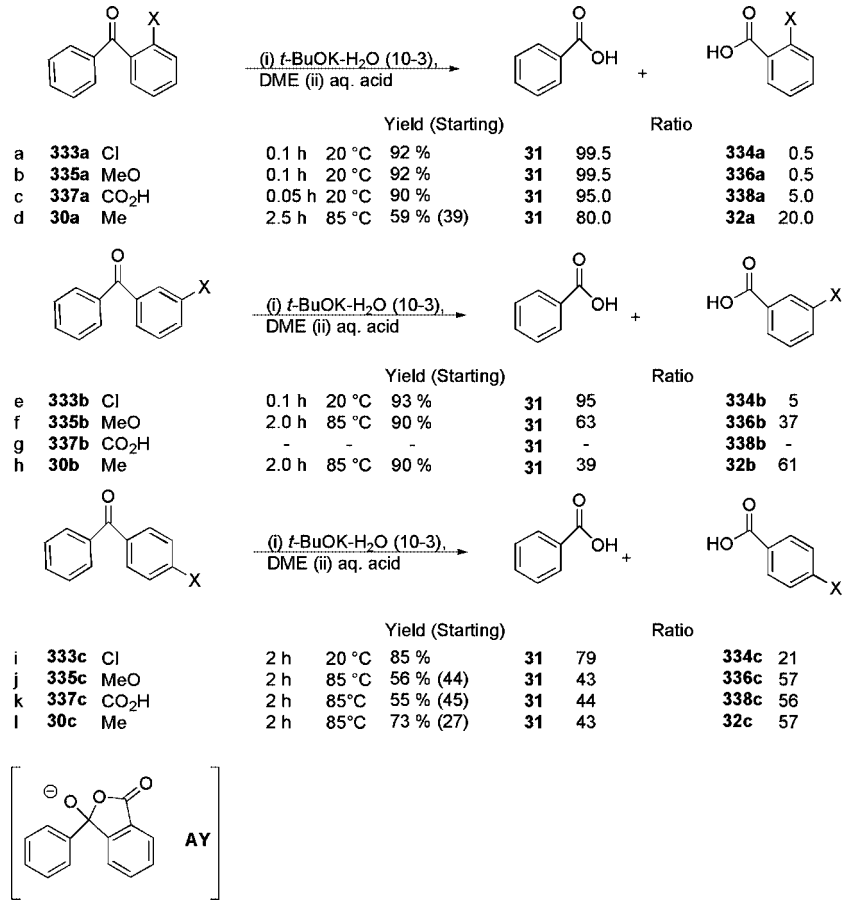
Successful C,C bond scission by "APH" has been also disclosed for other enolizable ketones such as the bicyclo[2.2.2]cyclooctanone **316** (Scheme 63, entry a) and for compounds **39** (Scheme 13, entry d),[34a] **117** (Scheme 35, entry c),[59] and **318** (Scheme 64, entry c)[109] bearing an enolizable cyclobutanone substructure. Metalation, however, occurs as already stressed on **115a** and **115b** (Scheme 35, entries a,b) possessing closely related structures.[59]

In this series of cleavages, the scission occurs to produce the more stable of the two possible carbanions. This is the case of (i) cyclobutanones **39** and **318**, which involve the α-phenylthiocarbanion **H** (Scheme 13)[34a] and the allylic carbanions **AU** (Scheme 64),[109] (ii) bicyclo[2.2.2]cyclooctanone **316**, which produces the diaryl-substituted carbanion **AS** (Scheme 63),[114] (iii) triphenyl ketone **322** (Scheme 65),[115] which leads to triphenylmethylcarbanion intermediate **AQ** (Scheme 62), (iv) bridged steroidal ketones **324** and **326** (Scheme 65, entries c,d),[116] which produce a primary alkyl instead of tertiary alkyl carbanions, and (v) norbornenone derivatives **328**[117] and **331**[118] (Scheme 66, entries a,c), whose transformation to **329** and **332a**, respectively, involves the allylic **AV** or biallylic **AX** intermediates.

In many cases, mixtures of regioisomeric unsaturated acids such as **329a** and **329b** are formed from unsaturated ketones able to produce, on cleavage, allylic carbanions. Reasonably high regioselectivity can be attained usually under aprotic conditions under which intermolecular protonation that normally favors the formation of **332b** (Scheme 66) can be suppressed.[117,118] (See section 4.2.7.5.)[109,119]

Finally, we have to recall that the scission of cyclobutanone **39** (Scheme 13, entry d)[34a] to **40** occurs with remarkable regio- and stereoselectivity because not only the *cis*-configuration of the two carbon chains on the cyclopentane ring is maintained but also protonation of the resulting

**Scheme 67**




α-phenylthiocarbanion **H** takes place with complete retention of configuration.[34a]

**4.2.7.3. Reactions of "Anhydrous Potassium Hydroxide" on Ketones Whose α and α′-Carbons Are Part of Aromatic and Heteroaromatic Rings.** Diaromatic ketones are usually efficiently cleaved by "APH" under mild conditions. This has been attributed to the generation of a quite stabilized arenide intermediate.[46,51,107] The reaction is reminiscent of the alkaline fission we already reported (Scheme 12)[33] but occurs at much lower temperature.

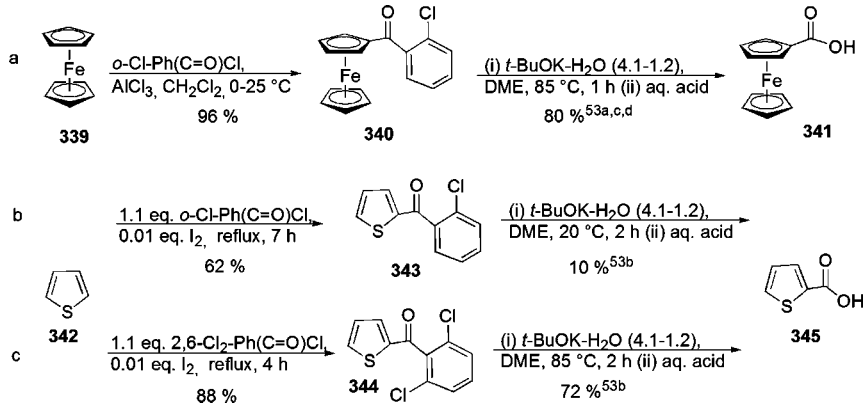
Successful cleavage has been reported on symmetrical diaromatic ketones such as (i) benzophenone **298** (Scheme 57),[46,51,107] (ii) 4,4′-dibromo- (dioxane, reflux, 13 h, 80% yield),[46] 4,4′-dimethoxy-[46,107] (dioxane, reflux, 13 h, 80% yield),[46] and 4,4′-bisdimethylamino- (dioxane, reflux, 13 h, 80% yield)[46] -benzophenone, and (iii) xanthone (dioxane, reflux, 13 h, 89% yield),[46] as well as on unsymmetrical aromatic ketones such as 4-bromobenzophenone and 4-methoxybenzophenone (dioxane, reflux, 13 h, benzoic acid/4-substituted benzoic acid ratio 80/20 and 47/53, respectively).[46]

More systematic work has been carried out by Hodge[107] on a series of benzophenones monosubstituted in various positions on one of the two aromatic rings (Scheme 67). The ease of scission and the regiochemistry of the reaction have been related to the strain in the starting material and the stabilization of the resulting carbanion. Thus, benzophenones bearing a substituent in *ortho*-position (release of the strain) react usually faster than the unsubstituted benzophenone **298** (Scheme 67, entries a−d) and than those that bear a substituent in another position.[107] The whole series of chloro-substituted benzophenones react faster than other benzophenones and produce benzoic acids resulting from the largely predominating scission of the carbonyl-carbon−aromatic-carbon bond whose aromatic ring bears a chlorine (Scheme 67, entries a,e,h).[107] It is still unclear if chloro-benzene produced concomitantly to benzoic acid **31** on reaction of 2-chlorobenzophenone **333a** with "APH" (Scheme 67, entry a)[107] results from protonation of the 2-chlorophenyl potassium intermediate originally formed or involves benzyne as an intermediate.[107] Concomitant formation of phenyl *t*-butyl ether (10%) does not exclude this pathway, and disambiguation using, for example, label experiments has not been carried out so far.[107]

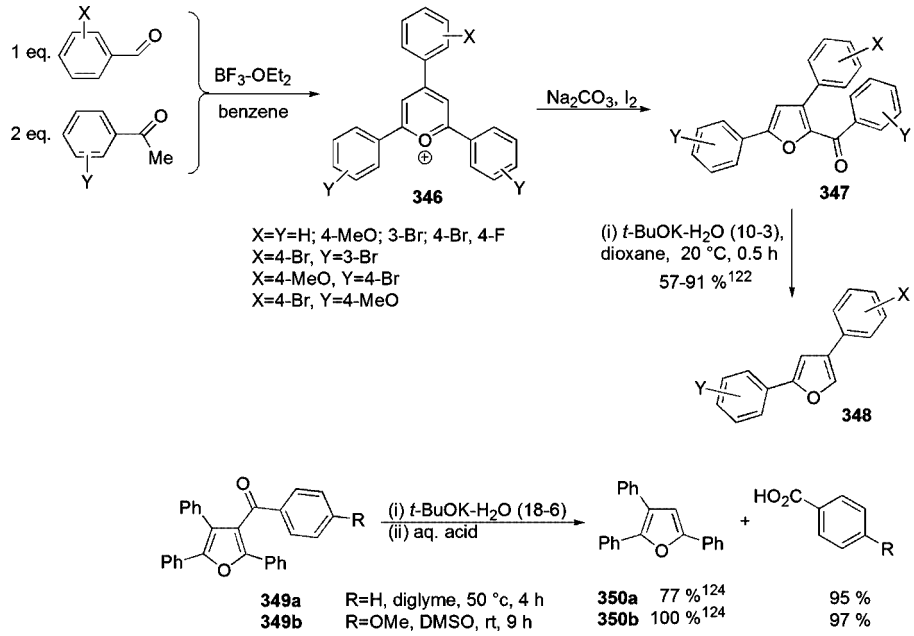
2-Methoxybenzophenone **335a** is also extremely rapidly cleaved and leads almost exclusively to the formation of benzoic acid **31** (Scheme 67, entry b).[107] This may account for the efficient stabilization of the *ortho*-metallo-anisole, which can be related to the ease with which anisole is metalated[120] to produce the same species. It has been also proposed that the highly regioselective cleavage of 2-carboxy benzophenone **337a**, which mainly produces benzoic acid **31** instead of phthalic acid **338a** (**31**/**338a**: 95/5, Scheme 67, entry c), might arise from the intermediate formation of a lactone (**AY**, Scheme 67) via an intramolecular process as well as from the extra stabilization of the resulting organometallics by the *ortho*-carboxylate.[107]

Finally, it is quite surprising that the reaction of "APH" with methyl benzophenones **30a** and **30b**, which takes place under relatively mild conditions (85 °C, <2.5 h), affords[107] a closely related benzoic acid/methylbenzoic acid **31/32** ratio as compared to one implying instead alkaline fusion,[33] which is carried out under more drastic conditions (200−300 °C, compare Scheme 67, entries d,h to Scheme 12, entries a,b).

**Scheme 68**




**Scheme 69**



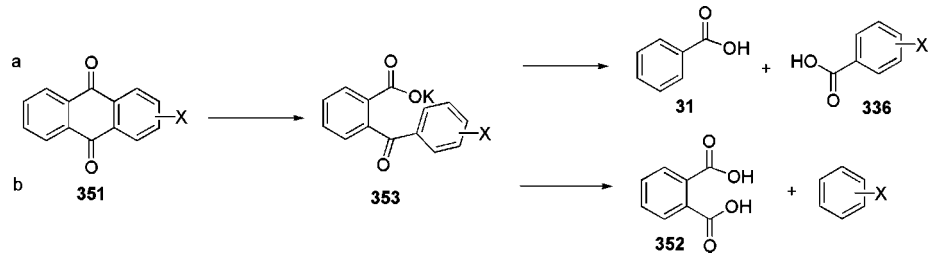

Fragmentation of diaryl ketones with "APH" has been used as a key step for the synthesis of aromatic and heteroaromatic carboxylic acids by a strategy that involves a Friedel−Craft acylation reaction and selective cleavage of the resulting diaromatic ketones in which the acyl group plays the role of a masked carboxyl group (Scheme 68). It has been found that 2-chlorobenzoyl chloride or even better 2,6-dichlorobenzoyl chloride should be advantageously used instead of, for example, benzoic acid due to the easy and selective cleavage of the resulting diaromatic ketones by "APH". It has been thus reported that ferrocenecarboxylic acid[53a,c,d] **341** can be produced from ferrocene **339** by acylation of the latter with 2-chlorobenzoic chloride and regioselective scission of the resulting ketone **340** (Scheme 68, entry a) and that a related reaction allows the efficient synthesis of carboxycyclopentadienyltricarbonylmanganese (79%)[53a] and of several substituted benzoic acids such as biphenyl-4-carboxylic acid (DME, 20 °C, 2 h, 91%, overall 64%),[53b] 3,4-dimethybenzoic acid (DME, 20 °C, 2 h, 57%),[53b] 2,4-dimethoxybenzoic acid (DME, 20 °C, 2 h, 69%, overall 60%),[53b] 3,4-dimethoxybenzoic acid (DME, 85 °C, 1 h, 77%, overall 73%),[53b] and 2,4,6-trimethoxybenzoic acid (DME, 85 °C, 1 h, 76%, overall 59%).[53b]

It has been reported that "APH" reacts with 2-chlorobenzoylthiophene **343** to deliver 2-thiophene carboxylic acid in poor yield (10%, Scheme 68, entry b) because it is cleaved to only a small extent in the desired direction.[53b] This is surprising because vinylic α-thiocarbanions are known to be quite stabilized.[121] Performing the same transformation using instead 2,6-dichlorobenzoyl chloride not only leads to an increased yield in the adduct resulting from the Friedel−Craft reaction but also produces efficiently 2-thiophene carboxylic acid (up to 72%, Scheme 68, entry c).[53b]

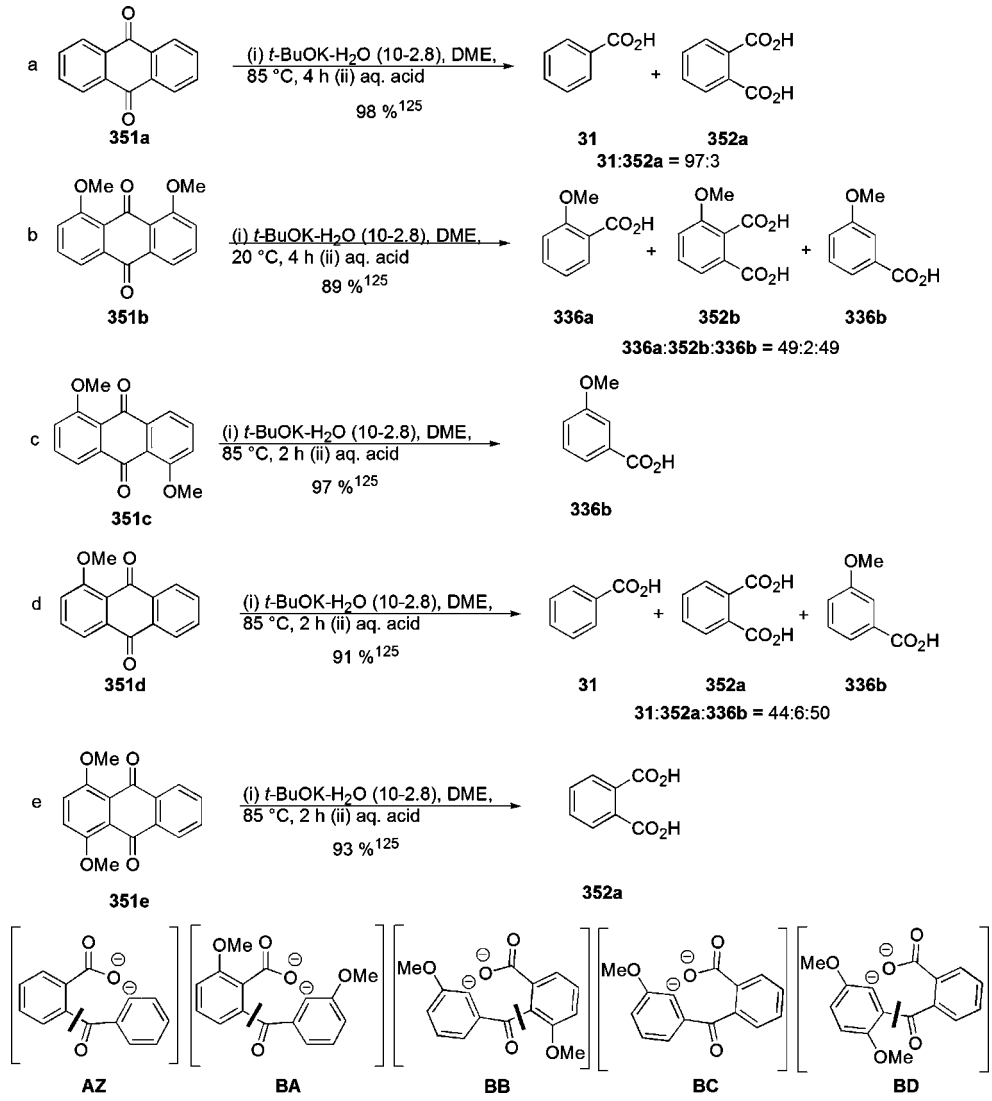
"APH" has been successfully reacted with 2-aroyl- **347**[122,123] and 3-aroyl furans **349**[124] and delivers the corresponding deacylated furanes **348** and **350** as well as the related benzoic acids in good yield and with extremely high regiocontrol (Scheme 69). In those cases, the nature of the substituants attached to the aryl group part of the aroyl moiety as well as the solvent used do not seem to play a crucial role in both yields and regiocontrols (compare Scheme 69 to Scheme 68, entry b). Thus, the cleavage of **347** (X, Y = H, Scheme 69)[122] has been carried out equally successfully in DMSO, DMF, *N*-methyl pyrrolidin-2-one, dioxane, or benzene and gave isolated yields of 72%, 95%, 85%, 80%, or 94%, respectively. In such case, dioxane has been selected because the desired compound crystallizes pure out of it.[122]

Anthraquinones **351**, which are more resistant to cleavage by base than other types of non enolizable ketones, are nevertheless cleaved in high yield when treated for up to

**Scheme 70**




**Scheme 71**




4 h with an excess of "APH" in DME at 85 °C (Schemes 70, 71).[46,125a] The reaction has been carried out on the parent compound **351a** as well as on alkyl-, chloro-, and methoxy-derivatives.[46,125]

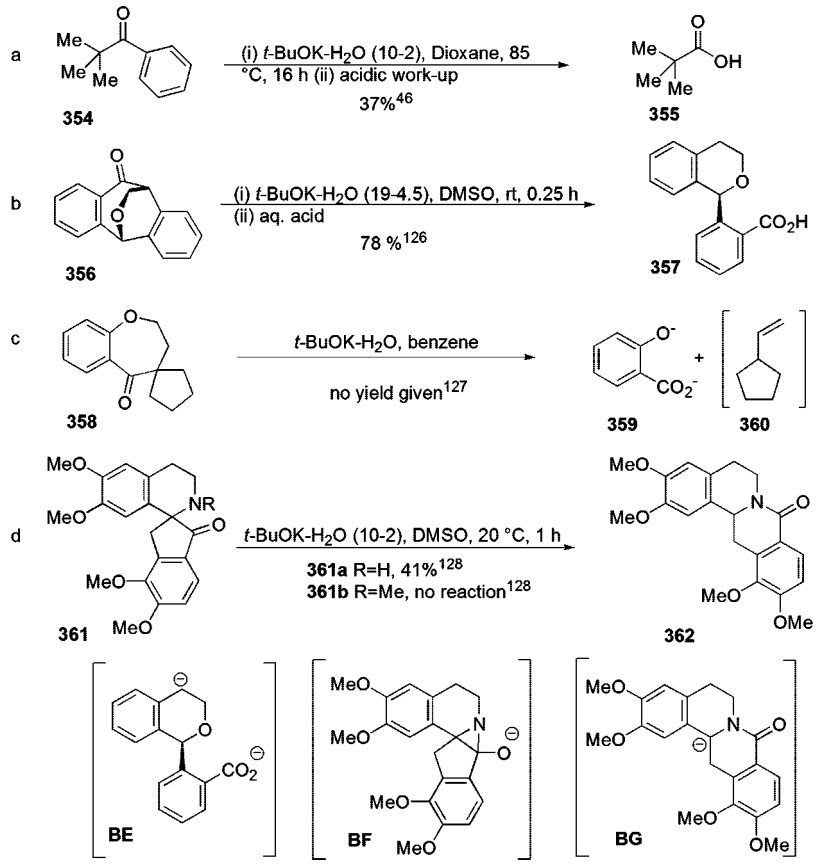
Reaction of anthraquinone **351a** with "APH" occurs under milder conditions (85 °C, DME) than the one involving alkali metal hydroxide in an inert solvent, which requires heating up to 250 °C[125a] to produce benzoic acid **31**. It is interesting that the Haller−Bauer reaction, involving sodamide instead, does not take place with anthraquinone when performed in refluxing toluene or xylene.[46,125a]

The reaction of anthraquinones **351** with "APH" takes place in two consecutive steps producing first the arylcarboxylates bearing in the *ortho*-position an acyl group **353** on which a second equivalent of "APH" reacts to produce either 2-benzoic acids **31** and **336** (Scheme 70, entry a) or phtalique acids **352** and arenes (Scheme 70, entry b).

The first reaction cleaves the carbonyl,α-carbon carbon bond and leads to the most stabilized carbanion. The second one involves the reaction of "APH" with the resulting diaryl ketone intermediate, which again is cleaved to produce a carboxylate and the most stabilized arenide anion.

Thus, the parent compound **351a** leads almost exclusively to benzoic acid **31** arising from the cleavage of the protonated **AZ** leading to the intermediate *ortho*-potassio potassium carboxylate whose carbanion has been already assessed to be stabilized intramolecularly (Scheme 71, entry a).[125]

**Scheme 72**




The reaction is much faster with **351b** (20 °C instead of 85 °C, 4 h), which possesses two methoxy groups on the aromatic ring ortho to the same carbonyl group, than with the parent compound **351a** (Scheme 71, entry b, as compared to entry a).[125]

The reactions of "APH" with anthraquinones **351d**, **351c**, and **351e** bear a methoxy group in the ortho position on a single aromatic ring or on each of the aromatic rings but in the ortho position of each of the two carbonyl groups, or two methoxy groups on the same aromatic ring and in the ortho position of each of the two carbonyl groups, respectively, are still faster than that of **351a** but less than that of **351b** (Scheme 71, entries d,c, respectively; compare to entries a,b).[125] Each of the two steps of the reaction occurs faster if they produce arylanions possessing stabilizing methoxy or carboxylate groups in the ortho position such as **BA**, **BB**, **BC**, and **BD** (Scheme 71). Those results are reminiscent of those already discussed for *ortho*-methoxy benzophenone **335a** and *ortho*-carboxy benzophenone **337a** (Scheme 67, entries b,c).[107]

**4.2.7.4. Reactions of "Anhydrous Potassium Hydroxide" on Aryl Aliphatic Ketones.** Acetophenone **305** (Figure 7) is recovered unchanged on admixing with "APH" in ether,[46] whereas benzopinacolone **314** (Scheme 62, entry c) generates benzoic acid **31** and triphenylmethane **315** quantitatively in less than 2 min by scission of the carbonyl−triphenylmethyl bond,[51] and *t*-butyl-phenyl ketone (*ω*-trimethyl acetophenone) **354** produces trimethyl acetic acid **355** in modest yield (Scheme 72, entry a).[46]

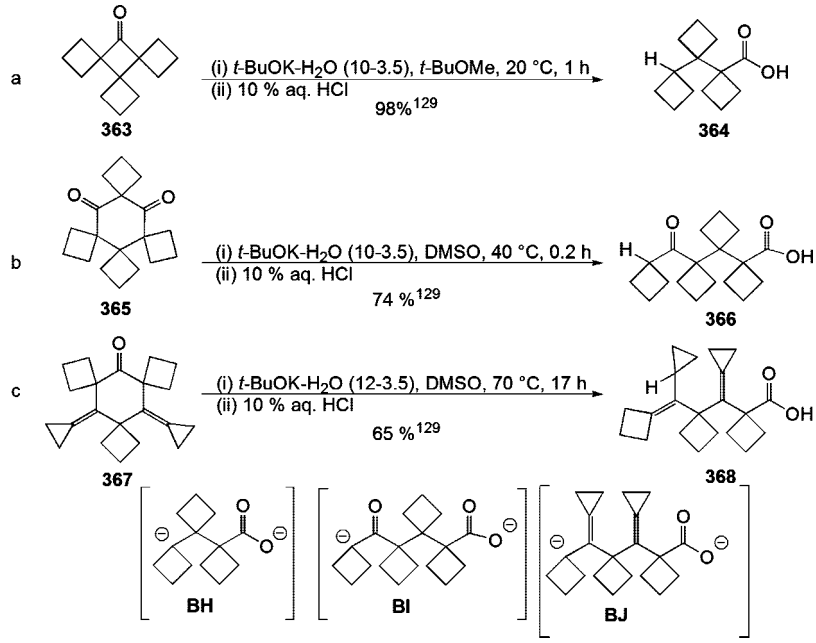
Apparently metalation takes place on **305**, whereas scission leading selectively to the best stabilized triphenylcarbinyl anion **AQ** and the phenyl anion **AR** (Scheme 62) takes place from benzopinacolone **314** and *t*-butyl-phenyl ketone **354**, respectively.

Selective scission leading to the carboxylic acid **357** has been observed from the aromatic ketone **356**, bearing an alkoxymethylene group at the bridgehead benzylic position (Scheme 72, entry b).[126] It involves the intermediate formation of the stabilized benzylic carbanion **BE**, which does not suffer the *β* elimination of its alkoxy moiety.[126] Reaction of benzooxepinone **358** has been reported to produce the salicylate **359**, whose yield has not been described and whose structure has not been unambiguously determined.[127] It apparently comes from a fragmentation reaction whose reported mechanism is not convincing.[127]

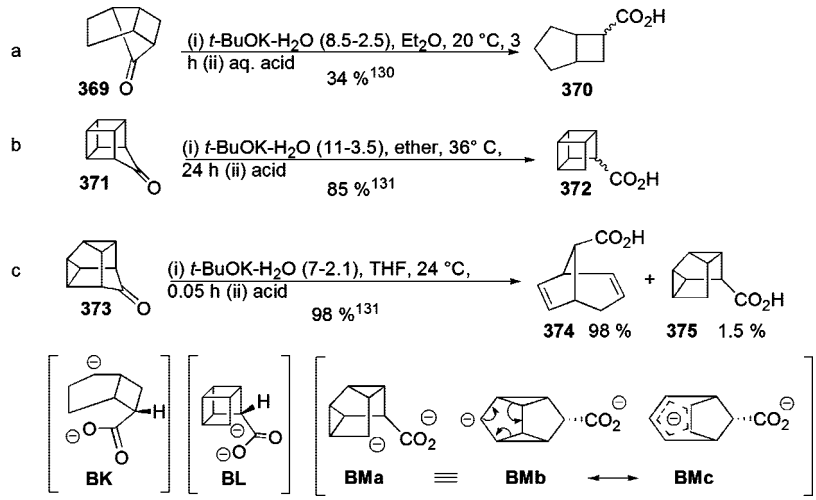
Reaction of the 2-indan-1-one bearing at the α-spirocarbon a secondary amino group **361** with "APH" leads to the bicyclic lactame **362**,[128] and although the scission of the carbonyl,carbon-benzylic carbon bond is taking place, the process is reported to involve *N*-metalation of **361a** and formation of the α-alkoxy aziridine **BF**, which then decomposes to the benzylic intermediate **BG** precursor of **362**.[128] Strong support for this process comes from the fact that anhydrous potassium *t*-butoxide does not react with its *N*-methyl analogue **361b**, which is unable to produce the aziridine intermediate related to **BF**.[128]

**4.2.7.5. Reactions of "Anhydrous Potassium Hydroxide" on Non Enolizable Dialiphatic Ketones.** "APH" has been reacted with several non enolizable dialiphatic ketones, but the scission reaction only takes place with compounds that possess strained carbonyl groups relatively accessible by the hydroxide ion and that are able to deliver beside the carboxylate a quite stabilized carbanion. Thus, as we already pointed out, di-*tert*-butyl ketone **306**,[46] fenchone **307**,[51b] the

**Scheme 73**




**Scheme 74**



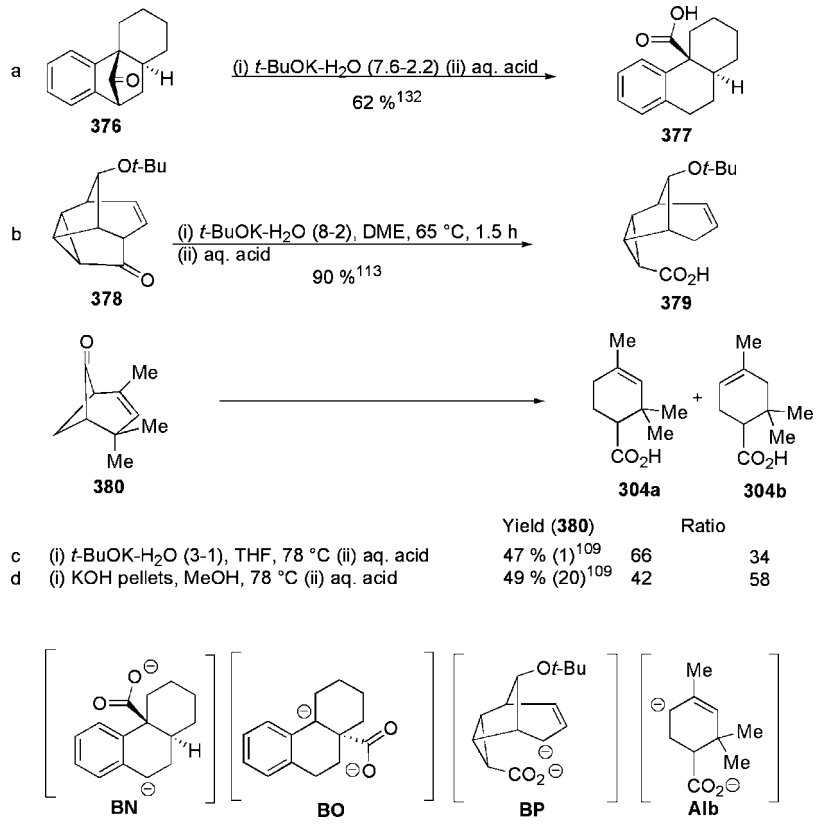

tetracyclic ketone **309**,[113] and di(1-phenylcyclopentyl) ketone **308**,[112] which miss some of those criteria, are all inert to "APH" (Figure 7). However, a series of cyclanones bearing spiro α-carbon atoms as part of four-membered rings **363**, **365**, and **367** have been successfully transformed,[129] under mild conditions, to the cyclobutane carboxylic acids **364**, **366**, and **368** in good yields (Scheme 73). Cyclobutanone **363** (Scheme 73, entry a), which is probably the most strained compound of the series, is the most reactive, although little stabilization is expected from the resulting carbanion intermediate **BH**.[129]

Cyclohexanedione **365** is far less strained, but the extremely good stabilization of the resulting enolate intermediate **BI** is without doubt responsible for the efficient cleavage and the complete regiocontrolled formation of **366** (Scheme 73, entry b).[129] The scission of **367** is far more difficult than those of **363** and **365** and requires heating up to 70 °C for 17 h to deliver the cyclobutane carboxylic acid **368** (Scheme 73, entry c).[129] Its formation implies the regioselective protonation of the allylic anion intermediate **BJ** at the cyclopropyl carbon and not at the cyclobutyl terminus as expected by the authors.[129]

Otherwise, "APH" has been used extensively to cleave polycyclic saturated, non enolizable ketones, bridgehead at least at one of their α-carbons.[4c] This is the case of the particularly strained camphelinone **310** (Scheme 62, entry a),[51] nortricyclanone **300** (Scheme 58),[51] tricyclanone **369** (Scheme 74, entry a),[130] homocubanone **371** (Scheme 74, entry b),[131] and homocuenone **373** (Scheme 74, entry c).[131]

Among this series, **310**, which only possesses a "moderately" strained carbonyl group, is by far the most difficult to cleave because the yield of the carboxylic acid **311** is very low (Scheme 62, entry a).[51] We have to recall that the homologuous **307** (Figure 7) whose carbonyl is fully alkylated on each of the two α carbon atoms is inert even to more drastic treatment.[51b] On the contrary, nortricyclanone **300**, which is more strained due to the presence of the cyclopropane ring (Scheme 58, entry a; compare to Scheme 62, entry a) and able to generate after scission a relatively stabilized cyclopropyl carbanion **AG** as compared to **AH** (Scheme 58, entry a,b), is cleaved.[51] The inertness of the cyclopropyl ketone **309** (Figure 7) even under more drastic conditions could be related to a lower strain.[113]

**Scheme 75**




Reaction of "APH" with strained ketones **369** (Scheme 74, entry a)[130] and **371** (Scheme 74, entry b)[131] delivers under mild conditions cyclobutane carboxylic acids **370** and **372** in modest to good yields. The presence of trace (3%)[130] and small (10%)[131] amounts of *exo*-carboxylic acids besides large quantities of their *endo*-isomer suggests that epimerization has taken place at the α carbon of the carboxylates **BK** and **BL** to provide the thermodynamically more stable stereoisomers.

On the contrary, scission of isomeric homocuneone cage compound **373** is so easy that 100 mg of sample is completely cleaved in less that 30 s by treatment with "APH".[131] It produces only a small amount (1.5%) of the expected cyclopentane carboxylic acid **375** besides large quantities of the carboxylic acid **374** possessing diunsaturated bicyclo[3.2.0]octanone skeleton resulting from the fragmentation of the intermediate carbanion **BMa** (Scheme 74, entry c).[131] This extraordinary reactivity has been attributed to the involvement of the bishomoaromatic anion **BMb**, **BMc** (Scheme 74) precursors of **374** (Scheme 74, entry c).[131]

Cleavage has been also efficiently carried out on strained bridged ketones bearing on their α-carbon aryl or vinyl groups. Those deliver after scission the expected carboxylates as well as benzylic- (Scheme 75, entry a)[132] or allylic- (Scheme 59;[109] Scheme 75, entries b−d;[109,113] Scheme 76[51,133,134]) carbanions, which offer extra stabilization and favor the scission.

In the case of benzonorbornanone **376**, a single regioisomeric carboxylic acid **377** is produced (Scheme 75, entry a).[132] It arises from the selective scission of the carbonyl,α-carbon carbon bond, which produces the secondary benzylic carbanion **BN** instead of the least stable tertiary benzylic carbanion **BO** (Scheme 75).[132]

Reaction of **378** with "APH" (Scheme 75, entry b)[113] is even more interesting because it produces the cyclopropane carboxylic acid **379** resulting from selective protonation of the allylic carbanion **BP** (Scheme 75). The presence of the C,C double bond is responsible for (i) the selective scission leading to **BP** possessing an allylic carbanion rather than to the regioisomeric intermediate bearing a cyclopropyl carbanion and (ii) the increased reactivity of **378** as compared to the dihydro compound **309** (Figure 7), which remains unchanged even under more drastic conditions.[113]

In only a few cases such as the one of the $\beta,\gamma$-unsaturated ketone **378** (Scheme 75, entry b) does protonation of the allylic carbanion intermediate (**BP**, Scheme 75) exclusively occur at the original site resulting from the scission.[113]

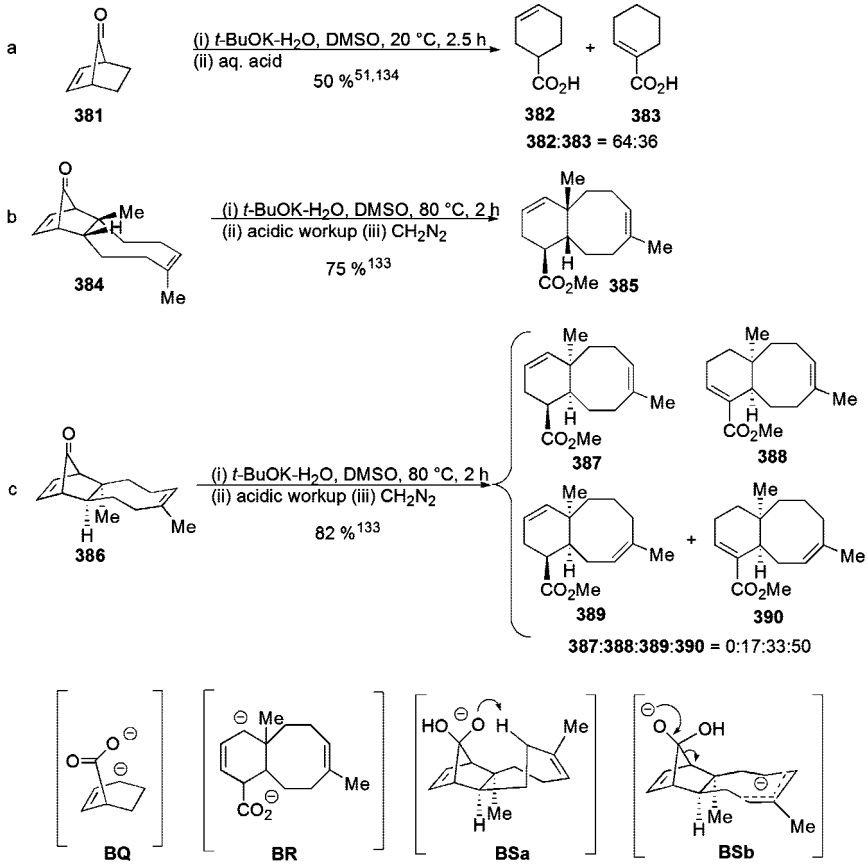
In some rare cases such as **331** (Scheme 66, entry c),[118] **367** (Scheme 73, entry c),[129] and **384** (Scheme 76, entry b),[133] protonation of the allylic anion intermediates **AX** (Scheme 66), **BJ** (Scheme 73), and **BR** (Scheme 76), respectively, exclusively takes place at the other terminus of the allylic system.

In the majority of the cases described, the process leads to a mixture of compounds that possess the C,C double bond at different positions. This is the case of **318** (Scheme 64, entry c),[109] **328** (Scheme 66, entry a),[117] chrysanthenone **380** (Scheme 75, entry c)[109] and its regioisomer **303** (Scheme 59, entries d,e),[109] dehydrocamphenilone **381** (Scheme 76, entry a),[51,134] and **386** (Scheme 76, entry c);[133] the stereoisomer of **384**, however, produces mixtures of regioisomeric cyclohexene carboxylic acids on reaction with "APH" and protonation of the resulting allylic anions.

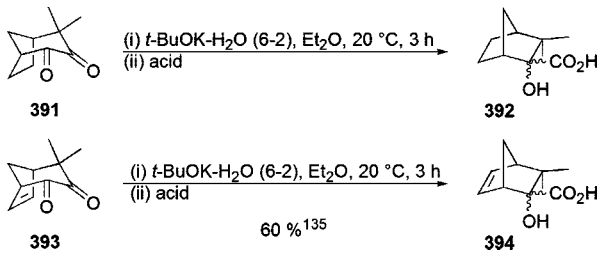
Models have been proposed[109] to explain the different ratios of **304a/304b** resulting from the scission of **303** (Scheme 59) and its regioisomer **380** (Scheme 75, entry c) under different conditions.

"APH" cleaves regioselectively the isomeric *endo*-**384** and *exo*-**386** tricyclanones because the C,C bond scission exclu-

**Scheme 76**




**Scheme 77**




sively takes place next to the quaternary carbon center bearing the methyl group (Scheme 76, entries b,c).[133] They, however, behave differently because the major products **389**, **390** resulting from the cleavage of the *exo*-tricyclanone **386** possess a C,C double bond in the eight-membered ring, which has shifted.[133] It has been proposed that this migration, which is not encountered in the *endo*-series, occurs through an intramolecular hydrogen abstraction on the conformationally flexible eight-membered ring as shown in **BSa** prior to the scission disclosed in **BSb** being achieved (Scheme 76).[133]

"APH" also reacts with carbocamphelinone **391** and dehydrocarbocamphelinone **393** possessing the α-diketone functional group and produces in an exothermal reaction regioselectively mixtures of stereoisomeric α-hydroxyacids **392** and **394**, respectively (Scheme 77).[135] Their formations have been reported to involve benzylic acid-type rearrangements.[135]

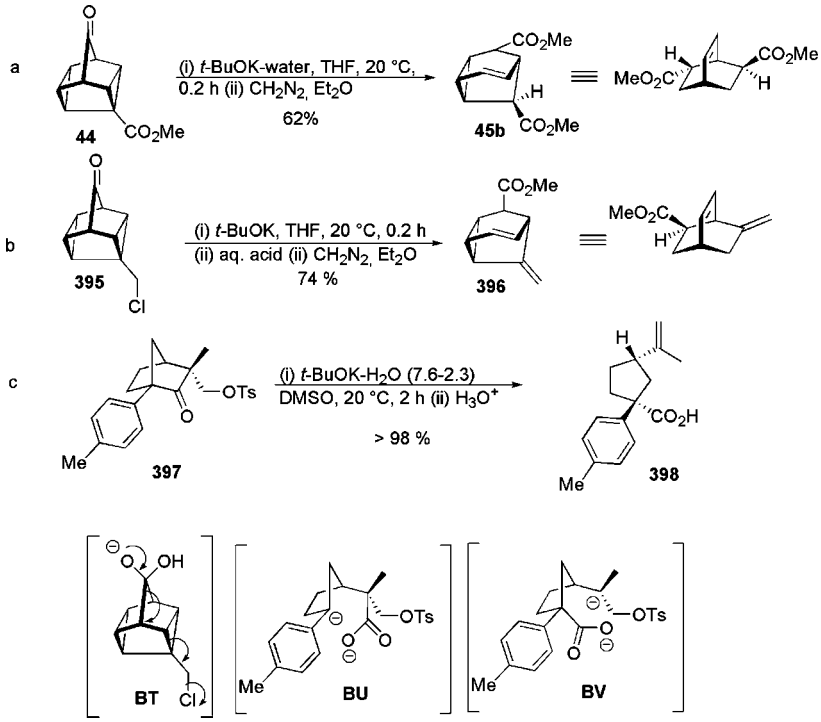
**4.2.7.6. Reactions of "Anhydrous Potassium Hydroxide" Involving Tandem Haller−Bauer Scission−Grob Fragmentation of Ketones Bearing a Carbanion Stabilizing Group or a Leaving Group in the *β*-Position.** *4.2.7.6.1. General Uses.* In some cases, the carbanion generated by the scission of the carbonyl carbon and the α-carbon reacts further. We have reported at the beginning of this Review some specific results using wet potassium hydroxide for that purpose [section 1.2 (Schemes 1, 4, 5, 6, 8);[22] section 2.1.2 (Schemes 15, 16, 17)]. "APH" has also been used for the same purpose, and, except in rare cases, the two methods have not yet been compared.

"APH" involves much milder conditions than those using instead wet metal hydroxides. This is effectively the case of **44**, **395**, and **397** (Scheme 78).[36,136]

For example, reaction of the γ-keto ester **44** with "APH" produces after acidic workup **45b** (Scheme 78, entry a). It results from a Haller−Bauer scission of the ketone α-carbon,carbonyl-group carbon bond followed by the fragmentation of the cyclopropane ring that finally produces the ester enolate whose protonation leads to **45b** expected to be the kinetic and least stable stereoisomer.[36] This result has to be compared to that already described that uses instead sodium hydroxide (50% aqueous solution in benzene), which requires heating at reflux for 10 h and only delivers the thermodynamically more stable diastereoisomer **45a** (Scheme 15, compare to Scheme 78).[36]

The tandem scission−fragmentation reaction disclosed above proceeds any time the scission is able to generate a carbanion, which can produce after a further C,C bond cleavage (i) a better stabilized carbanion such as (a) **44**, which produces the ester enolate **K** and at the same time allows strain release by cyclopropane ring-opening (Schemes 15 and 78), or (b) **373**, which leads to **374** through the formation of the stabilized anion **BM** that involves the sequential cleavage of two cyclopropane rings (Scheme 74, entry c), or (ii) a C,C double bond by a *β*-elimination reaction

**Scheme 78**




expelling a heteroatom $\gamma$ to the postulated carbanion (Scheme 78, entries b,c).[36,136] In the latter case, the tetrahedral intermediate **BT** formed through addition of hydroxide ion from the *syn*-face of **395** is perfectly poised, with *anti*-periplanar arrangement of the electrofugal and nucleofugal groups at the termini and the intervening C,C bonds, for a higher order fragmentation process (Scheme 78, entry b).[36] This mechanism has not, however, been proved to occur synchronously.[36]

The same *anti*-periplanar arrangement can be also achieved from **397** in the way to generate **398**. It is interesting that the terminal C,C double bond so generated does not migrate to produce the more stable disubstituted C,C double bond, during exposure of the strongly basic reaction conditions (Scheme 78, entry c).[136]

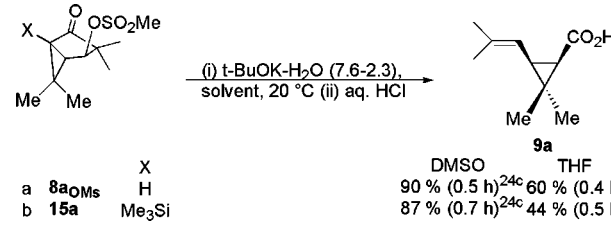
The structures of ketones **44**, **373**, and **395** possess a plane of symmetry, and therefore each of the two C,C bonds attached to the carbonyl group can be indistinctly cleaved. This is not the case for **397** whose cleavage exclusively leads to **398** via the putative **BV** intermediate, whereas it could have instead produced the particularly stable benzylic carbanion **BU** (Scheme 78).[136]

*4.2.7.6.2. Synthesis of cis-Chrysanthemic Acid Using "APH"*

The results described above, especially the ease with which "APH" promotes the scission and the fragmentation of ketone **44** to **45b**, encouraged us to test its reactivity toward the mesylate $\mathbf{8a_{OMs}}$, which produces, on reaction with KOH in aqueous DMSO ("WPH"), *cis*-chrysanthemic acid **9a** with a miserable yield via a tandem Haller−Bauer-scission−Grob-fragmentation reaction.[24c]

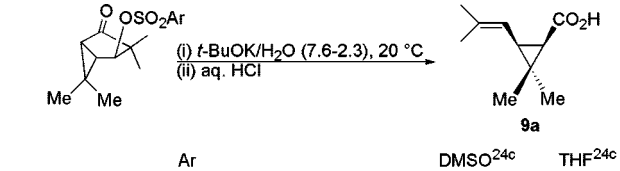
To our delight, we observed that "APH" promotes in DMSO the transformation of the bicyclic ketomesylate $\mathbf{8a_{OMs}}$ to *cis*-chrysanthemic acid **9a**. The transformation takes place under much milder conditions that with "WPH" (20 °C, 0.5 h instead of 70 °C, 2 h), with high reproducibility, in much higher yield (90% instead of 5%), and without the concomitant formation of polymeric compounds **14a** (Scheme 79, entry a, compare to Schemes 1 and 6).[24c] The same conditions

**Scheme 79**




| | | X | DMSO | THF |
|---|---|---|---|---|
| a | $\mathbf{8a_{OMs}}$ | H | 90 % (0.5 h)[24c] | 60 % (0.4 h)[24c] |
| b | **15a** | $Me_3Si$ | 87 % (0.7 h)[24c] | 44 % (0.5 h)[24c] |

**Scheme 80**




| | | Ar | DMSO[24c] | THF[24c] |
|---|---|---|---|---|
| a | $\mathbf{8a_{OTs}}$ | Ph | 86 % (0.3 h) | 84 % (1 h) |
| b | $\mathbf{8a_{MB}}$ | 2,4,6$(Me)_3$Ph | 80 % (0.75 h) | 95 % (0.5 h) |
| c | $\mathbf{8a_{PB}}$ | 2,4,6$(i\text{-}Pr)_3$Ph | 83 % (0.75 h) | |

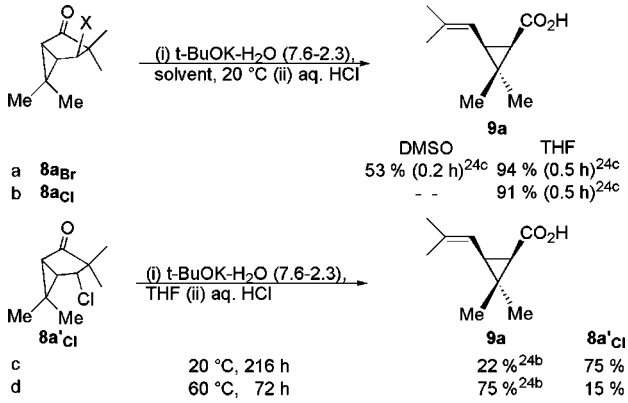
applied to the trimethylsilyl derivative **15a** also produced *cis*-chrysanthemic acid **9a** with similar yield (Scheme 79, entry b). The latter results imply that "APH" is also able to promote desilylation of **15a** (Scheme 79, entry b; compare to Scheme 7).[24c]

"APH" is also able to transform in THF rather than in DMSO the bicyclic ketomesylates $\mathbf{8a_{OMs}}$ and **15a** to *cis*-chrysanthemic acid **9a** at 20 °C, but the reaction proceeds in much lower yields unless it is carried out for longer time (Scheme 79).[24c]

Successful syntheses of *cis*-chrysanthemic acid **9a** have been achieved in even better yields from related arylsulfonyl derivatives (Scheme 80).[24c] As was already pointed out for the related mesylates, the reaction of tosylate $\mathbf{8a_{OTs}}$ is slightly slower in THF than in DMSO, but increasing the reaction time to 1 h results in similar yields (Scheme 80, entry a).

The more hindered 2,4,6-trimethyl- $\mathbf{8a_{MB}}$ and 2,4,6-triisopropyl sulfonyl $\mathbf{8a_{PB}}$ derivatives react much faster with

**Scheme 81**




"APH" than with "WPH" in DMSO (0.75 h at 20 °C instead of 48 h at 55 °C; Scheme 80, entries b,c)[24c] and contrary to the related mesylate $\mathbf{8a_{OMs}}$ and tosylate $\mathbf{8a_{OTs}}$ react faster with "APH" in THF than in DMSO (Scheme 80, entries b,c; compare to Scheme 79, entry a and Scheme 80, entry a).[24c]

The ratio of $\mathbf{8a_{OTs}}$/*t*-BuOK/$H_2O$ 1/7.6/2.3 used in this work, which is close to the one proposed by Swan[46] and Gassman,[51] provides **9a** in the highest yield and in the shortest time (Scheme 79). Performing the reaction in THF with (i) 1/4.4/2.2, (ii) 1/3.6/1.1, and (iii) 1/2.2/2.2 ratios implying lower amounts of *t*-BuOK or relatively higher percentage of water provides chrysanthemic acid **9a** in lower yields, much longer time, and with recovery of some starting material: **9a** (%)/recovered $\mathbf{8a_{OTs}}$ (%)/reaction time (h), (i) 60/6/24 h, (ii) 64/8/4 h, and (iii) 7/64/52 h, respectively (compare to Scheme 80, entry a).[24c]

The tandem scission−fragmentation reaction does not take place if *t*-BuONa is used instead of *t*-BuOK in THF (1/7.6/2.3 ratio) because $\mathbf{8a_{OTs}}$ is recovered, in up to 97%, after 36 h at 20 °C. It nevertheless occurs efficiently in DMSO but is slower than with *t*-BuOK (72/0/8 h, compare to Scheme 80, entry a). Reaction of $\mathbf{8a_{OTs}}$ with *t*-BuOLi in DMSO under the conditions described above for "APH" gives a symbolic yield of chrysanthemic acid **9a** (2%).[24c]

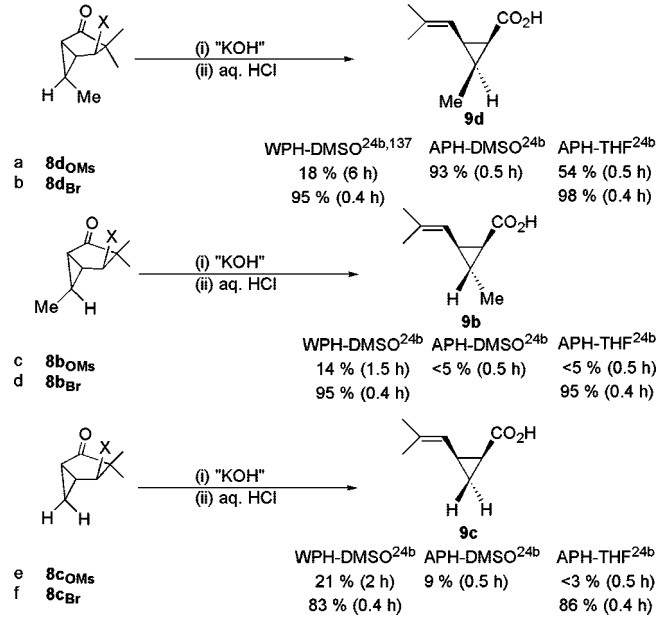
"APH" efficiently transforms the related $\beta$-bromo $\mathbf{8a_{Br}}$ and $\beta$-chloro $\mathbf{8a_{Cl}}$ ketones to *cis*-chrysanthemic acid **9a** (Scheme 81, entries a,b). Contrary to the related mesylate $\mathbf{8a_{OMs}}$ and tosylate $\mathbf{8a_{OTs}}$, the reaction of "APH" with the $\beta$-halogeno ketones **8a** is better achieved in THF than in DMSO (Scheme 81, entry a; see also Scheme 37, entry a), and both $\mathbf{8a_{Br}}$ and $\mathbf{8a_{Cl}}$ react at almost the same rate with "APH" in THF (Scheme 81, compare entries a and b).[24b]

"APH" also reacts with the *endo*-isomer $\mathbf{8a'_{Cl}}$ and produces chrysanthemic acid **9a**, but the reaction is much slower than that of its *exo*-isomer $\mathbf{8a_{Cl}}$ (Scheme 81, entries c,d, compare to entry b). Surprisingly, the transformation of $\mathbf{8a'_{Cl}}$ to **9a** cannot be achieved using instead "WPH" in DMSO, and $\mathbf{8a'_{Cl}}$ is completely destroyed within 2 h at 60 °C.

"WPH" in DMSO, however, transforms $\mathbf{8a_{Br}}$ to **9a**, but it requires higher temperature (70 °C) and longer time than when carried out with "APH" (Scheme 81, entry a, compare to Scheme 1, entry b).[22e,24b]

All of the *exo*-beta-bromo ketones $\mathbf{8b_{Br}}$, $\mathbf{8c_{Br}}$, and $\mathbf{8d_{Br}}$ missing one or two methyl groups on the cyclopropane react almost similarly to $\mathbf{8a_{Br}}$ toward both "APH" and "WPH" and deliver extremely good yields of the corresponding desmethyl- and didesmethyl-*cis*-chrysanthemic acids **9b**, **9c**, and **9d** with complete stereocontrol (Scheme 82, entries b,d,f, as compared to Scheme 81, entry a and Scheme 1, entry b).

**Scheme 82**[a]




[a] WPH: 6 equiv of KOH, DMSO−$H_2O$ (4:1), 70 °C. APH: *t*-BuOK/$H_2O$ (7.6:2.3), 20 °C.

This is different for the related *exo*-mesylates $\mathbf{8b_{OMs}}$, $\mathbf{8c_{OMs}}$, and $\mathbf{8d_{OMs}}$ (Scheme 82, entries a,c,e). The reactivity of "APH" and "WPH" toward $\mathbf{8d_{OMs}}$ parallels that of $\mathbf{8a_{OMs}}$, which also bears the *endo*-methyl group on the cyclopropane (Scheme 82, entry a, as compared to Scheme 79, entry a, and Scheme 6).

The reactivity of $\mathbf{8b_{OMs}}$ and $\mathbf{8c_{OMs}}$, which both miss the *endo*-methyl group, is different from that of $\mathbf{8d_{OMs}}$ (Scheme 82, compare entries c,e and compare also to entry a). In such cases, the yields of desmethyl- and didesmethyl-*cis*-chrysanthemic acids **9b** and **9c** using "WPH" as well as "APH" reagents are extremely poor and even poorer when "APH" is used, although the starting materials are consumed within a short reaction time (Scheme 82, entries c,e).

Thus, "WPH" and "APH" both allow the synthesis of *cis*-chrysanthemic acid analogues **9** from bromides $\mathbf{8b_{Br}}$ and $\mathbf{8c_{Br}}$ in excellent yields, whereas they both provide low yields of **9** from the corresponding mesylates $\mathbf{8b_{OMs}}$ and $\mathbf{8c_{OMs}}$.

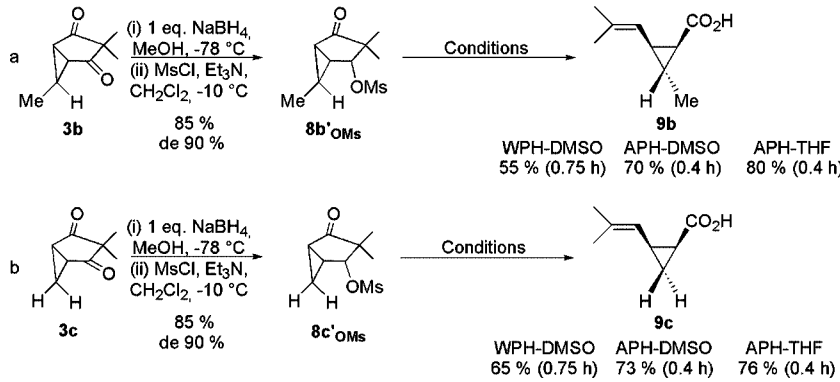
The *endo*-mesylates $\mathbf{8b'_{OMs}}$ and $\mathbf{8c'_{OMs}}$ behave similarly toward both "WPH" and "APH", but their behavior is different from that of their *exo*-stereoisomers $\mathbf{8b_{OMs}}$ and $\mathbf{8c_{OMs}}$ because they are transformed to desmethyl- and didesmethyl-*cis*-chrysanthemic acids **9b** and **9c** in good yields (Scheme 83).[24b,137]

Thus, whereas "WPH" is able to achieve the tandem scission−fragmentation in a short time (0.75 h, 70 °C), leading to desmethyl- and didesmethyl-*cis*-chrysanthemic acids **9b** and **9c** in reasonable yields,[137] "APH" in DMSO or THF does it better in one-half the time (0.4 h instead of 0.75 h) and at lower temperature (20 °C instead of 70 °C).[24b]

Finally, desmethyl- and didesmethyl-*endo*-mesylates $\mathbf{8c'_{OMs}}$ and $\mathbf{8d'_{OMs}}$ react very rapidly with "APH" (0.4 h, 20 °C, Scheme 83). Their behavior is different from that of the related *endo*-chloride $\mathbf{8a'_{Cl}}$, bearing a gem-dimethyl group on the cyclopropane ring, which reacts very slowly (72 h, 60 °C, Scheme 81, entries c,d).[24b]

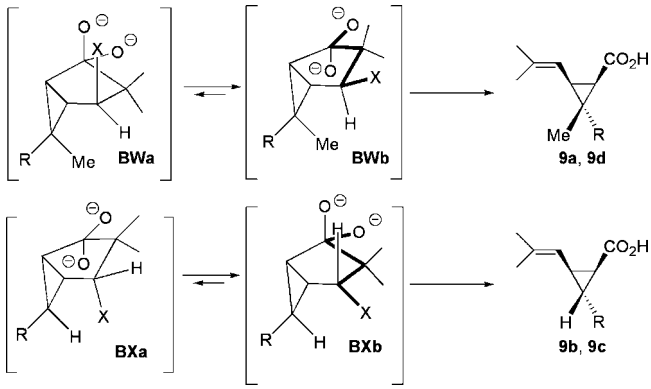
Thus, the best method for obtaining *cis*-vinyl-cyclopropane carboxylic acids **9** from mesylates **8** requires using "APH" and the (i) *exo*-mesylates $\mathbf{8a_{OMs}}$ and $\mathbf{8d_{OMs}}$, bearing an *endo*-

**Scheme 83**[a]




[a] WPH: 6 equiv of KOH, DMSO−$H_2O$ (4:1), 70 °C. APH: *t*-BuOK/$H_2O$ (7.6:2.3), 20 °C.

**Scheme 84**




methyl group on the cyclopropane ring, for the synthesis of *cis*-chrysanthemic acids **9a** (Scheme 79, entry a) and of its desmethyl analogue **9d** (Scheme 82, entry a), which possesses all of its groups on the cyclopropane ring cis to each other, respectively,[24b] and the (ii) *endo*-mesylates $\mathbf{8b'_{OMs}}$ and $\mathbf{8c'_{OMs}}$, bearing an *endo*-hydrogen on the cyclopropane ring, for the synthesis of didesmethyl *cis*-chrysanthemic acids **9c** (Scheme 83, entry b) and of its desmethyl anologue **9b**, which possesses one methyl group trans to each of the two other groups on the cyclopropane ring (Scheme 83, entry a).[24b]

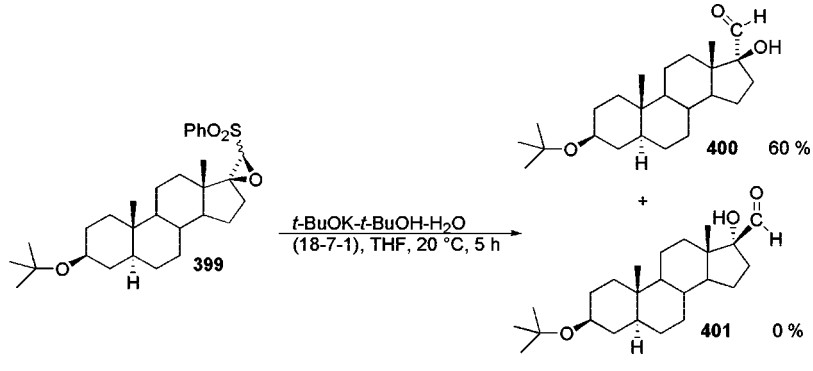
Those methods are surprisingly in complete agreement with the ease of synthesis of the diverse mesylates $\mathbf{8_{OMs}}$ from the related $\beta$-diketones **3**.

In fact, the endo mesylates $\mathbf{8a'_{OMs}}$ and $\mathbf{8d'_{OMs}}$ are extremely difficult to prepare because they are unstable and decompose around 0 °C.[137] The related alcohols **4a′** and **4d′** are, however, easy to produce stereoselectively from the diketones **3a** and **3d** and sodium borohydride in methanol if the reaction is carried out at −78 °C or lithium triethyl borohydride at 20 °C.[137] Their stereoisomeric mesylates $\mathbf{8a_{OMs}}$and $\mathbf{8d_{OMs}}$ are thermally stable but were much more difficult to get from the related diketones **3a** and **3d** because it requires reduction of one of their carbonyl groups, hindered by the *endo*-methyl group, stereoselectively by their most hindered *endo*-faces. Nevertheless, performing the reduction of the diketones **3a** and **3d** by sodium borohydride in the presence of 1 equiv of cerium trichloride in cold methanol (−78 °C, Scheme 1, entry a) allows the synthesis of the related *exo*-alcohols **4a** and **4d** in extremely high yield and extremely high stereocontrol.[137]

*endo*-Mesylates $\mathbf{8b'_{OMs}}$ and $\mathbf{8cpm'_{OMs}}$ bearing an *endo*-hydrogen on the cyclopropane ring are easy to get from the corresponding alcohols **4b′** and **4c′**, themselves produced by stereoselective reduction[137] of the diketones **3b** and **3c** by their least hindered face using sodium borohydride in methanol at −78 °C, as described above for **4a′** and **4d′**.[137] It is important to note that the reaction of cerium trichloride and sodium borohydride with diketones **3b** and **3c** is not stereoselective.[137]

It is difficult to rationalize all of these results, but we can assume that favored conformations **BWb** and **BXb** could be different when the *endo*-methyl group is present (**BWb**) or missing (**BXb**), and therefore the antiperiplanar arrangement, which is usually the preferred one in the fragmentation reactions, could be achieved with axial or equatorial leaving groups, respectively, especially if "APH" is used because dialkoxides can be generated (Scheme 84, compare to Scheme 28).

**Scheme 85**



### 4.3. "APH" Monitored Ring-Opening of Epoxy-sulfones to α-Hydroxy-aldehydes

"APH" proved to be an excellent nucleophilic reagent for the transformation of epoxy-sulfones to α-hydroxy-aldehydes.[138] In fact, exposure of epoxy-sulfones to hydroxide ion under various conditions lets the starting material be recovered ($NaOH-H_2O_2$) or produces intractable mixtures.[138] The success of "APH" in this process has been ascribed to the formation of base stable dimers of the α-hydroxy aldehydes, which in most cases revert to free α-hydroxy aldehydes on acidification at the end of the reaction.[138] The "APH" ring-opening of the epoxysulfone **399** proved to proceed by hydroxide attack at the α- and not at the β-position because it leads stereoselectively to **400** and not to its epimer **401** (Scheme 85).[138]

This reaction is a key step in the two-step homologation of ketones to α-hydroxy aldehydes.[138]

## 5. Conclusion

We have gathered certain evidence that reactions carried out with "naked hydroxide" ion whether produced by alkaline fusion, "anhydrous ammonium hydroxide", potassium hydroxide generated from potassium hydride and a stoichiometric amount of water, or potassium *t*-butoxide and water in the ratio of 3/1 ("APH") in non hydroxylated solvents behave differently in metal or ammonium hydroxide solutions containing water ("WPH"). "APH" proved to possess an exceptional reactivity among those "anhydrous hydroxides", but the best conditions involve an excess of reagent consisting of a strict ratio of potassium *t*-butoxide and water, so water is not present. Nevertheless, the synergetic role of the remaining potassium *t*-butoxide and of the potassium hydoxide and the *t*-butanol gererated has not yet been investigated. The success of the transformation of (i) carboxylic esters and tertiary amides to carboxylic acids, alcohols, and amines, respectively, (ii) carbamates to alcohols and amines, and (iii) ureas to amines has been attributed (a) to the high nucleophilicity of "APH" toward their carbonyl groups and (b) to the basicity of "APH", which is able to metalate the hydroxyl group of the resulting intermediate to generate a dialkoxide whose unfavorable interaction favors the scission (Scheme 28). Nevertheless, "APH" proved to be highly nucleophilic and comparatively less basic toward the reactant than the presence of potassium *t*-butoxide could have suggested. Gassman has pointed out that the latter compound is not the nucleophilic species and therefore remains, for that role, potassium hydroxide, naked or admixed with potassium *t*-butoxide, with just the amount of *t*-butanol to solubilize it at least partially. The exact nature of the basic species involved in the second step, however, has not been determined.

It is believed that other even more powerful reagents will be imagined on the model of "APH" and that proper tools will be used to determine the real nature of such reagent.

This Review is intended to (i) include in the proper context the original work[23d,24b,c] we have carried out with "APH" to synthesize vinyl cyclopropane carboxylic acids gem-dimethyl substituted on the vinyl group from 2,2-dimethylcyclohexanones bearing two leaving groups at the 3,4-position and from α,α-dimethyl cyclopentanones bearing a leaving group in the β-position and fused to a cyclopropane ring at α′,β′, and (ii) advertise and promote this unusual reagent discovered 61 years ago by Swan[46] who disclosed in a single and unique paper its exceptional reactivity and Gassman who rediscovered it and promote it.[47,51,52,95] It was also intended, in the context of EnCOrE project, to model the domain and to organize the data to extract the knowledge.[139]

## 6. Acknowledgments

This work is dedicated to Prof. Ytzak Apeloig on the occasion of his 65th birthday with extremely great appreciation for his scientific involvement in many facets.

## 7. References

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CR9003506