Tetrahedron 64 (2008) 10381–10387

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Development of intermolecular additive free Pauson–Khand reactions for estrone E-ring extension using microwaves

Erika Fager-Jokela [a], Emmi Kaasalainen [a], Kirsi Leppänen [b], Jan Tois [c], Juho Helaja [d,*]

[a] Laboratory of Organic Chemistry, Department of Chemistry, University of Helsinki, PO Box 55, FIN-00014, Finland
[b] Department of Physics, University of Helsinki, PO Box 64, FIN-00014, Finland
[c] Orion Pharma, PO Box 65, FIN-02101 Espoo, Finland
[d] Department of Chemistry, University of Helsinki, PO Box 55, FIN-00014, Finland

ARTICLE INFO

Article history:
Received 2 June 2008
Received in revised form 5 August 2008
Accepted 21 August 2008
Available online 28 August 2008

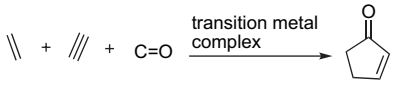
Keywords:
Pauson–Khand
Cycloaddition
Microwave
Estrone

ABSTRACT

Intermolecular additive free microwave (MW) promoted and cobalt octacarbonyl mediated Pauson–Khand reaction (PKR) performance was improved for estrone ring extension. The reaction development with norbornene and cyclopentene produced cyclopentenones in yields of comparable levels with those previously obtained with the aid of chemical additives as promoters. The PKRs with norbornene demonstrated that a low cobalt complex concentration increases yields, especially for the aliphatic alkynes. Furthermore, a boost for the MW PKR could be obtained by a gradual cobalt complex addition. These expedients combined with the use of an excess of free and cobalt complexed alkyne led to successful estrone ring system extension with various alkynes.

1. Introduction

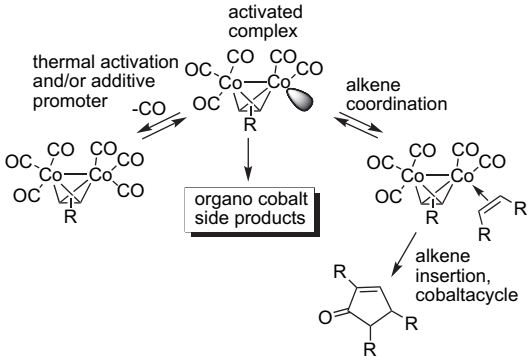
The Pauson–Khand reaction (PKR),[1] i.e., a formal [2+2+1] cycloaddition of an alkyne, an alkene and a carbonyl unit, is a powerful and versatile tool in the synthesis of complex molecules.[2]



It is well established that the intermolecular PKR suffers from the limitation of being applicable to a narrow range of reactive alkenes, which normally must feature a strained backbone.[3] Recently, the scope of the reaction has been expanded towards less strained alkenes with the aid of the development of various additives (amines, phosphates, *N*-oxides, sulphides and other Lewis bases), which serve as PKR promoters.[4] It is broadly recognised that the key role of an additive, in a general sense, is to accelerate the displacement of a CO ligand from the alkyl cobalt complex and thus create a vacant site for the coordination of the alkene (Scheme 1).

We have recently reported that cobalt catalysed PKR's can be applied effectively in the extension of estrone ring systems with phenyl substituted cyclopentenone rings (R=Ar, Scheme 2).[5] Driven by our interest in exploring the applicability and flexibility of the PKR in the chemical transformation of biologically active molecules, we applied this methodology towards the synthesis of other compounds potentially useful in steroidogenic enzyme inhibition.[6]

As a first modification attempt, we carried out the cycloaddition with alkynes bearing an aliphatic group in place of an aromatic system. To our surprise, under the reaction conditions that we had previously used,[5] and which rely on sulphide-promoted activation, no successful formation of the expected product was observed. This prompted us to explore a range of alternative conditions for the PKR to provide access to estrone ring extension with a broader range of employable alkynes (Scheme 2).



Scheme 1.

* Corresponding author. Tel.: +358 9 19150430; fax: +358 9 19150466.
E-mail address: juho.helaja@helsinki.fi (J. Helaja).

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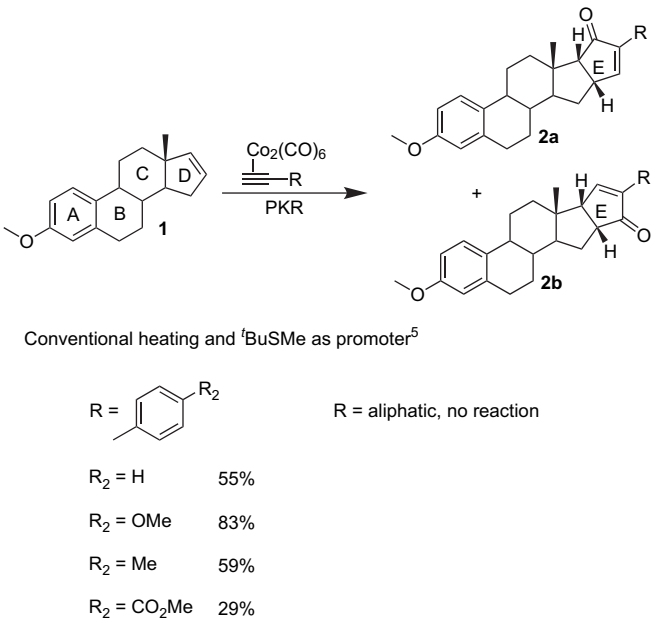
doi:10.1016/j.tet.2008.08.066



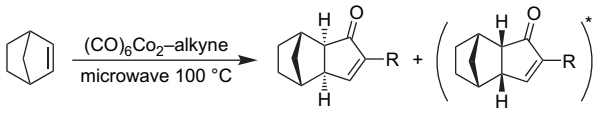
Scheme 2. Estrone ring system extension with PKR.[5]

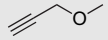
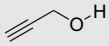
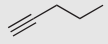
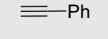
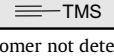
Microwave (MW) irradiations have also been shown to accelerate PKR's under promoter-free stoichiometric conditions,[7] as well as catalytically in the presence of a promoter.[8] In the latter case, best yields reported were obtained with 20% catalyst loadings.[8] Together these observations prompted us to reason whether a MW-promoted stoichiometric reaction could reach its optimal performance by simply maintaining the low ratio of the cobalt complex with respect to alkene over the course of the reaction.

2. Results and discussion

In the present study, the method development for MW-promoted PKR's was initially conducted on the inexpensive compound norbornene (Table 1), and successively repeated on cyclopentene (Table 2). With the former compound, the reaction development is performed with a stoichiometric amount of alkene, whereas for the more volatile cyclopentene, the reaction conditions were optimised

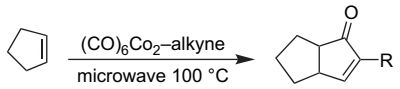
Table 1
MW PKR with 1 equiv norbornene

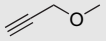
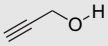
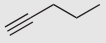
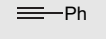
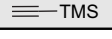


Entry	Alkyne	Mode of MW reaction and yield (%)[a]			
		Single addition (1×45 min)		4×0.25 equiv (4×10 min)	
		[0.18 M]	[0.072 M]		In charcoal
1		46	65	75	67
2		15	20	30	17
3		42	83	98	73
4		89	78	84	83
5		79	84	85	75

* *endo* isomer not detected.
[a] Yields after SiO_2 flash chromatographic purification.

Table 2
MW PKR with an excess of cyclopentene



Entry	Alkyne	Mode of reaction and isolated yield (%)[a]	
		Without charcoal (1 h)	In charcoal (1 h)
1		39	64
2		38	46
3		36	21
4		39	58
5		Not detected	Traces

[a] Yields after SiO_2 flash chromatographic purification.

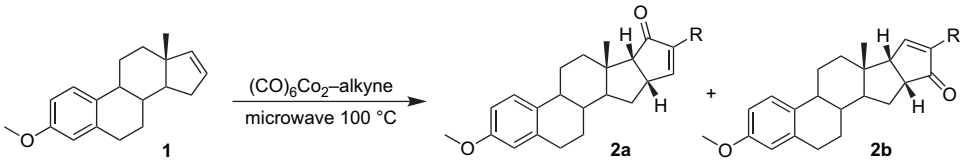
by use of an excess of alkene. Additionally, we carried out experiments with activated charcoal as an easy procedure for in situ removal of undesired organocobalt species.[9] In preliminary MW irradiation experiments we found out that the best yields can be obtained at about 100 °C. At more elevated temperatures, an increased decomposition was observed for the alkynyl–cobalt species, while in many cases also the MW reaction tubes exploded under the MW irradiation. Hence, in the reaction, time was the adjusted parameter for the different alkenes rather than the temperature.

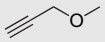
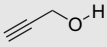
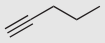
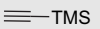
The MW PKR's with norbornene were first run with a single mode of addition, i.e., the alkynyl–cobalt species was added into reaction mixture in one portion (single addition, Table 1). In 0.18 M solution poor to fair yields were obtained with aliphatic alkynes (entries 1–3) and fair to good with aromatic and silyl alkynes (entries 4 and 5). Increased yields were obtained for aliphatic alkynes when reactions were run in more dilute solution (0.072 M). Accordingly, when the cobalt complex was added in portions (4×0.25 equiv), maintaining its concentration low, the yields were significantly improved for aliphatic alkynes, with best results approaching quantitative yields when pentyne was used without charcoal (entry 3). However, for the aromatic and silyl alkynes, no substantial effect was observed when using this method. When the gradual addition method was run in active charcoal suspension, slightly lower yields were obtained in all cases.

Overall, in most instances, the yields obtained for the MW reactions with the gradual addition method for norbornene without additives (Table 1) are approaching the best results reported in the literature for the corresponding PKR's with additives and conventional heating: 75% with nicotine *N*-oxide for pentyne[10] (entry 3, 98% with gradual addition), 67% with triethyl amine *N*-oxide dihydrate (TMANO) for propargyl alcohol[11] (entry 2, 30% with gradual addition), quantitative yield with NH_4OH for phenyl acetylene[12] (entry 4, 89%), 83% with polymer supported methyl sulphide for trimethylsilyl acetylene[13] (entry 5, 85% with gradual addition). In our experiments the stoichiometric use alkene makes the developed method even more valuable while the literature yields have been in part received in a presence of an excess of norbornene.[10,12,13]

In the case of cyclopentene, the MW-promoted reactions were run with an excess of alkene, implying a low relative alkynyl–cobalt/alkene ratio and therefore no requirement for the gradual addition mode.[14] To our surprise, poor to fair yields were obtained in absence of charcoal (entries 1–5, Table 2), whereas yields generally improved when reactions were run in the activated charcoal suspension. This clearly indicates that charcoal promotes the PKR's under MW irradiation with some substrates.

Table 3
MW PKR's with 1 equiv estrone derived alkene **1**



Entry	Alkyne	Yields[a] (%) versus addition mode of the cobalt-alkyl complex					Regioisomer ratio **a**/**b**[b]
		Single addition 1 equiv (150 min)	4×0.25 equiv (4×30 min)	6×0.25 equiv (6×1 h)	In charcoal		
					4×0.25 equiv (4×30 min)	6×0.25 equiv (6×1 h)	
1		24	33	60	28	63	1:1.3
2		14	16	44	7	33	1:2
3		10	8	33	21	32	1:1.7
4		28	32	57	23	62	1:1.3
5		Not detected		6			0:1

[a] Yields after SiO_2 flash chromatographic purification. In all the cases no estrone derived side products could be detected, except the recoverable starting material **1**.
[b] Regioisomer ratios are estimated from the product mixture based on integrals of characteristic ^1H NMR signals.

In terms of comparison with our results, up-to-date additive-promoted PKR's of cyclopentene found in the literature report yields of 53% for propargyl alcohol with TMANO additive[11] (Table 2, entry 2, 46% in charcoal suspension) and 75% for phenyl acetylene when refluxed for 3 days in DCM with methanol as an additive[15] (entry 4, 58% 1 h in charcoal suspension).

The encouraging effects of the gradual cobalt–alkyl complex addition (4×0.25 equiv) obtained with norbornene (Table 1) and those of the activated charcoal obtained for the cyclopentene inspired us to exploit these expedients for the estrone derivate **1**. Disappointingly, both of these methods produced poor yields for the ring extended estrone derivatives **2a** and **2b**, without any significant difference to the yields obtained with the single mode addition (Table 3). Nevertheless, absence of estrone side products was noted: all of the estrone derivative **1** that was not converted to the cyclopentenone products could essentially be recovered during the chromatographic purification. This encouraged us to further explore the boost for the reactions: the amount of added alkynyl–cobalt complex was increased to 1.5 equiv in the gradual mode addition procedure (6×0.25 equiv), the MW irradiation time period was increased from 30 to 60 min and an additional alkyne equivalent was added to the reaction mixture.[16] Gratifyingly, this technique increased the yields to fair-good level in gradual addition method (Table 3), except for the trimethylsilyl alkyne, which remained unreactive, as with cyclopentene (Table 2, entry 5).

The estrone (**2a**/**2b**) regioisomers obtained in the PKR's (Table 3, entries 1–5) were purified with HPLC and identified by NMR based on the characteristic chemical shifts and NOESY correlations, in a similar way to that reported earlier for the phenyl derivatives.[5] The inspection of the obtained regioisomer ratios indicates that the ring extended estrone regioisomer **2b** is predominantly formed in all cases (Table 3). This is in contradiction with our previous study in which, using ^{t}BuSMe additive as a promoter, the phenyl derivative formed in a 55% total yield with a 1.6:1 ratio (**2a**/**2b**). By applying the conditions described herein, the ratio inverted for the same conversion to 1:1.3 (**2a**/**2b**), while the yields reached even slightly higher level, being 57% for PKR performed without and 62% with the charcoal suspension.

The reactions carried out in activated carbon suspension produced generally cleaner product mixtures, and in some cases even a completely clear solution, free of colourful organocobalt species, was produced.[17] The charcoal evidently affected with some extent to the obtained yields and the mechanistic role of charcoal has yet to be unveiled. It has been shown that catalytically active cobalt nanoparticles can be synthesised on active charcoal when the cobalt octacarbonyl complex is thermally treated with active charcoal.[18] However, this was not the case in the present study: the wide angle X-ray scattering (WAXS) measurements of charcoal indicated no sign of cobalt nanoparticles but reflections originated from organocobalt species.[19] Our hypothesis is that the charcoal activates the alkynyl–cobalt complex similarly to how it occurs in thermal activation: impact between the hexacarbonylcobalt species and charcoal causes removal of one carbonyl group (Scheme 1) and creates the vacant site on the metal. In the absence of the stabilisation effect that an additive promoter could possibly provide, the produced activated species reacts readily either with available alkene in the PKR or with other cobalt species producing organocobalt side products (Scheme 1).

3. Conclusions

We have demonstrated in this work that additive free MW irradiations promote intermolecular PKR's for norbornene, cyclopentene and estrone derivative **1** with a range of alkynes. Moreover, the obtained yields for norbornene and cyclopentene PKR's are well comparable with the ones that have reported with various Lewis base additives as promoters. Based on this study low alkynyl–cobalt complex concentration is generally advantageous for the intermolecular MW-promoted PKR's. Overall, the gradual addition of cobalt complex method under MW irradiation can be a valid alternative to the use of substrate specific activators as PKR promoters.

The use of charcoal suspension in the reaction mixture is beneficial to obtain cleaner reaction mixtures, but with a remark that the yields may be, alkyne substrate dependently, negatively or positively affected.

4. Experimental

4.1. General

The following includes general experimental procedures, specific details for representative reactions and spectroscopic

information for new compounds. All reactions were performed in dry glassware under an argon atmosphere. Reaction solvents were either distilled over sodium and stored over 4 Å sieves (toluene) or used as received (1,2-dichloroethane). Propargyl alcohol was distilled prior to use and all other alkynes were used as received. Estrone derivate **1** was synthesised according to the previously published procedure.[5] Activated charcoal (p.a. Merck 2186) was used as received. Microwave reactions were performed using a Biotage Initiator 8 (400 W) and Biotage 5 ml sealed vials. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at room temperature using Varian Mercury 300 or Varian Inova 500 machine. ^{1}H spectra were referenced to tetramethylsilane (TMS, 0.0 ppm) and ^{13}C spectra were referenced to solvent carbon (77.0 ppm). No special notation is used for equivalent carbons. IR spectra were measured using FTIR PE Spectrum One spectrometer.

4.2. General procedure for norbornene reactions

(a) Single mode additions: The corresponding alkyne (0.36 mmol) and cobalt octacarbonyl (123 mg, 0.36 mmol) were stirred in toluene (2 ml or 5 ml) under argon for 30 min. Norbornene (34 mg, 0.36 mmol) was added to the dark red solution. The reaction mixture was heated with MW for 45 min at 100 °C. The reaction mixture was adsorbed on silica and purified by column chromatography.
(b) The gradual addition experiments were performed as above except that alkynyl–cobalt complex was formed in 4 ml of toluene, added in 0.25 equiv over the norbornene dissolved in toluene (1 ml) and irradiated with MW for 10 min after each addition (total 40 min).
(c) In charcoal experiments 100 mg of charcoal was suspended in the reaction mixture prior to first MW irradiation.

4.2.1. 3a,4,5,6,7,7a-Hexahydro-2-(methoxymethyl)-4,7-methano-1H-inden-1-one (Table 1, entry 1)

Following the general procedure, the single mode addition reaction of methyl propargyl ether (30.4 μl, 0.36 mmol) in 2 ml of toluene gave 32 mg (0.17 mmol, 46%) of the desired product after purification by column chromatography (hexane–ethyl acetate 5:1→1:1). R_f=0.21 (hexane–EtOAc=3:1); δ_H: 7.38 (1H, m, C*H*═), 4.10 (2H, m, CH_2OCH_3), 3.39 (3H, s, CH_3O–), 2.64 (1H, m, ═CHC*H*), 2.40 (1H, m), 2.21 (2H, m), 1.62 (2H, m), 1.29 (2H, m), 1.00 (2H, m); δ_C: 209.5, 160.4, 145.9, 66.2, 58.7, 54.1, 48.4, 38.8, 37.8, 31.0, 28.9, 28.2; FTIR (cm^{-1}) 2953 (m), 2872 (m), 1693 (s), 1637 (w); ESI HRMS $[C_{12}H_{16}O_2+Na]^+$ 215.1057, calcd 215.1048 (Δ=4.2 ppm).

Yields for the other addition modes were as follows: 45 mg (0.24 mmol, 65%) for reaction in 5 ml of toluene; 52 mg (0.27 mmol, 75%) for the gradual addition reaction; 45 mg (0.23 mmol, 67%) for gradual addition with charcoal.

4.2.2. 3a,4,5,6,7,7a-Hexahydro-2-(hydroxymethyl)-4,7-methano-1H-inden-1-one (Table 1, entry 2)

Following the general procedure, the single mode addition reaction of propargyl alcohol (21 μl, 0.36 mmol) in 2 ml of toluene gave 10 mg (0.05 mmol, 15%) of the desired product after purification by column chromatography (hexane–ethyl acetate 2:1→0:1). The recorded spectra corresponds well to the previously published data.[20] δ_H: 7.70 (2H, m), 7.64 (1H, d, *J*=2.9 Hz), 7.35 (3H, m), 2.70 (1H, m), 2.50 (1H, m), 2.37 (1H, m), 2.28 (1H, m), 1.78–1.51 (2H, m), 1.32 (2H, m), 1.12 (1H, m), 1.00 (1H, m); δ_C: 211.3, 159.9, 147.8, 57.6, 54.5, 48.6, 39.0, 37.9, 31.1, 29.1, 28.3.

Yields for the other addition modes were as follows: 13 mg (0.07 mmol, 20%) for reaction in 5 ml of toluene; 19 mg (0.11 mmol, 30%) for the gradual addition reaction; 11 mg (0.06 mmol, 17%) for gradual addition with charcoal.

4.2.3. 3a,4,5,6,7,7a-Hexahydro-2-propyl-4,7-methano-1H-inden-1-one (Table 1, entry 3)

Following the general procedure, the single mode addition reaction of 1-pentyne (35 μl, 0.36 mmol) in 2 ml of toluene gave 29 mg (0.15 mmol, 42%) of the desired product after purification by column chromatography (CH_2Cl_2). The recorded spectra corresponds well to the previously published data.[21] δ_H: 7.10 (1H, m, C*H*═), 2.56 (1H, m), 2.38 (1H, m), 2.14 (4H, m), 1.73–1.56 (2H, m), 1.50 (2H, m), 1.28 (2H, m), 1.04–0.85 (2H, m), 0.91 (3H, t, *J*=7.4 Hz); δ_C: 211.1, 158.7, 149.2, 53.8, 48.1, 38.9, 38.0, 30.9, 29.0, 28.4, 26.7, 21.0, 13.8.

Yields for the other addition modes were as follows: 57 mg (0.30 mmol, 83%) for reaction in 5 ml of toluene; 67 mg (0.35 mmol, 98%) for the gradual addition reaction; 50 mg (0.26 mmol, 73%) for gradual addition with charcoal.

4.2.4. 3a,4,5,6,7,7a-Hexahydro-2-phenyl-4,7-methano-1H-inden-1-one (Table 1, entry 4)

Following the general procedure, the single mode addition reaction of phenyl acetylene (40 μl, 0.36 mmol) in 2 ml of toluene gave 72 mg (0.32 mmol, 89%) of the desired product after purification by column chromatography (hexane–ethyl acetate 20:1→10:1). The recorded spectra corresponds well to the previously published data.[20] δ_H: 7.70 (2H, m), 7.64 (1H, d, *J*=2.9 Hz), 7.35 (3H, m), 2.70 (1H, m), 2.50 (1H, m), 2.37 (1H, m), 2.28 (1H, m), 1.78–1.51 (2H, m), 1.32 (2H, m), 1.12 (1H, m), 1.00 (1H, m); δ_C: 208.9, 160.1, 146.1, 131.5, 128.3 (3C), 127.0 (2C), 54.9, 47.7, 39.4, 38.3, 31.2, 29.1, 28.4.

Yields for the other addition modes were as follows: 63 mg (0.28 mmol, 78%) for reaction in 5 ml of toluene; 68 mg (0.30 mmol, 84%) for the gradual addition reaction; 67 mg (0.30 mmol, 83%) for gradual addition with charcoal.

4.2.5. 3a,4,5,6,7,7a-Hexahydro-2-(trimethylsilyl)-4,7-methano-1H-inden-1-one (Table 1, entry 5)

Following the general procedure, the single mode addition reaction of trimethylsilylacetylene (50 μl, 0.36 mmol) in 2 ml of toluene gave 63 mg (0.29 mmol, 79%) of the desired product after purification by column chromatography (hexane–ethyl acetate 20:1→10:1). The recorded spectra corresponds well to the previously published data.[22] δ_H: 7.54 (1H, d, *J*=2.5 Hz), 2.64 (1H, dd, *J*=5.3, 2.5 Hz), 2.36 (1H, m), 2.15 (1H, m), 2.10 (1H, d, *J*=5.3 Hz), 1.59 (2H, m), 1.26 (2H, m), 0.90 (2H, m), 0.15 (9H, s); δ_C: 214.9, 172.9, 150.1, 54.3, 51.9, 39.1, 38.0, 31.0, 29.0, 28.3, −1.8.

Yields for the other addition modes were as follows: 67 mg (0.30 mmol, 84%) for reaction in 5 ml of toluene; 68 mg (0.31 mmol, 85%) for the gradual addition reaction; 60 mg (0.27 mmol, 75%) for gradual addition with charcoal.

4.3. General procedure for cyclopentene reactions

(a) Single mode additions: The corresponding alkyne (0.36 mmol) and cobalt octacarbonyl (123 mg, 0.36 mmol) were stirred in toluene (2 ml) under argon for 30 min. Cyclopentene (0.5 ml, 5.46 mmol) was added to the dark red solution. The reaction mixture was heated with MW for 60 min at 100 °C. The reaction mixture was adsorbed on silica and purified by column chromatography.
(b) In charcoal experiments 100 mg of charcoal was suspended in the reaction mixture prior to MW irradiation and 4 ml of toluene was used.

4.3.1. cis-4,5,6,6a-Tetrahydro-2-(methoxymethyl)-pentalen-1(3aH)-one (Table 2, entry 1)

Following the general procedure, the single mode addition reaction of methyl propargyl ether (30 μl, 0.36 mmol) in 2 ml of

toluene gave 24 mg (0.14 mmol, 39%) of the desired product after purification by column chromatography (hexane–ethyl acetate 5:1). R_f=0.21 (hexane–EtOAc=3:1); δ_H: 7.39 (1H, m, C*H*=), 4.08 (2H, m, CH_2OCH$_3$), 3.39 (3H, s, CH$_3$O–), 3.30 (1H, m), 2.78 (1H, m), 1.89 (1H, m), 1.58–1.78 (4H, m), 1.25 (1H, m); δ_C: 211.5, 162.3, 143.4, 66.3, 58.8, 50.6, 44.4, 30.1, 29.4, 23.6; FTIR (cm^{-1}) 2938 (m), 2867 (m), 1695 (s), 1640 (w); ESI HRMS $[C_{10}H_{14}O_2+Na]^+$ 189.0892, calcd 189.0892 (Δ=0.5 ppm).

Yield for reaction with charcoal was 39 mg (0.23 mmol, 64%).

4.3.2. *cis-4,5,6,6a-Tetrahydro-2-(hydroxymethyl)-pentalen-1(3aH)-one (Table 2, entry 2)*

Following the general procedure, the single mode addition reaction of propargyl alcohol (21 μl, 0.36 mmol) in 2 ml of toluene gave 21 mg (0.14 mmol, 38%) of the desired product after purification by column chromatography (hexane–ethyl acetate 2:1→0:1). R_f=0.19 (hexane–EtOAc=1:1); δ_H: 7.34 (1H, m), 4.37 (2H, m), 3.30 (1H, m), 2.79 (1H, m), 2.56 (1H, m), 1.90 (1H, m), 1.67 (3H, m), 1.25 (1H, m); δ_C: 213.0, 161.5, 145.2, 57.5, 50.9, 44.5, 30.0, 29.3, 23.6; FTIR (cm^{-1}) 3406 (m, br), 2939 (m), 2868 (m), 1683 (s), 1635 (m); ESI HRMS $[C_9H_{12}O_2+Na]^+$ 175.0730, calcd 175.0730 (Δ=0.2 ppm).

Yield for reaction with charcoal was 25 mg (0.16 mmol, 46%).

4.3.3. *cis-4,5,6,6a-Tetrahydro-2-propyl-pentalen-1(3aH)-one (Table 2, entry 3)*

Following the general procedure, the single mode addition reaction of 1-pentyne (35 μl, 0.36 mmol) in 2 ml of toluene gave 21 mg (0.13 mmol, 36%) of the desired product after purification by column chromatography (CH_2Cl_2). R_f=0.47 (hexane–EtOAc=3:1); δ_H: 7.10 (1H, m), 3.21 (1H, m), 2.72 (1H, m), 2.13 (2H, m), 1.89 (1H, m), 1.77–1.42 (7H, m), 1.20 (1H, m), 0.90 (3H, t); δ_C: 213.0, 160.4, 146.6, 50.1, 43.9, 30.2, 29.7, 26.7, 23.5, 21.0, 13.8; FTIR (cm^{-1}) 2957 (m), 2936 (m), 2868 (m), 1699 (s), 1631 (w); ESI HRMS $[C_{11}H_{16}O+Na]^+$ 187.1097, calcd 187.1093 (Δ=1.7 ppm).

Yield for reaction with charcoal was 12 mg (0.07 mmol, 21%).

4.3.4. *cis-4,5,6,6a-Tetrahydro-2-phenyl-pentalen-1(3aH)-one (Table 2, entry 4)*

Following the general procedure, the single mode addition reaction of phenyl acetylene (40 μl, 0.36 mmol) in 2 ml of toluene gave 28 mg (0.14 mmol, 39%) of the desired product after purification by column chromatography (hexane–ethyl acetate 20:1→10:1). The recorded spectra corresponds well to the previously published data.[23] δ_H: 7.69 (3H, m), 7.36 (3H, m), 3.35 (1H, m), 2.92 (1H, m), 2.02 (1H, m), 1.88–1.58 (4H, m), 1.30 (1H, m); δ_C: 210.6, 161.7, 143.5, 131.5, 128.3, 127.0, 51.2, 43.5, 30.5, 29.8, 23.6.

Yield for reaction with charcoal was 41 mg (0.21 mmol, 58%).

4.4. General procedure for estrone derivative 1 reactions

(a) Single mode additions: The corresponding alkyne (0.36 mmol) and cobalt octacarbonyl (123 mg, 0.36 mmol) were stirred in 1,2-dichloroethane (2 ml) under argon for 30 min. 16-Ene-3-methoxyestra-1,3,5(10)-triene **1** (97 mg, 0.36 mmol) was added to the dark red solution. The reaction mixture was heated with MW for 150 min at 100 °C. The reaction mixture was adsorbed on silica and purified by column chromatography. Regioisomers were separated with preparative HPLC (Waters600 with LiChroCART SI60 column, detection at 280 nm), and identified with NOESY NMR measurements.

(b) The gradual addition experiments (4×0.25 equiv) were performed as above except that alkynyl–cobalt complex was formed in 4 ml of DCE, added in 0.25 equiv to the estrone derivate **1** in DCE (1 ml) and irradiated with MW for 30 min after each addition (total 120 min).

(c) In the gradual addition experiments (6×0.25 equiv), 3 equiv of the corresponding alkyne and 1.5 equiv of $Co_2(CO)_8$ were used. Half of the alkyne (0.54 mmol) and cobalt octacarbonyl (185 mg, 0.54 mmol) were stirred in DCE (3 ml) under argon for 30 min, added in 0.25 equiv to the solution of the estrone derivate **1** (97 mg, 0.36 mmol) and half of the alkyne (0.54 mmol) in DCE (2 ml), and irradiated with MW for 60 min after each addition (total 360 min).

(d) In charcoal experiments 100 mg of charcoal was suspended in the reaction mixture prior to first MW irradiation.

4.4.1. *1′-Oxo-2′-methoxymethylcyclopent-2′-enyl[4′,5′:16(S),17(R)]-3-methoxyestra-1,3,5(10)-triene (Table 3, entry 1)*

Following the general procedure, the single mode addition reaction of methyl propargyl ether (30 μl, 0.36 mmol) in 2 ml of DCE gave 32 mg (0.09 mmol, 24%) of the desired product after purification by column chromatography (hexane–ethyl acetate 5:1). Isomers were separated by HPLC.

(**a**) R_f=0.18 (hexane–EtOAc=3:1); δ_H: 7.41 (1H, m, C*H*=), 7.18 (1H, d, *J*=8.5 Hz), 6.70 (1H, dd, *J*=8.5, 2.7 Hz), 6.61 (1H, d, *J*=2.7 Hz), 4.10 (2H, m, CH_2OCH$_3$), 3.76 (3H, s, Ar–OCH_3), 3.40 (3H, s), 3.35 (1H, m), 2.81 (3H, m), 2.45 (1H, d, *J*=5.3 Hz, COC*H*), 2.31 (1H, dq, *J*=13.1, 3.2 Hz), 2.13 (1H, td, *J*=10.9, 3.8 Hz), 2.01 (1H, dt, *J*=13.0, 3.2 Hz), 1.83 (1H, m), 1.74–1.61 (3H, m), 1.59–1.08 (3H), 0.94 (3H, s, CH_3C); δ_C: 208.5, 161.6, 157.5, 144.2, 137.7, 132.5, 126.3, 113.8, 111.4, 66.5, 61.2, 58.9, 55.2, 48.1, 44.2, 43.4, 42.6, 38.4, 34.2, 29.8, 29.2, 27.9, 26.3, 20.8; FTIR (cm^{-1}) 2924, 2869, 1694 (s); ESI HRMS $[C_{24}H_{30}O_3+Na]^+$ 389.2077, calcd 389.2087 (Δ=2.6 ppm).

(**b**) R_f=0.17 (hexane–EtOAc=3:1); δ_H: 7.51 (1H, m, C*H*=), 7.16 (1H, d, *J*=8.5 Hz), 6.69 (1H, dd, *J*=8.5, 2.7 Hz), 6.61 (1H, d, *J*=2.7 Hz), 4.12 (2H, m, CH_2OCH$_3$), 3.76 (3H, s, Ar–OCH_3), 3.40 (3H, s), 2.94 (1H, m, =CHC*H*), 2.82 (3H, m), 2.31 (1H, m), 2.12 (1H, td, *J*=10.4, 4.0 Hz), 1.93 (2H, m), 1.84 (2H, m), 1.69 (1H, td, *J*=13.0, 10.3 Hz), 1.54–1.20 (3H, m), 1.07 (1H, m), 0.94 (3H, s, CH_3C); δ_C: 211.5, 159.6, 157.5, 145.2, 137.9, 132.3, 126.2, 113.7, 111.5, 66.7, 58.9, 55.9, 55.2, 48.7, 47.7, 43.4, 42.3, 38.3, 35.0, 29.9, 29.8, 27.9, 26.3, 20.6; FTIR (cm^{-1}) 2983 (w), 2927 (m), 2851 (m), 1698 (s), 1609 (m); ESI HRMS $[C_{24}H_{30}O_3+Na]^+$ 389.2080, calcd 389.2087 (Δ=1.9 ppm).

Yields for the other addition modes were as follows: 43 mg (0.12 mmol, 33%) for gradual addition reaction (4×0.25 equiv); 37 mg (0.10 mmol, 28%) for gradual addition (4×0.25 equiv) with charcoal; 80 mg (0.22 mmol, 60%) for gradual addition reaction (6×0.25 equiv); 83 mg (0.23 mmol, 63%) for gradual addition (6×0.25 equiv) with charcoal.

4.4.2. *1′-Oxo-2′-(hydroxymethyl)cyclopent-2′-enyl-[4′,5′:16(S),17(R)]-3-methoxyestra-1,3,5(10)-triene (Table 3, entry 2)*

Following the general procedure, the single mode addition reaction of propargyl alcohol (21 μl, 0.36 mmol) in 2 ml of DCE gave 18 mg (0.05 mmol, 14%) of the desired product after purification by column chromatography (hexane–ethyl acetate 2:1→0:1). Isomers were separated by HPLC.

(**a**) R_f=0.20 (hexane–EtOAc=1:1); δ_H: 7.35 (1H, m, C*H*=), 7.19 (1H, d, *J*=8.6 Hz), 6.70 (1H, dd, *J*=8.6, 2.7 Hz), 6.61 (1H, d, *J*=2.7 Hz), 4.37 (2H, m, CH_2OCH$_3$), 3.77 (3H, s, Ar–OCH_3), 3.36 (1H, m), 2.85 (3H, m), 2.47 (1H, d, *J*=5.3 Hz, COC*H*), 2.32 (2H, m), 2.14 (1H, td, *J*=11.1, 3.9 Hz), 2.01 (1H, dt, *J*=13.1, 3.2 Hz), 1.82 (1H, m), 1.68 (3H, m), 1.56–1.12 (2H), 1.08 (1H, m), 0.96 (3H, s, CH_3C); δ_C: 210.1, 160.9, 157.5, 145.6, 137.7, 132.5, 126.3, 113.8, 111.5, 61.4, 57.9, 55.2, 48.1, 44.3, 43.3, 42.6, 38.4, 34.2, 29.8, 29.1, 27.9, 26.3, 20.8; FTIR (cm^{-1}) 3434 (m, br), 2926 (s), 2870 (m), 1691 (s), 1500 (s); ESI HRMS $[C_{23}H_{28}O_3+H]^+$ 353.2107, calcd 353.2111 (Δ=1.1 ppm).

(**b**) R_f=0.19 (hexane–EtOAc=1:1); δ_H: 7.45 (1H, m, C*H*=), 7.16 (1H, d, *J*=8.5 Hz), 6.70 (1H, dd, *J*=8.5, 2.7 Hz), 6.62 (1H, d, *J*=2.7 Hz),

4.40 (2H, m, CH_2OH), 3.77 (3H, s, Ar–OCH_3), 2.95 (1H, m, =CHC*H*), 2.85 (3H, m), 2.32 (1H, m), 2.12 (1H, m), 1.93 (2H, m), 1.84 (1H, m), 1.70 (1H, m), 1.54–1.20 (5H, m), 1.08 (1H, m), 0.94 (3H, s, CH_3C); δ_C: 212.8, 158.8, 157.5, 146.9, 137.9, 132.2, 126.2, 113.8, 111.5, 58.0, 56.0, 55.2, 48.8, 47.6, 43.4, 42.3, 38.3, 35.0, 29.8, 29.7, 27.8, 26.3, 20.5; FTIR (cm^{-1}) 3430 (m, br), 2917 (s), 2850 (m), 1694 (s), 1500 (s); ESI HRMS $[C_{23}H_{28}O_3+H]^+$ 353.2111, calcd 353.2111 (Δ=0.03 ppm).

Yields for the other addition modes were as follows: 20 mg (0.06 mmol, 16%) for gradual addition reaction (4×0.25 equiv); 9 mg (0.025 mmol, 7%) for gradual addition (4×0.25 equiv) with charcoal; 56 mg (0.16 mmol, 44%) for gradual addition reaction (6×0.25 equiv); 42 mg (0.12 mmol, 33%) for gradual addition (6×0.25 equiv) with charcoal.

4.4.3. 1′-Oxo-2′-propylcyclopent-2′-enyl[4′,5′:16(S),17(R)]-3-methoxyestra-1,3,5(10)-triene (Table 3, entry 3)

Following the general procedure, the single mode addition reaction of 1-pentyne (35 μl, 0.36 mmol) in 2 ml of DCE gave 13 mg (0.04 mmol, 10%) of the desired product after purification by column chromatography (hexane–ethyl acetate 5:1). Isomers were separated by HPLC.

(**a**) R_f=0.44 (hexane–EtOAc=3:1); δ_H: 7.19 (1H, d, J=8.7 Hz), 7.13 (1H, m, C*H*=), 6.70 (1H, dd, J=8.7, 2.8 Hz), 6.61 (1H, d, J=2.8 Hz), 3.76 (3H, s, Ar–OCH_3), 3.27 (1H, m), 2.83 (3H, m), 2.41 (1H, d, J=5.4 Hz, COC*H*), 2.30 (1H, m), 2.14 (2H, m), 2.01 (1H, m), 1.83 (1H, m), 1.67–1.59 (3H, m), 1.56–1.08 (3H), 0.96–0.85 (9H, m); δ_C: 209.9, 160.0, 157.5, 147.3, 137.7, 132.6, 126.3, 113.8, 111.4, 60.7, 55.2, 48.0, 44.1, 43.5, 42.0, 38.4, 34.3, 29.8, 29.5, 28.0, 26.7, 26.3, 21.0, 20.8, 13.8; FTIR (cm^{-1}) 2922 (s), 2868 (m), 1694 (s); ESI HRMS $[C_{25}H_{32}O_2+H]^+$ 365.2480, calcd 365.2475 (Δ=1.5 ppm).

(**b**) R_f=0.42 (hexane–EtOAc=3:1); δ_H: 7.24 (1H, m, C*H*=), 7.17 (1H, d, J=8.6 Hz), 6.69 (1H, dd, J=8.6, 2.8 Hz), 6.61 (1H, d, J=2.8 Hz), 3.77 (3H, s, Ar–OCH_3), 2.83 (4H, m), 2.31 (1H, m), 2.18 (2H, m), 2.09 (1H, m), 1.95–1.79 (3H, m), 1.67 (1H, m), 1.60–1.21 (2H, m), 1.02 (1H, m), 0.92 (6H, m); δ_C: 212.9, 157.6, 157.5, 148.3, 137.9, 132.3, 126.2, 113.7, 111.5, 55.3, 55.2, 48.2, 47.5, 43.6, 42.1, 38.3, 35.0, 30.0, 29.8, 27.9, 27.0, 26.4, 21.0, 20.6, 13.8; FTIR (cm^{-1}) 2956 (m), 2929 (m), 2871 (m), 2851 (w), 1698 (s), 1609 (m); ESI HRMS $[C_{25}H_{32}O_2+H]^+$ 365.2484, calcd 365.2475 (Δ=2.4 ppm).

Yields for the other addition modes were as follows: 10 mg (0.03 mmol, 8%) for gradual addition reaction (4×0.25 equiv); 28 mg (0.08 mmol, 21%) for gradual addition (4×0.25 equiv) with charcoal; 40 mg (0.12 mmol, 33%) for gradual addition reaction (6×0.25 equiv); 39 mg (0.12 mmol, 32%) for gradual addition (6×0.25 equiv) with charcoal.

4.4.4. 1′-Oxo-2′-phenylcyclopent-2′-enyl[4′,5′:16(S),17(R)]-3-methoxyestra-1,3,5(10)-triene (Table 3, entry 4)

Following the general procedure, the single mode addition reaction of phenyl acetylene (40 μl, 0.36 mmol) in 2 ml of DCE gave 40 mg (0.10 mmol, 28%) of the desired product after purification by column chromatography (hexane–ethyl acetate 20:1→10:1). Isomers were separated by HPLC. The recorded spectra correspond well to the previously published data.[5]

(**a**) δ_H: 7.75 (2H, m), 7.71 (1H, d, J=3.2 Hz), 7.40–7.31 (3H, m), 7.19 (1H, d, J=8.6 Hz), 6.70 (1H, dd, J=8.6, 2.7 Hz), 6.61 (1H, m), 3.76 (3H, s), 3.42 (1H, m), 2.82 (2H, m), 2.61 (1H, d, J=5.5 Hz), 2.35 (1H, m), 2.19–2.00 (2H, m), 1.86 (1H, m), 1.77 (2H, m), 1.61–1.16 (5H, m), 1.00 (3H, s); δ_C: 207.6, 161.5, 157.5, 143.9, 137.7, 132.5, 131.5, 128.4, 126.3, 113.8, 111.4, 61.8, 55.2, 49.4, 48.3, 44.6, 43.4, 41.6, 38.4, 34.3, 29.7, 29.6, 27.9, 26.3, 20.9.

(**b**) δ_H: 7.81 (1H, m), 7.76 (2H, m), 7.39 (3H, m), 7.17 (1H, d, J=8.7 Hz), 6.70 (1H, m), 6.61 (1H, m), 3.76 (3H, s), 3.01 (2H, m), 2.83 (2H, m), 3.33 (1H, m), 2.16–1.98 (2H, m), 1.89–1.71 (3H, m), 1.62–1.40 (3H, m), 1.36–1.10 (2H, m), 0.98 (3H, s); δ_C: 210.6, 159.1, 157.5, 145.1, 137.9, 132.2, 131.5, 128.4, 127.1, 126.1, 113.8, 111.5, 55.2, 54.9, 49.4, 47.8, 43.4, 42.8, 38.4, 35.1, 30.4, 29.7, 27.8, 26.4, 20.6.

Yields for the other addition modes were as follows: 46 mg (0.12 mmol, 32%) for gradual addition reaction (4×0.25 equiv); 32 mg (0.08 mmol, 23%) for gradual addition (4×0.25 equiv) with charcoal; 91 mg (0.23 mmol, 63%) for gradual addition reaction (6×0.25 equiv); 82 mg (0.21 mmol, 57%) for gradual addition (6×0.25 equiv) with charcoal.

4.4.5. 1′-Oxo-2′-(trimethylsilyl)cyclopent-2′-enyl[4′,5′:16(S),17(R)]-3-methoxyestra-1,3,5(10)-triene (Table 3, entry 5)

Following the general procedure, the gradual addition experiment (6×0.25 equiv) of trimethylsilyl acetylene (150 μl, 0.36 mmol) in DCE gave 9 mg (0.02 mmol, 6%) of the desired product after purification by column chromatography (hexane–ethyl acetate 20:1→10:1). Only one isomer (**b**) was detected. ^{13}C NMR shifts of quaternary carbons were assigned from HMBC spectrum.

(**b**) R_f=0.48 (hexane–EtOAc=3:1); δ_H: 7.71 (1H, m, C*H*=), 7.16 (1H, d, J=8.5 Hz), 6.69 (1H, dd, J=8.5, 2.9 Hz), 6.61 (1H, d, J=2.9 Hz), 3.77 (3H, s, Ar–OCH_3), 3.72 (1H, m), 2.96 (1H, dd, J=5.6, 2.6 Hz), 2.83 (2H, m), 2.74 (1H, ddm, J=10.0, 5.5 Hz), 2.31 (1H, m), 2.10 (1H, m), 1.98–1.80 (3H, m), 1.66 (1H, m), 1.58–1.15 (5H, m), 0.95 (1H, m), 0.93 (1H, s), 0.19 (9H, s); δ_C: 216.8, 172.2, 157.5, 149.9, 138.0, 132.3, 126.2, 113.7, 111.5, 59.1, 55.2, 48.7, 43.5, 42.7, 38.3, 35.1, 30.1, 29.8, 27.9, 26.4, 20.8, −1.7; FTIR (cm^{-1}) 2929 (m), 2851 (w), 1690 (s), 1501 (s), 1246 (m), 841 (s); ESI HRMS $[C_{25}H_{34}O_2Si+H]^+$ 395.2399, calcd 395.2401 (Δ=0.4 ppm).

Acknowledgements

Mr. Antti Kivimäki and Ms. Jenni Kovanen are acknowledged for their technical assistance in the PKR optimisation. Dr. Petri Heinonen and Dr. Pirkko Karhunen are acknowledged for the HRMS measurements and expertise in HPLC purifications, respectively. Prof. Ritva Serimaa is gratefully accredited for her contribution in the WAX measurements. The authors kindly acknowledge the Academy of Finland for financial support (J.H., Project No. 215785).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.08.066.

References and notes

1. Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977–981; Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc., Perkin Trans. 1* **1973**, 975–977.
2. Representative PKR reviews: (a) synthesis of complex molecules: Blanko-Urgoiti, J.; Anorbe, L.; Perez-Serrano, L.; Dominguez, G.; Perez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32–42; (b) intermolecular reactions: Gibson, S. E.; Mainolfi, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 2–17; (c) catalytic reactions: Gibson, S. E.; Stevenazzi, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1800–1810.
3. de Bruin, T. J. M.; Milet, A.; Greene, A. E.; Gimbert, Y. *J. Org. Chem.* **2004**, *69*, 1075–1080.
4. Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263–3283.
5. Kaasalainen, E.; Tois, J.; Russo, L.; Rissanen, K.; Helaja, J. *Tetrahedron Lett.* **2006**, *47*, 5669–5672.
6. Bydal, P.; Auger, S.; Poirier, D. *Steroids* **2004**, *69*, 325–342; Fischer, D. S.; Allan, G. M.; Bubert, C.; Vicker, N.; Smith, A.; Tutill, H. J.; Purohi, A.; Wood, L.; Packham, G.; Mahon, F.; Reed, M. J.; Potter, B. V. L. *J. Med. Chem.* **2005**, *48*, 5749–5770.
7. Iqbal, M.; Vyse, N.; Dauvergne, J.; Evans, P. *Tetrahedron Lett.* **2002**, *43*, 7859–7862.
8. Fischer, S.; Groth, U.; Jung, M.; Schneider, A. *Synlett* **2002**, 2023–2026.
9. Active charcoal must be suspended into solution in order to avoid tube explosion under MW irradiation.
10. Derdau, V.; Laschat, S. *J. Organomet. Chem.* **2002**, *642*, 131–136.
11. Ford, J. G.; Kerr, W. J.; Kirk, G. G.; Lindsay, D. M.; Middlemiss, D. *Synlett* **2000**, 1415–1418.
12. Sugihara, T.; Yamada, M.; Ban, H.; Yamaguchi, M.; Kaneko, C. *Angew. Chem., Int. Ed.* **1997**, *36*, 2801–2804.
13. Kerr, W. J.; Lindsay, D. M.; McLaughlin, M.; Pauson, P. R. *Chem. Commun.* **2000**, 1467–1468.
14. The gradual addition had no influence on the yields in corresponding reference experiments.

15. Chung, Y. K.; Lee, B. Y.; Jeong, N.; Hudecek, M.; Pauson, P. L. *Organometallics* **1993**, *12*, 220–223.
16. The further increase of added alkynyl–cobalt complex and irradiation time improved still slightly the yields, but it led to laborious purification due to presence of large amounts of organocobalt species, whereas the addition of an uncomplexed alkyne equivalent raised yields up to 20% combined with the excess of added cobalt complex.
17. Referee's remark: in the case of compound **1** charcoal promoting effect on the yields is minor and could be inside error limits.
18. Son, S. U.; Lee, S. I.; Chung, Y. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 4158–4160; Son, S. U.; Park, K. H.; Chung, Y. K. *Org. Lett.* **2002**, *4*, 3983–3986.
19. The X-ray scattering setup consisted of a sealed copper anode X-ray tube, a multilayer monochromator (Incoatec, Germany) and an image plate detector (MAR345, Mar Research, Germany). Cu Kα radiation with the wavelength of 1.542 Å was used.
20. Hay, A. M.; Kerr, W. J.; Kirk, G. G.; Middlemiss, D. *Organometallics* **1995**, *14*, 4986–4988.
21. Derdau, V.; Laschat, S.; Jones, P. G. *Heterocycles* **1998**, *48*, 1445–1453.
22. Park, K. H.; Chung, Y. K. *Adv. Synth. Catal.* **2005**, *347*, 854–866.
23. Khand, I. U.; Pauson, P. L. *J. Chem. Res., Synop.* **1977**, 9; *J. Chem. Res., Miniprint* **1977**, 0168–0187; Billington, D. C.; Helps, I. M.; Pauson, P. L.; Thomson, W.; Willison, D. *J. Organomet. Chem.* **1988**, *354*, 233–242; Denmark, S. E.; Habermas, K. L.; Hite, G. A. *Helv. Chim. Acta* **1988**, *71*, 168–194.