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Dipartimento di Chimica

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Doctorate Course:

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Doctoral Thesis

Synthesis of molecules of pharmaceutical interest by organometallic catalysis

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Contents

Abstract

Nel presente lavoro di tesi, è riportato un nuovo approccio alla sintesi di furani-3-carbossilati tramite reazione di carbonilazione ossidativa palladio-catalizzata di composti 3-in-1,2-diolici, aventi un gruppo alcolico primario o secondario sul C-1. Tutte le reazioni sono state condotte in solvente alcolico (metanolo o etanolo) in condizioni relativamente blande (100°C e 40 atm di una miscela CO-aria 4:1). I rispettivi furani carbonilati sono stati ottenuti con rese eccellenti (56-93%) attraverso un processo di etero ciclizzazione-alcossicarbonilazione-deidratazione 5-*endo*-dig sequenziale, usando l'ossigeno come ossidante esterno. In condizioni simili, i derivati 2-metil-3-in-1,2-diolici, aventi un gruppo alcolico terziario, permettono la sintesi di 4-metilene-4,5-diidrofurani-3-carbossilati con rese soddisfacenti (58-60%).

I tiofeni sono una classe molto importante di composti eterociclici. Molte molecule contenenti il nucleo tiofenico mostrano una grande varietà di attività biologiche e trovano applicazione in campo farmaceutico e cosmetico. Inoltre, sono degli intermedi sintetici molto utili nella preparazione di nuovi materiali polimerici. Nel presente lavoro è stato realizzato un nuovo percorso sintetico per la sintesi di tiofeni sostituiti a partire da 1-mercapto-3-in-2-oli, tramite *S*-eterociclizzazione PdI_2/KI-catalizzata. Il sistema catalitico PdI_2/KI, sviluppato dal gruppo di ricerca in cui è stato svolto il Dottorato, ha già dimostrato la sua efficacia nel favorire reazioni simili.

La reazione di amminocarbonilazione ossidativa di alchini funzionalizzati è uno dei metodi più versatili per la sintesi diretta di eterocicli e carbocicli carbonilati. In particolare, il sistema catalitico PdI_2/KI è un ottimo promotore per queste reazioni, in presenza di ossigeno come ossidante.

Abstract

Nell'ultima parte del lavoro è stata sviluppata una nuova sintesi di indanilideni carbossilati, applicando la reazione di amminocarbonilazione ossidativa a esteri 2-etinilbenzilmalonici, per l'ottenimento di prodotti indanilidenici carbonilati con un alto grado di selettività nei confronti del diastereoisomero *E* che, in alcuni casi, è stato isolato in maniera totalmente selettiva.

Part I

Synthesis of Furan-3-carboxylic and 4-Methylene-4,5-dihydrofuran-3-carboxylic Esters by Direct Palladium Iodide-Catalyzed Oxidative Carbonylation of 3-yne-1,2-diol derivatives.

Gabriele, B.; Mancuso, R.; Maltese, V.; Veltri, L.; Salerno, G.; *J. Org. Chem.*, **2012**, 77 (19), 8657-8668.

Introduction

1.1 Pharmacological importance of furans

Furans represent one of the most important heterocyclic compound classes and have a main role in various biological processes. Furan ring can be found in many molecules of pharmacological interest such as anti-bacterical, anti-mycotic, anti-viral and anti-oxidant compounds. There are different muscarinic agonists, characterized by the presence of a pyrrolidinfuranic bridge in their molecular structure; between them, the most interesting one is S-(-)-2-(5-methyl-2-furyl)-1-methylpyrrolidine methyliodate (fig. 1.1), a partial agonist for M_2 receptor type.[1]

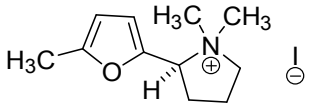
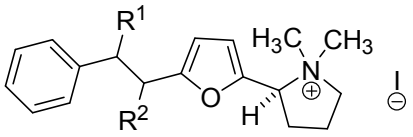


Fig. 1.1

On the other hand, pyrrolidinfuranic derivatives substituted with a hydrophobic group in position 5 of the ring behave like muscarinic antagonists (fig. 1.2), maybe because of the steric hindrance of the group mentioned above.



$R^1 = C_6H_5; C_6H_{11}$
$R^2 = H; OH$

Fig. 1.2

Recently, some heterocyclic isothioureas, bearing a furan ring in their macro-structure, showed anti-bacterical activity towards both Gram +, Gram – and yeast species; in particular S-2-(5-nitrofuran-2-yl-methyl)isothiourea (fig. 1.3) had excellent properties of gene-toxicity against all the bacterical strains tested.[2]

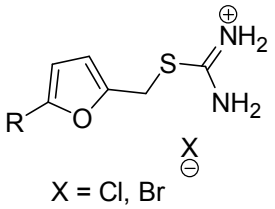


Fig. 1.3

Furan derivatives have a main role also in the inhibition of phosphodiesterase (PDE) enzymes, in particular PDE-7. This kind of compounds are used in dementia, cognitive disorders, depression and schizophrenia diseases.[3] They are also useful intermediates in organic synthesis and part of important therapeutic agents, such as ranitidine (fig. 1.4); it is one of the competitive antagonists of H_2 receptors for histamine, located on the base-lateral membrane of the parietal gastric cells. Ranitidine contrasts the effect of histamine, inhibiting the acid secretion of the gastric mucosa.[4]

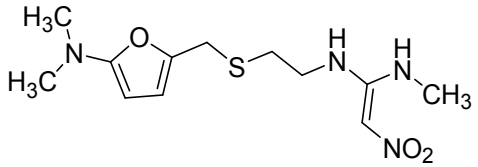


Fig. 1.4

Furan-2-carboxylic-(2-[4-[3-(4-cyclopropancarbonylphenoxy)-propyl]-pyperazin-1-yl]-1-methyl-2-oxaethyl)-amide acid (fig 1.5) is highly

selective for H_3 receptors, even if it is not an imidazolic-based compound, and it behaves as a backward agonist.[5]

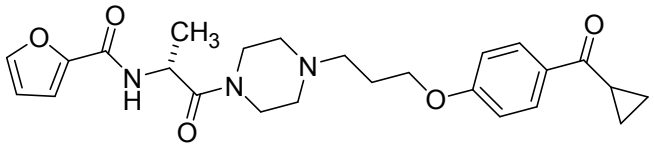


Fig. 1.5

Another commercial drug is furosemide (fig. 1.6), a diuretic molecule, through the inhibition of Na^+/K^+ flux in the kidney Henle loop. [6]

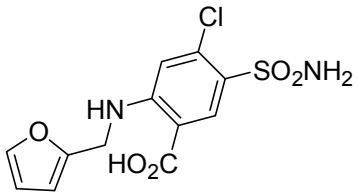


Fig. 1.6

Diloxanide furoate (fig 1.7) is an active drug in highly intestinal diseases from amaeba. [7]

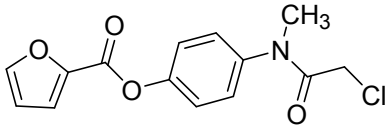


Fig. 1.7

2,5-*bis*(6-hydroxymethyl-2-thienyl)furan (fig. 1.8) (SOS, NSC 652287) is a new anti-cancer agent with a powerful and selective activity towards kidney tumoral cells.[8]

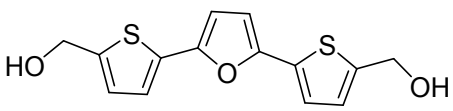


Fig. 1.8

Between the number of compounds synthesized with inhibitor effects on cyclo-oxygenase (COX) and 5-lipo-oxygenase (5-LOX), the best one on both enzymes is 1-furan-2-yl-3-pyridin-2-yl-propenone (FPP-3), (fig. 1.9).

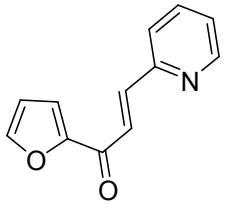


Fig. 1.9

In an in vitro study on FPP-3, its effect on pro-inflammatory citokynes was evacuate and this molecule decreases the expression of nitric oxide synthase enzyme and the production of tumor necrosis factor (TNF-α) too.[9]

1.2 Furans and pesticides

Pesticides are very important in farming, since they are used to eradicate a great number of parasites. There are many troubles in pesticide synthesis and toxicity towards mammals, but different studies were carried out and, in particular, furan derivatives showed lower toxicity towards mammal cells, in comparison with classical fosforamide-based compounds (fig 2.1; **a**, **b**).[10]

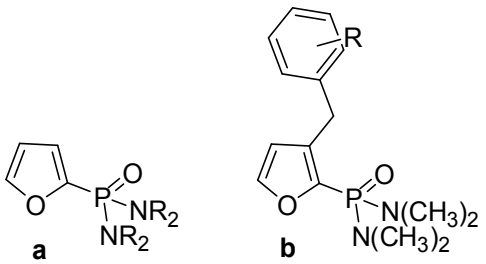


Fig 2.1

In the same field also weed-killers have a main role: a class of these compounds includes furan nucleus in its structure (fig. 2.2).[11]

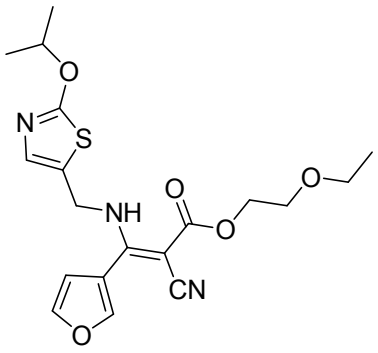
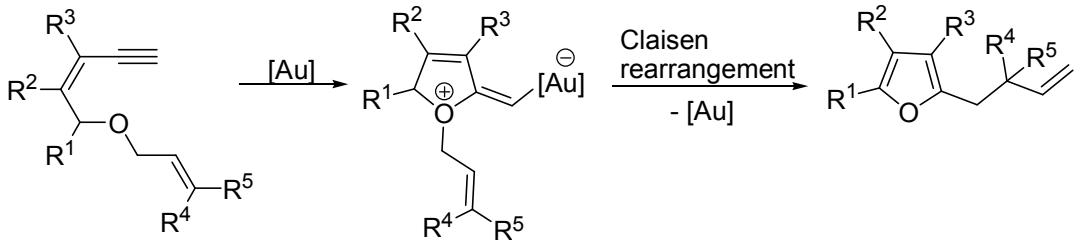


Fig 2.2

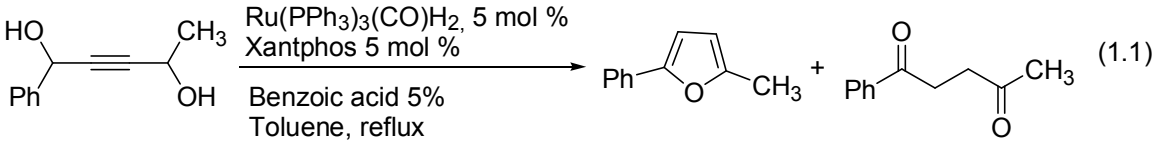
1.3 Synthesis of furan derivatives

There are many synthetic strategies known in literature to obtain substituted furan derivatives. Recently a procedure which includes meta-catalyzed cyclization of allenic and alkynyl derivatives to reach poly-substituted furans has been developed. The synthetic path consists in a Au-catalyzed cycloisomerization of ynenylallyl-ethers.[12] The following Scheme shows the Claisen rearrangement through a concerted mechanism which leads to the functionalized furan.



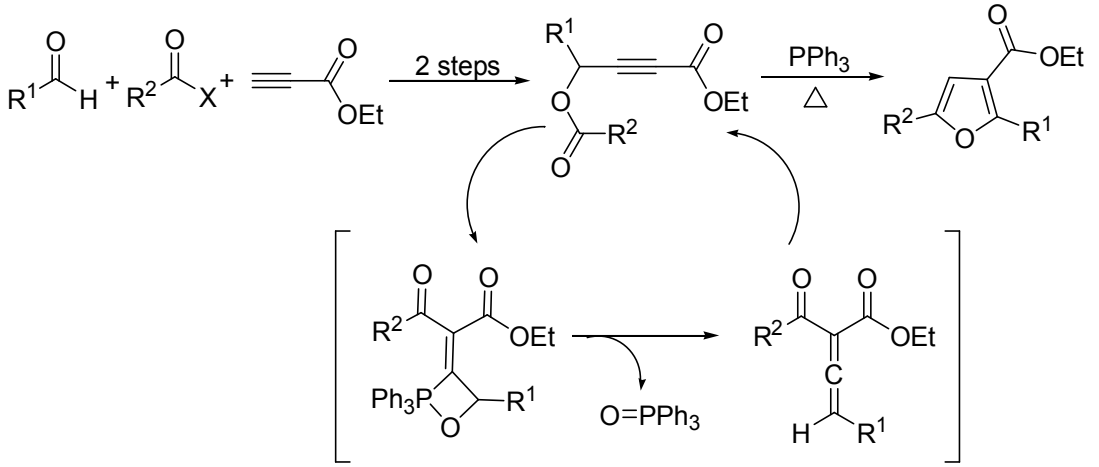
Scheme 1.1

An alkynyldiol derivative could also be used as substrate, in the presence of $Ru(PPh_3)_3(CO)H_2$/Xantphos, benzoic acid, at 80°C in toluene and then refluxing for 24h.[13]



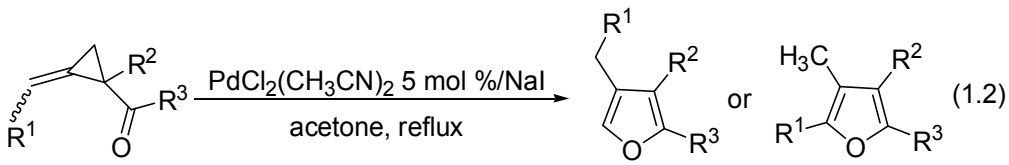
(1.1)

In another synthetic pathway, there was no need of metal catalysts, but the generation and isomerization *in situ* of allenic carbonyl compounds was observed. In Scheme 1.2 is reported a reaction with an acyloxybutynoate, which reacts with a stoichiometric amount of triarylphosphine and then, through a reductive condensation, leads to substituted furans.[14]



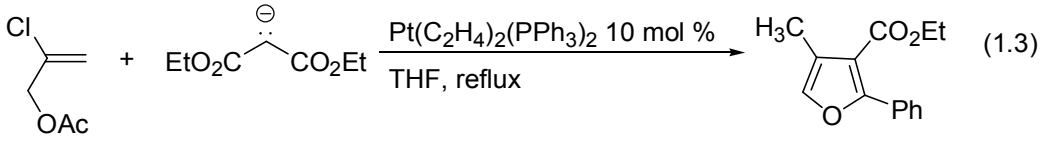
Scheme 1.2

Cyclopropene derivatives are very interesting, especially in the Pd(II)-catalyzed regio-selective cycloisomerization, to synthesize furans.[15]



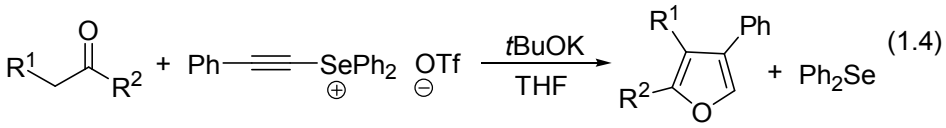
(1.2)

Pd-catalyzed reaction of 2-chloro-2-propenyl acetate with sodium ethylbenzoate in THF reflux leads to the formation of 3-(ethoxycarbonyl)-2-phenyl-4-methylfuran.



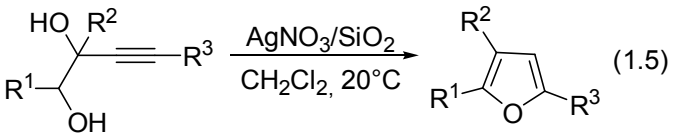
(1.3)

In this reaction platinum acts as an electronic acceptor with a similar function of a carbonyl group in the addition/elimination mechanism between hydrochloric acid and an alcoxy derivative.[16] We can obtain substituted furans from the reaction of diphenyl(phenylethynyl)-selenium triflate with molecules of the kind $R^1CH_2COR^2$.[17]



(1.4)

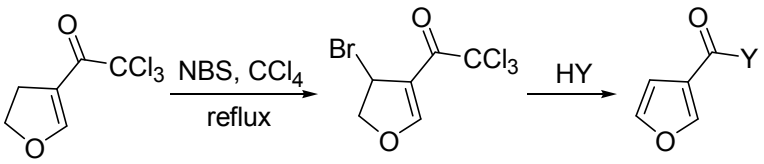
Silver salts are well known as allene activators in cyclization reactions. Conjugated allenes with ketones and alkynylpyrimidon derivatives are both converted in the corresponding furans by the use of silver (I) nitrate, following Marshall rules.[18]



(1.5)

These procedures involve the cyclization of acyclic compounds bearing a carboxylic group in suitable position. A simple method for the synthesis of furan-3-carboxylic acid and its derivatives, starts from 4-trichloroacetyl-2,3-dihydrofuran. The synthesis consists in two steps: first the dihydrofuran

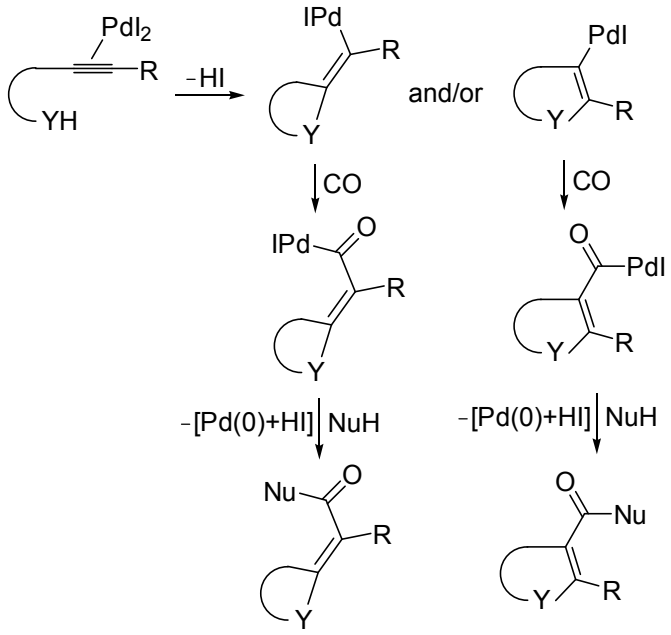
derivative reacts with N-bromosuccinimide in the presence of a peroxide as the catalyst to give 3-bromo-2,3-dihydrofuran intermediate (not isolated). Then is the turn of 3-chloroacetylenfuran and finally, after basic treatment, to the desired product.[19]



Scheme 1.3

Results and discussion.

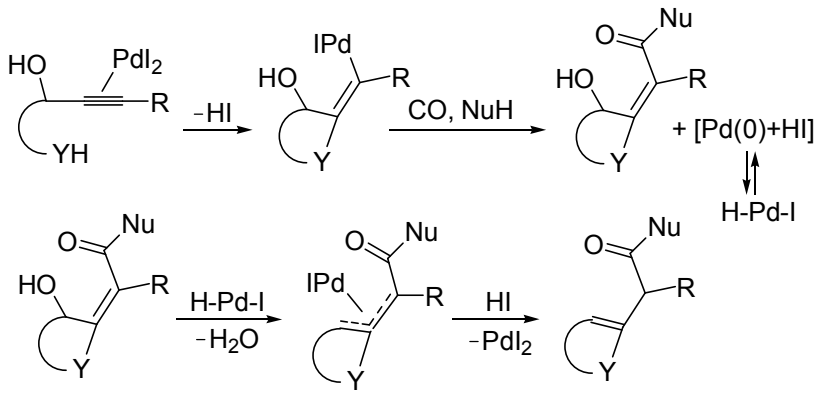
PdI_2/KI-catalyzed heterocyclization-alkoxycarbonylation or heterocyclization-aminocarbonylation of acetylenic substrates bearing a suitably placed nucleophilic group is a powerful methodology for the direct synthesis of important carbonylated heterocycles.[202122] The heterocyclization-carbonylation sequence is promoted by PdI_2, which is then reduced to Pd(0) at the end of the cycle (Scheme 2.1; in this and in the following schemes anionic iodide ligands are omitted for clarity).



Scheme 2.1. Mechanism of PdI_2-Promoted Heterocyclization-Carbonylation of Acetylenic Substrates Bearing a Suitably Placed Nucleophilic Group (Y = O or NR'; NuH = OH, NR")

Therefore, the presence of an oxidant is needed in order to make the process catalytic. In some particular cases, an external oxidant is not needed if the product initially ensuing from the carbonylation process still possess a reducible functional group able to reoxidize Pd(0) to Pd(II), as

exemplified in Scheme 2.2. Usually, however, the reaction is carried out under oxidative conditions, in the presence of oxygen as the external oxidant, which is able to reconvert Pd(0) to PdI_2 through the oxidation of HI (also ensuing from the carbonylation process) to I_2 followed by oxidative addition of the latter to Pd(0) (Scheme 2.3).



Scheme 2.2. Mechanism of PdI_2-Catalyzed Heterocyclization-Carbonylation of Acetylenic Substrates Bearing a Suitably Placed Nucleophilic Group and a Reducible Function (Y = O or NR'; NuH = OH, NR")

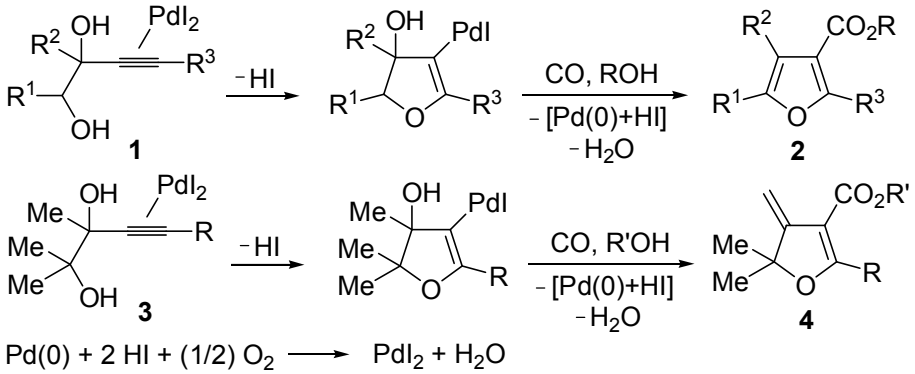
$$2\ HI + (1/2)\ O_2 \longrightarrow I_2 + H_2O$$
$$Pd(0) + I_2 \longrightarrow PdI_2$$

Scheme 2.3. Mechanism of Reoxidation of Pd(0) to PdI_2 in the Presence of O_2 as External Oxidant

A preliminary communication of this work was published recently,[23] in which was realized a novel synthesis of furan-3-carboxylic esters by PdI_2-catalyzed oxidative heterocyclization-alcoxycarbonylation of 3-yn-1,2-diol derivatives.

Here is reported a full account of the PdI_2/KI-catalyzed oxidative 5-*endo*-*dig* heterocyclodehydration-alkoxycarbonylation of readily available 3-yne-1,2-diol derivatives **1** and **3** to give furan-3-carboxylic and

methylenedihydrofuran-3-carboxylic esters **2** and **4**. In these cases, the heterocyclization-alkoxycarbonylation process is accompanied by dehydration, either from the CH(R^1)-C-OH moiety of **1** (resulting in aromatization and leading to **2**) or from the Me-C(2)-OH moiety of **3** (leading to **4**).

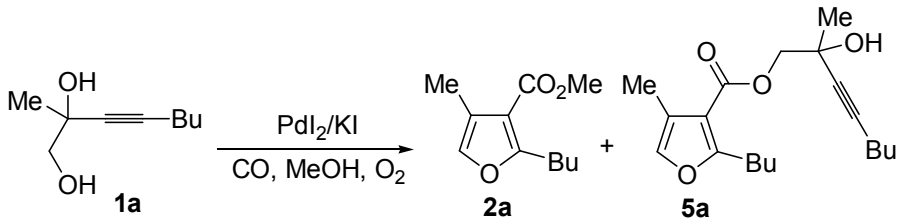


Scheme 2.4. Formation of Furan-3-carboxylic and 4-Methylene-5,6-dihydrofuran-3-carboxylic esters **2** and **4** by PdI_2-Catalyzed Oxidative Carbonylation of 3-yne-1,2-diol derivatives **1** and **3**, respectively.

2-Methyloct-3-yne-1,2-diol **1a** (R^1 = H, R^2 = Me, R^3 = Bu), readily available by alkynylation of hydroxyacetone, was chosen as model substrate to test the reactivity of 3-yne-1,2-diol derivatives **1** bearing a primary alcoholic group at C-1 under oxidative carboylation conditions in the presence of catalytic amounts of PdI_2/KI. The first attempt was carried at 80 °C in MeOH as the solvent (**1a** concentration = 0.25 mmol per mL of MeOH, **1a**:KI:PdI_2 molar ratio = 100:10:1) under 20 atm of a 4:1 mixture of CO-air. A mixture of the desired furan-carboxylic methyl ester derivative **2a** (28% GLC yield) and 2-hydroxy-2-methyloct-3-ynyl 2-butyl-4-methylfuran-3-carboxylate **5a** (derived from nucleophilic displacement by substrate **1a** rather than MeOH, 13 % GLC yield) at a substrate conversions of 70% was obtained under these conditions, as

shown in Table 1, entry 1. Although **5a** could not be isolated at the pure state by conventional chromatographic techniques.

Table 2.1. PdI_2/KI-Catalyzed Oxidative Carbonylation Reactions of 2-Methyloct-3-yne-1,2-diol 1a Under Different Conditions[a]



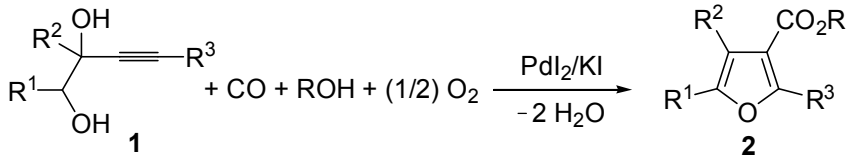
Entry	KI:PdI_2 molar ratio	T (°C)	substrate concentration [b]	P_{CO}/P_{air} (atm)	yield of **2a**[c] (%)	yield of **5a**[c] (%)	total yield (%)
1[d]	10	80	0.25	16/4	28	13	41
2	10	100	0.25	16/4	55	9	64
3	10	80	0.05	16/4	60	2	62
4	10	80	0.02	16/4	45	1	46
5	5	80	0.25	16/4	52	15	67
6	2	80	0.25	16/4	37	9	46
7	10	80	0.25	32/8	49	32	81

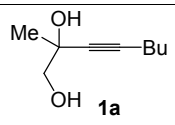
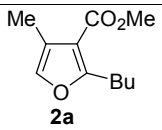
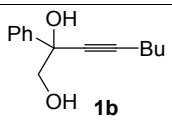
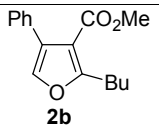
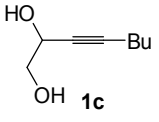
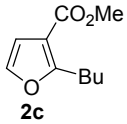
[a] All reactions were carried out in MeOH for 2 h in the presence of 1 mol % of PdI_2. Unless otherwise noted, substrate conversion was quantitative. [b] Mmol of starting **1a** per mL of MeOH. [c] Based on starting **1a**, by GLC. The formation of unidentified heavy products (chromatographically immobile materials) accounted for the difference between the substrate conversion and the product yield. [d] Substrate conversion was ca. 70% (determined by GLC).

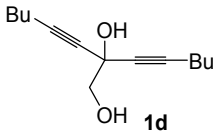
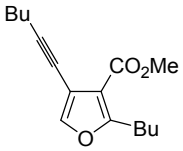
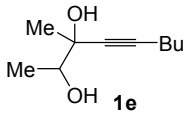
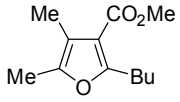
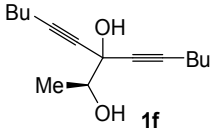
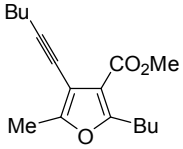
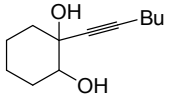
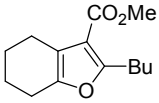
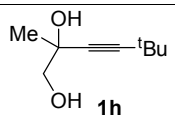
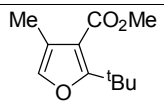
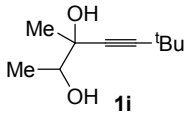
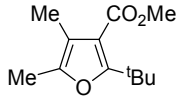
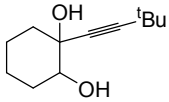
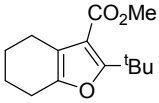
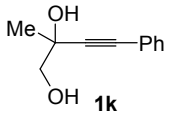
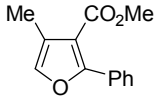
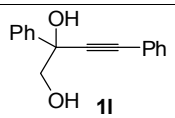
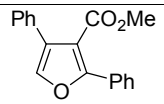
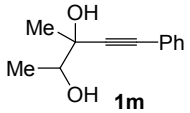
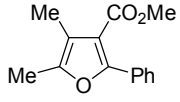
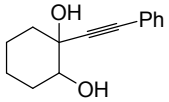
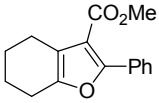
In order to improve this initial result, we then screened the reaction parameters; the results obtained are shown in Table 2.1, entries 2-7. As can be seen from Table 2.1, entry 2, an increase of the temperature to 100 °C

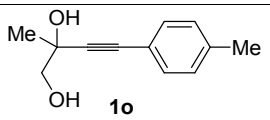
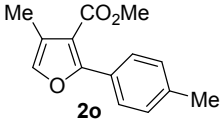
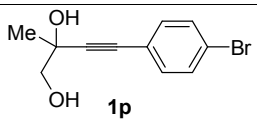
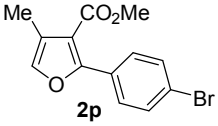
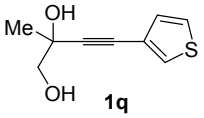
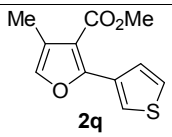
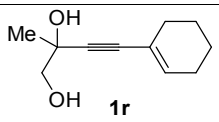
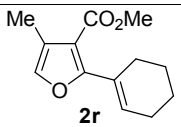
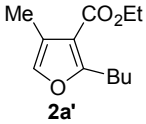
caused an improvement of both the total yield and the selectivity of the process toward the formation of **2a**. A similar effect was observed when substrate concentration was decreased (entry 3) and when the KI:PdI_2 ratio was lowered to 5 (entry 5). A significant increase of the total yield (81%, by GLC) was obtained when the total pressure was raised to 40 atm (entry 7). By carrying out the reaction under the optimized conditions (**1a**:KI:PdI_2 molar ratio = 100:5:1, 100 °C, 32 atm of CO, 8 atm of air, **1a** concentration = 0.05 mmol per mL of MeOH), methyl 2-butyl-4-methylfuran-3-carboxylate **2a** was selectively obtained in 76% GLC yield (69% isolated, Table 2.2, entry 1).

Table 2.2. Synthesis of Furan-3-Carboxylic Esters 2 by PdI_2/KI-Catalyzed Oxidative Carbonylation of 3-Yne-1,2-Diols 1 Bearing a Primary or Secondary Alcoholic Group at C-1[a]



Entry	**1**	R	PdI_2 (mol %)	*t* (h)	**2**	yield of **2**[b] (%)
1	 **1a**	Me	1	2	 **2a**	69[c]
2	 **1b**	Me	1	2	 **2b**	61
3	 **1c**	Me	1	2	 **2c**	72

4	 **1d**	Me	1	2	 **2d**	69
5	 **1e**	Me	1	2	 **2e**	65
6	 **1f**	Me	1	2	 **2f**	61
7	 **1g**	Me	1	5	 **2g**	62
8	 **1h**	Me	1	2	 **2h**	49
9	 **1i**	Me	1	2	 **2i**	40
10	 **1j**	Me	1	5	 **2j**	68
11	 **1k**	Me	1	2	 **2k**	60
12	 **1l**	Me	1	2	 **2l**	56
13	 **1m**	Me	1	2	 **2m**	42
14	 **1n**	Me	1	5	 **2n**	64

15	 **1o**	Me	1	2	 **2o**	62
16	 **1p**	Me	1	15	 **2p**	58
17	 **1q**	Me	1	2	 **2q**	75
18	 **1r**	Me	1	2	 **2r**	70
19	**1a**	Et	1	2	 **2a'**	66
20	**1a**	Me	2	2	**2a**	81
21	**1b**	Me	2	2	**2b**	74
22	**1c**	Me	2	2	**2c**	85
23	**1d**	Me	2	2	**2d**	80
24	**1e**	Me	2	2	**2e**	78
25	**1f**	Me	2	2	**2f**	73
26	**1g**	Me	2	2	**2g**	75
27	**1h**	Me	2	2	**2h**	60
28	**1i**	Me	2	2	**2i**	58
29	**1j**	Me	2	2	**2j**	75
30	**1k**	Me	2	2	**2k**	71
31	**1l**	Me	2	2	**2l**	65
32	**1m**	Me	2	2	**2m**	56
33	**1n**	Me	2	2	**2n**	70
34	**1o**	Me	2	2	**2o**	76
35	**1p**	Me	2	2	**2p**	81

36	**1q**	Me	2	2	**2q**	88
37	**1r**	Me	2	2	**2r**	93
38	**1a**	Et	2	2	**2a'**	78
39	**1g**	Et	2	2	**2g'**	69

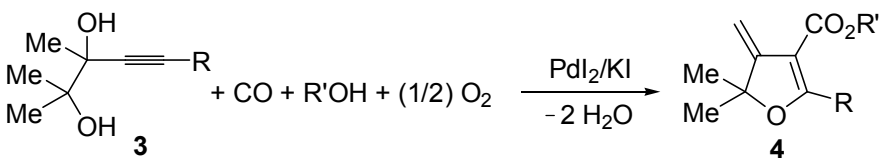
[a] All carbonylation reactions were carried out at 100 °C under 40 atm (at 25 °C) of a 4:1 mixture of CO-air, in ROH as the solvent (0.05 mmol of starting **1** per mL of solvent) and with a KI:PdI_2 molar ratio = 5. Conversion of **1** was quantitative in all cases. [b] Isolated yield based on starting **1**. [c] The GLC yield was 76%.

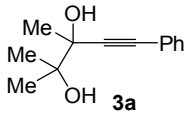
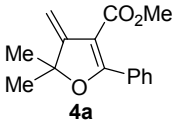
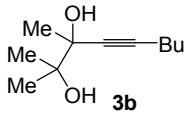
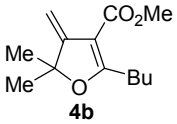
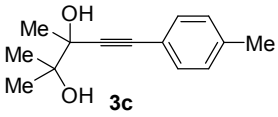
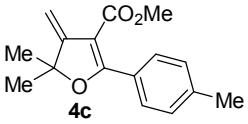
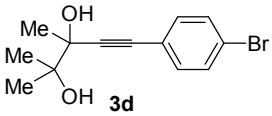
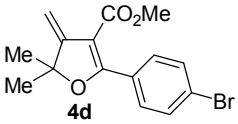
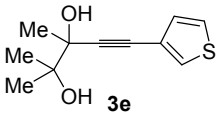
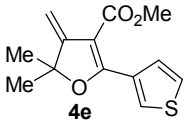
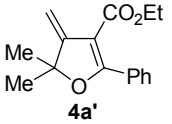
The generality of the process was then verified by testing the reactivity of other differently substituted 3-yne-1,2-diols **1b-r**, bearing a primary or secondary alcoholic group at C-1, as well as different substituents at C-2 and C-4. As can be seen from the results reported in Table 2.2, entries 1-18, the process was quite general, the corresponding furan-3-carboxylic esters **2a-r** being obtained in satisfactory yields. Only in the case of 2,5,5-trimethylhex-3-yne-1,2-diol **1h** and 3,6,6-trimethylhept-4-yne-2,3-diol **1i** (bearing a sterically hindered substituent on the triple bond) and 3-methyl-5-phenylpent-4-yne-2,3-diol **1m** the yields of the corresponding furan-3-carboxylic ester derivative **2h**, **2i** and **2m** were lower (49%, 40% and 42%, respectively, Table 2.2, entries 8, 9, and 13, respectively); these yields, however, could be raised to 60%, 58% and 56%, respectively, using a higher catalyst loading (2 mol %, Table 2.2, entries 27, 28, and 32, respectively). Indeed, the use of a **1**:PdI_2 molar ratio of 50 caused a significant improvement of the product yields with all the substrates tested (56-93%, entries 20-37; compare with entries 1-19, respectively). The reaction also worked well with dialkynyl substrates, such as 2-(hex-1-ynyl)oct-3-yne-1,2-diol **1d** and 3-(hex-1-ynyl)non-4-yne-2,3-diol **1f**, which were converted into the corresponding furan-3-carboxylic esters **2d** and **2f**

without affecting the alkynyl substituent at C-3 (Table 2.2, entries 4, 6, 23, 25), which would allow further functionalization at the furan ring. As can be seen from entries 19, 38, and 39 (Table 2.2), a higher alcohol, such as EtOH, could also be used instead of MeOH still with good results.

We also tested the reactivity of 2-methyl-3-yne-1,2-diols **3**, bearing a tertiary alcoholic group, for which aromatization is clearly not possible. Interestingly, when we allowed to react 2,3-dimethyl-5-phenylpent-4-yne-2,3-diol **3a** under the already optimized for substrates **1**, using 1 mol % of PdI_2 and for 2 h, methyl 5,5-dimethyl-4-methylene-2-phenyl-4,5-dihydrofuran-3-carboxylate **4a** was obtained in 67% isolated yield, resulting from 5-*endo-dig* cyclization-alkoxycarbonylation with simultaneous dehydration from the Me-C(3)-OH moiety of (Table 2.3, entry 1). This yield remained practically the same working with a higher catalyst loading (Table 2.3, entry 2). Then the same method was applied to other similar substrates **3b-e**, bearing different substituents on the triple bond. As shown in Table 2.3, entries 2-5, the corresponding 4-methylene-4,5-dihydrofuran-3-carboxylates **4b-e** were obtained in good yields with all the substrates tested. In the case of 2,3-dimethylnon-4-yne-2,3-diol **3b**, better results were obtained working at 80 °C under more concentrated conditions (Table 2.3, entry 2). The reaction could also be carried out successfully in EtOH as the solvent, as shown by entry 7 (Table 2.3).

Table 2.3. Synthesis of 4-Methylene-4,5-dihydrofuran-3-carboxylates 4 by PdI_2/KI-Catalyzed Oxidative Carbonylation of 2-Methyl-3-yne-1,2-Diols 3 Bearing a Tertiary Alcoholic Group at C-1[a]



Entry	**3**	**4**	yield of **4**[b] (%)
1	 **3a**	 **4a**	67
2[c]	**3a**	**4a**	66
3[d]	 **3b**	 **4b**	58
4	 **3c**	 **4c**	64
5	 **3d**	 **4d**	63
6	 **3e**	 **4e**	70
7	**3a**	 **4a'**	55

[a] Unless otherwise noted, all carbonylation reactions were carried out at 100 °C for 2 h under 40 atm (at 25 °C) of a 4:1 mixture of CO-air, in ROH as the solvent (0.05 mmol of starting **1** per mL of MeOH) and with a substrate:KI:PdI_2 molar ratio = 100:5:1. Conversion of **3** was quantitative in all cases. [b] Isolated yield based on starting **3**. [c] The reaction was carried out with 2 mol % of catalyst. [d] The reaction was carried out at 80 °C with a substrate concentration of 0.2 mmol of **3b** per mL of MeOH.

Conclusions.

In conclusion, we have reported a novel, general, and atom-economical method for the one-step synthesis of furan-3-carboxylic esters **2** and 4-methylene-4,5-dihydrofuran-3-carboxylic esters **4** starting from very simple building blocks (3-yne-1,2-diol derivatives **1** or **3**, respectively, CO, O_2, and ROH). The generality of the process has been assessed with different 3-yne-1,2-diols **1** and **3**, with the corresponding heterocyclic derivatives **2** and **4**, respectively, obtained in fair to excellent yields.

Part I

Part I

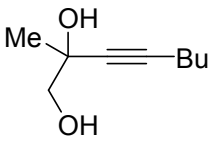
Experimental section

General Experimental Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ solutions at 300 or 500 MHz and 75 or 125 MHz, respectively, with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. IR spectra were taken with an FT-IR spectrometer. Mass spectra were obtained using a GC-MS apparatus at 70 eV ionization voltage or a mass spectrometer equipped with a turbo ion spray ionization source in the positive mode [ion spray voltage (IS) 4500 V; curtain gas 10 psi; temperature 25 °C; ion source gas (1) 20 psi; declustering and focusing potentials 50 and 400 V, respectively]. Microanalyses were carried out at our analytical laboratory. All reactions were analyzed by TLC on silica gel 60 F_{254} or on neutral alumina and by GLC using a gas chromatograph and capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase or using a gas chromatograph and a capillary columns with diethyl tertbutylsilyl-β-cyclodextrine as the stationary phase. Column chromatography was performed on silica gel 60 (70-230 mesh). Evaporation refers to the removal of solvent under reduced pressure.

Preparation of Substrates 1. Substrates **1** were prepared by alkynylation of the appropriate α-hydroxy aldehyde or α-hydroxy ketone using an excess of $R^3C{\equiv}CLi$ or $R^3C{\equiv}CMgBr$, as described below.

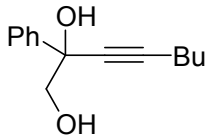
General Procedure for the Preparation of 3-yne-1,2-diols 1a, 1b, 1e, 1h, 1i, 1k-m, 1o-r. To a solution of BuLi in hexane (1.6 M) (25 mL, 40 mmol) was added anhydrous THF (6 mL) and hexane (25 mL) under nitrogen. The resulting mixture was cooled at -40 °C and maintained under stirring. A

solution of the 1-alkyne (44.5 mmol) (1-hexyne: 3.66 g; *tert*-butylacetylene: 3.66 g; phenylacetylene: 4.54 g; 3-ethynylthiophene: 4.81 g; 1-ethynylcyclohex-1-ene: 4.72 g; *p*-bromophenylacetylene: 8.06 g; *p*-methylphenylacetylene 5.17 g) in anhydrous THF (6 mL) was added dropwise under nitrogen to the cooled mixture followed by a solution of LiBr (1.56 g, 18.0 mmol) in anhydrous THF (6 mL). After stirring for 0.5 h at -40°C, a solution of the appropriate α-hydroxy ketone (17 mmol) [α-hydroxyacetone (purity 90%): 1.40 g; 3-hydroxybutan-2-one: 1.50 g; α-hydroxyacetophenone: 2.31 g] in anhydrous THF (5 mL) was added under nitrogen. The mixture was allowed to stir at the same temperature for 2 h, then it was allowed to warm up to room temperature. Satd aqueous NH_4Cl (40 mL) was added, followed by Et_2O (50 mL). Phases were separated and the aqueous phase extracted with Et_2O (50 mL × 3). The collected organic phases were washed with brine to neutral pH and dried over Na_2SO_4. After filtration and evaporation of the solvent, products **1b**, **1e**, **1i**, **1k**, **1l**, **1m**, **1p**, and **1q** were purified by column chromatography on silica gel using the following mixtures as eluent: 6:4 hexane-AcOEt (**1b**, **1l**), 7:3 hexane-AcOEt (**1e**, **1m**), 8:2 hexane-acetone (**1i**, **1q**), 9:1 hexane-acetone (**1k**), 95:5 hexane-acetone (**1p**). Crude products **1a**, **1h**, **1o** and **1r** were sufficiently pure to be used as such for the carbonylation reaction.

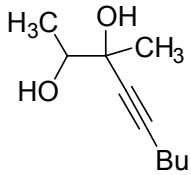


2-Methyloct-3-yne-1,2-diol (1a). Yield: 2.39 g, starting from 1.40 g of α-hydroxyacetone (90%). Colorless amorphous solid, mp 33-35 °C, lit.[9] 32-34 °C IR (KBr): ν = 3367 (m, br), 2937 (m), 2247 (w), 1469 (m), 1380 (m), 1256 (m), 1147 (m), 1111 (m), 1059 (m), 950 (m), 919 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.61 (distorted d, J = 11.0, 1 H), 3.47 (distorted d,

br, J = 11.0, 1 H), 3.30 (s, br, 2 H), 2.20 (t, J = 6.7, 2 H), 1.54-1.33 (m, 4 H), 1.43 (s, 3 H), 0.91 (t, J = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 85.3, 82.1, 71.0, 68.7, 30.9, 25.9, 22.0, 18.4, 13.5; GC-MS (EI, 70 eV): *m/z* = (absent) 156 [M^+], 125 (100), 95 (10), 91 (14), 81 (21), 79 (24), 69 (50), 67 (25), 55 (42); anal. calcd for $C_9H_{16}O_2$ (156.22): C, 69.19; H, 10.32; found C, 69.13; H, 10.35.

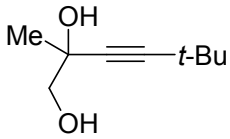


2-Phenyloct-3-yne-1,2-diol (1b). Yield: 3.33 g, starting from 2.31 g of α-hydroxyacetophenone (90%). Yellow oil. IR (film): ν = 3341 (m, br), 2931 (m), 2247 (w), 1588 (m), 1495 (m), 1385 (m), 1245 (s), 1074 (m), 1033 (m), 903 (m), 758 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65-7.58 (m, 2 H), 7.40-7.26 (m, 3 H), 3.69 (distorted dd, J = 10.9, 4.2, 1 H), 3.61 (distorted dd, J = 10.9, 6.3, 1 H), 3.23 (s, 1 H), 2.48-2.38 (m, 1 H), 2.29 (t, J = 6.9, 2 H), 1.60-1.36 (m, 4 H), 0.92 (t, J = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.5, 128.3, 128.0, 125.9, 87.8, 80.7, 73.9, 72.3, 30.7, 22.0, 18.5, 13.6; GC-MS (EI, 70 eV): *m/z* = 218 (absent) [M^+], 188 (52), 187 (100), 141 (11), 128 (26), 115 (53), 109 (58), 105 (67), 91 (37), 79 (46), 77 (52), 66 (38); anal. calcd for $C_{14}H_{18}O_2$ (218.29): C, 77.03; H, 8.31; found C, 77.12; H, 8.29.

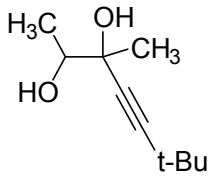


3-Methylnon-4-yne-2,3-diol (1e). Yield: 1.71 g, starting from 1.50 g of 3-hydroxybutan-2-one (59%). Mixture of diastereomers A+B, A:B ratio ca. 3:1, determined by ^{1}H NMR. Yellow oil. IR (film): ν = 3388 (s, br), 2962

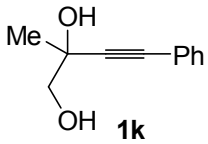
(m), 2235 (m), 1458 (m), 1372 (m), 1107 (m), 1076 (m), 929 (w), 904 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.77 [A (q, 1 H, J = 6.5, C*H*CH_3)], 3.59 [B (q, 1 H, J = 6.5, C*H*CH_3)], 3.13 [B, (s, br, 1 H, OH)], 2.78 [A (s, br, 1 H, OH)], 2.66 [A (s, br, 1 H, OH)], 2.42 [B (s, br, 1 H, OH)], 2.23 [B (t, J = 7.1, 2 H, C*H*$_2$$CH_2CH_2CH_3$)], 2.20 [A (t, J = 7.1, 2 H, C*H*$_2$$CH_2CH_2CH_3$)], 1.56-1.35 [A (m, 4 H, C*H*$_2$C*H*$_2$$CH_3$), + B (m, 4 H, C*H*$_2$C*H*$_2$$CH_3$)], 1.40 [B (s, 3 H, C*H*$_3$COH)], 1.39 [A (s, 3 H, C*H*$_3$COH)], 1.27 [B (d, J = 6.5, CHC*H*$_3$)], 1.22 [A (d, J = 6.5, CHC*H*$_3$)], 0.91 [A (t, J =7.3, 3 H, CH_2C*H*$_3$) + B (t, J =7.3, 3 H, CH_2C*H*$_3$)]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 86.1 (B), 85.5 (A), 82.5 (A + B), 74.5 (B), 74.0 (A), 72.1 (B), 71.3 (A), 30.9 (B), 30.8 (A), 26.1 (A + B), 23.7 (B), 22.0 (A), 18.3 (B), 16.7 (A), 13.6 (B), 13.5 (A); MS (ESI+, direct infusion) *m/z* = 193 [$(M+Na)^+$]; anal. calcd for $C_{10}H_{18}O_2$ (170.25): C, 70.55; H, 10.66; found C, 70.61; H, 10.64.



2,5,5-Trimethylhex-3-yne-1,2-diol (1h). Yield: 2.12 g, starting from 1.40 g of α-hydroxyacetone (80%). Colorless amorphous solid, mp 90-91 °C, lit.[10] 95.5-96. IR (KBr): ν = 3362 (m, br), 3222 (m, br), 2968 (m), 2226 (vw), 1458 (m), 1422 (m), 1360 (m), 1267 (m), 1188 (m), 1147 (m), 1059 (s), 960 (m), 716 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.61 (distorted d, J = 11.0, 1 H), 3.46 (distorted d, J = 11.0, 1 H), 3.39 (s, br, 1 H), 3.05 (s, br, 1 H), 1.43 (s, 3 H), 1.21 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 93.6, 80.3, 70.9, 68.6, 31.1, 27.3, 25.8; GC-MS (EI, 70 eV): *m/z* = 156 (M^+, absent), 125 (100), 107 (14), 95 (18), 91 (20), 79 (24), 69 (22), 67 (20), 57 (16); anal. calcd for $C_9H_{16}O_2$ (156.22): C, 69.19; H, 10.32; found C, 69.12; H, 10.34.



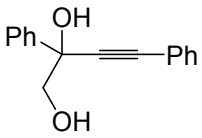
3,6,6-Trimethylhept-4-yne-2,3-diol (1i). Mixture of diastereomers A+B, A:B ratio ca. 2.5:1, determined by ^{1}H NMR. Yield: 1.88 g, starting from 1.50 g of 3-hydroxybutan-2-one (65%). Colorless amorphous solid, mp 50-52 °C. IR (KBr): ν = 3427 (s, br), 3231 (m, br), 2968 (m), 2225 (vw), 1631 (m), 1456 (m), 1384 (m), 1268 (m), 1099 (m), 1011 (w), 974 (m), 927 (m), 894 (w), 842 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.76 [A (q, J = 6.1, 1 H, C*H*CH$_3$)], 3.58 [B (q, J = 6.1, 1 H, C*H*CH$_3$)], 3.10 [B (s, br, 1 H, OH)], 2.78 [A (s, br, 1 H, OH)], 2.65 [A (s, br, 1 H, OH)], 2.35 [B (s, br, 1 H, OH)], 1.39 [B (s, 3 H, C*H*$_3$COH)], 1.38 [A (s, 3 H, C*H*$_3$COH)], 1.26 [B (d, J = 6.1, 3 H, CHC*H*$_3$)], 1.22 [B (s, 9 H, *t*-Bu)], 1.21 [A (s, 9 H, *t*-Bu)], 1.21 [A (d, J = 6.1, 3 H, CHC*H*$_3$)]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 94.4 (B), 93.9 (A), 80.9 (A + B), 74.4 (B), 74.0 (A), 71.8 (B), 71.2 (A), 31.1 (B), 31.0 (A), 27.3 (B), 26.2 (A), 23.6 (A + B), 18.4 (B), 16.8 (A); MS (ESI+, direct infusion): *m/z* = 193 [(M+Na)$^{+}$]; anal. calcd for $C_{10}H_{18}O_2$ (170.25): C, 70.55; H, 10.66; found C, 70.61; H, 10.63.



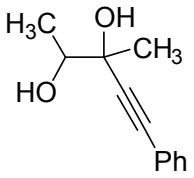
1k

2-Methyl-4-phenylbut-3-yne-1,2-diol (1k). Yield: 2.55 g, starting from 1.40 g of α-hydroxyacetone (85%). Colorless amorphous solid, mp. 105-106 °C, lit.[11] 105-106 °C. IR (KBr): ν = 3398 (s, br), 2977 (w), 2932 (m), 2232 (vw), 1491 (m), 1403 (m), 1376 (m), 1341 (m), 1283 (m), 1136 (m), 1090 (m), 1050 (s), 1028 (m), 986 (w), 900 (m), 764 (s), 696 (m), 677 (m) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.45-7.33 (m, 5 H, Ph), 5.42 (s, 1 H, CH$_3$CO*H*), 5.02 (t, J = 6.3, 1 H, CH$_2$O*H*), 3.52-3.26 (m, 2 H, C*H*$_2$OH),

1.42 (s, 3 H, Me); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 131.2, 128.5, 128.2, 122.7, 94.2, 81.9, 69.6, 67.8, 26.2; GC-MS (EI, 70 eV): *m/z* = 176 (3) [M^+], 146 (18), 145 (100), 129 (11), 115 (11), 102 (8), 77 (10); anal. calcd for $C_{11}H_{12}O_2$ (176.21): C, 74.98; H, 6.86; found C, 75.12; H, 6.84.

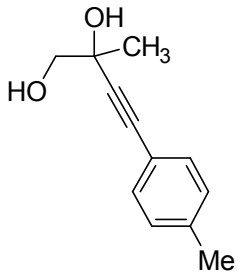


2,4-Diphenylbut-3-yne-1,2-diol (1l). Yield: 3.44 g, starting from 2.31 g of α-hydroxyacetophenone (85%). Colorless amorphous solid, mp 104-105 °C, lit.[12] 106 °C. IR (KBr): ν = 3352 (s, br), 3222 (s, br), 2213 (w), 1489 (m), 1412 (m), 1100 (m), 1069 (s), 1033 (m), 903 (m), 758 (s), 690 (m) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.70-7.64 (m, 2 H, aromatic), 7.51-7.45 (m, 2 H, aromatic), 7.42-7.26 (m, 6 H, aromatic), 3.89-3.67 (m, 2 H, C*H*$_2$OH), 3.54 (s, br, 1 H, PhCO*H*), 2.65 (s, br, 1 H, CH$_2$O*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 141.04, 141.01, 131.9, 128.8, 128.43, 128.38, 128.26, 126.0, 89.5, 86.7, 74.2, 72.2; GC-MS (EI, 70 eV): *m/z* = 238 (<0.5) [M^+], 208 (45), 207 (100), 191 (13), 189 (15), 178 (18), 130 (24), 129 (93), 105 (66), 77 (54); anal. calcd for $C_{16}H_{14}O_2$ (238.28): C, 80.65; H, 5.92; found C, 80.71; H, 5.90.



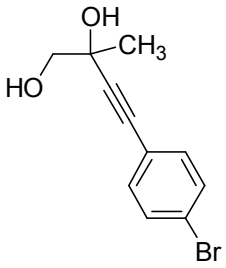
3-Methyl-5-phenylpent-4-yne-2,3-diol (1m). Mixture of diastereomers A+B, A:B ratio ca. 1.5:1, determined by ^{1}H NMR. Yield: 1.91 g, starting from 1.50 g of 3-hydroxybutan-2-one (59%). Colorless amorphous solid, mp 61-62 °C. IR (KBr): ν = 3568 (m, br), 3301 (m, br), 2986 (m), 2231 (w), 1598 (w), 1490 (m), 1443 (m), 1370 (m), 1123 (s), 1077 (m), 961 (m),

939 (m), 846 (w), 756 (s), 691 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.48-7.39 [A (m, 2 H, aromatic) + B (m, 2 H, aromatic)], 7.35-7.28 [A (m, 3 H, aromatic) + B (m, 3 H, aromatic)], 3.92 [A (q, J = 6.2, 1 H, C*H*CH_3)], 3.71 [B (q, J = 6.2, 1 H, C*H*CH_3)], 2.93 [B (s, br, 1 H, OH)], 2.44 [A (s, br, 1 H, OH)], 2.34 [A (s, br, 1 H, OH)], 2.03 [B (s, br, 1 H, OH)], 1.53 [B (s, 3 H, C*H*$_3$COH)], 1.52 [A (s, 3 H, C*H*$_3$COH)], 1.38 [B (distorted d, J = 6.2, 3 H, C*H*$_3$CH), 1.31 [A (distorted d, J = 6.1, C*H*$_3$CH)]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.86 (B), 131.82 (A), 128.61 (A), 128.56 (B), 128.4 (A + B), 122.6 (A or B), 122.5 (B or A), 91.2 (A), 89.9 (B), 85.5 (B), 84.9 (A), 74.6 (B), 73.9 (A), 72.5 (B), 71.8 (A), 25.9 (B), 23.6 (A), 18.6 (B), 16.8 (A); MS (ESI+, direct infusion): *m/z* = 213 [$(M+Na)^+$]; anal. calcd for $C_{12}H_{14}O_2$ (190.24): C, 75.76; H, 7.42; found C, 75.83; H, 7.40.

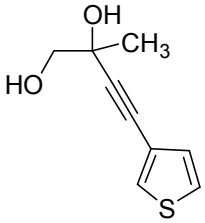


2-Methyl-4-*p*-tolyl-but-3-yne-1,2-diol (1o). Yield: 2.72 g, starting from 1.40 g of α-hydroxyacetone (84%). Colorless amorphous solid, mp= 88-90 °C; lit.[13] 88-90 °C. IR (KBr): ν = 3386 (s, br), 3312 (s, br), 2235 (vw), 1637 (m), 1510 (m), 1384 (m), 1265 (m), 1122 (m), 1057 (m), 951 (w), 815 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35-7.26 (m, 2 H, aromatic), 7.11-7.03 (m, 2 H, aromatic), 3.75 (distorted d, J = 11.2, 1 H, C*H*HOH), 3.57 (distorted d, J = 11.2, 1 H, CH*H*OH), 3.39 (s, br, 2 H, 2 OH), 2.31 (s, 3 H, C*H*$_3$C$_6$H$_4$), 1.52 (s, 3 H,C*H*$_3$COH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.6, 131.7, 129.0, 119.2, 89.9, 84.5, 70.6, 69.0, 25.4, 21.5; GC-MS (EI, 70 eV): *m/z* = 190 (6) [M^+], 172 (3), 159 (100), 143 (9), 128 (10), 115 (25), 91 (6),

89 (6), 77 (5); anal. calcd for $C_{12}H_{14}O_2$ (190.24): C, 75.76; H, 7.42; found C, 75.81; H, 7.41.

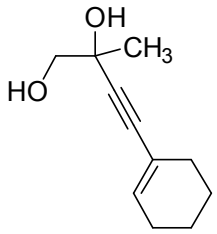


4-(4-Bromophenyl)-2-methylbut-3-yne-1,2-diol (1p). Yield: 3.47 g, starting from 1.40 g of α-hydroxyacetone (80%). Yellow amorphous solid, mp 84-85 °C. IR (KBr): ν = 3304 (s, br), 2930 (m), 2233 (vw), 1490 (m), 1384 (m), 1139 (m), 1064 (s), 755 (m), 669 (m) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 7.50-7.23 (m, 4 H, BrC_6H_4), 5.40 (s, 1 H, $CH_3CO\mathit{H}$), 5.00 (t, br, J = 6.2, 1 H, $CH_2O\mathit{H}$), 3.49-3-34 (m, 2 H, CH_2OH), 1.40 (s, 3 H, Me); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 131.2, 128.5, 125.8, 122.6, 94.2, 81.8, 69.5, 67.7, 26.2; GC-MS (EI, 70 eV): *m/z* = 176 (2), 145 (100), 129 (11), 115 (11), 112 (8), 89 (4), 77 (11); anal. calcd for $C_{11}H_{11}BrO_2$ (255.11): C, 75.76; H, 7.42; Br, 31.32; found C, 75.81; H, 7.41; Br, 31.30.



2-Methyl-4-thiophen-3-ylbut-3-yne-1,2-diol (1q). Yield: 2.63 g, starting from 1.40 g of α-hydroxyacetone (85%). Yellow amorphous solid, mp 81.0-83.0 °C. IR (KBr): ν = 3334 (s, br), 3237 (s, br), 2232 (vw), 1384 (m), 1357 (w), 1168 (m), 1127 (m), 1053 (s), 952 (w), 780 (s), 627 (m) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 7.74-7.64 (m, 1 H, H-2 on thiophene ring), 7.58 (dd, J = 4.9, 3.2, 1 H, H-5 on thiophene ring), 7.11 (d, br, J = 4.9, 1 H, H-4 on thiophene ring), 5.37 (s, 1H, $CH_3CO\mathit{H}$), 4.98 (t, J = 6.1, 1

H, CH_2OH), 3.50-3.31 (m, 2 H, CH_2OH), 1.38 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 129.5, 128.9, 126.4, 121.5, 93.4, 77.3, 69.5, 67.7, 26.2; GC-MS (EI, 70 eV): *m/z* = 182 (7) [M^+], 151 (100), 135 (9), 121 (5), 109 (11), 89 (5), 77 (6), 63 (14); anal. calcd for $C_9H_{10}O_2S$ (182.24): C, 59.32; H, 5.53; S, 17.59 ; found C, 59.39; H, 5.51; S; 17.58.

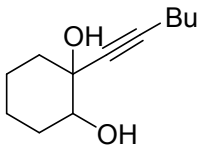


4-Cyclohex-1-enyl-2-methylbut-3-yne-1,2-diol (1r). Yield: 2.57 g, starting from 1.40 g of α-hydroxyacetone (84%). Yellow amorphous solid, mp 33-34 °C. IR (KBr): ν = 3447 (s, br), 2933 (w), 2218 (vw), 1631 (m), 1384 (s), 1056 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.17-7.04 (m, 1 H, =CH), 3.81-3.21 (m, 2 H, 2 OH), 3.66 (distorted d, *J* = 11.3, 1 H, C*H*HOH), 3.50 (distorted d, *J* = 11.3, 1 H, CH*H*OH), 2.17-2.01 (m, 4 H, =CHCH_2CH_2CH_2CH_2), 1.69-1.52 (m, 4 H, =CHCH_2CH_2CH_2CH_2), 1.46 (s, 3 H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.5, 119.9, 87.9, 86.1, 70.6, 68.8, 29.2, 25.6, 25.5, 22.2, 21.4; GC-MS (EI, 70 eV): *m/z* = 180 (9) [M^+], 150 (18), 149 (100), 115 (3), 105 (9), 91 (19), 79 (15), 77 (16), 65 (7); anal. calcd for $C_{11}H_{16}O_2$ (180.24): C, 73.30; H, 8.95; found C, 73.38; H, 8.93.

Preparation of oct-3-yne-1,2-diol 1c. To a suspension of Mg turnings (1.88 g, 77.4 mmol) in anhydrous THF (16 mL), maintained under nitrogen and under reflux, was added pure ethyl bromide (1.4 mL) to start the formation of the Grignard reagent. The remaining bromide was added dropwise in THF solution (4.0 mL of EtBr in 44 mL of THF; total amount of EtBr added: 7.88 g, 72.3 mmol). The mixture was then allowed to reflux

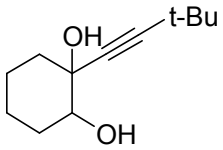
for additional 20 min. After cooling, the resulting solution of EtMgBr was transferred under nitrogen to a dropping funnel and added dropwise under nitrogen to a solution of 1-hexyne (5.91 g, 71.9 mmol) in anhydrous THF (21.6 mL) at 0 °C with stirring. After additional stirring at 0°C for 15 min, the mixture was allowed to warm up to room temperature and then maintained at 50 °C for 2 h. While warm (ca 40–45 °C), the solution of 1-hexynylmagnesium bromide thus obtained was then added dropwise under nitrogen to a pre-heated (50 °C) solution of glycolaldehyde (36 mmol) in anhydrous THF [obtained from glycolaldehyde dimer (2.16 g) in anhydrous THF (44 mL)]. The resulting mixture was allowed to stir at 50°C for additional 2 h. After cooling to room temperature, saturated NH_4Cl (100 mL) and AcOEt (40 ml) were sequentially added. Phases were separated, and the aqueous phase was extracted with AcOEt (3 × 100 mL). The collected organic layers were washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the product was purified by column chromatography on silica gel using 6:4 hexane-acetone as the eluent to give pure oct-3-yne-1,2-diol **1c**. Yield: 2.10 g, starting from 2.16 g of glycolaldehyde dimer (41%). Colorless oil. IR (film): ν = 3397 (m, br), 2957 (m), 2239 (w), 1647 (m), 1464 (w), 1148 (m), 1087 (m), 1039 (m), 876 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.48-4.41 (m, 1 H), 3.71 (distorted dd, J = 11.3, 3.4, 1 H), 3.61 (distorted dd, J = 11.3, 7.3, 1 H), 3.51 (s, br, 1 H), 3.29 (s, br, 1 H), 2.21 (td, J = 7.1, 2.0, 2 H), 1.55-1.32 (m, 4 H), 0.91 (t, J = 7.3, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 87.2, 78.0, 67.0, 63.6, 30.7, 22.0, 18.4, 13.5; GC-MS (EI, 70 eV): m/z = 142 (absent) [M^+], 125 (77), 111 (43), 110 (11), 107 (16), 95 (20), 93 (47), 91 (37), 83 (27), 79 (27), 77 (29), 71 (40); anal. calcd for $C_{18}H_{14}O_2$ (142.20): C, 67.57; H, 9.92; found C, 67.53; H, 9.90.

Preparation of 3-yne-1,2-diols 1g, 1j, 1n. To a cooled (0 °C), stirred solution of the 1-alkyne (30.8 mmol) (1-hexyne: 3.66 g; *tert*-butylacetylene: 3.66 g; phenylacetylene: 4.54 g; 3-ethynylthiophene: 4.81 g; 1-ethynylcyclohex-1-ene: 4.72 g; *p*-bromophenylacetylene: 8.06 g; *p*-methylphenylacetylene 5.17 g) in anhydrous THF (75 mL) maintained under nitrogen and was added dropwise a solution of BuLi in hexane (1.6 M) (19.3 mL, 30.9 mmol). The resulting mixture was allowed to stir at 0 °C for 0.5 h. Dodecahydrodibenzo[*b*,*e*][1,4]dioxine-4a,9a-diol (2-hydroxycyclohexanone dimer) (1.60 g, 7.0 mmol, corresponding to 14.0 mmol of 2-hydroxycyclohexanone) was added under nitrogen in portions. After additional stirring at 0 °C for additional 0.5 h, the mixture was allowed to warm up to room temperature and then satd. aqueous NH_4Cl was added followed by Et_2O (50 mL). Phases were separated and the aqueous phase extracted with Et_2O (50 mL × 3). The collected organic phases were washed with brine to neutral pH and dried over Na_2SO_4. After filtration and evaporation of the solvent, crude products **1g**, **1j**, and **1n** were sufficiently pure to be used as such for the carbonylation reaction.



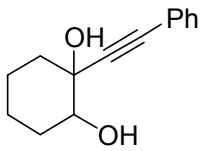
1-Hex-1-ynylcyclohexane-1,2-diol (1g). Mixture of diastereomers A+B, A:B ratio ca. 1.1:1, determined by ^{1}H NMR. Yield: 2.39 g, starting from 1.60 g of 2-hydroxycyclohexanone dimer (87%). Yellow oil. IR (film): ν = 3410 (m, br), 2934 (s), 2854 (m), 2238 (w), 1449 (s), 1250 (w), 1171 (w), 1063 (s), 1000 (m), 866 (m), cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.70 [A (dd, *J* = 7.3, 4.0, 1 H, C*H*OH)], 3.39 [B (dd, *J* = 11.3, 4.4, 1 H, C*H*OH)], 2.89 [A (s, br, 2 H, 2 OH) + B (s, br, 2 H, 2 OH)], 2.26 [B (t, *J* = 6.9, 2 H, ≡CCH_2)], 2.21 [B (t, *J* = 6.7, 2 H, ≡CCH_2)], 2.06-1.85 [A (m, 2 H,

C*H*$_2$COH) + B (m, 2 H, C*H*$_2$COH)], 1.83-1.23 [A (m, 10 H, C*H*$_2$C*H*$_2$C*H*$_2$CHOH + C*H*$_2$C*H*$_2$CH$_3$) + B (m, 10 H, C*H*$_2$C*H*$_2$C*H*$_2$CHOH + C*H*$_2$C*H*$_2$CH$_3$)], 0.92 [B (t, J = 7.3, 3 H, Me)], 0.91 [A (t, J = 7.3, 3 H, Me)]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 88.1 (A or B), 85.5 (B or A), 82.6 (A or B), 79.6 (B or A), 77.0 (A or B), 74.2 (B or A), 74.0 (A or B), 70.3 (B or A), 38.0 (A or B), 35.6 (B or A), 32.1 (A or B), 30.9 (B or A), 30.8 (A or B), 28.7 (B or A), 24.2 (A or B), 23.3 (B or A), 22.02 (A or B), 21.98 (B or A), 21.61 (A or B), 21.56 (B or A), 18.4 (A + B), 13.6 (A + B); GC-MS (EI, 70 eV): A: *m/z* = 196 (absent) [M^+], 168 (3), 154 (86), 149 (9), 137 (46), 136 (30), 121 (27), 118 (44), 108 (71), 107 (60), 97 (31), 95 (56), 94 (39), 93 (57), 91 (52), 81 (54), 79 (98), 68 (71), 67 (70), 55 (100); B: *m/z* = 196 (absent) [M^+], 168 (3) 154 (91), 149 (7), 137 (42), 136 (28), 121 (28), 118 (48), 108 (68), 107 (60), 97 (37), 95 (55), 94 (34), 93 (56), 91 (47), 81 (54), 79 (90), 77 (48), 69 (55), 68 (75), 67 (69), 55 (100); anal. calcd for $C_{12}H_{20}O_2$ (196.29): C, 73.43; H, 10.27; found C, 73.51; H, 10.25.



1-(3,3-Dimethylbut-1-ynyl)cyclohexane-1,2-diol (**1j**). Mixture of diastereomers A+B, A:B ratio ca. 1:1, determined by ^{1}H NMR. Yield: 2.28 g, starting from 1.60 g of 2-hydroxycyclohexanone dimer (83%). Colorless amorphous solid, mp 67-68 °C. IR (KBr): ν = 3387 (s, br), 2966 (m), 2939 (m), 2861 (m), 2233 (vw), 1633 (m), 1384 (m), 1361 (w), 1263 (m), 1078 (m), 997 (w), 866 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.70 [A (dd, J = 6.5, 4.0, 1 H, C*H*OH)], 3.38 [B (dd, J = 11.1, 4.2, 1 H, C*H*OH)], 2.90 [A (s, br, 2 H, 2 OH) + B (s, br, 2 H, 2 OH)], 2.07-1.85 [A (m, 2 H, C*H*$_2$COH) + B (m, 2 H, C*H*$_2$COH)], 1.83-1.23 [A (m, 6 H, C*H*$_2$C*H*$_2$C*H*$_2$CHOH) + B (m, 6 H, C*H*$_2$C*H*$_2$C*H*$_2$CHOH)], 1.25 [A or B (s, 9 H, *t*-Bu)], 1.22 [B or A

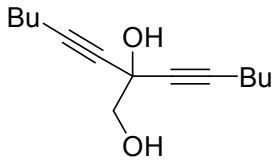
(s, 9 H, *t*-Bu)]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 96.7 (A or B), 94.1 (B or A), 80.8 (A or B), 77.9 (B or A), 77.5 (A or B), 74.0 (B or A), 73.8 (A or B), 70.1 (B or A), 38.0 (A or B), 35.3 (B or A), 32.2 (A or B), 31.1 (B or A), 31.0 (A or B), 28.7 (B or A), 27.4 (A or B), 27.3 (B or A), 24.2 (A or B), 23.3 (B or A), 22.0 (A or B), 21.1 (B or A); GC-MS (EI, 70 eV): A or B: *m/z* = 181 (3), 163 (6), 145 (4), 135 (14), 126 (22), 111 (100), 109 (24), 107 (21), 95 (20), 93 (29), 91 (28), 83 (25), 81 (22), 79 (31), 77 (24), 67 (36), 57 (37), 55 (37); B or A: *m/z* = 181 (4), 163 (8), 145 (5), 137 (13), 135 (16), 126 (22), 111 (100), 109 (28), 107 (25), 95 (21), 93 (30), 91 (30), 83 (24), 81 (24), 79 (33), 77 (25), 67 (37), 57 (35), 55 (38); anal. calcd for $C_{12}H_{20}O_2$ (196.29): C, 73.43; H, 10.27; found C, 73.52; H, 10.25.



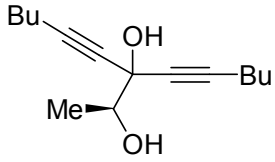
1-Phenylethynylcyclohexane-1,2-diol (1n). Mixture of diastereomers A+B, A:B ratio ca. 1:1, determined by ^{1}H NMR. Yield: 2.39 g, starting from 1.60 g of 2-hydroxycyclohexanone dimer (79%). Yellow oil. IR (film): ν = 3369 (m, br), 2937 (s), 2860 (m), 2225 (vw), 1598 (w), 1489 (m), 1443 (m), 1385 (m), 1353 (m), 1268 (m), 1059 (s), 1008 (m), 972 (w), 949 (w), 867 (m), 755 (s), 691 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51-7.39 [A (m, 2 H, aromatic), + B (m, 2 H, aromatic)], 7.35-7.20 [A (m, 3 H, aromatic), + B (m, 3 H, aromatic)], 3.85 [A (dd, *J* = 7.3, 4.0, 1 H, C*H*OH)], 3.52 [B (dd, *J* = 11.3, 4.4, 1 H, C*H*OH)], 3.37 [A (s, br, 2 H, 2 OH) + B (s, br, 2 H, 2 OH)], 2.21-1.15 [A (m, 8 H, $CH_2CH_2CH_2CH_2$) + B (m, 8 H, $CH_2CH_2CH_2CH_2$)]; ^{13}C NMR (75 MHz, CDCl3): δ = 132.1 (A or B), 131.8 (B or A), 131.7 (A or B), 128.41 (B or A), 128.37 (A or B), 128.28 (B or A), 128.23 (A or B), 122.5 (B or A), 91.6 (A or B), 88.8 (B or A), 87.3 (A or B), 84.8 (B or A), 77.2 (A or B), 74.4 (B or A), 73.9 (A or

B), 70.6 (B or A), 37.9 (A or B), 35.4 (B or A), 32.0 (A or B), 28.9 (B or A), 24.2 (A or B), 23.3 (B or A), 21.56 (A or B), 21.47 (B or A); GC-MS (EI, 70 eV): A or B: *m/z* = 216 (13) [M^+], 198 (5), 187 (12), 170 (20), 157 (42), 154 (20), 146 (100), 145 (57), 141 (39), 131 (78), 129 (93), 115 (85), 103 (37), 102 (45), 97 (28), 91 (42), 77 (45), 75 (23), 55 (43); B: *m/z* = 216 (16) [M^+], 198 (6), 187 (15), 170 (24), 157 (49), 146 (97), 145 (56), 142 (31), 141 (45), 131 (79), 129 (100), 115 (97), 103 (38), 102 (50), 97 (34), 91 (46), 77 (50), 55 (48); anal. calcd for $C_{14}H_{16}O_2$ (216.28): C, 77.75; H, 7.46; found C, 77.82; H, 7.44.

Preparation of 1,1-dialkynyl-1,2-diols 1d, 1f. A solution of 1-hexyne (4.19 g, 51.0 mmol) in anhydrous THF (8 mL) was added dropwise under nitrogen to a stirred, cooled (–78°C) mixture of BuLi (34 mL of a 1.6 M solution in hexanes, 54.4 mmol) in anhydrous THF (22 mL) and anhydrous hexane (34 mL). To the resulting mixture, maintained at – 78°C, was added, with stirring, a solution of LiBr (2.13 g, 24.5 mmol) in THF (7 mL). After 0.5 h, the appropriate α-hydroxyacetic acid ester (α-hydroxyacetic acid methyl ester, 1.53 g, or (*S*)-α-hydroxypropionic acid ethyl ester, 2.01 g, 17 mmol), diluted in anhydrous THF (5 mL) was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 2 h, and then allowed to warm up to room temperature. After quenching with a saturated solution of NH_4Cl (20 mL), the mixture was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with water (40 mL) and then dried oven Na_2SO_4. After filtration and evaporation of the solvent, the crude products were purified by column chromatography using 8:2 hexane-AcOEt as eluent.

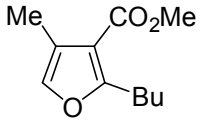


2-Hex-1-ynyloct-3-yne-1,2-diol (1d). Yield: 2.80 g, starting from 1.53 g of α-hydroxyacetic acid methyl ester (74%). Yellow solid, mp 30-32°C. IR (KBr): ν = 3339 (m, br), 2934 (m), 2241 (w), 1465 (w), 1382 (w), 1263 (m), 1175 (m), 1084 (m), 912 (w), 678 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.70 (s, 2 H), 3.00 (s, br, 2 H), 2.24 (t, J = 6.9, 4 H), 1.60-1.30 (m, 8 H), 0.91 (t, J = 7.1, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 85.4, 78.5, 71.0, 64.5, 30.5, 22.0, 18.4, 13.6; GC-MS (EI, 70 eV): *m/z* = 222 (absent) [M^+], 192 (15), 191 (100), 135 (3), 115 (4), 105 (7), 91 (17), 79 (20), 77 (12); anal. calcd for $C_{14}H_{22}O_2$ (222.16): C, 75.63; H, 9.97; found C, 75.55; H, 9.99.



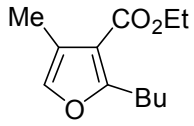
(*S*)-3-Hex-1-ynylnon-4-yne-2,3-diol (1f). Yield: 3.21 g, 80% based on (*S*)-α-hydroxypropionic acid ethyl ester. Yellow oil. $[\alpha]^{25}_D$ (MeOH, $c = 9.1\times10^{-3}$ g mL^{-1}) -22°. IR (film): ν = 3399 (m, br), 2933 (m), 2237 (w), 1466 (w), 1378 (w), 1363 (w), 1270 (w), 1119 (m), 1012 (m), 889 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.90-3.77 (m, 1H), 3.37 (s, br, 1 H), 2.70 (s, br, 1H), 2.29-2.19 (m, 4 H), 1.58-1.33 (m, 8 H), 1.36 (d, J = 6.5, 3H), 0.96-0.87 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 85.9, 85.4, 79.1, 77.8, 74.4, 68.0, 30.5, 30.4, 22.00, 21.97, 18.44, 18.40, 17.5, 13.6; GC-MS (EI, 70 eV): *m/z* = 236 (absent) [M^+], 191 (73), 150 (16), 131 (28), 121 (75), 117 (50), 108 (100), 107 (61), 91 (99), 79 (81); anal. calcd for $C_{15}H_{24}O_2$ (236.35): C, 76.23; H, 10.24; found C, 76.13; H, 10.25.

General Procedure for the Synthesis of Furan-3-carboxylic Esters 2a-r. A 250 mL stainless steel autoclave was charged in the presence of air with PdI_2 (5.0 mg, 1.39×10^{-2} mmol or 10.0 mg, 2.78×10^{-2} mmol, see Table 2.2), KI (11.5 mg, 6.93×10^{-2} mmol or 23.0 mg, 0.14 mmol, see Table 2.2), anhydrous ROH (R = Me or Et, 28 mL) and the 3-yne-1,2-diol **1a-r** (1.39 mmol). The autoclave was sealed and, while the mixture was stirred, the autoclave was pressurized with CO (32 atm) and air (up to 40 atm). After being stirred at 100 °C for the required time (see Table 2.2), the autoclave was cooled, degassed and opened. The solvent was evaporated, and the products **2a-r** were purified by column chromatography on silica gel using the following mixtures as eluent: 9:1 hexane-acetone (**2a**, **2e**, **2k**, **2p**, **2r**), 98:2 hexane-AcOEt (**2a'**), 95:5 hexane-AcOEt (**2b**, **2h**, **2l**), 6:4 hexane-acetone (**2c**), 99:1 hexane-AcOEt (**2d**, **2f**), 9:1 hexane-AcOEt (**2g**, **2n**, **2o**), 8:2 hexane-acetone (**2i**, **2j**), 8:2 hexane-AcOEt (**2m**), 7:3 hexane-acetone (**2q**).

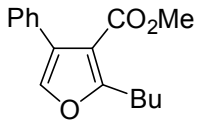


Methyl 2-butyl-4-methylfuran-3-carboxylate (2a).Yield: 220 mg, starting from 217.0 mg of **1a** (81%) (Table 2.2, entry 20). Yellow oil. IR (film): ν = 2957 (m), 1739 (s), 1442 (m), 1391 (w), 1256 (m), 971 (w), 763 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.04 (s, br, 1 H), 3.82 (s, 3 H), 2.98-2.90 (m, 2 H), 2.13 (s, br, 3 H), 1.69-1.57 (m, 2 H), 1.42-1.28 (m, 2 H), 0.92 (t, J = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2, 164.3, 137.9, 121.2, 113.2, 50.8, 30.2, 27.9, 22.4, 13.7, 9.9; GC-MS (EI, 70 eV): m/z = 196 (25) [M^+], 167 (11), 165 (12), 154 (32), 153 (100), 139 (32), 137 (16), 135 (44), 123 (47), 122 (17), 121 (29), 95 (15), 79 (11), 77 (18), 65

(45); anal. calcd for $C_{11}H_{16}O_3$ (196.24): C, 67.32; H, 8.22; found C, 67.23; H, 8.24.

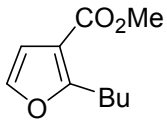


Ethyl 2-butyl-4-methylfuran-3-carboxylate (2a'). Yield: 228 mg, starting from 217.0 mg of **1a** (78%) (Table 2.2, entry 38). Colorless oil. IR (film): ν = 2960 (m), 2932 (m), 1722 (s), 1608 (w), 1557 (w), 1383 (w), 1267 (m), 1073 (m), 1028 (w), 787 (w), cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.04 (q, J = 1.3, 1 H), 4.29 (q, J = 7.2, 2 H), 2.98-2.91 (m, 2 H), 2.14 (d, J = 1.3, 3 H), 1.69-1.58 (m, 2 H), 1.42-1.26 (m, 2 H), 1.35 (t, J = 7.2, 3 H), 0.92 (t, J = 7.5, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8, 164.1, 137.8, 121.2, 113.2, 59.8, 30.3, 28.0, 22.4, 14.4, 13.8, 10.0; GC-MS (EI, 70 eV): m/z = 210 (29) [M^+], 181 (18), 168 (14), 167 (13), 165 (12), 140 (11), 139 (100), 135 (15), 123 (13), 121 (10), 95 (6), 77 (6), 65 (9); anal. calcd for $C_{12}H_{18}O_3$ (210.27): C, 68.54; H, 8.63; found C, 68.53; H, 8.64.

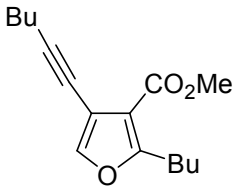


Methyl 2-butyl-4-phenylfuran-3-carboxylate (2b). Yield: 265 mg, starting from 303.5 mg of **1b** (74%) (Table 2.2, entry 21). Colorless oil. IR (film): ν = 2963 (m), 1718 (s), 1438 (m), 1391 (m), 1292 (m), 1121 (m), 1038 (w), 758 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38-7.29 (m, 5 H), 7.27 (s, 1 H), 3.70 (s, 3 H), 3.04-2.96 (m, 2 H), 1.76-1.64 (m, 2 H), 1.47-1.33 (m, 2 H), 0.95 (t, J = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6, 164.2, 138.4, 132.2, 129.2, 127.9, 127.3, 112.3, 51.0, 30.2, 27.9, 22.4, 13.8; GC-MS (EI, 70 eV): m/z = 258 (41) [M^+], 226 (17), 215 (39), 197 (100), 183 (54), 155 (23), 141 (12), 128 (34), 127 (49), 115 (28), 77

(19); anal. calcd for $C_{16}H_{18}O_3$ (258.31): C, 74.39; H, 7.02; found C, 74.19; H, 7.03.

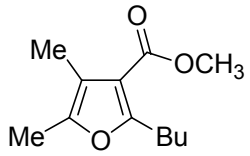


Methyl 2-butylfuran-3-carboxylate (2c). Yield: 215 mg, starting from 197.5 mg of **1c** (85%) (Table 2.2, entry 22). Colorless oil. IR (film): ν = 2962 (m), 1720 (s), 1605 (m), 1442 (m), 1307 (m), 1201 (m), 1123 (w), 1039 (m), 736 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, J = 2.0, 1 H), 6.63 (d, J = 2.0, 1 H), 3.82 (s, 3 H), 3.00 (t, J = 7.7, 2 H), 1.72-1.59 (m, 2 H), 1.42-1.29 (m, 2 H), 0.93 (t, J = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.5, 163.5, 140.4, 113.0, 110.7, 51.2, 30.1, 27.3, 22.3, 13.7; GC-MS (EI, 70 eV): *m/z* = 182 (56) [M^+], 153 (42), 151 (25), 140 (96), 139 (87), 125 (47), 121 (74), 109 (100), 81 (23); anal. calcd for $C_{10}H_{14}O_3$ (182.22): C, 65.91; H, 7.74; found C, 65.79; H, 7.72.

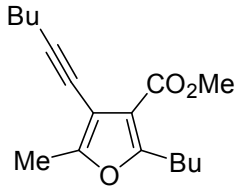


Methyl 2-butyl-4-hex-1-ynylfuran-3-carboxylic acid methyl ester (2d). Yield: 290 mg, starting from 309.5 mg of **1d** (80%) (Table 2.2, entry 23). Yellow oil. IR (film): ν = 2958 (m), 1719 (s), 1438 (m), 1320 (w), 1231 (m), 970 (w), 764 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40 (s, 1 H), 3.84 (s, 3 H), 2.95 (t, J = 7.7, 2 H), 2.42 (t, J = 6.9, 2 H), 1.70-1.25 (m, 8 H), 0.94 (t, J = 7.3, 3 H), 0.91 (t, J = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.9, 163.8, 143.9, 113.4, 108.5, 93.8, 70.4, 51.3, 30.8, 29.9, 27.6, 22.2, 21.9, 19.3, 13.7, 13.6 ; GC-MS (EI, 70 eV): *m/z* = 262 (77) [M^+], 233 (26), 231 (26), 220 (77), 219 (50), 201 (100), 191 (54), 188 (62),

176 (23), 173 (33), 161 (23), 160 (36), 145 (40), 131 (42), 117 (42), 116 (23), 115 (49), 105 (32), 91 (84), 89 (40), 77 (57); anal. calcd for $C_{16}H_{22}O_3$ (262.34): C, 73.25; H, 8.45; found C, 73.23; H, 8.44.

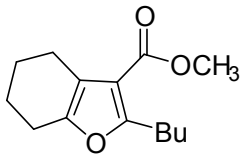


Methyl 2-Butyl-4,5-dimethylfuran-3-carboxylate (2e). Yield: 228 mg, starting from 237 mg of **1e** (78%) (Table 2.2, entry 24). Yellow oil. IR (film): ν = 2969 (m), 2931 (m), 2864 (w), 1715 (s), 1577 (m), 1439 (m), 1382 (w), 1294 (m), 1211 (m), 1077 (m), 736 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3 H, CO_2Me), 2.90 (t, J =7.5, 2 H, $CH_2CH_2CH_2CH_3$), 2.16 (s, 3 H, Me at C-4), 2.05 (s, 3H, Me at C-5), 1.68-1.55 (m, 2 H, $CH_2CH_2CH_3$), 1.43-1.28 (m, 2 H, CH_2CH_3), 0.92 (t, J = 7.5, 3 H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 161.5, 145.8, 114.4, 113.1, 50.8, 30.4, 27.7, 22.4, 13.8, 11.0, 9.9; GC-MS (EI, 70 eV): *m/z* = 210 (55) [M^+], 179 (17), 167 (100), 153 (33), 151 (38), 137 (27), 135 (57), 109 (14), 97 (6), 77 (13), 65 (16), 55 (18); anal. calcd for $C_{12}H_{18}O_3$ (210.27): C, 68.54; H, 8.63; found C, 65.64; H, 8.61.

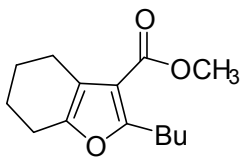


Methyl 2-Butyl-4-hex-1-ynyl-5-methylfuran-3-carboxylate (2f). Yield: 280 mg, starting from 329.0 mg of **1f** (73%) (Table 2.2, entry 25). Yellow oil. IR (film): ν = 2960 (m), 1712 (s), 1439 (m), 1216 (s), 1147 (w),1060 (w), 754 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.82 (s, 3 H), 2.90 (t, J = 7.4, 2 H), 2.44 (t, J = 6.9, 2 H), 2.30 (s, 3 H), 1.67-1.24 (m, 8 H), 0.95 (t, J = 7.1, 3 H), 0.91 (t, J = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.1,

161.5, 154.4, 113.4, 103.9, 94.4, 71.5, 51.1, 31.0, 30.2, 27.4, 22.3, 21.9, 19.4, 13.8, 13.7, 12.3; GC-MS (EI, 70 eV): *m/z* = 276 (51) [M^+], 245 (15), 233 (73), 219 (17), 215 (25), 205 (17), 202 (24), 191 (16), 187 (15), 175 (24), 173 (21), 159 (13), 147 (11), 131 (13), 115 (16), 91 (16), 77 (14); anal. calcd for $C_{17}H_{24}O_3$ (276.37): C, 73.88; H, 8.75; found C, 73.83; H, 8.73.

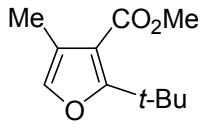


Methyl 2-Butyl-4,5,6,7-tetrahydrobenzofuran-3-carboxylate (2g). Yield: 246 mg, starting from 273 mg of **1g** (75%) (Table 2.2, entry 26). Yellow oil. IR (film): ν = 2935 (m), 2857 (m), 1719 (s), 1577 (m), 1440 (m), 1345 (w), 1273 (m), 1213 (m), 1056 (m), 956 (w), 869 (w), 784 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 3 H, CO_2Me), 2.93 (t, *J* = 7.7, 2 H, $CH_2CH_2CH_2CH_3$), 2.62-2.49 (m, 4 H, $CH_2CH_2CH_2CH_2$), 1.86-1.56 (m, 6 H, $CH_2CH_2CH_2CH_2$ + $CH_2CH_2CH_3$), 1.44-1.29 (m, 2 H, CH_2CH_3), 0.92 (t, *J* = 7.3, 3 H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 161.9, 149.2, 117.2, 112.2, 50.8, 30.5, 27.6, 22.9, 22.7, 22.43, 22.36, 13.8; GC-MS (EI, 70 eV): *m/z* = 236 (M^+, 26), 221 (3), 205 (7), 193 (100), 179 (16), 177 (24), 161 (17), 146 (4), 133 (9), 119 (3), 105 (12), 91 (16), 79 (11), 77 (12); anal. calcd for $C_{14}H_{20}O_3$ (236.31): C, 71.16; H, 8.53; found C, 71.20; H, 8.51.

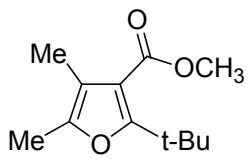


Ethyl 2-butyl-4,5,6,7-tetrahydrobenzofuran-3-carboxylate (2g'). Yield: 240 mg, starting from 273 mg of **1g** (69%) (Table 2.2, entry 39). Yellow

oil. IR (film): ν = 2935 (m), 2857 (m), 1719 (s), 1577 (m), 1440 (m), 1345 (w), 1273 (m), 1213 (m), 1056 (m), 956 (w), 869 (w), 784 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 3 H, CO_2Me), 2.93 (t, J = 7.7, 2 H, $CH_2CH_2CH_2CH_3$), 2.62-2.49 (m, 4 H, $CH_2CH_2CH_2CH_2$), 1.86-1.56 (m, 6 H, $CH_2CH_2CH_2CH_2 + CH_2CH_2CH_3$), 1.44-1.29 (m, 2 H, CH_2CH_3), 0.92 (t, J = 7.3, 3 H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 161.9, 149.2, 117.2, 112.2, 50.8, 30.5, 27.6, 22.9, 22.7, 22.43, 22.36, 13.8; GC-MS (EI, 70 eV): *m/z* = 236 (M^+, 26), 221 (3), 205 (7), 193 (100), 179 (16), 177 (24), 161 (17), 146 (4), 133 (9), 119 (3), 105 (12), 91 (16), 79 (11), 77 (12); anal. calcd for $C_{14}H_{20}O_3$ (236.31): C, 71.16; H, 8.53; found C, 71.20; H, 8.51.

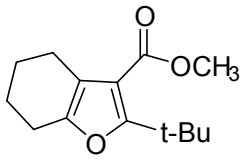


Methyl 2-*tert*-Butyl-4-methylfuran-3-carboxylate (2h). Yield: 165 mg, starting from 217.0 mg of **1h** (60%) (Table 2.2, entry 27). Yellow oil. IR (film): *v* = 2958 (m), 1720 (s), 1531 (m), 1435 (w), 1364 (w), 1283 (m), 1228 (m), 1084 (m), 750 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.00 (q, J = 1.3, 1 H), 3.83 (s, 3 H), 2.07 (d, J = 1.3, 3 H), 1.38 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.5, 165.6, 136.4, 121.7, 112.9, 51.0, 34.7, 28.5, 9.9; GC-MS (EI, 70 eV): *m/z* = 196 (13) [M^+], 181 (38), 165 (9), 149 (100), 122 (6), 107 (5), 93 (8), 91 (19), 79 (12), 77 (24); anal. calcd for $C_{11}H_{16}O_3$ (196.24): C, 67.32; H, 8.22; found C, 67.28; H, 8.23.

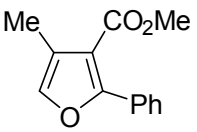


Methyl 2-*tert*-Butyl-4,5-dimethylfuran-3-carboxylate (2i). Yield: 170 mg, starting from 237 mg of **1i** (58%) (Table 2.2, entry 28). Yellow oil. IR

(KBr): ν = 1714 (s), 1643 (w), 1436 (m), 1364 (m), 1222 (m), 1083 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 3H, CO_2Me), 2.15 (q, *J* = 1.0, 3 H, Me at C-4), 1.98 (d, *J* = 1.0, 3H, Me at C-5), 1.36 (s, 9 H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 164.3, 144.4, 115.1, 113.3, 51.0, 34.4, 28.7, 11.0, 9.8; GC-MS (EI, 70 eV): *m/z* = 210 (16) [M^+], 195 (42), 179 (8), 163 (100), 135 (4), 121 (2), 107 (3), 91 (9), 77 (8), 65 (5); anal. calcd for $C_{12}H_{18}O_3$ (210.27): C, 68.54; H, 8.63; found C, 65.59; H, 8.61.

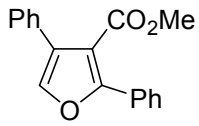


2-tert-Butyl-4,5,6,7-tetrahydro-benzofuran-3-carboxylic acid methyl ester (2j). Yield: 246 mg, starting from 273 mg of **1j** (75%) (Table 2.2, entry 29). Colorless amorphous solid, mp 39-40 °C. IR (KBr): ν = 2939 (s), 2851 (m), 1718 (s), 1537 (m), 1435 (w), 1384 (w), 1316 (m), 1282 (m), 1244 (m), 1218 (m), 1117 (m), 1051 (m), 1027 (w), 936 (w), 803 (w), 789 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 3 H, CO_2Me), 2.58-2.48 (m, 4 H, $CH_2CH_2CH_2CH_2$), 1.84-1.65 (m, 4 H, $CH_2CH_2CH_2CH_2$), 1.40 (s, 9 H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 165.5, 147.6, 118.2, 111.6, 51.0, 34.5, 28.4, 23.0, 22.9, 22.7, 22.6; GC-MS (EI, 70 eV): *m/z* = 236 (22) [M^+], 221 (77), 205 (9), 189 (100), 161 (5), 147 (2), 134 (3), 119 (3), 105 (8), 91 (16), 77 (9), 65 (6); anal. calcd for $C_{14}H_{20}O_3$ (236.31): C, 71.16; H, 8.53; found C, 71.23; H, 8.52.

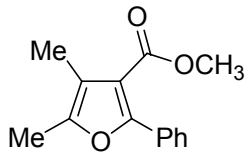


Methyl 4-methyl-2-phenylfuran-3-carboxylate (2k). Yield: 214 mg, starting from 245.0 mg of **1k** (71%) (Table 2.2, entry 30). Yellow oil. IR (film): *v* = 3030 (m), 2957 (m), 1728 (s), 1448 (m), 1386 (w), 1225 (m),

960 (w), 758 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.79-7.74 (m, 1 H), 7.45-7.36 (m, 4 H), 7.24 (q, J = 0.9, 1 H), 3.80 (s, 3 H), 2.20 (d, J = 0.9, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 158.0, 139.2, 129.4, 129.1, 128.4, 128.1, 128.0, 122.6, 51.2, 10.0; GC-MS (EI, 70 eV): *m/z* = 216 (82) [M^+], 185 (100), 156 (16), 129 (23), 128 (53), 127 (33), 115 (10), 102 (15), 77 (38); anal. calcd for $C_{13}H_{12}O_3$ (216.23): C, 72.21; H, 5.59; found C, 72.30; H, 5.60.

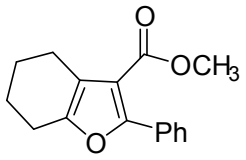


Methyl 2,4-diphenylfuran-3-carboxylate (2l). Yield: 215.8 mg, starting from 250 mg of **1l** (65%) (Table 2.2, entry 31). Yellow solid, m.p. = 27-28°C. IR (KBr): *v* = 3051 (m), 2942 (m), 1717 (s), 1540 (m), 1482 (m), 1385 (m), 1266 (m), 1152 (m), 924 (m), 768 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.83-7.77 (m, 2 H), 7.50 (s, 1 H), 7.47-7.30 (m, 8 H), 3.68 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1, 156.6, 139.2, 131.7, 130.1, 129.2, 128.6, 128.33, 128.26, 127.7, 127.6, 113.7, 51.6; GC-MS (EI, 70 eV): *m/z* = 278 (100) [M^+], 247 (92), 191 (42), 189 (55), 165 (15), 139 (12), 105 (42), 94 (19), 77 (42), 63 (20); anal. calcd for $C_{18}H_{14}O_3$ (278.30): C, 77.68; H, 5.07; found C, 77.60; H, 5.07.

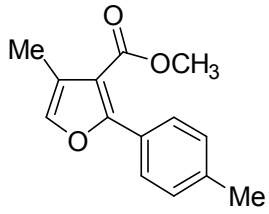


4,5-Dimethyl-2-phenyl-furan-3-carboxylic acid methyl ester (2m). Yield: 180 mg, starting from 265 mg of **1m** (56%) (Table 2.2, entry 32) Yellow oil. IR (film): ν = 2957 (w), 1717 (s), 1603 (w), 1449 (m), 1242 (m), 1112 (w), 757 (m), 697 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.76-7.71 (m, 2 H, aromatic), 7.42-7.28 (m, 3 H, aromatic), 3.77 (s, 3 H,

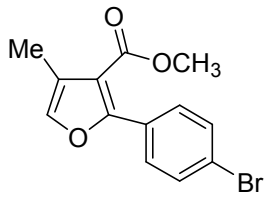
CO_2Me), 2.25 (s, 3 H, Me at C-4), 2.10 (s, 3 H, Me at C-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2, 155.2, 147.7, 130.6, 128.6, 128.1, 128.0, 116.3, 114.4, 51.1, 11.2, 10.0; GC-MS (EI, 70 eV): *m/z* = 230 (100) [M^+], 215 (4), 199 (62), 170 (15), 159 (6), 143 (4), 128 (17), 115 (7), 105 (21), 77 (27); anal. calcd for $C_{14}H_{14}O_3$ (230.26): C, 73.03; H, 6.13; found C, 73.14; H, 6.11.



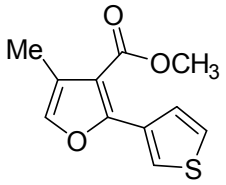
2-Phenyl-4,5,6,7-tetrahydro-benzofuran-3-carboxylic acid methyl ester (2n). Yield: 250 mg, starting from 300 mg of **1n** (70%) (Table 2.2, entry 33). Colorless amorphous solid, mp. 49-50 °C. IR (KBr): ν = 2939 (m), 2851 (w), 1714 (s), 1636 (w), 1547 (m), 1497 (m), 1437 (m), 1384 (w), 1326 (w), 1282 (m), 1218 (s), 1090 (s), 1021 (w), 920 (w), 774 (m), 758 (m), 688 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.87-7.78 (m, 2 H, aromatic), 7.45-7.31 (m, 3 H, aromatic), 3.79 (s, 3 H, CO_2Me), 2.70-2.58 (m, 4 H, $CH_2CH_2CH_2CH_2$), 1.91-1.71 (m, 4 H, $CH_2CH_2CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 155.9, 150.9, 130.6, 128.7, 128.2, 128.0, 119.1, 113.2, 51.2, 23.1, 22.9, 22.62, 22.55; GC-MS (EI, 70 eV): *m/z* = 256 (100) [M^+], 241 (4), 228 (26), 196 (16), 170 (38), 141 (15), 128 (11), 115 (19), 105 (34), 91 (11), 77 (37); anal. calcd for $C_{16}H_{16}O_3$ (256.30): C, 74.98; H, 6.29; found C, 75.07; H, 6.27.



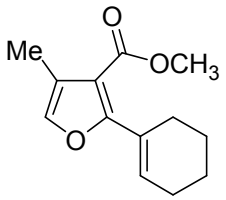
Methyl 2-*tert*-Butyl-4,5,6,7-tetrahydrobenzofuran-3-carboxylate (2o). Yield: 243 mg, starting from 264 mg of **1o** (76%) (Table 2.2, entry 34). Yellow oil. IR (film): ν = 3415 (m, br), 2953 (w), 1717 (s) 1616 (w), 1500 (w), 1436 (m), 1291 (m), 1120 (m), 1074 (m), 821 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.70-7.61 (m, 2 H, tolyl), 7.28-7.13 (m, 3 H, tolyl + H-5), 3.78 (s, 3 H, CO_2Me), 2.36 (s, 3 H, $CH_3C_6H_4$), 2.17 (s, 3 H, Me at C-4); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 158.3, 139.1, 138.9, 128.7, 128.3, 127.7, 122.4, 113.5, 51.1, 21.4, 10.1; GC-MS (EI, 70 eV): *m/z* = 230 (100) [M^+], 199 (80), 170 (19), 159 (4), 141 (26), 128 (36), 115 (35), 91 (13); anal. calcd for $C_{14}H_{14}O_3$ (230.26): C, 73.03; H, 6.13; found C, 73.15; H, 6.12.



Methyl 2-(4-bromophenyl)-4-methylfuran-3-carboxylate (2p). Yield: 332 mg, starting from 355 mg of **1p** (81%) (Table 2.2, entry 35). Yellow oil. IR (KBr): ν = 1719 (s), 1547 (w), 1490 (w), 1290 (m), 1213 (m), 1085 (m), 1066 (w), 766 (m), 693 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65-7.25 (m, 5 H, aromatic), 3.73 (s, 3 H, CO_2Me), 2.23 (s, 3 H, Me at C-4); GC-MS (EI, 70 eV): *m/z* = 216 (81), 185 (100), 156 (16), 129 (24), 128 (57), 127 (34), 115 (9), 102 (15), 77 (31); anal. calcd for $C_{13}H_{11}BrO_3$ (295.13): C, 52.91; H, 3.76; Br, 27.07; found C, 52.99; H, 3.75; Br, 27.09.



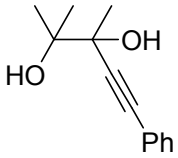
Methyl-4-methyl-2-(thiophen-3-yl)furan-3-carboxylate (2q). Yield: 272 mg, starting from 253 mg of **1q** (88%) (Table 2.2, entry 36). Yellow oil. IR (film): ν = 2953 (m), 1718 (s), 1619 (w), 1521 (w), 1438 (m), 1242 (m), 1075 (m), 864 (w), 806 (m), 784 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.19 (d, J = 3.2, 1 H, H-2 on thiophene ring), 7.62 (d, J = 5.3, 1 H, H-4 on thiophene ring), 7.30 (dd, J = 5.3, 3.2, 1 H, H-5 on thiophene ring), 7.16 (s, 1 H, H-5 on furan ring), 3.85 (s, 3 H, CO_2Me), 2.17 (s, 3 H, Me at C-4); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 154.6, 138.3, 131.2, 127.3, 125.9, 124.9, 122.3, 113.0, 51.2, 10.4; GC-MS (EI, 70 eV): m/z = 222 (100) [M^+], 207 (4), 191 (87), 179 (4), 165 (15), 162 (29), 151 (6), 135 (34), 134 (27), 121 (4), 111 (12), 91 (34), 89 (18); anal. calcd for $C_{11}H_{10}O_3S$ (222.26): C, 59.44; H, 4.53; S, 14.43; found C, 59.51; H, 4.54; S, 14.44.



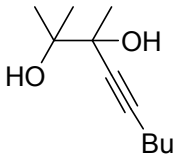
2-Cyclohex-1-enyl-4-methyl-furan-3-carboxylic acid methyl ester (2r). Yield: 285 mg, starting from 250 mg of **1r** (93%) (Table 2.2, entry 37). Yellow oil. IR (film): α = 2936 (s), 2862 (m), 1719 (s), 1602 (w), 1534 (m), 1436 (m), 1379 (w), 1286 (w), 1205 (w), 1087 (m), 805 (w), 787 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.06 (s, 1 H, H-5), 6.42-6.34 (m, 1 H, =CH), 3.81 (s, 3 H, CO_2Me), 2.42-2.29 (m, 2 H, =CHCH_2), 2.28-2.16 (m, 2 H, =CHCH_2CH_2CH_2), 2.11 (s, 3 H, Me at C-4), 1.80-1.58 (m, 4 H, =CHCH_2CH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.3, 160.3, 137.5, 131.5, 128.4, 121.7, 112.7, 51.2, 26.3, 25.6, 22.5, 21.8, 10.0; GC-MS (EI,

70 eV): *m/z* = 220 (100) [M^+], 205 (17), 188 (77), 187 (57), 173 (12), 166 (31), 161 (25), 160 (27), 159 (24), 145 (15), 133 (24), 132 (18), 131 (21), 117 (20), 115 (23), 105 (24), 103 (14), 91 (45), 79 (22), 77 (38), 65 (19); anal. calcd for $C_{13}H_{16}O_3$ (220.26): C, 70.89; H, 7.32; found C, 70.95; H, 7.30.

General Procedure for the Preparation of 2-methyl-3-yne-1,2-diols 3a-e. To a solution of BuLi in hexane (1.6 M) (25 mL, 40 mmol) was added anhydrous THF (6 mL) and hexane (25 mL) under nitrogen. The resulting mixture was cooled at -40 °C and maintained under stirring. A solution of the 1-alkyne (44.5 mmol) (1-hexyne: 3.66 g; phenylacetylene: 4.54 g; 3-ethynylthiophene: 4.81 g; *p*-bromophenylacetylene: 8.06 g; *p*-methylphenylacetylene 5.17 g) in anhydrous THF (6 mL) was added dropwise under nitrogen to the cooled mixture followed by a solution of LiBr (1.56 g, 18.0 mmol) in anhydrous THF (6 mL). After stirring for 0.5 h at -40°C, a solution of the of 3-hydroxy-3-methylbutan-2-one (1.74 g, 17 mmol) in anhydrous THF (5 mL) was added under nitrogen. The mixture was allowed to stir at the same temperature for 2 h, then it was allowed to warm up to room temperature. Satd aqueous NH_4Cl (40 mL) was added, followed by Et_2O (50 mL). Phases were separated and the aqueous phase extracted with Et_2O (50 mL × 3). The collected organic phases were washed with brine to neutral pH and dried over Na_2SO_4. After filtration and evaporation of the solvent, products **3a-e** were purified by column chromatography on silica gel using the following mixtures as eluent: 85:15 hexane-AcOEt (**3a**), 9:1 hexane-AcOEt (**3b**, **3d**), 95:5 hexane-AcOEt (**3c**), 8:2 hexane-AcOEt (**3e**).

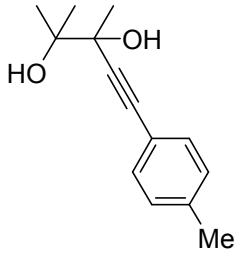


2,3-Dimethyl-5-phenylpent-4-yne-2,3-diol (3a). Yield: 2.64 g, starting from 1.74 g of 3-hydroxy-3-methylbutan-2-one (76%). Yellow oil. IR (film): ν = 3568 (m, br), 3301 (m, br), 2986 (m), 2231 (vw), 1598 (w), 1490 (w), 1443 (w), 1370 (m), 1338 (m), 1266 (w), 1123 (m), 1077 (m), 961 (w), 939 (w), 903. (w), 846 (w), 756 (m), 691 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44-7.38 (m, 2 H, aromatic), 7.32-7.26 (m, 3 H, aromatic), 3.16 (s, br, 1 H, OH), 2.42 (s, br, 1 H, OH), 1.56 [s, 3 H, PhC≡CC(CH_3)OH], 1.45 [s, 3 H, $CH_3C(CH_3)OH$] 1.33 [s, 3 H, $CH_3C(CH_3)OH$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.7, 128.4, 128.3, 122.6, 91.6, 84.8, 75.5, 74.4, 25.8, 24.5, 23.3; GC-MS (EI, 70 eV): *m/z* = 204 (absent) [M^+], 171 (8), 146 (93), 145 (84), 131 (100), 128 (42), 115 (13), 103 (29), 102 (19), 77 (17), 59 (53); anal. calcd for $C_{13}H_{16}O_2$ (204.26): C, 76.44; H, 7.90; found C, 76.51; H, 7.89.

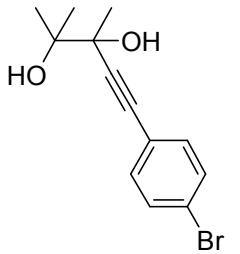


2,3-Dimethylnon-4-yne-2,3-diol (3b). Yield: 2.16 g, starting from 1.74 g of 3-hydroxy-3-methylbutan-2-one (74%). Colorless oil. IR (film): ν = 3420 (s, br), 2963 (m), 2933 (m), 2242 (vw), 1636 (m), 1461 (m), 1368 (m), 1175 (m), 1084 (m), 960 (w), 917 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.87 (s, br, 1 H, OH), 2.27 (s, br, 1 H, OH), 2.22 (t, J = 7.0, 2 H, ≡CCH_2), 1.56-1.32 (m, 4 H, $CH_2CH_2CH_3$), 1.44 [s, 3 H, BuC≡CC(CH_3)OH], 1.37 [s, 3 H, $CH_3C(CH_3)OH$] 1.27 [s, 3 H, $CH_3C(CH_3)OH$], 0.91 (t, J = 7.3, 3 H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 85.4, 82.4, 75.3, 74.0, 30.7, 25.7, 24.6, 22.9, 22.0, 18.3, 13.6;

GC-MS (EI, 70 eV): *m/z* = 184 (absent) [M^+], 151 (1), 125 (10), 109 (3), 97 (12), 84 (100), 79 (11), 69 (59), 59 (52); anal. calcd for $C_{11}H_{20}O_2$ (184.28): C, 71.70; H, 10.94; found C, 71.79; H, 10.93.

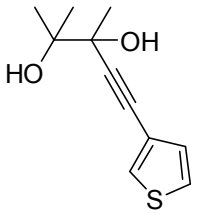


2,3-Dimethyl-5-*p*-tolylpent-4-yne-2,3-diol (3c). Yield: 2.63 g, starting from 1.74 g of 3-hydroxy-3-methylbutan-2-one (71%). Pale yellow solid, mp 64-65 °C. IR (KBr): ν = 3419 (s, br), 2985 (m), 2234 (w), 1665 (w), 1511 (m), 1369 (m), 1267 (w), 1121 (s), 939 (m), 903 (w), 816 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35-7.27 (m, 2 H, aromatic), 7.14-7.06 (m, 2 H, aromatic), 2.93 (s, br, 1 H, OH), 2.34 (s, 3 H, $CH_3C_6H_4$), 2.25 (s, br, 1 H, OH), 1.55 [s, 3 H, $MeC_6H_4C{\equiv}CC(CH_3)OH$], 1.45 [s, 3 H, $CH_3C(CH_3)OH$] 1.33 [s, 3 H, $CH_3C(CH_3)OH$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.6, 131.6, 129.1, 119.4, 90.6, 84.9, 75.5, 74.4, 25.8, 24.4, 23.1, 21.5; GC-MS (EI, 70 eV): *m/z* = 218 (1) [M^+], 185 (5), 160 (56), 159 (38), 145 (100), 142 (21), 141 (19), 128 (4), 117 (13), 115 (22), 91 (6), 59 (22); anal. calcd for $C_{14}H_{18}O_2$ (218.29): C, 77.03; H, 8.31; found C, 77.14; H, 8.30.



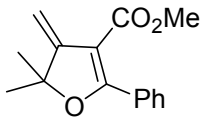
5-(4-bromophenyl)-2,3-Dimethylpent-4-yne-2,3-diol (3d). Yield: 2.84 g, starting from 1.74 g of 3-hydroxy-3-methylbutan-2-one (59%). Yellow oil. IR (film): ν = 3398 (s, br), 3302 (m, br), 2932 (w), 2230 (vw), 1484 (m),

1384 (m), 1249 (m), 1123 (m), 1048 (s), 948 (w), 899 (m), 821 (m), 764 (m), 695 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.47-7.37 (m, 2 H, aromatic), 7.33-7.25 (m, 2 H, aromatic), 3.15 (s, br, 1 H, OH), 2.38 (s, br, 1 H, OH), 1.56 [s, 3 H, $BrC_6H_4C{\equiv}CC(CH_3)OH$], 1.46 [s, 3 H, $CH_3C(CH_3)OH$] 1.34 [s, 3 H, $CH_3C(CH_3)OH$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.1, 131.7, 128.3, 122.5, 91.3, 84.7, 75.5, 74.4, 25.8, 24.4, 23.2; GC-MS (EI, 70 eV): *m/z* = 282 (absent) [M^+], 251 (6), 249 (6), 226 (58) 224 (60), 211 (63), 209 (72), 183 (8), 181 (7), 145 (37), 127 (19), 115 (9), 102 (13), 101 (10), 75 (9), 59 (100); anal. calcd for $C_{13}H_{15}BrO_2$ (283.16): C, 55.14; H, 5.34, Br, 28.22; found C, 65.21; H, 5.33, 28.24.

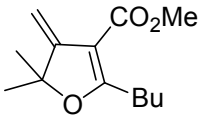


2,3-Dimethyl-5-thiophen-3-ylpent-4-yne-2,3-diol (3e). Yield: 2.82 g, starting from 1.74 g of 3-hydroxy-3-methylbutan-2-one (79%). Yellow oil. IR (KBr): ν = 3410 (s, br), 2984 (m), 2935 (w), 2234 (w), 1633 (w), 1459 (m), 1370 (m), 1182 (m), 1122 (m), 1080 (m), 963 (m), 919 (m), 866 (w), 840 (w), 782 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.43 (distorted dd, *J* = 3.0, 1.2, 1 H, H-2 on thiophene ring), 7.25 (distorted dd, *J* = 4.9, 3.0, 1 H, H-5 on thiophene ring), 7.09 (dd, *J* = 4.9, 1.2, 1 H, H-4 on thiophene ring), 2.42 (s, br, 2 H, 2 OH), 1.55 [s, 3 H, $C{\equiv}CC(CH_3)OH$], 1.45 [s, 3 H, $CH_3C(CH_3)OH$] 1.33 [s, 3 H, $CH_3C(CH_3)OH$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 129.9, 129.0, 125.4, 121.5, 90.9, 80.0, 75.4, 74.5, 25.8, 24.4, 23.1; GC-MS (EI, 70 eV): *m/z* = 210 (absent) [M^+], 195 (1), 177 (6), 152 (97), 151 (38), 137 (100), 134 (30), 109 (30), 89 (5), 77 (3), 69 (5), 59 (54); anal. calcd for $C_{11}H_{14}O_2S$ (210.29): C, 62.83; H, 6.71, S, 15.25; found C, 62.91; H, 6.70, S, 15.23.

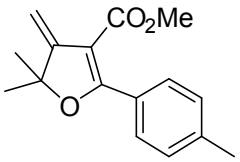
General Procedure for the Synthesis of 4-Methylene-4,5-dihydrofuran-3-carboxylic Esters 4a-e. A 250 mL stainless steel autoclave was charged in the presence of air with PdI_2 (5.0 mg, 1.39×10^{-2} mmol), KI (11.5 mg, 6.93×10^{-2} mmol), anhydrous MeOH (28 mL) and the 2-methyl-3-yne-1,2-diol **3a-e** (1.39 mmol). The autoclave was sealed and, while the mixture was stirred, the autoclave was pressurized with CO (32 atm) and air (up to 40 atm). After being stirred at 100 °C for the required time (see Table 3), the autoclave was cooled, degassed and opened. The solvent was evaporated, and the products **4a-e** were purified by column chromatography on silica gel using 95:5 hexane-AcOEt as eluent.



Methyl 5,5-dimethyl-4-methylene-2-phenyl-4,5-dihydrofuran-3-carboxylate (4a). Yield: 228 mg, starting from 284 mg of **3a** (67%) (Table 2.3, entry 1). Pale yellow amorphous solid, mp 53-55 °C. IR (KBr): ν = 1699 (s), 1589 (m), 1436 (w), 1384 (s), 1272 (m), 1193 (w), 1160 (w), 1098 (w), 1072 (m), 859 (m), 763 (m), 694 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.70-7.62 (m, 2 H, aromatic), 7.47-7.34 (m, 3 H, aromatic), 5.49 (s, 1 H, C*H*H), 4.68 (s, 1 H, CH*H*), 3.70 (s, 3 H, CO_2Me), 1.50 (s, 6 H, CH_3CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.2, 165.2, 153.1, 130.7, 130.6, 129.1, 127.7, 105.4, 99.7, 89.3, 50.9, 28.5; GC-MS (EI, 70 eV): *m/z* = 244 (92) [M^+], 228 (42), 212 (19), 199 (18), 197 (23), 185 (24), 184 (20), 171 (15), 155 (13), 144 (23), 141 (20), 127 (17), 115 (18), 105 (84), 77 (100); anal. calcd for $C_{15}H_{16}O_3$ (244.29): C, 73.75; H, 6.60; found C, 73.82; H, 6.58.

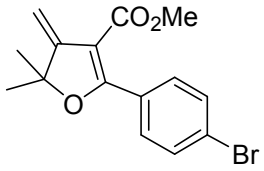


Methyl 2-butyl-5,5-dimethyl-4-methylene-4,5-dihydrofuran-3-carboxylate (4b). Yield: 180 mg, starting from 256 mg of **3b** (58%) (Table 2.3, entry 3). Yellow oil. IR (film): ν = 2957 (m), 2932 (m), 2872 (w), 1705 (s), 1598 (m), 1437 (m), 1383 (m), 1274 (m), 1198 (w), 1172 (w), 1077 (m), 1032 (w), 866 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.37 (s, 1 H, C*H*H), 4.51 (s, 1 H, CH*H*), 3.78 (s, 3 H, CO_2Me), 2.75 (t, J = 7.6, 2 H, $CH_2CH_2CH_2CH_3$), 1.66-1.31 (m, 2 H, $CH_2CH_2CH_3$), 1.47-1.24 (m, 2 H, CH_2CH_3), 1.39 (s, 6 H, CH_3CCH_3), 0.92 (t, J = 7.3, 3 H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.6, 165.7, 152.4, 104.6, 97.7, 89.6, 50.7, 29.0, 28.8, 28.3, 22.4, 13.8; GC-MS (EI, 70 eV): *m/z* = 224 (47) [M^+], 209 (29), 195 (100), 177 (9), 167 (17), 149 (9), 135 (18), 107 (14), 79 (20); anal. calcd for $C_{13}H_{20}O_3$ (224.30): C, 69.61; H, 8.99; found C, 69.70; H, 8.97.

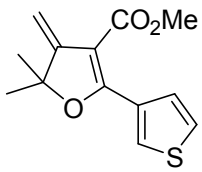


Methyl 5,5-dimethyl-4-methylene-2-p-tolyl-4,5-dihydrofuran-3-carboxylate (4c). Yield: 230 mg, starting from 303 mg of **3c** (64%) (Table 2.3, entry 4). Yellow solid, mp. 77-78 °C. IR (KBr): ν = 2978 (w), 1698 (s), 1592 (m), 1505 (w), 1438 (m), 1383 (m), 1266 (m), 1192 (w), 1154 (w), 1093 (m), 1074 (m), 955 (w), 863 (m), 824 (m), 787 (m), 623 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.62-7.52 (m, 2 H, aromatic), 7.24-7.12 (m, 2 H, aromatic), 5.47 (s, 1 H, C*H*H), 4.65 (s, 1 H, CH*H*), 3.70 (s, 3 H, CO_2Me), 2.37 (s, 3 H, $CH_3C_6H_4$), 1.48 (s, 6 H, CH_3CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.3, 165.3, 153.3, 140.9, 129.1, 128.4, 127.8, 104.9, 99.3, 89.1, 50.8, 28.5, 21.5; GC-MS (EI, 70 eV): *m/z* = 258 (100) [M^+], 243

(41), 227 (10), 211 (32), 199 (10), 185 (11), 183 (8), 169 (6), 158 (10), 155 (9), 141 (9), 119 (57), 91 (35), 65 (12); anal. calcd for $C_{16}H_{18}O_3$ (258.31): C, 74.39; H, 7.02; found C, 74.45; H, 7.01.

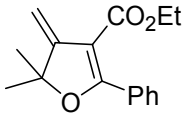


Methyl 2-(4-bromophenyl)-5,5-dimethyl-4-methylene-4,5-dihydrofuran-3-carboxylate (4d). Yield: 284 mg, starting from 394 mg of **3d** (63%) (Table 2.3, entry 5). Yellow oil. IR (film): ν = 2978 (w), 1709 (s), 1589 (m), 1485 (w), 1436 (m), 1383 (m), 1366 (w), 1277 (m), 1195 (w), 1153 (w), 1094 (m), 1072 (m), 865 (m), 831 (w), 766 (m), 694 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.70-7.64 (m, 1 H, aromatic), 7.57-7.51 (m, 1 H, aromatic), 7.45-7.35 (m, 2 H, aromatic), 5.49 (s, 1 H, C*H*H), 4.68 (s, 1 H, CH*H*), 3.70 (s, 3 H, CO_2Me), 1.50 (s, 6 H, CH_3CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1, 165.2, 153.2, 130.8, 130.5, 129.1, 127.7, 100.3, 99.7, 89.3, 50.9, 28.5; GC-MS (EI, 70 eV): *m/z* = 324 (99) [$(M+2)^+$], 322 (100) [M^+], 309 (42), 307 (43), 291 (16), 277 (17), 264 (15), 224 (12), 222 (12), 211 (15), 202 (11), 185 (57), 183 (62), 169 (8), 157 (27), 155 (40), 143 (12), 141 (11), 126 (17), 76 (18); anal. calcd for $C_{15}H_{15}BrO_3$ (323.18): C, 55.75; H, 4.68; Br, 24.72; found C, 55.82; H, 4.69; Br, 24.69.



Methyl 5,5-Dimethyl-4-methylene-2-thiophen-3-yl-4,5-dihydrofuran-3-carboxylate (4e). Yield: 245 mg, starting from 292 mg of **3e** (70%) (Table 2.3, entry 6). Yellow oil. IR (film): ν = 2977 (w), 1703 (s), 1579 (m), 1438 (m), 1364 (w), 1263 (m), 1192 (w), 1144 (w), 1097 (m), 1077 (m), 878

(m), 853 (m), 788 (m), 650 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.26 (d, J = 3.0, 1 H, H-2 on thiophene ring), 7.60 (distorted d, J = 5.5, 1 H, H-4 on thiophene ring), 7.29 (distorted dd, J = 5.5, 3.0, 1 H, H-5 on thiophene ring), 5.45 (s, 1 H, C*H*H), 4.66 (s, 1 H, CH*H*), 3.81 (s, 3 H, CO_2Me), 1.48 (s, 6 H, CH_3CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 163.8, 153.1, 131.4, 130.7, 128.5, 124.5, 104.5, 99.7, 88.6, 51.0, 28.6; GC-MS (EI, 70 eV): *m/z* = 250 (100) [M^+], 235 (35), 218 (12), 205 (13), 203 (21), 190 (11), 177 (11), 161 (9) 150 (11), 147 (11), 111 (64), 97 (8), 83 (13); anal. calcd for $C_{13}H_{14}O_3S$ (250.31): C, 62.38; H, 5.64; S, 12.81; found C, 62.44; H, 5.62; S, 12.80.



Ethyl 5,5-dimethyl-4-methylene-2-phenyl-4,5-dihydrofuran-3-carboxylate (4a'). Yield: 198 mg, starting from 284 mg of **3a** (55%) (Table 2.3, entry 7). Pale yellow amorphous solid, mp 82-83 °C. IR (KBr): ν = 1687 (s), 1589 (m), 1405 (w), 1383 (s), 1275 (m), 1190 (w), 1167 (w), 1095 (m), 1073 (s), 862 (m), 765 (w), 699 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.70-7.62 (m, 2 H, aromatic), 7.47-7.34 (m, 3 H, aromatic), 5.49 (s, 1 H, C*H*H), 4.68 (s, 1 H, CH*H*), 3.70 (s, 3 H, CO_2Me), 1.50 (s, 6 H, CH_3CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.2, 165.2, 153.1, 130.7, 130.6, 129.1, 127.7, 105.4, 99.7, 89.3, 50.9, 28.5; GC-MS (EI, 70 eV): *m/z* = 258 (58) [M^+], 243 (8), 229 (7), 215 (21), 197 (17), 186 (22), 185 (17), 184 (13), 171 (25), 144 (18), 136 (12), 115 (8), 105 (100), 77 (63); anal. calcd for $C_{16}H_{18}O_3$ (258.31): C, 74.39; H, 7.02; found C, 74.45; H, 7.01.

Part II

Synthesis of substituted thiophenes by Palladium-catalyzed heterocyclodehydration of 1-mercapto-3-yn-2-ols.

Gabriele, B.; Mancuso, R.; Veltri, L.; Maltese, V.; Salerno, G.; *J. Org. Chem.*, **2012**, 77 (21), 9905-9909.

Part II

Introduction

1.1 Pharmacological importance of thiophenes

Organic compounds containing five-member aromatic heterocycle rings are very common in nature and play important biological roles. The thiophene core, in particular, is a structural motif present in many pharmaceutical compounds.

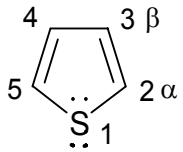


Fig. 1

The reasons of this great interest are mainly due to the fact that thiphene is an aromatic system almost similar to benzene; anyway, the presence of an heteroatom could improve the therapeutic profile, with few toxic effects. Different thiophene derivatives are biologically active , [24] such as ticlopidine and clopidogrel, platelet anti-aggregating drugs.

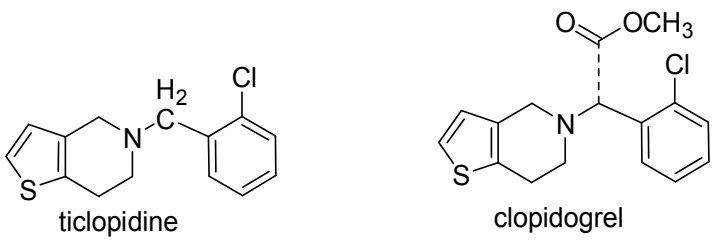
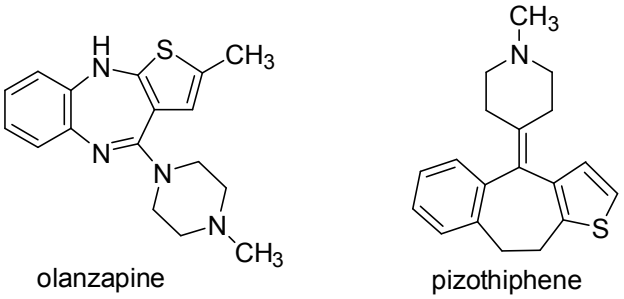


Fig. 2

Both of them are thienopyridine derivatives and they are used in the treatment of cardiovascular diseases, such as acute coronaryc syndromes (heart attack, instable angina). [25]

Olanzapine is an atypical anti-psychotic drug, delivered for schizophrenia treatment and bipolar disturb. [26]



olanzapine pizothiphene

Fig. 3

Olanzapine presents a thiophene ring condensed with a 1,5-benzodiazepine ring, which is responsible, according to a number of hypothesis, for the antagonistic activity towards D_2 dopaminergic receptors. Pizothiphene shows a good efficacy in the prevention of some migraine conditions. [27]

From recent pharmacological studies, it was clear that thiophene derivatives have also anti-inflammatory activity.[28] In all the studies it was demonstrated that acetylenic thiophene derivatives produce a powerful anti-inflammatory effect by reducing an edema burned out by carragenin, a vegetable gelatin used in food processing industry.

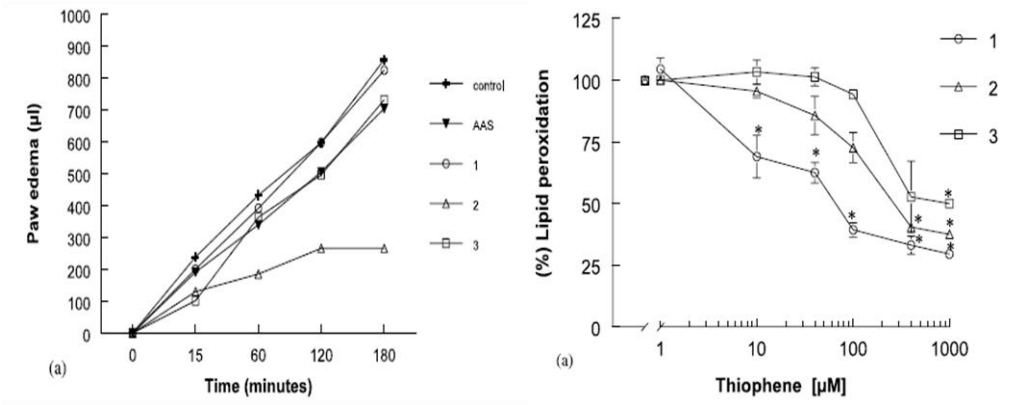
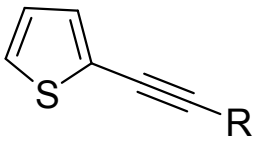


Fig. 4 a) Thiophene effect in the carrigenin induced edema in rats. b) Thiophene effect on lipidic peroxidation induced by Fe^{2+}/EDTA in rat liver. This class of compounds inhibits the normal activity of ALA-D enzyme (δ-aminolevulinate de-hydrogenase); in particular thiophene 1 and 2, have, respectively, anti-oxidant and anti-inflammatory activity (fig. 5).



1. R=CH_2OH
2. R=$(CH_2)_2CH_2OH$
3. R=$(CH_3)C(OH)(CH_2)_4CH_3$

Fig. 5

A significant example of anti-bacterical drug based on thiophene nucleus is Ticarcillin (fig. 6), a penicillin with a wide spread activity, indicated in Gram – infections.

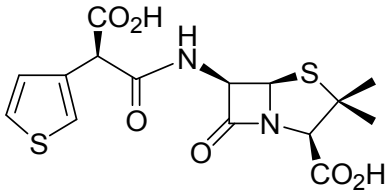


Fig.6 Ticarcillin structure.

(Thiophene-2-carbonyl)-thiourea derivatives have some biological activities, especially anti-bacterical and anti-mycotic ones, tested towards many bacterical and mycotic species, such as: *Staphylococcus (S.) aureus, Bacillus (B.) subtilis, Pseudomonas (P.) aeruginosa, Escherichia (E.) coli, Klebsiella (K.) pneumoniae, Candida (C.) albicans* e *Aspergillus (A.) Niger.*[29]

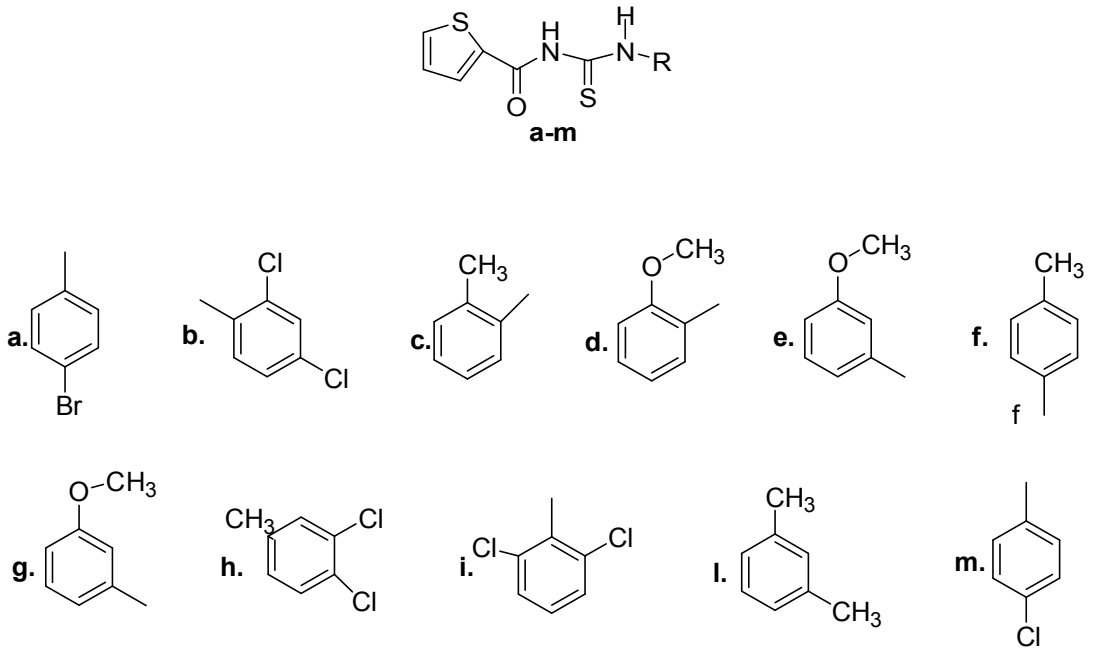
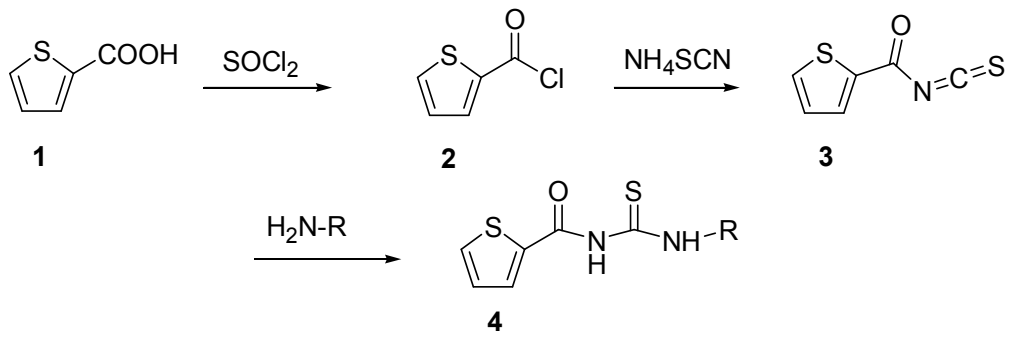


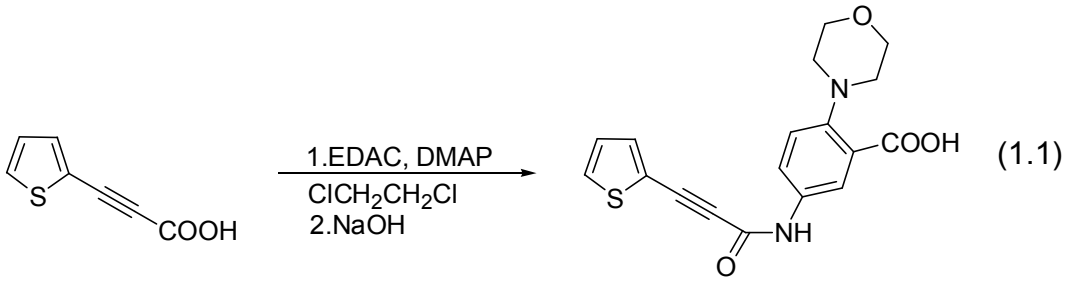
Fig. 7 Thioureic derivatives substituents.

These molecules can be obtained through a simple synthetic path, illustrated in the following Scheme:



Scheme 1.1

A variety of *Staphylococcus aureus* Sortase A inhibitors was obtained through different synthetic methodologies, as follows (eq. 1.1)



(1.1)

There are many expectations about thiophenes in pharmacology especially, after recent studies, in their potential anti-tumoral activity (thienopyridine derivatives)[30] and the therapy of Alzheimer disease.[31]

1.2 Thiophenes in material chemistry.

Synthetic applications of thiophenes were investigated in the last 60-70 years and are even now constantly in evolution. Many fundamental aspects, such as thiophene aromaticity, have been discussed since now.[32] In the last years, by simple modifications of common plastic materials, new materials were synthesized, called conductive polymers, which conjugate the electric properties of metals with the advantages of plastics (lightness and corrosion resistance). A structural require of these materials is that they should be conjugated polymers. Electrical conductivity and optical properties of conjugated polymers depend on the orbitals which, if in a sufficient number, create valency and conduction bands practically continuous. The valency band is constituted by π-orbitals, while conduction one by π^*-orbitals. The two bands are separated by an energy gap (Eg), which decreases with the increasing of conjugated double bonds. The energy gap is of 2.5 eV or more for insulating materials, less than 2.5 eV for semi-

conductors and worthless for conductors ones. Traditional polymers have an elevated energy gap.

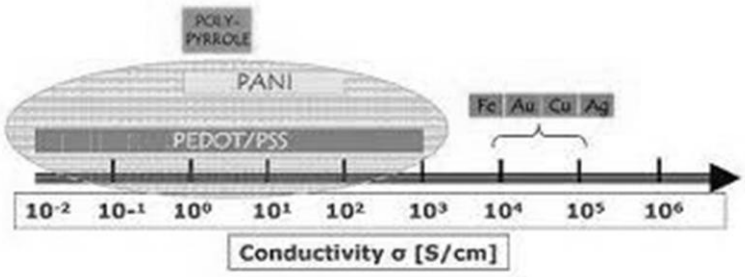


Fig. 8 Specific conductivity of organic polymers and conventional metals.

It is necessary to decrease the distance between valency and conduction orbitals, allowing the electrons to be excited on the conduction band. This can be possible through the reversible doping process on the neutral polymer by oxidation or reduction.

In the first case the polymer is oxidated by an electron-withdrawing species, generating a radical-cation; we talk about p-doping, or positive, since the molecules acquires a positive charge.

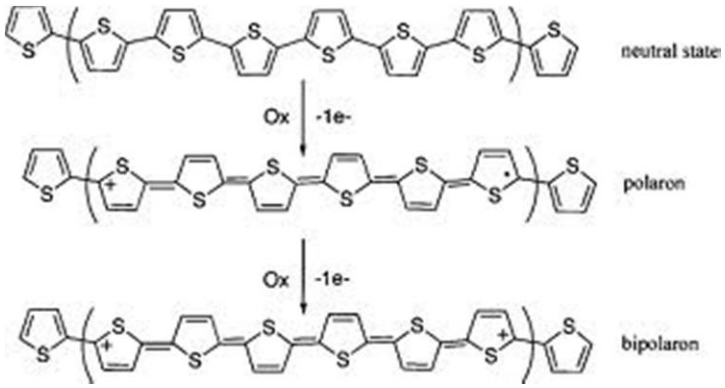


Fig. 9 p-doping of polythiophenes.

The most useful species for oxidative p-doping are Lewis acids ($AlCl_3$, $FeCl_3$), strong protic acids (or salts) and halogens. The radical-cation intermediate is instable, giving life to a chinoid-type structure extended

along 4 or 5 thiophene rings. Two radical cations could interact between them making a di-cation. If a neutral polymer is reducted with electron-donating species, such as alkaline metals (Na, K), making di-anions, the polymer acquires a negative charge (n-doping).

Polythiophenes (PT) are the most studied class because of their elevated conductivity, cheap synthesis cost, high temperatures resistances, no toxicity and high stability. In the neutral state, polythiophene is stable until 350°C exposed to air and until 900°C in inert atmosphere; the reason of this stability is explained by the high redox potential. The presence of alkylic chains bearing more than four carbon atoms in position 3 highly increases the solubility in common organic solvents. Furthermore, a region-regular polymer, due to a head-tail coupling (HT-HT, fig. 10), is provided of higher conductivity but less solubility.

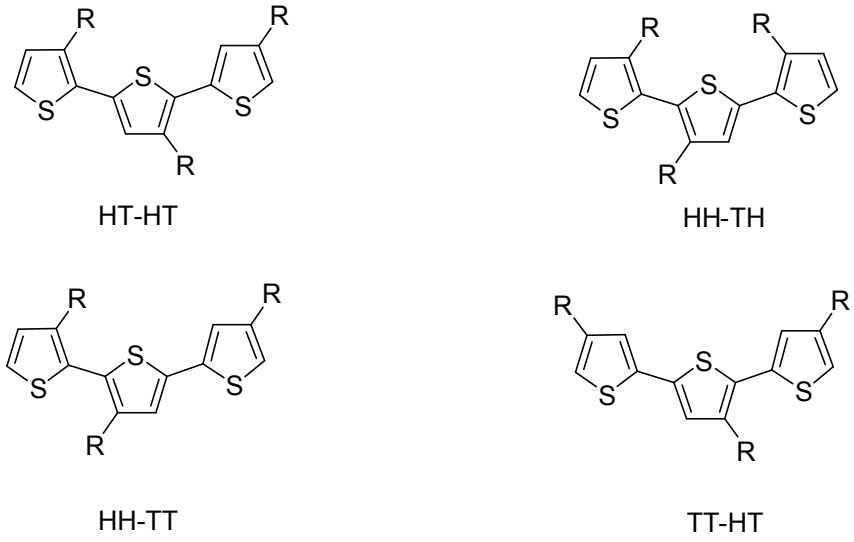


Fig. 10 Permitted configurations of 3-substituted polythiophenes.

All the chemical modifications of the polymeric structure are aimed at decreasing the bandgap, determined by contribution of the relative energy to bond length ($E^{\delta r}$), planarity deviation (E^{φ}), resonance energy (E^{Res}), inductive electronic effects of the substituents (E^{Sub}), intermolecular coupling (E^{int}). The novel syntheses of PT are dealing mainly in the

developing light emitting diodes (LEDs), transistors (FETs) and photovoltaic cells.[33]

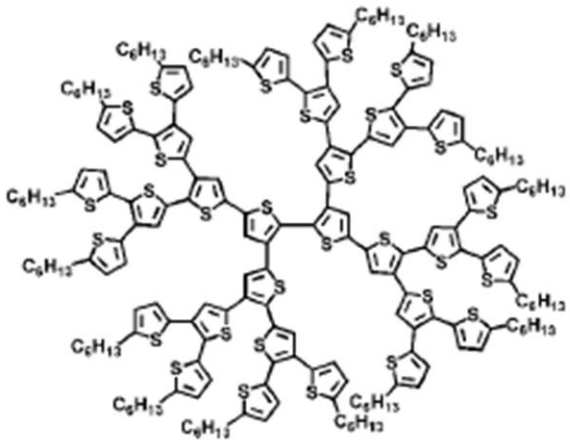


Fig. 11 Dendrimeric polythiophene.

Organometallic-based LEDs are quite studied, since many industries found a great potential in PT used in these kind of applications.[34] An electron-phosphorescence study on doped PT with iridium and platinum complexes was recently reported, underlining the troubles linked to this research field.[35] A diode which shows a record luminance of 10500 Cd/m^2 (fig. 12) was obtained by substitution of the *S*,*S*-dioxide oligothiophene with a branched structure based on benzo[b]thiophene, showing better film properties.

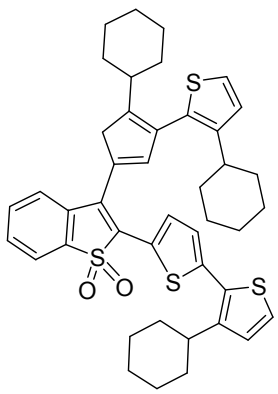


Fig. 12 Molecular structure o fan oligothiophene with high electro-luminance.

This class of materials has an intermediate band gap, which allows the inter-band transition to be close in the visible spectral region. Consequently, PTs show a coloured aspect in the neutral state, while they become more opaque after oxidation. One of the best examples is poly(3,4-ethylendioxithiophene), commonly known as PEDOT, developed with the final goal to increase the deposition of the polymers. This compound has a band gap of about 1,6 eV, less than any other alkyl-substituted polythiophene. PEDOT occupies a central place among electrochromic materials, since it has a reductive state with high absorption in the visible region, with an intense blue-coloration and a high-transmitting oxidative state, with NIR-absorption. The spectroelectrochemistry of a PEDOT film, settled from a 0,1 M solution of TBAP (tetrabutylamonium perchlorate) in PC (polycarbonate) and analyzed in a TBAP solution of acetonitrile is shown in the next figure (on the right). The voltammograms registered during the electro-deposition at 100 mV/s scansion are shown in the left: they show the EDOT oxidation semi-wave, its potential and oxidation/reduction semi-waves of deposited PEDOT. All the potential reported are based on the Ag/Ag+ couple.

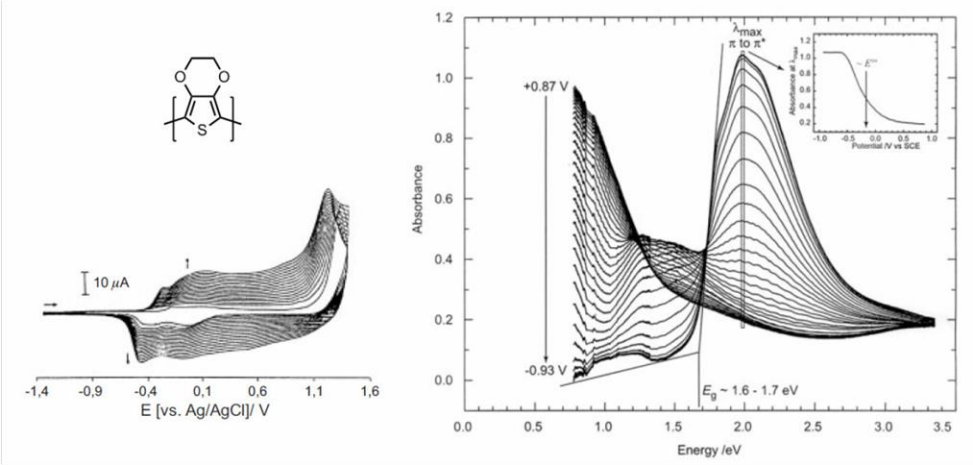


Fig. 13 PEDOT cyclo-voltammogram and electronic spectrum.

There are many improvements in electrochromic device field thanks to the synthesis of polymers with few HOMO-LUMO gap, by forming a covered film on indium-tin oxide (ITO), obtaining three primary colors (blue, red and green) from functionalized PTs.

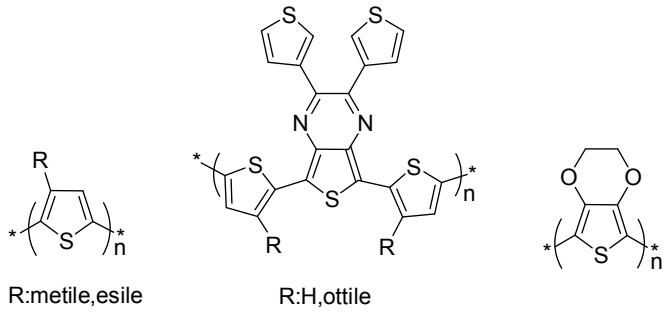


Fig. 14 Structures of blue, green and red electrochromic polythiophenes.

These results lead to a new class of electrochromic molecules based on semi-conductors polymers. Thiophene-based materials are used to detect biological molecules, such as DNA and proteins.[36] Been small and definite molecules, oligomers could be functionalized with particular groups, reacting spontaneously with protein functional groups (for example, mono-clonal antibodies) without changing the biological activity and forming stable conjugates.[37] Alternatively polythiophenes could easily prepared with positive or negative charge substituents, able to electrostatically interact with opposite charges on DNA or proteins, with a color change due to that interaction. For that reason many thiophene-based fluorescence markers were developed, functionalized with isothiocyanate group.[38] Recently many improvements were studied, which allow an efficient linkage with antibodies and oligonucleotides, by using simple standard ways and testing their specificity towards DNA sequences.[39]

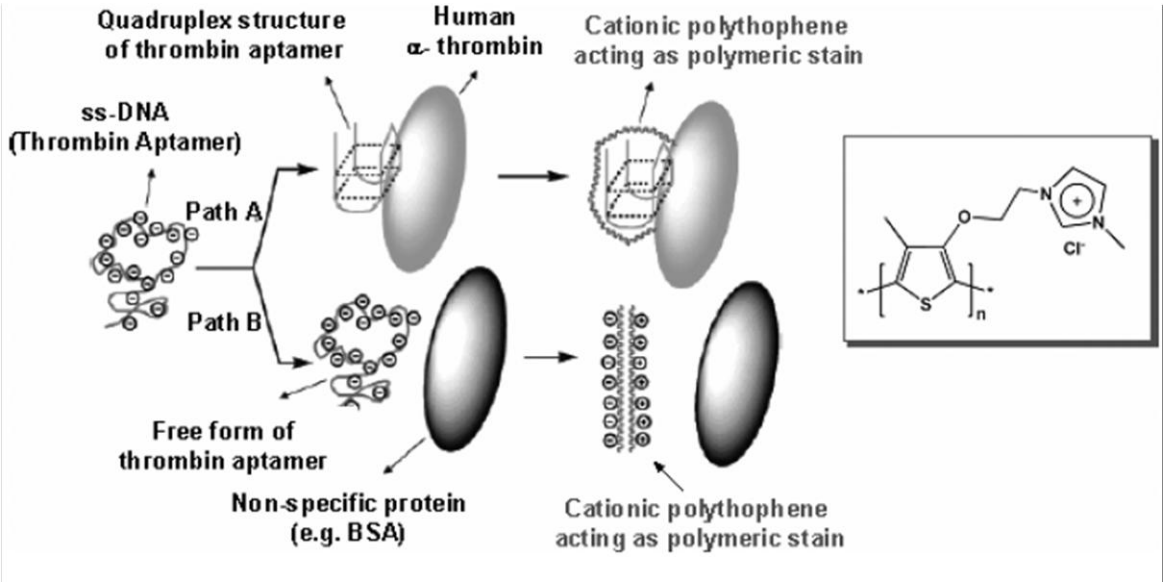


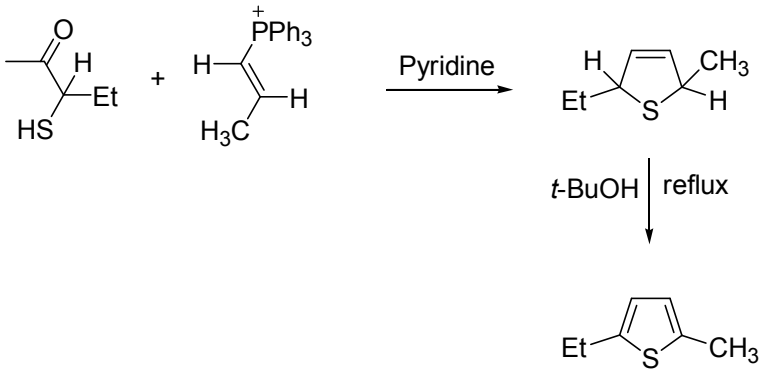
Fig. 15 Protein detecting (BSA e α-trombine) from a polythiophene marker.

Accordingly with the results of these studies, polythiophenes could generate new ways and instruments in diagnostic field and drug screening.[40]

1.3 Synthesis of thiophene derivatives.

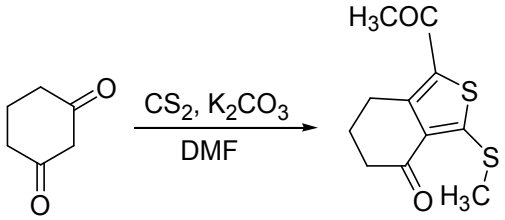
1) From thiocarbonylic compounds

2-Ketothiol derivatives, when reacted with alkenylphosphonium ions, lead to 2,5-dihydrothiophenes after ring closure through Wittig reaction. The corresponding thiophene is obtained by de-hydrogenation.



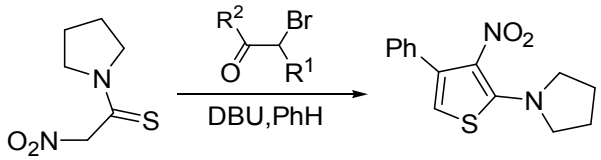
2) With carbon disulfide

2-Alkylthiophenes can be synthesized from addition of a carbanion to carbon disulfide, followed by *S*-alkylation.



3) From thionitroacetamides

S-alkylation of thionitroacetamides with 2-bromoketones leads to the formation of 2-amino-3-nitrothiophenes.



Classical methods

Thiophenes and their derivatives can be obtained through different synthetic approaches. Thiophene ring can be built from non-heterocyclic precursors following two different paths.

1. Ring building from open chained suitable precursors:

This method involves the introduction of the sulfur atom in the starting material bearing the entire carbon skeleton.

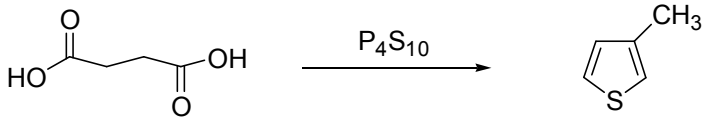
2. α and β position functionalization towards the *S*-atom with right precursors:

In this method the authors carried out the reaction between a mercaptoacetate and a 1,3-dicarbonylic compound or the reaction between a thiodiacetate and a 1,2-dicarbonylic compound.

The most known classical procedures in organic synthesis are Paal-Knorr (a), Fiesselmann (b), Gewald (c) and Hinsberg (d) syntheses:

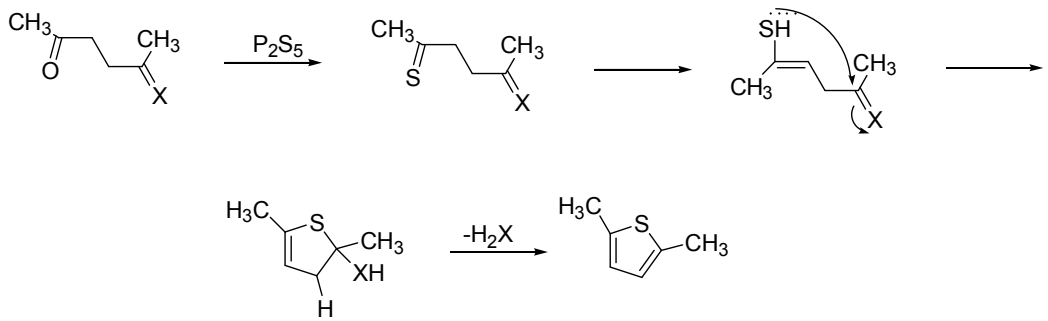
a) Paal-Knorr synthesis of thiophenes.

This reaction is better known as Paal synthesis. 1,4-dicarbonylic compounds react with a sulfur atoms source, to give thiophenes.



Paal synthesis

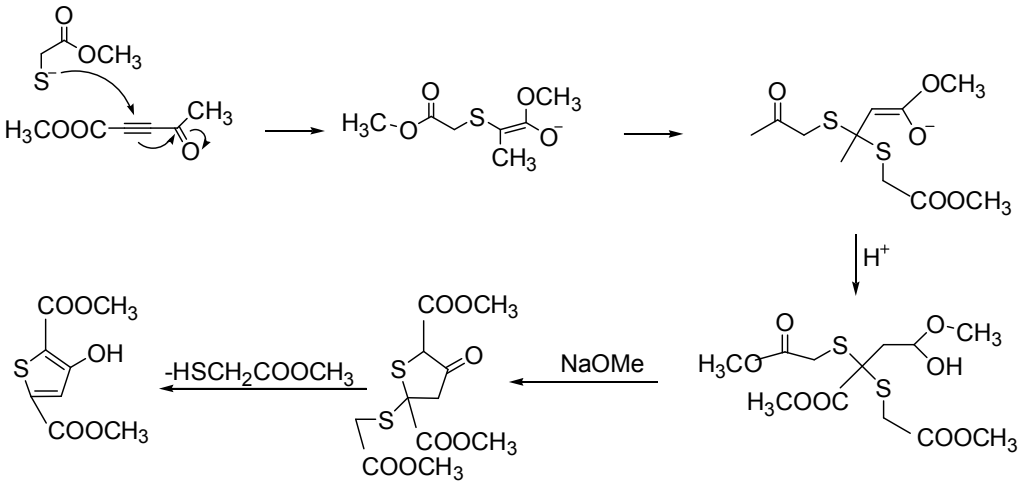
Phosphorus pentasulfide (P_2S_5), Lawesson reagent and bis(trimethylsilyl)sulfide are the commonly used sulfur sources. The reaction mechanism involves the initial formation of a thione, followed by tautomerization and cyclization. The consequent aromaticity leads to H_2O or H_2S elimination.



Reaction mechanism of the Paal synthesis.

b) Fiesselmann synthesis.

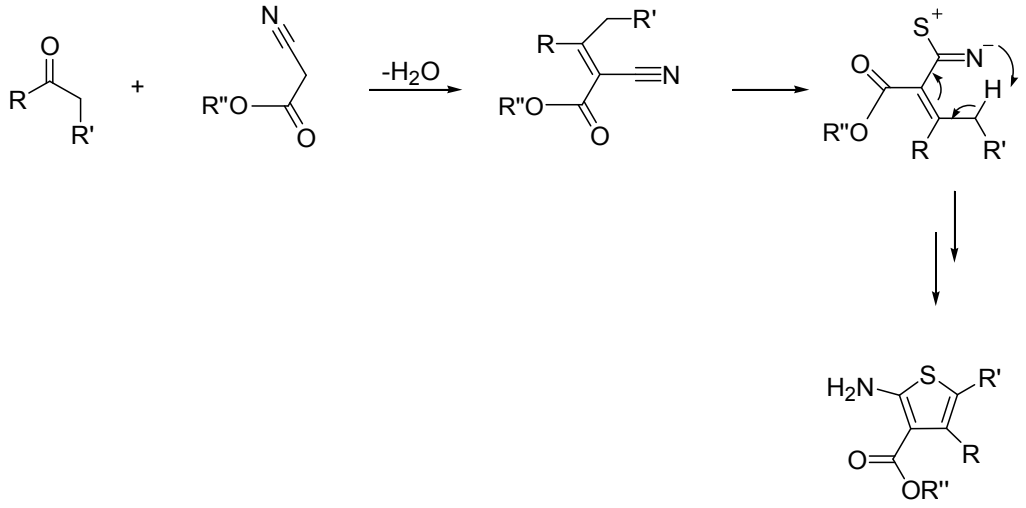
In this synthesis there is a condensation between thioglicolic acid (or its derivatives) with α,β-acetylenic esters which, after base treatment, leads to 3-hydroxy-2-thiophenecarboxylic acids (or their derivatives). The reaction works through a base-catalyzed 1,4-addition to form a thioacetal derivative. Treatment with a stronger base allows the formation of an enolate, while intramolecolar reaction (a Dieckman condensation), leads to a ketone. The final product is obtained after thioglicolate elimination, followed by aromatization.



Reaction mechanism of the Fiesselmann synthesis.

c) Gewald synthesis.

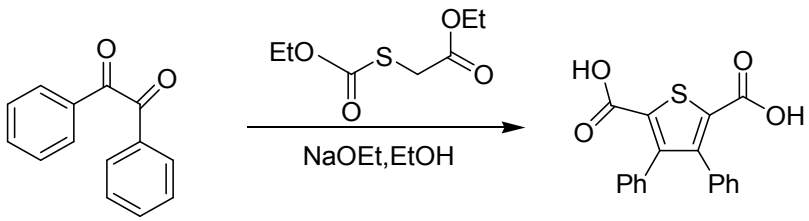
The gewald synthesis is a useful method for the synthesis of 2-aminothiophenes. It consists in the base-catalyzed condensation of a ketone bearing a $-CH_2$ group with a β-ketonitrile, able to form an olefin, following by elemental sulfur cyclization. In the first step occurs a Knoevenagel condensation between an activated nitrile and a ketone (or an aldehyde) to form an acrylonitrile. This condensation product is sulfurated on the nitrilic carbon atom. After the sulfuration, this compound converts into a mercaptide, which undergoes cyclization through an intramolecular attack.



Reaction mechanism of the Gewald synthesis.

d) Hinsberg synthesis.

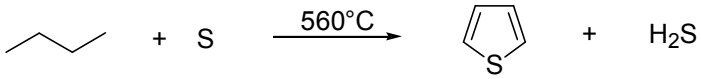
Two consecutive aldolic condensations between a 1,2-dicarbonylic compound and diethyldithioacetate lead to thiophene formation.



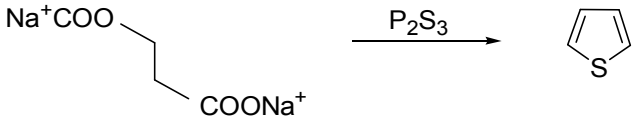
Hinsberg synthesis.

Industrial scale synthesis.

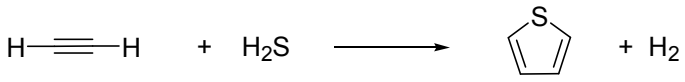
i) At elevated temperatures thiophene can be synthesized thanks to the reaction between *n*-butane and elemental sulfur.



ii) Another method includes the reaction between sodium succinate and phosphorous trisulfide under heating.

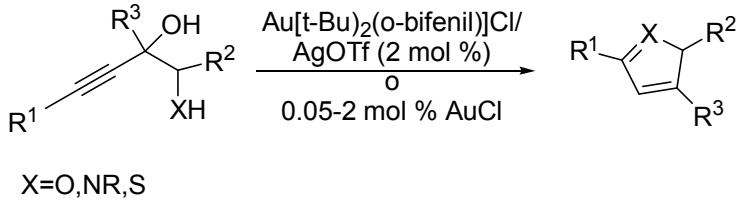


iii) Thiophene can be synthesized by passing an acetylene and sulfidric acid through a tube containing alumina at 400°C.



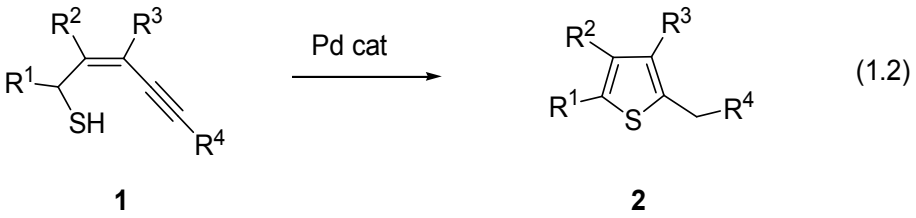
Metal-catalyzed syntheses of substituted thiophenes.

In the following Scheme is reported a synthetic strategy for the synthesis of heterocyclic derivatives through an Au-catalyzed heterocyclodehydration starting from a propargylic alcohol (one step reaction).[41]



Scheme 1.2

Another method occurs through a Pd-catalyzed cycloisomerization mechanism of (*Z*)-2-en-4-yne-1-thiols (**1**), to obtain thiophene derivatives (**2**).[42]



(1.2)

Table 1.1 Synthesis of thiophenes (**2**) by Pd-catalyzed cycloisomerization of (*Z*)-2-en-4-yne-1-thiols (**1**).[a]

Entry	**1**	R^1	R^2	R^3	R^4	Time (h)	Yield (%)[b]
1[c,d]	**1a**	H	H	Me	H	2	45 (36)
2[c]	**1b**	Et	H	Me	H	1	80 (71)
3	**1c**	Ph	H	Me	H	1.5	65 (58)
4	**1d**	H	H	Me	Bu	15	52 (44)
5	**1e**	H	H	Me	Ph	8	64 (56)
6[e]	**1f**	H	Et	H	Bu	1	94 (89)

[a] Unless otherwise noted, the reactions were carried out in inert atmosphere, in anhydrous DMA (2 mmol of 1/ mLof DMA), at 100°C, with a PdI_2/KI/substrate = 1/2/100 molar ratio.

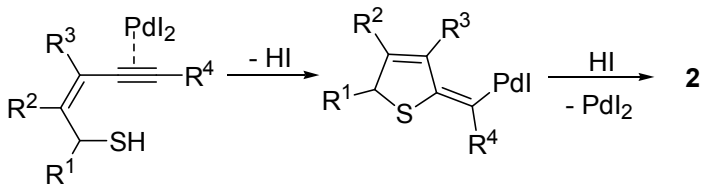
[b] GLC yield (isolated yield) based on **1**.

[c] The reaction was carried out in the absence of solvent.

[d] PdI_2/substrate = 1/50 molar ratio.

[e] The reaction was carried out at 25°C.

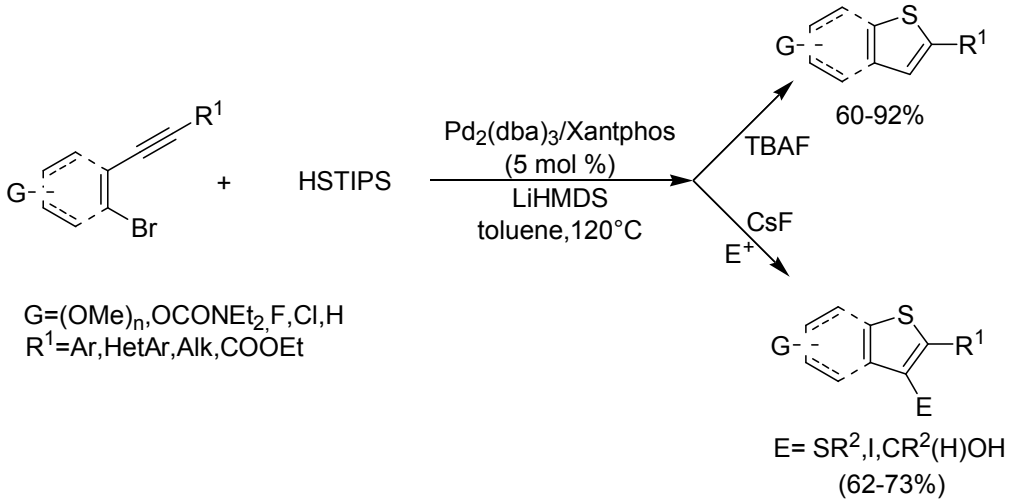
The reaction mechanism starts with the electrophilic activation of the triple bond by Pd(II), followed by an intramolecular nucleophilic attack of –SH group, protonolysis and aromatization (Scheme 1.3).



Scheme 1.3

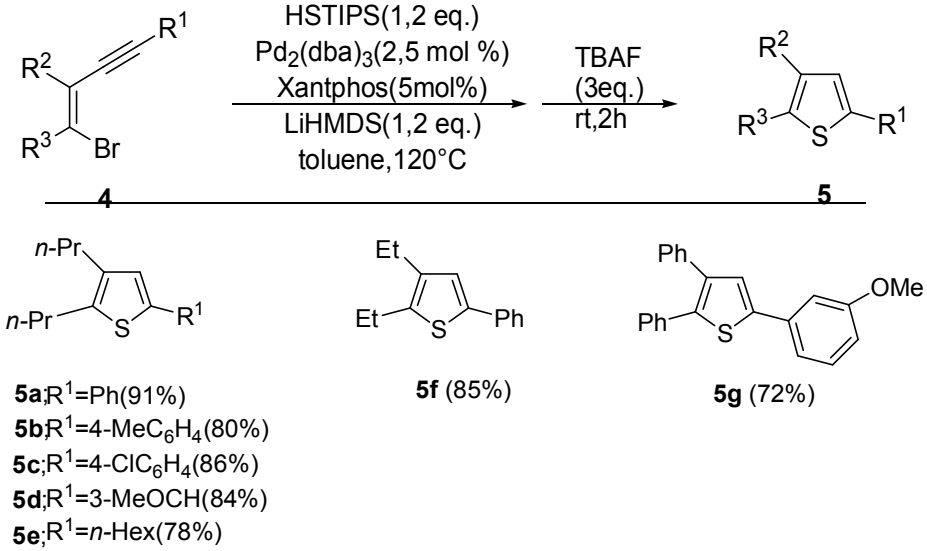
An efficient synthesis of thiophenes and benzothiophenes was developed starting from available molecules, such as bromoenynes and o-

alkynylbromobenzine derivatives (Scheme 1.4). This innovative one-pot procedure involves the formation of a C-S bond Pd-catalyzed by a HS surrogate, followed by an hetercyclization. Furthermore, the successive functionalization with suitable electrophilic species expands the potential of this methodology.[43]



Scheme 1.4

By using this synthetic strategy it is possible to synthesize 2,3,5-trisubstituted thiophenes, starting from bromoenyne derivatives:

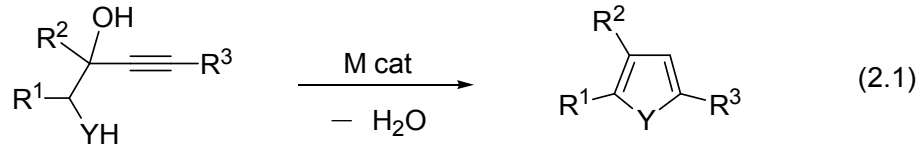


Scheme 1.5

Part II

Results and discussion

The general interest for metal-catalyzed reactions in organic synthesis is increasing year by year. In particular, the preparation, starting from simple and available substrates, of substituted heterocyclic compounds is acquiring an increasing importance. These compounds could be prepared by functionalization of the ring, through classical reactions, such as α-metallation o β-alogenation. Anyway, heterocyclization reactions from acyclic precursors are an alternative methodology which directly allows obtaining the desired molecule in a regioselective way. Recently different methods were developed: all of them show the utility of this approach. [44,45]

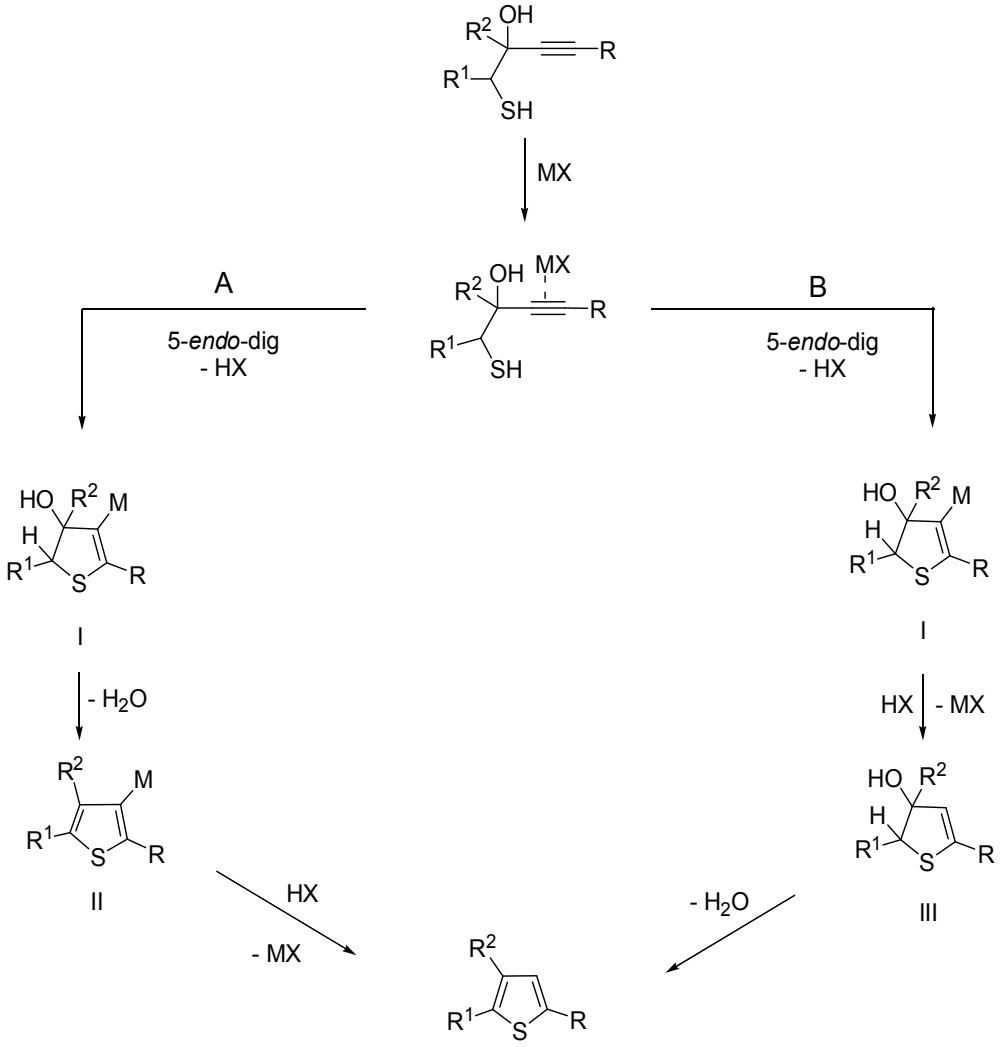


(2.1)

Y=O, NR, S

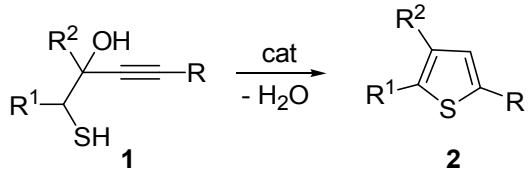
In the present thesis, our aim was to verify the possibility to extend the synthetic methodology described above with Y = O and NR (eq. 2.1) to 1-mercapto-3-yn-2-ol derivatives, in order to obtain new synthesized substituted thiophenes (eq. 2.1, Y = S). This strategy is very interesting because allows the one-step synthesis of useful molecules, under mild conditions and starting from simple starting materials. The reaction mechanism, in the presence of an appropriate catalyst, starts with the triple bond coordination to a metal center. After the coordination, the reaction could undergo two different mechanistic paths (A and B), leading to the same product through the formation of two different reaction intermediates: in path A, cyclic intermediate I is formed from the 5-*endo*-dig

intramolecular nucleophilic attack of the sulfur atom on the triple bond, with ring closure; intermediate I then undergoes spontaneous dehydration to give aromatic intermediate II followed by protonolysis. In path B the vice versa occurs: after the nucleophilic attack, there is first the protonolysis (intermediate III) and then the aromatization with loss of water. In both ways we observe the formation of the same final product and the regeneration of the catalytic species.



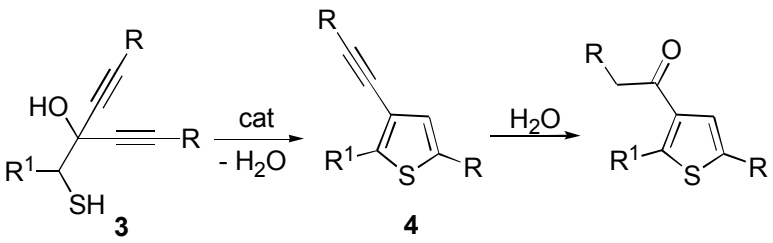
Scheme 2.1

On the basis of the already realized furan and pyrrole syntheses,[46] our work hypothesis was based on the use of 1-mercapto-3-yn-2-ol (**1**) derivatives, according to Scheme 2.2.



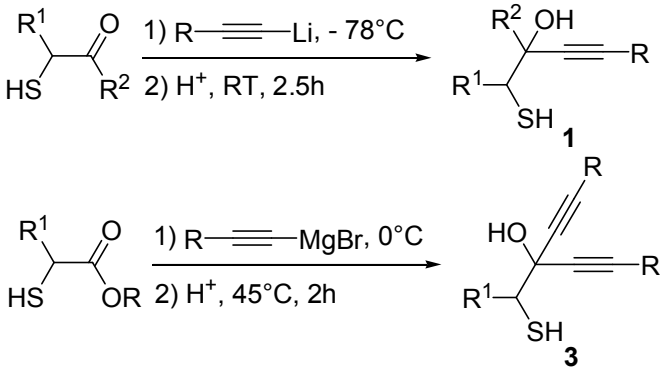
Scheme 2.2

The synthetic path already described could be extended to 1-mercapto-3,3-diyn-2-ol (**3**) derivatives. This alternative methodology could allow the further functionalization of the triple bond in position 3, with the introduction of a carbonyl group, after hydration of the alkynyl function of the initially formed species **4** (Scheme 2.3):



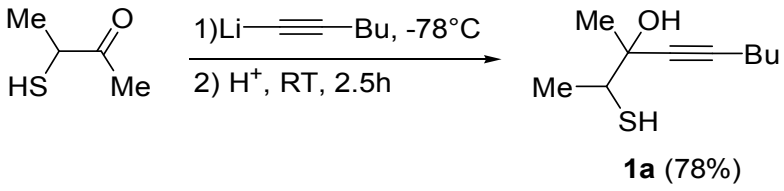
Scheme 2.3

This innovative methodology is of great interest also in view of the availability of the starting substrates, whose precursors (α-mercaptoketones and α-mercaptoesters) are commercially available and unexpensive (Scheme 2.4).

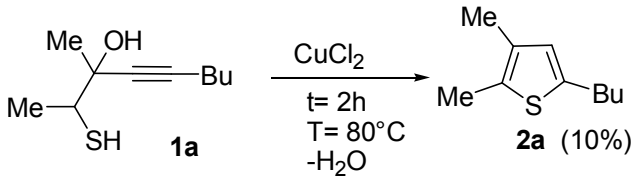


Scheme 2.4

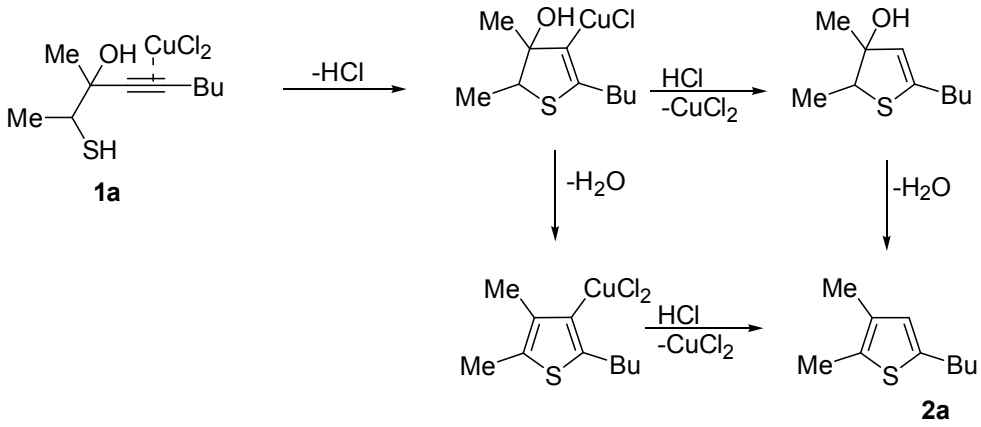
2-Mercapto-3-methylnon-4-yn-3-ol **1a** (R = Bu, R^1 = Me, R^2 = Me), readily available by alkynylation of 3-mercapto-2-butanone (Scheme 2.5; the preparation is reported the experimental section), was chosen as model substrate to test the reactivity of 1-mercapto-3-yn-2-ol derivatives **1** in the same optimized conditions already tested in the process of heterocyclo-dehydration of *N*-protected 1-amino-3-yn-2-ol and 3-yne-1,2-diol derivatives. The first attempt was carried at 80 °C in MeOH as the solvent (**1a** concentration = 0.2 mmol per mL of MeOH, **1a**:$CuCl_2$ molar ratio = 100:1) in a Schlenk flask. The reaction mixture was monitored during time through GLC and TLC: both analyses showed a partial conversion of the substrate (30%) with the formation of 5-butyl-2,3-dimethylthiophene (**2a**) as the product, purified through distillation and completely characterized, according to our initial hypothesis.



Scheme 2.5



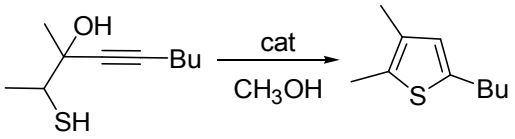
Scheme 2.6



Scheme 2.7

As shown in Scheme 2.6, the yield obtained after distillation was not too high (10%), maybe because of the formation of heavy products not detectable in GLC. In order to improve this initial result, we then screened the reaction parameters by using different catalytic systems. Excepted for $PdCl_2(PPh_3)_2$ (entry 5), analyzing the results reported in the table, we can note that, with all the catalytic system tested, the process is slower or has a low selectivity; the most efficient is surely PdI_2/KI (entry 2). So, considering these last results, we moved to PdI_2/KI as the catalytic system: thanks to it, in the last years, many heterocyclization processes were developed.[47]

Table 2.1. Metal-catalyzed heterocyclo-dehydration reaction of 2-mercapto-3-methylnon-4-yn-3-ol 1a with different catalytic systems.[a]



1a **2a**

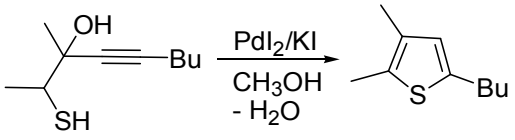
Entry	Catalyst	Conversion (%)[b]	Yield **2a** (%)[b]
1	$CuCl_2$	30	10
2	PdI_2+10KI	40	39
3	CuCl	24	2
4	CuI	18	3
5	$PdCl_2(PPh_3)_2$	38	20
6	$Pd(PPh_3)_4$	11	8
7	$Pd(dba)_2$	7	1
8	ZnI_2	9	2
9	$PdCl_2$	27	10
	$PdCl_2$+10 KCl	27	13

[a] All reactions were carried out in MeOH, for 2h, at 80°C (**1a** concentration = 0.2 mmol per mL of MeOH; **1a**:catalyst molar ratio = 100:1).

[b] Based on starting **1a**, by GLC.

We then screened the reaction parameters; the results obtained are shown in Table 2.2, entries 2-8.

Table 2.2 PdI_2/KI-catalyzed heterocyclo-dehydration reaction of 2-mercapto-3-methylnon-4-yn-3-ol 1a under different conditions. [a]



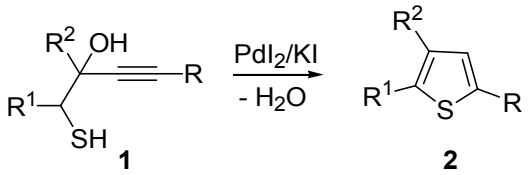
1a **2a**

Entry	KI/PdI_2 molar ratio	T (°C)	Sub. concentration [b]	Conversion (%)[c]	yield of **2a**[c] (%)
1	10	50	0.2	40	39
2	10	80	0.2	100	77
3	10	50	0.5	87	78
4	10	50	1	81	70
5	10	50	0.05	27	25
6	5	50	0.2	34	33
7	100	50	0.2	65	59
8[d]	10	50	0.2	56	37

[a] All reactions were carried out in MeOH for 2 h in the presence of 1 mol % of PdI_2. [b] Mmol of starting **1a** per mL of MeOH. [c] Based on starting **1a**, by GLC. [d] The reaction was carried out with DMA as the solvent.

As can be seen from Table 2.2, entry 2, an increase of the temperature to 80 °C caused an improvement of the total yield of **2a** and a complete conversion of the substrate. A similar effect on the yield was observed when substrate concentration was increased (entry 3) and when the KI:PdI_2 ratio was elevated to 100 (entry 7) even if with some loss of substrate. Finally, as shown in entry 8, methanol is the best solvent to promote this kind of reaction. By carrying out the reaction under the optimized conditions (**1a**:KI:PdI_2 molar ratio = 100:10:1, 50 °C, **1a** concentration = 0.5 mmol per mL of MeOH) and until complete conversion of the substrate (3h), 5-butyl-2,3-dimethylthiophene **2a** was obtained in 88% isolated yield (Table 2.3, entry 1).

Table 2.3 Synthesis of substituted thiophenes 2 by PdI_2/KI-catalyzed heterocyclo-dehydration of 1-mercapto-3-yn-2-ols 1.[a]



1 **2**

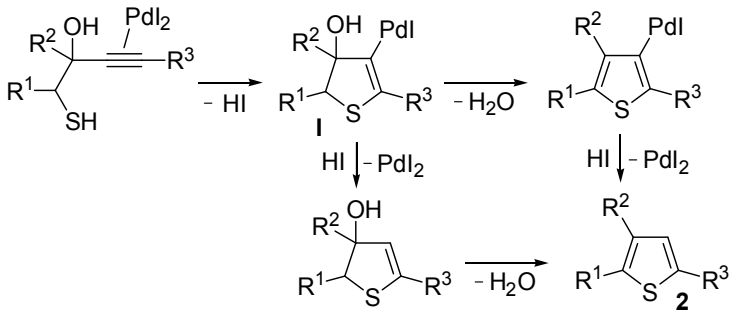
Entry	**1**	R	R^1	R^2	PdI_2 (mol %)	T (°C)	t (h)	**2**	Yield of **2** (%)[b]
1	**1a**	Bu	Me	Me	1	50	3	**2a**	88
2	**1b**	Ph	Me	Me	1	80	1	**2b**	89
3	**1c**	3-thienyl	Me	Me	1	80	16	**2c**	76
4	**1d**	Tolyl	Me	Me	2	50	12	**2d**	75
5	**1e**	*p*-$O_2NC_6H_5$	Me	Me	1	50	1	**2e**	78
6	**1f**	1-cyclohexenyl	Me	Me	2	80	24	**2f**	50
7	**1g**	Ph	H	H	2	100	6	**2g**	50

[a] All reactions were carried out in MeOH as the solvent (0.5 mmol of starting **1** per mL of MeOH) and with a KI:PdI_2 molar ratio = 10. Conversion of **1** was quantitative in all cases. [b] Isolated yield based on starting **1**.

The generality of the process was then verified by testing the reactivity of other differently substituted 1-mercapto-3-yn-2-ols **1b-g**, bearing different substituents on the triple bond, both aromatic and aliphatic ones. As can be seen from the results reported in Table 2.3, entries 1-6, the process is quite general, the corresponding substituted thiophenes **2a-g** being consistently obtained in satisfactory isolated yields. Only in the case of 1-mercapto-4-phenyl-but-3-yn-2-ol **1g** the yield of the corresponding thiophene derivative **2g**, was lower (50%, Table 2.3, entry 6).

The reaction also worked well with a substrate bearing a triple bond conjugated with a phenyl group, such as 4-mercapto-3-methyl-1-phenyl-pent-1-yn-3-ol **1b**, which led to the formation of 2,3-dimethyl-5-phenylthiophene **2b** in 72% yield. The reaction time could be reduced to 1 h working at 80 °C, with an isolated yield of of 89% (Table 2.3, entry 2). However, the heterocyclodehydration process was slower when the R^3 was an aromatic ring substituted with an electron-releasing group at the *para* position, as in the case of 4-mercapto-3-methyl-1-*p*-tolylpent-1-yn-3-ol **1d**, whose conversion was not complete even after 20 h working at 50 °C, with a yield of 2,3-dimethyl-5-*p*-tolylthiophene **2d** of 50 %. This result could, however, be improved working for 12 h with a higher catalyst loading (2% rather than 1%), with a yield of **2d** of 75% at total substrate conversion (Table 2.3, entry 4). Complete substrate conversion was also achieved working at 80 °C for 8 h, but this caused extensive substrate decomposition, with a yield of **2d** of only 22%. As expected in view of the results obtained with **1d**, a *para*-electron-withdrawing group caused an augment of the reaction rate. Thus, 4-mercapto-3-methyl-1-(4-nitrophenyl)pent-1-yn-3-ol **1e**, under the same conditions as those of entry 1, was converted into 2,3-dimethyl-5-(4-nitrophenyl)thiophene **2e** in 80% yield after only 1 h reaction time (Table 2.3, entry 5). On the other hand, a substrate bearing a π-excessive heteroaromatic substituent on the triple bond, such as 4-mercapto-3-methyl-1-(thiophen-3-yl)pent-1-yn-3-ol **1c**, was less reactive than **1b**, affording, under the same conditions, the corresponding 2,3-dimethyl-5-(thiophen-3-yl)thiophene **2c** in 78% yield after 24 h (Table 2.3, entry 3). These results show that the heterocyclodehydration process is quite sensitive to the electrophilicity of the coordinated triple bond undergoing the intramolecular nucleophilic attack by the mercapto group, which leads to the formation of a vinylpalladium species as intermediate **I** (Scheme 2; anionic iodide ligands

are omitted for clarity). The latter then undergoes protonolysis followed by dehydration or vice versa to give the final product with regeneration of PdI_2 (Scheme 2.8).



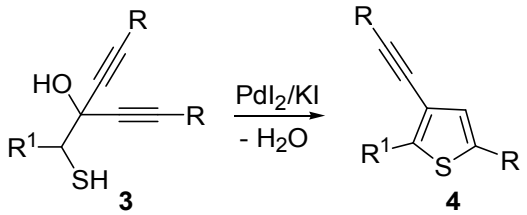
Scheme 2.8 Proposed Mechanism for the PdI_2/KI-Catalyzed Heterocyclodehydration of 1-Mercapto-3-yn-2-ols **1** to Substituted Thiophenes **2**.

The reaction of a 1,2-unsubstituted 1-mercapto-3-yn-2-ol, such as 1-mercapto-4-phenylbut-3-yn-2-ol **1g** turned out to be much slower with respect to the analogous 1,2-dimethyl-substituted substrate **1b**. In order to achieve complete conversion of **1g**, it was necessary to work at 100 °C for 6 h with 2 mol % of catalyst, with a yield of 2-phenylthiophene **2g** of 50% (Table 2.3, entry 7). This result clearly shows that the reactive rotamer effect[48] is at work under our conditions.

We also tested the reactivity of 1-mercapto-2,2-dialkynyl-2-ols **3a-c**, bearing an additional alkynyl substituent at C-2 (Table 2.4, entries 1-3). The reaction of 7-(1-mercaptoethyl)trideca-5,8-diyn-7-ol **3a**, carried out under the same conditions optimized for **1a** (Table 2.3, entry 1), afforded 5-butyl-3-(hex-1-ynyl)-2-methylthiophene **4a** in 85% yield after 8 h (Table 2.4, entry 1), without affecting the alkynyl substituent. As expected in view of the reactive rotamer effect, an analogous substrate lacking the alkyl substituent at C-1, such as 7-(mercaptomethyl)trideca-5,8-diyn-7-ol **3c** was

less reactive than **3a**, leading to the corresponding alkynylthiophene **4c** in 52% yield after 8 h at 74% substrate conversion (Table 2.4, entry 3). This result could not be improved by increasing the reaction time and temperature or the catalyst loading. On the other hand, 3-(1-mercaptoethyl)-1,5-diphenylpenta-1,4-diyn-3-ol **3b** led to the corresponding thiophene derivative **4b** in high yield working at 80 °C for 3 h with 2 mol % of catalyst (85%, Table 2.4, entry 2).

Table 2.4 Synthesis of 3-alkynyl substituted thiophenes 4 by PdI_2/KI-catalyzed heterocyclo-dehydration of 1-mercapto-3,3-diyne-2-ols 3.[a]



Entry	**3**	R	R^1	PdI_2 (mol %)	T (°C)	t (h)	**4**	Yield of **4** (%)[b]
1	**3a**	Bu	Me	1	50	3	**4a**	85
2	**3b**	Ph	Me	2	80	3	**4b**	85
3	**3c**	Bu	H	1	50	8	**4c**	52

[a] All reactions were carried out in MeOH as the solvent (0.5 mmol of starting **1** per mL of MeOH) and with a KI:PdI_2 molar ratio = 10. Conversion of **3** was quantitative in all cases. [b] Isolated yield based on starting **3**.

Conclusions.

In conclusion, we have reported a convenient and general method for the heterocyclodehydration of readily available 1-mercapto-3-yn-2-ols **1** to substituted thiophenes **2**. The process is catalyzed by a simple catalytic system, consisting of PdI_2 in conjunction with an excess of KI, under mild reaction conditions (MeOH as the solvent at 50−80 °C) and can be applied to a variety of substrates, including 1-mercapto-2,2- dialkynyl-2-ols. The latter were converted into the corresponding thiophene derivatives without affecting the additional alkynyl substituent, which would allow further functionalization at the thiophene ring.

Part II

Part II

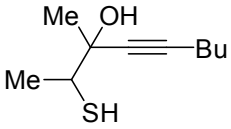
Experimental section

General Experimental Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ solutions at 300 or 500 MHz and 75 or 125 MHz, respectively, with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. IR spectra were taken with an FT-IR spectrometer. Mass spectra were obtained using a GC-MS apparatus at 70 eV ionization voltage or a mass spectrometer equipped with a turbo ion spray ionization source in the positive mode [ion spray voltage (IS) 4500 V; curtain gas 10 psi; temperature 25 °C; ion source gas (1) 20 psi; declustering and focusing potentials 50 and 400 V, respectively]. Microanalyses were carried out at our analytical laboratory. All reactions were analyzed by TLC on silica gel 60 F_{254} or on neutral alumina and by GLC using a gas chromatograph and capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase or using a gas chromatograph and a capillary columns with diethyl tertbutylsilyl-β-cyclodextrine as the stationary phase. Column chromatography was performed on silica gel 60 (70-230 mesh). Evaporation refers to the removal of solvent under reduced pressure.

Preparation of substrates 1. Substrates **1** were prepared by alkynylation of the appropriate or α-mercapto ketone using an excess of RC≡CLi, as described below.

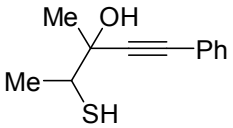
General procedure for the preparation of 1-mercapto-3-yn-2-ols 1a-f. To a solution of BuLi in hexane (1.6 M) (25 mL, 40 mmol) was added anhydrous THF (6 mL) and hexane (25 mL) under nitrogen. The resulting

mixture was cooled at -40 °C and maintained under stirring. A solution of the 1-alkyne (44.5 mmol) (1-hexyne: 3.66 g; phenylacetylene: 4.54 g; 3-ethynylthiophene: 4.81 g; *p*-tolylacetylene: 5.17 g; *p*-nitrophenylacetylene: 6.55 g; 4-ethynylcyclohexene: 4.72 g) in anhydrous THF (6 mL) was added dropwise under nitrogen to the cooled mixture followed by a solution of LiBr (1.56 g, 18.0 mmol) in anhydrous THF (6 mL). After stirring for 0.5 h at -40°C, a solution of the of the appropriate α-mercapto ketone (17 mmol) [3-mercapto-2-butanone (purity 88%): 1.77 g] in anhydrous THF (5 mL) was added under nitrogen. The mixture was allowed to stir at the same temperature for 2 h, then it was allowed to warm up to room temperature. Satd aqueous NH_4Cl (40 mL) was added, followed by Et_2O (50 mL). Phases were separated and the aqueous phase extracted with Et_2O (50 mL × 3). The collected organic phases were washed with brine to neutral pH and dried over Na_2SO_4. After filtration and evaporation of the solvent, products **1a-e** were purified by column chromatography on silica gel using 95/5 hexane-AcOEt mixture as the eluent in every case.

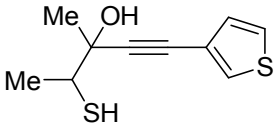


2-Mercapto-3-methyl-non-4-yn-3-ol (1a) Yield: 2.47 g, starting from 1.77 g of 3-mercaptobutan-2-one (78%). Mixture of diastereomers A+B, A:B ratio ca. 7:3, determined by GLC. Yellow pale oil; $C_{10}H_{18}OS$ (186.31). IR (film): ν = 3447 (s, br), 2960 (m), 2933 (s), 2872 (m), 2240 (w), 1458 (m), 1371 (m), 1343 (m), 1192 (w), 1118 (m), 1048 (m), 701 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.22 (s, br, 1H, OH, B), 3.14 (q, J = 6.9, 1H, C*H*CH_3, A), 2.91-2.80 (m, 1H, C*H*CH_3, B), 2.75 (s broad, 1H, OH, A), 2.25-2.17 (m, 4H, C*H*$_2$$CH_2CH_2CH_3$, A+B), 1.89 (d, J = 10.5, 3H, CHC*H*$_3$, B), 1.71(d, J = 6.5, 1H, SH, B), 1.55 (s, 3H, C*H*$_3$COH, B), 1.51 (s, 3H, C*H*$_3$COH, A), 1.46 (d, J = 6.9, 1H, SH, A), 1.35 (d, J = 6.9, 3H, CHC*H*$_3$,

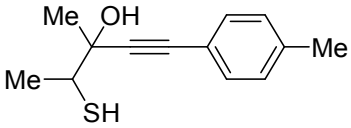
A), 1.55-1.40 (m, 8H, $CH_2CH_2CH_2CH_3$, A+B), 0.91 (td, J = 1.6, 7.3, 6H, $CH_2CH_2CH_2CH_3$, A+B); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 85.6 (B), 85.1 (A), 82.5 (A), 80.6 (B), 71.6 (B), 71.0 (A); 40.4 (B), 46.4 (A), 30.8 (B), 30.7 (A), 27.0 (B), 26.0 (A); 21.9 (A), 21.8 (B), 18.6 (A+B), 18.3 (A+B), 13.6 (A+B). GC-MS (EI, 70 eV) A : *m/z* = 186 (0.1) [M^+]; 126 (9); 125 (95); 91 (12); 82(9); 81 (10); 79 (13); 70 (20); 61 (19); 55(13); 43 (100); 41 (25); B : *m/z* = 187 (0.1) [M^{+1}]; 186 (0.6) [M^+]; 125 (98); 79 (10); 69 (18); 61 (20); 55 (12); 43 (100); 41 (24).



4-Mercapto-3-methyl-1-phenyl-pent-1-yn-3-ol (1b) Yield: 2.98 g, starting from 1.77 g of 3-mercaptobutan-2-one (85%). Mixture of diastereomers A+B, A:B ratio ca. 6:4, determined by GLC. Yellow oil; $C_{12}H_{14}OS$ (206.30). IR (film): ν = 3448 (s, br), 2974 (m), 2932 (m), 2557 (m), 2230 (w), 1598 (m), 1489 (m), 1372 (m), 1262 (w), 1106 (m), 1070 (m), 756 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47-7.40 (m, 4H arom, A+B), 7.37-7.28 (m, 6H arom, A+B), 3.37 (s, 1H, OH, B), 3.3 (q, J = 6.9, 1H, $CHCH_3$, A), 3.0-2.92 (m, 1H, $CHCH_3$, B), 2.81 (s, 1H, OH, A), 1.96 (d, J = 10.9, 3H, $CHCH_3$, B), 1.77 (dd, J = 0.8, 6.5, 1H, SH, B), 1.65 (s, 3H, CH_3COH, B), 1.63 (s, 3H, CH_3COH, A), 1.66 (d, J = 6.9, 3H, $CHCH_3$, A), 1.43 (dd, J = 0.8, 6.9, 1H, SH, A); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.7 (B), 131.68 (A), 128.5 (B+A), 128.3 (B+A), 122.3 (B), 122.28 (A), 91.3 (A), 89.4 (B), 85.0 (B), 84.4 (A), 72.0 (B), 71.2 (A), 40.5 (B), 46.3 (A), 26.8 (B), 25.5 (A); 22.0 (B), 18.4 (A). GC-MS (EI, 70 eV) A : *m/z* = 206 (0.5) [M^+]; 146 (11); 145 (100); 129 (14); 115 (10); 77 (8); 75 (5); 43 (72); B : *m/z* = 207 (0.14) [M^{+1}]; 137 (0.6) [M^+]; 188 (14); 173 (10); 145 (100); 129 (15); 115 (12); 77 (11); 43 (80).

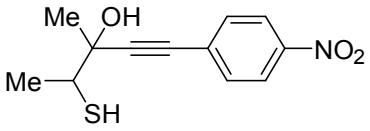


4-Mercapto-3-methyl-1-thiophen-3-yl-pent-1-yn-3-ol (1c) Yield: 3.32 g, starting from 1.77 g of 3-mercaptobutan-2-one (92%). Mixture of diastereomers A+B, A:B ratio ca. 9:1, determined by GLC. Yellow oil; $C_{10}H_{12}OS_2$ (212.33). IR (film): ν = 3419 (s, br), 3107 (m), 2976 (m), 2932 (m), 2561 (w), 2231 (w), 1769 (w), 1592 (w), 1450 (m), 1358 (m), 1242 (w), 1137 (m), 1036 (m), 783 (s), 627 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.43 (td distorted, J = 1.2, 3.0, 2H, on thiophen ring , A+B), 7.25 (td distorted, J = 1.2, 3.0, 2H, on thiophen ring, A+B), 7.12-7.07 (m, 2H, on thiophen ring, A+B), 3.5-3.39 (m, 1H, OH, B), 3.26 (q, J = 6.7, 1H, C*H*CH_3, A), 3.04-2.90 (m, 1H, C*H*CH_3, B), 1.94 (d, J = 6.7, 3H, CHC*H*$_3$, B), 1.76 (d, J = 10.3, 1H, SH, B), 1.63 (s, 3H, C*H*$_3$COH, B), 1.61 (s, 3H, C*H*$_3$COH, A), 1.52 (d, J = 6.7, 1H, SH, A), 1.41(d, J = 6.7, 3H, CHC*H*$_3$, A); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 129.8 (B+A), 129.0 (B+A), 125.4 (A+B), 121.3 (A+B), 91.0 (A), 89.1 (B), 80.1 (B), 79.5 (A), 72.0 (B), 71.3 (A), 48.2 (B), 46.1 (A), 26.8 (B), 25.5 (A); 21.82 (B), 18.6 (A). GC-MS (EI, 70 eV) A : *m/z* = 212 (0.48) [M^+]; 183 (6); 152 (6); 151 (62); 135 (7); 109 (5); 63 (6); 61 (8); 45 (11); 43 (100); B : *m/z* = 212 (0.8) [M^+]; 183 (7); 151 (70); 135 (8); 109 (7); 61 (8); 45 (11); 43 (100).



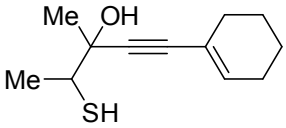
4-Mercapto-3-methyl-1-*p*-tolyl-pent-1-yn-3-ol (1d) Yield: 2.10 g, starting from 1.77 g of 3-mercaptobutan-2-one (56%). Mixture of diastereomers A+B, A:B ratio ca. 6:4, determined by GLC. Yellow oil; $C_{13}H_{16}OS$ (220.33). IR (film): ν = 3433 (s, br), 2974 (m), 2926 (m), 2566 (w), 2229 (w), 1510 (s), 1450 (m), 1372 (m), 1267 (w), 1146 (m), 1036 (m), 816 (s)

771 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36-7.27 (m, 4H arom, A+B), 7.10 (d, J = 7.34, 4H arom, A+B), 3.48 (s broad, 1H, OH, B), 3.27 (q, J = 6.6, 1H, C*H*CH_3, A), 3.0-2.85 (m, 1H, C*H*CH_3, B), 2.33 (s, 6H, PhCH_3, A+B), 1.96 (d, J = 10.3, 3H, CHC*H*$_3$, B), 1.78 (d, J = 5.86, 1H, SH, B), 1.64 (s, 3H, C*H*$_3$COH, B), 1.62 (s, 3H, C*H*$_3$COH, A), 1.53 (d, J = 6.6, 1H, SH, A), 1.42(d, J = 6.6, 3H, CHC*H*$_3$, A). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.6 (A+B), 131.6 (B), 131.58 (A), 129.0(B+A), 119.2 (B+A), 90.6 (A), 88.7 (B), 85.1 (A), 84.5 (B), 72.0 (B), 71.3 (A), 48.5 (B), 46.3 (A), 26.8 (B), 25.6 (A), 21.9 (B), 21.5 (A), 18.5 (A+B). GC-MS (EI, 70 eV) A : *m/z* = 220 (1) [M^+]; 202 (5); 160 (13); 159 (100); 143 (7); 115 (11); B : *m/z* = 220 (1) [M^+]; 205 (5); 160 (14); 159 (100); 143 (7); 115 (11); 61 (3).



4-Mercapto-3-methyl-1-(4-nitrophenyl)-pent-1-yn-3-ol (1e) Yield: 4.06 g, starting from 1.77 g of 3-mercaptobutan-2-one (95%). Mixture of diastereomers A+B, A:B ratio ca. 3:1, determined by ^1H NMR. Yellow oil; $C_{12}H_{13}O_3S$ (251.30). IR (film): v = 3393 (s, br), 2975 (m), 2930 (m), 2198 (w), 1709 (m), 1592 (s), 1449 (w), 1342 (s), 1107 (m), 918 (w), 854 (m), 752 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.24 [(d, J = 8.9, 2 H, H-3 + H-5 on the benzene ring) B], 8.14 [(d, J = 8.9, 2 H, H-3 + H-5 on the benzene ring) A], 7.71 [(d, J = 8.9, 2 H, H-2 + H-6 on the benzene ring) B], 7.62 [(d, J = 8.9, 2 H, H-2 + H-6 on the benzene ring) A], 4.15-4.06 [(m, 1 H, C*H*SH) B] + 3.83-3.69 [(m, 1 H, C*H*SH) A], 1.47 [(d, J = 7.0, 3 H, C*H*$_3$CH) A], 1.44 [(s, 3 H, C*H*$_3$COH) A + (s, 3 H, C*H*$_3$COH) B], 1.42 [(d, J = 7.1, 3 H, C*H*$_3$CH) B], 1.28-1.22 [(m, 1 H, SH) A + (m, 1 H, SH) B]. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 130.7 (A or B), 129.2 (A), 129.0 (B), 127.0 (A), 126.6 (B), 123.7 (A), 123.6 (B), 86.7 (A+B), 84.2 (A+B), 23.6 (A+B), 18.6 (A+B), 14.8 (A), 13.7 (B), 12.3 (A+B). GC-MS (EI, 70 eV) A

: *m/z* = 251 (absent) [M^+]; 234 (14); 233 (100); 232 (20); 218 (56); 172 (36); 171 (36); 115 (13); 59 (15); B : *m/z* = 251 (absent) [M^+]; 234 (13); 233 (100); 232 (19); 218 (64); 172 (36); 171 (37); 115 (13); 59 (14).



1-Cyclohex-1-enyl-4-mercapto-3-methyl-pent-1-yn-3-ol (1f) Yield: 3.08 g, starting from 1.77 g of 3-mercaptobutan-2-one (86%). Mixture of diastereomers A+B, A:B ratio ca. 8:2, determined by ^{1}H NMR. Yellow oil; $C_{12}H_{18}OS$ (210.34). IR (film): *v* = 3434 (s, br), 2977 (m), 2931 (s), 2215 (w), 1663 (w), 1583 (w), 1447 (s), 1341 (m), 1104 (m), 919 (s), 841 (m), 610 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.16-6.06 (m, 2H, cycloexenyl ring, A+B), 3.30 (s broad, 1H, OH, B), 3.19 (q, *J* = 6.6, 1H, C*H*CH_3, A), 2.95-2.85 (m, 1H, C*H*CH_3, B), 2.82 (s broad, 1H, OH, A), 2.15-2.03 (m, 10H, cycloexenyl ring, A+B), 1.92 (d, J=10.3, 3H, CHC*H*$_3$, B), 1.73 (d, *J* = 6.6, 1H, SH, B), 1.60-1.53 (m, 6H, cycloexenyl ring, A+B),1.61 (s, 3H, C*H*$_3$COH, B), 1.59 (s, 3H, C*H*$_3$COH, A), 1.48 (d, *J* = 7.3, 1H, SH, A), 1.37(d, *J* = 7.3, 3H, CHC*H*$_3$, A).^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.5 (A+B), 120.0 (A+B), 88.6 (A), 86.8 (B), 86.6 (B), 86.2 (A), 71.9 (B), 71.2 (A), 48.5 (B),46.3 (A), 29.2 (B); 29.1 (A), 26.8 (A); 25.6 (B), 25.58 (A+B), 22.32 (A+B), 22.0 (B), 21.4 (A+B), 18.5 (A). GC-MS (EI, 70 eV) A : *m/z* = 210 (1); 181 (4); 150 (12); 149 (100); 105(4); 91 (7); 79 (5); 77 (6); B : *m/z* = 210 (1); 181 (4); 150 (12); 149 (100); 195 (4); 91 (8); 79 (5); 77 (6).

Preparation of 1-mercapto-4-phenylbut-3-yn-2-ol (1g).[49]

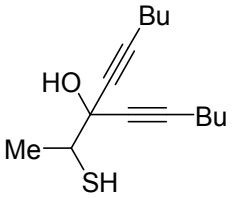
According to a similar known procedure, sodium hydrosulfide (560 mg, 10.0 mmol) was dissolved in methanol (2.0 mL), then 2-(phenylethynyl)-oxirane (144 mg, 1.0 mmol) in carbon disulfide (1.0 mL) was added slowly

over 25 min maintaining the temperature at 25 - 30°C. After 1 h, 20 mL ice water was added, then 2 N hydrochloric acid was added until the mixture had a pH near 6. The organic materials were extracted with CH_2Cl_2 (2 x 10 mL). The organic layer was separated, washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and further purification was carried out by short-column chromatography on silica gel, using 95/5 hexane-AcOEt mixture as the eluent, to afford **1g** as yellow oil (296 mg, 42%); $C_{10}H_{10}OS$ (178.25). IR (film): ν = 3381 (s, br), 3057 (w), 2932 (w), 2567 (w), 2231 (w), 1598 (w), 1490 (m), 1053 (m), 757 (s), 691 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.47-7.43 (m, 2H), 7.35-7.29 (m, 3H), 4.73 (dt, J = 7.2, 5.4 Hz, 1H), 3.00-2.84 (m, 2H), 2.61 (d, J = 7.2 Hz, 1H), 1.70 (dd, J = 9.3, 8.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 131.7, 128.7, 128.3, 122.0, 87.8, 85.9, 63.6, 32.6. HRMS (ESI) Calcd for $C_{10}H_{10}NaOS$ (M + Na) + 201.0345, found 201.0361.

Preparation of substrates 3. Substrates **3** were prepared by alkynylation of the appropriate or α-mercapto ester using an excess of RC≡CMgBr, as described below.

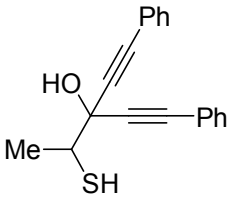
General procedure for the preparation of 1-mercapto-3,3-diyne-2-ols 3a-c. To a suspension of Mg turnings (2.1 g, 86.4 mmol) in anhydrous THF (9 mL), maintained under nitrogen and under reflux, was added pure ethyl bromide (1.8 mL) to start the formation of the Grignard reagent. The remaining bromide was added dropwise in THF solution (4.5 mL of EtBr in 48 mL of THF; total amount of EtBr added: 9.2 g, 6.3 mL 84.2 mmol). The mixture was then allowed to reflux for additional 20 min. After cooling, the resulting solution of EtMgBr was transferred under nitrogen to a dropping

funnel and added dropwise under nitrogen to a solution of 1-alkyne (88 mmol) (71-hexyne: 7.29 g; phenylacetylene: 8.99 g) in anhydrous THF (24 mL) at 0 °C with stirring. After additional stirring at 0°C for 15 min, the mixture was allowed to warm up to room temperature and then maintained at 45 °C for 2 h. While warm (ca 25-30 °C), the solution of 1-hexynylmagnesium bromide thus obtained was then added dropwise under nitrogen to a pre-heated (45 °C) solution of the appropriate α-mercaptoester (22 mmol) (ethyl 2-mercaptopropionate: 2.95 g; ethyl thioglicolate: 2.64 g) in anhydrous THF (6 mL). The resulting mixture was allowed to stir at 45°C for additional 2 h. After cooling to room temperature, saturated NH_4Cl (100 mL) and Et_2O (40 ml) were sequentially added. Phases were separated, and the aqueous phase was extracted with Et_2O (3 × 100 mL). The collected organic layers were washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, products **3a-c** were purified by column chromatography on silica gel using 95/5 hexane-AcOEt mixture as the eluent in every case.

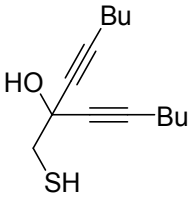


7-(1-mercaptoethyl)-trideca-5,8-diyne-7-ol (3a). Yield: 2.39 g, starting from 2.95 g of ethyl 2-mercaptopropionate (43%). Yellow oil; $C_{15}H_{24}OS$ (252.42). IR (film): ν = 3427 (m, br), 2958 (s), 2931 (s), 2237 (w), 1672 (m), 1556 (m), 1455 (m), 1376 (m), 1175 (w), 999 (w), 833 (w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.21-3.08 (m, 1H, C*H*SH), 2.27 (t, J = 6.9, 2H, $CH_2CH_2CH_2CH_3$), 2.25 (t, J = 6.9, 2H, $CH_2CH_2CH_2CH_3$), 1.87 (d, J = 8.5, 1H, -S*H)* ,1.64-1.35 (m, 8H, 2 $CH_2CH_2CH_2CH_3$), 1.52 (S, 3H, Me at C-2), 0.92 (t, J = 7.3, 3H, $CH_2CH_2CH_2CH_3$),0.91(t, J =7.3, 3H,

$CH_2CH_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 85.7, 85.2, 79.2, 78.1, 67.8, 47.8, 30.5, 30.4, 22.0, 20.4, 18.4, 13.6. GC-MS (EI, 70 eV): *m/z* = 252 (absent) [M^+], 234 (29); 192 (16); 191 (100); 148 (8); 147 (16); 135 (6); 115 (9); 91 (5); 59 (5).



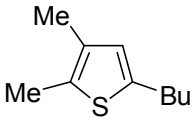
3-(1-mercaptoethyl)-1,5-diphenyl-pent-1,4-diyne-7-ol (3b). Yield: 2.83 g, starting from 2.95 g of ethyl 2-mercaptopropionate (44%). Yellow oil; $C_{19}H_{16}OS$ (292.39). IR (film): *v* = 3436 (s, br), 2977 (w), 2932 (w), 2227 (w), 1640 (m), 1598 (m), 1490 (s), 1376 (m), 1120 (w), 917 (w), 755 (s), 668 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.67-7.01 (m, 10H aromatics), 3.54-3.33. (m, 1H, C*H*CH_3), 1.68 (d, *J* = 4.9, 3H, C*H*$_3$), 1.28-1.17 (m, 1H, SH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.0, 131.9, 128.93, 128.9, 128.3, 128.26, 121.8, 87.3, 86.3, 85.2, 84.7, 65.8, 47.7, 20.5. GC-MS (EI, 70 eV): *m/z* = 292 (absent) [M^+], 276 (7); 275 (21); 274 (100); 273 (28); 271 (10); 241 (9); 240 (8) ;239 (15).



7-mercaptomethyl-trideca-5,8-diyne-7-ol (3c). Yield: 2.39 g, starting from 2.31 g of ethyl thioglicolate (44%). Yellow oil; $C_{14}H_{22}OS$ (238.39). IR (film): *v* = 3426 (m, br), 2957 (s), 2930 (s), 2231 (w), 1701 (m), 1636 (w), 1577 (w), 1458 (m), 1379 (m), 1157 (w), 1041 (m), 927 (w), 816 (w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.08 (s broad, 1H, OH), 2.96 (d distorted, J = 8.8, 2H, SHC*H*$_2$), 2.25 (t, J = 7.0, 4H, 2 C*H*$_2$$CH_2CH_2CH_3$),

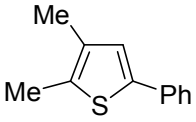
1.78 (t, J = 8.8, 1H, S*H*CH_2), 1.58-1.33 (m, J = 7.3, 8H, 2 $CH_2CH_2CH_2CH_3$), 0.91 (t, J = 1.6, 6H, 2 $CH_2CH_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 85.2, 79.4, 63.7, 39.5, 30.4, 22.0, 18.4, 13.6. GC-MS (EI, 70 eV): *m/z* = 238 (absent) [M^+], 220 (24); 192 (16); 191 (100); 178 (11); 177 (54); 135 (17); 134 (11); 115 (17); 105 (10); 91 (34); 81 (17); 79 (30); 77 (27).

General procedure for the synthesis of substituted thiophenes 2a-g and 3-alkynylthiophenes 4a-c. A Schlenk flask was charged in inert atmosphere with PdI_2 (3.6 mg, 1×10^{-2} mmol or 7.2 mg, 2×10^{-2} mmol, see Table 2.3 and 2.4), KI (16.6 mg, 0.1 mmol or 33.2 mg, 0.2 mmol, see Table 2.3 and 2.4), anhydrous MeOH (2 mL) and the 1-mercapto-3-yne-2-ols **1** (1.0 mmol) (**1a**, 186 mg; **1b**, 206 mg; **1c**, 212 mg; **1d**, 220 mg; **1e**, 251 mg; **1f**, 178 mg) or the 1-mercapto-3,3-diyne-2-ols **3** (1.0 mmol) (**3a**, 252 mg; **3b**, 292 mg, **3c**, 238 mg) respectively. After being stirred at 50 or 80°C for the required time (see Table 2.3 and 2.4), the Schlenk flask was cooled and opened. The solvent was evaporated, and the products **2b-f** and **4a-c** were purified by column chromatography on silica gel using the following mixtures as the eluent: hexane (**2c**, **4c**), 98:2 hexane-acetone (**4b**), 9:1 hexane-acetone (**2b**), 98:2 hexane-AcOEt (**2d**, **4a**), 95:5 hexane-AcOEt (**2e**, **2f**). Product **2a** was obtained by distillation because of its low boiling point.

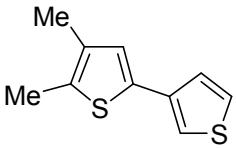


5-butyl-2,3-dimethylthiophene (2a).[50] Yield: 795.3 mg, starting from 1 g of **1a** (81%) (Table 2.3, entry 1). Colorless oil; $C_{10}H_{16}S$ (168.30). IR (film): ν = 2948 (m), 2834 (m), 1653 (w), 1449 (w), 1086 (w), 1028 (s), 875 (w), 758 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.44, (s, 1 H, H-4), 2.69 (t,

J = 7.7, 2 H), 2.27 (s, 3 H, Me), 2.06 (s, 3 H, Me), 1.66-1.53 (m, 2 H), 1.45-1.30 (m, 2 H), 0.92 (t, *J* = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.9, 132.3, 129.8, 126.9, 33.9, 29.6, 22.2, 13.9, 13.5, 12.9. GC-MS (EI, 70 eV): *m/z* = 168 (26) [M^+], 126 (12), 125 (100), 91 (13), 59 (9), 41 (9).

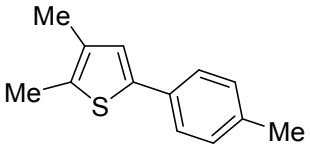


5-phenyl-2,3-dimethylthiophene (2b). [51] Yield: 167.6 mg, starting from 206.3 mg of **1b** (89%) (Table 2.3, entry 2). Yellow solid; m.p. = 46-47 °C; lit. 46-47°C; $C_{12}H_{12}S$ (188.29). IR (KBr): ν = 2914 (m), 2855 (m), 1665 (w), 1597 (m), 1443 (m), 1202 (w), 1072 (w), 832 (m), 754 (s) 689 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54-7.47 (m, 2H, on phenyl ring), 7.35-7.25 (m, 3H, on phenyl ring), 7.23-7.15 (m, 2H, on phenyl ring), 6.99 (s, 1H, H-4), 2.33 (s, 3H, Me at C-2), 2.12 (s, 3H, Me at C-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.1, 134.7, 134.1, 131.4, 128.7, 126.8, 126.0, 125.3, 13.6, 13.1.GC-MS (EI, 70 eV): *m/z* = 189 (16) [M^{+1}], 188 (100) [M^+], 187 (54), 173 (69), 128 (15), 77 (18) 59 (13), 51 (16).

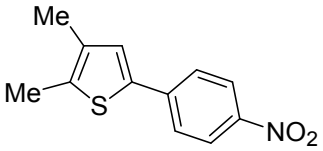


2,3-Dimethyl-5-(thiophen-3-yl)thiophene (2c).Yield: 147.7 mg, starting from 212.3 mg of **1c** (76%) (Table 2.3, entry 3). Yellow amorphous solid; m.p. = 52-53°C; $C_{10}H_{10}S_2$ (194.32). IR (KBr): ν = 2918 (m), 2857 (m), 1638 (w), 1516 (m), 1446 (w), 1215 (w), 944 (w), 811 (s), 757 (m) 484 (w) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27-7.24 (m, 1 H, H-3 on thienyl group), 7.23-7.19 (m, 2 H, H-4 + H-5 on thiophene ring), 6.85 (s, 1 H, H-4), 2.30 (s, 3 H, Me at C-2), 2.10 (s, 3 H, Me at C-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.9, 134.1, 133.6, 131.4, 126.03, 125.96, 125.8, 118.4, 13.6,

13.0. GC-MS (EI, 70 eV): *m/z* = 195 (17) [M^{+1}], 194 (100) [M^{+}], 193 (58), 179 (67), 161 (15), 134 (10) 97 (10), 45 (15), 44 (21).

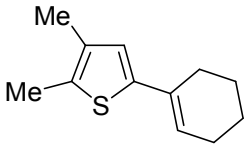


2,3-dimethyl-5-*p*-tolylthiophene (2d).Yield: 151.7 mg, starting from 220.3 mg of **1d** (75%) (Table 2.3, entry 4). Yellow amorphous solid; m.p. = 46-47°C; $C_{13}H_{14}S$ (202.32). IR (KBr): *v* = 2918 (m), 2857 (m), 1638 (w), 1516 (m), 1446 (w), 1215 (w), 944 (w), 811 (s), 757 (m), 484 (w) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.1, 2 H, H-2 + H-6 on thiophene ring), 7.12 (d, *J* = 8.1, 2 H, H-3 + H-5 on phenyl ring), 6.94 (s, 1 H, H-4), 2.33 (s, 3 H, Me at C-2), 2.12 (s, 3 H, Me at C-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.3, 136.6, 133.9, 132.0, 131.3, 129.4, 125.5, 125.3, 21.1, 13.6, 13.1. GC-MS (EI, 70 eV): *m/z* = 203 (17) [M^{+1}], 202 (100) [M^{+}], 201 (54), 187 (50), 153 (5), 128 (6) 115 (6).

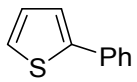


2,3-dimethyl-5-(4-nitrophenyl)-thiophene (2e).Yield: 182 mg, starting from 251.3 mg of **1e** (78%) (Table 2.3, entry 5). Yellow amorphous solid; m.p. = 78-79°C; $C_{12}H_{11}NO_2S$ (233.29). IR (KBr): *v* = 2952 (m), 2917 (m), 1660 (w), 1593 (m), 1513 (m), 1449 (w), 1346 (s), 1102 (w), 851 (s), 735 (m), 698 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.9, 2 H, H-3 + H-5 on phenyl ring), 7.51 (d, *J* = 8.9, 2 H, H-2 + H-6 on phenyl ring), 7.07 (s, 1 H, H-4), 2.42 (s, 3 H, Me at C-2), 2.13 (s, 3 H, Me at C-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.5, 141.5, 135.1, 131.1, 129.3, 123.6, 120.4, 13.7, 13.0. GC-MS (EI, 70 eV): *m/z* = 234 (15) [M^{+1}], 233 (100)

[M^+], 232 (21), 218 (56), 186 (16), 172 (37) 171 (37), 153 (12), 115 (14), 59 (16).

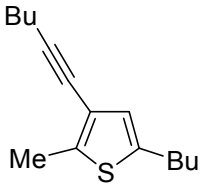


5-Cyclohex-1-enyl-2,3-dimethylthiophene (2f).Yield: 96 mg, starting from 210.3 mg of **1f** (50%) (Table 2.3, entry 6). Yellow oil; $C_{12}H_{16}S$ (192.32). IR (KBr): v = 2927 (m), 2857 (m), 1660 (w), 1567 (w), 1446 (m), 1435 (m), 1348 (w), 1135 (w), 819 (m), 797 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.60 (s, 1 H, on thienyl ring), 6.06-5.96 (m, 1 H, H-2 on cyclohexenyl ring), 2.28 (s, 3 H, Me at C-5), 2.31-2.11 (m, 4 H, CH_2C=$CCHCH_2$), 2.06 (s, 3 H, Me at C-4), 1.77-1.68 (m, 2 H, =$CHCH_2CH_2CH_2$ or =$CHCH_2CH_2CH_2$), 1.68-1.55 (m, 2 H, =$CHCH_2CH_2CH_2$ or =$CHCH_2CH_2CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.0, 132.9, 131.2, 130.0, 124.2, 122.6, 27.2, 25.6, 25.5, 22.4, 22.2. GC-MS (EI, 70 eV): m/z = 193 (14) [M^{+1}], 192 (100) [M^+], 177 (86), 164 (40), 163 (26), 149 (68) 135 (17), 125 (14), 115 (14), 91 (17), 79 (14), 77 (17), 59 (18).

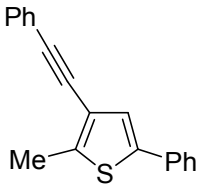


2-phenylthiophene (2g).[52] Yield: 80.1 mg, starting from 178.3 mg of **1f** (50%) (Table 2.3, entry 7). Yellow solid; m.p. = 34-35°C; lit. 33-34°C; $C_{10}H_8S$ (160.24). IR (KBr): v = 3062 (m), 2924 (m), 1727 (w), 1600 (s), 1488 (m), 1256 (w), 1072 (w), 849 (w), 755 (s) 693 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.63-7.54 (m, 2 H), 7.39-7.20 (m, 5 H), 7.07-7.01 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.4, 134.4, 128.9, 128.0, 127.4,

125.9, 124.8, 123.1. GC-MS (EI, 70 eV): *m/z* = 161 (12) [M^{+1}], 160 (100) [M^{+}], 128 (15), 116 (14), 115 (42), 89 (10) 63 (8), 51 (8).

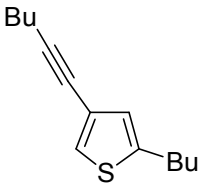


5-butyl-3-hex-1-ynyl-2-methylthiophene (4a). Yield: 199.2 mg, starting from 252.3 mg of **3a** (85%) (Table 2.4, entry 1). Yellow oil; $C_{15}H_{22}S$ (234.40). IR (film): *v* = 2964 (s), 2931 (s), 2858 (m), 2229 (w), 1465 (m), 1378 (m), 1249 (w), 1142 (w), 831 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.56 (S, 1H, H-4),2.66 (t, *J* = 7.5, 2H, -C$H_2$$CH_2CH_2CH_3$),2.41 (s, 3H, Me at C-2), 2.40 (t, *J* = 6.9, 2H, -≡C$H_2$$CH_2CH_2CH_3$), 1.64-1.24 (m, 8H, ≡CCH_2CH_2C$H_2$$CH_3$ + -CH_2CH_2C$H_2$$CH_3$), 0.94(t, *J* = 7.3, 3H, $CH_2CH_2CH_2$CH_3), 0.91 (t, *J* = 7.3, 3H, -≡$CH_2CH_2CH_2$CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.9, 163.8, 143.9, 113.4, 108.5, 93.8, 70.4, 51.3, 30.8, 29.9, 27.6, 22.2, 21.9, 19.3, 13.7, 13.6. GC-MS (EI, 70 eV): *m/z* = 234 (19) [M^{+}], 192 (15), 191 (100), 161 (16), 148 (18), 147 (42), 115 (31), 91 (16), 59 (22), 51 (15), 43 (40), 41 (73).



5-phenyl-3-phenylethynyl-2-methylthiophene (4b). Yield: 233.2 mg, starting from 292.3 mg of **3b** (85%) (Table 2.4, entry 2). Yellow solid; m.p. = 124-125°C; $C_{19}H_{14}S$ (274.38). IR (KBr): *v* = 2959 (s), 2923 (s), 2854 (m), 2204 (w), 1734 (w), 1442 (w), 1384 (m), 1069 (w), 752 (s), 686 (m).) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 – 7.49 (m, 4 H, on thiophen ring), 7.39 – 7.30 (m, 5 H, on phenyl ring), 7.29 – 7.21 (m, 1 H, on phenyl ring + H-4), 2.59 (s, 3 H, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.0, 140.3,

133.9, 131.4, 128.9, 128.4, 128.1, 127.5, 125.5, 125.1, 123.4, 120.7, 91.6, 84.1, 14.6. GC-MS (EI, 70 eV): *m/z* = 275 (31) [M^{+1}], 274 (86) [M^{+}], 273 (28), 240 (30), 239 (40), 197 (46), 152 (50), 121 (31), 93 (33), 89 (39), 77 (100), 59 (77), 51 (81).



2-butyl-4-hex-1-ynyl-thiophene (4c). Yield: 114.6 mg, starting from 238.3 mg of **3c** (52%) (Table 2.4, entry 3). Yellow oil; $C_{14}H_{20}S$ (220.37). IR (film): *v* = 2966 (s), 2930 (s), 2856 (m), 2232 (w), 1545 (m), 1464 (s), 1357 (m), 1141 (w), 834 (m), 737 (s), 628 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.10 (d, *J* = 0.9, 1 H, H-5), 6.73 (q, *J* = 0.9, 1 H, H-3), 2.74 (td, *J* = 0.9, 2 H, ≡CCH_2), 2.36 (t, *J* = 7.0, 2 H, C$H_2$$CH_2CH_2CH_3$ C$H_2$$CH_2CH_2CH_3$), 1.68 -1.29 (m, 8 H, 2 CH_2CH_2C$H_2$$CH_3$), 0.93 (t, *J* = 7.3, 3 H, $CH_2CH_2CH_2$CH_3 or ≡$CCH_2CH_2CH_2$CH_3), 0.91 (t, *J* = 7.3, 3 H, ≡$CCH_2CH_2CH_2$CH_3 or $CH_2CH_2CH_2$CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.3, 126.8, 125.2, 122.3, 89.0, 76.1, 33.6, 30.9, 29.6, 22.1, 22.0, 19.1, 13.8, 13.7. GC-MS (EI, 70 eV): *m/z* = 220 (45) [M^{+}], 178 (18), 177 (100), 163 (16), 135 (29), 134 (22), 91 (13), 41 (13).

Part III

Synthesis of indanylidene derivatives by Pd-catalyzed oxidative aminocarbonylation carbocyclization of 2-(2-ethynylbenzyl)-malonic ester derivatives.

Manuscript in preparation

Part III

Introduction

1.1 Pharmacological properties of indane derivatives.

Indane (fig. 1.1) is a cyclic hydrocarbon molecule composed of a benzene ring fused with a cyclopentane.

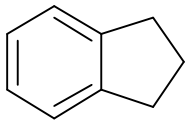
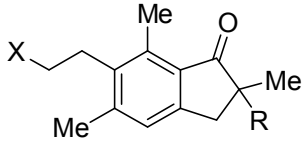


Fig. 1.1

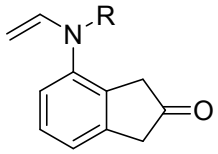
Indane derivatives are very interesting molecules in their pharmacological activities, since they have a wide activity spectrum. The existence of drugs and endogenous molecules with indane-like structure opened the way to pharmacological experimentation of various molecules. Nowadays, experimental results show that many indane derivatives are molecules with good pharmacokinetic and pharmacodynamic characteristics, with better values of K_d, B_{max}, EC_{50}, despite different commercially drugs. An importance source of indane derivatives is Nature. Pterosynes are a class of secondary metabolites, with great pharmacological interest; their basic nucleus is an indane one (fig.1.2):



X = OH ; OCH_3
R = CH_3 ; H

Fig. 1.2

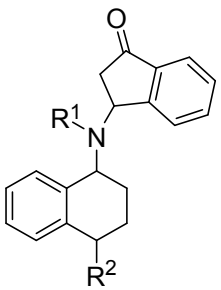
In different studies, Pterosyne Z and Onytine (phenolic illudoid sesquiterpene), were identified as myo-relaxant compounds. Successively, was demonstrated that, pterosyne synthetic derivatives have liver-protective activity together with and mast-cells stabilizing effects (fig. 1.3).[53]



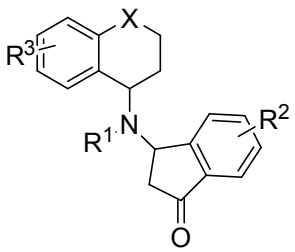
a R = 1-indane
b R = 2-indane

Fig. 1.3

The activity of a series of indan-1-ylaminic derivatives was evaluated by changing the spatial position of both cyclic substituents, R-group nature and carbonyl group position (fig.1.4):



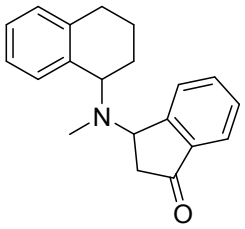
$R^1 = CH_3$; CH_2CHCH_3
R^2 = Carbonyl



X = O; C
$R^1 = CH_3$; H
$R^2 = OCH_3$; OAc
R^3 = H ; OMe

Fig.1.4

From the results of *in vitro* tests, indane derivative shown in figure 1.5 resulted the better one in stabilizing mast-cells.



3-[Methyl-(1,2,3,4-tetrahydro-naphtalen-1-yl)-amino]-indan-1-one

Fig. 1.5

Recent studies showed that tricyclic indane derivatives, bearing a condensed dihydrofuran ring (fig. 1.6), have a certain affinity for MT_1-melatonin receptor.[54]

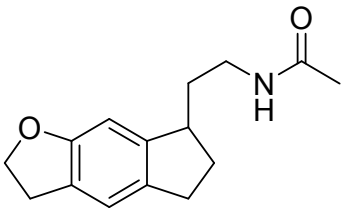


Fig. 1.6

After structure-activity studies, the tricyclic indane derivative, which possess the best structural characteristics for MT_1 receptor is:

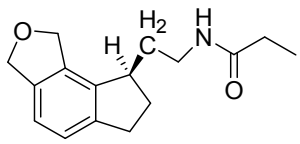
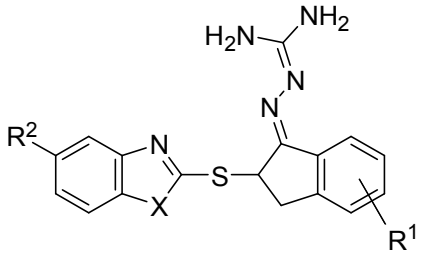


Fig. 1.7

Some of indane derivatives, in particular amino-guanidine ones, showed to be useful therapeutic agents in the treatment of myocardic disease; they are powerful inhibitors of Na^+/H^+ pump.[55] A number of indan-1-ylideneamino-

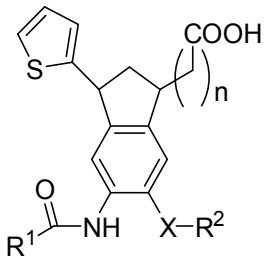
guanidine derivatives were synthesized with the aim of finding new drugs (fig. 1.8).



R ^{1} = H; 5Cl; 6-OCH_3; 4,5,6 -OCH_3; 5,6-OCH_3
R^2 = H ; NO_2 ; -OCH_3
X = N ; S

Fig. 1.8

Indane nucleus was used also for scheduling a new class of non-peptidic antagonists of endothelin ET_A-receptor.[56] An hypothetic pharmacophor led to choose indane derivatives as the right class on this basic skeleton (fig. 1.9).



n = 0,1,2
X = O, CH_2
R^1= i-Pr ; i-Bu ecc

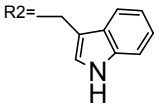


Fig 1.9

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The best inhibitory activity was obtained with *cis*-indane derivatives (fig. 1.10).

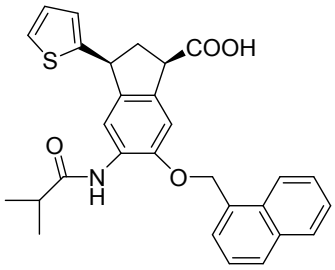
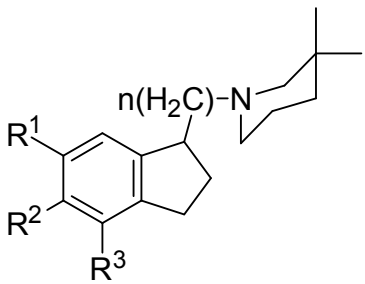


Fig. 1.10

Some recently discovered indane compounds are active in central nervous system as neuro-protective agents, specific for σ_1 receptors. The structural characteristic of these new molecules (fig. 1.11) is the tertiary aminic function, separated through an alkylic chain from the main rings.[57]

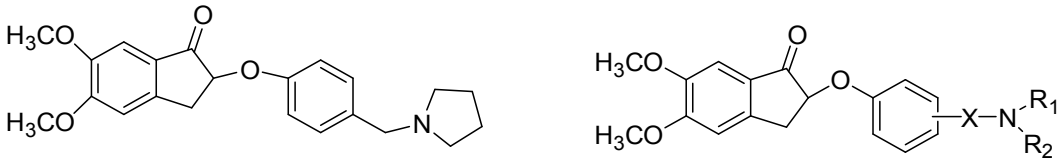


a R^1 = H ; R^2 = H ; R^3= H ; n = 4
b R^1 = H ; R^2 = H ; R^3 = H ; n = 5
c R^1= H ; R^2 = H ; R^3 = H ; n = 6
d R^1= H ; R^2 = H ; R^3 = OCH_3 ; n = 4
e R^1= H ; R^2 = OCH_3 ;R^3 = H ; n = 3
f R^1 = H ; R^2 = OCH_3; R^3= H ; n =4
g R^1= H ; R^2= OCH_3 ; R^3 = H ; n = 5
h R^1= H ; R^2= OCH_3 ; R^3 = H ; n = 6

Fig. 1.11

Indane derivatives were useful for Alzheimer disease treatment[58] and as inhibitors of acetylcolinesterase enzyme (AchE), especially

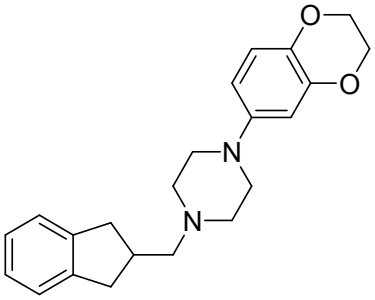
2-phenoxyindan-1-one ones (fig. 1.12).[59]



5,6-Dimethoxy-2-(4-pyrrolidin-1-ylmethyl-phenoxy)-indan-1-one

Fig. 1.12

In order to prevent collateral effects of traditional antipsychotics, new neuroleptic drugs were disclosed, for example a benzylindane compound (fig. 1.13).[60]



1-(2,3-Dihydro-benzo[1,4]dioxan-6-yl)-4-indan-2-ylmethyl-pyperazine

Fig. 1.13

Indane derivatives are also involved as inhibitors of HIV-integrase enzyme (IN). According to previous studies which identified sulfurate natural compounds,[61] three indane-based molecules resulted with more activity with respect to those last mentioned (fig. 1.14).[62]

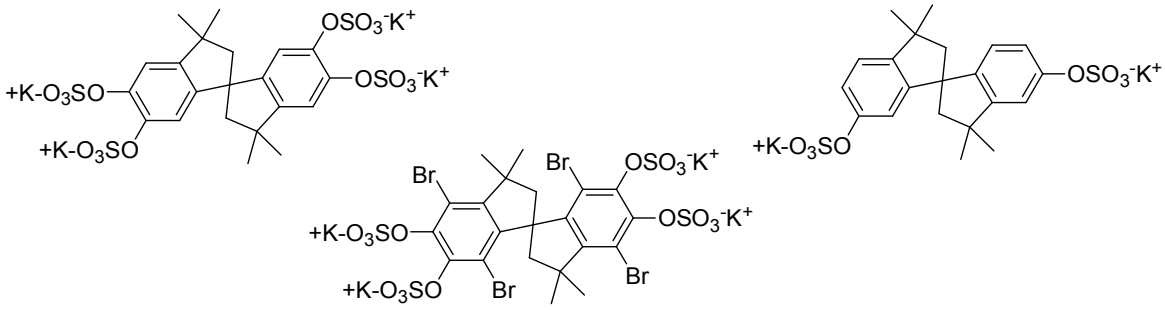
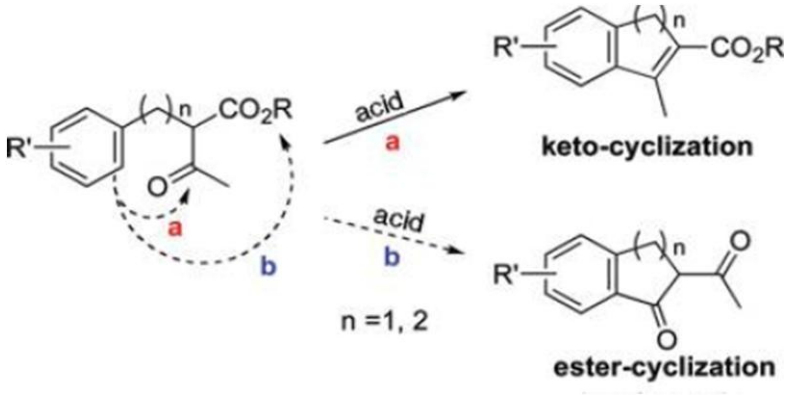


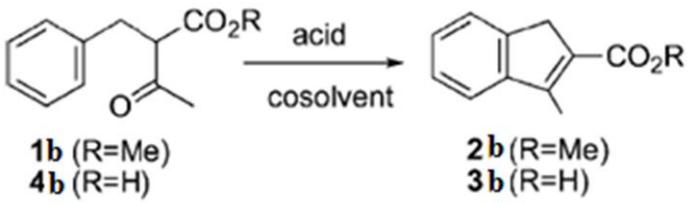
Fig. 1.14

In literature have been reported several studies on acid catalyzed cyclization of 2-aceto-4-phenylbutanoates[63] leading to a six member derivative of 3,4-dihydronaphtalene.[64] Basing on these studies some reactions were carried out under acid conditions starting from 2-aceto-3-arylpropanoates to obtain indane derivatives (Scheme 1.1); this synthetic methodology was recently used to synthesize many bioactive molecules.[65]



Scheme 1.1

In order to form six member rings, the aromatic ring of the substrate was substituted with an halogen atom (R' = X). On the contrary, to form indane derivatives, the substitution was limited to electron releasing groups, such as the hydroxylic one. The best reaction conditions (kind and amount of acid, co-solvent, temperature and reaction time) were tested on the model substrate, that is, methyl 2-benzyl-3-oxo-butyrrate (**1b**).



Scheme 1.2

Sulfuric acid is able to transform substrate **1b**, leading to the formation of 3-methyl-1*H*-indene-2-carboxylic acid methyl ester (**2b**) and 3-methyl-1*H*-indene-2-carboxylic acid (**3b**) with a 49% yield (Scheme 1.2). The same cyclization was studied using trifluoromethansolfonic acid (TFSA): in the presence of TFSA, the combined yield raised up to 80-90%. The reaction did not lead to the selective formation of one final product, for this reason they changed the starting material, employing 2-benzyl-3-oxo-butyrric acid (**4b**). This substrate led to the selective formation of product **3b** (70%), but its utilization is limited because of low stability. Furthermore, indanylidene derivatives possess powerful analgesic and anti-inflammatory activities.[66] An example of these compounds reported in literature is (*E*)-2-(4,6-difluoro-1-indanylidene)acetamide (fig. 1.15).

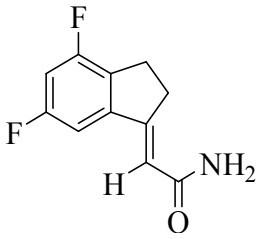


Fig. 1.15

On the other hand (*E*)-2-(4,7-difluoro-1-indanylidene)acetamide is a myo-relaxant agent. Other derivatives (fig. 1.16) are selective inhibitors of CYP11B2 and CYP11B1 enzymes.[67]

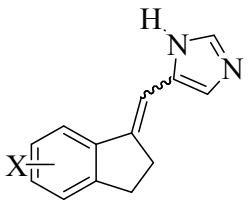
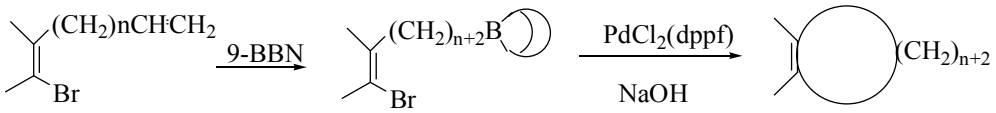


Fig. 1.16

1.2 Synthetic pathways.

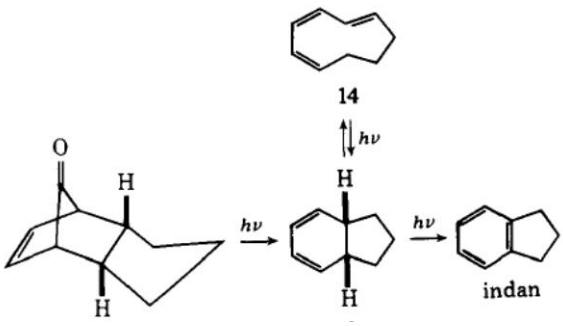
A combination of hydroboration reaction and cross-coupling offers a versatile method to synthesize benzo-fused cycloalkenes and cycloalkanes (Scheme 1.3). Five and six member rings (6) can be obtained in good yields by hydroboration of haloalkenes (4) with 9-BBN, followed by treatment with $PdCl_2$(dppf) and sodium hydroxide. Boron addition to the triple bond occurs exclusively in terminal position.[68]



4 5 6

Scheme 1.3

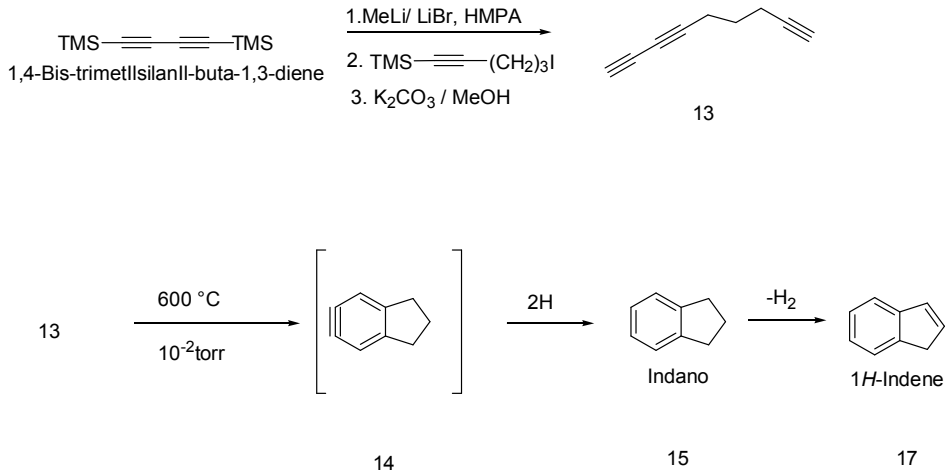
The indane nucleus can be easily obtained by photochemical activation of particular *cis* bicyclo-2,4-dienic compounds (1,3-hexaline analogous), which have flexible conformations in the fundamental state (Scheme 1.4).[69]



Scheme 1.4

In another synthetic approach, 1,3,8-nonantriyne was employed as the starting compound. Alkylation of 1,4-bis(trimethylsilyl)butadiyne and subsequent removal of TMS, gives a 50% yield.[70] In literature it was known a previous attempt carried out under the same conditions.[71] The

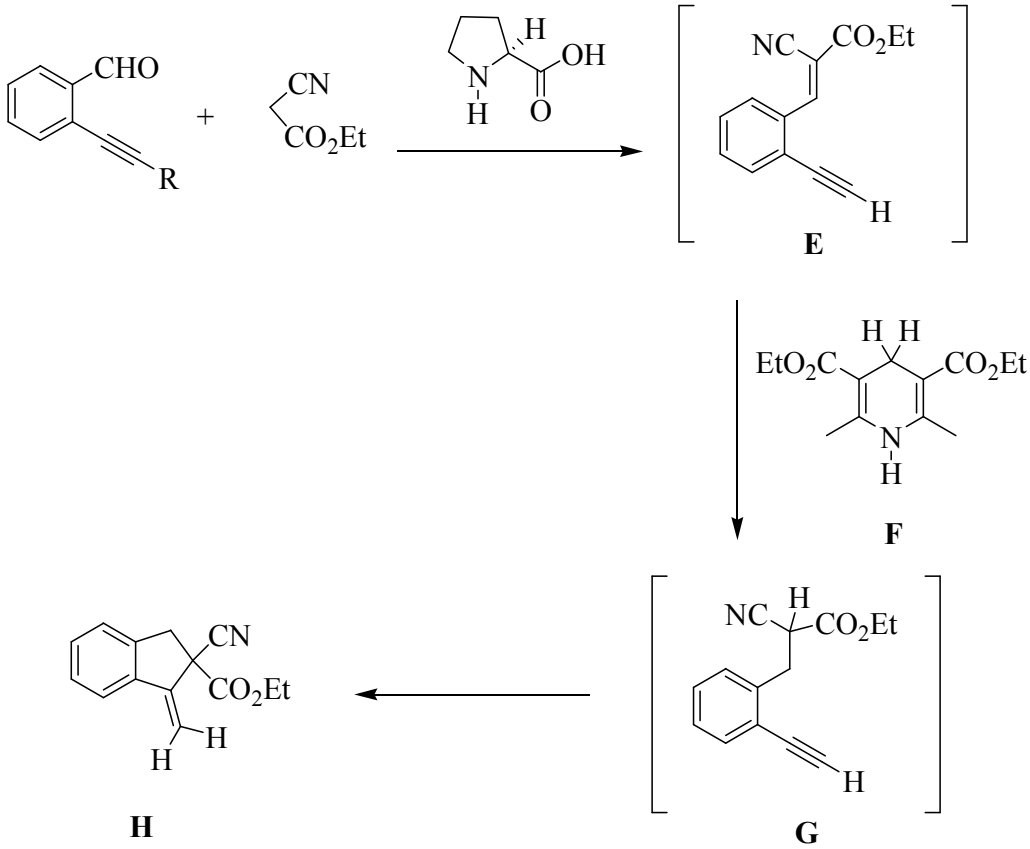
simpler way to obtain the desired product involves an intramolecular cyclo-addiction [2+4], with formation of benzyne derivative (Scheme 1.5); successive reactions lead to indane formation with a little percentage of indene.[72] There are several examples of benzynes reduction under pyrolytic conditions.[73]



Scheme 1.5

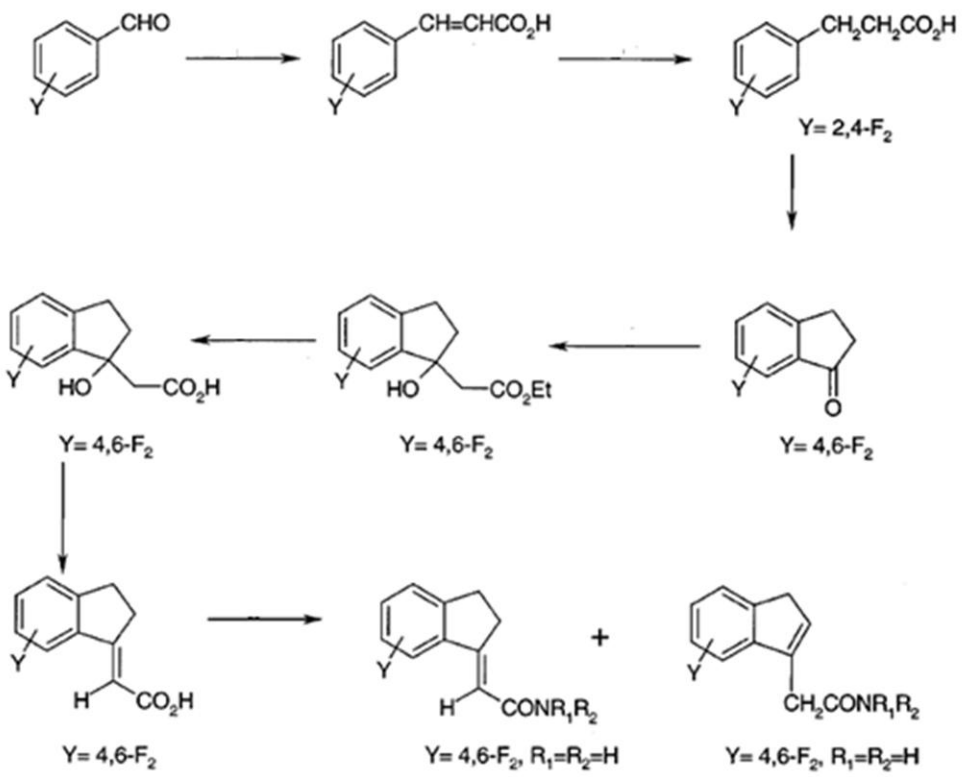
Several synthetic methods of substituted indanilydene derivatives have been reported in literature so far. They are an important class of carbocycles, since they constitute the basic moiety of biological and pharmacological compounds. The developing of novel and general catalytic pathways for their preparation results of great interest. In a recent study,[74] an innovative carbocyclization process was reported, the Conia-Ene reaction. This process is a multi-catalyzed cascade (MCC) reaction, which includes both an organic catalysis by an aminoacid such as proline and a transition metal catalysis by a soft metal ion, for example Cu^{+}. The substrate should bear an alkynylic function in suitable position for cyclization. In Scheme 1.6, the synthetic process leading to ethyl 2-cyano-1-methyleneindane-2-carboxylate (**H**) is described. L-proline catalyzes the olefination of 2-ethynylbenzaldehyde with ethyl ethynylcianoacetate to

give the activated olefin (**E**) which, after treatment with 2,6-dimethyl-3,5-dicarboxyethyl-1,4-dihydropyridine (Hantzsch ester **F**) gives ethyl 2-cyano-3-(2-ethynylphenyl)propionate (**G**). The following reaction, carried out under the optimized conditions (15 mol% of l-proline, 10 mol% of CuI and 2 eq. of Cs_2CO_3), leads to the formation of the final product.



Scheme 1.6

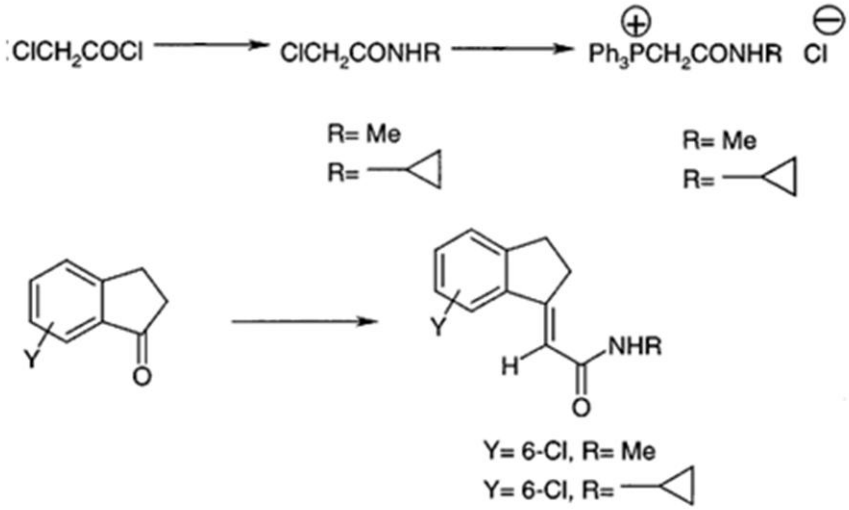
Another widely used method involves the corresponding substituted indanone derivative as key intermediate (Scheme 1.7). Indanones can be commercially available or can be prepared from the respective dihydrocinnamic acid by Friedel-Crafts acylation.[75] A method for the preparation of dihydrocinnamic acids occurs with a substituted benzaldehyde which, after Knoevenagal reaction, gives the respective cinnamic acid, which finally undergoes catalytic hydrogenation.



Scheme 1.7

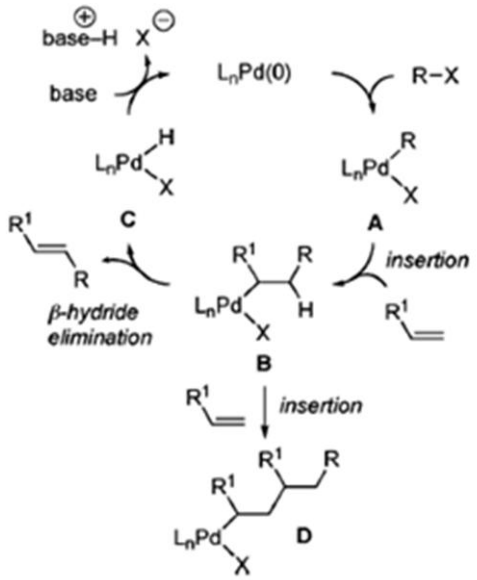
Indanones are converted into (*E*)-indanilydene acids through two different paths. The first one includes the formation of Reformatsky reactant from ethyl bromoacetate and zinc. The resulting β-hydroxy ester is hydrolized to the β-hydroxy acid and immediately dehydrated with trifluoroacetic acid leading to (*E*)-indanylic acid. It was verified that, leaving the hydroxyl acid in a closed container, it dehydrates spontaneously, even avoiding acidic treatment. An alternative method for the synthesis of hydroxyesters is the condensation of indanones with ethyl acetate lithium enolate. (*E*)-indanylidene acids were converted to the respective acyl chlorides through a reaction with oxalyl chloride or thionyl chloride and then condensed with different amines, leading to amide derivatives. Some indanylidenes were prepared directly from indanones by a Wittig reaction; phosphonium

chloride derivatives were synthesized starting from 2-chloro-*N*-alkylacetamide and triphenylphosphine (Scheme 1.8).



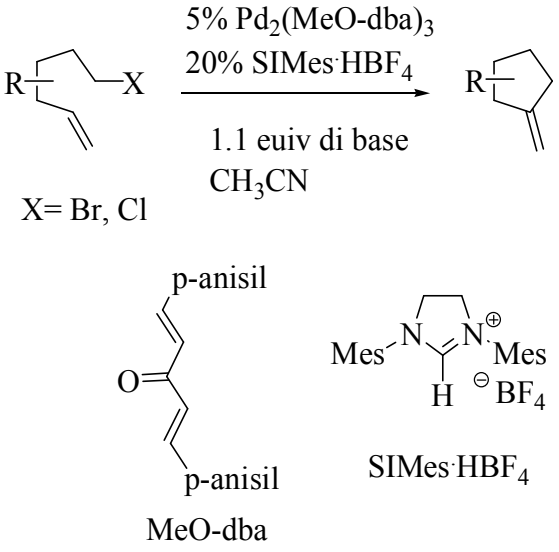
Scheme 1.8

Recently, some methods were reported, including an intramolecular Heck reaction between an olefin and an alkylic halide. The Pd-catalyzed Heck reaction of olefins is normally carried out using arylic and vinylic halides and it is one of the most efficient methodology for the formation of a new C-C bond. This process can be extended to double bond alkylation,[76] only if it could be possible to control β-hydride elimination towards insertion in the fundamental step of Heck reaction, that is the oxidative addition of the alkylic halide leading to the formation of an alkylpalladium intermediate. In the case of the Heck reaction with an alkyl halide (Scheme 1.9), if β-hydride elimination of **A** intermediate is simple, the olefin insertion forming **B** intermediate cannot occur. To carry out the coupling, **A** and **B** should have a quite different reactivity: **A** intermediate should prefer insertion instead of β-elimination and vice versa about **B**.



Scheme 1.9

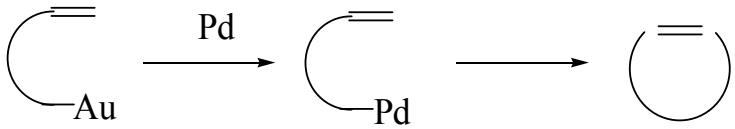
This particular condition could be realized by an intramolecular alkylation of the double bond using Pd/N heterocyclocarbenes catalytic systems. By this way, several derivatives of 6-bromo-1-hexene were converted in the corresponding methylencyclopentane with good yields, by $Pd_2(MeO\text{-}dba)_3$/ SIMes·HBF_4 catalysis (Scheme 1.10).



Scheme 1.10

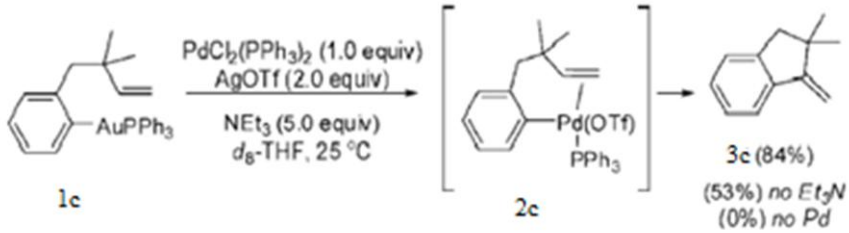
The use of 2-(2-bromoethyl)styrene allows the direct formation of 1-methylenindane with a 81% yield.

Recently another application of Heck reaction was studied.[77] The starting substrate is a gold organic complex. The last one is inert to olefin insertion, on the contrary this insertion works very well with palladium, so the transmetallation of the organic moiety from gold to Pd allows, successively, the migration insertion (eq. 1.1).



(1.1)

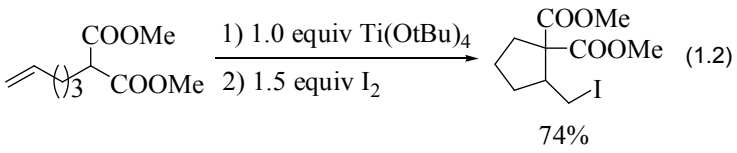
The reaction was studied starting from substrate **1c** treated with $PdCl_2(PPh_3)_2$ and AgOTf in THF, at room temperature (Scheme 1.11). The cyclized product **3** was obtained with a 84% yield, using triethylamine as base. In the absence of Pd, the reaction does not lead to the formation of product **3**, to confirm the fact that the reaction mechanism passes through a Au/Pd transmetallation reaction to form the organopalladium intermediate **2c**.



Scheme 1.11

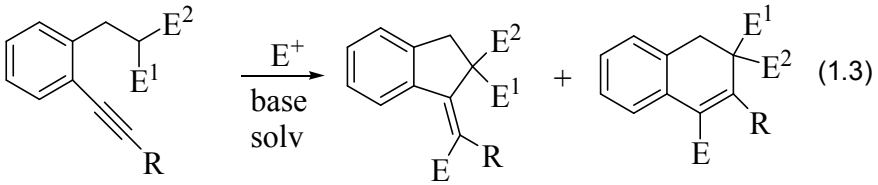
Furthermore, milder conditions and simpler methods have been used to synthesize indanes by electrophilic iodocyclization reactions of

alkynylmalonic derivatives. Electrophilic iodocyclizations of nucleophilic hetero-atoms such as oxygen, nitrogen, sulfur and phosphorous with an alkynylic moiety in suitable position for ring closure, showed to be an efficient method to obtain a wide variety of heterocyclic compounds. However very few examples of electrophilic cyclization using carbon nucleophiles have been reported in literature. Taguchi and coworkers demonstrated that iodocyclization of 4-alkenylmalonates in the presence of I_2 and $Ti(OtBu)_4$ proceeded with high regio and stereoselectivity (eq. 1.2), leading to iodomethylencyclopentane derivatives.[78]



(1.2)

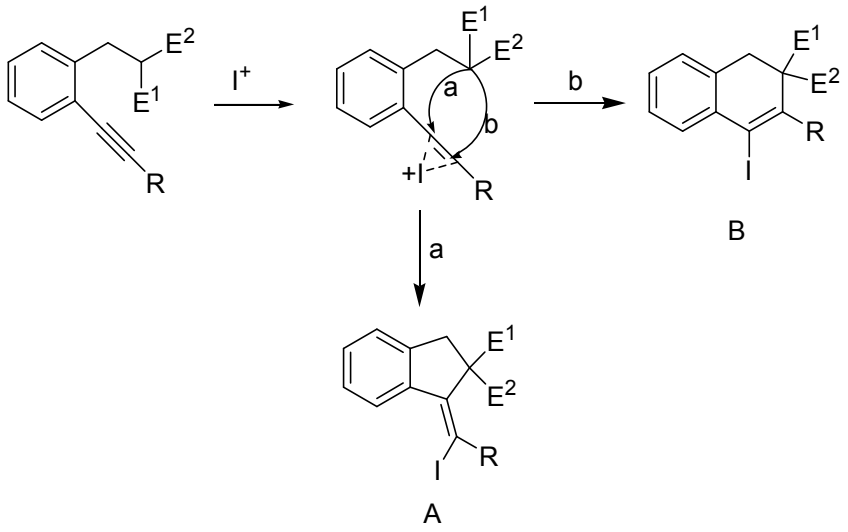
This particular kind of reactivity was applied to the regio and stereoselective synthesis of indane derivatives by iodocyclization starting from acetylmalonates and ketones (eq. 1.3).[79]



(1.3)

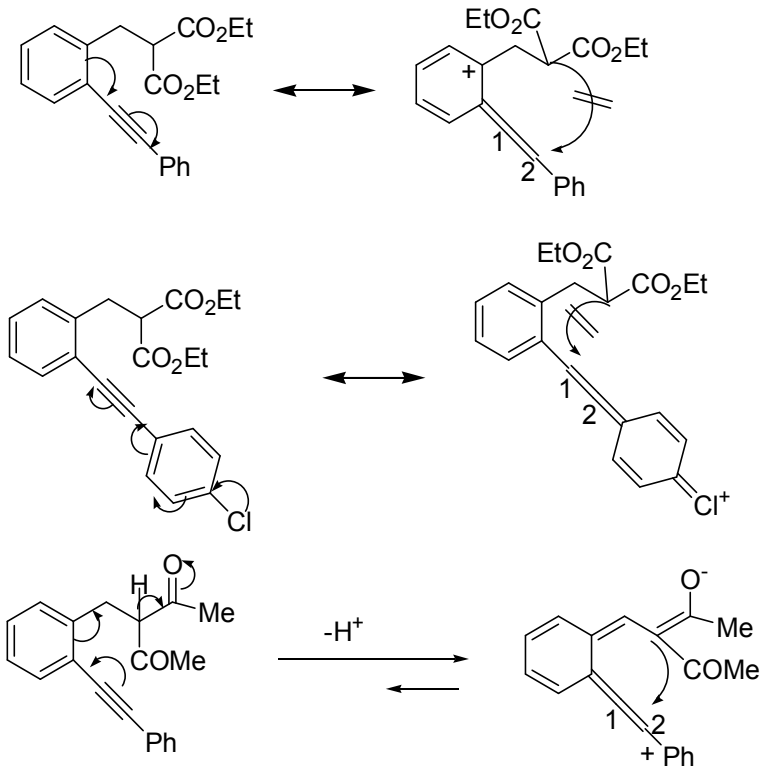
$E^1 = E^2$ = COOMe, COOEt, COMe
R = alchil, aril
$E^+ = I_2$, NIS, ICI

The hypothetic mechanism proposed for the reaction is illustrated below (Scheme 1.12):



Scheme 1.12

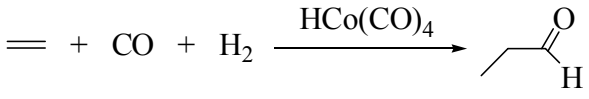
The explanation of the two mechanistic pathways was found in the influence on the resonance and electronic effect by the different substituents: this driving force facilitated, time by time, C_1 or C_2 closure, with formation of five or six member ring respectively (Scheme 1.13).



Scheme 1.13

1.3 Carbonylation

The carbonylic group represents one of the most versatile functionalities in organic synthesis.[80] For this reason, the direct introduction of the carbon monoxide molecule in a particular substrate, in order to obtain carbonylic compounds is of great interest on industrial scale too. All these processes are known as carbonylation reactions.[81] Carbon monoxide is a widely available reagent with a reactivity which promotes a convenient application. The first carbonylation reaction was carried out by Otto Roelen in 1938.[82] Roelen observed as octacarbonyldicobalt, $Co_2(CO)_8$, was able to catalyze the reaction between ethylene and synthetic gas ($CO + H_2$) to give propionaldehyde with high yields (eq. 1.4)

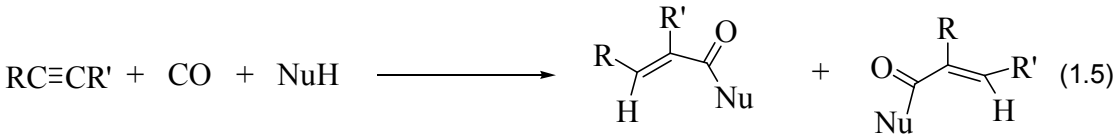


(1.4)

This reaction, successively named as hydroformylation, found wide industrial application to synthesize aldehydes from olefins (from C-2 to C-20).[83] These reactions need a catalytic system to work out: the most active and selective, which allow to operate in mild conditions and high catalycity, not volatile and air stable, are palladium and rhodium derivatives. Then many other carbonylation processes were studied and developed, leading to the synthesis not only of aldehydes but of carboxylic acids, esters, amides and ketones too. All the processes mentioned above utilize organohalides, mainly aryl, vinyl and allyl halides, in addition to unsaturated substrates such as olefins, 1,3-dienes, 1,2-dienes and alkynes as starting materials.

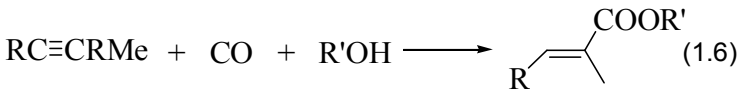
1.4 Alkyne carbonylation.

Alkyne derivatives are widely used substrates in the carbonylation reaction, leading mainly to the formation of carboxylic acids and their derivatives and ketones. Generally alkynes are more reactive than alkenes in transition metal catalyzed carbonylation reactions; for this reason the reactions can be carried out under milder conditions than the analogous with alkenes. The most used metal complexes for alkyne carbonylation reactions are Ni, Co, Pd and Pt-based. The carbonylation of alkynes can be divided into three types: additive, oxidative and reductive carbonylation. Additive carbonylation gives α,β-unsaturated compounds following next equation:



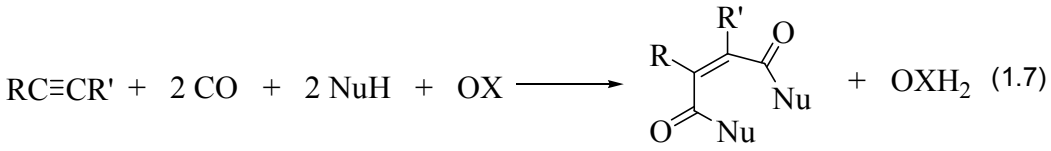
(1.5)

With internal alkynes, the reaction leads to a miscellaneous of products, deriving from the different regiochemistry of addition to the triple bond. Unlike the analogous alkene reaction, in this case it is not observed triple bond isomerization during the carbonylation. Terminal alkynes generally are more reactive than internal ones. It was reported that additive carbonylation of 2-alkynes to α,β-unsaturated esters could be realized under mild conditions (room temperature and atmospheric pressure) in a regioselective and stereoselective way, using $PdCl_2$ in the presence of $CuCl_2/HCl/O_2$ (eq. 1.6).



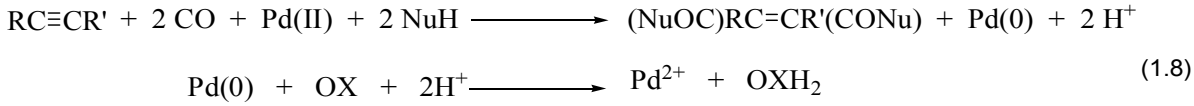
(1.6)

Oxidative carbonylation of alkynes usually leads to the formation of diacids or their α,β-unsaturated derivatives (esters and amides), according to equation 1.7:



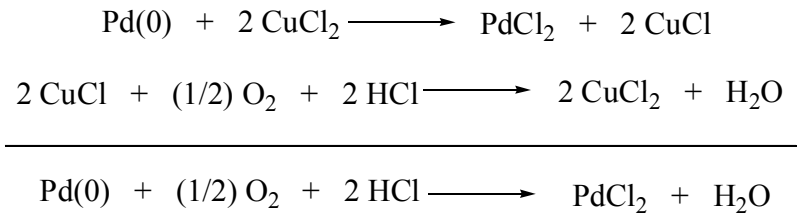
(1.7)

The stereochemistry of the addition on the triple bond is of *syn* type. The most used metal complexes are Pd(II)-based. The total process is given from the combination of the two reaction reported in the following equation.



(1.8)

It is therefore possible to realize a catalytic process only in the presence of an oxidative agent able to re-oxidize Pd (0) to Pd (II). An oxidant able to do that is Cu (II), which reduces itself to Cu (I). The oxidation of the last one by oxygen makes the process catalytic also for copper (Scheme 1.14).



Scheme 1.14

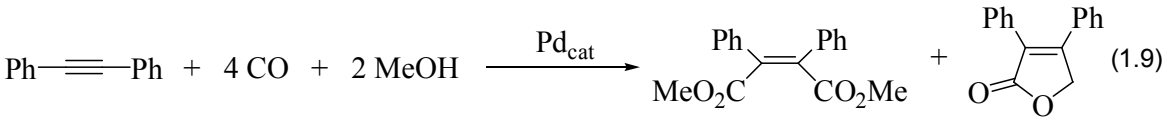
A quick and effective reoxidation of Pd (0) in the alkyne oxidative carbonylation can be carried out by using PdI_2. In this case, HI is produced from the reaction, which is oxidized by the oxygen to form iodine,

suddenly able to give oxidative addition, with the reoxidation of Pd (0) to Pd (II).

$$2\,HI + (1/2)\,O_2 \longrightarrow I_2 + H_2O$$
$$I_2 + Pd(0) \longrightarrow PdI_2$$
$$2\,HI + (1/2)\,O_2 + Pd(0) \longrightarrow PdI_2 + H_2O$$

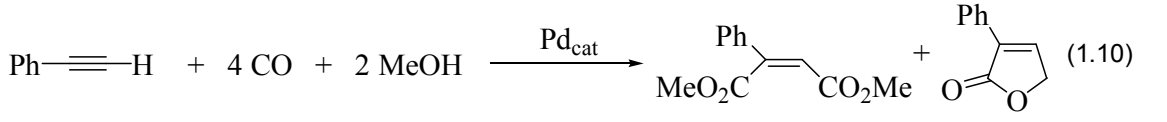
Scheme 1.15

Oxidative carbonylation of alkynes can occur also in the absence of an external oxidative agent, if coupled to a reductive carbonylation process on the acetylenic substrate. The first example of this reactivity was reported by Tsuji and Nogi in 1966, in the $PdCl_2$-catalyzed diphenylacetylene carbonylation in methanol, in the presence of HCl, at 100 °C and 100 atm. At the end of the reaction, they observed the formation of both dimethyl diphenylmaleate and diphenyl-γ-butenolactone, the oxidative dicarbonylation product and the reductive dicarbonylation one, respectively (eq. 1.9).



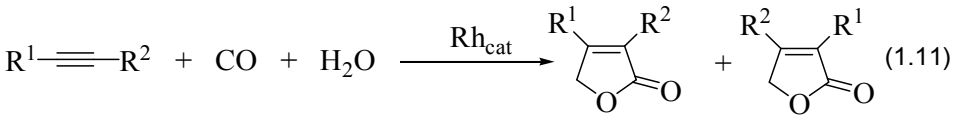
(1.9)

Using the $[Pd(tu)_4]Cl_2$ (tu= thiourea) complex as the catalyst, it is possible to realize the combination oxidative/reductive carbonylation of phenylacetylene, with the formation or dimethyl phenylmaleate and phenyl-γ-butenolactone (eq. 1.10).[84]



(1.10)

The reductive carbonylation of internal alkynes to 2-(5*H*)-furanones in the absence of contemporary oxidative carbonylation was realized through rhodium-carbonyl clusters [$Rh_4(CO)_{12}$ or $Rh_6(CO)_{16}$], in the presence of secondary or tertiary amines (eq. 1.11).

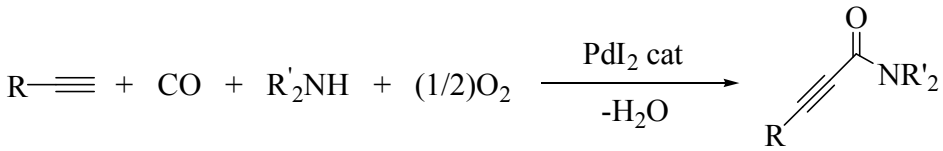


(1.11)

Part III

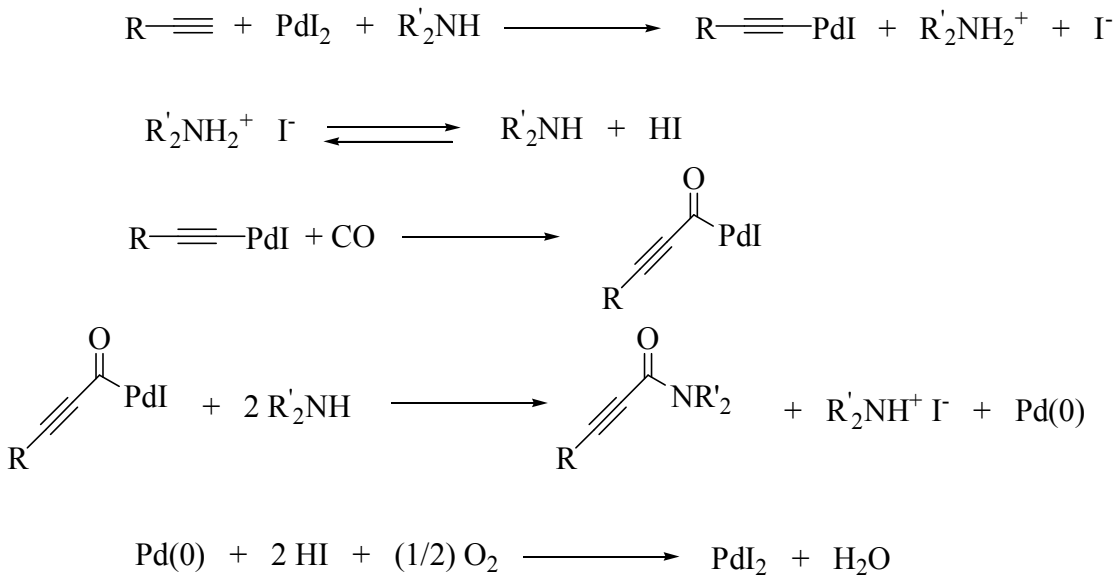
Results and discussion.

Pd-catalyzed carbonylations of unsaturated substrates represent an interesting methodology to synthesize functionalized heterocyclic compounds, even if they occur with CO incorporation in the cycle[85] or bearing a exocyclic carbonyl group.[86] PdI_2/KI in conjunction with oxygen as oxidant showed to be a simple and economic catalytic system for this kind of reactions. In general, the utilization of PdI_2 in conjunction with KI allowed the realization of various heterocyclization, oxidative alkoxycarbonylation and aminocarbonylation process of alkynic compounds suitably functionalized. It is known in literature that PdI_2-catalyzed oxidative aminocarbonylation of terminal alkynes triple bond leads directly to the formation of 2-ynamides (scheme 2.1).[87]



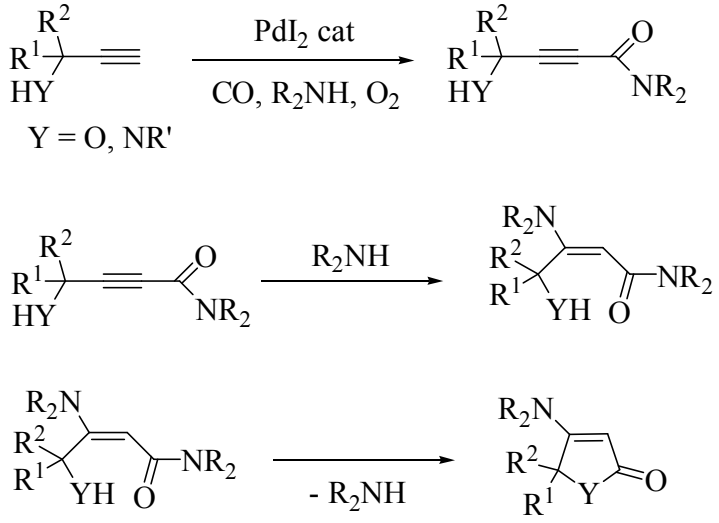
Scheme 2.1

The process involves the formation of an alkynylpalladium complex, which, successively, inserts carbon monoxide with the formation of an acylpalladium that undergoes nucleophilic attack from a secondary amine with final formation of an alkynylamide (Scheme 2.2). Hydrogen iodide, formed during the intermediate states, reacts with oxygen giving molecular iodine. Oxidative addiction of I_2 to Pd(0) newly forms PdI_2 species, ready to realize another cycle.



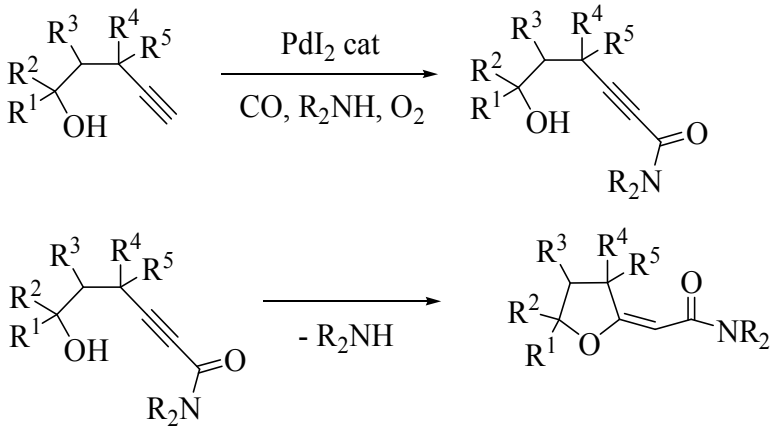
Scheme 2.2

This particular oxidative aminocarbonylation reaction leading to alkynylamides was employed to synthesize functionalized heterocycles, if applied to substituted 1-alkynes. Our research group already realized the syntheses of 4-dialkylamino-5*H*-furan-2-ones and 4-dialkylamino-1,5-dialkylpyrrol-2-ones, starting respectively from propynyl alcohols and amines, by oxidative aminocarbonylation, intermolecular conjugated addiction and intramolecular alcoholysis (Scheme 2.3).



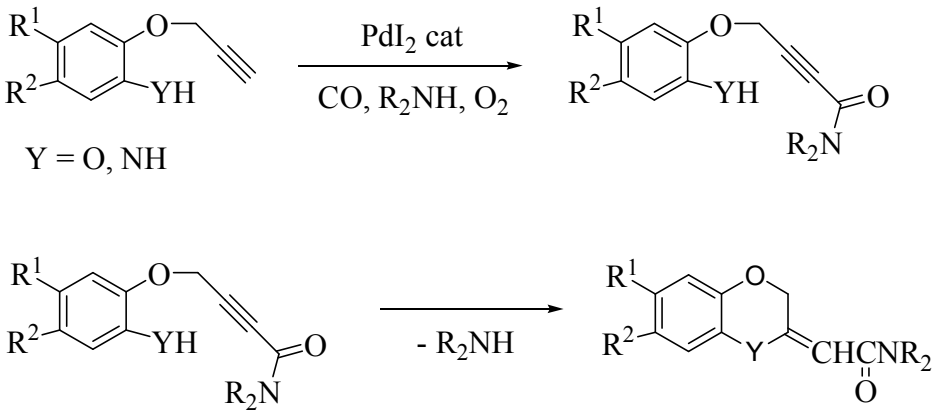
Scheme 2.3

Furthermore the synthesis of 2- [(dialkylcarbamoyl)methylene] tetrahydrofuran derivatives was realized starting from 4-yne-1-ols through an oxidative aminocarbonylation and intramolecular conjugated addition sequence (Scheme 2.4).



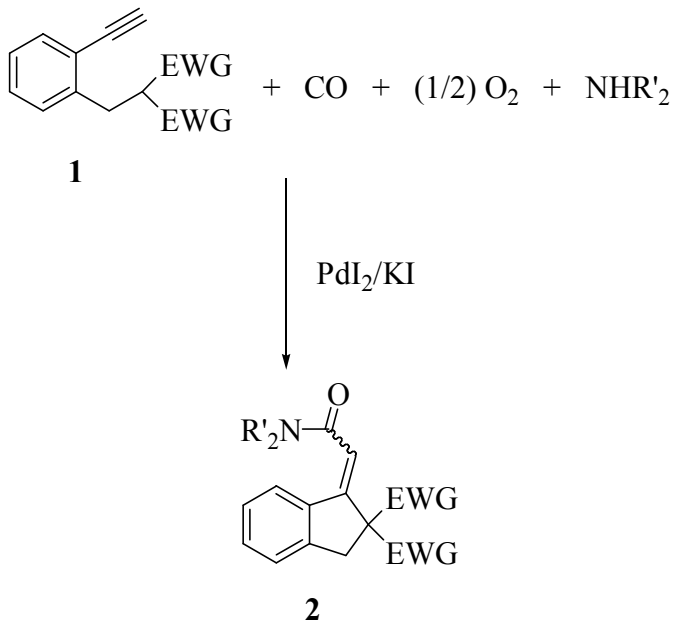
Scheme 2.4

The same reactivity was extended for the preparation of 2-[(dialkylcarbamoyl)methylene]-2,3-dihydrobenzo[1,4]dioxins and 3-[(dialkylcarbamoyl)methylene]-3,4-dihydro-2*H*-benzo[1,4]oxazines, starting respectively from 2-prop-2-ynyloxyphenols or 2-prop-2-ynyloxanilines (Scheme 2.5).



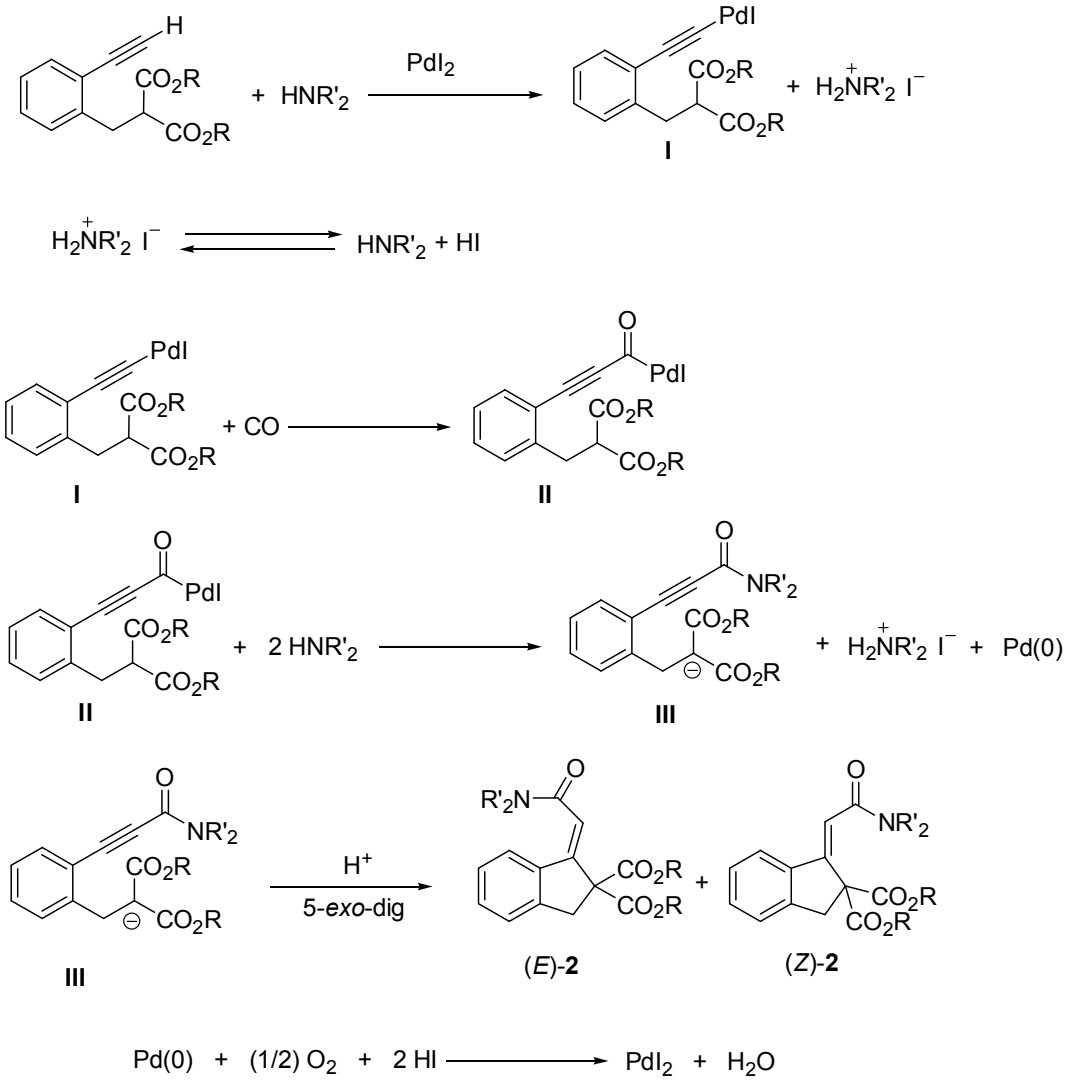
Scheme 2.5

On the base of these examples, we planned to carry out a Pd-catalyzed oxidative aminocarbonylation reaction for the synthesis of functionalized carbocycles instead of heterocycles. So we tested the reactivity of substrates **1** in the classic Pd-catalyzed oxidative aminocarbonylation conditions, leading to carbonylated indane derivatives **2** (Scheme 2.6).



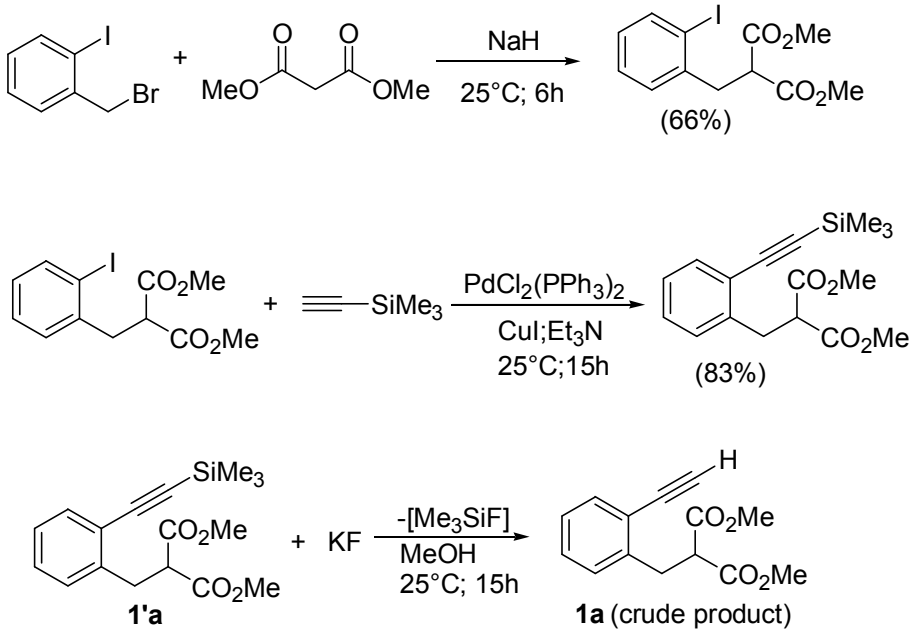
Scheme 2.6

According to previous studies, indanylidene derivatives **2** could be obtained after the formation of palladium acetylide **I** with amine protonation, CO insertion and formation of acylic intermediate **II**, followed by nucleophilic attack of the amine leading to the formation of 2-yne-1-amide species **III** and Pd (0) elimination, intramolecular Michael reaction and re-oxidation of the Pd (0) species to Pd (II).



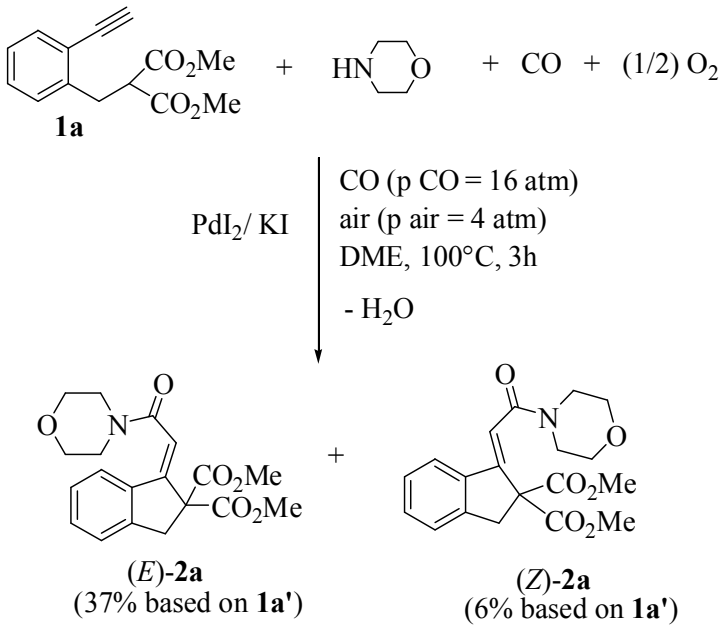
Scheme 2.7

Dimethyl 2-(2-ethynylbenzyl)malonate **1a**, obtained by malonic synthesis between 2-iodo-2-benzylbromide and the dimethyl malonate, followed by Sonogashira coupling with ethynyltrimethylsilane and finally de-protection with potassium fluoride (Scheme 2.8; the preparation is reported the experimental section), was chosen as model substrate to test the reactivity of derivatives **1** towards Pd-catalyzed oxidative aminocarbonylation carbocyclization. Compound **1a**, shown to be not stable, so it was used crude, without further purification.



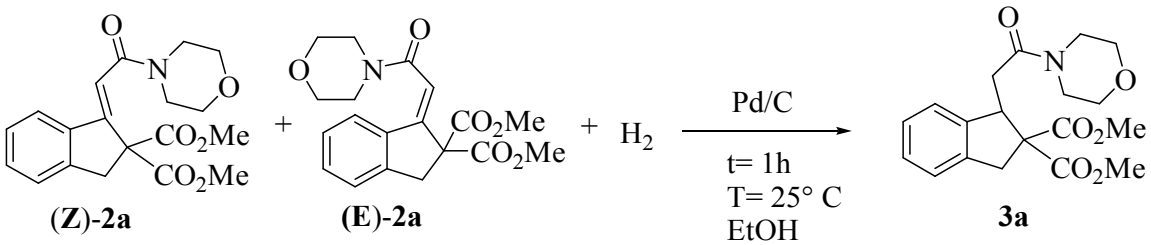
Scheme 2.8

The first experiment was carried at 100 °C in DME as the solvent (**1a** concentration = 0.22 mmol per mL of DME, **1a**/morpholine/KI/PdI_2 molar ratio = 100/200/10/1) under 20 atm of a 4:1 mixture of CO-air. The reaction mixture was monitored, and after three h GLC and TLC analyses revealed the absence of the substrate with the formation of two products, which were purified by chromatographic column, separated and characterized by IR, NMR and GC-MS. As hypothesized at the beginning, the two products were identified as the *E* and *Z* isomers of dimethyl 1-(2-morpholine-4-yl-2-oxoethylydene)-indan-2,2-dicarboxylate **2a** (Scheme 2.9). The two isomers were recovered with a 37% and 6% yield respectively, based on starting **1a'**.



Scheme 2.9

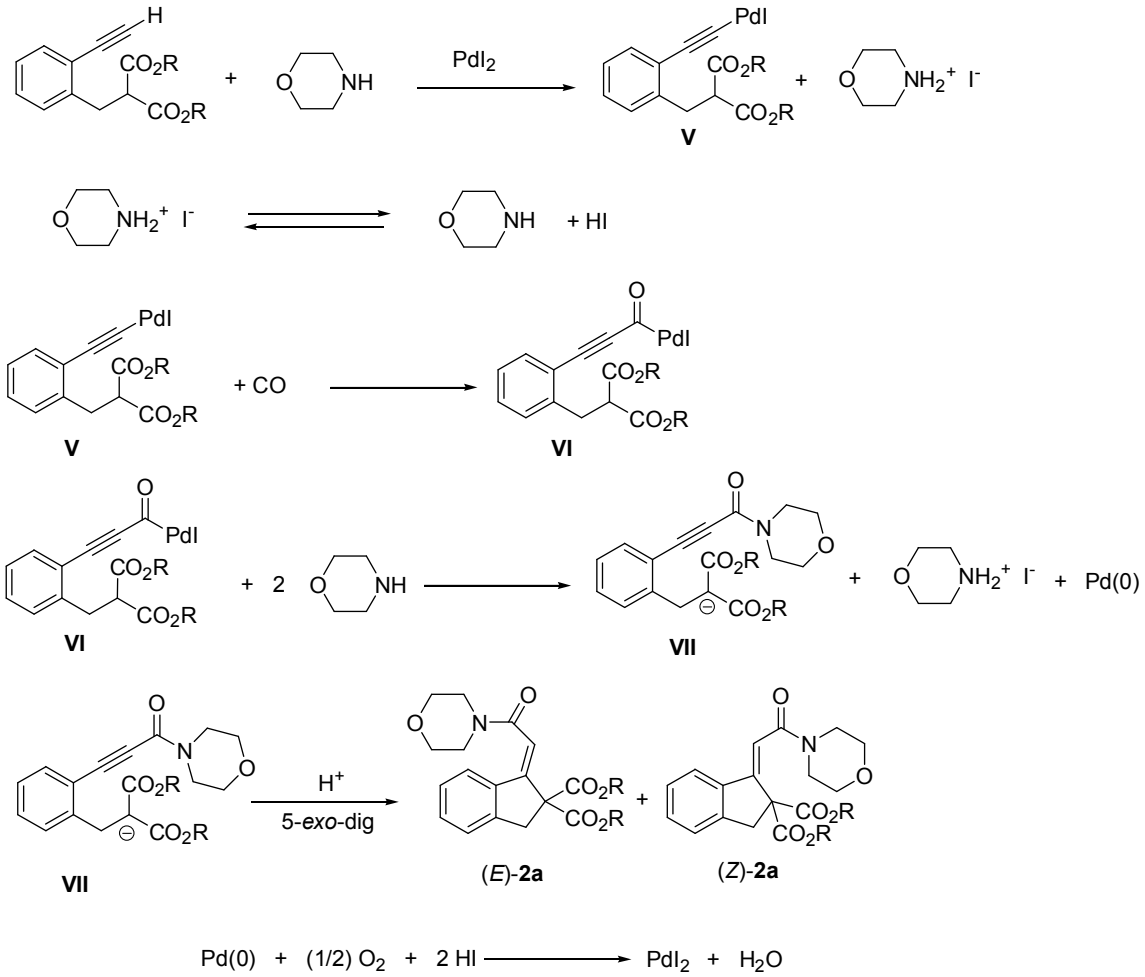
Through NMR bi-dimensional analyses (Noesy and Cosy), we were able to attribute *E* and *Z* stereochemistry, respectively to the main product and to secondary one. To further confirm the proposed structures, we carried out a Pd/C catalyzed hydrogenation: the GC-MS analysis of the reaction mixture showed the absence of the starting **2a** with exclusive formation of the hydrogenation product **3a** (Scheme 2.10), whose structure was confirmed by NMR analysis.



Scheme 2.10

(*Z*)**-2a** and (*E*)**-2a** compounds were plausibly obtained, as supposed previously, through the formation of the dimethyl 2-[2-(3-morpholine-4-yl-

3-oxoprop-1-ynyl)benzyl]-malonate, followed by intramolecular Michael reaction (Scheme 2.11).



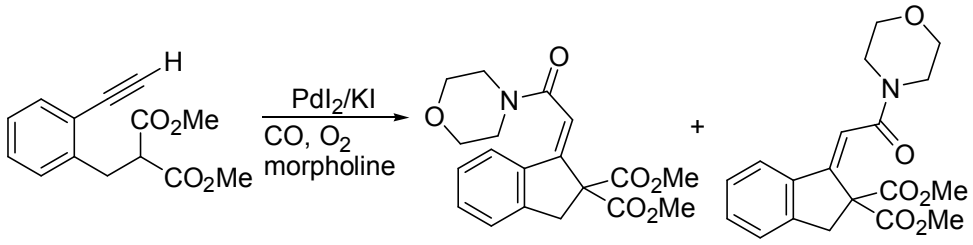
Scheme 2.11

A confirm of the exposed mechanistic hypothesis was obtained by testing a substrate with an internal triple bond. In particular we let to react dimethyl 2-(2-hex-1-ynylbenzyl)-malonate **1a** at 100 °C in DME as the solvent (**1a** concentration = 0.22 mmol per mL of DME, **1a**/morpholine/KI/PdI_2 molar ratio = 100/200/10/1) under 20 atm of a 4:1 mixture of CO-air. The reaction mixture was monitored after three hours through GLC and TLC, revealing only the presence of the substrate without the formation of any product. Even by conducing the reaction for a longer time (15 h) we did not observe the formation of any product. This result supports our mechanistic

hypothesis, since it is not possible to form the ynylamidic species from substrates bearing an internal triple bond.

In order to improve our initial result, we then screened the reaction parameters; the results obtained are shown in Table 2.1, entries 2-18.

Table 2.1. PdI_2/KI-catalyzed oxidative aminocarbonylation carbocyclization reaction of dimethyl 2-(2-ethynylbenzyl)-malonate 1a under different conditions. [a]



1a **2a** (*E*) **2a** (*Z*)

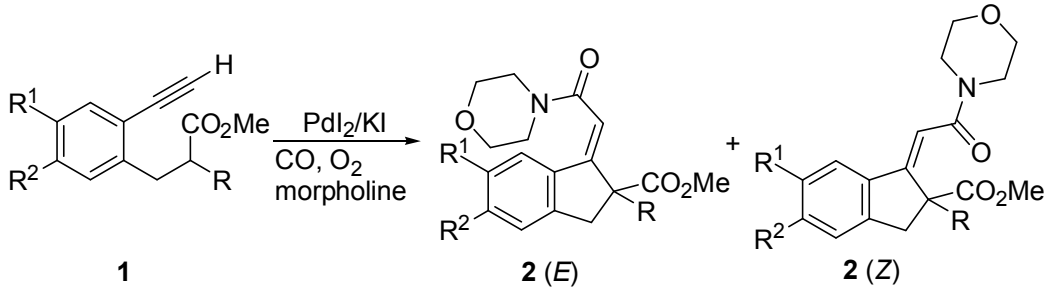
Entry	morpholine/KI/ PdI_2 molar ratio	Solv.	[Sub.] [b]	T(°C)	Conv.(%)[c]	Yield of **2a**[c] (%)	
						E	*Z*
1	200/10	DME	0.22	100	100	37	6
2	200/10	DME	0.22	80	100	39	9
3	200/10	DME	0.22	70	95	29	6
4	200/10	DME	0.22	50	55	18	5
6	200/5	DME	0.22	100	100	33	8
7	200/20	DME	0.22	100	100	32	7
8	200/50	DME	0.22	100	100	39	8
9	100/10	DME	0.22	100	95	39	9
10	150/10	DME	0.22	100	95	32	10
11	200/10	DME	0.1	100	100	42	8
12	200/10	DME	0.5	100	100	34	12

13	200/10	DME	0.05	100	75	35	7
14[d]	200/10	DME	0.22	100	100	45	11
15	200/10	DIOX	0.22	100	100	55	12
16	200/10	MeOH	0.22	100	100	41	23
17	200/10	MeCN	0.22	100	100	56	11
18	200/10	DMA	0.22	100	80	12	3

[a] All carbonylation reactions were carried out under 20 atm (at 25 °C) of a 4:1 mixture of CO-air, for 3 h in the presence of 1 mol % of PdI_2. [b] Mmol of starting **1a** per mL of solvent. [c] Based on starting **1'a**, by GLC. [d] The reaction was carried out under 40 atm (at 25 °C) of a 4:1 mixture of CO-air.

As can be seen from Table 2.1, entry 2-4, a decrease of the temperature from 80 °C to 70 and 50 °C caused a decrese of both the total yield and the selectivity of the process toward the formation of **2a**. A similar effect was observed when the KI:PdI_2 ratio was lowered to 5 (entry 6) and also raised respectively to 20 and 50 (entries 7-8) and when substrate concentration was decreased (entry 13). On the other hand, a sensible increase of the total yield was obtained when the substrate concentration was increased until 0.1 (entry 11), the total pressure was raised to 40 atm (entry 14) and also by using acetonitrile as the solvent (entry 17). By carrying out the reaction under the optimized conditions (**1a**:morpholine:KI:PdI_2 molar ratio = 100:200:10:1, 100 °C, 32 atm of CO, 8 atm of air, **1a** concentration = 0.1 mmol per mL of CH_3CN), dimethyl (*E*)-1-(2-morpholine-4-yl-2-oxoethylydene)-indane-2,2-dicarboxylate **2a** and dimethyl (*Z*)-1-(2-morpholine-4-yl-2-oxoethylydene)-indane-2,2-dicarboxylate **2a** were respectively obtained in 62% and 3% isolated yield, based on starting **1'a** (Table 2.2, entry 1).

Table 2.2. Synthesis of indanylidene derivatives 2 by PdI_2/KI-catalyzed oxidative aminocarbonylation carbocyclization reaction of methyl 2-(2-ethynylbenzyl)-esters derivatives 1 bearing different groups on the aromatic ring and on the ester moiety. [a]



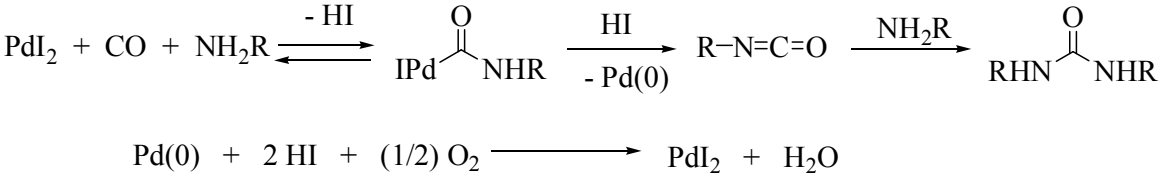
1 **2** (*E*) **2** (*Z*)

Entry	**1**	R	R^1	R^2	**2**	Yield of **2**[b] (%)	
						E	*Z*
1	**1a**	CO_2Me	H	H	**2a**	62	3
2	**1b**	CO_2Me	OMe	OMe	**2b**	70	3
3	**1c**	CO_2Me	Me	Me	**2c**	60	6
4	**1d**	CO_2Me	OMe	H	**2d**	60	4
5	**1e**	CO_2Me	Cl	H	**2e**	62	/
6	**1f**	COMe	H	H	**2f**	67	/
7	**1g**	CN	H	H	**2g**	35	18

[a] All carbonylation reactions were carried out at 100 °C under 40 atm (at 25 °C) of a 4:1 mixture of CO-air, in acetonitrile as the solvent (0.1 mmol of starting **1** per mL of solvent) and with a **1**:morpholine:KI:PdI_2 molar ratio = 100/200/10/1. Conversion of **1** was quantitative in all cases. [b] Isolated yield based on starting **1'**.

The generality of the process was then verified by testing the reactivity of other differently substituted substrates **1b-g**, bearing different substituents on the aromatic ring, as well as different electron withdrawing groups on the ester moiety of the molecule. As can be seen from the results reported

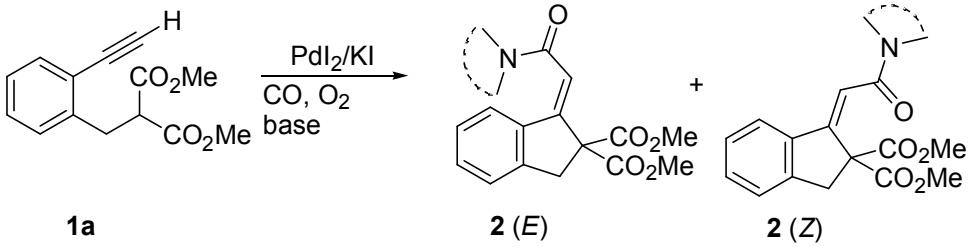
in Table 2.2, entries 1-7, the process was quite general, the corresponding carbonylated indanylidene derivatives **2a-g** being obtained in satisfactory yields and good selectivity towards the *E* diatereoisomer. Only in the case of 2-cyano-3-(2-ethynyl-phenyl)-propionate**1g** (bearing a cyano group on the enolic moiety), the total yield and selectivity of the corresponding products were lower (53%, 35% and 18%, respectively, Table 2.2, entry 7). We also tested the reactivity of dimethyl 2-(2-ethynylbenzyl)-malonate **1a**, carrying out the reaction with different secondary amines as bases, both linear and cyclic ones (we already knew from previous works[88] that primary amines undergoing PdI_2-catalyzed oxidative carbonylation reaction, give symmetrically disubstituted ureas with satisfactory yields; Scheme 2.12)



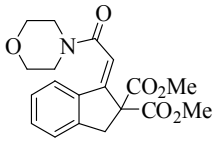
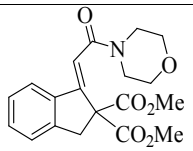
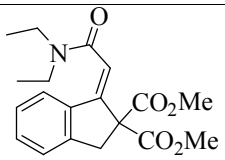
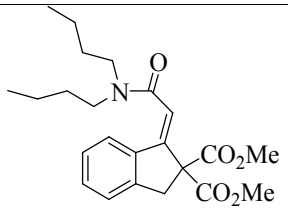
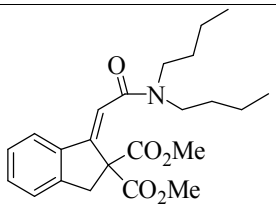
Scheme 2.12

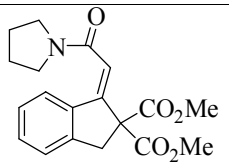
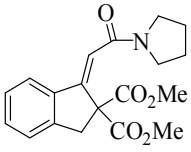
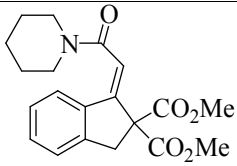
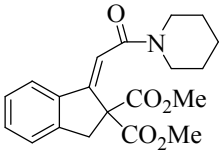
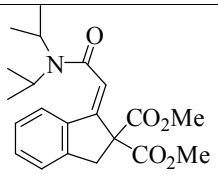
As can be seen from the results reported in Table 2.3, entries 1-5, the process is general with reproducible results with all the amine used. It is noteworthy that the reaction with a bulky amine such as diisopropylamine (Table 2.3, entry 6) is totally selective towards the *E* diastereoisomer with a satisfactory yield. In the case of the cyclic amines pyrrolidine and piperidine (Table 2.3, entries 4-5 respectively), the selectivity was lower so, to obtain a complete selectivity towards the main product, we decreased substrate concentration to 0.05 carrying out the reaction for a longer time (5h): in such a way, the yields of the corresponding carbonylated indanylidene derivatives **2j** and **2k** were always good (54% and 45%, respectively, Table 2.3, entries 7 and 8, respectively).

Table 2.3. PdI_2/KI-catalyzed oxidative aminocarbonylation carbocyclization reaction of dimethyl 2-(2-ethynylbenzyl)-malonate 1a using cyclic and linear secondary amines as bases. [a]



1a **2** (*E*) **2** (*Z*)

Entry	Amine	**2**		Yield of **2**[b] (%)	
				E	*Z*
1	Morpholine	 (*E*)-**2a**	 (*Z*)-**2a**	62	3
2	Diethylamine	 (*E*)-**2h**	/	70	/
3	Dibutylamine	 (*E*)-**2i**	 (*Z*)-**2i**	73	7

4	Pyrrolidine	 (*E*)-**2j**	 (*Z*)-**2j**	40	28
5	Piperidine	 (*E*)-**2k**	 (*Z*)-**2k**	50	15
6	Diisopropylamine	 (*E*)-**2l**	/	46	/
7[c]	Pyrrolidine	**2j**		54	/
8[c]	Piperidine	**2k**		45	/

[a] All carbonylation reactions were carried out at 100 °C under 40 atm (at 25 °C) of a 4:1 mixture of CO-air, in CH_3CN as the solvent (0.1 mmol of starting **1a** per mL of solvent), for 3h and with a sub:base:KI:PdI_2 molar ratio = 100:200:10:1. Conversion of **1a** was quantitative in all cases. [b] Isolated yield based on starting **1'a**. [c] The reaction was carried out in CH_3CN as the solvent (0.05 mmol of starting **1a** per mL of solvent), for 5h.

Part III

Conclusions.

In conclusion, we have disclosed a novel, general and innovative method for the one-step synthesis of carbonylated indanylidene derivatives **2** by PdI_2-catalyzed oxidative aminocarbonylation of the triple bond followed by intramolecular conjugated addition, starting from very simple building blocks such as CO, O_2 and ethynylbenzyl malonates, ethynyl oxobutyrrates and ethynyl cyanopropionates **1**. All the products were obtained with satisfactory yields (53-73%) and the reaction showed a high stereoselective grade towards the formation of *E* isomer, which, in some cases, was isolated in a totally selective way. Finally, it has been demonstrated that PdI_2-catalyzed oxidative aminocarbonylation is a powerful methodology leading to the one-step synthesis of functionalized cyclic derivatives of remarkable interest in pharmacology.

Part III

Part III

Experimental section.

General Experimental Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ solutions at 300 or 500 MHz and 75 or 125 MHz, respectively, with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. IR spectra were taken with an FT-IR spectrometer. Mass spectra were obtained using a GC-MS apparatus at 70 eV ionization voltage or a mass spectrometer equipped with a turbo ion spray ionization source in the positive mode [ion spray voltage (IS) 4500 V; curtain gas 10 psi; temperature 25 °C; ion source gas (1) 20 psi; declustering and focusing potentials 50 and 400 V, respectively]. Microanalyses were carried out at our analytical laboratory. All reactions were analyzed by TLC on silica gel 60 F_{254} or on neutral alumina and by GLC using a gas chromatograph and capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase or using a gas chromatograph and a capillary columns with diethyl tertbutylsilyl-β-cyclodextrine as the stationary phase. Column chromatography was performed on silica gel 60 (70-230 mesh). Evaporation refers to the removal of solvent under reduced pressure.

General procedure of iodination for the preparation of substituted 2-iodobenzyl alcohols 5b-d.[89] A solution of I_2 (1 mmol, 250 mg) in dry $CHCl_3$ (30 mL) was added over a suspension of CF_3COOAg (1 mmol, 220 mg) and benzyl alcohols (1 mmol) (3,4-dimethoxybenzyl alcohol: 168.2 mg; 3,4-dimethylbenzyl alcohol: 136.2 mg; 4-methoxybenzyl alcohol: 138.2 mg) in $CHCl_3$ (5 mL). The reaction mixture was stirred at room temperature during 30 min, the resulting AgI precipitate was filtered, and

the resulting solution was washed with saturated $Na_2S_2O_3$. Evaporation of the solvent afforded iodinated benzyl alcohols **5b-d**, which were crystallized from Et_2O.

Procedure for the preparation of 2-bromo-4-chlorotoluene 5e.[90] To a mixture of *p*-chlorotoluene (79.00 mmol, 10.0 g) and powdered Fe (79.00 mmol, 4.41 g) Br_2 (98.73 mmol, 5.06 mL) was slowly added, after 3.5 hours at room temperature, the mixture was filtered and the filtrate was distilled to give 6.71 g of 2-bromo-4-chlorotoluene **5e** as a colorless oil, (b.p. = 80-100 °C at 2 mmHg) (40% yield).

General procedure for the preparation of substituted 2-iodobenzylbromides 4a-d.[91] PBr_3 (20 mmol, 0.38 mL) was added over a solution of benzyl alcohols (10 mmol) (2-iodobenzyl alcohol: 2.43 g; 2-iodo-4,5-dimethoxybenzyl alcohol **5b**: 2.94 g; 2-iodo-4,5-dimethylbenzyl alcohol **5c**: 2.62 g; 2-iodo-4-methoxybenzyl alcohol **5d**: 2.64 g) in dry CH_2Cl_2 (100 mL), and the reaction mixture was stirred at room temperature for 16 h. Solvent was evaporated, and the resulting oil was treated with saturated $NaHCO_3$. The resulting aqueous phase was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo, yielding bromides **4a-d**, which were crystallized from Et_2O.

Procedure for the preparation of 2-bromo-4-chlorobenzylbromide 4e.[92] *N*-bromosuccinimide (32.68 mmol, 5.82 g) and α,α'-azoisobutyrronitrile (0.65 mmol, 107.20 mg) were added to a solution of 2-bromo-4-chlorotoluene **5e** (32.68 mmol, 6.71 g) in carbon tetrachloride (100 mL); the resulting mixture was heated at reflux for 4 hours under stirring. After cooling the solution was filtered and the filtrate was washed with 5%

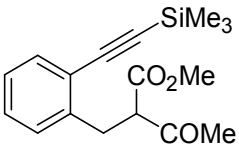
aqueous sodium thiosulphate. The organic layer was dried over anhydrous sodium sulphate and the carbon tetrachloride was evaporated under vacuum. The oily crude product was purified by means of a flash chromatography (*n*-hexane) to afford 6.00 g of 2-bromo-4-chlorobenzylbromide **4e** as colorless oil (64% yield).

General procedure for the preparation of 2-halobenzyl malonates 3a-e.[93] 2-halobenzyl bromide derivative (11 mmol) (2-iodobenzylbromide **4a**: 3.27 g; 1-bromomethyl-2-iodo-4,5-dimethoxy-benzene **4b**: 3.93 g; 1-bromomethyl-2-iodo-4,5-dimethyl-benzene **4c**: 3.57 g; 1-bromomethyl-2-iodo-4-methoxy-benzene **4d**: 3.60 g; 2-bromo-1-bromomethyl-4-chloro-benzene **4e**: 3.13 g) was added to a solution of NaH (15 mmol, 0.60 g) and dimethylmalonate (17 mmol, 2.25 g, 1.94 mL) in anhydrous THF (30 mL), then the reaction mixture was refluxed for 6h. The mixture was poured into 10% HCl (15 mL) and extracted with ether (20 mL x 3). The collected organic phases were washed with brine to neutral pH, dried over $MgSO_4$ and evaporated to dryness. After filtration and evaporation of the solvent, products **3a-e** were purified by column chromatography on silica gel using the following mixtures as eluent: 9:1 hexane-acetone (**3a**), 8:2 hexane-acetone (**3b-d**), 8:2 hexane-AcOEt (**3e**).

General procedure for the preparation of methyl 2-(*o*-iodobenzyl)acetoacetate 3f and methyl 2-(*o*-iodobenzyl)cyanoacetate 3g.[94] To a suspension of NaH (12 mmol, 0.29 g) in anhydrous THF (20 mL) and HMPA (24 mmol, 4.2 mL) were sequentially added acetate derivatives (12 mmol) (methyl acetoacetate: 1.39 g; methyl cyanoacetate: 1.19 g) in anhydrous THF (20 mL, 23°C, 30 min.) and 2-iodobenzylbromide **4a** (12 mmol, 3.56 g, 23°C, 2h). Then saturated NH_4Cl (50 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 ×

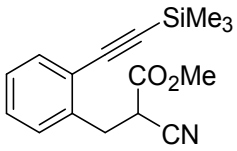
50 mL). The collected organic layers were washed with brine and dried over Na_2SO_4. After filtration and evaporation, products **3f-g** were purified by column chromatography on silica gel using the following mixtures as eluent: 9:1 hexane-AcOEt (**3f**), 95:5 hexane-AcOEt (**3g**).

General procedure for the preparation of 2-(2-trimethylsilanylethynyl)benzyl ester derivatives 1'a-g. [95] To a stirred solution of the 2-halobenzyl ester derivatives (8.06 mmol) [dimethyl 2-(2-iodo-benzyl)-malonate **3a**: 2.81 g; dimethyl 2-(2-iodo-4,5-dimethoxy-benzyl)-malonate **3b**: 3.29 g; dimethyl 2-(2-iodo-4,5-dimethyl-benzyl)-malonate **3c**: 3.03 g; dimethyl 2-(2-iodo-4-methoxy-benzyl)-malonate **3d**: 3.05 g; dimethyl 2-(4-chloro-2-bromo-benzyl)-malonate **3e**: 2.70 g; methyl 2-(*o*-iodobenzyl)acetoacetate **3f**: 2.68 g; methyl 2-(*o*-iodobenzyl)cyanoacetate **3g**: 2.54 g] and ethynyltrimethylsilane (9.67 mmol, 0.95 g), in NEt_3 (30 mL), was added under nitrogen $PdCl_2(PPh_3)_2$ (0.161 mmol 113.1 mg). The mixture was stirred for 5 min and CuI (0.081 mmol 15.4 mg) was added. The resulting mixture was then stirred at room temperature for 12h. The ammonium salt was removed by filtration and the solvent was removed under reduced pressure. Products were purified by column chromatography on silica gel using the following mixtures as eluent: 95:5 hexane-AcOEt (**1'a-1'e**), 8:2 hexane-acetone (**1'b-d**), 98:2 hexane-AcOEt (**1'f-g**).



Mehyl 3-oxo-2-(2-trimethylsilanylethynyl-benzyl)-butyrrate (1'f). Yield: 1.90 g, starting from 2.68 g of methyl 2-(*o*-iodobenzyl)acetoacetate **3f** (78%). Yellow oil, $C_{17}H_{22}O_3Si$ (302.44). IR (KBr): ν = 2955 (m), 2156

(w), 1739 (s), 1436 (m), 1251 (m), 1152 (m), 872 (m), 842 (m), 761 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.44 (dt, J = 7.0, 1.3, 1H-6), 7.25-7.13 (m, 3H, aromatic), 4.10 (t, J = 7.5, 1H-CH_2CH), 3.70 (s, 3H, CO_2CH_3), 3.40-3.21 (m, 2H, CH_2CH), 1.97 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.3, 169.5, 140.4, 132.7, 130.0, 128.8, 126.7, 122.6, 103.2, 99.2, 59.4, 52.3, 33.1, 29.6, -0.1. GC-MS (EI, 70 eV): *m/z* = 302 (4) [M^+], 288 (20), 287 (83), 259 (45), 243 (34), 227 (51), 213 (34), 185 (32), 183 (23), 173 (50), 169 (26), 156 (23), 153 (24), 145 (24), 128 (21), 127 (27), 115 (21), 89 (100), 75 (39), 73 (92).

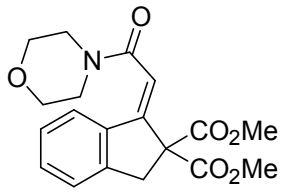


Methyl 2-cyano-3-(2-trimethylsilanylethynyl-phenyl)-propionate (1'g). Yield: 1.63 g, starting from 2.54 g of methyl 2-(*o*-iodobenzyl)cyanoacetate **3g** (71%). Yellow oil, $C_{16}H_{19}NO_2Si$ (285.41). IR (KBr): v = 2957 (m), 2156 (w), 1752 (s), 1437 (m), 1251 (m), 1159 (w), 874 (m), 843 (m), 760 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.49 (d, J = 7.1, 1H-6), 7.35-7.21 (m, 3H, aromatic), 4.07 (dd, J = 6.0,9.6 1H-CH_2CH), 3.81 (s, 3H, CO_2CH_3), 3.58 (dd, J=13.3, 6.0, 1H, C*H*HCH), 3.17 (dd, J= 13.3, 9.6 1H, CH*H*CH), 0.23 (s, 9 H, $SiMe_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 137.8, 132.9, 130.3, 129.3, 128.0, 123.0, 116.2, 102.4, 100.6, 53.6, 37.9, 35.3, 0.2. GC-MS (EI, 70 eV): *m/z* = 285 (5) [M^+], 271 (21), 270 (100), 240 (90), 238 (37), 213 (26), 183 (13), 172 (42), 155 (10), 145 (18), 129 (12), 115 (15), 89 (67).

General procedure for the preparation of 2-(2-ethynyl)benzyl ester derivatives 1a-g. To a solution of the trimethylsilanyl protected precursors (1 mmol) [dimethyl 2-(2-trimethylsilanylethynyl-benzyl)-malonate **1'a**:

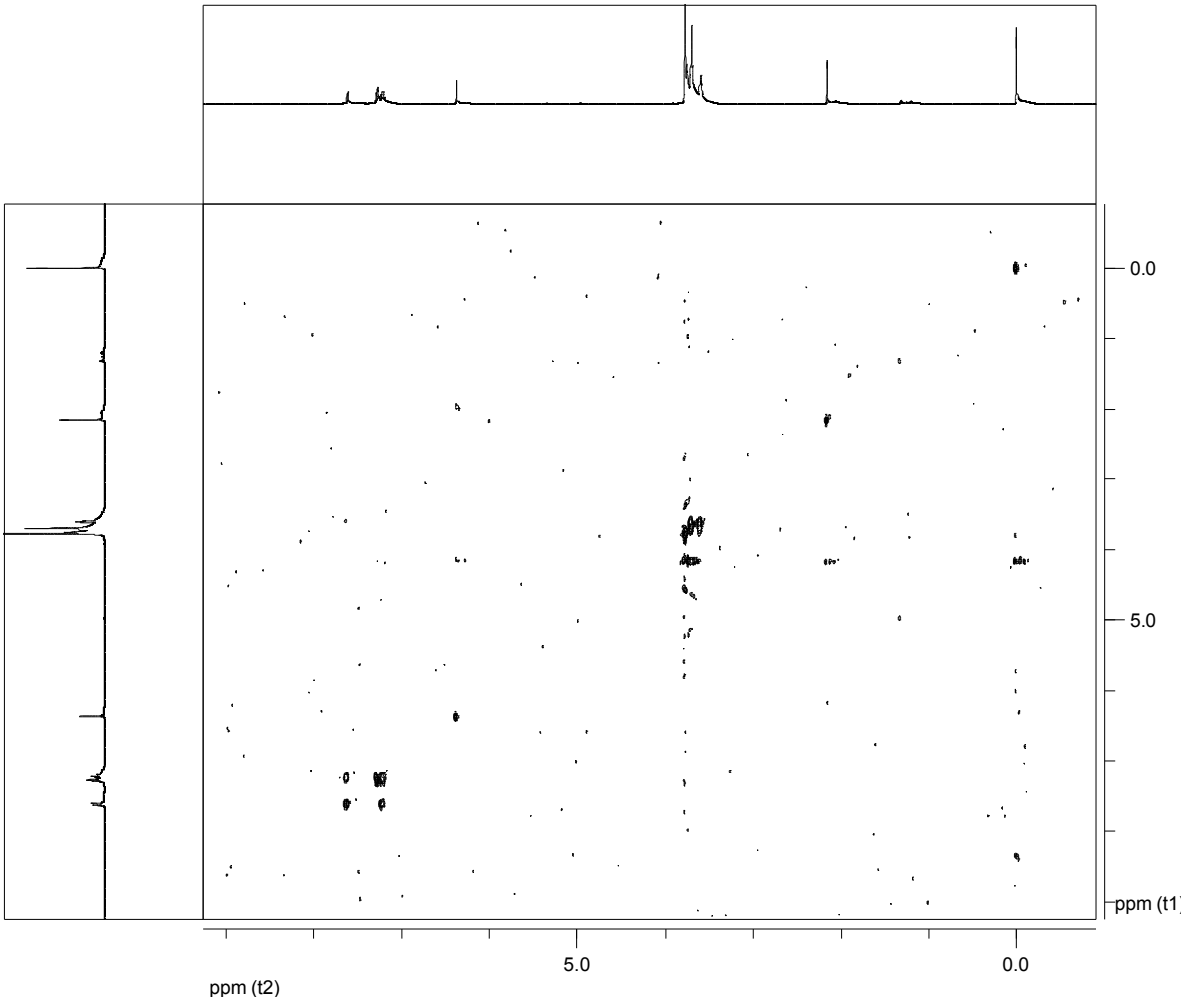
318.4 mg; dimethyl 2-(4,5-dimethoxy-2-trimethylsilanylethynyl-benzyl)-malonate **1'b**: 378.5 mg; dimethyl 2-(4,5-dimethyl-2-trimethylsilanylethynyl-benzyl)-malonate **1'c**: 346.5 mg; dimethyl 2-(4-methoxy-2-trimethylsilanylethynyl-benzyl)-malonate **1'd**: 348.5 mg; dimethyl 2-(4-chloro-2-trimethylsilanylethynyl-benzyl)-malonate **1'e**: 353.9 mg; methyl 3-oxo-2-(2-trimethylsilanylethynyl-benzyl)-butyrrate **1'f**: 302.4 mg; methyl 2-cyano-3-(2-trimethylsilanylethynyl-phenyl)-propionate **1'g**: 285.4 mg] in methanol (8 mL) was added potassium fluoride (3.5 mmol, 203.4 mg) at room temperature. The resulting mixture was stirred for 15h. Then water was added (25 mL) and the solution extracted with diethyl ether (30 mL x 3) and the collected organic layers dried over anhydrous Na_2SO_4. Crude products **1a-g** were sufficiently pure to be used as such for the carbonylation reaction.

General procedure for the synthesis of indanylidene amide derivatives 2a-l. A 250 mL stainless steel autoclave was charged in the presence of air with PdI_2 (5.4 mg, 1.5×10^{-2} mmol, see Table 2.2 and Table 2.3), KI (24.9 mg, 1.5×10^{-1} mmol, see Table 2.2 and Table 2.3), anhydrous CH_3CN (15 mL, see Table 2.2 or 30 mL, see Table 2.3, entries 7-8) and the 2-(2-ethynyl)benzyl ester derivatives **1a-g** (1.5 mmol). The autoclave was sealed and, while the mixture was stirred, the autoclave was pressurized with CO (32 atm) and air (up to 40 atm). After being stirred at 100 °C for the required time (see Table 2.2 and Table 2.3), the autoclave was cooled, degassed and opened. The solvent was evaporated, and the products **2a-l** were purified by column chromatography on silica gel using the following mixtures as eluent: 7:3 hexane-acetone (**2a-c**), 8:2 hexane-acetone (**2d**), 95:5 hexane-AcOEt (**2f-g**), hexane (**2h**), 7:3 hexane-AcOEt (**2i-l**).



Dimethyl (*E*)-1-(2-morpholin-4-yl-2-oxo-ethylidene)-indan-2,2-dicarboxylate (2a). Yield: 334 mg, starting from 477.7 mg of dimethyl 2-(2-trimethylsilanylethynyl-benzyl)-malonate **1'a** (62%). Yellow oil, $C_{19}H_{21}NO_6$ (359.14). IR (KBr): ν = 3426 (m, br), 2958 (w), 2859 (w), 1733 (s), 1622 (s), 1435 (s), 1216(m), 1114 (m), 1055 (w), 985 (w), 849 (w), 754 (s), 668 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, J = 7.33, 1H aromatic), 7.40-7.15 (m, 3H, aromatic), 6.38 (s, 1H, C*H*CO), 3.83-3.69 (m, 8H morpholine), 3.71 (s, 6H, $2CO_2Me$), 3.64-3.56 [m, 2H, $CH_2(CO_2Me)_2$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 166.5, 143.4, 142.8, 135.8, 130.1, 127.6, 124.9, 124.5, 120.3, 114.4, 67.0, 66.6, 63.7, 53.4, 46.5, 41.7, 39.3. GC-MS (EI, 70 eV): *m/z* = 360 (5) [M^{+1}], 359 (26) [M^+], 300 (22), 274 (16), 273 (94), 214 (16), 213 (100), 186 (17), 181 (13), 171 (14), 155 (25), 141 (12), 128 (11), 127 (35), 126 (11), 115 (13), 86 (12).

NMR-COESY



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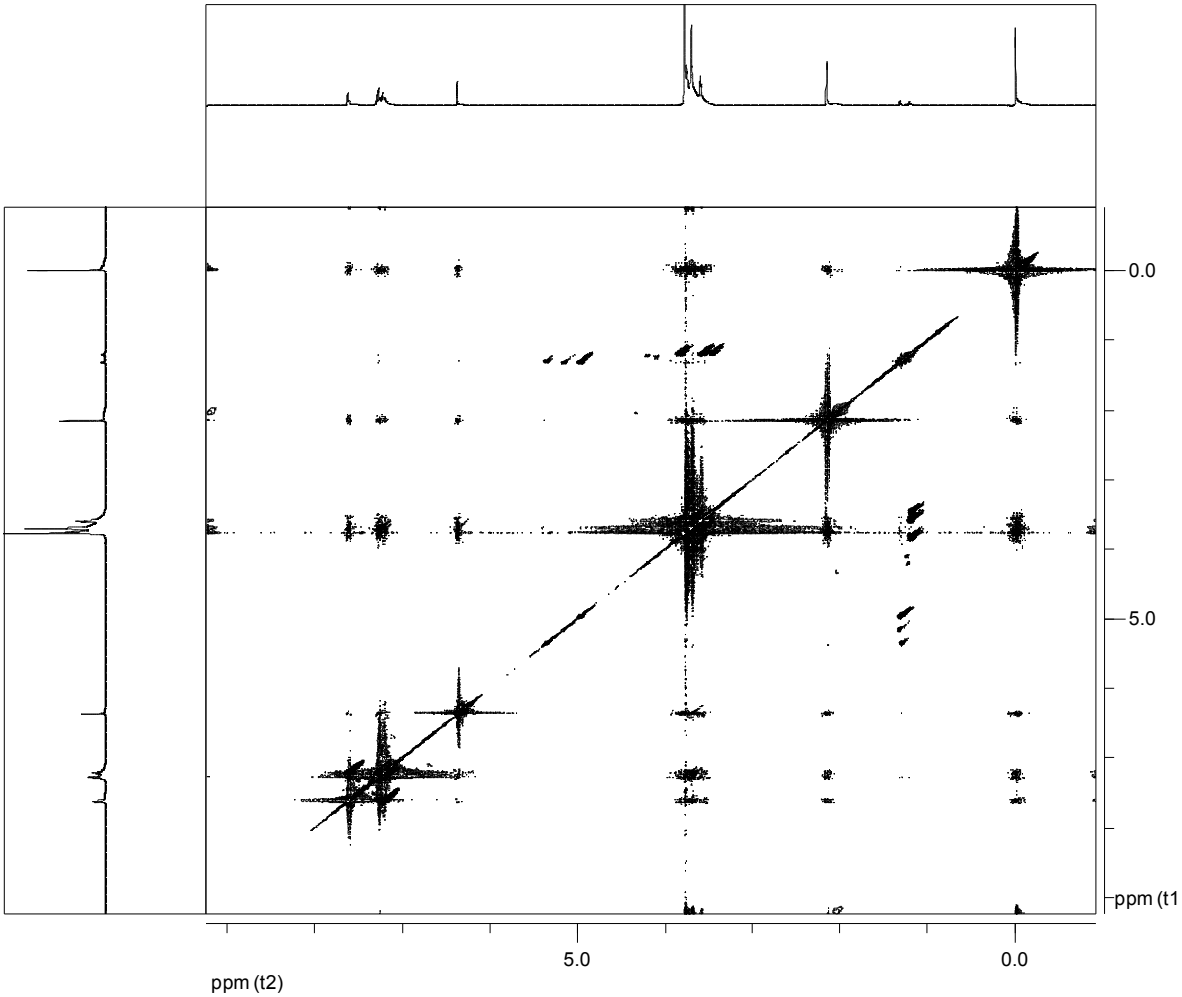
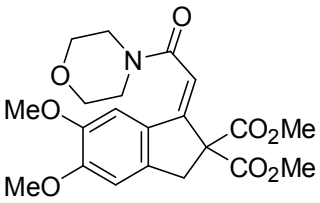
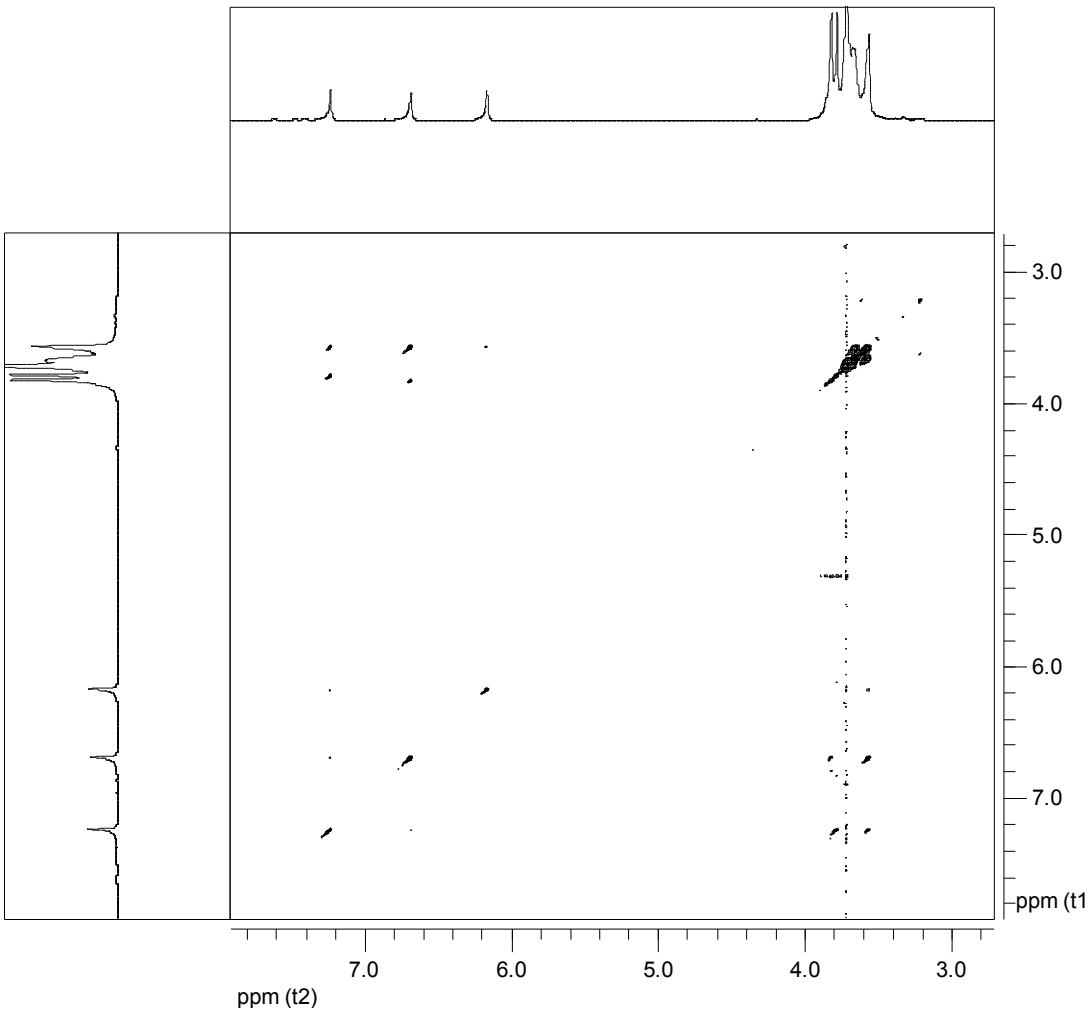




Dimethyl (*E*)-5,6-Dimethoxy-1-(2-morpholin-4-yl-2-oxo-ethylidene)-indan-2,2-dicarboxylate (2b). Yield: 440.1 mg, starting from 567.7 mg of dimethyl 2-(4,5-dimethoxy-2-trimethylsilanylethynyl-benzyl)-malonate **1'b** (70%). Yellow oil, $C_{21}H_{25}NO_8$ (419.16). IR (KBr): ν = 3471 (m, br), 3016 (w), 2856 (w), 1735 (s), 1639 (s), 1434 (s), 1244 (m), 1222 (m), 1115 (m), 1083 (m), 973 (w), 850 (w), 753 (s), 667 (m) cm^{-1}. ^1H NMR (300 MHz,

$CDCl_3$): δ = 7.28 (s, 1H aromatic), 6.74 (s, 1H aromatic), 6.23 (s, 1H, C*H*CO), 3.89 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.80-3.70 (m, 8H morpholine), 3.78 (s, 6H, CO_2Me), 3.66-3.61 [m, 2H, $CH_2(CO_2Me)_2$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 166.7, 151.5, 148.9, 143.8, 137.1, 128.3, 117.2, 106.9, 106.6, 67.1, 66.8, 64.4, 55.9, 53.3, 46.6, 41.7, 39.2. 29.3. GC-MS (EI, 70 eV): *m/z* = 420 (7) [M^{+1}], 419 (30) [M^+], 360 (11), 334 (12), 333 (65), 274 (20), 273 (100), 246 (22), 241 (23), 231 (13), 215 (15), 172 (10), 171 (13), 115 (11).

NMR-COESY



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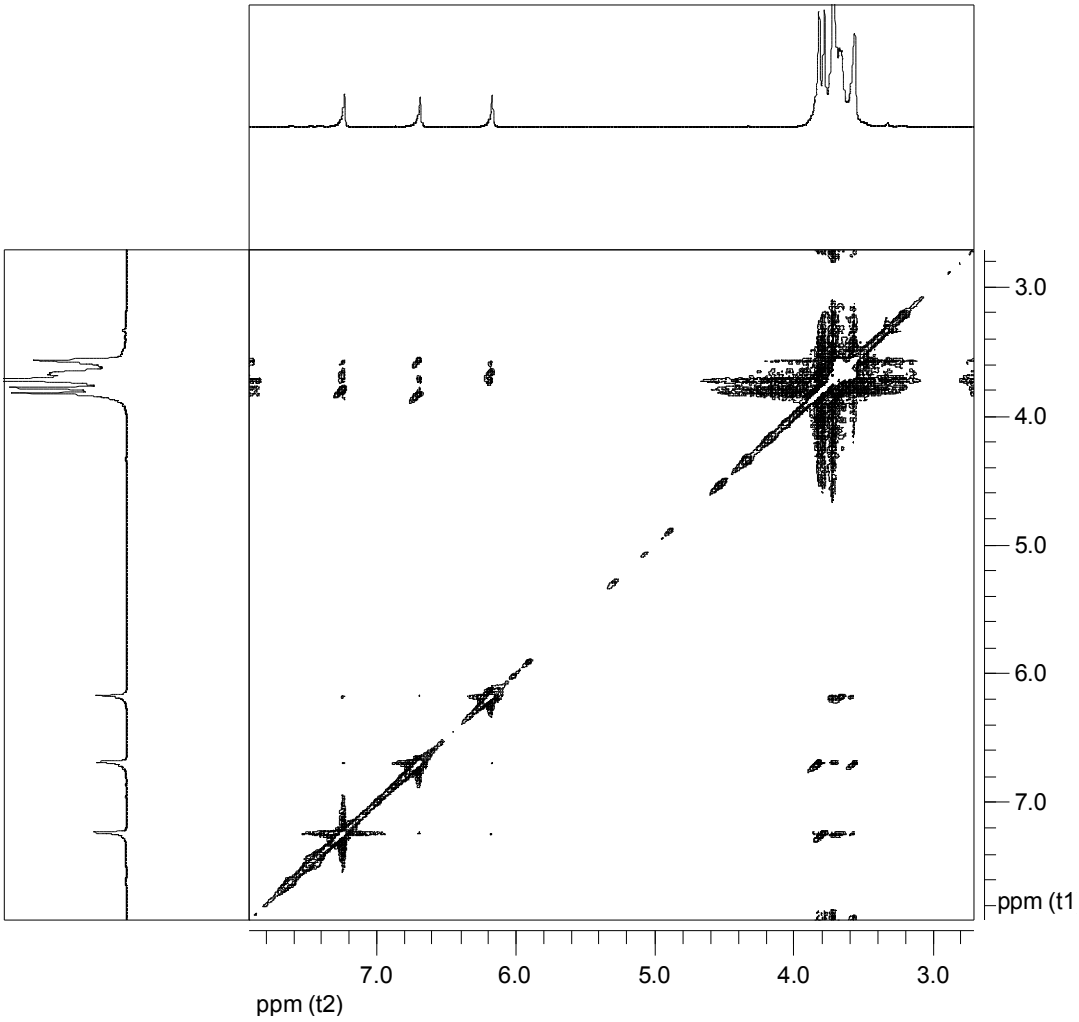
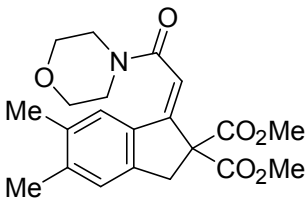
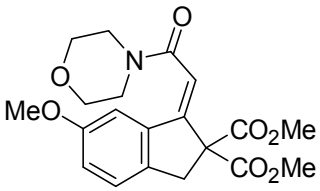


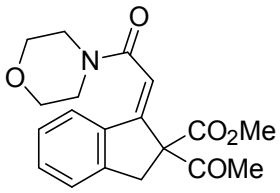


Dimethyl (*E*)-5,6-Dimethyl-1-(2-morpholin-4-yl-2-oxo-ethylidene)-indan-2,2-dicarboxylate (2c). Yield: 340.4 mg, starting from 519.7 mg of dimethyl 2-(4,5-dimethyl-2-trimethylsilanylethynyl-benzyl)-malonate **1'c** (60%). Yellow oil, $C_{21}H_{25}NO_6$ (387.17). IR (KBr): ν = 2923 (w), 2859 (w), 1737 (s), 1628 (s), 1435 (s), 1272 (m), 1198 (m), 1109 (m), 885 (w), 806 (w), 684 (w), 569 (m), 413 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.28 (s, 1H aromatic), 6.74 (s, 1H aromatic), 6.23 (s, 1H, C*H*CO), 3.89 (s, 3H,

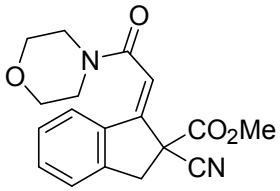
Me), 3.85 (s, 3H, Me), 3.80-3.70 (m, 8H morpholine), 3.78 (s, 6H, CO_2Me), 3.66-3.61 [m, 2H, $CH_2(CO_2Me)_2$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 166.8, 143.0, 141.3, 139.5, 136.0, 133.8, 125.8, 125.2, 118.7, 67.1, 66.7, 64.1, 53.3, 46.5, 41.7, 39.1, 30.9, 20.2. GC-MS (EI, 70 eV): *m/z* = 388 (3) [M^{+1}], 387 (16) [M^+], 328 (14), 302 (12), 301 (58), 242 (15), 241 (100), 214 (13), 209 (17), 199 (12), 183 (18), 155 (13), 153 (12).



Dimethyl (*E*)-6-Methoxy-1-(2-morpholin-4-yl-2-oxo-ethylidene)-indan-2,2-dicarboxylate (2d). Yield: 350.2 mg, starting from 522.7 mg of dimethyl 2-(4-methoxy-2-trimethylsilanylethynyl-benzyl)-malonate **1'd** (60%). Yellow oil, $C_{20}H_{23}NO_7$ (389.15). IR (KBr): ν = 2955 (w), 2857 (w), 1733 (s), 1639 (s), 1435 (s), 1255 (m), 1090 (m), 1051 (m), 968 (w), 852 (w), 730 (w), 618 (w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 7.8, 1H aromatic), 6.81-6.71 (m, 3H, aromatic), 6.23 (s, 1H, C*H*CO), 3.85-3.75 (m, 8H morpholine), 3.81 (s, 3H, OCH_3), 3.78 (s, 6H, CO_2Me), 3.72-3.65 [m, 2H, $CH_2(CO_2Me)_2$].; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 166.8, 161.6, 145.8, 143.0, 128.8, 126.0, 117.4, 114.6, 109.0, 67.1, 66.8, 64.4, 55.4, 53.3, 46.6, 41.7, 39.4, 30.9. GC-MS (EI, 70 eV): *m/z* = 390 (7) [M^{+1}], 389 (28) [M^+], 330 (12), 304 (18), 303 (100), 244 (12), 243 (79), 216 (20), 211 (11), 201 (13), 185 (23), 157 (10), 142 (10), 114 (12).

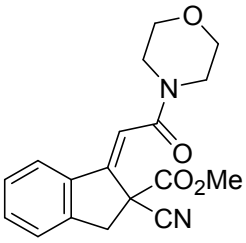


Methyl (*E*)-2-Acetyl-1-(2-morpholin-4-yl-2-oxo-ethylidene)-indan-2-carboxylate (2f). Yield: 345.1 mg, starting from 543.7 mg of methyl 3-oxo-2-(2-trimethylsilanylethynyl-benzyl)-butyrrate **1'f** (67%). Yellow oil, $C_{19}H_{21}NO_5$ (343.37). IR (KBr): ν = 2856 (m), 1714 (s), 1633 (s), 1434 (m), 1359 (m), 1238 (m), 1114 (m), 760 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.67-7.61 (m, 2H, aromatic), 7.39-7.19 (m, 3H, aromatic), 6.25 (s, 1H, C*H*=C), 3.89-3.54 (m, 10H, $OCH_2CH_2NCH_2CH_2$ + $CH_2CCO_2CH_3$), 3.81 (s, 3H, CO_2CH_3), 2.24 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.5, 170.3, 168.1, 166.4, 143.3, 130.3, 128.0, 127.7, 125.0, 124.9, 120.4, 77.4, 67.0, 66.7, 53.2, 46.6, 41.7, 38.1, 26.1. GC-MS (EI, 70 eV): *m/z* = 343 (absent) [M^+], 302 (12), 301 (64), 269 (14), 215 (54), 214 (100), 187 (21), 186 (96), 183 (28), 171 (18), 156 (25), 155 (64), 128 (35), 127 (48), 114 (12), 88 (25), 86 (13), 70 (13).

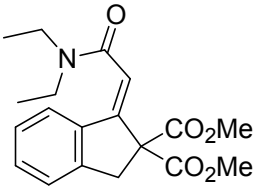


Methyl (*E*)-2-Cyano-1-(2-morpholin-4-yl-2-oxo-ethylidene)-indan-2-carboxylate (2g). Yield: 171.3 mg, starting from 428.1 mg of methyl 2-cyano-3-(2-trimethylsilanylethynyl-phenyl)-propionate **1'g** (35%). Yellow oil, $C_{18}H_{18}N_2O_4$ (326.25). IR (KBr): ν = 2968 (m), 2923 (m), 2864 (m), 2244 (w), 1742 (s), 1646 (s), 1597 (s), 1447 (m), 1273 (m), 1237 (m), 1214 (m), 1114 (m), 854 (m), 762 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.63 (d, J = 7.8, 1H, aromatic), 7.47-7.27 (m, 3H, aromatic), 6.51 (s, 1H, C*H*=C), 3.90 (s, 3H, CO_2CH_3), 3.84 (s, 2H, $CH_2CCO_2CH_3$), 3.79-3.61 (m,

8H, OCH_2CH_2NCH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.4, 162.9, 142.2, 138.0, 131.8, 128.3, 125.3, 121.9, 111.7, 67.3, 66.9, 46.6, 44.4, 41.6, 40.8. GC-MS (EI, 70 eV): *m/z* = 326 (26) [M^+], 295 (9), 267 (41), 241 (20), 240 (100), 214 (14), 196 (27), 181 (26), 180 (37), 155 (59), 153 (55), 127 (34), 126 (21), 105 (3), 86 (72).

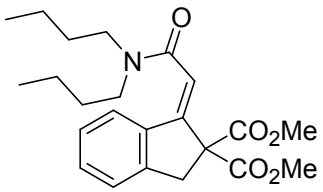


Methyl (*Z*)-2-Cyano-1-(2-morpholin-4-yl-2-oxo-ethylidene)-indan-2-carboxylate (2g). Yield: 88.1 mg, starting from 428.1 mg of methyl 2-cyano-3-(2-trimethylsilanylethynyl-phenyl)-propionate **1'g** (18%). Yellow oil, $C_{18}H_{18}N_2O_4$ (326.25). IR (KBr): ν = 2850 (m), 2209 (w), 1741 (s), 1645 (s), 1596 (m), 1437 (m), 1298 (m), 1213 (m), 1115 (m), 854 (m), 774 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 7.7, 1H, aromatic), 7.46-7.29 (m, 3H, aromatic), 6.90 (s, 1H, C*H*=C), 3.86 (s, 3H, CO_2CH_3), 3.84 (s, 2H, $CH_2CO_2CH_3$), 3.77-3.61 (m, 8H, OCH_2CH_2NCH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.5, 163.0, 142.3, 137.9, 131.8, 128.3, 125.7, 125.4, 121.9, 119.0, 111.9, 67.0, 66.7, 53.6, 46.7, 44.5, 41.7. GC-MS (EI, 70 eV): *m/z* = 326 (26) [M^+], 296 (5), 267 (48), 241 (20), 240 (100), 214 (14), 196 (29), 181 (26), 180 (40), 155 (60), 153 (57), 127 (34), 126 (25), 105 (1), 86 (93).



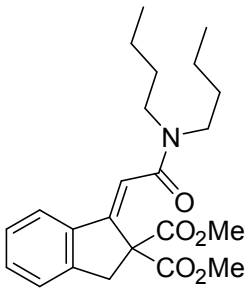
Dimethyl (*E*)-1-Diethylcarbamoylmethylene-indan-2,2-dicarboxylate (2h). Yield: 362.7 mg, starting from 477.6 mg of dimethyl 2-(2-

trimethylsilanylethynyl-benzyl)-malonate **1'a** (70%). Yellow oil, $C_{19}H_{23}NO_5$ (345.39). IR (KBr): ν = 2976 (m), 2940 (m), 1736 (s), 1634 (s), 1465 (m), 1432 (m), 1257 (m), 1171 (m), 1098 (m), 1056 (m), 786 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, J = 7.7, 1H, aromatic), 7.31-7.15 (m, 3H, aromatic), 6.45 (s, 1H, C*H*=C), 3.78 (s, 6H, 2 CO_2CH_3), 3.71 (s, 2H, $CH_2CO_2CH_3$), 3.55 (q, J = 7.1, 2H, NCH_2CH_3), 3.49 (q, J = 7.1, 2H, NCH_2CH_3), 1.25 (t, J = 7.1, 3H, NCH_2CH_3), 1.11 (t, J = 7.1, 3H, NCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 167.1, 143.3, 142.1, 136.2, 129.8, 127.4, 124.9, 124.7, 121.5, 64.0, 53.2, 42.7, 39.4, 39.3, 14.3, 12.9. GC-MS (EI, 70 eV): *m/z* = 346 (4) [M^+], 345 (17), 286 (19), 274 (10), 273 (60), 254 (7), 214 (21), 213 (100), 186 (23), 181 (12), 171 (12), 155 (23), 128 (11), 127 (28), 115 (10), 100 (5), 72 (39).

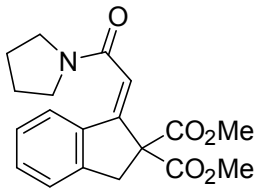


Dimethyl (*E*)-1-Dibutylcarbamoylmethylene-indan-2,2-dicarboxylate (2i). Yield: 439.3 mg, starting from 477.6 mg of dimethyl 2-(2-trimethylsilanylethynyl-benzyl)-malonate **1'a** (73%). Yellow oil, $C_{23}H_{31}NO_5$ (401.22). IR (KBr): ν = 2958 (m), 2930 (m), 2873 (m), 1764 (s), 1639 (s), 1591 (m), 1435 (m), 1264 (m), 1191 (w), 1153 (m), 1063 (m), 779 (m), 754 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, J = 7.8, 1H, aromatic), 7.30-7014 (m, 3H, aromatic), 6.44 (s, 1H, C*H*=C), 3.77 (s, 6H, 2 CO_2CH_3), 3.70 (s, 2H, $CH_2CO_2CH_3$), 3.51-3.34 (m, 4H, 2 $NCH_2CH_2CH_2CH_3$), 1.71-1.20 (m, 8H, 2 $NCH_2CH_2CH_2CH_3$ + 2 $NCH_2CH_2CH_2CH_3$), 0.98 (t, J = 7.3, 3H, $NCH_2CH_2CH_2CH_3$), 0.86 (t, J = 7.3, 3H, $NCH_2CH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 167.4, 143.3, 142.3, 136.4, 129.8, 127.4, 125.2, 124.6, 121.7, 64.2, 53.1, 48.3, 43.8, 39.6, 30.9, 29.7, 20.5, 13.9. GC-MS (EI, 70 eV): *m/z* = 401

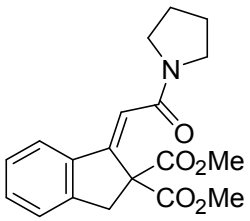
(absent) [M^+], 344 (12), 342 (29), 310 (41), 274 (18), 273 (100), 214 (21), 213 (97), 186 (26), 181 (14), 171 (16), 155 (27), 141 (12), 128 (65), 127 (26), 115 (10), 86 (11).



Dimethyl (*Z*)-1-Dibutylcarbamoylmethylene-indan-2,2-dicarboxylate (2i). Yield: 42.1 mg, starting from 477.6 mg of dimethyl 2-(2-trimethylsilanylethynyl-benzyl)-malonate **1'a** (7%). Yellow oil, $C_{23}H_{31}NO_5$ (401.22). IR (KBr): ν = 2957 (m), 2934 (m), 2873 (m), 1738 (s), 1633 (s), 1532 (m), 1460 (m), 1433 (m), 1378 (m), 1254 (m), 1170 (m), 1098 (m), 1063 (m), 785 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.60-7.52 (m, 1H, aromatic), 7.37-7.22 (m, 3H, aromatic), 6.87 (s, 1H, C*H*=C), 3.72 (s, 6H, 2 CO_2CH_3), 3.68 (s, 2H, $CH_2CO_2CH_3$), 3.42-3.31 (m, 4H, 2 $NCH_2CH_2CH_2CH_3$), 1.71-1.59 (m, 2H, $NCH_2CH_2CH_2CH_3$), 1.58-1.45 (m, 2H, $NCH_2CH_2CH_2CH_3$), 1.44-1.24 (m, 4H, 2 $NCH_2CH_2CH_2CH_3$), 0.99 (t, J = 7.3, 3H, $NCH_2CH_2CH_2CH_3$), 0.91 (t, J = 7.3, 3H, $NCH_2CH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 166.0, 143.2, 139.8, 130.4, 127.5, 125.3, 125.1, 121.1, 113.7, 63.1, 52.6, 48.3, 46.0, 43.5, 31.8, 30.2, 20.3, 13.9. GC-MS (EI, 70 eV): *m/z* = 401 (absent) [M^+], 342 (24), 310 (44), 274 (18), 273 (96), 254 (7), 214 (18), 213 (100), 186 (22), 181 (14), 171 (15), 155 (25), 141 (11), 128 (52), 127 (26), 115 (10), 86 (9).

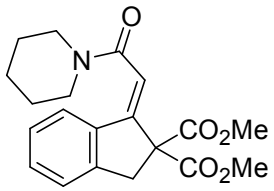


Dimethyl (*E*)-1-(2-Oxo-2-pyrrolidin-1-yl-ethylidene)-indan-2,2-dicarboxylate (2j). Yield: 206.0 mg, starting from 477.6 mg of dimethyl 2-(2-trimethylsilanylethynyl-benzyl)-malonate **1'a** (40%). Yellow oil, $C_{19}H_{21}NO_5$ (343.37). IR (KBr): ν = 2977 (m), 2954 (m), 2877 (m), 1737 (s), 1616 (s), 1435 (m), 1248 (m), 1172 (m), 1056 (m), 754 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.86 (d, J = 7.7, 1H, aromatic), 7.30-7.16 (m, 3H, aromatic), 6.42 (s, 1H, C*H*=C), 3.77 (s, 6H, 2 CO_2CH_3), 3.70 (s, 2H, $CH_2CO_2CH_3$), 3.65-3.57 (m, 2H, CH_2NCH_2 or CH_2NCH_2), 3.54-3.46 (m, 2H, CH_2NCH_2 or CH_2NCH_2), 1.99-1.83 (m, 4H, $CH_2CH_2NCH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 165.8, 143.6, 143.5, 136.3, 130.1, 127.5, 125.4, 124.6, 121.5, 67.1, 53.2, 47.1, 45.5, 39.5, 26.1, 24.5. GC-MS (EI, 70 eV): *m/z* = 343 (24) [M^+], 284 (24), 274 (15), 273 (79), 214 (18), 213 (100), 186 (15), 181 (14), 171 (13), 155 (21), 141 (9), 127 (28), 98 (5), 70 (16).

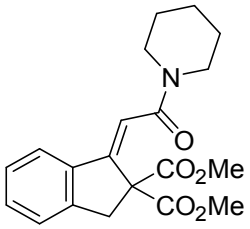


Dimethyl (*Z*)-1-(2-Oxo-2-pyrrolidin-1-yl-ethylidene)-indan-2,2-dicarboxylate (2j). Yield: 144.2 mg, starting from 477.6 mg of dimethyl 2-(2-trimethylsilanylethynyl-benzyl)-malonate **1'a** (28%). Yellow oil, $C_{19}H_{21}NO_5$ (343.37). IR (KBr): ν = 2956 (m), 2880 (m), 1738 (s), 1634 (s), 1483 (m), 1403 (m), 1266 (m), 1170 (m), 1066 (m), 764 (m), 700 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65-7.61 (m, 1H, aromatic), 7.38-7.24 (m, 3H, aromatic), 6.81 (s, 1H, C*H*=C), 3.74 (s, 6H, 2 CO_2CH_3), 3.68 (s,

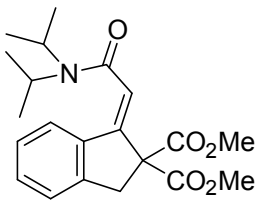
2H, C*H*$_2$CO$_2$CH$_3$), 3.57-3.47 (m, 4H, C*H*$_2$NCH$_2$ + CH$_2$NC*H*$_2$), 1.98-1.87 (m, 4H, C*H*$_2$CH$_2$NCH$_2$C*H*$_2$); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 170.1, 164.7, 163.4, 143.4, 139.5, 130.7, 127.5, 125.0, 121.4, 113.9, 67.0, 52.7, 46.9, 45.8, 43.5, 25.9, 24.5. GC-MS (EI, 70 eV): *m/z* = 343 (4) [M$^+$], 300 (14), 274 (14), 273 (77), 214 (16), 213 (100), 186 (15), 181 (13), 171 (12), 155 (20), 141 (10), 127 (30), 115 (11), 86 (11).



Dimethyl (*E*)-1-(2-Oxo-2-piperidin-1-yl-ethylidene)-indan-2,2-dicarboxylate (2k). Yield: 267.9 mg, starting from 477.6 mg of dimethyl 2-(2-trimethylsilanylethynyl-benzyl)-malonate **1'a** (50%). Yellow solid, m.p. = 104-105 °C, $C_{20}H_{23}NO_5$ (357.16). IR (KBr): *v* = 2925 (m), 2857 (m), 1736 (s), 1618 (s), 1426 (m), 1280 (m), 1152 (m), 1079 (m), 1024 (m), 953 (m), 850 (m), 785 (m), 763 (m) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.61 (d, *J* = 7.7, 1H, aromatic), 7.30-7.16 (m, 3H, aromatic), 6.41 (s, 1H, C*H*=C), 3.78 (s, 6H, 2 CO$_2$C*H*$_3$), 3.74-3.67 (m, 2H, C*H*$_2$NCH$_2$ or CH$_2$NC*H*$_2$), 3.70 (s, 2H, C*H*$_2$CO$_2$CH$_3$), 3.66-3.55 (m, 2H, C*H*$_2$NCH$_2$ or CH$_2$NC*H*$_2$), 1.71-1.57 (m, 4H, C*H*$_2$CH$_2$NCH$_2$CH$_2$ + CH$_2$CH$_2$NCH$_2$C*H*$_2$), 1.55-1.44 (m, 2H, C*H*$_2$CH$_2$CH$_2$N); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 170.5, 166.2, 143.3, 142.1, 136.4, 129.8, 127.5, 125.0, 124.7, 121.6, 53.1, 47.3, 39.6, 26.5, 25.7, 24.8. GC-MS (EI, 70 eV): *m/z* = 357 (absent) [M$^+$], 298 (15), 273 (63), 238 (19), 214 (21), 213 (100), 186 (24), 181 (16), 171 (16), 155 (30), 141 (13), 128 (15), 127 (39), 115 (13), 84 (58).



Dimethyl (*Z*)-1-(2-Oxo-2-piperidin-1-yl-ethylidene)-indan-2,2-dicarboxylate (2k). Yield: 80.4 mg, starting from 477.6 mg of dimethyl 2-(2-trimethylsilanylethynyl-benzyl)-malonate **1'a** (15%). Yellow solid, m.p. = 70-71 °C, $C_{20}H_{23}NO_5$ (357.16). IR (KBr): ν = 2937 (m), 2858 (m), 1738 (s), 1652 (s), 1431 (m), 1281 (m), 1134 (m), 1065 (m), 999 (m), 853 (m), 763 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.62-7.56 (m, 1H, aromatic), 7.37-7.23 (m, 3H, aromatic), 6.89 (s, 1H, C*H*=C), 3.74 (s, 6H, 2 CO_2CH_3), 3.69 (s, 2H, $CH_2CO_2CH_3$), 3.66-3.56 (m, 2H, CH_2NCH_2 or CH_2NCH_2), 3.42-3.33 (m, 2H, CH_2NCH_2 or CH_2NCH_2), 1.78-1.55 (m, 6H, $CH_2CH_2NCH_2CH_2$ + $CH_2CH_2NCH_2CH_2$ + $CH_2CH_2CH_2N$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 165.5, 163.7, 142.3, 139.6, 130.3, 127.4, 124.9, 121.2, 114.2, 52.8, 47.3, 41.9, 26.5, 25.4, 24.5. GC-MS (EI, 70 eV): *m/z* = 357 (absent) [M^+], 298 (22), 273 (50), 266 (12), 238 (18), 214 (20), 213 (100), 186 (25), 181 (14), 171 (15), 155 (28), 141 (12), 128 (15), 127 (35), 115 (12), 84 (60).



Dimethyl (*E*)-1-[(Diisopropylcarbamoyl)-methylene]-indan-2,2-dicarboxylate (2l). Yield: 257.7 mg, starting from 477.6 mg of dimethyl 2-(2-trimethylsilanylethynyl-benzyl)-malonate **1'a** (46%). Yellow solid, m.p. = 105-107°C, $C_{21}H_{27}NO_5$ (373.44). IR (KBr): ν 2970 (m), 1737 (s), 1623 (s), 1438 (m), 1371 (m), 1324 (m), 1255 (m), 1170 (m), 1098 (m), 1045 (m), 757 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, J = 7.7, 1H,

aromatic), 7.34-7.13 (m, 3H, aromatic), 6.40 (s br, 1H, C*H*=C), 4.46 (hept, *J* = 6.7, 1H, CH_3CHCH_3), 3.81-3.58 (m, 3H, $CH_2CO_2CH_3$ + CH_3NCHCH_3), 3.77 (s, 6H, 2 CO_2CH_3), 1.55 (d, *J* = 6.7, 6H, CH_3NCHCH_3), 1.15 (d, *J* = 6.7, 6H, CH_3CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 167.1, 143.0, 140.7, 136.5, 130.6, 127.2, 124.73, 124.68, 123.2, 53.1, 50.0, 45.7, 39.5, 21.5, 21.1, 20.5. GC-MS (EI, 70 eV): *m/z* = 373 (absent) [M^+], 274 (17), 273 (95), 214 (24), 213 (100), 207 (10), 186 (27), 181 (14), 171 (16), 155 (26), 141 (12), 128 (13), 127 (32), 115 (14), 100 (76), 91 (11), 86 (10), 84 (14).

Appendix

1. List of publications.

- "Versatile Synthesis of Isoquinolines and Isochromenes by Pd-Catalyzed Oxidative Carbonylation of (2-Alkynyl)benzylideneamine Derivatives." Gabriele, B.; Veltri, L.; Maltese, V.; Spina, R.; Mancuso, R.; Salerno, G.; *Eur. J. Org. Chem.*, **2011**, 5626–5635.
- "Synthesis of Furan-3-carboxylic and 4-Methylene-4,5-dihydrofuran-3-carboxylic Esters by Direct Palladium Iodide-Catalyzed Oxidative Carbonylation of 3-yne-1,2-diol derivatives." Gabriele, B.; Mancuso, R.; Maltese, V.; Veltri, L.; Salerno, G.; *J. Org. Chem.*, **2012**, 77 (19), 8657-8668.
- "Synthesis of Substituted Thiophenes by Palladium-Catalyzed Heterocyclodehydration of 1-Mercapto-3-yn-2-ols in Conventional and Non-conventional Solvents." Gabriele, B.; Mancuso, R.; Veltri, L.; Maltese, V.; Salerno, G.; *J. Org. Chem.*, **2012**, 77 (21), 9905-9909

2. Participation in PhD Schools and Conferences.

- E-WISPOC 2011, European Winter School on Physical Organic Chemistry, Material Science, Bressanone, January 30-February 4 2011.
- Nanostructured Hybrid Materials for Energy Conversion and Storage, Ostuni (Br), 5-10 June 2011.
- XXIV Congresso Nazionale della "Società Chimica Italiana", Lecce, 11-16 Settembre, 2011.

- E-WISPOC 2012, European Winter School on Physical Organic Chemistry, Catalysis, Bressanone, January 29-February 3 2012.
- XIII RSC-SCI Joint Meeting on Heterocyclic Chemistry 2012, Catania, 10-12 May 2012.

3. Scientific contribution in PhD Schools and Conferences.

- Maltese V. and Gabriele B. and Veltri L. and Mancuso R. and Plastina P. and Salerno G., "A Simple and Convenient Approach to Functionalized Thiophenes by Heterocyclodehydration of 1-Mercapto-3-yn-2ol Derivatives". "Atti del convegno European Winter School on Physical Organic Chemistry (e-WISPOC 2012)", Bressanone, January 29th-Februar, 2012, 2012, pp. 476-476.
- Mancuso R. and Gabriele B. and Maltese V. and Veltri L. and Salerno G., "Palladium-catalyzed oxidative aminocarbonylation-carbocyclization of 2-(2-ethynylbenzyl)malonates and related substrates: a novel synthetic approach to functionalized 1-[2-(dialkylamino)-2-oxoethylidene]-1,3-dihydroindenes". "Atti del convegno X Congresso del Gruppo Interdivisionale di Chimica Organometallica", Padova, 5-8 Giugno, 2012, 2012, pp. 48-48.
- Gabriele B. and Mancuso R. and Maltese V. and Salerno G., "Synthesis of furan-3-carboxylic and 4methylene-4,5-dihydrofuran-3-carboxylic esters by direct palladium iodide-catalyzed oxidative carbonylation of 3-yne-1,2-diol derivatives". "Atti del convegno XIII RSC-SCI Joint Meeting on Heterocyclic Chemistry", Catania, May 10-12, 2012, 2012, 2012, pp. 60-60.
- Mancuso R. and Gabriele B. and Veltri L. and Maltese V. and Salerno G., "Novel Heterocyclizations Leading to Thiophene and Benzothiophene Derivatives". "Atti del convegno XXIV Congresso

Nazionale della Società Chimica Italiana", Lecce, 11-16 Settembre 2011, 2011, 2011, pp. 948-948.

- Gabriele B.and Veltri L. and Maltese V. and Spina R. and Mancuso R. and Salerno G., "A New Approach to Functionalized Isoquinoline and Isochromene by Carbonylation of(2-Alkynyl)benzylideneamine Derivatives". "Atti del convegno XXIV Congresso Nazionale della Società Chimica Italiana", Lecce, 11-16 Settembre, 2011, pp. 952-952.
- Mancuso R. and Gabriele B. and Maltese V. and Veltri L. and Salerno G., "Nuove sintesi di derivati tiofenici mediante processi di eterociclizzazione". "Atti del convegno Convegno congiunto delle Sezioni SCI Calabria e Sicilia 2011", Messina, 1-2 Dicembre, 2011.

Appendix

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