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Synthesis of functionalized isoindolinones: Addition of *in situ* generated organoalanes to acyliminium ions

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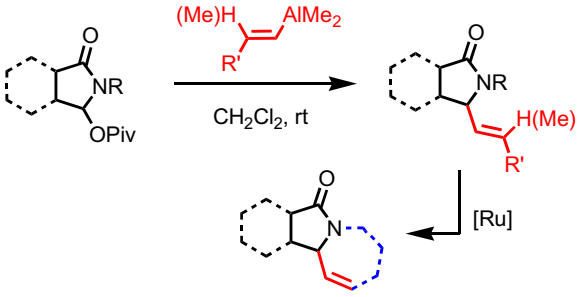
Dedicated to Prof. Gerhard Erker in celebration of his 60th birthday and in recognition of his pioneering contributions to transition metal chemistry.

Abstract

Addition of *in situ* generated di- or trisubstituted alkenylalanes to *N*-acyliminium ions provides rapid access to functionalized isoindolinones. Subsequent ring closing metathesis leads to tricyclic products. These transformations proceed under mild conditions and allow for the convergent synthesis of biologically significant scaffolds from readily available starting materials.



Keywords: Isoindolinone; Aluminum; Zirconium; Hydrozirconation; Carbometallation; *N*-Acyliminium ion

1. Introduction

Isoindolinones constitute the core structures of numerous naturally occurring biologically active compounds such as magallanesine **1** [1] and lennoxamine **2** [2] as well as many drug candidates such as pagoclone **3** [3] (Fig. 1). Isoindolinones demonstrate a remarkably wide array of biological activities, including anti-inflammatory [4], antihypertensive [5], antipsychotic [6], vasodilatory [7] and antileukemic [8] effects, which renders the development of new synthetic routes toward these heterocycles particularly attractive. While several methods have been reported for the preparation of isoindolinones [9], some leading to the synthesis of natural products [10] and compound libraries [11], many approaches suffer from a lack of generality or functional group compatibility.

In view of the potent and diverse biological spectrum of isoindolinones, we initiated studies directed at their preparation as part of our program for the synthesis of

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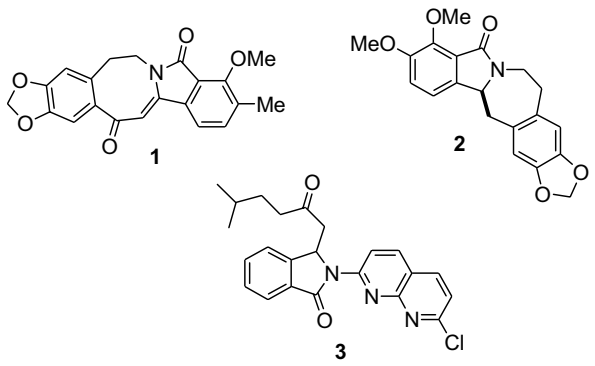
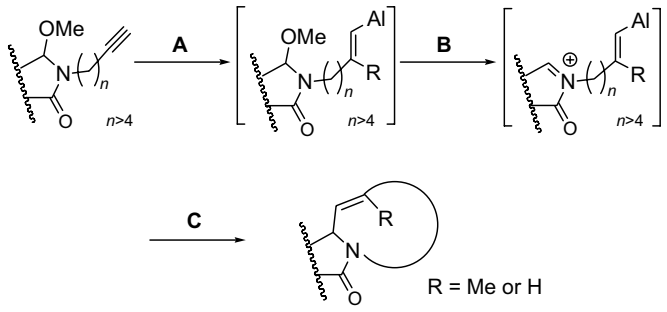


Fig. 1. Biologically active isoindolinones.



Scheme 1. Proposed intramolecular addition of alkenylalanes to *N*-acyliminium ions. (A) Zirconium-catalyzed, water-accelerated carboalumination or hydrozirconation/transmetallation; (B) elimination; (C) addition/ring closure.

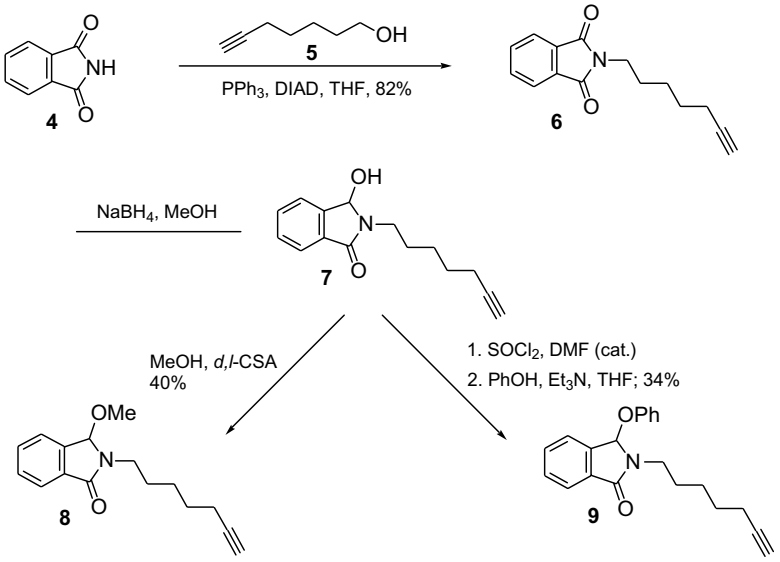
nitrogen containing heterocycles [12]. We initially proposed combining our water-accelerated carboalumination [13] or hydrozirconation [14] with an intramolecular *N*-acyliminium ion addition in a cascade process that would generate medium-ring containing isoindolinones (Scheme 1). *N*-Acyliminium ions are versatile synthetic intermediates [15] and have previously been employed in the formation of simple isoindolinones [16]; however, with the exception of allylsilanes, the addition of functionalized organometallic reagents to these systems has not yet been exploited. Moreover, the intramolecular addition would potentially provide an entry toward strained medium-rings containing (*E*)-alkenes.

2. Results and discussion

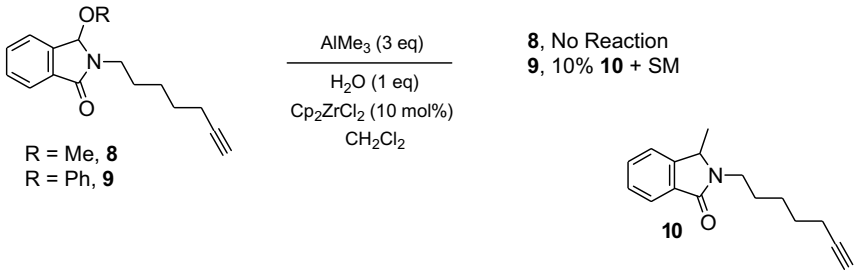
Our investigations began with the synthesis of methoxy-**8** and phenoxy lactam **9** (Scheme 2). Alcohol **5** was obtained in 85% yield by the isomerization of the commercially available hept-3-yne-1-ol with KAPA reagent in 85% yield [17]. Imide **6** could then be constructed by a Mitsunobu alkylation with alkynol **5**, which proceeded in 82% yield. Reduction with sodium borohydride was followed by a methanol exchange to give methoxylactam **8** in 40% overall yield (Scheme 1). With the key substrate in hand, we submitted **8** to our water-accelerated carboalumination conditions ($AlMe_3$ (3 equiv.), H_2O (1 equiv.), zirconocene dichloride (10 mol%)) which only returned starting material with no evidence for elimination of methanol or carboalumination of the alkyne moiety (Scheme 3).

We anticipated the need for a better leaving group and hence prepared phenoxy lactam **9**, which was generated by treatment of **7** with $SOCl_2$ and catalytic DMF. The resulting unstable chloride intermediate was immediately treated with phenol in the presence of triethylamine to yield **9** in 34% yield [18]. When **9** was subjected to the carboalumination conditions, only alkylated lactam **10** (10%), starting material (52%), and decomposition products were observed by NMR analysis (Scheme 3).

These experiments suggested that the functionality present in these lactam acetals was inhibiting the



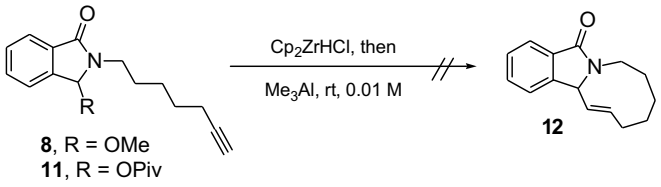
Scheme 2. Synthesis of lactam precursors.



Scheme 3. Attempted cascade cyclization of **8** and **9**.

carboalumination step. We postulated that the lactam group was responsible for the observed inhibition, as highly Lewis basic functionality has been noted to decrease the reactivity of aluminoxanes [19]. Therefore, we performed a series of GC experiments to test this hypothesis with 1-heptyne, which is known to undergo rapid water-accelerated carboalumination. A control experiment demonstrated that the carboalumination of heptyne with $AlMe_3$ (3 equiv.), H_2O (1 equiv.), and Cp_2ZrCl_2 (10 mol%) proceeded to completion in less than 5 min at low temperatures (−78 °C to −25 °C) to furnish a 97:3 mixture of regioisomers by GC analysis (Scheme 4). Conducting the identical experiment in the presence of 1 equiv. of methoxylactam **8** dramatically inhibited carboalumination, with only 4.4% of heptyne undergoing conversion after 1 h at ambient temperature. Most likely, this inhibition is due to the coordination of Lewis basic functional groups to $AlMe_3$ oligomers, thus preventing alkyne carboalumination.

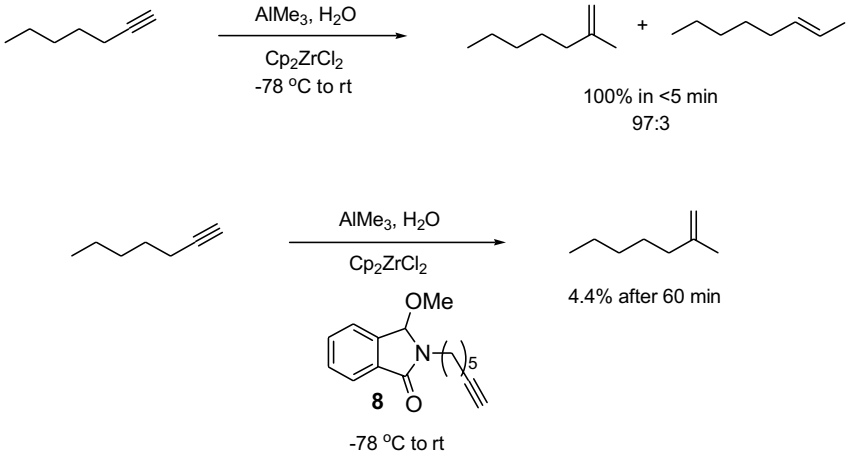
Due to the lack of reactivity in the carboalumination approach, we turned to hydrozirconation, known to be quite tolerant of diverse functionality [14]. When lactam **8** was treated with Cp_2ZrHCl, only the corresponding alkene was recovered (Scheme 5). Treatment of the intermediate alkenylzirconocene with $AgClO_4$ or trimethylaluminum also provided no desired cyclization products. Our attempts to enhance leaving group ability by using pivaloate **11** also failed to promote cyclization under any



Scheme 5. Attempted hydrozirconation and medium-ring formation.

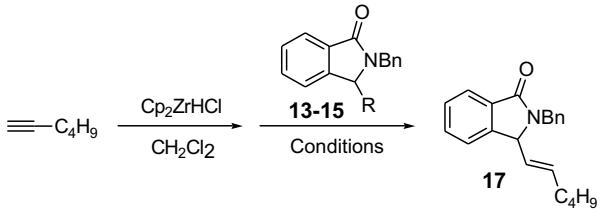
of the above conditions. Highly concentrated reaction mixtures or prolonged heating resulted only in slow methyl group addition. Possibly, the ring strain present in the desired products is too high to allow the reaction to proceed under these experimental conditions.

Because the intramolecular cyclizations proved elusive, we turned our attention toward an alternative construction of these systems starting with an intermolecular addition process. Alkenylation of *N*-acyliminium ions can often require harsh reaction conditions [20] or unusual anomeric leaving groups [21]; a noteworthy exception is the mild intermolecular addition of alkenyl boronates reported by Batey et al. [22] We first explored the hydrozirconation of terminal alkynes as a method to generate alkenyl nucleophiles (Table 1). Hydrozirconation of 1-hexyne, followed by treatment with silver perchlorate [23] and lactam **13** yielded only a trace of addition product after 24 h at r.t. (entry 1, Table 1). Transmetallation to dimethylzinc also proved unsuccessful (entry 2, Table 1). Gratifyingly,



Scheme 4. GC analysis of the water-accelerated carboalumination of heptyne in the presence and absence of **8**.

Table 1
Reaction optimization for the addition of hexenylzirconocene to lactams **13–15**



Entry	Conditions	R (lactam acetal)	**17** [%]
1	$AgClO_4$, 24 h, r.t.	OMe (**13**)	Trace[a]
2	Me_2Zn, 12 h, r.t.	OMe (**13**)	–
3	Me_3Al, 12 h, r.t.	OMe (**13**)	43[b]
4	Me_3Al, 4 h, r.t.	OAc (**14**)	30
5	Me_3Al, 4 h, r.t.	OPiv (**15**)	81
6	$AgClO_4$, 12 h, r.t.	OPiv (**15**)	Complex mixture

[a] Product was formed as a mixture of alkene isomers.
[b] Starting material observed after 12 h.

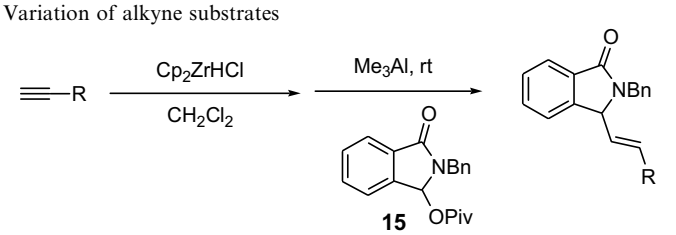
hydrozirconation-transmetallation to trimethylaluminum [24] generated an alkenylalane that reacted with lactam **13** in a moderate 43% yield (entry 3, Table 1). We further increased the leaving group ability by using acetate **14**; however, product **17** was only formed in 30% yield while the remaining starting material was consumed (entry 4, Table 1). Attempts to perform this reaction in THF or toluene led to recovered starting material. In an effort to prevent decomposition pathways while retaining good leaving group ability, pivaloate **15** was synthesized and treated with the *in situ* generated alane to provide hexenyl isoindolinone **17** in 81% yield without any observed isomerization of the alkene moiety (entry 5, Table 1). Attempts to achieve this transformation under cationic conditions with silver perchlorate [20] led to complex mixtures, seemingly arising from alkene isomerization. The mild conditions under which the addition proceeds and the ability to utilize readily available alkynes and pivaloate iminium ion precursors encouraged us to explore this process further.

Among the numerous methods known for the synthesis of substituted isoindolinones, only a few examples of Heck-type cyclizations install an alkenyl moiety at the 3-position [25]. The modularity of our approach warranted further investigation, and therefore we evaluated the substrate scope of this process. As shown in Table 2, silyl ether, carbamate, and sulfonamide functionalities are well tolerated, generating functionalized isoindolinones in a high yielding, one-pot procedure.

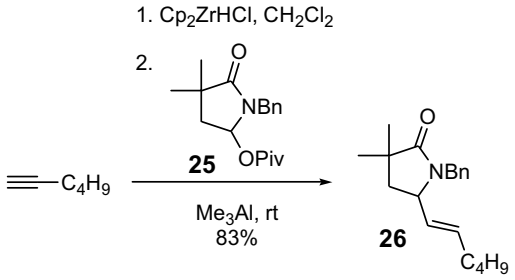
To further probe the scope of this reaction, we synthesized succinimide-derived pivaloate **25** from 1-benzyl-3,3-dimethylpyrrolidine-2,5-dione (**24**) and subjected it to our optimized conditions (Scheme 6). Addition product **26** was isolated in 83% yield. This success bodes well for the extension of the cyclic iminium ion alkenylation methodology toward a broad class of heterocyclic electrophiles.

We also explored the use of trisubstituted alkenes in this transformation. Although the lactam functionality had prevented an intramolecular addition, pre-forming the

Table 2
Variation of alkyne substrates



Entry	R (alkyne)	Product [%]
1	C_4H_9 (**16**)	**17** [81]
2	*c*-C_6H_{11} (**18**)	**19** [79]
3	$CH_2CH_2OTBDPS$ (**20**)	**21** [71]
4	$CH_2CH_2N(CO_2Me)Ts$ (**22**)	**23** [62]



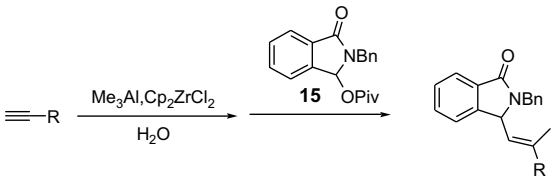
Scheme 6. Addition to succinimide-derived iminium ion precursor.

alkenylalane under our water-accelerated conditions, followed by addition of **15**, provided isoindolinones **27** and **29** in 77% yield after only 15 min (Table 3). The flexibility and mild nature of these transformations are well suited for their application in the synthesis of biologically interesting target molecules and libraries.

Since this strategy provided a rapid access toward alkenyl-functionalized phthalimides, we sought to revisit our initial goal of generating medium-rings. As a model system, we synthesized alkyne **30** and allyl-pivaloate **31** and subjected them to our hydrozirconation-transmetallation conditions to generate **32** in 55% yield accompanied by considerable amounts of methyl addition side product (Scheme 7). It should be noted that carbometallation of **30** failed and the rate of addition for the alkenylalane generated via the transmetallation reaction was diminished due to the presence of the ether functionality. With **32** in hand, we screened conditions to form the desired 12-membered macrocycle. Although ring closing metathesis methodology [23] has been demonstrated to perform well for the synthesis of a variety of macrocycles [26], rapid formation of the five-membered ring **33** was observed (Scheme 7) [27]. Increasing dilution, change of metathesis catalyst, addition of $Ti(O^iPr)_4$ [28], or varying solvents did not influence the reaction pathway.

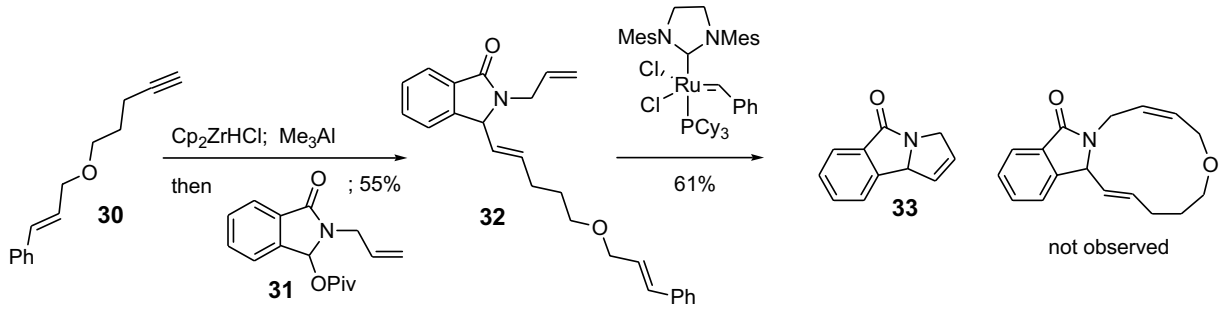
Due to the ease of formation of pyrrolizidine **33**, we explored the synthesis of this compound via addition of hexyne to **31** and subsequent ring closing metathesis to provide tricycle **33** in 75% yield (Scheme 8). Extension of this approach to the synthesis of fused azepines was achieved

Table 3
Water-accelerated carboalumination – addition to lactam **15**

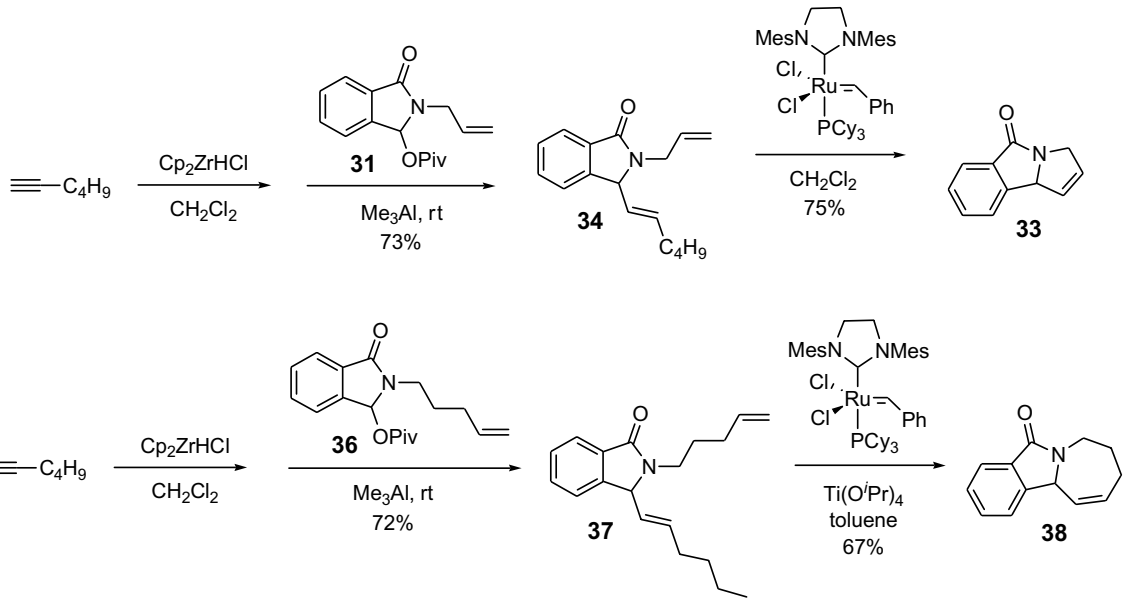


Entry	R	Product [%]
1	C_4H_9 (**16**)	**27** [77]
2	Ph (**28**)	**29** [77][a]

[a] Product contains ~5% of a carbometallation regioisomer.



Scheme 7. Attempted medium-ring formation via ring closing metathesis.



Scheme 8. Application of ring closing metathesis to generate five- and seven-membered fused ring systems.

from indolinone **37**, prepared from 2-(pent-4-enyl)isoindoline-1,3-dione (**35**) via pivaloate **36** and 1-hexyne in 72% yield. Ring closing metathesis of **37** proved to be problematic in CH_2Cl_2 with several ruthenium catalysts, yielding only starting material or decomposition products. Addition of $Ti(O^iPr)_4$ in toluene at room temperature resolved these issues and yielded 67% of **38**. Possible deactivation of the metathesis intermediate by the neighboring amide carbonyl could explain the difficulty in this transformation [29]. While not fully optimized, these reactions provide proof of concept for the conversion of our phthalimide substrates to structurally diverse tricyclic products.

3. Conclusions

We have demonstrated that *in situ* generated alkenylalanes represent versatile nucleophiles for additions to *N*-acyliminium ions. While direct intramolecular cyclization strategies currently suffer from inhibition of the carboalumination reaction by Lewis basic functional groups, pre-forming alkenylalanes via hydrozirconation–transmetallation or carboalumination and subsequent addition to the lactam acetal substrates yields functionalized isoindolinones. This method applies easily prepared or commercially available starting materials that provide opportunities for diversification at numerous points and yields synthetically useful heterocyclic products in a one-pot transformation. Further elaboration of the alkenyl heterocycles through the use of ring closing metathesis leads to tricyclic products that are common motifs in natural products and drug-like molecules.

4. Experimental

4.1. General details

All reactions were performed under an N_2 atmosphere and all glassware was dried in an oven at 140 °C for 2 h prior to use. THF and Et_2O was distilled over sodium/benzophenone ketyl, Et_3N was distilled from CaH_2, and CH_2Cl_2 and toluene were purified using an alumina filtration system. Cp_2ZrHCl [30], **18** [31], **20** [32], and **22** [24] were prepared according to literature procedures and all other compounds were purchased and used as received.

Reactions were monitored by TLC analysis (EM Science pre-coated silica gel 60 F_{254} plates, 250 mm layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with a PMA solution (5 g of phosphomolybdic acid in 100 mL of 95% EtOH), *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH), Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and 0.2 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 N H_2SO_4 solution) or a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution). Flash chromatography on SiO_2 was used to purify the crude reaction mixtures.

Melting points were determined using a Laboratory Devices Mel-Temp II. Infrared spectra were determined on a Nicolet Avatar 360 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were obtained on a Bruker Avance 300 instrument in $CDCl_3$ unless otherwise noted. Chemical shifts were reported in parts per million with the residual solvent peak used as an internal standard. ^1H NMR spectra were run at 300 MHz and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), number of protons, and coupling constant(s). ^{13}C NMR spectra were run at 76 MHz using a proton-decoupled pulse sequence with a d_1 of 3 s, and are tabulated by observed peak. Mass spectra were obtained on a Micromass Autospec double focusing instrument.

4.2. 2-(Hept-6-ynyl)isoindoline-1,3-dione (6)

A solution of hept-6-yn-1-ol (**5**) (228 mg, 2.04 mmol), phthalimide **4** (302 mg, 2.04 mmol), and PPh_3 (540 mg, 2.04 mmol) in THF (20 mL) was cooled to 0 °C and treated with DIAD (403 μL, 2.04 mmol) over 5 min. The reaction mixture was warmed to r.t. and stirred for 6 h. The solvent was evaporated, the residue was dissolved in EtOAc/hexanes (1:1, 10 mL) and the solids were filtered off. The filtrate was concentrated and chromatographed on SiO_2 (EtOAc:hexanes, 1:5) to yield imide **6** (407 mg, 1.69 mmol, 82%) as a colorless oil: IR (neat) 3466, 3283, 2941, 2862, 2115, 1772, 1709, 1615, 1397, 1046, 720 cm^{-1}; ^1H NMR δ 7.84–7.79 (m, 2H), 7.72–7.67 (m, 2H), 3.67 (t, 2H, $J = 7.1$ Hz), 2.17 (td, 2H, $J = 6.8$, 2.6 Hz), 1.91 (t, 1H, $J = 2.6$ Hz), 1.75–1.61 (m, 2H), 1.58–1.51 (m, 2H), 1.49–1.38 (m, 2H); ^{13}C NMR δ 168.3 (2C), 133.8 (2C), 132.1 (2C), 123.1 (2C), 84.2, 68.4, 37.7, 28.0, 27.9, 25.8, 18.2; MS (EI) *m*/*z* (rel. intensity) 241 ($[M]^+$, 11), 186 (6), 173 (10), 160 (100), 148 (31), 130 (29), 104 (27); HRMS (EI) *m*/*z* calcd. for $C_{15}H_{15}NO_2$ 241.1103, found 241.1107.

4.3. 2-(Hept-6-ynyl)-3-methoxyisoindolin-1-one (8)

To a 0 °C solution of imide **6** (40.0 mg, 0.166 mmol) in MeOH (4 mL) was added $NaBH_4$ (5.00 mg, 0.125 mmol). The reaction mixture was stirred at r.t. for 2.5 h, quenched with H_2O (1 mL) and the MeOH was removed *in vacuo*. The residue was extracted with CH_2Cl_2 (5 × 3 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to provide crude hydroxylactam **7** which was immediately dissolved in MeOH (4 mL), treated with *d*,*l*-camphorsulfonic acid (3.85 mg, 0.0166 mmol) and stirred for 16 h. The solvent was removed *in vacuo* and the residue was partitioned between H_2O (5 mL) and CH_2Cl_2 (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), concentrated and chromatographed on SiO_2 (EtOAc:hexanes, 1:4) to yield methoxy lactam **8** (17.0 mg, 0.0661 mmol, 40% over two steps) as a colorless oil: IR (neat) 3298, 2925, 2854, 2115, 1702, 1466, 1412, 1059, 746 cm^{-1}; ^1H NMR δ 7.84–7.80 (m, 1H), 7.61–7.49 (m, 3H), 5.88 (s, 1H), 3.79 (ddd, 1H, $J = 13.7$, 8.1, 7.3 Hz), 3.24 (ddd, 1H, $J = 14.0$, 8.0, 6.3 Hz), 2.87 (s, 3H), 2.19 (td, 2H, $J = 6.7$, 2.6 Hz), 1.92 (t, 1H, $J = 2.6$ Hz), 1.75–1.63 (m, 2H), 1.62–1.43 (m, 4H); ^{13}C NMR δ 167.6, 140.3, 133.2, 131.9, 129.9, 123.4 (2C), 86.2, 84.3, 68.4, 49.1, 39.3, 28.0, 27.6, 26.0, 18.3; MS (EI) *m*/*z* (rel. intensity) 257 ($[M]^+$, 18), 242 (17), 226 (20), 176 (66), 146 (100), 132 (39), 117 (21); HRMS (EI) *m*/*z* calcd. for $C_{16}H_{19}NO_2$ 257.1416, found 257.1419.

4.4. 2-(Hept-6-ynyl)-3-phenoxyisoindolin-1-one (**9**)

A 0 °C solution of imide **6** (307 mg, 1.27 mmol) in MeOH (20 mL) was treated with $NaBH_4$ (36.3 mg, 0.953 mmol), warmed to r.t. and stirred for 1 h. The reaction mixture was quenched with H_2O (10 mL) and the MeOH was removed *in vacuo*. The residue was extracted with CH_2Cl_2 (6 × 10 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to yield crude hydroxylactam **7** as a colorless oil. A portion of the crude hydroxylactam (101 mg, 0.416 mmol) was immediately dissolved in THF (5 mL) at r.t. and treated with $SOCl_2$ (30.3 μL, 0.416 mmol) and DMF (1 drop) and stirred for 14 h. The volatiles were removed under reduced pressure and the residue was dried *in vacuo* for 12 h. The unstable crude chloride was obtained as a colorless oil and immediately dissolved in THF (4.1 mL) at ambient temperature. This solution was treated with phenol (58.0 mg, 0.620 mmol) and Et_3N (288 μL, 2.07 mmol) and stirred for 2 h. The reaction mixture was quenched with H_2O (1 mL) and the THF was removed *in vacuo*. The residue was extracted with CH_2Cl_2 (4 × 5 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on SiO_2 (EtOAc:hexanes, 1:3) to yield phenoxylactam **9** (45.0 mg, 1.41 mmol, 34% over two steps) as a colorless oil: IR (neat) 3296, 2936, 2115, 1707, 1588, 1491, 1415, 1222, 992, 780 cm^{-1}; ^1H NMR δ 7.85–7.79 (m, 1H), 7.53–7.46 (m, 3H), 7.33–7.27 (m, 2H), 7.08–6.98 (m, 3H), 6.42 (s, 1H), 3.80 (dt, 1H, $J = 14.2$, 7.4 Hz), 3.44 (ddd, 1H, $J = 14.0$, 7.8, 6.4 Hz), 2.16 (td, 2H, $J = 6.7$, 2.6 Hz), 1.91 (t, 1H, $J = 2.6$ Hz), 1.78–1.61 (m, 2H), 1.57–1.39 (m, 4H); ^{13}C NMR δ 167.4, 156.3, 141.3, 132.3, 132.0, 130.0, 129.7 (2C), 123.5, 123.3, 123.1, 118.1 (2C), 86.8, 84.2, 68.4, 40.0, 27.9, 27.6, 25.9, 18.2; MS (EI) *m/z* (rel. intensity) 319 ($[M]^+$, 70), 265 (28), 226 (100), 198 (8), 146 (52), 132 (65); HRMS (EI) *m/z* calcd. for $C_{21}H_{21}NO_2$ 319.1572, found 319.1573.

4.5. 2-Benzyl-3-oxoisoindolin-1-yl pivaloate (**15**)

To a solution of benzyl phthalimide (8.89 g, 37.5 mmol) in MeOH (130 mL) was added sodium borohydride (1.42 g, 37.5 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 2 h and carefully quenched with H_2O. The aqueous layer was extracted with EtOAc (2×) and the organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was dried to yield a white solid which was carried on to the next step without further purification. To a solution of the crude reduced phthalamide (1.00 g, 4.20 mmol) in THF (30 mL) was added Et_3N (1.17 mL, 8.40 mmol) and pivaloyl chloride (621 μL, 5.04 mmol) at 0 °C and the reaction mixture was allowed to warm to r.t. and stirred at this temperature for 4 h. The mixture was quenched with sat. aq. $NaHCO_3$, extracted with EtOAc (2×), dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc:hexanes, 3:7) to yield 1.09 g (80% over 2 steps) of **15** as a colorless solid: m.p. 88.1–89.0 °C (CH_2Cl_2); IR (neat) 3419, 3062, 3031, 2973, 2934, 2872, 1717, 1408, 1276, 1122, 959, 751 cm^{-1}; ^1H NMR δ 7.92–7.84 (m, 1H), 7.61–7.53 (m, 2H), 7.50–7.43 (m, 1H), 7.38–7.22 (m, 5H), 6.89 (s, 1H), 5.01 (d, 1H, $J = 15$ Hz), 4.44 (d, 1H, $J = 15$ Hz), 1.13 (s, 9H); ^{13}C NMR δ 178.4, 167.9, 141.3, 136.8, 132.5, 131.9, 130.2, 128.7, 128.1, 127.7, 123.7, 123.7, 81.0, 44.2, 39.0, 26.8; MS (EI) *m/z* (rel. intensity) 323 ($[M]^+$, 35), 221 (100), 133 (65), 91 (100); HRMS (EI) *m/z* calcd. for $C_{21}H_{23}NO$ 323.1521, found 323.1515.

4.6. (E)-2-Benzyl-3-(hex-1-enyl)isoindolin-1-one (**17**)

General protocol A. To a solution of 1-hexyne (**16**) (60.5 μL, 0.526 mmol) in CH_2Cl_2 (1.5 mL) was added zirconocene hydrochloride (156 mg, 0.605 mmol) and the resulting suspension was stirred at r.t. for 10 min. The resulting yellow solution was cooled to 0 °C and Me_3Al (1.0 M in CH_2Cl_2, 0.605 mL, 0.605 mmol) and **15** (85.0 mg, 0.263 mmol) were added. The mixture was warmed to r.t. and stirred at this temperature for 1 h, quenched with sat. aq. NH_4Cl, and extracted with CH_2Cl_2. The organic layers were separated, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc:hexanes, 3:7) to yield 65.1 mg (81%) of **17** as a colorless oil: IR (neat) 3479, 3031, 2927, 2857, 1694, 1615, 1400, 972 cm^{-1}; ^1H NMR δ 7.91–7.86 (m, 1H), 7.56–7.42 (m, 2H), 7.36–7.21 (m, 6H), 5.90 (dt, 1H, $J = 15.0$, 6.8 Hz), 5.30 (d, 1H, $J = 14.8$ Hz), 5.09 (dd, 1H, $J = 15.2$, 9.2 Hz), 4.70 (d, 1H, $J = 9.2$ Hz), 4.17 (d, 1H, $J = 14.9$ Hz), 2.13 (app q, 2 H, $J = 6.7$ Hz), 1.50–1.30 (m, 4H), 0.94 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR δ 167.9, 145.1, 138.3, 137.5, 131.8, 131.5, 128.6, 128.3, 127.3, 126.1, 123.6, 123.0, 62.7, 43.8, 31.8, 31.1, 22.1, 13.8; MS (EI) *m/z* (rel. intensity) 305 ($[M]^+$, 100), 248 (40), 237 (70), 214 (40); HRMS (EI) *m/z* calcd. for $C_{21}H_{23}NO$ 305.1780, found 305.1785.

4.7. (E)-2-Benzyl-3-(2-cyclohexylvinyl)isoindolin-1-one (**19**)

According to general protocol A, alkyne **18** (66.9 mg, 0.618 mmol), CH_2Cl_2 (1.5 mL), zirconocene hydrochloride (183 mg, 0.711 mmol), Me_3Al (1.0 M in CH_2Cl_2, 0.711 mL, 0.711 mmol) and **15** (100 mg, 0.309 mmol) afforded 80.8 mg (79%) of **19** as a colorless oil after purification on SiO_2 (EtOAc:hexanes, 3:7): IR (neat) 3375, 3030, 2921, 2851, 2243, 1220, 1200, 1097, 844 cm^{-1}; ^1H NMR δ 7.92–7.86 (m, 1 H), 7.54–7.41 (m, 2H), 7.35–7.20 (m, 6H), 5.85 (dd, 1H, $J = 15.3$, 6.6 Hz), 5.28 (d, 1H, $J = 14.8$ Hz), 5.02 (ddd, 1H, $J = 15.3$, 9.2, 1.2 Hz), 4.67 (d, 1H, $J = 9.2$ Hz), 4.18 (d, 1H, $J = 14.8$ Hz), 2.14–1.96 (m, 1H), 1.85–1.60 (m, 4H), 1.42–1.00 (m, 6H); ^{13}C NMR δ 167.9, 145.1, 144.1, 137.4, 131.8, 131.4, 128.5, 128.3, 128.2, 127.3, 123.6, 122.9, 62.8, 43.8, 40.3, 32.6, 26.0, 25.8; MS (EI) *m/z* (rel. intensity) 331 ($[M]^+$, 86), 248 (40), 237

(100); HRMS (EI) *m/z* calcd. for $C_{23}H_{25}NO$ 331.1936, found 331.1951.

4.8. (*E*)-2-Benzyl-3-(4-(*tert*-butyldiphenylsilyloxy)but-1-enyl)isoindolin-1-one (**21**)

According to general protocol A, alkyne **20** (94.4 mg, 0.306 mmol), CH_2Cl_2 (1 mL), zirconocene hydrochloride (78.9 mg, 0.306 mmol), Me_3Al (1.0 M in CH_2Cl_2, 0.306 mL, 0.306 mmol) and **15** (50.0 mg, 0.153) afforded 57.6 mg (71%) of **21** as a colorless oil after purification on SiO_2 (EtOAc:hexanes, 2:8): IR (neat) 3450, 2930, 2857, 1692, 1428, 1111, 735, 701 cm^{-1}; ^1H NMR δ 7.92–7.86 (m, 1H), 7.72–7.65 (m, 4H), 7.53–7.35 (m, 9H), 7.32–7.21 (m, 5H), 5.96 (dt, 1H, $J = 15.3$, 6.8 Hz), 5.27 (d, 1H, $J = 14.9$ Hz), 5.16 (dddd, 1H, $J = 15.3$, 9.1, 1.2, 1.2 Hz), 4.71 (d, 1H, $J = 9.1$ Hz), 4.16 (d, 1H, $J = 14.9$ Hz), 3.77 (dt, 2H, $J = 6.3$, 1.2 Hz), 2.37 (app q, 2H, $J = 6.6$ Hz), 1.08 (s, 9H); ^{13}C NMR δ 168.0, 144.9, 137.5, 135.6, 134.8, 133.8, 131.9, 131.5, 129.7, 128.6, 128.4, 128.2, 127.7, 127.4, 123.6, 123.1, 63.2, 62.6, 43.9, 35.6, 26.9, 19.2; MS (EI) *m/z* (rel. intensity) 532 ($[M]^+$, 35), 488 (100), 474 (45), 306 (65), 252 (75); HRMS (EI) *m/z* calcd. for $C_{35}H_{37}NO_2Si$ 532.2664, found 532.2664.

4.9. (*E*)-Methyl 4-(2-benzyl-3-oxoisoindolin-1-yl)but-3-enyl(tosyl)carbamate (**23**)

According to general protocol A, alkyne **22** (174 mg, 0.618 mmol), CH_2Cl_2 (1.5 mL), zirconocene hydrochloride (183 mg, 0.711 mmol), Me_3Al (1.0 M in CH_2Cl_2, 0.711 mL, 0.711 mmol) and **15** (100 mg, 0.309) afforded 95.1 mg (62%) of **23** as a colorless oil after purification on SiO_2 (acetone:CH_2Cl_2, 0.3:9.7): IR (neat) 3467, 3032, 2957, 2245, 1735, 1686, 1359, 1168, 733 cm^{-1}; ^1H NMR δ 7.92–7.78 (m, 3H), 7.56–7.41 (m, 2H), 7.39–7.18 (m, 9H), 5.93 (dt, 1H, $J = 15.2$, 7.0 Hz), 5.26 (d, 1H, $J = 14.9$ Hz), 5.21 (dd, 1H, $J = 15.1$, 9.1 Hz), 4.73 (d, 1H, $J = 9.0$), 4.18 (d, 1H, $J = 14.9$ Hz), 3.95 (t, 2H, $J = 7.0$ Hz), 3.69 (s, 3H), 2.58 (app q, 2 H, $J = 7.0$ Hz), 2.43 (s, 3H); ^{13}C NMR δ 168.0, 152.8, 144.8, 144.6, 137.4, 136.5, 133.0, 131.7, 131.6, 129.7, 129.4, 128.6, 128.3, 128.3, 127.4, 123.6, 123.2, 62.3, 53.8, 46.5, 43.8, 32.9, 21.6; MS (EI) *m/z* (rel. intensity) 504 ($[M]^+$, 50), 262 (40), 155 (100); HRMS (EI) *m/z* calcd. for $C_{28}H_{28}N_2O_5S$ 504.1719, found 504.1724.

4.10. 1-Benzyl-3,3-dimethylpyrrolidine-2,5-dione (**24**)

A mixture of 2,2-dimethylsuccinic anhydride (710 mg, 5.55 mmol) and benzyl amine (712 mg, 6.66 mmol, 1.2 equiv.) was heated over a bunsen burner for ~1 min. The cooled mixture was purified by chromatography on SiO_2 (EtOAc:hexanes, 1:1) to furnish 1.14 g (95%) of **24** as a colorless oil: IR (neat) 2969, 2933, 1777, 1702, 1344, 1142, 709 cm^{-1}; ^1H NMR δ 7.29–7.21 (m, 5H), 4.57 (s, 2H), 2.47 (s, 2H), 1.22 (s, 6H); ^{13}C NMR δ 182.5, 175.1, 135.8, 128.3, 128.1, 127.5, 43.2, 42.0, 39.7, 25.1; MS (EI) *m/z* (rel intensity) 217 ($[M]^+$, 100), 174 (33), 133 (22); HRMS (EI) *m/z* calcd. for $C_{13}H_{15}NO_2$ 217.1103, found 217.1104.

4.11. 1-Benzyl-4,4-dimethyl-5-oxopyrrolidin-2-yl pivaloate (**25**)

A solution of imide **24** (1.14 g, 5.25 mmol) in MeOH (53 mL) was treated with $NaBH_4$ (200 mg, 2.62 mmol) at ambient temperature. After 6 h, the reaction mixture was concentrated, the residue dissolved in CH_2Cl_2 (50 mL) and treated with sat. aq. NH_4Cl. The aqueous layer was separated and washed with CH_2Cl_2 (2×) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated and the resulting oil used without further purification. A solution of the crude oil in CH_2Cl_2 (50 mL) was treated sequentially with Et_3N (2.19 mL, 15.7 mmol, 3 equiv.), DMAP (128 mg, 1.05 mmol, 20 mol %) and pivaloyl chloride (1.29 mL, 10.5 mmol, 2 equiv.) at ambient temperature. After 6 h, the reaction mixture was quenched with 3 M HCl and the aqueous layer washed with CH_2Cl_2 (3×). The combined organic layers were washed with H_2O, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc:hexanes, 1:2) to yield 398 mg (25%) of **25** as a colorless oil: IR (neat) 2971, 1710, 1419, 1125, 707 cm^{-1}; ^1H NMR δ 7.33–7.21 (m, 5H), 5.99 (d, 1H, $J = 6.3$ Hz), 4.74 (d, 1H, $J = 14.7$ Hz), 4.15 (d, 1H, $J = 14.7$ Hz), 2.14 (dd, 1H, $J = 14.1$, 6.3 Hz), 1.87 (d, 1H, $J = 14.4$ Hz), 1.32 (s, 3H), 1.22 (s, 3H), 1.10 (s, 9H); ^{13}C NMR δ 180.6, 177.9, 136.6, 128.7, 128.2, 127.6, 82.1, 44.8, 41.5, 39.3, 38.7, 26.8, 26.5, 25.6; MS (EI) *m/z* (rel. intensity) 303 ($[M]^+$, 36), 275 (15), 202 (85), 158 (46); HRMS (EI) *m/z* calcd. for $C_{18}H_{25}NO_3$ 303.1834, found 303.1827.

4.12. (*E*)-1-Benzyl-5-(hex-1-enyl)-3,3-dimethylpyrrolidin-2-one (**26**)

According to general protocol A, hexyne (**16**) (9.77 mg, 0.119 mmol), CH_2Cl_2 (1 mL), zirconocene hydrochloride (30.7 mg, 0.119 mmol), Me_3Al (1.0 M in CH_2Cl_2, 0.119 mL, 0.119 mmol) and **25** (18.0 mg, 0.0593 mmol) afforded 14.0 mg (83%) of **26** as a colorless oil after purification on SiO_2 (EtOAc:hexanes, 2.5:7.5): IR (neat) 2958, 2928, 2868, 1692, 1411, 1262, 972, 752 cm^{-1}; ^1H NMR δ 7.35–7.23 (m, 3H), 7.21–7.13 (m, 2H), 5.53 (dt, 1H, $J = 15.0$, 6.6 Hz), 5.16 (dd, 1H, $J = 15.3$, 9.0 Hz), 4.94 (d, 1H, $J = 14.4$ Hz), 3.88 (d, 1H, $J = 14.4$ Hz), 3.73 (app q, 1H, $J = 7.8$ Hz), 2.10–1.98 (m, 2H), 1.99 (dd, 1H, $J = 12.9$, 7.2 Hz), 1.58 (dd, 1H, $J = 12.9$, 8.1 Hz), 1.42–1.28 (m, 4H), 1.24 (s, 3H), 1.11 (s, 3H), 0.92 (t, 3H, $J = 6.9$ Hz); ^{13}C NMR δ 179.6, 137.2, 135.8, 129.8, 128.4, 128.3, 127.2, 56.9, 44.2, 42.0, 40.3, 31.8, 31.2, 25.5, 24.7, 22.2, 13.9; MS (EI) *m/z* (rel. intensity) 285 ($[M]^+$, 20), 228 (20), 175 (30), 91 (100); HRMS (EI) *m/z* calcd. for $C_{19}H_{27}NO$ 285.2093, found 285.2090.

4.13. (*E*)-2-Benzyl-3-(2-methylhex-1-enyl)isoindolin-1-one (**27**)

General protocol B. To a −30 °C solution of $AlMe_3$ (89.0 mg, 1.24 mmol) and Cp_2ZrCl_2 (9.00 mg, 0.0309 mmol) in CH_2Cl_2 (1.5 mL) was added H_2O (11.1 mg, 0.619 mmol) dropwise. The reaction mixture was warmed to ambient temperature, cooled to 0 °C, treated with 1-hexyne (**16**) (71.0 μL, 0.619 mmol), stirred for 30 min and treated with **15** (100 mg, 0.309 mmol). The reaction mixture was warmed to r.t. and stirred at this temperature for 1 h, quenched with sat. aq. NH_4Cl, and extracted with CH_2Cl_2. The organic layers were separated, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc:hexanes, 3:7) to yield 76.0 mg (77%) of **27** as a colorless oil: IR (neat) 2956, 2929, 2858, 1694, 1468, 1401, 749, 703 cm^{-1}; ^1H NMR δ 7.89–7.50 (m, 1H), 7.53–7.40 (m, 2H), 7.35–7.20 (m, 6H), 5.31 (d, 1H, $J = 14.9$ Hz), 5.06 (d, 1H, $J = 9.8$), 4.81 (dq, 1H, $J = 9.8$, 1.2 Hz), 4.09 (d, 1H, $J = 14.9$ Hz), 2.07 (t, 2H, $J = 7.1$ Hz), 1.67 (d, 3H, $J = 1.3$ Hz), 1.50–1.22 (m, 4H), 0.91 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR δ 168.1, 145.7, 143.4, 137.5, 132.0, 131.4, 128.5, 128.2, 128.0, 127.3, 123.6, 122.8, 120.6, 57.9, 43.9, 39.3, 29.8, 22.2, 16.5, 13.8; MS (EI) *m*/*z* (rel. intensity) 319 ($[M]^+$, 100), 221 (40); HRMS (EI) *m*/*z* calcd. for $C_{22}H_{25}NO$ 319.1936, found 319.1921.

4.14. (*E*)-2-Benzyl-3-(2-phenylprop-1-enyl)isoindolin-1-one (**29**)

According to general protocol B, alkyne **28** (68.0 μL, 0.619 mmol), $AlMe_3$ (89.0 mg, 1.24 mmol), Cp_2ZrCl_2 (9.00 mg, 0.0309 mmol), CH_2Cl_2 (1.5 mL), H_2O (11.1 mg, 0.619 mmol) and **15** (100 mg, 0.309 mmol) afforded 81.0 mg (77%) of **29** as a colorless oil and a 95:5 mixture of regioisomers after purification on SiO_2 (EtOAc:hexanes, 1:3): Major isomer: IR (neat) 3030, 2918, 1693, 1602, 1432, 1400, 1250, 749 cm^{-1}; ^1H NMR δ 7.93 (dd, 1H, $J = 6.3$, 2.1 Hz), 7.54–7.46 (m, 2H), 7.35–7.26 (m, 11H), 5.41 (dd, 1H, $J = 9.6$, 0.9 Hz), 5.35 (d, 1H, $J = 15.0$ Hz), 5.27 (d, 1H, $J = 9.9$ Hz), 4.21 (d, 1H, $J = 15.0$ Hz), 2.12 (d, 3H, $J = 0.9$ Hz); ^{13}C NMR δ 168.1, 145.0, 142.0, 141.3, 137.4, 132.0, 131.6, 128.6, 128.3, 127.8, 127.5, 125.8, 123.8, 123.7, 122.9, 58.2, 44.3, 16.3; MS (EI) *m*/*z* (rel. intensity) 339 ($[M]^+$, 41), 248 (47), 234 (77), 91 (100); HRMS (EI) *m*/*z* calcd. for $C_{24}H_{21}NO$ 339.1623, found 339.1631. Minor isomer (characteristic peaks): ^1H NMR δ 1.44 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR δ 128.0, 121.9, 18.0.

4.15. (*E*)-(3-(Pent-4-ynyloxy)prop-1-enyl)benzene (**30**)

To a solution of 4-pentyn-1-ol (4.03 mL, 43.3 mmol) in hexanes (75 mL) was added 50% NaOH (75 mL), TBAI (801 mg, 2.17 mmol) and cinnamyl bromide (8.97 g, 45.5 mmol). The reaction mixture was rapidly stirred for 10 h. The organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc:hexanes, 1:9) to yield 9.00 g (69%) of **30** as a colorless oil: IR (neat) 3298, 3027, 2951, 2854, 2117, 1478, 1365, 1111, 967 cm^{-1}; ^1H NMR δ 7.44-7.37 (m, 2H), 7.37–7.27 (m, 2H), 7.27–7.21 (m, 1H), 6.62 (d, 1H, $J = 15.9$Hz), 6.30 (dt, 1H, $J = 15.9$, 6.0), 4.15 (dd, 2H, $J = 6.0$, 0.9 Hz), 3.60 (t, 2 H, $J = 6.3$ Hz), 2.34 (dt, 2H, $J = 7.2$, 2.7 Hz), 1.96 (t, 1H, $J = 2.7$ Hz), 1.85 (app p, 2H, $J = 6.6$ Hz); ^{13}C NMR δ 136.5, 131.8, 128.3, 127.4, 126.2, 126.0, 83.7, 71.2, 68.5, 68.3, 28.5, 15.1; MS (EI) *m*/*z* (rel. intensity) 199 ($[M]^+$, 100), 186 (35), 173 (35), 131 (100); HRMS (EI) *m*/*z* calcd. for $C_{14}H_{16}O$ 199.1123, found 199.1126.

4.16. 2-Allyl-3-oxoisoindolin-1-yl pivaloate (**31**)

To a solution of 2-allylisoindoline-1,3-dione (3.64 g, 19.4 mmol) in MeOH (100 mL) was added sodium borohydride (734 mg, 19.4 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 2 h and carefully quenched with H_2O. The aqueous layer was extracted with EtOAc (2×) and the organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was dried to yield a white solid which was carried on to the next step without further purification. To a solution of the crude reduced phthalamide (3.60 g, 19.0 mmol) in THF (100 mL) was added Et_3N (7.90 mL, 57.0 mmol) and pivaloyl chloride (2.81 mL, 22.8 mmol) at 0 °C and the reaction mixture was allowed to warm to r.t. and stirred at this temperature for 4 h. The mixture was quenched with sat. aq. $NaHCO_3$, extracted with EtOAc (2x), dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc:hexanes, 2.5:7.5) to yield 4.40 g (83% over 2 steps) of **31** as a colorless oil: IR (neat) 2976, 1716, 1405, 1135, 753 cm^{-1}; ^1H NMR δ 7.88–7.80 (m, 1H), 7.62–7.46 (m, 3H), 6.99 (s, 1H), 5.94–5.77 (m, 1H), 5.29–5.15 (m, 2H), 4.44 (dd, 1H, $J = 15.9$, 5.1 Hz), 3.88 (dd, 1H, $J = 15.3$, 6.6 Hz), 1.23 (s, 9H); ^{13}C NMR δ 178.3, 167.5, 141.2, 132.4, 132.4, 131.8, 130.0, 123.6, 123.5, 118.0, 80.9, 42.8, 39.0, 26.9; MS (EI) *m*/*z* (rel. intensity) 273 ($[M]^+$, 60), 172 (100); HRMS (EI) *m*/*z* calcd. for $C_{16}H_{19}NO_3$ 273.1365, found 273.1358.

4.17. 2-Allyl-3-((*E*)-5-(cinnamyloxy)pent-1-enyl)isoindolin-1-one (**32**)

According to general protocol A, alkyne **30** (733 mg, 3.66 mmol), CH_2Cl_2 (10 mL), zirconocene hydrochloride (944 mg, 3.66 mmol), Me_3Al (1.0 M in CH_2Cl_2, 3.66 mL, 3.66 mmol) and **31** (500 mg, 1.83 mmol) (reaction time increased to 12 h) afforded 376 mg (55%) of **32** as a colorless oil after purification on SiO_2 (acetone:CH_2Cl_2, 0.7:9.3): IR (neat) 2924, 2853, 1694, 1468, 1289, 1098, 968, 746 cm^{-1}; ^1H NMR δ 7.85 (d, 1H, $J = 6.6$ Hz), 7.57–7.20 (m, 8H), 6.61 (d, 1H, $J = 15.9$ Hz), 6.29 (dt, 1H, $J = 15.9$, 6.0 Hz), 6.02 (dt, 1H, $J = 13.8$, 6.9 Hz), 5.90–5.73 (m, 1 H), 5.25–5.07 (m, 3H), 4.87 (d, 1H,

$J = 9.0$ Hz), 4.60 (ddd, 1H, $J = 15.6$, 4.5, 2.7 Hz), 4.15 (dd, 2H, $J = 6.0$, 1.2 Hz), 3.70 (dd, 1H, $J = 15.3$, 7.2 Hz), 3.53 (t, 2H, $J = 6.3$ Hz), 2.25 (app q, 2H, $J = 6.9$ Hz), 1.77 (app p, 2H, $J = 7.8$ Hz); ^{13}C NMR δ 167.7, 144.9, 137.2, 136.6, 133.2, 132.3, 131.8, 131.4, 128.5, 128.3, 127.6, 126.7, 126.4, 126.1, 123.5, 122.9, 117.5, 71.5, 69.4, 62.9, 42.5, 29.2, 28.9; MS (ESI) *m/z* (rel. intensity) 396 ($[M + Na]^+$, 100), 307 (20), 297 (20); HRMS (ESI) *m/z* calcd. for $C_{25}H_{27}NO_2Na$ 396.1939, found 396.1928.

4.18. 3H-Pyrrolo[2,1-a]isoindol-5(9bH)-one (**33**)

To a solution of **32** (41.7 mg, 0.112 mmol) in CH_2Cl_2 (6 mL) was added Grubbs 2nd generation catalyst (4.75 mg, 5.60 μmol) and the red solution was heated at 50 °C for 1 h, cooled to r.t. and concentrated. The residue was purified by chromatography on SiO_2 (acetone:CH_2Cl_2, 0.4:9.6) to yield 11.7 mg (61%) of **33** as a colorless oil: IR (neat) 2872, 1614, 1468, 1395, 1366, 1080, 746 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 7.74-7.66 (m, 2H), 7.66–7.58 (m, 1 H), 7.54–7.45 (m, 1H), 6.28–6.20 (m, 1H), 6.08–5.99 (m, 1H), 5.53 (app d, 1H, $J = 1.8$ Hz), 4.57–4.43 (m, 1H), 3.98–3.83 (m, 1H); ^{13}C NMR (acetone-d_6) δ 175.4, 148.4, 133.6, 133.1, 131.9, 129.4, 129.2, 124.6, 124.0, 71.1, 52.0; MS (EI) *m/z* (rel. intensity) 171 ($[M]^+$, 60), 160 (70), 130 (55), 105 (60), 83 (100); HRMS (EI) *m/z* calcd. for $C_{11}H_9NO$ 171.0684, found 171.0676.

4.19. (E)-2-Allyl-3-(hex-1-enyl)isoindolin-1-one (**34**)

According to general protocol A, 1-hexyne (**16**) (420 μL, 3.66 mmol), CH_2Cl_2 (10 mL), zirconocene hydrochloride (944 mg, 3.66 mmol), Me_3Al (1.0 M in CH_2Cl_2, 3.66 mL, 3.66 mmol) and **31** (500 mg, 1.83 mmol) afforded 341 mg (73%) of **34** as a colorless oil after purification on SiO_2 (EtOAc:hexanes, 3:7): IR (neat) 2957, 2926, 1697, 1468, 1396, 971, 748 cm^{-1}; ^{1}H NMR δ 7.83 (d, 1H, $J = 7.2$ Hz), 7.57–7.38 (m, 2H), 7.33 (d, 1H, $J = 7.5$ Hz), 5.97 (dt, 1H, $J = 15.0$, 6.9 Hz), 5.88–5.71 (m, 1H), 5.22–4.97 (m, 3H), 4.85 (d, 1H, $J = 9.3$ Hz), 4.59 (dd, 1H, $J = 15.6$, 4.5 Hz), 3.69 (dd, 1H, $J = 15.3$, 7.2 Hz), 2.12 (app q, 2H, $J = 6.6$ Hz), 1.48–1.28 (m, 4H), 0.91 (t, 3H, $J = 6.9$ Hz); ^{13}C NMR δ 167.7, 145.0, 138.2, 133.1, 131.7, 131.4, 128.2, 126.0, 123.4, 122.9, 117.4, 62.9, 42.5, 31.8, 31.1, 27.0, 22.0, 13.8; MS (EI) *m/z* (rel intensity) 255 ($[M]^+$, 30), 198 (100), 172 (55); HRMS (EI) *m/z* calcd. for $C_{17}H_{21}NO$ 255.1623, found 255.1627.

4.20. 2-(Pent-4-enyl)isoindoline-1,3-dione (**35**)

A solution of 4-penten-1-ol (3.51 mL, 34.0 mmol), phthalimide **4** (5.00 mg, 34.0 mmol), and PPh_3 (8.92 g, 34.0 mmol) in THF (220 mL) was cooled to 0 °C and treated with DIAD (6.69 mL, 34.0 mmol) over 5 min. The reaction mixture was warmed to r.t. and stirred for 6 h. The solvent was evaporated, the residue was dissolved in EtOAc/hexanes (1:1, 100 mL) and the solids were filtered off. The filtrate was concentrated and chromatographed on SiO_2 (EtOAc:hexanes, 1:5) to yield 6.44 g (88%) of imide **35** as a colorless oil: IR (neat) 3466, 3077, 2939, 1773, 1641, 1397, 995, 720 cm^{-1}; ^{1}H NMR δ 7.88–7.81 (m, 2H), 7.76–7.67 (m, 2H), 5.90–5.73 (m, 1H), 5.12–4.94 (m, 2H), 3.70 (dt, 2H, $J = 7.5$, 4.5 Hz), 2.20–2.07 (m, 2H), 1.87–1.73 (m, 2H); ^{13}C NMR δ 168.1, 137.1, 133.7, 131.9, 122.9, 115.1, 37.3, 30.8, 27.4; MS (EI) *m/z* (rel. intensity) 215 ($[M]^+$, 45), 173 (70), 160 (100), 148 (80), 130 (80), 104 (90); HRMS (EI) *m/z* calcd. for $C_{13}H_{13}NO_2$ 215.0946, found 215.0946.

4.21. 3-Oxo-2-(pent-4-enyl)isoindolin-1-yl pivalate (**36**)

To a solution of imide **35** (4.42 g, 20.5 mmol) in MeOH (100 mL) was added sodium borohydride (776 mg, 20.5 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 2 h and carefully quenched with H_2O. The aqueous layer was extracted with EtOAc (2×) and the organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was dried to yield a white solid which was carried on to the next step without further purification. To a solution of the crude reduced phthalamide (4.23 g, 19.5 mmol) in THF (100 mL) was added Et_3N (8.15 mL, 58.5 mmol), pivaloyl chloride (3.61 mL, 29.3 mmol) and DMAP (119 mg, 0.975 mmol) at 0 °C and the reaction mixture was allowed to warm to r.t. and stirred at this temperature for 8 h. The mixture was quenched with sat. aq. $NaHCO_3$, extracted with EtOAc (2×), dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc:hexanes, 1:5) to yield 4.70 g (76% over 2 steps) of **36** as a colorless oil: IR (neat) 3077, 2974, 2873, 1739, 1641, 1618, 1369, 1208, 1141, 959, 751 cm^{-1}; ^{1}H NMR δ 7.67 (d, 1H, $J = 6.0$ Hz), 7.49–7.32 (m, 3H), 6.89 (s, 1H), 5.79–5.58 (m, 1H), 4.91 (d, 1H, $J = 17.1$ Hz), 4.84 (d, 1H, $J = 10.5$ Hz), 3.73–3.55 (m, 1H), 3.27–3.09 (m, 1H), 2.07–1.93 (m, 2H), 1.77–1.50 (m, 2H), 1.11 (s, 9H); ^{13}C NMR δ 178.2, 167.4, 140.9, 137.1, 132.0, 131.8, 129.8, 123.2, 123.1, 114.9, 80.8, 39.5, 38.7, 30.7, 27.1, 26.6; MS (EI) *m/z* (rel intensity) 301 ($[M]^+$, 15), 246 (45), 216 (65), 200 (85), 146 (85), 133 (65); HRMS (EI) *m/z* calcd. for $C_{18}H_{23}NO_3$ 301.1678, found 301.1681.

4.22. (E)-3-(Hex-1-enyl)-2-(pent-4-enyl)isoindolin-1-one (**37**)

According to general protocol A, hexyne (**16**) (420 μL, 3.66 mmol), CH_2Cl_2 (10 mL), zirconocene hydrochloride (944 mg, 3.66 mmol), Me_3Al (1.0 M in CH_2Cl_2, 3.66 mL, 3.66 mmol) and **36** (552 mg, 1.83 mmol) afforded 368 mg (72%) of **37** as a colorless oil after purification on SiO_2 (EtOAc:hexanes, 3:7): IR (neat) 3076, 2967, 2928, 2860, 1693, 1468, 1404, 972, 749 cm^{-1}; ^{1}H NMR δ 7.72 (d, 1H, $J = 7.5$ Hz), 7.44–7.28 (m, 2H), 7.23 (d, 1H, $J = 7.2$ Hz), 5.94 (dt, 1H, $J = 14.4$, 6.6 Hz), 5.80–5.63

(m, 1H), 5.03–4.82 (m, 3H), 4.75 (d, 1H, $J = 9.0$ Hz), 3.83–3.65 (m, 1H), 3.23–3.07 (m, 1H), 2.13–1.93 (m, 4H), 1.75–1.51 (m, 2H), 1.42–1.19 (m, 4H), 0.83 (t, 3H, $J = 6.9$ Hz); ^{13}C NMR δ 167.6, 144.6, 137.5, 137.3, 131.7, 131.0, 127.9, 126.2, 122.9, 122.6, 114.7, 63.2, 39.4, 31.5, 30.8, 30.7, 27.3, 26.9, 21.8, 13.5; MS (EI) *m/z* (rel. intensity) 283 ([M]$^+$, 20), 228 (70), 160 (100), 146 (50), 76 (50); HRMS (EI) *m/z* calcd. for $C_{19}H_{25}NO$ 283.1936, found 283.1934.

*4.23. (Z)-7,8,9,11a-Tetrahydro-5H-azepino[2,1-a]isoindol-5-one (**38**)*

To a solution of **37** (150 mg, 0.529 mmol) in toluene (100 mL) was added Ti(O^{i}Pr)$_4$ (157 μL, 0.529 mmol) and Grubbs 2nd generation catalyst (22.5 mg, 0.0265 mmol) and the red solution was stirred at r.t. for 12 h and concentrated. The residue was purified by chromatography on SiO_2 (acetone:CH_2Cl_2, 0.4:9.6) to yield 70.7 mg (67%) of **38** as a colorless oil: IR (neat) 3024, 2926, 1680, 1469, 1419, 1298, 938, 709 cm^{-1}; ^{1}H NMR (CD_2Cl_2) δ 7.76 (dd, 1H, $J = 6.9$, 1.2 Hz), 7.58–7.51 (m, 1H), 7.46 (app t, 2H, 7.2 Hz), 6.13–6.02 (m, 1H), 6.02–5.91 (m, 1H), 4.49 (dd, 1H, $J = 11.4$, 2.1 Hz), 4.26 (ddd, 1H, $J = 13.5$, 6.6, 3.0 Hz), 3.22 (ddd, 1H, $J = 12.6$, 9.6, 2.7 Hz), 2.81 (app ddd, 1H, $J = 15.9$, 7.8, 2.4 Hz), 2.53–2.26 (m, 2H), 2.25–2.09 (m, 1H); ^{13}C NMR (CD_2Cl_2) δ 167.5, 145.9, 133.0, 132.7, 131.6, 128.8, 128.5, 123.5, 122.4, 60.6, 41.6, 35.2, 28.2; MS (EI) *m/z* (rel. intensity) 199 ([M]$^+$, 45), 145 (100), 117 (40), 90 (35); HRMS (EI) *m/z* calcd. for $C_{13}H_{13}NO$ 199.0997, found 199.0991.

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References

[1] E. Valencia, V. Fajardo, A.J. Freyer, M. Shamma, Tetrahedron Lett. 26 (1985) 993.
[2] E. Valencia, A.J. Freyer, M. Shamma, V. Fajardo, Tetrahedron Lett. 25 (1984) 599.
[3] L.A. Sorbera, P.A. Leeson, J. Silvestre, J. Castaner, Drugs Fut. 26 (2001) 651.
[4] S. Li, X. Wang, H. Guo, L. Chen, Yiyano Gongye 16 (1985) 543; Chem Abstr. 105 (1985) 3788.
[5] J.M. Ferland, C.A. Demerson, L.G. Humber, Can. J. Chem. 63 (1985) 361.
[6] (a) M. Linden, D. Hadler, S. Hofmann, Hum. Psychopharmacol. 12 (1997) 445;
(b) Z.-P. Zhuang, M.-P. Kung, M. Mu, H.F. Kung, J. Med. Chem. 41 (1998) 157;
(c) M.H. Norman, D.J. Minick, G.C. Rigdon, J. Med. Chem. 39 (1996) 149.
[7] Achinami K, Ashizawa N, Kobayasui F. Japanese Patent 03,133,955, 1991;
Chem. Abstr. 115 (1991) 255977j.
[8] E.C. Taylor, P. Zhou, L.D. Jennings, Z. Mao, B. Hu, J.-G. Jun, Tetrahedron Lett. 38 (1997) 521.
[9] For recent racemic syntheses, see: T. Yao, R.C. Larock, J. Org. Chem. 70 (2005) 1432;
L. Shen, R.P. Hsung, Org. Lett. 7 (2005) 775, and references cited therein;
For recent asymmetric syntheses, see: D.L. Comins, S. Schilling, Y. Zhang, Org. Lett. 7 (2005) 95, and references cited therein.
[10] (a) For recent examples, see: D.L. Comins, S. Schilling, Y. Zhang, Org. Lett. 7 (2005) 95;
(b) H. Heaney, K.F. Shuhaibar, Synlett (1995) 47;
(c) M. Othman, B. Decroix, Synth. Commun. 26 (1996) 2803;
(d) M. Othman, P. Pigeon, B. Decroix, Tetrahedron 53 (1997) 2495.
[11] D.L. Boger, J.K. Lee, J. Goldberg, Q. Jin, J. Org. Chem. 65 (2000) 1467.
[12] (a) For recent examples, see: P. Wipf, T.H. Graham, Org. Biomol. Chem. 3 (2005) 31;
(b) P. Wipf, J.M. Fletcher, L. Scarone, Tetrahedron Lett. 46 (2005) 5463, and references cited therein.
[13] (a) P. Wipf, S. Lim, Angew. Chem., Int. Ed. Engl. 32 (1993) 1068;
(b) P. Wipf, R.L. Nunes, S. Ribe, Helv. Chim. Acta 85 (2002) 3478;
(c) E.-I. Negishi, Bull. Chem. Soc. Jpn. 80 (2007) 233.
[14] (a) For reviews, see: P. Wipf, H. Jahn, Tetrahedron 52 (1996) 12853;
(b) P. Wipf, R.L. Nunes, Tetrahedron 60 (2004) 1269;
(c) P. Wipf, C. Kendall, Top. Organomet. Chem. 8 (2005) 1.
[15] (a) H. Hiemstra, W.N. Speckamp, in: B.M. Trost, I. Fleming (Eds.), Comprehensive Organic Synthesis, vol. 2, Pergamon, Oxford, 1991 (Chapter 4.5);
(b) B.E. Maryanoff, H.C. Zhang, J.H. Cohen, I.J. Turchi, C.A. Maryanoff, Chem. Rev. 104 (2004) 1431, and references cited therein.
[16] (a) K.V. Nikitin, N.P. Andryukhova, Can. J. Chem. 78 (2000) 1285;
(b) M.-J. Tranchant, C. Moine, R. Ben Othman, T. Bousquet, M. Othman, V. Dalla, Tetrahedron Lett. 47 (2006) 4477;
(c) R. Ben Othman, T. Bousquet, A. Fousse, M. Othman, V. Dalla, Org. Lett. 7 (2005) 2825;
(d) S.M. Allin, C.J. Northfield, M.I. Page, A.M.Z. Slawin, Tetrahedron Lett. 40 (1999) 141;
(e) Y. Ukaji, K. Tsukamoto, Y. Nasada, M. Shimizu, T. Fujisawa, Chem. Lett. 2 (1993) 221.
[17] S.R. Abrams, Can. J. Chem. 62 (1984) 1333.
[18] M.S. Kitching, W. Clegg, M.R.J. Elsegood, R.J. Griffin, B.T. Golding, Synlett 1 (1999) 997.
[19] P. Wipf, D.L. Waller, J.T. Reeves, J. Org. Chem. 70 (2005) 8096.
[20] S. Coulton, L. Francois, R. Southgate, Tetrahedron Lett. 31 (1990) 6923.
[21] (a) D.G. Washburn, R.W. Heidbrecht Jr., S.F. Martin, Org. Lett. 5 (2003) 3523;
(b) C.E. Neipp, S.F. Martin, J. Org. Chem. 68 (2003) 8867.
[22] (a) R.A. Batey, D.B. MacKay, V. Santhakumar, J. Am. Chem. Soc. 121 (1999) 5075;
(b) R.A. Batey, D.B. MacKay, Tetrahedron Lett. 41 (2000) 9935.
[23] For recent applications of cationic zirconocenes, see: P. Wipf, J.G. Pierce, N. Zhuang, Org. Lett. 7 (2005) 483, and references cited therein.
[24] P. Wipf, J.G. Pierce, Org. Lett. 8 (2006) 3375.
[25] (a) C.S. Cho, X. Wu, L.-H. Jiang, S.-C. Shim, H.-J. Choi, J. Kim Tae, J. Het. Chem. 35 (1998) 265;
(b) B. Burns, R. Grigg, V. Santhakumar, V. Sridharan, P. Stevenson, T. Worakun, Tetrahedron 48 (1992) 7297.
[26] For a review, see: A. Fürstner, Angew. Chem., Int. Ed. Engl. 39 (2000) 3012.
[27] (a) For related examples, see: J.-B. Ahn, C.-S. Yun, K.H. Kim, D.-C. Ha, J. Org. Chem. 65 (2000) 9249;
(b) I.S. Kim, O.P. Zee, Y.H. Jung, Org. Lett. 8 (2006) 4101.

[28] A. Fürstner, K. Langemann, J. Am. Chem. Soc. 119 (1997) 9130.
[29] (a) J.D. White, P. Hrnciar, A.F.T. Yokoshi, J. Am. Chem. Soc. 120 (1998) 7359;
(b) S.F. Martin, Y. Liao, H.-J. Chen, M. Patzel, M.N. Ramser, Tetrahedron Lett. 35 (1994) 6005.
[30] S.L. Buchwald, S.J. LaMaire, R.B. Nielsen, B.T. Watson, S.M. King, Org. Synth. 71 (1993) 77.
[31] P. Wipf, J. Janjic, C.R.J. Stephenson, J. Org. Biomol. Chem. 2 (2004) 443.
[32] (a) V. Theus, H. Schinz, Helv. Chem. Acta 39 (1956) 1290;
(b) R.A. Aitken, J.I. Atherton, J. Chem. Soc. Perkin Trans. 1 (1994) 1281.