

Synthesis of 2-alkenylidene-3-oxoindolines: cascade reactions of 4*H*-furo [3,2-*b*]indoles with diazoacetates catalyzed by a Cu(I) macrocyclic pyridine-containing ligand (PcL) complex

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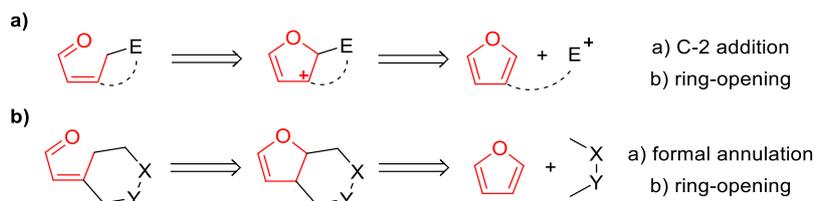
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Abstract: A highly reactive and selective catalytic system comprising Cu(I) and a macrocyclic pyridine-containing ligand (Pc-L) for the synthesis of 2-(penta-2,4-dien-1-ylidene) 3-oxoindolines from 4*H*-furo[3,2-*b*]indoles and diazoalkane is reported herein. The reaction sequence involves the initial formation of a copper-carbene by Cu(I)-catalyzed decomposition of a diazoalkane followed by copper-carbene to furoindole addition and successive furan ring-opening affording the final products. The reaction proved to be quite general, tolerating EWG as well as EDG substituents on the indole scaffold as well as acceptor or donor/acceptor carbene precursors and products were obtained in good to excellent yields. The proposed methodology allows to overcome some selectivity issues encountered performing similar transformations in the presence of gold(I)-carbenes. Interestingly, two of the 2-alkenylidene-3-oxoindolines are characterized by a second-order nonlinear optical response higher than that of Disperse Red One

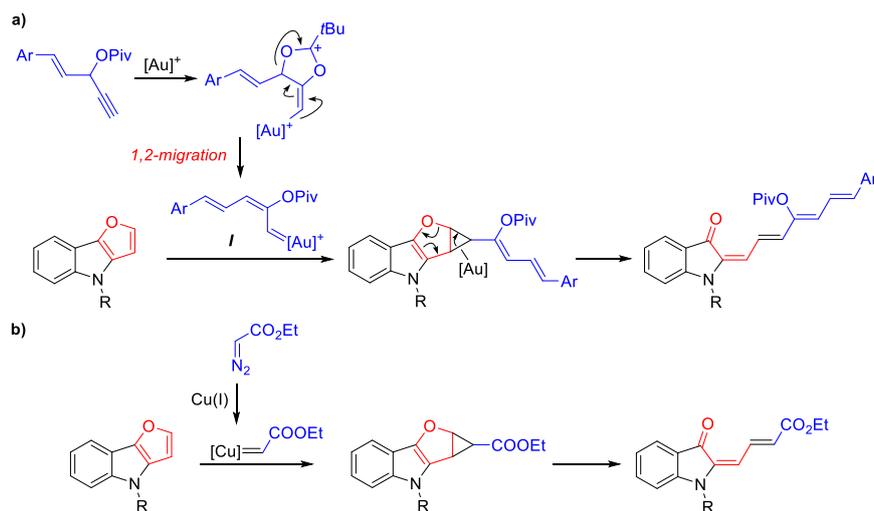
Introduction

Ring opening reactions of furans are a class of organic transformations well documented in the literature.^[1] Mostly they occur by intra- or intermolecular addition of electrophiles at C2, followed by a ring-opening event,^[2] scheme 1a, or involve the C2-C3 bond in annulation reactions with suitable partners followed by ring rearrangement,^[3] scheme 1b.



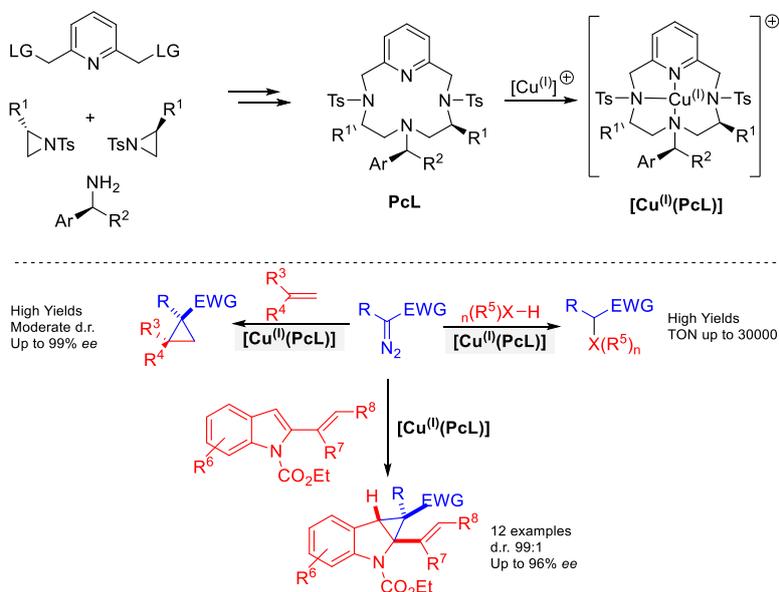
Scheme 1. Ring opening reactions of furans.

Recently, we extended this kind of reactivity to 4*H*-furo[3,2-*b*]indoles, wherein the furan ring is embedded in a tricyclic framework.^[4] For example,^[4b] scheme 2a, *E,E,Z,E*-(hepta-2,4,6-trien-1-ylidene)-3-oxoindolines were synthesized from 4*H*-furo[3,2-*b*]indoles via a cascade sequence involving gold-carbene complexes *I* as reactive intermediates. The reaction involves initial formation of a gold-carbene species via cationic gold(I) catalyzed 1,2-acyloxy migration of properly substituted propargyl esters followed by gold-carbene to furoindole addition and successive furan ring-opening affording the final products.



Scheme 2. Reactivity of 4H-furo[3,2-b]indoles with: a) gold-carbene (ref [4b]) and b) copper-carbene complexes (this work).

However, satisfactory yields could be obtained only working with α -stiryl substituted propargyl esters whereas alkyl or aryl substituted derivatives gave rise to the corresponding alkyliden-3-oxindolines in poor yields. Thus, in order to extend the scope of these transformations we decided to test copper-carbene complexes generated in situ from diazoalkanes under copper(I) catalysis for the synthesis of 2-(penta-2,4-dien-1-ylidene) 3-oxindolines, scheme 2b. In this field, we have recently disclosed the coordination chemistry of pyridine containing macrocyclic cyclen-type ligands (PcL)^[5] and the catalytic activity of their copper(I) complexes.^[6] Given the relevance of reactions involving metal catalyzed carbene transfer starting from diazoalkanes in organic synthesis^[7], a series of [Cu^(I)(PcL)] complexes was evaluated in alkene cyclopropanation^[8] and X-H bond insertion reactions.^[9] More recently, we also demonstrated the ability of those [Cu^(I)(PcL)] complexes to efficiently catalyze the reaction between 2-vinylindoles and diazoesters to yield a series of 2-vinylcyclopropa[b]indolines with excellent levels of regio- and stereocontrol.^[10] The synthetic path used to obtain the target macrocyclic complexes, including chiral non racemic ones, is flexible and high yielding, starting from cheap materials, scheme 3.



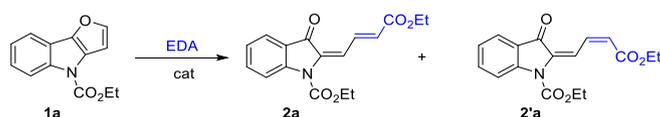
Scheme 3. Synthesis of pyridine-containing ligands (PcL) and their applications in copper(I)-catalyzed cyclopropanations with diazo compounds (Ref [8-10]).

Results and Discussion

At the outset, we tested the reactivity of furoindole **1a** with EDA (EDA = ethyldiazoacetate), by screening several metal catalysts, Table 1. In the presence of classical rhodium(II) octanoate dimer complex (Rh₂(Oct)₄, 2.5 mol%) a well-established precursor for the Rh(II)-carbenoid mediated cyclopropanation of alkenes in the presence of diazocarbonyl compounds,^[11] slow addition of EDA to a

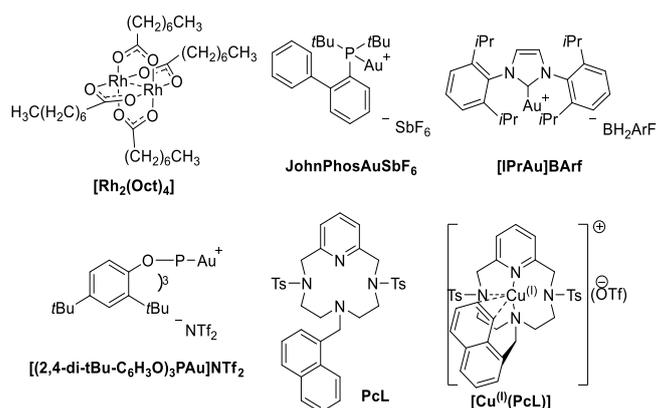
dichloromethane solution of furoindole **1a** resulted in the isolation in good yield of a separable 2.5:1 mixture of *E/Z* isomeric 2-(penta-2,4-dien-1-ylidene) 3-oxoindolines **2a** and **2'a** (entry 1, Table 1). The structure of the isolated compounds was confirmed by analytical (HRMS) and spectral data (1D NMR). Lowering the catalyst loading to 1.0 mol% resulted in a slight decrease of the yields (entry 2, Table 1). We next run the model reaction, in the presence of 5 mol% of preformed cationic JohnPhosAuSbF₆ catalyst,^[12] but no traces of products were detected and only starting furoindole **1a** was quantitatively recovered (entry 3, Table 1). Other cationic gold(I) catalyst, namely chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I), [IPrAu]BARf, and [(2,4-di-*t*Bu-C₆H₃O)₃PAu]NTf₂ were also ineffective, even in refluxing DCM (Table 1 entries 4 and 5).

Table 1. Optimization of the reaction conditions.^[a]



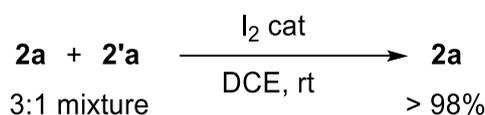
Entry	Catalyst	Solvent (M)	Equiv EDA	T (°C)	t (h)	2a ^[b] (%)	2'a ^[b] (%)
1	Rh ₂ (Oct) ₄ 2.5 mol%	DCM 0.05	2 ^[c]	rt	1.5	49	20
2	Rh ₂ (Oct) ₄ 1.0 mol%	DCM 0.05	2 ^[c]	rt	1.5	41	17
3	JohnPhosAuSbF ₆ 5 mol%	DCM 0.05	2 ^[c]	rt	1.5	/ ^[d]	/
4	IPrAuCl 5 mol% NaBARf 5 mol%	DCM 0.1	2 ^[e]	rt(2h) 40 (3h)	5	/ ^[d]	/
5	(ArO) ₃ PAuNTf ₂ ^[f] 5 mol%	DCM 0.1	2 ^[e]	rt(2h) 40 (3h)	5	/ ^[d]	/
6	Cu(OTf) ₂ 15 mol% Ph-NHNH ₂ 15 mol%	DCM 0.05	2 ^[c]	rt	1.5	29	12
7	Cu(OTf) ₂ 8 mol%	DCE 0.07	1.5 ^[g]	rt	2	19	6
8	[Cu(OTf) ₂] ₂ ·C ₆ H ₆ (5 mol%) PcL (10 mol%)	DCE 0.07	2.5 ^[g]	rt	1	75	12
9	[Cu ^(I) (PcL)] (8 mol%)	DCE 0.07	1 ^[g]	rt	1	30	6
10	[Cu ^(I) (PcL)] (8 mol%)	DCE 0.07	1.5 ^[h]	rt	2	74	25

[a] All reactions were carried out using **1a** (0.2 mmol) and EDA (0.2-0.5 mmol) in the stated solvent (0.1-0.05 M) in the presence of 4 Å MS. [b] Isolated yield. [c] EDA added with syringe pump in 1h in 1 ml of solvent. [d] **1a** and EDA recovered unreacted at the end of the reactions. [e] EDA added manually dropwise. [f] Ar = (2,4-di-*t*Bu-C₆H₃). [g] EDA added with syringe pump in 1h in 2 ml of solvent. [h] EDA added with syringe pump in 2h in 2 ml of solvent.



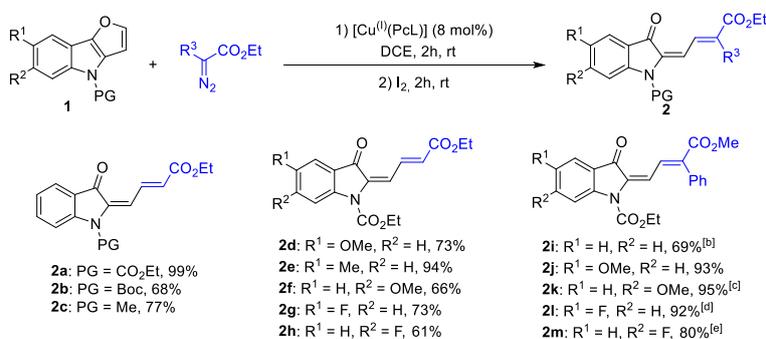
Instead, using copper(II) triflate without the presence of any reducing agent, the yield was lower (entry 7).

To our pleasure, when we used the copper(I)/PcL complex formed in situ,^[8b] the yield of the desired oxoindolines **2** was increased to 87% with a diastereoisomeric *E/Z* ratio of 6.25 to 1 (entry 8, Table 1). The reaction conditions could be further optimized by using the isolated copper complex by slow addition of a 1.5 fold molar ratio of the starting EDA. Under those conditions, an almost quantitative yield of the desired products was obtained, in a d.r. of 3 (entry 10, Table 1). As already reported by us in the case of 3-oxo-2-(hepta-2,4,6-trien-1-ylidene)indolines,^[4b] it is possible to obtain **2a** as a single isomer just treating the solution after the complete addition of EDA with a catalytic amount of iodine. The conversion of a mixture of **2a/2a'** stereoisomers to the **2a** isomer was completed (>98%) in 2h, scheme 4.



Scheme 4. Isomerization of a **2a/2'a** mixture to pure **2a**.

Once having optimized the reaction conditions, we next explored the scope of the reaction. All the reactions were performed under the conditions reported in the footnote of Table 1 (entry 10). Compounds **2a-m** were isolated and characterized after chromatographic purification, once the reaction mixture was treated with iodine in order to fully convert the *Z* isomer into the more stable *E* compound, scheme 5.



Reaction condition: **1** (0.2 mmol) and diazo compound (0.3 mmol) in DCE (0.07 M), *E/Z* > 98:2. [b] *E/Z* = 95:5. [c] *E/Z* 88:12. [d] *E/Z* = 85:15. [e] *E/Z* = 94:6.

Scheme 5. Reaction scope.

We firstly performed the reaction between **1a** and EDA obtaining **2a** in almost quantitative yield as a single isomer. Then a study of the influence of the protecting group at the nitrogen position on the yield was undertaken. In particular, we observed that a bulkier electron-withdrawing group such as N-Boc led to the formation of the corresponding product **2b** in lower yield (68%). On the other hand, the substitution of the starting furoindole with an electron-donating N-methyl group was tolerated and compound **2c** was obtained in 77% yield.

Next, we investigated the influence of the substitution pattern of the starting furoindole. The introduction of a methyl substituent at C7 of the indole core didn't alter the reaction outcome and **2e** was obtained in very good yield (94%), while the presence of the more coordinating methoxy group at the same position led to a decrease of the isolated yield for **2d** (73%). The same effect on the yield was observed also when the methoxy group was in C8 position, leading to the desired product **2f** in 66% yield. A drop in the isolated yield of the product was observed also when electron-withdrawing groups were present on the indole core, either at C7 or at C8, and the corresponding product **2g** and **2h** were obtained in 73% and 61% respectively. In both cases, the substituent in C8 is less tolerated than in C7 position, regardless the nature of substituent.

Finally, we tested the reactivity of a donor/acceptor carbenoid precursor, namely methyl phenyl diazoacetate, which, due to its superior stability, is well known to be far less susceptible to dimer formation.^[14] Good to excellent yields were observed with all tested furoindoles. Thus, the model furoindole **1a**, reacting with methyl phenyldiazoacetate, gave rise to the single isomer **2i** in good 69% yield. Whereas, excellent yields were obtained for all C7 and C8 substituted furoindoles. In these cases, significant differences on the outcome of the reaction were not noticed changing the position of the methoxy group and the corresponding product **2j** and **2k** were obtained in 93% and 95% yield, respectively. For the fluorine derivatives the same trend reported for EDA was observed with a lower yield for compound **2m** than for **2l** (80% and 92% yield respectively). It is worth to note that for all methoxy and fluorine derivative products the yield was higher than the corresponding compound obtained using EDA, showing enhanced selectivity of methyl phenyldiazoacetate.

The peculiar structure of the target 2-(penta-2,4-dien-1-ylidene) 3-oxoindolines **2**, in which a quite long π -conjugated system with enforced coplanarity is accompanied by the presence of both electron donor and electron acceptor groups, prompted us to investigate their second-order nonlinear optical (NLO) properties. It is known that chromophores with second-order NLO properties are important as molecular building block materials for the field of molecular photonics, in particular for optical communications, optical data processing and electro-optical devices.^[15] In order to have a second-order NLO response, a molecule must not be centrosymmetric. *Push-pull* 1D dipolar molecules, in which an electron donor group (EDG) is separated from an electron acceptor (EWG) group by means of a π -conjugated polarizable spacer, are characterized by good quadratic hyperpolarizabilities, β . As a general rule, the use of strong electron donors and acceptors and the incorporation of a bridge with a large conjugation length lead to a strong second-order NLO response.^[15,16]

Thus, we studied the NLO properties in solution of a selection of the prepared 2-(penta-2,4-dien-1-ylidene) 3-oxoindolines **2** by means of the EFISH (Electric Field Induced Second Harmonic generation) technique, which affords the product $\mu\beta$ where μ is the ground state dipole moment.^[17] UV-visible absorption spectra and $\mu\beta$ measurements were carried out on compounds **2a**, **2c**, **2d**, **2e**, **2g**, **2h**, **2l** and **2m** in chloroform solution. Results are summarized in Table 2. The main absorption maxima are reported in Table 2. In Figure 1 a relevant red shift of the band at lower energy is observed going from **2a** to **2c**, by changing the substituent on the nitrogen atom from an ethyl-ester to a methyl group. Comparing the spectra of **2a**, **2g** and **2h**, it is possible to see the effect of a fluorine atom as substituent on the phenyl ring: in both **2g** and **2h**, with the fluorine atom, the epsilon values increase.

Figure 1b shows the effect of MeO compared to Me (**2d** and **2e**): with the Me substituent, the epsilon values increase. The introduction of a phenyl substituent on the terminal double bond causes a red-shift of the band at lower energy (compare **2g** with **2l** and **2h** with **2m**).

Table 2. Main absorption bands in the UV-visible spectra and second-order NLO response.

Compound	Absorption ^[a] $\lambda_{\text{max}}/\text{nm}$ ($\epsilon/\text{M}^{-1} \text{cm}^{-1}$)	$\mu\beta$ ($\times 10^{-48}$ esu) ^[b]
2a	246(14898), 283(13033), 317(8362), 396(2993)	230
2c	247(5379), 308(19024), 316(1849), 509(3929)	190
2d	287(18279), 317(7274), 330(6598), 426(2793)	410
2e	246(18388), 310(10333), 322(18326), 417(5029)	400
2g	284(14646), 295(15141), 320sh (11436), 413(3559)	480
2h	250(19419), 289(25362), 315 sh(16742), 330sh(10016), 393(5291)	540
2l	289(15846), 343(11980), 416sh(8861), 432(9516)	640
2m	252(2218), 289(26299), 332(19758), 409(17182)	680

[a] In CHCl_3 ; UV-vis spectra recorded in toluene are almost identical to the ones recorded in chloroform solution. [b] In CHCl_3 10^{-3} M working at $1.907 \mu\text{m}$; estimated uncertainty in EFISH measurements is $\pm 20\%$.

As shown in Table 2, all molecules are characterized by a fair to good second-order NLO response.

A clear dependence from the substituents on the core of the investigated compounds on the $\mu\beta$ values is present. Comparing compounds **2a** and **2d**, it is evident that it is better to have a donor group (MeO) on the phenyl ring ($\mu\beta$ goes from 230×10^{-48} to 410×10^{-48} esu). However, even a slightly donor group such as Me (**2e**) gives a good response (400×10^{-48} esu). As previously observed,^[18] substitution of methyl by fluorine has a significant positive effect on the NLO properties (for **2g**, $\mu\beta$ is 480×10^{-48} esu). Also the position of the fluorine substituent has an influence: going from **2g** to **2h**, $\mu\beta$ goes from 480×10^{-48} to 540×10^{-48} esu. As expected,^[15,16] a larger π -delocalization, reached by adding a phenyl group on the terminal double bond, leads to a good increase of the second-order NLO response: $\mu\beta$ is 640×10^{-48} and 680×10^{-48} esu for **2l** and **2m**, respectively. The best second-order NLO response is obtained with the two compounds characterized by the most intense bands at low energy in the UV-visible region (Table 2), in agreement with the two-level model.^[19] Finally, it is worth pointing out that the $\mu\beta$ values of **2l** and **2m** are of particular interest from an application point of view, being superior to the value reached by Disperse Red One (*trans*-4,4'- $\text{O}_2\text{NC}_6\text{H}_4\text{N} = \text{NC}_6\text{H}_4\text{NE}(\text{CH}_2\text{CH}_2\text{OH})$), 500×10^{-48} esu) which has been used in electrooptic polymeric poled films.^[20] Finally, a mechanism could be easily underlined looking at the literature on both the reactivity of copper carbene complexes^[21] and on the electrophiles-driven furan ring opening reactions,^[4a] scheme 6.

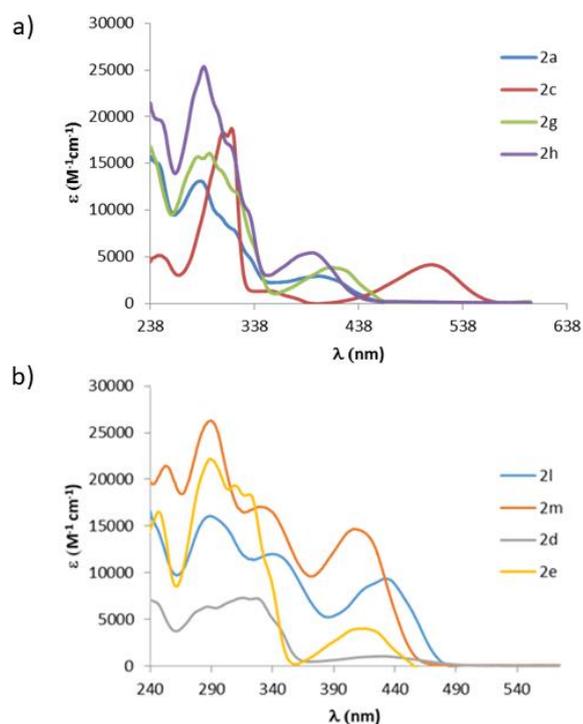
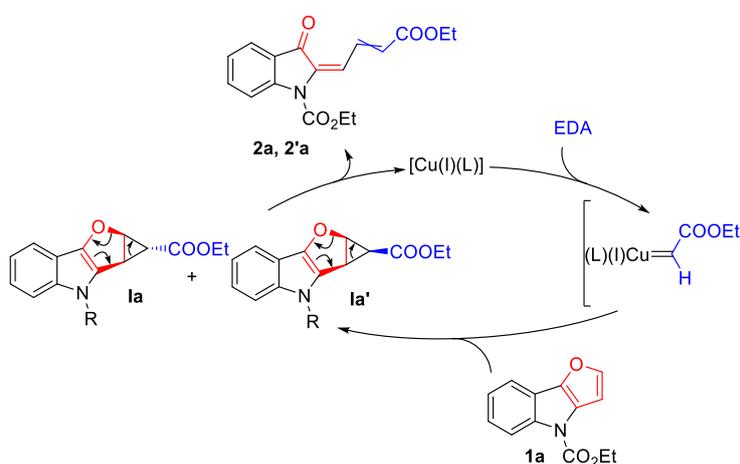


Figure 1. Absorption spectra in chloroform solution of compounds a) **2a**, **2c**, **2g**, **2h** and b) **2l**, **2m**, **2d**, **2e**.

Activation of the diazoacetate by means of cationic copper(I) catalyst leads to the formation of the copper-carbene complex that reacts with the nucleophilic C2-C3 furan carbons of **1a** to give the corresponding cyclopropanated species **la/la'**, which evolves via furan ring-opening to final products **2a/2'a**.



Scheme 6. Proposed reaction mechanism.

Conclusion

In summary, we have demonstrated that several differently substituted 2-alkenylidene-3-oxindolines can be efficiently and selectively synthesized by using a catalytic system comprising Cu(I) and a pyridine-containing ligand (Pc-L). The obtained results represent a further improvement and expansion of the synthetic concept reported in our previous research^[4] for the gold(I)catalyzed cascade reaction yielding to highly conjugated oxindolines. In particular, the reported methodology allows for the installation of a double conjugated system at the C2 carbon atom of the oxindoline which resulted unfeasible with gold(I)carbenes. The catalytic system used rely on the use of an economic metal source coordinated to an easy to assemble macrocyclic ligand under extremely mild reaction conditions. Substitution of the starting furoindole is well tolerated and, especially when using a donor/acceptor carbenoid precursor, excellent yields are obtained regardless if an electron-donating (OMe) or an electron-withdrawing (F) atom are present.

Interestingly, two of our 2-(penta-2,4-dien-1-ylidene) 3-oxindolines are characterized by a second-order nonlinear optical response higher than that of Disperse Red One which found application in electrooptic polymeric poled films.

Experimental Section

General procedure for the synthesis of compounds 2

To a N₂-flushed solution of 4*H*-furo[3,2-*b*]indole **1** (0.2 mmol, 1 equiv), [Cu^{II}(PcL)] (8 mol%) and 4 Å molecular sieves (200 mg) in anhydrous DCE (1 mL), a solution of diazo compound (1.5 equiv.) in anhydrous DCE (2 mL) was added dropwise in 2 h with a syringe pump at room temperature. Then the reaction mixture was warmed to room temperature and further stirred for 2 h in the presence of one crystal of I₂. Then, the solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography to yield the desired product **2**.

EFISH measurements

EFISH measurements were carried out by using a non-resonant incident wavelength of 1.907 μm, achieved by Raman-shifting the fundamental 1.064 μm wavelength given by a Q-switched, mode-locked Nd³⁺:YAG laser (from Atalaser). All compounds were dissolved in chloroform at a concentration of 10⁻³ M. The reported μβ_{1,907} values are the mean values of 16 measurements performed on the same sample.

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Keywords: Indoles • Copper • Carbenes • Macrocyclic ligands • Nonlinear optics

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