Accepted Manuscript

Palladium-catalyzed allylation and deacylative allylation of 3-acetyl-2-oxindoles with allylic alcohols

Aitor Ortega-Martínez, Rocco de Lorenzo, José M. Sansano, Carmen Nájera

PII: S0040-4020(17)31189-4

DOI: 10.1016/j.tet.2017.11.041

Reference: TET 29121

To appear in: *Tetrahedron*

Received Date: 14 October 2017

Revised Date: 13 November 2017

Accepted Date: 14 November 2017

Please cite this article as: Ortega-Martínez A, de Lorenzo R, Sansano JoséM, Nájera C, Palladium-catalyzed allylation and deacylative allylation of 3-acetyl-2-oxindoles with allylic alcohols, *Tetrahedron* (2017), doi: 10.1016/j.tet.2017.11.041.

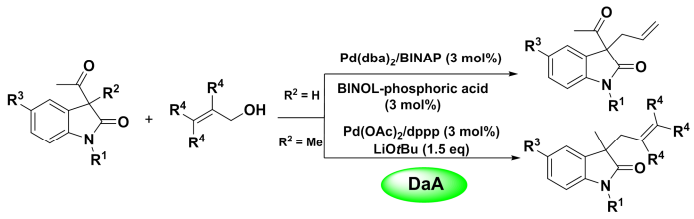
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Palladium-catalyzed allylation and deacylative allylation of 3-acetyl-2-oxindoles with allylic alcohols

Leave this area blank for abstract info.

Aitor Ortega-Martínez, Rocco de Lorenzo, José M. Sansano,* and Carmen Nájera*



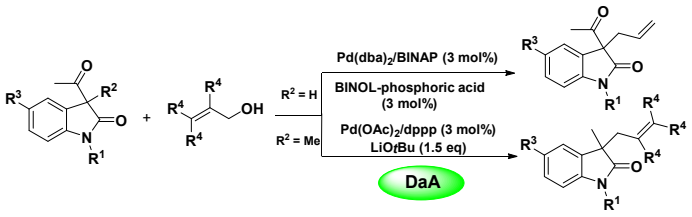
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Palladium-catalyzed allylation and deacylative allylation of 3-acetyl-2-oxindoles with allylic alcohols

Leave this area blank for abstract info.

Aitor Ortega-Martínez, Rocco de Lorenzo, José M. Sansano,* and Carmen Nájera*



Tetrahedron
journal homepage: www.elsevier.com

Palladium-catalyzed allylation and deacylative allylation of 3-acetyl-2-oxindoles with allylic alcohols

Aitor Ortega-Martínez,[a,b] Rocco de Lorenzo,[a,b] José M. Sansano,[a,b]* and Carmen Nájera[a]*

[a] *Department of Organic Chemistry and Centro de Innovación en Química Avanzada (ORFEO-CINQA). Faculty of Sciences, University of Alicante, E-03080 Alicante, Spain. Fax: +34 965903549*
[b] *Instituto de Síntesis Orgánica, University of Alicante.*

E-mail: jmsansano@ua.es, cnajera@ua.es

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

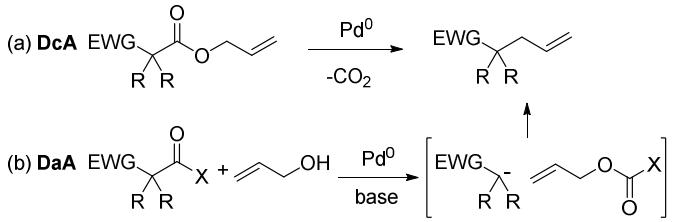
Keywords:
oxindoles
allylic alcohols
palladium
catalysis
deacylation

ABSTRACT

The Pd-catalyzed allylation of 3-acetyl-2-oxindoles with allyl alcohol is performed using 3 mol% of $Pd(dba)_2$, rac-BINAP and BINOL phosphoric acid as catalytic mixture. This procedure allows the in situ synthesis of 3-allyl-2-oxindole by adding Triton B to the reaction mixture. The deacylative allylation of 3-acetyl-3-methyl-2-oxindoles with allylic alcohols is carried out with 3 mol% of $Pd(OAc)_2$, dppp and 1.5 equiv. of Li*O*t*Bu as base affording the corresponding 3,3-disubstituted 2-oxindoles in good yields. Both methodologies can be combined for the preparation of unsymmetrical 3,3-diallylated 2-oxindoles such as compound **7**. The DaA must be carried out in the absence of oxygen in order to avoid the competitive formation of 3-alkyl-3-hydroxy-2-indoles. The later compounds can be easily obtained by deacylative oxidation of 3-alkylated 3-acetyl-2-oxindoles with LiOEt at rt under air.

1. Introduction

Pd-catalyzed allylation of nucleophiles with allylic alcohols is a direct methodology for the formation of C-C bonds.[1] Allylic alcohols are commercially available compounds and their direct use avoids the preparation of their derivatives, normally acetates, carbonates and phosphates, to generate the corresponding π-allyl Pd electrophilic intermediates. Due to the poor leaving group ability of the OH group it has to be activated by means of Lewis or Brønsted acids or by forming in situ the corresponding esters. Alternatively, two main strategies can be used for the Pd-catalyzed allylation of active methylene derivatives: (a) decarboxylative allylation (DcA)[2] of allyl esters and (b) deacylative allylation (DaA)[3] with allylic alcohols of acylated substrates (Scheme 1). Intramolecular DcA requires an anion stabilizing group for the decarboxylative metalation of the starting allyl esters, which has to be previously formed by transesterification with Otera's catalyst[4] ($XR_2SnOSnR_2X$) using a large excess of the allylic alcohol. Intermolecular deacylative metalation needs the introduction of the acetyl or a carboxylate group, which react with the alcoholate under basic conditions generating, in situ, the acetate or carbonate, respectively. This DaA takes place in THF or DMSO at 60 ºC and has been studied with α-nitro and α-cyano ketones, 1,3-diketones, and α-cyanoacetates.



Scheme 1. Pd-Catalyzed allylation of active methylene compounds by DcA and DaA

3,3-Disubstituted 2-oxindoles are important class of heterocyclic compounds occurring in natural alkaloids and biologically active compounds,[5] for instance the alkaloid horsfiline[6] and also esermethole,[7] which is an intermediate for the synthesis of acetylcholinesterase inhibitors physostigmine and phenserine[8] (Figure 1). This family of compounds have been synthetized from 3-allyl-3-methyloxindoles. The Pd-catalyzed prenylation and geranylation of 3-substituted 2-oxindoles has been performed with the corresponding allylic carbonates of the monoalkylated oxindole.[9] The resulting compounds are synthetic intermediates of flustramides A and B with skeletal and smooth muscle relaxant activity.

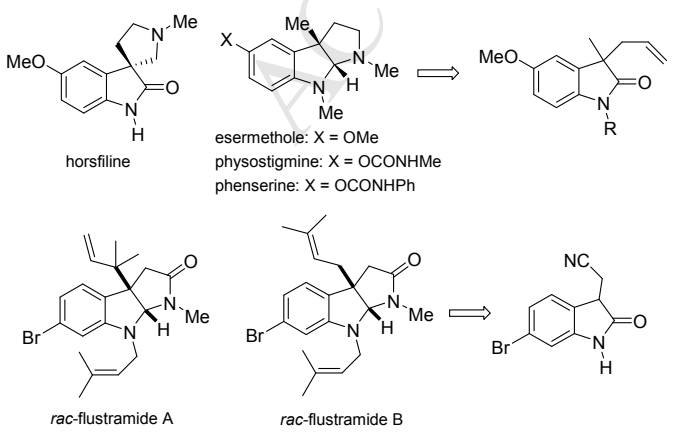
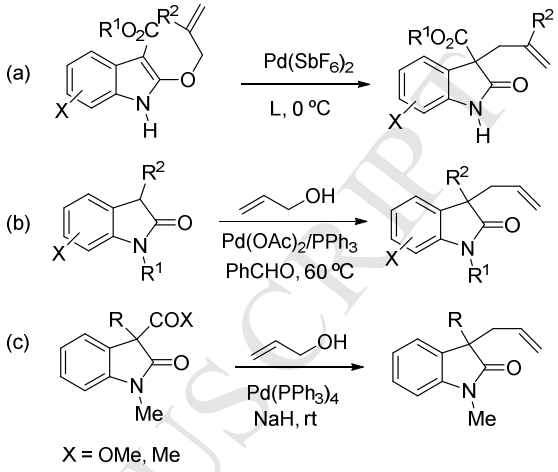


Figure 1. Biologically active 3,3-disubstituted oxindoles

For the Pd-catalyzed synthesis of 3-allyl-2-oxindoles, two alternative methodologies have been described: (a) one intramolecular process based on the Meerwein–Eschenmoser Claisen rearrangement of 2-allyloxyindoles[10]; (b) direct allylic alkylation of oxindoles with simple allylic alcohols co-catalyzed by $Pd(OAc)_2/Ph_3P$ and $PhCO_2H$;[11a] and c) the DaA of 3-acyl-2-oxindoles with allylic alcohols[11b] (Scheme 2).



Scheme 2. Synthesis of 3-allyl-2-oxindoles by Pd-catalyzed methodologies

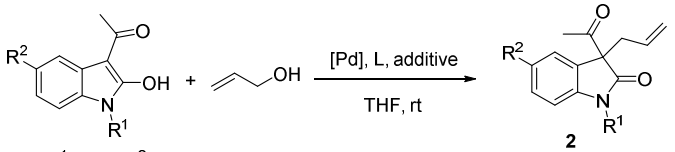
We have recently described the synthesis of 3,3-disubstituted 2-oxindoles by deacylative alkylation of 3-acetyl-2-oxindoles with alkyl halides and electrophilic alkenes under basic conditions.[12] Independently, Bisai and co-workers published a palladium-catalyzed allylation of 3-acetyl-2-oxindoles during the elaboration of this manuscript.[11b] Herein, we report our findings about the synthesis of 3,3-disubstituted 2-oxindoles by Pd-catalyzed direct allylation of 3-acetyl-2-oxindoles and by deacylative allylation. The main objectives of this study are: a) evaluate the possible palladium-catalyzed monoallylation of 3-acetyl-1-methyl-2-oxindole **1a**; b) study the DaA using similar conditions from 3-acetyl-1,3-methyl-2-oxindole (**4a**); c) the oxidation of heterocycles **4** under a mild process avoiding oxidizing agents.

2. Results and Discussion

Initially studies about the allylation of 3-acetyl-1-methyl-2-oxindole (**1a**)[12] were performed with allyl alcohol in the presence of different additives (Table 1). The selection of the *N*-methylated structure obeyed to this arrangement is present in many natural compounds (Figure 1). Using the Tamaru reaction conditions for the allylation of active methylene compounds,[13] 3 mol% of $Pd(OAc)_2$ and 1,3-bis(diphenylphosphino)propane (dppp), in the presence of triethylborane (60 mol%), gave compound **2aa** in 99% isolated crude yield (Table 1, entry 1). In order to diminish the amount of additive 3 mol% of *p*-toluenesulfonic acid (TsOH) was employed instead of Et_3B affording **2aa** in only 3% yield (Table 1, entry 2). Next, $Pd(dba)_2$ was employed instead of $Pd(OAc)_2$ without success (Table 1, entry 3). However, by changing the dppp ligand by *rac*-BINAP product **2aa** was obtained in 66% yield (Table 1, entry 4). Using *rac*-BINOL phosphoric acid instead of TsOH gave a 98% of product **2aa** (Table 1 entry 5). These reaction conditions: 3 mol%

of Pd(dba)$_2$/*rac*-BINAP//*rac*-BINOL phosphoric acid in THF at rt, were used for the allylation of 3-acetyl-2-oxindoles **1b** and **1c** providing the corresponding allylated compounds **2ba** and **2ca** in 61 and 89% yield, respectively (Table 1, entries 6 and 7). To the best of our knowledge, this is the first palladium-catalyzed allylation of 3-acetyl-1-methyl-2-oxindoles from allyl alcohol.

Table 1. Pd-Catalyzed allylation of 3-acetyl-2-oxindoles

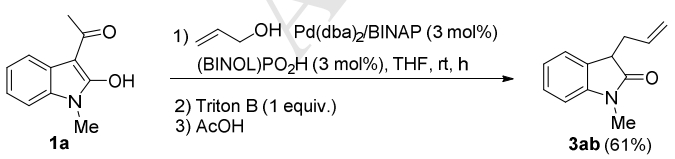


1a: R^1 = Me, R^2 = H
1b: R^1 = Me, R^2 = OMe
1c: R^1 = Bn, R^2 = OMe

Ent.	Cat (3 mol%)	Ligand (3 mol%)	Additive (mol%)	**2**	Yield (%)[b]
1	$Pd(OAc)_2$	dppp	Et_3B (60)	**2aa**	99
2	$Pd(OAc)_2$	dppp	TsOH (3)	**2aa**	3
3	$Pd(dba)_2$	dppp	TsOH (3)	**2aa**	-
4	$Pd(dba)_2$	*rac*-BINAP	TsOH (3)	**2aa**	66
5	$Pd(dba)_2$	*rac*-BINAP	(BINOL)PO_2H (3)[c]	**2aa**	98 (96)
6	$Pd(dba)_2$	*rac*-BINAP	(BINOL)PO_2H (3)[c]	**2ba**	91 (61)
7	$Pd(dba)_2$	*rac*-BINAP	(BINOL)PO_2H (3)[c]	**2ca**	99 (89)

[a] Reaction conditions: **1** (0.3 mmol), allyl alcohol (0.45 mmol), Pd (3 mol%), ligand (3 mol%), additive (see column), THF (1.5 mL), 60 h.
[b] Isolated crude yield. In parenthesis, yield after flash chromatography.
[c] Racemic (BINOL)PO_2H was employed.

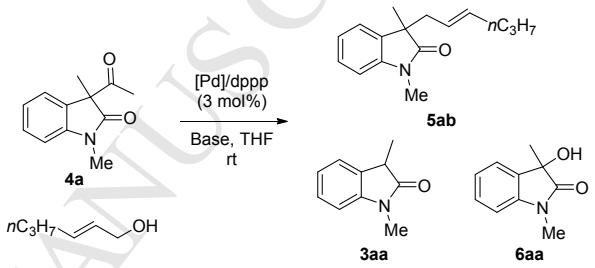
The synthesis of 3-allyl-1-methyl-2-oxindole (**3ab**) was carried out by in situ addition of a solution of benzyltrimethylammonium hydroxide (Triton B) (40% in MeOH) (1 equiv) followed by addition of AcOH (0.85 mL) in 61% yield (Scheme 3). Attempts to prepare this compound by allylation of *N*-methyl-2-oxindole with allyl bromide and Triton B as base gave the corresponding 3,3-diallylated 2-oxindole.[12] Therefore, this one-pot procedure can be used for the synthesis of 3-monoallylated oxindoles instead of using LiHMDS at -78 °C during the allylation of *N*-alkyloxindole or sodium hydride at different temperatures.[14]



Scheme 3. One-pot synthesis of 3-allyl-1-methyl-2-oxindole (**3ab**).

Next, the Pd-catalyzed deacylative allylation of 3-acetyl-1,3-methyl-2-oxindole (**4a**) was attempted. The reaction conditions study was carried out with compound **4a**[12] and hex-2-en-1-ol (Table 2). Using $Pd(OAc)_2$ and dppp (3 mol%) as catalysts and KO*t*Bu (1.1 equiv) as base in THF, after 15 h at rt under Ar atmosphere, a 3:1 mixture of **5ab** and also the oxidized 3-hydroxy-1,3-dimethyl-2-oxindole **6aa** were obtained, compound **5ab** being isolated after flash chromatography in 54% yield (Table 2, entry 1). The same process was repeated in the absence of oxygen (freezing-pump) and using LiO*t*Bu instead of KO*t*Bu giving a 95:5 mixture of both products, but also a 17% of 1,3-dimethyl-2-oxindole (**3aa**) (Table 2, entry 2). After increasing the amount of dppp to 6 mol% a 60:40 mixture of product **5ab** and **3aa** was formed (Table 2, entry 3). Changing $Pd(OAc)_2$ by $Pd_2(dba)_3$ increased the amount of deacetylated product (Table 2, entry 4). Finally increasing the amount of LiO*t*Bu to 1.5 equiv the formation of a mixture of 86% of the expected product **5ab** together with 10% of **3aa** and only 3% of **6aa** was observed (Table 2, entry 5).

Table 2. Reaction conditions study for the Pd-catalyzed DaA of 3-acetyl-1-methyloxindole (**4a**).[a]



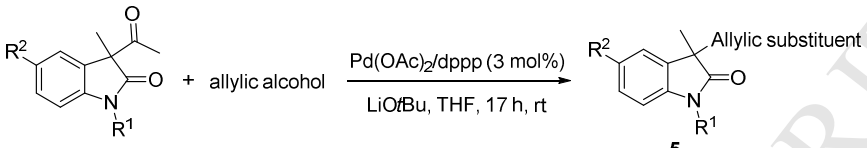
Entry	Cat (3 mol%)	Base (equiv)	Products ratio (%)[b]	Yield (%)[c]
1[d]	$Pd(OAc)_2$	KO*t*Bu (1.1)	**5ab** (76), **6aa** (24)	54
2[e]	$Pd(OAc)_2$	LiO*t*Bu (1.1)	**5ab** (79), **3aa** (17), **6aa** (4)	66
3[e]	$Pd(OAc)_2$[f]	LiO*t*Bu (1.1)	**5ab** (61), **3aa** (39)	-
4[e]	$Pd_2(dba)_3$[g]	LiO*t*Bu (1.1)	**5ab** (49), **3aa** (51)	-
5[e]	$Pd(OAc)_2$	LiO*t*Bu (1.5)	**5ab** (86), **3aa** (10), **6aa** (3)	70

[a] Reaction conditions: **4a** (0.3 mmol), allyl alcohol (0.45 mmol), Pd (3 mol%), ligand (3 mol%), THF (1.5 mL), 15 h, argon atmosphere.
[b] Determined by 300Mhz ^{1}H NMR on the crude product.
[c] Isolated crude yield. In parenthesis, yield after flash chromatography.
[d] Without using freezing pump.
[e] After using freezing pump.
[f] 6 mol% dppp was used.
[g] 1.5 mol% of $Pd_2(dba)_3$ was used

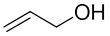
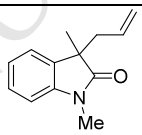
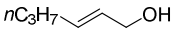
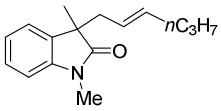
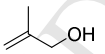
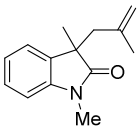
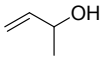
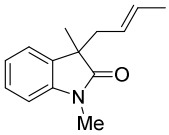
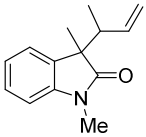
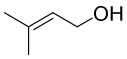
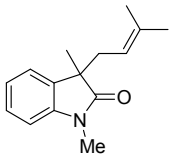
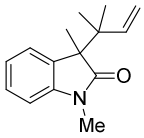
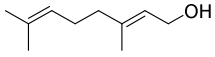
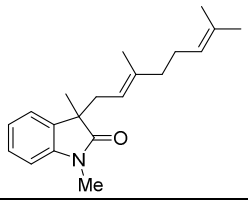
For the scope studies of this DaA process, different substituted oxindoles **4** and allylic alcohols were assayed using the optimal reaction conditions described on Table 2, entry 5 but 17 h instead of 15 h were needed as reaction time (Table 3). The reaction of **4a** with primary allylic alcohols such as allyl alcohol, hex-2-enol and methallyl alcohol gave the corresponding products **5aa**, **5ab** and **5ac** in good yields (Table 3, entries 1-3). The same occurred with geraniol giving product **5af** in moderate 45% yield (Table 3, entry 6). However, 1-methylallyl alcohol afforded a ca. 2:1 inseparable mixture of the γ- and the α-allylated products **5ad** and **5ad'** in 45% overall yield (Table 3, entry 4). Similar results were observed with prenyl alcohol affording a separable mixture of γ- and α-products **5ae** and **5ae'** in 51% and 16% yields, respectively (Table 3, entry 5). In the case of pent-1,4-dien-3-ol, a 8:1 mixture of γ- and α-products **5ag** and **5ag'** was obtained in 62% overall yield (Table 3, entry 7). The DaA of **4a** with cyclohex-2-ol gave dialkylated 2-

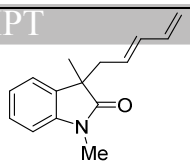
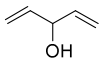
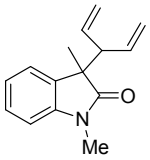
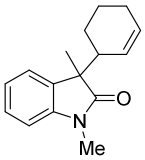
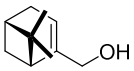
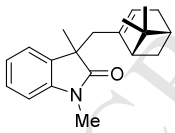
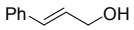
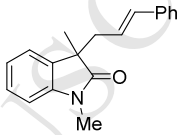
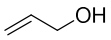
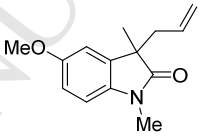
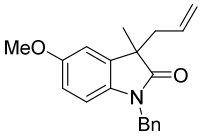
oxindole **5ah** in 75% yield as a 1:1 mixture of diastereomers (Table 3, entry 8). Primary alcohols such as (–)-myrtenol and cinnamyl alcohol provided compounds **5ai** and **5aj** in 56 and 51% yields, respectively (Table 3, entries 9 and 10). Compound **5ai** was obtained as an inseparable 5.5:1 mixture of diastereomers. Reactions of allyl alcohol with oxindoles **4b** and **4c** gave the corresponding products **5ba** and **5ca** in 72% and 77% yields, respectively (Table 3, entries 11 and 12). It is remarkable that compounds **5ab**, **5ad**, **5af**, **5ag** and **5aj** were isolated as unique *E*-stereoisomers.

Table 3. Palladium-catalyzed DaA of 3-acetyl-2-oxindoles **4**.[a]



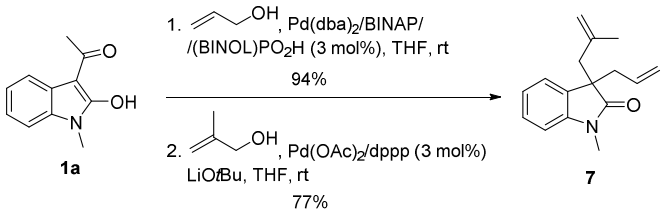
4a: R^1 = Me, R^2 = H
4b: R^1 = Me, R^2 = OMe
4c: R^1 = Bn, R^2 = OMe

Entry	**4**	Allylic Alcohol	**No.**	Product	Yield (%)[b]
1	**4a**		**5aa**		80
2	**4a**		**5ab**		70
3	**4a**		**5ac**		74
4	**4a**		**5ad**		45[c]
			5ad'		
5	**4a**		**5ae**		51
			5ae'		16
6	**4a**		**5af**		45

			5ag		55[d]
7	**4a**		**5ag'**		7
8	**4a**		**5ah**[e]		75
9	**4a**		**5ai**		56[f]
10[g]	**4a**		**5aj**		51
11	**4b**		**5ba**		72
12	**4c**		**5ca**		77

[a] Reaction conditions: **4** (0.3 mmol), allylic alcohol (0.45 mmol), $Pd(OAc)_2$ (3 mol%), dppp (3 mol%), LiO*t*Bu (0.45 mmol), THF (1.5 mL), 17 h at rt under argon atmosphere using freezing-pump.
[b] Isolated yields after flash chromatography
[c] An inseparable mixture of compounds **5ad** (68%) and **5ad'** (32%) was obtained.
[d] A 8:1 mixture of compounds **5ag** and **5ag'** was obtained.
[e] A *ca.* 1:1 mixture of diastereomers was obtained.
[f] A 5.5:1 mixture of diastereomers was obtained.
[g] 24 h reaction time.

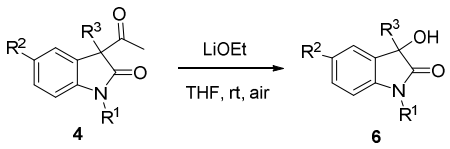
The synthesis of the unsymmetrically disubstituted 3,3-diallylated oxindole 7 was performed first by allylation of **1a** affording product **2aa** followed by Pd-catalyzed deacylative allylation with methallyl alcohol affording product **7** in 72% overall yield (Scheme 4).



Scheme 4. Sequential synthesis of 3-allyl-3-methallyl-1-methyl-2-oxindole (**7**).

The formation of 3-hydroxy-1,3-dimethyl-2-oxindoles as secondary products when oxygen was presented in the medium prompt us to study the best reaction conditions for the synthesis of 3-hydroxy oxindoles. 3-Substituted-3-hydroxy-2-oxindoles are important structural components of pharmacological active alkaloids such as convolutamydines and other useful intermediates for the synthesis of biological active compounds.[15] For the synthesis of these type of compounds 3-substituted-2-oxindoles together with oxygenating reagents are used.[16] Bisai and co-workers[11] recently reported that 3-alkyl-3-methoxycarbonyl-2-oxindoles can be transformed into the corresponding 3-hydroxy derivatives, by treatment with NaH and an oxygen balloon. In our case the reaction of compounds **4**[12] with 1 equiv of LiOEt in THF at rt under air atmosphere gave the corresponding 3-alkyl-3-hydroxy-2-oxindoles in good yields (Table 4).

Table 4. Synthesis of 3-alkyl-3-hydroxy-2-oxindoles **6**.[a]



4 **6**

Entry	R^1	R^2	R^3	Product	Yield (%)[b]
1	Me	H	Me	**6aa**	70
2	Me	H	Bn	**6ab**	68
3	Me	H	allyl	**6ac**	68
4	Me	H	propargyl	**6ad**	70
5	Me	OMe	Me	**6ba**	57
6	Bn	OMe	Me	**6ca**	58

[a] Reaction conditions: **4** (0.15 mmol), LiOEt (0.15 mmol), THF (1.5 mL), 12 h, rt under air.
[b] Isolated yield after flash chromatography.

3. Conclusions

The Pd-catalyzed allylation of 3-acetyl-2-oxindoles with allyl alcohol can be performed under BINOL-derived phosphoric as co-catalyst in THF at rt in good yields. This methodology allows the synthesis of monoallylated 2-oxindoles by in situ deacetylation with Triton B. For the deacylative allylation of 3-acetyl-3-methyl-2-oxindoles with allylic alcohols, $Pd(OAc)_2$/dppp and Li*O*t*B*u as base (1.5 equiv) gave the best results affording the corresponding 3,3-disubstituted 2-oxindoles in moderate to good yields. The mildness of both transformations allows to prepare no-easily accessible unsymmetrical 3,3-diallylated-1-methyl-2-oxindoles as has been demonstrated for compound **7**. By treatment of 3-alkyl-3-acetyl-2-oxindoles with LiOEt under air the corresponding 3-alkyl-3-hydroxy-2-oxindoles can be easily prepared. These reaction conditions are very mild, the selective substitution and the high tolerance of the reagents to many functional groups convert this process in an *a priori* useful tool for the synthesis of natural products.

4. Experimental section

4.1. General

Melting point was determined with a Marienfeld melting point meter (MPM-H2) apparatus and are uncorrected. For flash chromatography, silica gel 60 (40-60 μm) was employed. 300 and 400 MHz ^{1}H NMR and 75 and 101 MHz ^{13}C NMR (spectra were recorded using Bruker AV300 and Bruker AV400, respectively, with $CDCl_3$ as solvent and TMS as internal standard for ^{1}H NMR, and the own chloroform signal for ^{13}C NMR, and chemical shifts are given in ppm. IR spectra were recorded using a Jasco FT/IR-4100 Fourier Transform Infrared Spectrometer and a Nicolet Avatar 320 FT-IR Spectrometer. Low-resolution electron impact (GC-EI) mass spectra were obtained at 70 eV using a Agilent 6890N Network GC system and Agilent 5973 Network Mass Selective Detector. High-resolution mass spectra (GC-EI) were recorded using a QTOF Agilent 7200 instrument for the exact mass and Agilent 7890B for the GC. Analytical TLC was performed using ALUGRAM® Xtra SIL G/UV_{254} silica gel plates, and the spots were determined under UV light (λ=254 nm). Allylic alcohols were purchased as pure *E*-stereoisomers.

4.2. General procedure for the synthesis of 3-acetyl-3-allyl-2-oxindoles 2.

To a round-bottom flask was added $Pd(dba)_2$ (3 mol%, 5.2 mg, 0.009 mmol), *rac*-BINAP (3 mol%, 5.6 mg, 0.009 mmol), and dry THF (1.5 mL) and the mixture stirred for 30 min. Then, the oxindole **1** (0.3 mmol), the BINOL derived phosphoric acid (3 mol%, 3.1 mg, 0.009 mmol) and allyl alcohol (31 μL, 0.45 mmol) were added. The resulting mixture was stirred at rt for 60 h, and afterwards extracted with EtOAc (3x10 mL) and the organic phases washed with H_2O (10 mL), dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography (EtOAc/hexane) affording pure products **2**.

*3-Acetyl-3-allyl-1-methylindolin-2-one (**2aa**):* Yield 96%; Orange oil; R_f 0.19 (hexane/EtOAc 9/1); IR (neat) ν : 3521, 3410, 3078, 3057, 3006, 2923, 1738, 1724, 1609 cm^{-1}; ^{1}H NMR (400 MHz) δ_H: 7.36 (td, *J* = 7.7, 1.3 Hz, 1H), 7.19–7.17 (m, 1H), 7.10 (td, *J* = 7.5, 0.9 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 5.30 (dddd, *J* = 16.9, 10.1, 7.8, 6.7 Hz, 1H), 5.00 (dq, *J* = 17.0, 1.3 Hz, 1H), 4.90–4.87 (m, 1H), 3.28 (s, 3H), 2.95 (ddt, *J* = 13.8, 6.7, 1.1 Hz, 1H), 2.86 (dd, *J* = 13.9, 7.9 Hz, 1H), 1.99 (s, 3H); ^{13}C NMR (101 MHz) δ_C: 200.7, 174.5, 144.3, 131.5, 129.3, 127.0, 124.2, 123.2, 119.5, 108.5, 66.4, 37.5, 26.6; LRMS (EI) *m/z* (%): 229 (8) (M^+), 188 (14), 187 (100), 186 (24), 172 (14), 160 (24), 158 (16), 144 (13), 143 (13), 130 (12), 128 (10); HRMS (ESI): calcd. for $C_{14}H_{15}NO_2$ 229.1103; found 229.1101.

*3-Acetyl-3-allyl-5-methoxy-1-methylindolin-2-one (**2ba**):* Yield 61%; Orange oil; R_f 0.10 (hexane/EtOAc 9/1); IR (neat) ν : 3077, 3003, 2941, 2836, 1745, 1729, 1601 cm^{-1}; ^{1}H NMR (400 MHz) δ_H: 6.88 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.82–6.79 (m, 2H), 5.31 (dddd, *J* = 16.9, 10.1, 7.8, 6.7 Hz, 1H), 5.04–4.99 (m, 1H), 4.91–4.88 (m, 1H), 3.79 (s, 3H), 3.25 (s, 3H), 2.96–2.83 (m, 2H), 2.00 (s, 3H); ^{13}C NMR (101 MHz) δ_C: 200.8, 174.2, 156.4, 137.8, 131.5, 128.2, 119.5, 113.8, 111.2, 108.9, 66.8, 55.9, 37.6, 26.7, 26.6; LRMS (EI) *m/z* (%): 259 (28) (M^+), 218 (15), 217 (100), 216 (21), 202 (37), 190 (12), 188 (16), 176 (10), 174 (29), 173 (11), 144 (18), 115 (21), 77 (11); HRMS (ESI): calcd. for $C_{15}H_{17}NO_3$ 259.1208; found 259.1206.

*3-Acetyl-3-allyl-1-benzyl-5-methoxyindolin-2-one (**2ca**):* Yield 89%; Pale orange oil; R_f 0.21 (hexane/EtOAc 9/1); IR (neat) ν : 3065, 3032, 2922, 2836, 1745, 1723, 1600 cm^{-1}; ^{1}H NMR (300

MHz) δ_H: 7.33–7.27 (m, 5H), 6.78–6.74 (m, 2H), 6.69 (dd, *J* = 8.3, 0.6 Hz, 1H), 5.33 (dddd, *J* = 16.6, 10.0, 8.0, 6.5 Hz, 1H), 5.07 (ddd, *J* = 17.0, 3.1, 1.2 Hz, 1H), 5.01–4.86 (m, 3H), 3.75 (s, 3H), 3.03–2.88 (m, 2H), 2.01 (s, 3H); ^{13}C NMR (75 MHz) δ_C: 200.7, 174.3, 156.4, 136.9, 135.7, 131.6, 128.9, 128.2, 127.9, 127.6, 119.8, 113.8, 111.1, 110.1, 66.8, 55.9, 44.3, 37.6, 26.7; LRMS (EI) *m/z* (%): 335 (10) (M^+), 294 (11), 293 (47), 91 (100); HRMS (ESI): calcd. for $C_{21}H_{21}NO_3$ 335.1521; found 335.1521.

4.3. Typical procedure for the synthesis of 3-allyl-1-methylindolin-2-one (3ab).[17]

After performing the Pd-catalyzed allylation of compound **1a** (see, Section 4.2), a solution of benzyltrimethylammonium hydroxide (Triton B) in MeOH (40 wt%, 136µL, 0.3 mmol) was added and, immediately, acetic acid (0.85 mL, 15 mmol). Immediately, the extractive work-up was performed with EtOAc (3x10 mL), the organic phases were washed with H_2O (10 mL), dried with $MgSO_4$, filtered and concentrated. The resulting crude was purified by flash chromatography (hexane/EtOAc) to afford pure compound **3ab** in 61% yield.

4.4. General procedure for the Pd-catalyzed deacylative allylation of compounds 4. Synthesis of 3-allylated 3-methyl-2-oxindoles 5.

To a mixture of $Pd(OAc)_2$ (3 mol%, 2.0 mg, 0.009 mmol) and 1,3-bis(diphenylphosphino)propane (3 mol%, 3.7 mg, 0.009 mmol), was added dry THF (1 mL) under Ar and stirring continued for 30 min. This mixture was added to a solution of oxindole **4** (0.3 mmol) in dry THF (0.5 mL). Finally, the allylic alcohol (0.45 mmol) was added and the mixture was degassed by three cycles of freeze-pump-thaw and filled with Ar before the addition of Li*O*t*B*u (36 mg, 0.45 mmol). The solution was stirred at rt for 14 h and then extracted with EtOAc (3x10 mL). The organic phases were washed with water (10 mL), dried over $MgSO_4$, and evaporated under vacuum. The pure compounds **5** were obtained after flash chromatography (hexane/EtOAc).

Compounds **5aa**,[18] **5ac**,[11] **5ae**,[19] **5'ae**,[19] **5ai**,[11] **5aj**,[18] **5ba**[14] and **5ca**[12] are known, new compounds follow:

*(*E*)-3-(Hex-2-en-1-yl)-1,3-dimethylindolin-2-one (**5ab**):* Yield 70%; Yellow oil; R_f 0.17 (hexane/EtOAc 9.5/0.5); IR (neat) ν : 3055, 2962, 2927, 2872, 1713, 1613 cm^{-1}; ^{1}H NMR (400 MHz) δ_C: 7.27–7.23 (m, 1H), 7.19–7.16 (m, 1H), 7.05 (td, *J* = 7.5, 0.9 Hz, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 5.40–5.32 (m, 1H), 5.08–4.99 (m, 1H), 3.18 (s, 3H), 2.50–2.39 (m, 2H), 1.81 (q, *J* = 7.0 Hz, 2H), 1.35 (s, 3H), 1.20 (q, *J* = 7.3 Hz, 2H), 0.73 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz) δ_C: 180.5, 143.3, 134.9, 134.0, 127.7, 123.9, 123.0, 122.3, 107.9, 48.7, 41.5, 34.5, 26.1, 22.6, 22.5, 13.5; LRMS (EI) *m/z* (%): 243 (8) (M^+), 162 (9), 161 (80), 160 (100), 130 (8), 117 (9); HRMS (ESI): calcd. for $C_{16}H_{21}NO$ 243.1623; found 243.1621.

*(*E*)-3-(But-2-en-1-yl)-1,3-dimethylindolin-2-one (**5ad**) and isomers:* Yield 45%; Brown oil; R_f 0.22 (hexane/EtOAc 9/1); IR (neat) ν : 3054, 3025, 2965, 2927, 1716, 1613 cm^{-1}; ^{1}H NMR (400 MHz) δ_H: 7.29–7.24 (m, 1.7H), 7.21 (d, *J* = 7.3 Hz, 0.3H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1.5H), 6.83 (d, *J* = 7.7 Hz, 1.4H), 5.87 (dt, *J* = 17.3, 9.4 Hz, 0.2H), 5.67–5.54 (m, 0.3H), 5.42 (dq, *J* = 12.8, 6.3 Hz, 1H), 5.16–4.99 (m, 1.4H), 4.90 (d, *J* = 10.1 Hz, 0.1H), 3.24 (s, 0.4H), 3.22 (s, 0.7H), 3.20 (s, 3H), 3.18 (s, 0.3H), 2.70–2.47 (m, 0.7H), 2.43 (d, *J* = 7.2 Hz, 1.6H), 1.66 (d, *J* = 6.7 Hz, 0.3H), 1.52 (d, *J* = 6.3 Hz, 3H), 1.45 (s, 0.3H), 1.39 (s, 0.6H), 1.35 (s, 3H), 0.99 (d, *J* = 6.9 Hz, 0.3H), 0.68 (d, *J* = 6.7 Hz, 0.5H); ^{13}C NMR (101 MHz) δ_C: 180.6, 143.3, 143.2, 139.2, 138.6, 134.0, 134.0, 129.4, 127.9, 127.8, 127.8, 127.7, 127.4, 124.9, 124.2, 123.9, 123.2, 123.2, 123.0, 122.9, 122.4, 122.3, 122.3, 121.1, 117.0, 115.8, 108.1, 107.9, 107.9, 107.8, 51.3, 51.2, 48.6, 48.4, 45.9, 44.9, 41.4, 35.5, 26.2, 22.8, 22.6, 22.2, 21.6, 18.0, 15.3, 15.0, 13.1; LRMS (EI) *m/z* (%): 215 (10) (M^+), 161 (32), 161 (100), 160 (100), 132 (11), 130 (14), 117 (16) 77 (11), 55 (13); HRMS (ESI): calcd. for $C_{16}H_{21}NO$ 215.1310; found 215.1309.

*(*E*)-3-(3,7-Dimethylocta-2,6-dien-1-yl)-1,3-dimethylindolin-2-one (**5af**):* Yield 45%; Pale yellow oil; R_f 0.32 (hexane/EtOAc 9/1); IR (neat) ν : 3055, 2967, 2927, 1713, 1613 cm^{-1}; ^{1}H NMR (400 MHz) δ_H: 7.27–7.22 (m, 1H), 7.21–7.17 (m, 1H), 7.03 (td, *J* = 7.5, 0.9 Hz, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 5.00–4.93 (m, 1H), 4.89–4.82 (m, 1H), 3.19 (s, 3H), 2.47 (d, *J* = 7.6 Hz, 2H), 1.95–1.82 (m, 4H), 1.64 (s, 3H), 1.54 (s, 3H), 1.50 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (101 MHz) δ_C: 180.8, 143.3, 138.9, 134.2, 131.5, 127.7, 124.3, 123.1, 122.3, 118.3, 107.8, 48.7, 39.9, 36.8, 26.8, 26.2, 25.8, 22.4, 17.8, 16.4; LRMS (EI) *m/z* (%): 297 (1) (M^+), 162 (11), 161 (100), 160 (30), 130 (8), 117 (8), 69 (27); HRMS (ESI): calcd. for $C_{20}H_{27}NO$ 297.2093; found 297.2093.

*(*E*)-1,3-Dimethyl-3-(penta-2,4-dien-1-yl)indolin-2-one (**5ag**):* Mixture of isomers (major *trans* isomer); Yield 55%; Pale yellow wax; R_f 0.24 (hexane/EtOAc 9/1); IR (KBr) ν : 2924, 2852, 1713, 1612 cm^{-1}; ^{1}H NMR (300 MHz) δ_H: 7.26 (td, *J* = 7.9, 1.3 Hz, 1H), 7.21–7.16 (m, 1H), 7.06 (td, *J* = 7.5, 1.0 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 6.21–5.96 (m, 2H), 5.36 (dt, *J* = 15.0, 7.7 Hz, 1H), 5.09–5.02 (m, 1H), 4.96–4.92 (m, 1H), 3.19 (s, 3H), 2.53 (d, *J* = 7.7 Hz, 2H), 1.37 (s, 3H); ^{13}C NMR (75 MHz) δ_C: 180.2, 143.2, 136.7, 134.8, 133.7, 128.3, 127.9, 123.0, 122.5, 116.3, 108.0, 48.5, 41.3, 26.2, 22.7; LRMS (EI) *m/z* (%): 227 (5) (M^+), 174 (9), 161 (13), 160 (100), 132 (11), 130 (13), 117 (15), 77 (10), 67 (10); HRMS (ESI): calcd. for $C_{15}H_{17}NO$ 227.1310; found 227.1305.

*1,3-Dimethyl-3-(penta-1,4-dien-3-yl)indolin-2-one (**5ag'**):* Yield 7%; Colorless oil; R_f 0.28 (hexane/EtOAc 9/1); IR (neat) ν : 3076, 2962, 2926, 1712.8, 1613 cm^{-1}; ^{1}H NMR (300 MHz) δ_H: 7.31–7.25 (m, 1H), 7.22–7.20 (m, 1H), 7.05 (td, *J* = 7.5, 1.0 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 5.86 (ddd, *J* = 17.0, 10.4, 8.3 Hz, 1H), 5.39 (ddd, *J* = 17.1, 10.2, 8.7 Hz, 1H), 5.19–5.01 (m, 3H), 4.93 (dd, *J* = 10.1, 1.9 Hz, 1H), 3.22–3.14 (m, 4H), 1.36 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C: 179.9, 143.7, 135.7, 135.6, 132.4, 128.0, 123.7, 122.3, 118.2, 117.4, 107.9, 55.6, 51.2, 26.2, 21.8; LRMS (EI) *m/z* (%): 227 (5) (M^+), 161 (11), 160 (100), 132 (10), 130 (11), 117 (13), 77 (7), 67 (5), 65 (5); HRMS (ESI): calcd. for $C_{15}H_{17}NO$ 227.1310; found 227.1309.

*3-(Cyclohex-2-en-1-yl)-1,3-dimethylindolin-2-one (**5ah**):* Mixture of diastereoisomers; Yield 55%; Pale yellow oil; R_f 0.28 (hexane/EtOAc 9/1); IR (Major diastereoisomer, neat) ν : 2930, 2866, 1712, 1611 1492.6, cm^{-1}; ^{1}H NMR (major diastereoisomer, 300 MHz) δ_H: 7.29–7.23 (m, 1H), 7.21–7.18 (m, 1H), 7.02 (td, *J* = 7.5, 1.0 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 5.88–5.74 (m, 2H), 3.21 (s, 3H), 2.72–2.63 (m, 1H), 1.95–1.72 (m, 2H), 1.64–1.33 (m, 6H), 0.95–0.83 (m, 1H); ^{13}C NMR (major diastereoisomer, 75 MHz) δ_C: 180.5, 143.7, 133.1, 130.8, 127.7, 126.0, 123.8, 122.3, 107.7, 51.0, 43.0, 26.2, 25.1, 24.5, 21.8, 21.5; LRMS (EI)

m/z (%): 241 (8) (M^+), 162 (20), 161 (100), 160 (73), 130 (11), 117 (11), 81 (22); HRMS (ESI): calcd. for $C_{16}H_{19}NO$ 241.1467; found 241.1464.

4.5. General procedure for the deacylative oxidation of compounds 4. Synthesis of 3-alkyl-3-hydroxy-2-oxindoles 6.

To a solution of oxindole **4** (0.15 mmol) in dry THF (1.5 mL) was added dropwise a solution of LiOEt (0.1 M in THF, 150 µL, 0.15 mmol) and the mixture was stirred at rt for 12 h. Then was extracted with EtOAc (3x10 mL), the organic phases were washed with water (10 mL), dried over $MgSO_4$, and evaporated under vacuum. The pure compounds **6** were obtained after flash chromatography (hexane/EtOAc).

Compounds **6aa**,[20] **6ab**,[21] **6ac**,[22] **6ad**,[23] and **6ba**[24] are known, a new compound follow:

1-Benzyl-3-hydroxy-5-methoxy-3-methylindolin-2-one ***(6ca)****:* Yield 58%; Orange solid; m.p. 135–137 °C (hexane/EtOAc); R_f 0.12 (hexane/EtOAc 7/3); IR (KBr) ν : 3347, 3028, 2927, 2833, 1704 cm^{-1}; ^1H NMR (400 MHz) δ_H: 7.32–7.23 (m, 5H), 7.04 (d, *J* = 2.6 Hz, 1H), 6.70 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.60 (d, *J* = 8.5 Hz, 1H), 4.93 (d, *J* = 15.7 Hz, 1H), 4.78 (d, *J* = 15.7 Hz, 1H), 3.75 (s, 3H), 3.17 (br s, 1H), 1.67 (s, 3H); ^{13}C NMR (101 MHz) δ_C: 178.8, 156.6, 135.6, 135.1, 132.9, 128.9, 127.8, 127.3, 114.2, 110.6, 110.3, 74.3, 55.9, 43.9, 25.3; LRMS (EI) *m/z* (%): 283 (39) (M^+), 267 (8), 192 (7), 174 (5), 146 (8), 106 (7), 92 (10), 91 (100), 89 (6), 77 (7), 65 (19) 63 (5), 51 (5); HRMS (ESI): calcd. for $C_{17}H_{17}NO_3$ 283.1208; found 283.1203.

4.6. General procedure for the combined double allylation of 1a. Synthesis of 3-allyl-3-methallyl-1-methyl-2-oxindole 7.

The first step was carried out following the description of section 4.2. for the synthesis of intermediate **2aa**. The second step was run according to section 4.4. and, after purification, product **7**[25] was isolated in 72% yield.

Acknowledgments

We gratefully acknowledge financial support from the Spanish Ministerio de Economía y Competitividad (MINECO) (projects CTQ2013-43446-P and CTQ2014-51912-REDC), the Spanish Ministerio de Economía, Industria y Competitividad, Agencia Estatal de Investigación (AEI) and Fondo Europeo de Desarrollo Regional (FEDER, EU) (projects CTQ2016-76782-P and CTQ2016-81797-REDC), the Generalitat Valenciana (PROMETEO2009/039 and PROMETEOII/2014/017) and the University of Alicante. A. O.-M. thanks MINECO for a predoctoral fellowship.

Supplentary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.

References and notes

1. For a review, see: Muzart J. *Eur. J. Org. Chem.* 2007; 3077-3089.
2. For a review, see: Weaver JD, Recio AIII, Grenning AJ, Tunge JA. *Chem. Rev.* 2011; 111: 1846-1913.
3. (a) Grenning AJ, Tunge JA. *Angew. Chem. Int. Ed.* 2011; 50: 1688-1699; (b) Grenning AJ, Tunge JA. *J. Am. Chem. Soc.* 2011; 133: 14785-14794; (c) Grenning AJ, Van Allen CK, Maji T, Lang SB, Tunge JA. *J. Org. Chem.* 2013; 78: 7281-7287.
4. (a) Otera J, Ioka S, Nozaki H. *J. Org. Chem.* 1989; 54: 4013-4014; (b) Otera J, Dan-oh N, Nozaki H. *J. Org. Chem.* 1991; 56: 5307-5311; (c) Orita A, Sakamoto K, Hamada Y, Mitsutome A, Otera J. *Tetrahedron* 1999; 55: 2899-2910.
5. For recent reviews, see: (a) Cao ZY, Wang YH, Zeng YP, Zhou J. *Tetrahedron Lett.* 2014; 55: 2571-2584; (b) Shen K, Liu X, Feng X. *Chem. Sci*. 2012; 3: 327-334; (c) Singh GS, Desta ZY. *Chem. Rev.* 2012; 112: 6104-6155; (d) Dalpozzo R, Bartoli G, Bencivenni G. *Chem. Soc. Rev.* 2012; 41: 7247-7290; (e) Zhou F, Liu YL, Zhou J. *Adv. Synth. Catal.* 2010; 352: 1381-1407; (f) Galliford CV, Scheidt KA. *Angew. Chem. Int. Ed.* 2007; 46: 8748-8758.
6. Trost BM, Brennan MK. *Org. Lett.* 2006; 8: 2027-2030.
7. Trost BM, Zhang Y. *J. Am. Chem. Soc*. 2006; 128: 4590-4591.
8. Huang A, Kodanko JJ, Overman LE. *J. Am. Chem. Soc.* 2004; 126: 14043-14053.
9. Trost BM, Malhotra S, Chan WH. *J. Am. Chem. Soc*. 2011; 133: 7328-7331.
10. Linton EC, Kozlowski MC. *J. Am. Chem. Soc*. 2008; 130: 16162-16163.
11. (a) Yang H, Zhou H, Yin H, Xia C, Jiang G. *Synlett* 2014; 25: 2149-2154; (b) Kumar N, Das MK, Ghosh S, Bisai A. *Chem. Commun.* 2017, 53, 2170-2170.
12. Ortega-Martínez A, Molina C, Moreno-Cabrerizo C, Sansano JM, Nájera C. *Synthesis* 2017, DOI: 10.1055/s-0036-1590880.
13. (a) Tamaru Y, Horino Y, Araki M, Tanaka S, Kimura M. *Tetrahedron Lett.* 2000; 41: 5705-5709; (b) Kimura M, Mukai R, Tanigawa N, Tanaka S, Tamaru, Y. *Tetrahedron* 2003; 59: 7767-7777.
14. (a) Trost BM, Zhang Y. *Chem. Eur. J*. 2011; 17: 2916-2922; (b) Reisch J, Mueller M, Labitzke H. *Arch Pharm*. 1984; 317: 639-646.
15. (a) Matsuda H, Yoshida K, Miyagawa K, Asao Y, Takayama S, Nakashima S, Xu F, Yoshikawa M. *Bioorg. Med. Chem.* 2007; 15: 1539-1546; (b) Lucas-López C, Patterson S, Blum T, Straight AF, Toth J, Slawin AMZ, Mitchison TJ, Sellers JR, Westwood NJ. *Eur. J. Org. Chem*. 2005; 1736-1740.
16. Ohmatsu K, Ando Y, Ooi T. *Synlett* 2017; 28: 1291-1294 and references cited therein.
17. Jang YJ, Yoon H, Lautens M. *Org. Lett*. 2015; 17: 3895-3897.
18. Zhou Y, Zhao Y, Dai X, Liu J, Li L, Zhang H. *Org. Biomol. Chem.* 2011; 9: 4091-4097.
19. Zhou B, Hou W, Yang Y, Feng H, Li Y. *Org. Lett.* 2014; 16: 1322-1325.
20. Shin I, Ramgren SD, Krische MJ. *Tetrahedron* 2015, 71, 5776-5780.
21. Ghandi M, Feizi S, Ziaie F, Notash B. *Tetrahedron* 2014; 70: 2563-2569.
22. Zhao C, Tan Z, Liang Z, Deng W, Gong H. *Synthesis* 2014; 46: 1901-1907.
23. Alcaide B, Almendros P, Rodríguez-Acebes R. *J. Org. Chem*. 2005; 70: 3198-3204.
24. Wanh H, Li Y, Wang G, Zhang H, Yang SD. *Asian J. Org. Chem.* 2013; 2: 486-490.
25. Kinthada LK, Medisetty SR, Parida A, Babu KN, Bisai A. *J. Org. Chem*. 2017; 82: 8548-8567.