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Synthetic Applications of the Nickel-Catalyzed Cyclization of Alkynes Combined with Addition Reactions in a Domino Process

Muriel Durandetti,* Lucie Hardou, Rudy Lhermet, Mathieu Rouen, and Jacques Maddaluno*[a]

Abstract: Carbonickelations of alkynes and functionalization of the resulting vinylnickel moiety have been performed efficiently in a nickel-catalyzed domino cyclization–condensation process. This reaction, which does not require the preparation of any other organometallic reagent, proceeds only by *exo*-dig cyclization. This convenient and mild method constitutes a one-pot synthesis of substituted dihydrobenzofurans, chromans, isochromans, indoles, or indanes. Theses valuable products are generally obtained in good yields and high stereoselectivity. They are shown to be useful synthons for rapid access to functionalized polycyclic skeletons.

Keywords: alkynes · carbonickelation · domino reactions · nickel · vinylnickel

Introduction

For several decades, nickel catalysis has been successfully applied in a number of industrial processes, particularly in the oligomerization of alkenes and alkynes, as well as carbonylation reactions.[1] However, nickel chemistry has found sporadic use among organic chemists, relative to palladium chemistry. Nickel-catalyzed couplings originated with the reaction of Grignard reagents with vinyl and aryl halides, as reported by Kumada et al.[2] and Corriu and Masse.[3] Since these pioneer works, various organometallic reagents, such as organomagnesium,[4] organozinc,[5] organoborane,[6] or organotin[7] compounds, have also been employed in nickel-catalyzed couplings. The complementary role of nickel salts in the activation of organometallic compounds is clear in the Nozaki–Hiyama–Kishi (NHK) reaction, in which the reactive vinylchromium reagents are obtained by transmetalation of the corresponding vinylnickel precursors,[8] and also in the carbozincation of aryl-substituted alkynes.[9]

A survey of recent literature[10] shows that nickel is becoming increasingly popular in the organic chemistry community. This new "nickel rush" has probably been triggered by the development of alternatives to catalytic [Ni(cod)$_2$] (cod = 1,5-cyclooctadiene), which is relatively difficult to handle, or to less-reactive nickel–phosphine complex precatalysts. For example, nucleophilic N-heterocyclic carbenes have attracted attention as possible ligands for Ni^0, recently demonstrated by Montgomery in the reductive coupling of aldehydes and alkynes,[11a–c] or in the cross-coupling of aryl bromides with organomanganese reagents.[11d] Despite these advances, cross-coupling reactions that involve nickel still rely on the preparation of an organometallic reagent on the one hand and the addition of nickel salts on the other. Therefore, the development of direct procedures that allow C–C bond formation, yet avoid a preliminary preparation of sensitive organometallic species, remains of great interest, especially when functionalized precursors are at stake. A few years ago, we developed electrochemical cross-coupling reactions based on the sacrificial anode process in the presence of catalytic amount of [NiBr$_2$bipy] (bipy = 2,2'-bipyridyl), which is reduced in situ to active Ni^0.[12] Although these methods lead to good yields of heterocoupling product, electrochemical syntheses lie outside the scope of standard organic protocols and are rarely used on greater than laboratory scale. Thus, a conventional chemical route is often preferred. Our group, and others, have developed novel chemical processes to avoid an electrochemical step or preliminary formation of organometallic reagents through a direct activation of organic halides. The cross-coupling occurs in the presence of a complex of Ni^0 generated in situ by a metal reducing agent. For example, an intermolecular sequence catalyzed solely by nickel was recently brought to the fore by Cheng et al., who showed that arylnickels add efficiently to triple bonds[13a–b] to afford functionalized quinolines and isoquinolines.[13c–e] Also, a nickel-catalyzed cross-coupling of aryl halides with alkyl halides has been developed that does not require the preparation of any other organometallic compounds.[14] We have described a tandem sequence that relies on: 1) intramolecular carbonickelation of alkynes to give nucleophilic vinylnickel reagents; 2) inter-

[a] Dr. M. Durandetti, Dr. L. Hardou, R. Lhermet, M. Rouen, Dr. J. Maddaluno
Laboratoire des Fonctions Azotées & Oxygénées Complexes de l'IRCOF
CNRS UMR 6014 & FR 3038
Université de Rouen et INSA de Rouen
76821 Mont St Aignan Cedex (France)
Fax: (+33) 235-522-971
E-mail: muriel.durandetti@univ-rouen.fr
jmaddalu@crihan.fr

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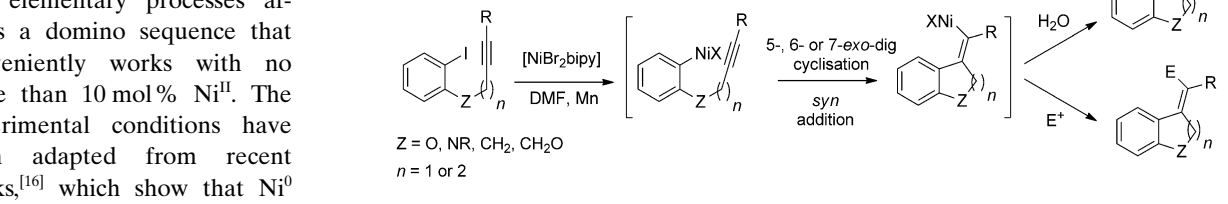
molecular trapping of these nickel intermediates by various electrophiles. This nickel-catalyzed reaction, which does not require the preparation of any other organometallic reagent, provides a convenient and mild method for the one-pot synthesis of substituted benzofurans and chromans.[15] Furthermore, the combination of these two elementary processes affords a domino sequence that conveniently works with no more than 10 mol% Ni^{II}. The experimental conditions have been adapted from recent works,[16] which show that Ni^0 can be easily engendered by reduction of [$NiBr_2$bipy] by Mn^0, employed as a finely ground metallic powder. Under these conditions, no other organometallic reagent has to be employed in conjunction with the nickel catalysis. Good overall yields and selectivities were returned in most cases. The mild conditions under which this sequence proceeds made us confident for its extension to other important targets, for example, indoles, benzothiophenes, or carbocycles, such as indanes.

Results and Discussion

Very little is known about the "pure" carbonickelation of triple bonds; to our knowledge, the recent papers by Cheng[13] and ourselves[15] are the only reports in the field. In contrast, nucleophilic organolithium entities are prone to undergo addition to C≡C triple bonds.[17] Hence, we have described a method that provides highly functionalized heterocycles by intramolecular carbolithiation of an acetylenic triple bond. This efficient and stereocontroled reaction, which most likely proceeds through a carbolithiation–elimination sequence, transforms phenyl propargyl ethers into 3-vinylbenzofurans, furopyridines, and indoles (Scheme 1).[18]

However, an acetal moiety on the propargylic chain was shown to be essential for the cyclization to occur. For substrates bearing a homopropargylic chain, another restriction was that 6-*exo*-dig cyclizations were impossible. To evade these limitations, we developed a new procedure based on the carbonickelation of similar alkynes.

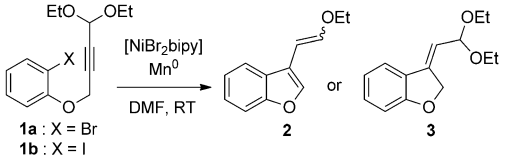
Here we discuss the details and applications of Ni^0-catalyzed *syn* intramolecular carbonickelation of the triple bond of iodoaryl propargylic compounds to afford nucleophilic vinylnickel reagents, which can be trapped, in a tandem process, by various electrophiles introduced at the onset of the reaction (Scheme 2).



Scheme 1. Anionic heterocyclization of propargylic acetal in benzofuran.

Scheme 2. Heterocyclization by carbonickelation.

Practicability and optimization of the process: Our first experiments were run with bromoaryl **1a**, a substrate easily prepared by methodology directly inspired from our previous paper concerned with carbolithiation.[18a] Following a protocol optimized for the arylnickel reagent synthesis, we exposed **1a** to a mixture of [$NiBr_2$bipy] (1 equiv), finely ground manganese (2 equiv), and trace amounts of trifluoroacetic acid in DMF at room temperature. Disappointingly, the only new product recovered was *o*-bromophenol. This suggested that the Ni^0 formed in situ was probably complexed by the triple bond and underwent a competitive oxidative addition into the propargyl C–O bond, similar to π-allyl-complex chemistry, and described previously by Olivero and Dunach.[19] To favor oxidative addition into the aryl–halogen bond, we applied the same conditions to iodoaryl **1b**. This time, the heterocyclization–rearomatization–elimination product **2** (Scheme 3) was identified after

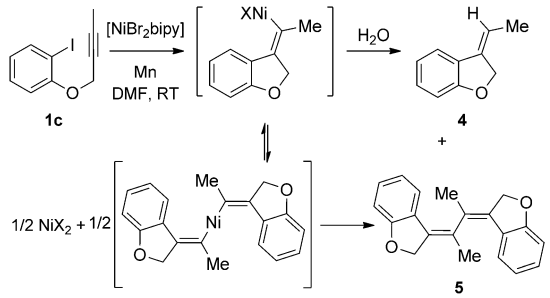


Scheme 3. Carbonickelation of propargylic ether **1**.

30 min and a mild acidic workup (50% yield, $Z/E = 50:50$). Thus, a 5-*exo-dig* ring closure, followed by elimination of ethoxide comparable to that observed with aryllithiums, was the only process observed. The acidic workup was the most likely origin of the elimination, so we repeated the reaction and ran the final hydrolysis under neutral conditions. The expected 5-*exo-dig* cyclization product **3** was obtained quantitatively after 30 min, as a single isomer.[20] The ^{1}H NMR spectra of the crude product recorded in $CDCl_3$ and C_6D_6, as well as a 2D NOESY experiment, showed that this isomer exhibits a *Z* configuration, a result of *syn* addition of the arylnickel intermediate to the triple bond. Therefore,

lithium and nickel appear to be very complementary metals, and provide the *E*- or *Z*-olefin, respectively.

The scope of this cyclization was next extended to other aryl propargylic ethers. Because the carbolithiation required a propargylic acetal moiety, we wondered if the carbonickelation could remove this restriction. We prepared butynol-derived ether **1c** and submitted it to the carbonickelation procedure (Scheme 4). The temperature and the amount of ligand were varied and the results are reported in Table 1.



Scheme 4. Carbonickelation of compound **1c**.

Thus, [$NiBr_2$bipy] (1 equiv) was added to aryl halide **1c** and manganese metal in DMF. After 30 min, no starting material remained and we isolated the expected dihydrobenzofuran **4** as a single isomer but in moderate yield (46%, $Z/E = 100:0$, Table 1, entry 1). Again, a *syn* carbonickelation occurs after oxidative addition of the in situ generated Ni^0. This demonstrates that the acetal moiety is not necessary to the nickel-catalyzed process.

Table 1. Optimization of the carbonickelation reaction of aryl iodide **1c** catalyzed by [$NiBr_2$bipy].[a]

Entry	Extra 2,2′-bipy	**4** [%][b]	**5** [%][b]
1	none added	60 (46)	40 (36)
2[c]	none added	50	50
3	+1 mmol	0[d]	0
4	+0.3 mmol	80 (65)	20 (20)
5	no [$NiBr_2$bipy]	0[e]	0

[a] Typical procedure: aryl iodide **1c** (1 mmol), manganese metal (2 mmol), [$NiBr_2$bipy] (1 mmol), 2,2′-bipy (see table), DMF (5 mL), under argon. [b] GC yields, based on initial aryl iodide **1c**. Isolated yields in parentheses. [c] Reaction conducted at 0°C. [d] Iodophenol was obtained as the major product. [e] Compound **1c** was recovered after 3 d and 10% of reduction product ArH was obtained.

However, significant amounts of the dimeric byproduct **5** were also obtained (≈40%, single isomer). The formation of this symmetrical dimer suggests that a slow disproportionation of the vinylnickel intermediate occurs, which leads to $(vinyl)_2Ni$ and [$NiBr_2$bipy] (Scheme 4).[12d,21]

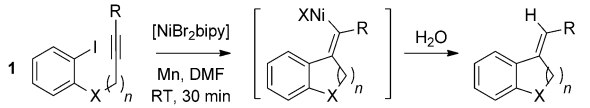
Stabilizing the vinylnickel intermediate was expected to avoid the formation of dimer **5**. Thus, we tried to run the reaction at lower temperature, or in the presence of an excess of bipy ligand. At 0°C, the rate of the oxidative addition of Ni^0 to aryl iodide **1c** decreased rapidly and a longer reaction time (≈1 h) became necessary. Under these conditions, a metathesis process has time to occur, which led to a large amount of dimer **5** (Table 1, entry 2). In the presence of a 1 equiv excess of bipy, no cyclization was observed (Table 1, entry 3) and the only product obtained was iodophenol, as previously observed with aryl bromides. This could be due to the decrease of the rate constant of the oxidative addition of ArI to Ni^0 in the presence of additional bipy. As a consequence, when the bipy/nickel ratio is increased, the complexation of the triple bond to Ni^0 prevails over the formation of ArNiX, and ArOH becomes the main product. Finally, with only a 0.3 mmol excess of bipy, the chemical yield is enhanced (Table 1, entry 4), whereas the stereoselectivity is unchanged. Note that the reaction does not proceed by direct insertion of Mn^0; the cyclization of **1c** does not proceed in the absence of the [$NiBr_2$bipy] catalyst, even after 3 days at RT (Table 1, entry 5).

The investigation of the effects of the various parameters led us to employ an experimental procedure fully described in the Experimental section. Note that even though the best results obtained for **1c** required 1.3 equiv of bipy, we prefered to run the reaction with equimolar bipy to avoid reoptimization of this parameter for each substrate considered.[22]

Synthetic applications: Because the benzofuran and indole moieties are present in an extremely large number of natural products, in particular alkaloids, new methods to access to these binuclear heterocycles represent a perpetual challenge in organic chemistry. Mainly, two processes are employed that rely on heteroannulation[23] or carbometalation.[17] In particular, palladium-catalyzed cyclization is one of the most powerful methods for the construction of heterocycles.[24] This process generally involves oxidative addition of Pd^0 to afford a σ-arylpalladium(II), which undergoes rapid insertion into a double or triple bond.[18b,25] Subsequent tandem cross-coupling can sometimes occur.[26] Other metals, for example magnesium[27] and lithium,[18a,28] are also known to promote cyclization by carbometalation. Indium,[29] chromium,[30] gold,[31] and rhodium[32] can all be used for carbometalations of multiple bonds; the latter allows the carbometalation of triple bonds by arylzinc derivatives, which leads to indolinones in good yield. Finally, intramolecular radical cyclization reactions have been proven efficient for the generation of heterocyclic compounds, but generally lead to lower stereocontrol of the double bond that results from addition to an alkyne.[33] Electrochemical reactions involving the reductive generation of Ni^I intermediates, which induce a radical-type reactivity, constitute a convenient alternative method.[34]

Scope of the reaction: We began our study by varying the substituents on the substrate. The problem of the sensitivity of the propargylic ether skeleton to the presence of "critical" functional groups remained to be tackled. The first series of variations we attempted is summarized in Table 2.

Table 2. Scope of the cyclization of iodoaryls **1** by intramolecular carbonickelation of the triple bond.[a]

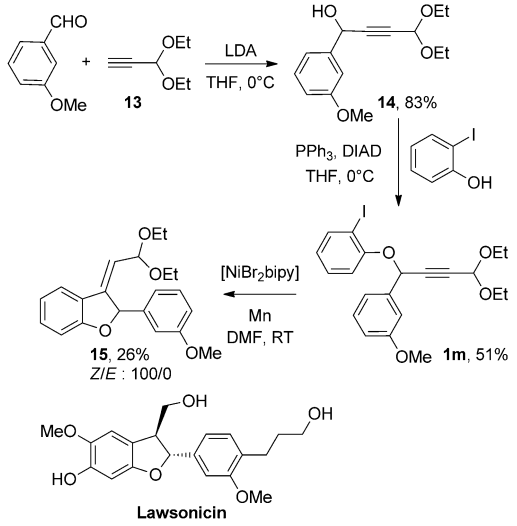


Entry	ArI	X	R	*n*	Product	Yield [%]	*Z*/*E*
1	**1b**	O	$CH(OEt)_2$	1	**3**[b]	53	100:0
2	**1c**	O	Me	1	**4**	65[c]	100:0
3	**1d**	O	Ph	1	**6**	54	83:17
4	**1e**	O	H	1	–	0	–
5	**1f**	O	Me	2	**7**	62	0:100
6	**1g**	O	Me	3	**8**	28	0:100
7	**1h**	CO_2	Me	1	–	0[d]	–
8	**1i**	CH_2O	Me	1	**9**	44	85:15
9	**1j**	CH_2	Me	1	**10**	39	0:100
10	**1k**	NBoc[e]	Me	1	**11**	34	100:0
11	**1k**	NBoc[e]	Me	1	**11**	50[c]	92:8
12	**1l**	NH	Me	1	**12**	39[f]	100:0

[a] A typical procedure is described in Table 1 and the Experimental section. [b] Compound **3** is the only product in the crude mixture but is contaminated with **2** (29%) during purification (see text and Ref. [20]). [c] Extra bipy (0.3 equiv) was added. [d] ArH (30%) was the only product isolated in this case. [e] The synthesis of the starting *N*-Boc-iodoaniline **55** is described in the Supporting Information. [f] 3-Ethylene indoline rearranged quickly into 3-ethylindol **12** during workup.

In all cases, the conversion is complete and the selectivity is high to total *syn* addition.[35] The incomplete selectivities observed for reaction of **1d** and **1i** (Table 2, entries 3 and 8) are probably due to postcylization isomerization of the vinylnickel intermediate, previously described for styrylnickel reagents.[36] Unfortunately, our isolated yields are fair to medium. Two factors can explain these disapointing figures: 1) the tendency of the vinylnickel intermediates to dimerize, as noted above (Scheme 4); 2) the limited stability of these dihydrobenzo-furanylidenes in the presence of silica gel (the uncontrolled migration of the exocyclic double bond is probably the origin of the polymerization of part of the material). Notably, neither terminal alkyne **1e** nor *o*-iodobenzoate **1h** are substrates for this transformation (Table 2, entries 4 and 7). The failure of the latter is probably related to intramolecular coordination of the arylnickel moiety to the oxygen of the ester carbonyl group. On the other hand, the method is relatively general because it can be applied to the synthesis of dihydrobenzofurans **3**, **4**, and **6** (Table 2, entries 1–3), dihydrochroman **7** and isochroman **9** (Table 2, entries 5 and 8), tetrahydrobenzoxepine **8** (Table 2, entry 6), indane **10** (Table 2, entry 9), and protected indoline **11** (Table 2, entries 10 and 11). In fact, the indoline nitrogen atom does not need to be protected; free indole **12** was recovered in similar yield to protected indole **11** (Table 2, entry 12). Note that all these yields can most likely be improved by fine-tuning the excess of bipy (compare Table 2, entries 10 and 11). The 6-*exo-dig* and, particularly, 7-*exo-dig* character of the cyclizations of **1f** and **1g** (Table 2, entries 5 and 6, respectively) are worth underlining because, to our knowledge, there are only a limited number of comparable examples in literature, and they principally use palladium catalysis[37] or radical cyclization.[33a–d,38]

Complementarily, we probed the influence of a substituent on the propargylic position α to X (for X = O, Scheme 5).



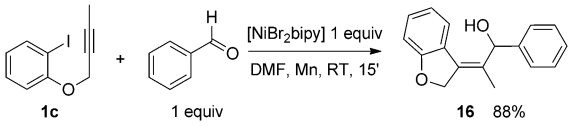
Scheme 5. Synthesis and cyclization of α-substituted substrate **1m** (LDA = lithium diisopropylamide, DIAD = diisopropyl azodicarboxylate).

Thus, we prepared substrate **1m**, which bears a *m*-methoxyphenyl appendage, from the perspective of a formal synthesis of lawsonicin, a natural product that exhibits some antimicrobial activity.[39] Compound **1m** was readily prepared by reaction of anisaldehyde with the acetylide **13** (derived from 3,3-diethoxypropyne), then Mitsunobu condensation between the resulting alcohol **14** and 2-iodophenol. However, the isolated yield of the desired product **15** was disappointingly low (26%), even though a single *Z* isomer was obtained. The elimination product and the aldehyde were found as byproducts after purification. Again, the purification process is probably responsible for this low yield; a tandem sequence that involved the same substrate was extremely efficient (see below, Table 3, entry 11).

The dimerization of the vinylnickel intermediate remains a problem that tends to diminish the efficiency of these transformations (20–40% of **5**-like dimers is recovered from these reactions) independently of the poor stability of the methylidene dihydrobenzofuran skeleton. This prompted us to take advantage of these highly reactive intermediates by trapping them, in a tandem process, with electrophiles introduced to the medium at the onset of the reaction.

Tandem processes: The nucleophilic character of the intermediate vinylnickel species was first assessed with benzaldehyde, a highly reactive electrophile, supposedly inert toward Ni^0. We cyclized **1c** (1 equiv) in the presence of benzaldehyde (1 equiv) under Barbier conditions [Ni^{II} (1 equiv) and

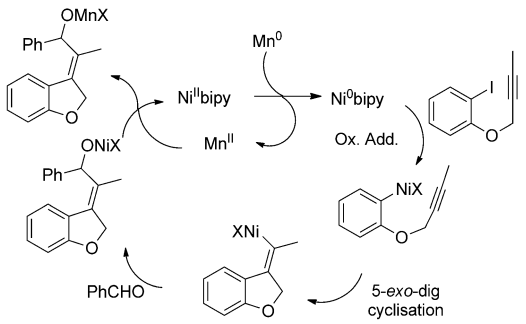
Mn^0 (2 equiv)] and the expected alcohol **16** was recovered in 88% isolated yield after 15 min at room temperature (Scheme 6).



Scheme 6. Domino process involving substrate **1c** and benzaldehyde.

Despite this interesting preliminary result, we wanted to reduce the use of significant amounts of nickel salts and decided to explore the possibility of developing a substoichiometric catalytic version of this transformation.

The most important condition for such a catalytic cycle to be efficient is that the nickel alkoxide that results from the condensation has to be transmetallated by Mn^{II}, this will reinject Ni^{II} back into the catalytic cycle (Scheme 7). Such a hypothesis has already been successfully tested in the nickel-catalyzed Reformatsky reaction.[16a]

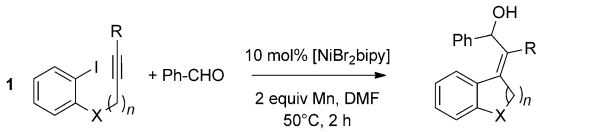


Scheme 7. Proposed catalytic cycle involving a $Ni^{II} \rightarrow Mn^{II}$ transmetallation.

Thus, we repeated the experiment described in Scheme 6 but with only 10 mol% [$NiBr_2$bipy]. A comparable yield could be obtained after 2 h in DMF, provided the reaction temperature was raised to 50 °C. Most substrates tested in the first examples of stoiochiometric cyclization (Table 2) were re-employed in the tandem process under these new catalytic conditions. The results are displayed in Table 3.

Overall, the yields are comparable or better than those presented in Table 2 (Table 3, entries 2, 8, and 10), probably because of the inhibition of the vinylnickel dimerization route. The selectivity of the addition remains in complete accord with a *syn* carbonickelation of the alkyne, the *Z* to *E* inversions noted in Table 3 correspond to the Cahn–Ingold–Prelog rule priorities. Note, however, that the terminal phenyl group prevents the aldehyde condensation; product **6** (cyclization stopped before condensation occurs) was recovered in amounts proportional to the Ni^{II} salt (Table 3, entry 3). In contrast, the presence of an aryl group α to the oxygen atom does not prevent the domino sequence

Table 3. Scope of the domino cyclization–condensation process of iodoaryls **1** and benzaldehyde by catalytic substoichiometric intramolecular carbonickelation of the triple bond.[a]



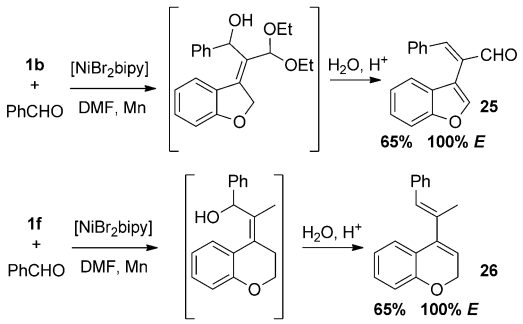
Entry	ArI	X	R	*n*	Product	Yield [%][b]	*Z*/*E*
1	**1b**	O	$CH(OEt)_2$	1	**17**	48 (94)	100:0
2	**1c**	O	Me	1	**16**	91	0:100
3	**1d**	O	Ph	1	**6**	10	73:27
4	**1e**	O	H	1	–	0	–
5	**1f**	O	Me	2	**18**	59	100:0
6	**1g**	O	Me	3	**19**	60	100:0
7	**1i**	CH_2O	Me	1	**20**	43	0:100
8	**1j**	CH_2	Me	1	**21**	54	100:0
9	**1k**	NBoc	Me	1	**22**	64	0:100
10	**1l**	NH	Me	1	**23**	66[c]	0:100
11	**1m**[d]	O	$CH(OEt)_2$	1	**24**	92	100:0

[a] For a typical procedure, see the Experimental section. [b] Isolated yields (quantitative GC yields in parentheses, based on an internal standard). [c] Reaction carried out in MeCN/DMF (9:1) to facilitate purification. [d] See Scheme 5 for the structure of **1m**.

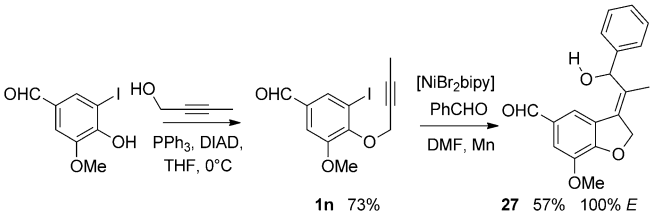
(Table 3, entry 11). The result of the cyclization–condensation of **1m** is much more satisfying than that given by the simple cyclization (92% **24** versus 26% **15**, Table 3, entry 11 and Scheme 5). This is probably due to the fact that **24** is a solid, therefore flash chromatographic purification can be avoided. The same remark applies to product **16** (Table 3, entry 2), also a solid. The detrimental effect of silica gel purification is also apparent for compound **17**; a 94% yield in the crude mixture (quantitative GC data) translates to a 48% isolated yield (Table 3, entry 1). In fact, in all cases, the ^1H NMR spectrum of the crude mixture suggests that the conversion is almost quantitative. Note that the terminal alkyne **1e** does not cyclize, as already underlined above (Table 2). On the other hand, this procedure is applicable to the 5-, 6-, and 7-*exo-dig* cyclizations of **1c**, **1f**, and **1g** (Table 3, entries 2, 5, and 6), as well as to the synthesis of indane and indoline skeletons **22**–**24** (Table 3, entries 8–10).

Varying the workup conditions can lead to different products: acid-sensitive products **17** and **18** can be directly transformed into the corresponding dienes **25** and **26** (Scheme 8), following a dehydration/double-bond migration process (plus hydrolysis of the acetal in the case of **17**). These new products are more stable, therefore the overall yields are improved.

Another important aspect of this work was to examine the chemical tolerance of the sequence to aryl substituents. We prepared aryliodide **1n** by a Mitsunobu condensation of commercially available 5-iodovanillin and 2-butynol. Substrate **1n** was employed in the tandem protocol described above (PhCHO (1 equiv), [$NiBr_2$bipy] (10 mol%), DMF, 50 °C; Scheme 9). The expected alcohol **27** was isolated in 57% yield, which shows that the sensitive carboxaldehyde function is perfectly compatible with the tandem intermolecular process, without the necessity for any protection.



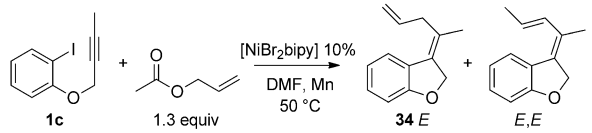
Scheme 8. Formation of dienes **25** and **26** upon acidic workup of the tandem process applied to **17** and **18**.



Scheme 9. Application of the tandem process to the synthesis of functionalized alcohol **27**.

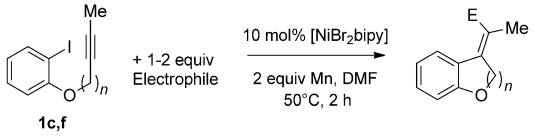
Clearly, the next step of this study was to replace benzaldehyde with a series of other electrophiles (Table 4). This investigation was restricted, in most cases, to iodoaryls **1c** (dihydrobenzofuran products) and **1f** (dihydrobenzopyran products). Aliphatic aldehydes are good substrates for the sequence, as shown by the GC yields (Table 4, entries 1–4). The isolated yields, after purification, are limited to 50–60%. Activated alkyl halides and acetates are also reactive (Table 4, entries 5–12). Note, however, that 1.3 equiv of electrophile had to be employed (1.8 equiv in the case of benzyl chloride, which is prone to a Ni^0-catalyzed dimerization side reaction). As expected, methyl chloropropionate give slightly better yields than methyl chloroacetate because of the sensitivity of these electrophiles toward Ni^0.[12c] Note that the *syn*-addition products are always the major isomers. However, with milder electrophiles, such as benzyl chloride, the reaction lasted 1 h and a mixture of *E*- and *Z*-isomers was recovered (Table 4, entries 5 and 6), probably due to isomerization of the vinylnickel intermediate before the reaction occured.[36] The chroman-derived vinylnickel reagent, which seems less reactive than the benzofuran-derived counterpart, also undergoes an isomerization before cross-coupling.

Similar results were obtained with allyl acetate (Table 4, entries 7 and 8). In this latter case, the desired product was obtained as a mixture of regioisomers due to reconjugation of the double bond in varying proportions (Scheme 10). A series of unsaturated esters were also employed with aryl iodide **1c** to assess the ability of vinylnickel reagents to promote conjugate additions (Table 4, entries 13–15). Under standard conditions ([$NiBr_2$bipy] (10 mol%), activated olefin (1.3 equiv), 50°C), the desired products of the tandem cyclization–conjugate addition were contaminated with 50% starting material and benzofuran **4**. Thus, the vinylnickel intermediate seems relatively sluggish toward this kind of electrophile. Conversions were increased by raising the temperature (80 versus 50°C) and use of 40 mol% Ni salt (Table 4, entries 13 and 14). The substitution pattern on the unsaturated ester also plays a role. Methyl methacrylate is relatively less reactive than ethyl acrylate, and ethyl crotonate was revealed to be totally inert under our conditions (Table 4, entry 15).



Scheme 10. Application of the tandem process to allyl acetate and aryl iodide **1c**.

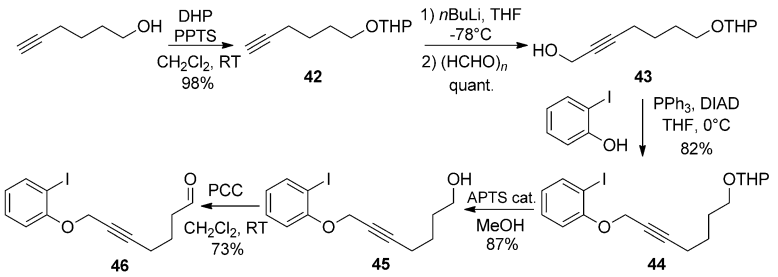
Table 4. Scope of the electrophile in the domino cyclization–condensation of iodoaryls by catalytic substoichiometric intramolecular carbonickelation of the triple bond.



Entry	ArI	Electrophile	Product	Yield [%][a]		*Z*/*E*
1	**1c**	*n*-C_8H_{17}–CHO	**28**	47	(84)	0:100
2	**1f**	*n*-C_8H_{17}–CHO	**29**	56	(70)	100:0
3	**1j**	*n*-C_8H_{17}–CHO	**30**	53	(62)	100:0
4	**1k**	*n*-C_8H_{17}–CHO	**31**	58	(66)	0:100
5	**1c**	BnCl	**32**	60	(70)	15:85
6	**1f**	BnCl	**33**	64	(80)	70:30
7	**1c**	allyl–OAc	**34**	69	(81)[b]	0:100
8	**1f**	allyl–OAc	**35**	71	(86)[b]	85:15
9	**1c**	$ClCH_2CO_2Me$	**36**	42	(70)	0:100
10	**1f**	$ClCH_2CO_2Me$	**37**	23	–	79:21
11	**1c**	$ClCH(CH_3)CO_2Me$	**38**	54	(80)	0:100
12	**1f**	$ClCH(CH_3)CO_2Me$	**39**	44	(60)	70:30
13	**1c**	CH_2=CH–CO_2Et[c]	**40**	28	(65)	15:85
14	**1c**	CH_2=CHMe–CO_2Me[c]	**41**	26	(40)	42:58
15	**1c**	Me-CH=CH–CO_2Et[c]	–	–	–	–

[a] Isolated yields (quantitative GC yields in parentheses, based on an internal standard). [b] A mixture of the nonconjugated and conjugated dienic isomers was obtained (70:30– 85:15, see Scheme 10). [c] Reaction was conducted with activated olefin (4.0 equiv) at 80°C in presence of Ni^{II} salt (40 mol%).

Tandem intramolecular processes: Next, we tried to develop an intramolecular version of this tandem reaction by application of our protocol to aldehyde **46**. The substrate was prepared from commercially available hex-5-yn-1-ol, by a route reported by Hogdson and Wells.[30] The alcohol was first protected as its tetrahydropyran (THP) derivative **42**, the lithium acetylide of which was condensed onto formaldehyde to afford propargyl alcohol **43**. Subsequent Mitsunobu condensation, then THP deprotection and oxidation of



Scheme 11. Synthesis of aldehyde **46** (DHP = 3,4-dihydropyran, PPTS = pyridinium *p*-toluenesulfonate, DIAD = diisopropyl azodicarboxylate, PTSA = *p*-toluenesulfonic acid, PCC = pyridinium chlorochromate).

the intermediate alcohol **45** with PCC led to the expected aldehyde **46** in 52% overall yield (Scheme 11).

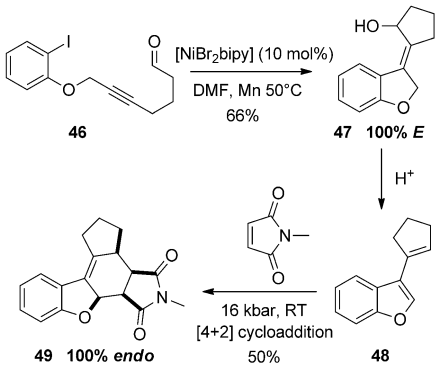
Aldehyde **46** was employed in the tandem cyclization process described above with 10 mol% of Ni^{II}. The resulting bicyclic alcohol **47** was obtained in 66% yield, as a single *E* isomer. Note that the cyclization of this substrate in a NHK-type sequence had been studied by the same team whose procedure we followed for its preparation.[30] The same product was obtained by these authors, but in only 11% yield.

Dehydration of this alcohol under acidic conditions led to the expected benzofuran **48**, albeit in modest yield. To further illustrate the synthetic potential of such 3-vinylbenzofurans as dienes,[18c] **48** was reacted in a [4+2] cycloaddition with *N*-methyl maleimide under hyperbaric conditions (16 kbar, 50°C; Scheme 12). A single *endo* isomer was obtained in 50% yield.

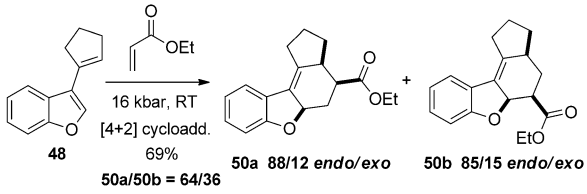
The same reaction conducted under similar conditions (16 kbar, 50°C) in the presence of ethyl acrylate as the dienophile led to the tetracyclic adduct **50** in a good isolated yield of 69%, but as a mixture of four inseparable isomers in the ratio 56:8:31:5 (Scheme 13). Several bi-dimensional NMR spectroscopic analyses were needed to determine the structure of the four isomers. Overall, a good *endo*/*exo* selectivity of about 9:1 was observed, but associated with a moderate regioselectivity of 64:36. This downside is probably due to the modest polarization of the diene in **48**, which is 1,4-substituted by two antagonistic electron-donating groups.[18c]

The limits of the intramolecular tandem process were reached with aldehydes **52a**, **52b**, and **53** (Scheme 14). Aryl iodides **52a** and **52b** were prepared by a Mitsunobu condensation between 2-iodo-isovanillin (**51**; obtained by iodination of commercially available isovanillin) and but-2-yn-1-ol or pent-3-yn-1-ol, respectively. Homologue **53** was obtained, in modest yield, from aldehyde **52a** through a Wittig reaction and acidic hydrolysis.

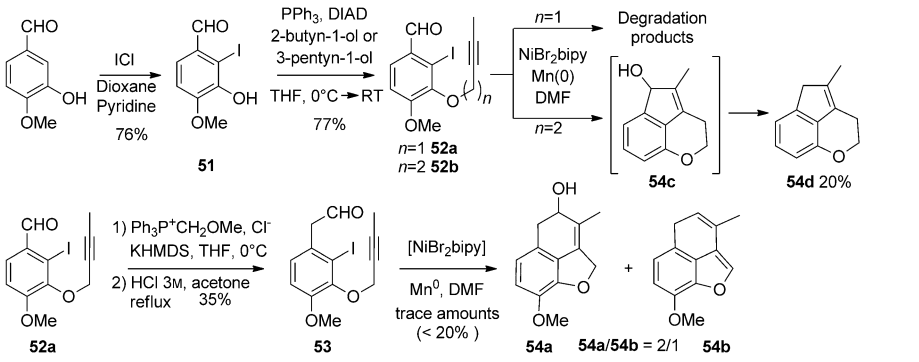
Under the conditions of the carbonickelation described above, iodoaldehyde **52a** provides a mixture of unidentified products (trace amounts of the cyclized product were observed). The results obtained with the *meta* isomer **1n** (Scheme 9) suggest that it is the *ortho* position of the carboxaldehyde moiety that is troublesome in this case. The homologue **53** led to the expected cyclization–condensation tricy-



Scheme 12. Cycloaddition of benzofuran **48** and *N*-methyl maleimide under hyperbaric conditions.



Scheme 13. Cycloaddition of benzofuran **48** and ethyl acrylate under hyperbaric conditions.



Scheme 14. Synthesis of aldehydes **52** and **53** from isovanillin (DIAD = diisopropyl azodicarboxylate, KHMDS = potassium bis(trimethylsilyl)amide)).

clic product **54**, albeit in low yield (≈20% as an inseparable mixture with the dehydrated form **54b**; Scheme 14). Note that this skeleton displays interesting similarities with indole analogues, such as those found in the hapalindoles series, a family of alkaloids extracted from the blue-green algae *Hapalosiphon fontinalis*.[40] The expected coordination of nickel by the carbonyl group in the arylnickel intermediate is probably responsible for these failures. Finally, the best results were obtained for the homopropargyl iodoaldehyde **52b**, for which the cyclization–condensation sequence seems to be effective. However, the product isolated after purification was not the expected alcohol **54c**, nor its dehydrated analogue, but the dehydroxylated product **54d** (20% isolated yield). The origin of the surprising reduction of this benzylic position is not known yet.

Conclusion

The optimized domino cyclization–condensation process of alkynes described in this paper proceeds by using catalytic amounts (10 mol%) of simple, shelf-stable reagents ([$NiBr_2$bipy], Mn). Neither glovebox chemistry, nor tedious preparation of sophisticated intermediate organometallic derivatives is required. This domino process gives access to a large set of useful fused bicycles and heterocycles, such as dihydrobenzofurans, chromans, isochromans, tetrahydrobenzoxepines, dihydroindoles, indolines, and indanes. The tandem aspect of this reaction has been shown to apply to a significant variety of activated electrophiles, and products that bear quite diverse functionalities can be obtained in generally good yields, albeit limited by purification issues of these delicate vinylidenic heterocycles. When the substrate bears an aldehyde, either on the side chain or on the aromatic nucleus, an intramolecular trapping of the vinylnickel intermediate takes place, which affords the expected tricyclic aldol products. In one case, the dehydration of this latter function provided a diene that could be employed in a Diels–Alder cycloaddition with a classical dienophile, despite the aromatic character of one of the double bonds. This supplementary step gives access to functionalized tetracyclic structures of interest from the perspective of natural product synthesis.

Interesting preliminary results have been obtained with alkenes, and they suggest that an extension of comparable chemistry in that direction could be envisaged; details will be disclosed in due time.

Experimental Section

General: GC analysis was carried out by using a 24 m HP-methyl silicon capillary column. Mass spectra were recorded with a quadrupolar MS instrument coupled to a gas chromatograph. Elemental analyses were performed by the Laboratoire de Microanalyse Organique (CNRS, IRCOF, Rouen). Column chromatography was performed on standard silica gel (230–400 mesh) or basic alumina. ^{1}H NMR spectra were recorded in $CDCl_3$, C_6D_6, or [D_6]DMSO at 300 MHz, and ^{13}C NMR spectra were recorded at 75 MHz; chemical shifts (δ) are given in parts per million (ppm) and the coupling constants (J) in hertz (Hz).

General procedure for the intramolecular carbonickelation of alkynes (Schemes 3 and 4 and Table 2): Aryl halide **1a–l** (1 mmol) was added to DMF (5 mL) in a stirred flask under argon at RT. Finely ground Mn (0.11 g, 2 mmol) and [$NiBr_2$bipy] (0.374 g, 1 mmol) were introduced sequentially, followed by CF_3CO_2H (20 μL) to activate the Mn. The reaction was conducted at RT, monitored by GC, and stopped after **1** was consumed (ca. 30 min). The mixture was hydrolyzed with water (10 mL) and diluted with diethyl ether (10 mL). The crude mixture was filtered through Celite. The aqueous layer was extracted with diethyl ether (2× 10 mL), the combined organic layers were washed with water (to ensure complete removal of DMF) and saturated NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated under vacuum . The crude oil was purified by column chromatography (pentane/diethyl ether) to give compounds **3–12** and **15**.

Compound 11: ^{1}H NMR (300 MHz, $CDCl_3$): δ (*Z* isomer) = 1.60 (s, 9H), 1.77 (dt, J = 7.2, 2.1 Hz, 3H), 4.52 (s, 2H), 5.94 (qt, J = 7.1, 3.2 Hz, 1H), 6.93 (td, J = 7.7, 1.0 Hz, 1H), 7.16 (t, J = 7.7 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.78 ppm (s, 1H); δ (*E* isomer) = 1.57 (s, 9H), 2.02 (dt, J = 7.5, 2.4 Hz, 3H), 4.52 (s, 2H), 5.63 (qt, J = 7.1, 3.2 Hz, 1H), 6.99 (td, J = 7.7, 1.0 Hz, 1H), 7.16 (t, J = 7.7 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.55 ppm (d, J = 7.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (*Z* isomer) = 14.7, 28.6 (3C), 51.7, 77.4, 112.7, 115.2, 115.3, 119.4, 122.4, 128.8, 133.9, 142.9, 155.9 ppm; 2D NOESY NMR *Z* isomer correlation between 1.77 (dt, J = 7.2, 2.1 Hz, 3H) and 4.50 (s, 2H), between 5.94 (m, 1H) and 7.35 ppm (d, J = 7.8 Hz, 1H); *m/z*: 245 [M^+], 189, 174, 144 (base), 130, 115, 77, 57; elemental analysis calcd (%) for $C_{15}H_{19}NO_2$: C 73.44, H 7.81, N 5.71; found: C 77.35, H 7.63, N 5.35.

Compound 15: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02–1.32 (m, 6H), 3.12–3.74 (m, 4H), 3.77 (s, 3H), 4.79 (d, J = 6.3 Hz, 1H), 6.03 (dd, J = 6.3, 3 Hz, 1H), 6.22 (d, J = 3 Hz, 1H), 6.83–7.08 (m, 5H), 7.21–7.27 (m, 2H), 7.43 ppm (dd, J = 7.5, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.5 (2C), 55.3, 60.0 (2C), 61.6, 86.2, 98.5, 110.7, 113.7, 114.5, 116.6, 120.4, 121.0, 121.1, 125.7, 129.6, 131.1, 140.1, 142.4, 160.0, 161.9 ppm; 2D NOESY NMR correlation between 4.79 (d, J = 6.3 Hz, 1H) and 6.22 (d, J = 3 Hz, 1H), between 6.03 (dd, J = 6.3, 3 Hz, 1H) and 7.43 ppm (dd, J = 7.5, 0.9 Hz, 1H); *m/z*: 340 [M^+], 294 (base), 265, 248, 237, 222, 205, 194, 178, 165; IR: $\tilde{\nu}$ = 3422, 2975, 1597, 1466, 1265, 1051, 747 cm^{-1}; HRMS (API+): *m/z* calcd for $C_{19}H_{19}O_3$: 295.1334 [M+H$^+$−EtOH]; found: 295.1342.

General procedure for the domino cyclisation–condensation of iodoaryl (Tables 3 and 4): Aryl iodide **1b–m** (1 mmol) and electrophile (1.3–1.8 mmol) were added to a stirred flask under argon at 50 °C with DMF (5 mL). Mn (0.11 g, 2 mmol) and [$NiBr_2$bipy] (0.0374 g, 0.1 mmol) were introduced sequentially, followed by CF_3CO_2H (20 μL) to activate manganese metal. The reaction was conducted at 50 °C, monitored by GC-analysis, and quenched after the aryl halide was consumed (ca. 2 h). The mixture was then hydrolyzed with water (10 mL) and diluted with ethyl acetate (10 mL). The crude mixture was filtered through Celite. The aqueous layer was extracted with ethyl acetate (2×10 mL), the combined organic layers were washed with water (to ensure complete removal of DMF) and saturated NaCl solution, dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The product was isolated by column chromatography (pentane/ethyl acetate) to give compounds **16–24** and **27–41**.

Compound 19: M.p. 92–94 °C.^{1}H NMR (300 MHz, [D_6]DMSO, 60 °C): δ = 1.56 (s, 3H), 1.78–2.01 (m, 2H), 2.19 (brs, 1H), 2.68 (brs, 1H), 3.95 (brs, 1H), 4.23 (brs, 1H), 5.18 (d, J = 4.1 Hz, 1H), 5.42 (d, J = 4.1 Hz, 1H), 6.97–7.03 (m, 2H), 7.16–7.41 ppm (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.8, 29.5, 30.6, 72.4, 73.3, 121.5 (2C), 123.3, 125.3, 126.7, 128.2 (2C), 128.5, 129.7, 133.2, 134.6, 136.9, 142.9, 157.7 ppm; NMR 2D NOESY correlation between 1.56 (s, 3H) and 1.78–2.01 (m, 2H); *m/z*: 280 [M^+], 262 [M−H_2O], 247 [M−H_2O−CH_3], 147 (base); IR: $\tilde{\nu}$ = 3424, 3025, 2930, 1599, 1480, 1228, 1054, 1008 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{19}H_{20}O_2$: 280.1463; found: 280.1477.

Compound 20: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.66 (s, 3H), 2.09 (brs, 1H), 4.56 (s, 2H), 4.62 (s, 2H), 6.09 (d, J = 2.1 Hz, 1H), 7.15–7.40 ppm

(m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.1, 67.5, 68.6, 73.1, 125.0, 126.3 (2C), 127.1, 127.3, 127.4, 128.1, 128.6 (2C), 130.6, 132.37, 132.44, 137.7, 142.2 ppm; NMR 2D NOESY correlation between 1.66 (s, 3H) and 4.56 (s, 2H), between 6.09 (d, J=2.1 Hz, 1H) and 7.15–7.40 ppm (m, 9H); m/z: 266 [M^+], 248 [M^+-H_2O], 233, 205, 144, 132, 105 (base), 91, 77; IR: $\tilde{\nu}$=3417, 2914, 2852, 1449, 1105, 1021, 761, 700 cm^{-1}; HRMS (EI): m/z calcd for $C_{18}H_{16}O$: 248.1201 [M^+-H_2O]; found: 248.1199.

Compound 21: ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.72 (s, 3H), 2.35 (d, J=3.9 Hz, 1H), 2.74–2.89 (m, 2H), 2.98–3.03 (m, 2H), 6.37 (d, J=3.9 Hz, 1H), 7.14–7.39 (m, 6H), 7.45–7.56 (m, 2H), 7.53 ppm (d, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=15.4, 30.2, 31.8, 71.8, 124.5, 125.5, 126.1 (2C), 126.5, 127.1, 127.5, 128.4 (2C), 130.0, 140.2, 140.3, 142.1, 148.1 ppm; NMR 2D NOESY correlation between 1.72 (s, 3H) and 2.74–2.89 (m, 2H), between 6.37 (d, J=3.9 Hz, 1H) and 7.53 ppm (d, J=7.5 Hz, 1H); m/z: 250 [M^+], 232 [M^+-H_2O], 217 (base), 202, 115; IR: $\tilde{\nu}$=3405, 2919, 1447, 1016, 754 cm^{-1}; HRMS (EI): m/z calcd for $C_{18}H_{16}$: 232.1252 [M^+-H_2O]; found: 232.1260.

Compound 22: ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.60 (s, 9H), 1.68 (t, J=1.7 Hz, 3H), 1.99 (s, 1H), 4.53 (s, 2H), 6.38 (s, 1H), 6.93 (td, J=7.8, 0.9 Hz, 1H), 7.21 (d, J=8.1 Hz, 1H), 7.30–7.35 (m, 3H), 7.43 (d, J=7.4 Hz, 2H), 7.57 (d, J=7.8 Hz, 1H), 7.92 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=15.2, 28.5 (3C), 53.0, 70.6, 81.2, 115.3, 122.4, 123.9, 125.8 (2C), 127.0, 127.3, 128.4 (2C), 128.8, 129.7, 130.5, 141.5, 145.8, 151.9 ppm, NMR 2D NOESY correlation between 1.65 (s, 3H) and 4.34–4.50 ppm (m, 2H); m/z: 350 [M^+–H], 349, 233 (base), 218; IR: $\tilde{\nu}$=3412, 3052, 2980, 1703, 1472, 1383, 1163, 725 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{25}NO_3$: C 75.19, H 7.17, N 3.99; found: C 74.91, H 7.69, N 3.90.

Compound 23: ^{1}H NMR (300 MHz, [D_6]DMSO): δ=1.48 (s, 3H), 4.10 (s, 2H), 5.54 (d, J=4.2 Hz, 1H), 6.01 (s, 1H), 6.13 (d, J=4.2 Hz, 1H), 6.51 (t, J=7.5 Hz, 1H), 6.58 (d, J=7.9 Hz, 1H), 6.97 (t, J=7.6 Hz, 1H), 7.21 (t, J=7H, 1H), 7.31 (t, J=7.5 Hz, 2H), 7.35–7.39 ppm (m, 3H); ^{13}C NMR (75 MHz, [D_6]DMSO): δ=14.7, 51.1, 69.3, 109.4, 116.6, 123.9, 125.5, 125.6 (2C) 126.5, 128.0 (2C), 128.5, 128.6, 133.1, 143.5, 156.1 ppm; NMR 2D NOESY correlation between 1.47 (s, 3H) and 4.09 ppm (s, 2H); m/z: 233 [M^+-H_2O] (base), 218, 144, 116, 90, 77; elemental analysis calcd (%) for $C_{17}H_{17}NO$: C 81.24, H 6.82, N 5.57; found: C 80.81, H 7.23, N 5.64.

Compound 24: Isolated as a 1:1 mixture of two inseparable diastereoisomers ratio. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.83 (brs, 1H), 1.05–1.23 (m, 13H), 3.40–3.54 (m, 8H), 3.64 (s, 3H), 3.70 (s, 3H), 3.92 (s, 1H), 3.95 (s, 1H), 4.75–4.80 (m, 2H), 5.16 (s, 1H), 5.28 (s, 1H), 6.55–6.95 (m, 10H), 7.05–7.30 (m, 15H), 7.59 ppm (dd, J=7.8, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=15.05 (2C), 15.10 (2C), 46.9, 47.8, 55.15, 55.20, 60.6, 60.79, 60.84, 60.93, 77.75, 77.82, 91.3, 91.4, 113.1, 113.3, 114.1, 114.3, 115.2, 120.9, 121.2, 122.2, 126.6, 127.1, 127.8, 127.99 (2C), 128.02 (2C), 129.3, 129.5, 130.0, 138.6, 138.7, 138.8, 140.7, 140.8, 155.2, 159.4, 159.6 ppm, m/z: 202 (base), 174, 145, 115, 103, 77; IR: $\tilde{\nu}$=3422, 2970, 1601, 1455, 1048, 700 cm^{-1}.

Compound 27: ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.62 (t, J=1.6 Hz, 3H), 2.67 (s, 1H), 3.95 (s, 3H), 5.25 (q, J=1.6 Hz, 2H), 6.34 (s, 1H), 7.27–7.38 (m, 4H), 7.43 (d, J=7.4 Hz, 2H), 7.70 (d, J=0.9 Hz, 1H), 9.73 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=15.1, 56.2, 71.1, 76.7, 111.1, 121.1, 125.6 (2C), 126.1, 127.6, 128.6 (2C), 130.7, 130.8, 131.0, 141.2, 145.8, 158.8, 190.8 ppm; NMR 2D NOESY correlation between 1.62 (t, J=1.6 Hz, 3H) and 5.25 (q, J=1.6 Hz, 2H), between 6.34 (s, 1H) and 7.70 ppm (d, J=0.9 Hz, 1H); m/z: 309 [M^+–H], 292 [M^+-H_2O] (base), 277, 261, 249, 231, 218, 204, 189, 178, 165; elemental analysis calcd (%) for $C_{19}H_{18}O_4$: C 73.53, H 5.85; found: C 73.63, H 5.89.

Compound 30: ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.87–0.90 (m, 3H), 1.20–1.30 (m, 14H), 1.85 (s, 3H), 2.30 (brs, 1H), 2.68–2.75 (m, 2H), 2.94 (t, J=6.9 Hz, 2H), 5.13–5.17 (m, 1H), 7.16–7.28 (m, 3H), 7.49–7.52 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.2, 14.6, 22.8, 26.1, 29.4, 29.7, 29.9, 30.2, 31.7, 32.0, 35.0, 70.7, 124.9, 125.4, 126.3, 127.1, 131.6, 138.6, 140.3, 147.9 ppm; NMR 2D NOESY correlation between 1.84 (s, 3H) and 2.72 (m, 2H), between 5.12 (m, 1H) and 7.48 ppm (d, J=7.2 Hz, 1H); m/z: 268 [M^+-H_2O], 183, 169 (base), 155, 141, 128, 115, 91; IR: $\tilde{\nu}$=3418, 2919, 1684, 1542, 1461, 1030 cm^{-1}; HRMS (EI): m/z: calcd for $C_{20}H_{28}$: 268.2191 [M^+-H_2O]; found: 268.2180.

Compound 31: ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (brs, 3H), 1.20–1.40 (m, 15H), 1.59 (s, 9H), 1.78 (s, 3H), 4.45 (s, 2H), 5.17 (s, 1H), 6.95 (t, J=7.7 Hz, 1H), 7.18 (t, J=7.7 Hz, 1H), 7.47 (d, J=7.8 Hz, 1H), 7.86–7.87 ppm (brs, 1H); ^{13}C NMR (75 MHz, [D_6]DMSO): δ=14.0, 14.6, 22.1, 25.2, 28.0 (3C), 28.7, 29.0, 29.2, 31.3, 34.8, 52.6, 68.0, 74.2, 114.5, 122.2, 124.3, 125.5, 127.9, 128.3, 129.9, 134.2, 150.9 ppm, NMR 2D NOESY correlation between 1.78 (s, 3H) and 4.45 (s, 2H), between 5.17 (s, 1H) and 7.47 (d, J=7.8 Hz, 1H); elemental analysis calcd (%) for $C_{24}H_{37}NO_3$: C 74.38, H 9.62, N 3.61; found: C 74.50, H 9.39, N 3.50.

Compound 37: ^{1}H NMR (300 MHz, $CDCl_3$): δ Z isomer=1.90 (s, 3H), 2.63 (t, J=5.8 Hz, 2H), 3.44 (s, 2H), 3.77 (s, 3H), 4.28 (t, J=5.8 Hz, 2H), 6.83 (t, J=8 Hz, 1H), 6.86 (d, J=7.6 Hz, 1H), 7.14 (td, J=8, 1.8 Hz, 1H), 7.30 ppm (dd, J=7.6, 1.8 Hz, 1H); δ E isomer=2.11 (s, 3H), 2.59 (t, J=5.8 Hz, 2H), 3.24 (s, 2H), 3.65 (s, 3H), 4.05 (t, J=5.8 Hz, 2H), 6.83 (t, J=8.0 Hz, 1H), 6.86 (d, J=7.6 Hz, 1H), 7.14 (td, J=8.0, 1.8 Hz, 1H), 7.30 ppm (dd, J=7.6, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ Z isomer=19.6, 27.9, 41.1, 52.1, 66.9, 116.7, 119.8, 122.7, 123.4, 128.5, 128.8, 129.3, 154.8, 172.9 ppm, δ E isomer=21.7, 29.8, 40.4, 52.0, 67.6, 116.6, 119.2, 122.8, 123.3, 123.5, 128.6, 128.7, 154.7, 171.9 ppm, NMR 2D NOESY Z isomer: correlation between 1.90 (s, 3H) and 2.63 (t, J=5.8 Hz, 2H), between 3.44 (s, 2H) and 7.30 ppm (dd, J=7.6, 1.8 Hz, 1H); E isomer correlation between 2.11 (s, 3H) and 7.28 ppm (dd, J=7.6, 1.8 Hz, 1H); m/z: 232 [M^+] (base), 173, 158, 145, 131, 91, 77, 59; IR: $\tilde{\nu}$=2976, 2872, 2242, 1731, 1448, 1382, 1113, 909, 737 cm^{-1}.

Compound 39: ^{1}H NMR (300 MHz, $CDCl_3$): δ Z isomer=1.30 (d, J=6.9 Hz, 3H), 1.95 (s, 3H), 2.50–2.60 (m, 1H), 2.75–2.84 (m, 1H), 3.68 (s, 3H), 3.75 (q, J=6.9 Hz, 1H), 4.18–4.26 (m, 1H), 4.28–4.37 (m, 1H), 6.79–6.88 (m, 2H), 7.12 (td, J=7.5, 1.8 Hz, 1H), 7.28 ppm (dd, J=8.4, 1.5 Hz, 1H), δ E isomer=1.29 (d, J=6.9 Hz, 3H), 1.76 (s, 3H), 2.50–2.60 (m, 1H), 2.62–2.68 (m, 1H), 3.69 (q, J=6.9 Hz, 1H), 3.71 (s, 3H), 4.18–4.26 (m, 1H), 4.28–4.37 (m, 1H), 6.79–6.88 (m, 2H), 7.19 (td, J=7.5, 1.5 Hz, 1H), 7.37 ppm (dd, J=7.5, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ Z isomer=14.9, 16.8, 27.6, 42.6, 52.0, 67.6, 116.5, 119.1, 123.6, 127.7, 128.1, 128.7, 129.5, 154.7, 174.8 ppm; δE isomer=14.8, 15.9, 27.9, 42.7, 52.1, 67.8, 116.8, 119.7, 123.5, 128.1, 128.3, 128.4, 128.8, 154.8, 175.2 ppm; NMR 2D NOESY: Z isomer correlation between 1.95 (s, 3H) and 4.28–4.37 ppm (m, 1H); m/z: 246 [M^+] (base), 215, 187, 163, 145, 120, 91; IR: $\tilde{\nu}$=2977, 2872, 2242, 1731, 1448, 1111, 910, 741 cm^{-1}; HRMS (EI): m/z calcd for $C_{15}H_{18}O_3$: 246.1256; Z isomer found: 246.1256, E isomer found: 246.1264.

Compound 48: ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.08 (quint, J=7.5 Hz, 2H), 2.58–2.65 (m, 2H), 2.69–2.76 (m, 2H), 6.33 (m, 1H), 7.29–7.36 (m, 2H), 7.51 (dd, J=7.8, 1.8 Hz, 1H), 7.57 (s, 1H), 7.85 ppm (dd, J=7.8, 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.8, 33.6, 34.4, 111.7, 118.6, 121.4, 123.0, 124.5, 126.3, 126.6, 133.8, 142.2, 155.8 ppm; m/z: 184 [M^+] (base), 169, 165, 141, 127, 115, 102, 89, 77, 63, 51; HRMS (EI): m/z: calcd for $C_{13}H_{12}O$: 184.0888; found: 184.0888.

Cycloadduct *endo*-49: Diene **48** (0.088 g, 0.48 mmol) and *N*-methylmaleimide (0.111 g, 2 equiv, 1 mmol) were added to THF (5 mL). After 24 h under hyperbaric conditions (16 kbar) at RT, the solvent was concentrated under reduced pressure and the crude solid was purified by column chromatography on silica gel (pentane/AcOEt, 50:50) to provide ***endo*-49** as a white solid (0.071 g, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.76–1.88 (m, 2H), 2.05–2.16 (m, 1H), 2.38–2.59 (m, 4H), 2.78 (s, 3H), 3.19 (t, J=8.1 Hz, 1H), 3.71 (t, J=8.0 Hz, 1H), 5.11–5.16 (m, 1H), 6.91 (t, J=7.5 Hz, 1H), 7.01 (d, J=8.1 Hz, 1H), 7.18 (t, J=7.7 Hz, 1H), 7.29 ppm (d, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.1, 27.1, 27.7, 29.9, 39.7, 41.9, 44.1, 80.9, 110.7, 121.3, 122.6, 124.1, 127.4, 129.6, 134.0, 163.4, 174.1, 177.0 ppm; NMR 2D NOESY: correlation between 2.38–2.59 (m, 4H) and 5.11–5.16 (m, 1H), between 3.19 (t, J=8.1 Hz, 1H) and 5.11–5.16 (m, 1H), between 3.71 (t, J=8.0 Hz, 1H) and 5.11–5.16 ppm (m, 1H); m/z: 295 [M^+], 210 [$M-C_2O_2NMe$], 197, 184 (base), 165, 152, 128, 112; HRMS (ESI+): m/z calcd for $C_{18}H_{18}NO_3$: 296.1287 [M+H^+]; found: 296.1297.

Cycloadduct 50: The cycloaddition reaction was conducted under similar conditions to those described above for ***endo*-49** (16 kbar, RT) in pres-

ence of ethyl acrylate as dienophile. Tetracyclic adduct **50** was obtained in 69% yield as a mixture of four inseparable isomers (56:8:31:5).

Adduct *endo*-50a: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15–1.23 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.69–1.86 (m, 4H), 2.44 (dt, J = 11.8, 4.5 Hz, 1H), 2.49–2.70 (m, 2H), 2.82–2.87 (m, 1H), 2.94 (ddd, J = 12.8, 8.8, 4.2 Hz, 1H), 4.18 (q, 7.1 Hz, 2H), 5.02–5.13 (m, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.90 (td, J = 7.5, 1.2 Hz, 1H), 7.15 (td, J = 7.8, 1.2 Hz, 1H), 7.25 ppm (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 23.2, 27.4, 28.4, 28.8, 37.6, 41.6, 60.6, 83.3, 109.8, 120.7, 123.0, 126.0, 129.0, 130.7, 134.7, 162.1, 173.9 ppm, NMR 2D NOESY: correlation between 2.94 (ddd, J = 12.8, 8.8, 4.2 Hz, 1H) and 5.02–5.13 (m, 1H), between 2.82–2.87 (m, 1H) and 2.94 ppm (ddd, J = 12.8, 8.8, 4.2 Hz, 1H); m/z: 284 [M^+], 211 (base), 183, 165, 141, 131, 115; HRMS (ESI+): m/z calcd for $C_{18}H_{21}O_3$: 285.1491 [M+H$^+$]; found: 285.1485.

Adduct *exo*-50a: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15–1.23 (m, 1H), 1.29 (t, J = 7.1 Hz 3H), 1.69–1.86 (m, 4H), 2.44 (dt, J = 11.8, 4.5 Hz, 1H), 2.49–2.70 (m, 2H), 2.82–2.87 (m, 1H), 2.94 (ddd, J = 12.8, 8.8, 4.2 Hz, 1H), 4.26 (q, 7.2 Hz, 2H), 5.25–5.29 (m, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.90 (td, J = 7.5, 1.2 Hz, 1H), 7.15 (td, J = 7.8, 1.2 Hz, 1H), 7.25 ppm (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 24.8, 29.2, 29.8, 31.0, 40.0, 45.0, 61.0, 84.1, 110.1, 120.7, 122.6, 126.0, 128.7, 129.8, 136.3, 162.0, 174.9 ppm; m/z: 284 [M^+], 211 (base), 183, 165, 141, 131, 115.

Adduct *endo*-50b: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, J = 7.1 Hz, 3H), 1.34–1.44 (m, 1H), 1.60 (ddd, J = 13.8, 7.1, 5.0 Hz, 1H), 1.69–1.86 (m, 1H), 1.89–1.96 (m, 1H), 2.09 (dt, J = 13.8, 7.9 Hz, 1H), 2.04–2.14 (m, 1H), 2.28–2.37 (m, 1H), 2.49–2.70 (m, 2H), 3.39 (td, J = 7.5, 4.9 Hz, 1H), 3.96 (qd, J = 7.2, 4.1 Hz, 2H), 5.02–5.13 (m, 1H), 6.83 (d, J = 8.1 Hz, 1H), 6.89 (td, J = 7.5, 0.9 Hz, 1H), 7.11 (td, J = 7.8, 1.2 Hz, 1H), 7.28 ppm (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 25.7, 26.8, 29.3, 33.5, 39.7, 42.8, 60.4, 81.9, 109.8, 120.8, 122.4, 126.3, 126.6, 128.4, 137.0, 162.4, 172.5 ppm; NMR 2D NOESY: correlation between 3.39 (td, J = 7.5, 4.9 Hz, 1H) and 5.02–5.13 ppm (m, 1H); m/z: 284 [M^+], 211 (base), 183, 165, 141, 131, 115; HRMS (ESI+): m/z calcd for $C_{18}H_{21}O_3$: 285.1491 [M+H$^+$]; found: 285.1485.

Adduct *exo*-50b: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, J = 7.2 Hz, 3H), 1.34–1.44 (m, 1H), 1.60 (ddd, J = 13.8, 7.1, 5.0 Hz, 1H), 1.69–1.86 (m, 1H), 1.89–1.96 (m, 1H), 2.09 (dt, J = 13.8, 7.9 Hz, 1H), 2.04–2.14 (m, 1H), 2.28–2.37 (m, 1H), 2.49–2.70 (m, 2H), 3.39 (td, J = 7.5, 4.9 Hz, 1H), 3.96 (qd, J = 7.2, 4.1 Hz, 2H), 5.02–5.13 (m, 1H), 6.83 (d, J = 8.1 Hz, 1H), 6.89 (td, J = 7.5, 0.9 Hz, 1H), 7.11 (td, J = 7.8, 1.2 Hz, 1H), 7.28 ppm (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 25.5, 26.6, 33.1, 33.2, 41.0, 43.5, 60.8, 81.2, 110.0, 120.8, 122.6, 125.7, 125.8, 128.0, 135.0, 162.3, 176.1 ppm; m/z: 284 [M^+], 211 (base), 183, 165, 141, 131, 115.

Compound 54d: M.p. 102–103 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.01 (s, 3H), 2.71–2.79 (m, 2H), 3.28 (s, 2H), 3.88 (s, 3H), 4.30 (t, J = 5.7 Hz, 2H), 6.62 (d, J = 7.9 Hz, 1H), 6.88 ppm (d, J = 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 24.4, 42.8, 56.4, 67.7, 108.3, 115.9, 127.2, 134.0, 134.1, 134.4, 139.1, 145.7 ppm; m/z: 202 [M^+] (base), 187 [M^+−Me], 171 [M^+−OMe], 115; IR: $\tilde{\nu}$ = 3054, 2930, 1500, 1265 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{14}IO_2$: C 77.20, H 6.98; found: C 77.36, H 6.97.

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